NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Year 5 Report

2022

Prepared by the Task Force for
Combating Antibiotic-Resistant Bacteria

Contents

Executive Summary

The National Action Plan for Combating Antibiotic-Resistant Bacteria 2015 – 2020 (2015 Plan) has guided the U.S. Government's response to combating antibiotic-resistant infections since its establishment in 2015. The U.S. Government's Interagency Task Force for Combating Antibiotic-Resistant Bacteria (CARB) has produced four previous reports on progress toward the 2015 Plan. This Year 5 Report presents highlights of activities achieved during the last year of the 2015 Plan and summarizes major accomplishments achieved between 2015 and 2020. In addition to the specific activities, this report discusses challenges and barriers faced in their implementation.

Since 2015, the U.S. Government has pursued strategic domestic action and catalytic global leadership to strengthen efforts to prevent, detect, and control illness and death related to infections caused by antibiotic-resistant bacteria. These actions have supported human and animal health by promoting antibiotic stewardship to improve antibiotic use in a variety of human healthcare settings and by eliminating the use of medically important antibiotics for growth promotion in animals in the United States; created and expanded surveillance networks and improved monitoring of antibiotic resistance as well as antibiotic use; supported the development and use of new diagnostics and treatments; and promoted strong national, regional, and international dialogue and political commitments to address antibiotic resistance.

While these achievements have generated significant progress toward the 2015 Plan's five goals, antibiotic resistance remains an urgent threat in the United States and abroad. In 2020, the CARB Task Force issued an updated National Action Plan to be implemented between 2020 and 2025 (2020 Plan) that describes continuing and new high priority actions for reducing antibiotic resistance in the next five years. This 2020 Plan builds on the achievements described in this report, addresses ongoing and emerging barriers and challenges, is responsive to the evolving domestic and international landscape, and outlines aspirational targets (to be updated and/or added to annually) that the U.S. Government will undertake to continue to reduce the emergence, spread, and impact of antibiotic resistance.

Introduction

The discovery of antibiotics in the early 20th century fundamentally transformed human and veterinary medicine. However, bacterial and fungal pathogens have evolved to develop resistance to many of these lifesaving products. Any time an antibiotic is used, there is a chance for resistance to develop and decrease the usefulness of that antibiotic. Both appropriate and inappropriate use of antibiotic products—in humans, animals, plants and crops, and the environment—can drive the evolution of resistance. Emerging resistant pathogens can spread undetected and contribute to the development and prevalence of resistance. Currently, Centers for Disease Control and Prevention (CDC) estimates that more than 3 million people in the U.S. acquire a resistant infection or *Clostridioides difficile* (*C. difficile*)—an infection that can happen after taking antibiotics—and nearly 50,000 people in the U.S. die as a result each year. When pathogens develop resistance to first-line antibiotics, our drug choices become limited, and some patients have no effective treatment options at all. If antibiotic resistance is left unaddressed, we face a future world with few effective antibiotics, undermining human and animal health, economic development, and national security. Ongoing awareness and action are essential to combat the development of antibiotic resistance, contain its spread, and mitigate its impact.

In recognition of the threat that antibiotic resistance poses, the U.S. Government developed the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB Strategy) in 2014. Issued concurrently, Executive Order 13676 called for the development of a National Action Plan for CARB to coordinate five years of federal action in collaboration with a broad range of partners to prevent, detect, and control illness and death related to infections caused by antibiotic-resistant bacteria. The CARB Strategy and subsequent 2015 Plan established five interrelated goals, pursued through a One Health approach recognizing the interconnectedness of human health, animal health, and the environment:

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 research and development for new antibiotics, other therapeutics, and vaccines.

Goal 5: Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control and antibiotic research and development.

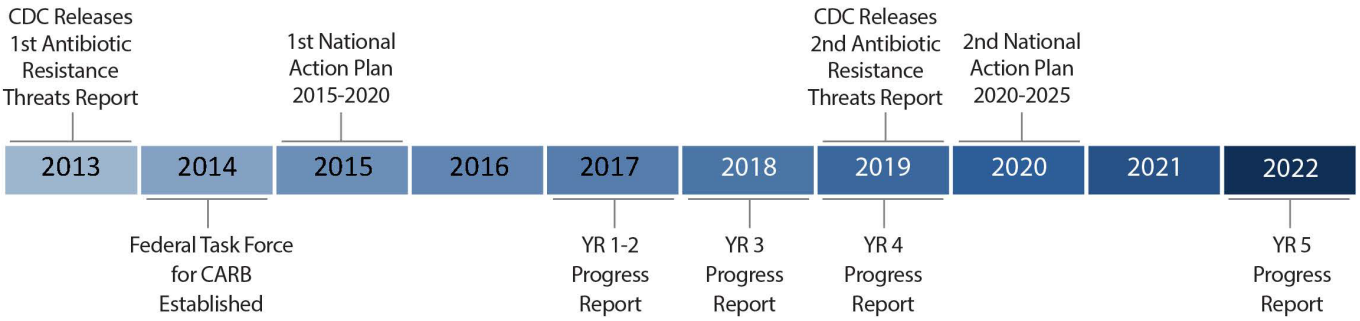
The 2015 Plan goals are further divided into objectives and sub-objectives, with specific milestones to be completed by Year 1, Year 3, and Year 5.

The federal CARB Task Force was established by Executive Order 13676 to facilitate and monitor implementation of the Executive Order and the CARB Strategy, and is co-chaired by the Secretaries of

Health and Human Services (HHS), Agriculture (USDA), and Defense (DoD). The CARB Task Force also includes the Department of Homeland Security (DHS), the Department of Interior (DoI), the Department of State (State), the Department of Veterans Affairs (VA), the Environmental Protection Agency (EPA), and the U.S. Agency for International Development (USAID).

Throughout implementation of the 2015 Plan, the CARB Task Force has published progress reports to inform stakeholders about these activities.[1] This document will be the final report on activities under the original 2015 Plan, and therefore includes a summary of accomplishments for Year 5 as well as highlights from earlier years of implementation.

[1] https://aspe.hhs.gov/reports/national-action-plan-combating-antibiotic-resistant-bacteria-progress-report-years-1-2
https://aspe.hhs.gov/reports/national-action-plan-combating-antibiotic-resistant-bacteria-progress-report-year-3
https://aspe.hhs.gov/reports/national-action-plan-combating-antibiotic-resistant-bacteria-progress-report-year-4



In addition to outlining these achievements by goal, this report also describes the barriers and challenges faced by U.S. agencies as they combat antibiotic resistance. Most of these challenges caused delays or complications to implementation but were eventually overcome. The majority of milestones were achieved within the specified timeline, and very few milestones were not implemented.[2] In addition to the goal-specific barriers and challenges described below, the activities within the 2015 Plan were subject to capacity limitations and availability of appropriations. Lessons learned from these challenges informed the development of the National Action Plan for CARB, 2020 – 2025, recognizing that many of these challenges persist as implementation of this new phase of work begins. The Next Steps section at the end of this report describes the 2020 Plan and how the lessons learned from the first five years are informing the U.S. Government's effort to combat antibiotic resistance for the next five years.

In addition to the CARB Task Force progress reports, other entities have reviewed and summarized the U.S. Government's response to antibiotic resistance. Of note are multiple reports developed by the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), a 2020 review with recommendations from the U.S. Government Accountability Office (GAO), and the 2021 review from the National Academies of Science, Engineering, and Medicine (NASEM). These reports and their associated activities (e.g., stakeholder meetings) play an important role in how the CARB Task Force monitors the impact of its ongoing activities and plans future activities.

Since the issuance of the CARB Strategy in 2014, the U.S. Government has continued to recognize the threat that antibiotic resistance poses to health, economic security, development, and national security, and further codified its commitment to action through the 2018 National Biodefense Strategy and the 2019 U.S. Government Global Health Security Strategy.

The activities described in this report demonstrate the strength of the 2015 Plan in guiding the U.S. Government's response to antibiotic resistance, leading to improved infection prevention and antibiotic stewardship in human and animal health; expanding surveillance for drug-resistant bacteria in humans and animals; supporting hundreds of new products to detect, prevent, and treat infections; and translating these advances across the globe through effective partnerships. These coordinated efforts implemented by the members of the CARB Task Force are working to slow the spread of resistance: CDC reports 18% fewer deaths overall within the U.S. from resistant infections between their 2013 and 2019 reports. Hospital-acquired resistant infections have dropped by nearly 30%. However, 2021 estimates indicated

[2] For additional detail, please see https://www.nap.edu/resource/26350/Background_Analysis.pdf

that the Coronavirus Disease 2019 (COVID-19) pandemic reversed some of these gains with substantial increases in several Healthcare-associated infections (HAIs) such as methicillin-resistant *Staphylococcus aureus* (MRSA). Antibiotic resistance continues to harm too many people, both within the U.S. and across the globe; and these estimates also show that new threats are emerging. A continued implementation of many of the ongoing and expanded activities described above will be essential to detect and mitigate antibiotic resistance and its impact in the future.

Collaborating for Greater Impact

Members of the CARB Task Force work within their own missions and complement each other's strengths through interagency collaborations. Many of these collaborations underscore the value of a One Health approach toward combating antibiotic resistance.

TABLE 1: Significant and Ongoing Interagency Activities

Antimicrobial Resistance (AMR) Challenge CDC, along with the HHS Office of Global Affairs, led this year-long, international effort that resulted in more than 350 organizations committing to slow the impact of AMR globally. This Challenge was initiated and concluded during the 2018 and 2019 United Nations General Assemblies, respectively.
Antimicrobial Resistance (AMR) Diagnostic Challenge The AMR Diagnostic Challenge was a joint effort between CDC, Food and Drug Administration (FDA), National Institutes of Health (NIH), and the Office of Assistant Secretary for Preparedness and Response (ASPR)/Biomedical Advanced Research and Development Authority (BARDA) to identify innovative and rapid point-of-need diagnostic tests, starting in 2016. The final prize of $19 million was awarded in 2020 to Visby Medical, Inc. for their device that detects the bacteria that cause gonorrhea and determines its susceptibility to ciprofloxacin in under 30 minutes.
CDC & FDA Antibiotic Resistance Isolate Bank CDC and FDA launched the Antibiotic Resistance Isolate Bank in 2015 and have continued to expand and increase the diversity of resistant bacterial and fungal pathogens available for research and development of new therapeutics, testing, or other innovations.
Combating Antibiotic-Resistant Bacteria Accelerator (CARB-X) The National Institute of Allergy and Infectious Diseases (NIH/NIAID) and ASPR/BARDA launched CARB-X in partnership with the Wellcome Trust in 2016. Subsequent partners include the Gates Foundation and the United Kingdom and German Governments. CARB-X supports global innovation and enhances the preclinical antibacterial and diagnostic product pipeline. Between 2016 and 2020, CARB-X received $483 million from funders to support 75 projects, including 9 new classes of antibiotics, 16 non-traditional therapies, 8 vaccines, and 6 rapid diagnostics.
FDA Guidance for Industry (GFI) #213 The FDA implemented Guidance for Industry (GFI) #213 in 2017 after extensive collaboration with the animal pharmaceutical industry, veterinary organizations, animal producer organizations, the animal feed industry, and others. As a result, 100% of the affected medically important antimicrobial drugs approved for use in or on the feed or water of food-producing animals were either withdrawn from the marketplace or voluntarily transitioned from over-the-counter marketing status to veterinary oversight or prescription status, and the use of these products in food-producing animals for production (e.g., growth promotion) purposes was eliminated. FDA and USDA/Animal and Plant Health Inspection Service (APHIS)/National Veterinary Accreditation Program (NVAP) collaborated to develop a new module on the Veterinary Feed Directive (VFD) to educate veterinarians about these policy changes. Along with FDA, USDA and CDC continue to monitor antimicrobial sales, use, and resistance after implementation of GFI #213.
Genomics for Food Safety (Gen-FS) Consortium The Gen-FS consortium includes FDA, CDC, USDA/Food Safety and Inspection Service (FSIS), USDA/Agricultural Research Service (ARS), USDA/APHIS, and NIH/National Library of Medicine (NLM)/National Center for Biotechnology Information (NCBI). The consortium coordinates, strengthens, and leads whole-genome sequencing efforts, focusing on crosscutting priorities for molecular sequencing of foodborne and other zoonotic

pathogens and data collection and analysis. The Consortium then uses information gathered to support surveillance and outbreak investigations.
Global Health Security Agenda (GHSA) Multiple U.S. departments and agencies, including USAID, HHS Office of Global Affairs (OGA), CDC, State, and USDA work together through the GHSA AMR Action Package (AP) to strengthen national capacities to address antimicrobial resistance, including through multisectoral coordination, surveillance, infection prevention and control, and antimicrobial stewardship.
National Antimicrobial Resistance Monitoring System (NARMS) NARMS is the U.S. public health surveillance system that tracks the antimicrobial susceptibility of certain enteric (intestinal) bacteria found in ill people (CDC), retail meats (FDA), and food animals (USDA).
NCBI National Database of Antibiotic-Resistant Organisms (NDARO) The NIH/NLM/NCBI NDARO is a collaborative, cross-agency, centralized hub for researchers to access AMR data to facilitate real-time surveillance of pathogenic organisms, which currently contains genomic data for nearly one million pathogen isolates collected from publicly available information. As part of the 2015 Plan, NIH/NLM/NCBI partnered with several agencies, including FDA, CDC, USDA, World Health Organization (WHO), Public Health England (PHE), and others to take steps to develop and maintain a curated database of antimicrobial resistance genes.

Emerging Issues

The 2015 Plan generated investments that not only served to combat antibiotic resistance, but also have been pivotal in the public health response for the COVID-19 pandemic. For example, past U.S. investments and ongoing U.S. programs and partnerships to strengthen infection prevention and control capacity, which helps to contain and prevent antibiotic-resistant infections, were paramount in addressing the rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, across the country and internationally. In 2020 alone, CDC programs provided more than 18,000 local responses or consultations to address confirmed or possible outbreaks involving antibiotic-resistant threats, COVID-19, other healthcare-associated infections and antibiotic-resistant (HAI/AR) infections, or serious infection control breaches in healthcare settings. Among these responses and consultations, CDC's HAI/AR Programs provided more than 3,800 reports of emerging resistance, including more than 420 antibiotic-resistant containment responses that involved onsite infection control assessment and/or screening, nearly 14,000 reports of possible COVID-19 outbreaks in healthcare settings, and more than 450 reports involving other types of HAI/AR outbreaks or infection control breaches. Additionally, these programs engaged more than 2,300 clinical laboratories to improve testing of targeted microorganisms to detect antibiotic resistance rapidly. The Armed Forces Health Surveillance Division Global Emerging Infections Surveillance Branch (AFHSD-GEIS) implements a robust surveillance network and pre-pandemic organism sequencing strategy that became a rapidly deployable asset in response to the COVID-19 pandemic. In addition, GEIS maintained a strong AMR surveillance platform with many activities continuing in support of ongoing DoD global surveillance throughout the pandemic. Internationally, U.S. investments in capacities and systems to address antibiotic resistance were also leveraged for COVID-19 response. U.S. programs in infectious disease prevention and control were significantly expanded to help improve triage and isolation; water, sanitation, and hygiene; and waste management in key health facilities.

Additionally, antibiotic resistance has the potential to affect people at any stage of life, as well as the healthcare, veterinary, and agriculture industries, making it one of the world's most urgent public health threats. However, risks of contracting antibiotic-resistant infections are tied to various external factors including where you live, how often you engage with health care (comorbidities, chronic illness, etc.), environmental exposures, and various other considerations related to health equity that can lead to disparities in health outcomes. The CARB Task Force is currently working to better understand disparities related to antibiotic resistance across health care, the community, and the environment, as well as the relationship between health equity and antibiotic use and resistance to determine community- or population-level trends that could inform better stewardship or prescribing practices in high-risk communities. For example, CDC aims to characterize health inequities related to key bacterial pathogens across incidence, infection outcome, and antibiotic resistance at a geospatial level, linking inequities to indicators of social determinants of health; Agency for Healthcare Research and Quality (AHRQ) has requested that researchers specifically plan for how priority populations may be affected by proposed studies; and all National Institutes of Health (NIH)-funded clinical research studies, including for antibiotic resistance (AR), must address plans for the inclusion of women and minority groups. The CARB Task Force is looking closely at lessons learned during the COVID-19 pandemic for how to improve and innovate in the fight against antibiotic resistance, including how to prepare for and respond to future pandemics and how to address disparities related to AR.

Progress Toward National Targets set in 2015 for CDC's Recognized Urgent and Serious Threats

CDC released its first AR Threats Report in 2013 to quantify the burden of bacterial and fungal resistance in the United States. The report assessed several aspects of antibiotic resistance, including clinical impact, economic impact, current rates, projections of incidence, transmissibility, availability of effective antibiotics, and barriers to reduction. The 2015 Plan included eight national targets for pathogens listed in the 2013 AR Threats Report as "Urgent Threats" and "Serious Threats." These targets represented goals to be achieved by 2020.

TABLE 2: Progress Toward 2015 Plan Targets

2015 National Action Plan Target	2020 Status
Reduce by 50% the incidence of overall *Clostridioides difficile* (*C. difficile*) infection compared to estimates from 2011	The adjusted estimate of the national burden of health care–associated *C. difficile* infection decreased by 36%. The adjusted estimate of the national burden of community-associated *C. difficile* infection is unchanged.
Reduce by 60% carbapenem-resistant *Enterobacterales* infections acquired during hospitalization compared to estimates	There was no significant change in the incidence of hospital-onset carbapenem-resistant *Enterobacterales*.
Maintain the prevalence of ceftriaxone-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)* below 2% compared to estimates from 2013	The percentage of isolates from the Gonococcal Isolate Surveillance Project (GISP) with reduced susceptibility to ceftriaxone in 2019 was 0.02%.*
Reduce by 35% multidrug-resistant (MDR) *Pseudomonas spp.* infections acquired during hospitalization compared to estimates from 2011	Hospital-onset MDR *Pseudomonas aeruginosa* decreased by 41%.
Reduce by at least 50% overall methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections by 2020 as compared to 2011	MRSA hospital-onset bloodstream infections decreased approximately 31.5% between 2012 and 2019 and community-onset bloodstream infections remained stable.**
Reduce by 25% MDR non-typhoidal *Salmonella* infections compared to estimates from 2010-2012	There was no significant change in the incidence of MDR non-typhoidal *Salmonella.*
Reduce by 15% the number of MDR tuberculosis (TB) infections in the United States[3]	Multidrug-resistant TB continues to remain stable at 1% of overall reported TB cases in the United States.
Reduce by at least 25% the rate of antibiotic-resistant invasive pneumococcal disease among <5 year-olds compared to estimates from 2008	Analyses on these trends are pending.
Reduce by at least 25% the rate of antibiotic-resistant invasive pneumococcal disease among >65 year-olds compared to estimates from 2008	Analyses on these trends are pending.

** Early data indicate that the COVID-19 pandemic has reversed some of these gains.

* The prevalence of ceftriaxone-reduced susceptible *N. gonorrhoeae* is defined as the percentage of isolates from the 2019 Gonococcal Isolate Surveillance Project exhibiting reduced susceptibility to ceftriaxone (defined as having a minimum inhibitory concentration ≥0.5µg/ml).

[3] While tuberculosis (TB) falls outside of the scope of the CARB Strategy and 2015 Plan, TB activities identified in the 2015 Plan are included as they represent critical near-term public health activities that will support progress to reduce the burden of drug-resistant TB in the United States. U.S. government activities during the 2015-2020 time period to address drug- resistant TB domestically and internationally were managed through efforts such as the U.S. National Action Plan for Combating Multidrug-Resistant TB.

Goal 1
Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections

Given that both appropriate and inappropriate use of antibiotics can generate resistance, preventing the overuse of antibiotics in both healthcare and agricultural settings is essential to slowing the emergence of resistant bacteria and extending the lifetime of effective antibiotics. Infection prevention and control can help avoid the need for antibiotic use in the first place, thereby reducing opportunities for antibiotic resistance to develop. Antibiotic stewardship is the practice of carefully evaluating the need for antibiotic use in human and animal health, with the goal of using the right antibiotic for each patient, at the right dosage, and for the right duration. The U.S. Government works to enhance infection prevention and control and antibiotic stewardship in human and animal care settings and foster broader stewardship of antibiotics in agricultural settings to reduce or eliminate the inappropriate use of antibiotics.

Barriers and Challenges

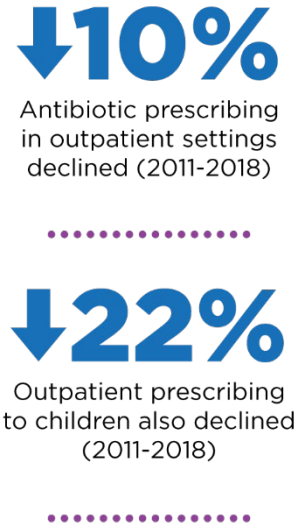
Many of the actions required to slow the emergence and spread of antibiotic-resistant bacteria require collaboration with various non-federal stakeholders, from healthcare facilities and systems to laboratories to state governments and animal and environmental health sectors. To address this complexity, CARB Task Force agencies work through multiple fora to enhance engagement and coordination of these activities. DoD/GEIS/WRAIR recently stood up a new One Health Branch to coordinate AMR One Health activities across the DoD.

Objective 1.1

Implement public health programs and reporting policies that advance antibiotic-resistance prevention and foster antibiotic stewardship in healthcare settings and the community.

Preventing infections in the first place is a key strategy to slow the spread of antibiotic resistance and reduce the need for antibiotics, which can drive the development of resistance. CDC has made significant investments to support HAI and antibiotic-resistant infection prevention programs that detect, respond to, and contain emerging antibiotic-resistant threats across healthcare, the food supply, the community, and the environment in all 50 states, DC, several large cities, and territories. Health departments continue to target their response and prevention actions using data from the CDC's National Healthcare Safety Network (NHSN), outbreak investigations, and the Antibiotic Resistance Laboratory Network (AR Lab Network). CDC also provided technical support to CMS's Hospital Improvement Innovation Networks, including prevention tools and expertise to target hospital-acquired and antibiotic-resistant infections in acute care and critical access hospitals. AHRQ has supported the creation of new interventions, along with

implementation toolkits for practitioners, that apply evidence-based practices to prevent the spread of infections within a variety of healthcare settings. Through its Emerging Infection Program (EIP) platform, CDC conducted assessments of antibiotic use in hospitals and nursing homes as part of HAI prevalence surveys in 2015 and 2017, quantifying the extent to which several common HAIs drive inappropriate antibiotic use, and identifying priority targets for stewardship programs.



Antibiotic stewardship programs improve how antibiotics are prescribed and are a critical prevention tool for combating the spread of antibiotic resistance. To guide efforts to implement antibiotic stewardship programs, CDC developed the Core Elements of Antibiotic Stewardship for inpatient, outpatient, long-term care, and resource-limited settings. The Core Elements define the components of high-quality, successful antibiotic stewardship programs, and provide guidance on how these components can be incorporated into their practice. CDC updated the Core Elements in 2019 to add new recommendations that prospective audits with feedback and pre-authorizations (review of therapy before initiation) of prescriptions be implemented as priority actions for stewardship programs.

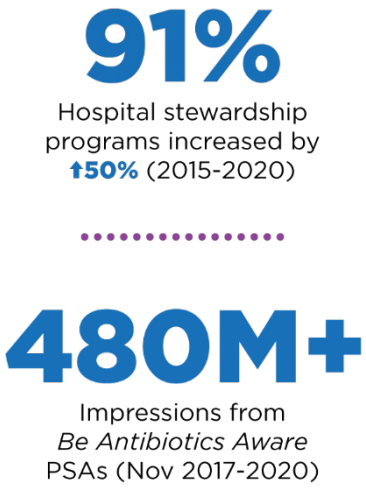
One component of antibiotic stewardship focuses on choosing the right antibiotic for each patient, and antimicrobial susceptibility testing (AST) devices can support these decisions by informing clinicians about whether a patient's infection is susceptible to specific antibiotic products. The U.S. Government also took steps to increase the availability of AST devices by streamlining regulatory processes and updating relevant interpretive criteria. In 2019, Food and Drug Administration (FDA) published guidance on Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Tests to assist drug sponsors and device manufacturers who are planning to develop new antimicrobial drugs and AST devices and who seek to coordinate development of these products, thereby helping to foster timely availability of AST devices at the time of new antibiotic approval or soon thereafter.

Even with evidence-based guidance from the Core Elements and informative diagnostics, implementing antibiotic stewardship programs can be complex and costly for healthcare providers, so the U.S. Government has pursued several strategies to support implementation of robust antibiotic stewardship programs in a variety of healthcare settings. Between 2015 and 2020, AHRQ greatly increased its support for investigator-initiated research to develop improved interventions and tools for combating antibiotic-resistant HAIs and promoting antibiotic stewardship. AHRQ developed its Safety Program for Improving Antibiotic Use, which adapted AHRQ's Comprehensive Unit-based Safety Program (CUSP), previously used to successfully reduce several HAIs, and applied CUSP principles to promote antibiotic stewardship in acute care hospitals, long-term care, and ambulatory care across the country. This program resulted in a reduction in antibiotic use of 30.3 days of therapy per 1000 patient days in 402 acute care hospitals and a 0.41 reduction antibiotic starts per 1000 resident days in 439 long-term care facilities. Educational toolkits tailored to acute care and long-term care settings are available, with ambulatory setting results and materials forthcoming. AHRQ developed the Nursing Home Antimicrobial Stewardship Guide and the Safety Program for Long-Term Care, which achieved a 54 percent reduction in catheter-associated urinary

tract infections in over 400 nursing homes. AHRQ also collaborated with the NIH/the National Institute of Allergy and Infectious Diseases (NIAID) to apply findings from the NIH/NIAID-sponsored Active Bathing to Eliminate Infection Trial to develop a toolkit for decolonization of patients with indwelling devices in hospital non-ICU settings to prevent resistant infections.

CDC further supports the detection, prevention, and response to antibiotic-resistant infections in health care, the community, and the environment through its Antibiotic Resistance Solutions Initiative. From 2016 to 2020, CDC invested more than $160 million in nearly 100 institutions to research innovative approaches to addressing antibiotic-resistant infections through the Broad Agency Announcement (BAA), the Modeling Infectious Diseases in Healthcare Network (MInD-Healthcare), the Prevention Epicenters Program, Safety and Healthcare Epidemiology Prevention Research Development (SHEPheRD), and the Small Business Innovation Research (SBIR) Program. Additionally, from 2016 to 2020, the Antibiotic Resistance Solutions Initiative invested more than $550 million to 59 state and local health departments through the Epidemiology and Laboratory Capacity program to sustain core laboratory and epidemiological capacity to address AR infections related to healthcare, foodborne, and community infections across the U.S. CDC also supports laboratory capacity in all 50 states, several large cities, and Puerto Rico to detect resistant threats through the AR Lab Network as well as seven Regional Laboratories to assist state outbreak response, detect existing and emerging resistance rapidly, and support innovations in antibiotic and diagnostic development.

To incentivize the implementation of antibiotic stewardship programs, CMS revised and finalized relevant aspects of the Conditions of Participation (CoPs) and the long-term care (LTC) facility requirements in Medicare, requiring all participating hospitals, critical access hospitals, and LTC facilities (such as nursing homes) to develop and maintain antibiotic stewardship programs to improve their antibiotic prescribing practices and reduce patient risks for antibiotic-resistant infections. To support effective implementation of the revised CoPs, CMS provided interpretive guidance and training webinars for these new requirements. CMS also incentivizes antibiotic stewardship programs through its Merit-Based Incentive Payment System. VA formalized the development of antimicrobial stewardship programs at all VA Medical Centers by January 2016. Between 2015 and 2020, the number of hospitals that have implemented CDC's Core Elements increased from 46% to nearly 90%.



Healthcare providers, hospitals, systems, and government agencies at all levels can best target their antibiotic stewardship efforts when they have accurate, timely, and actionable data about how antibiotics are being used. State and local health departments work to not only stop transmission of antibiotic-resistant pathogens and *C. difficile* between healthcare settings, but also to build and strengthen partnerships to improve antibiotic prescribing in acute care, including critical access hospitals, nursing homes, and in outpatient settings. More than 2,000 acute care hospitals across the United States have reported data on antibiotic use and more than 900 have reported data on antibiotic resistance to CDC's NHSN. NHSN now includes analytic features that enable hospitals to assess antibiotic use data according to type of ward or unit, benchmark their antibiotic use against nationally aggregated data, and display

antibiotic use data for specific antimicrobial agents. CDC tracks prescribing trends over time and geographically to target interventions and education and continues to provide annual reporting of outpatient prescribing by state. CDC also specifically tracks outpatient antibiotic use and has established a baseline of unnecessary antibiotic use in outpatient settings. For example, CDC reported in 2016 that only 52% of patients received the first-line recommended antibiotic for three common outpatient conditions, demonstrating another important opportunity to improve antibiotic use. CDC tracks national trends in quality of outpatient antibiotic prescribing to assess progress and identify where additional opportunities exist to improve prescribing. CDC recommends leveraging quality measures and antibiotic prescribing performance to provide individual prescriber-level feedback. CDC supports state and local health departments and other partners (health systems, payers) to support interventions that target individual prescribers for quality improvement. DoD conducts similar tracking of outpatient antibiotic use data for all military treatment facilities using a centralized database, and has produced summaries, reports, and analyses, including quarterly reports on outpatient prescribing rates using these data.

Public awareness of antibiotic resistance issues can also help to prevent infections and support the appropriate use of antibiotics. CDC's annual public awareness weeks (*Get Smart About Antibiotics*, subsequently renamed *Be Antibiotics Aware*) and healthcare-provider education aimed to raise awareness about the importance of appropriate antibiotic prescribing. Between 2017 and 2020, CDC's *Be Antibiotics Aware* public service announcements garnered more than 480 million impressions.

Objective 1.2

Eliminate the use of medically important antibiotics for growth promotion in animals and bring under veterinary oversight other uses of medically important antibiotics.

With the goal to eliminate the use of medically important antibiotics for growth promotion and bring medically important antibiotic drugs under veterinary oversight, FDA completed implementation of Guidance for Industry (GFI) #213 in 2017. As a result of the strategy outlined in GFI #213, medically important antibiotic drugs approved for use in or on the feed or water of food-producing animals shifted from over-the-counter marketing status to Veterinary Feed Directive (VFD) or prescription status, and affected drug sponsors voluntarily removed production (e.g., growth promotion) claims from approved drug products. This guidance was implemented through collaborations between FDA and the animal pharmaceutical industry, veterinary organizations, animal producer organizations, the animal feed industry, and others. USDA/Animal and Plant Health Inspection Service (APHIS)/National Veterinary Accreditation Program (NVAP) collaborated with FDA to develop a new module on the VFD to educate veterinarians about the policy changes implemented by FDA.

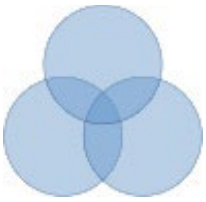
Building on previous efforts, in 2019 FDA announced draft guidance intended to bring all dosage forms (injectable, intramammary, etc.) of medically important antimicrobial drugs approved for use in food-producing animals under the oversight of a licensed veterinarian. As the agency did with GFI #213, FDA is committed to working with affected stakeholders to transition the remaining products by June 2023 to minimize impacts on animal health.

Objective 1.3

Identify and implement measures to foster stewardship of antibiotics in animals.

To further foster stewardship efforts within animal health settings, USDA supported research through the National Institute of Food and Agriculture (NIFA) Agriculture and Food Research Initiative, including the Understanding Antimicrobial Resistance, Animal Health, and Animal Well-Being programs. Researchers supported by USDA are developing models to reduce transmission of drug-resistant pathogens, to help identify critical control points for the spread of drug-resistant pathogens in feedlots and calving operations. USDA also supported applied research in field settings to demonstrate the feasibility and effectiveness of stewardship programs and to test alternatives to traditional uses of antibiotics in animals. On-farm data on antibiotic use and resistance are crucial to support antibiotic stewardship efforts and to evaluate changes over time, and such data are collected with voluntary participation by producers in multiple animal commodities, including on swine operations, cattle feedlots, and poultry operations by USDA/APHIS National Animal Health Monitoring System (NAHMS) and their partners.

USDA and FDA have developed, implemented, and measured the effectiveness of educational outreach to relevant stakeholders on judicious use of antibiotics and antibiotic stewardship, including engagement with livestock and veterinary organizations. USDA/APHIS/NVAP developed a module on the use of antibiotics in animals to provide antimicrobial stewardship information to veterinarians. FDA/Center for Veterinary Medicine (CVM) developed several brochures, videos, presentations, and other supporting documents that can be found on their Judicious Use of Antimicrobials page or Veterinary Feed Directive page. To further distribute this information, FDA/CVM participated in more than 200 stakeholder meetings and webinars regarding its antimicrobial resistance strategy, including the VFD final rule. Additionally, FDA's Veterinary Laboratory Investigation and Response Network (Vet-LIRN) promotes antimicrobial stewardship through educational capacity-building grants at veterinary schools. Through a collaboration with FDA's Office of Regulatory Affairs, FDA/CVM found that nearly 95% of inspected stakeholders are in compliance with the VFD rule. This overwhelming compliance rate indicates that veterinarians are involved in the judicious use of VFD feeds and serves as a signal that education and outreach related to VFD are achieving their goals.



Goal 2
Strengthen National One Health Surveillance Efforts to Combat Resistance

Since 2015, the U.S. Government has created a regional public health laboratory network, expanded national infrastructure for public health surveillance, enhanced the capacity of veterinary/food safety laboratories, and improved monitoring of antibiotic resistance patterns, as well as antibiotic sales, usage, and management practices. These surveillance activities generate a vast amount of detailed data that inform federal, state, and local public health efforts, crucial research aimed at understanding antibiotic resistance and mitigating its effects, and the development of innovative, new preventative strategies, diagnostics, and treatments.

Barriers and Challenges

Comprehensive surveillance for antibiotic-resistant pathogens and infections presents challenges in establishing, scaling up, and optimizing data systems. Data availability, collection, and harmonization were ongoing challenges to these efforts throughout the past five years, from initial difficulty in recruiting participants in data collection, to challenges in analyzing complex operation records. Surveillance is a resource- and time-intensive activity, and implementation of the Goal 2 milestones was impacted by burden to agency staff. For example, establishing communication *between* data systems is extremely time-intensive, given the need to expand the capabilities of each system and develop new workflows for communication. To address this challenge, DoD/GEIS, with input from the Multidrug-Resistant Organism Repository and Surveillance Network (MRSN), has developed a harmonized plan for reporting of AMR genomic data across the DoD. The Defense Health Agency is working on enhancing existing electronic communication between the DoD MHS and VA Health system. Other challenges included concerns regarding confidentiality, especially for the patients or owners of the animals from which samples were voluntarily obtained. For example, although there are many efforts underway to collect individual streams of antimicrobial use data from animals, there is not currently a national quantitative data repository or guideline for how to capture and compare such data. This makes synthesizing meaningful relationships between antimicrobial use and resistance from animals a continuing challenge. Recognizing this data gap, FDA/CVM is working with the Reagan-Udall Foundation for the FDA to seek input from a variety of affected stakeholders on strategies for collecting data regarding antimicrobial use in food-producing animals.

Objective 2.1

Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains and create a specimen repository to facilitate development and evaluation of diagnostic tests and treatments.

Antibiotic-resistant infections cannot be contained unless they are detected. To detect resistant bacterial strains more quickly and more broadly, CDC invested in foundational capacity to detect antibiotic-resistant

threats across One Health in the United States through the creation of the AR Lab Network, which includes public health labs in 50 states, multiple cities and territories, and seven regions. Since its development in 2016, the AR Lab Network performed more than 500,000 tests, including more than 150,000 isolate characterizations, 100,000 colonization screenings, and 250,000 whole genome sequences. Additionally, in 2020, CDC programs provided more than 18,000 local responses to address confirmed or possible outbreaks involving HAIs, including antibiotic-resistant infections and COVID-19, or serious infection control breaches in healthcare settings. Among these responses, the programs provided more than 3,800 reports of emerging resistance, including more than 420 antibiotic-resistant containment responses that involved onsite infection control assessment and/or screening. Similarly, in 2016, DoD established the MRSN as its official reference laboratory network for reporting antibiotic resistance and antibiotic use data for tri-service military treatment facilities. The MRSN collected and performed antibiotic susceptibility testing on 53,000 multidrug-resistant (MDR) bacteria and conducted whole genome sequencing on 46,000 of those samples, including sequencing of nearly 400 gonococcal isolates via the DoD/GEIS-funded Gonococcal Reference Laboratory and Repository. From 2017 to 2020, the MRSN has responded to 315 outbreak requests from 22 different medical facilities. When emerging antibiotic-resistant threats or trends are identified, DoD and CDC have established procedures to facilitate interactions between military healthcare facilities, MRSN, regional laboratories, and CDC.

Diagnostic tests and devices allow clinicians and researchers to accurately identify bacterial pathogens and their susceptibility or resistance to existing antibiotics. An important aspect of diagnostic test innovation is the use of isolates, pure samples of bacteria recovered from a patient, animal, or environmental specimen. CDC and FDA launched the AR Isolate Bank in 2015 and have continued to expand and increase the diversity of resistant bacterial and fungal pathogens available for research and development of new therapeutics, diagnostics, or other innovations. As of the end of 2020, the AR Isolate Bank has shipped more than 5,000 isolate panels composed of more than 200,000 isolate samples. FDA has observed that an increasing number of product developers cite the AR Isolate Bank as a valuable resource that has facilitated development and validation of new devices.

The MRSN Antimicrobial Resistance Monitoring and Research Database (ARMoR-D) houses clinical and demographic data for more than 64,000 patients with more than 6 million results from phenotypic and genotypic testing platforms. MRSN designed, developed, and validated sets of diversity panels consisting of 100 *Acinetobacter baumannii*, 100 *Klebsiella pneumoniae*, and 100 *Pseudomonas aeruginosa*, which have been deposited in the NIH/NIAID-funded Biodefense and Emerging Infections Research Resources Repository. These panels are available, at no additional cost, to any interested parties that are testing new diagnostics, therapeutics, or disinfectants, and pertinent meta-data are available, including the collection site where bacteria were cultured, susceptibility to antibiotics, and the complete genome sequence of all isolates. MRSN is adding additional diversity panels for *Enterobacter cloacae*, *Escherichia coli (E. coli)*, and *Staphylococcus aureus*.

Other key databases have also been established or expanded, allowing scientists from all over the world to access and leverage information to foster understanding of resistance mechanisms and inform development of improved diagnostics, therapeutics, vaccines, and antibiotic strategies. NIH and CDC continue to sequence high priority reference strains of bacteria and other pathogens, and genome sequences are rapidly released to the public through the free open-database GenBank, which is published

by NIH/National Library of Medicine (NLM)/National Center for Biotechnology Information (NCBI), and the Bioinformatics Resource Center Pathosystems Resource Integration Center (PATRIC), which is funded by NIH/NIAID. NIH has partnered with FDA and CDC to expand the web-based open-access NIH/NLM/NCBI National Database of Antibiotic-Resistant Organisms, which currently contains genomic data for nearly one million pathogen isolates collected from publicly available information, including high priority bacterial threats. Many of these isolate entries include integrated antibiotic susceptibility phenotypic data, antibiotic resistance genotypic data, and detailed information on the sequences encoding resistance genes found in these isolates.

Objective 2.2

Expand and strengthen the national infrastructure for public health surveillance and data reporting, and provide incentives for timely reporting of antibiotic resistance and antibiotic use in all healthcare settings.

NARMS was established in 1996 as a collaboration between CDC, USDA, FDA, and state and local health departments. NARMS currently tracks resistance in enteric bacteria from humans, retail meats, and food-producing animals at the time of slaughter. In October 2020, NARMS published a new Strategic Plan that outlines a dynamic roadmap for future enhancements to achieve One Health antibiotic resistance surveillance, including greater emphasis on pathogens affecting animal health and a pilot environmental effort based on both watershed and national scale monitoring of surface waters. With the implementation of whole-genome sequencing, NARMS resistance data are shared online in real time for use by stakeholders globally. The application of genomics to One Health surveillance has become the framework for best practices in antibiotic resistance monitoring. The whole-genome sequencing (WGS) data are being generated and uploaded into the public domain at NCBI at NIH/NLM/NCBI where resistance is predicted from the genomic sequences and incorporated into NDARO and PATRIC databases. This has greatly shortened the time from sample collection to data sharing and analysis online. Since 2015, through NARMS, CDC, FDA and USDA/FSIS sequenced over 98,000 bacterial isolates (approximately 40,000 by CDC, approximately 19,000 by FDA, and approximately 39,000 by USDA/FSIS) and deposited the sequences into NIH/NLM/NCBI for public access.

To better track antibiotic resistance and antibiotic use in human health settings, CDC, DoD, and VA have collaborated to continuously expand reporting into the NHSN Antibiotic Use and Resistance (AUR) module. CDC's NHSN is the nation's most comprehensive and widely used system for healthcare quality measurement and improvement. Data from NHSN drive improvement of quality and patient safety by enabling healthcare facilities to track, report, assess gaps, and take quality improvement actions related to a range of urgent health threats, including HAIs, antibiotic-resistant infections, and antibiotic use. NHSN currently covers 100% of eligible VA facilities, 160 military treatment facilities including Pacific and European military hospitals, and more than 37,000 civilian U.S. healthcare facilities, including nearly every hospital (~6,900), ambulatory surgery center (~4,700), dialysis facility (~7,900), and CMS-certified nursing home (~15,400) across all 50 states, several large cities, and Puerto Rico. As noted under Goal 1, as of 2020, nearly 2,000 of these facilities were reporting antibiotic use information and nearly 900 facilities were reporting antibiotic resistance data to the NHSN antibiotic use Option. Additional federal actions to provide guidance, support, and incentives for timely reporting of relevant data to NHSN are discussed under Goal 1.

Aggregated national and state-specific NHSN summary data are publicly available through CDC's Antibiotic Resistance & Patient Safety Portal (AR&PSP), originally released in 2016, which is a user-friendly electronic portal that facilitates integrated analyses of state and regional trends and practices. Specific healthcare facilities can also use NHSN data to determine where to focus their antibiotic stewardship efforts by calculating their own Standardized Antimicrobial Administration Ratio (SAAR), a risk-adjusted summary measure of antibiotic use that CDC developed in close collaboration with health system partners. The SAAR was originally endorsed by the National Quality Forum (NQF) in December 2015, and this endorsement was renewed in 2019 for an additional three years (NQF #2729). NQF-endorsed measures are evaluated by expert committees using rigorous criteria to ensure that they are highly relevant and reliable. To expand the number of facilities that have access to critical benchmarking tools like the SAAR, CDC and CMS worked to promote hospital reporting of AUR data under the Promoting Interoperability program by including AUR reporting to public health registries as one of the measures available for hospitals to earn points under public health and clinical data exchange requirements.

Surveillance has also been expanded through gathering detailed information that can help target interventions. CDC collaborates with EIP sites to conduct active, laboratory-confirmed population-based surveillance for infections caused by multiple threat organisms[4], generating surveillance and microbiologic data that allow researchers to understand the range of resistance genotypes and mechanisms, estimate burden and detailed risk factors to inform prevention and containment strategies, and monitor the impact of existing interventions and programs. CDC also expanded its work to combat resistant gonorrhea through the Gonococcal Isolate Surveillance Project (GISP) and the Strengthening the U.S. Response to Resistant Gonorrhea (SURRG) project. GISP collects samples from men diagnosed with gonorrhea at sexually transmitted infection (STI) clinics, and participating Antibiotic Resistance Laboratory Network laboratories test these isolates for resistance to several antibiotics. CDC has been supporting SURRG since 2016 in eight areas around the country through expanded sample collection, local and rapid testing for resistance, and swift and robust response to identified potential resistant cases. A subset of samples collected in the GISP and SURRG programs are whole-genome sequenced to monitor the diversity of antimicrobial resistance genetic markers among U.S. *Neisseria gonorrhoeae* (*N. gonorrhoeae*) isolates. WGS recently identified one strain with novel resistance variants which accounted for the increased prevalence of isolates with azithromycin decreased susceptibility; this information along with GISP annual reports supported the recommended change of clinical treatment guidelines in 2021. Annual analysis of sequences document how *N. gonorrhoeae* strain populations associated with specific antibiotic susceptibility patterns change over time and have supported recent changes in clinical treatment guidelines.

[4] Including drug-resistant *Candida* species, *C. difficile*, MRSA, extended spectrum beta-lactamase-resistant or carbapenem-resistant *Enterobacterales*, and *Acinetobacter baumannii.*

Objective 2.3

Develop, expand, and maintain capacity in veterinary/food safety laboratories to conduct standardized susceptibility testing/characterize select zoonotic pathogens.

To improve the timely identification of zoonotic and animal health pathogens, both USDA/APHIS and FDA/CVM have established and expanded the antimicrobial resistance monitoring, including building and expanding capacity for whole-genome sequencing. Through the Vet-LIRN AMR monitoring program, FDA/CVM has collected susceptibility testing data from over 8,000 animal pathogens routinely isolated by veterinary diagnostic laboratories across the U.S. and Canada, and WGS data from over 3,500 of those isolates, with publicly available results. To enhance communications and identify mechanisms for sharing and reporting antibiotic-susceptibility data from the National Animal Health Laboratory Network (NAHLN) AMR Pilot Project, USDA/APHIS published an interactive interface for external users to visualize antimicrobial resistance data. Given the challenges with standardizing antibiotic susceptibility and bacterial characterization in animal populations, USDA/APHIS National Veterinary Services Laboratories created a pilot antibiotic susceptibility testing proficiency test in 2018. Goals of this pilot included providing summary data for publication, sharing individual reports back to the participants, and creating a formalized, graded AST proficiency test to encourage and evaluate the standardization of ASTs.

Objective 2.4

Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain for food animals and retail meat.

Antibiotic resistance in the food chain is tracked by the NARMS. Over the past several years, NARMS has expanded to look at a broader scope of animals and commodities that may be produced using antibiotics, such as shrimp, tilapia, salmon, Siluriformes fish/catfish, veal, lamb, sheep, and goats. At the same time, additional bacterial species were added to surveillance (e.g., *Aeromonas* species, additional lactose fermenters, carbapenem resistant Enterobacteriaceae - CRE). To better understand bacterial AMR in food animal sources, FDA and USDA/FSIS together analyzed over 300,000 samples under the NARMS program between 2015 and 2020. Specifically, USDA/FSIS contributed results from over 230,000 food and animal samples (food products and cecal/intestinal content samples) and FDA contributed results from over 72,000 in commerce food product samples collected at retail. All of the 75,000 isolates retrieved under NARMS by USDA/FSIS (56,000) and FDA (19,000) were subjected to Antimicrobial Susceptibility Testing. Of these, 58,000 isolates were also whole genome sequenced and deposited in real time into NCBI for public access. The NARMS AMR findings from *E. coli* and *Enterococcus* from food animal sources are unique, as these provided a continued glimpse into the emerging AMR trends, including their potential for transfer and spread to pathogenic bacteria and eventually to humans.

FDA's actions over the past several years, including implementation of GFI #213 and the VFD final rule, have fundamentally changed the way animal producers obtain and use medically important antibiotics in food animals. In 2017, FDA saw a substantial reduction in the quantity of such drugs sold or distributed,

which demonstrates that ongoing stewardship efforts are having a measurable impact. Four years after completing implementation of GFI #213, data from the 2020 Sales and Distribution Report indicate that sales volume of medically-important antibiotics for use in food-producing animals remain considerably lower than previous years.

Beyond the quantity of antimicrobial products sold each year, FDA continues to work with federal, academic, and industry partners to obtain more information about how, when, and why animal producers and veterinarians use medically important antibiotic drugs to better understand progress toward judicious antimicrobial use. Since 2016, FDA/CVM has funded two cooperative agreements with university researchers to develop approaches for collecting data on antibiotic use in cattle, swine, and poultry. An initial report related to the poultry pilot project was recently published. In addition, USDA's NAHMS has collected data about antibiotic use, stewardship, and resistance in multiple animal commodities over the past five years, including horses, small ruminants, poultry, dairy cattle, feedlot cattle, beef cow/calf, and swine. NAHMS has published summary reports of its surveys on antibiotic use and stewardship on U.S. feedlots and swine operations, and is collecting updated antibiotic use, stewardship, and resistance data in 2021. These data collection efforts are intended to provide needed information on antimicrobial use practices in various animal production settings and to inform the development of long-term strategies for collecting and reporting such data in a sustainable and nationally representative manner. More information gathered from these cooperative agreements was highlighted in the November 2020 special issue of Zoonoses and Public Health

USDA/APHIS NAHMS collected antibiotic use and stewardship data on cattle feedlots and swine operations during 2016, with summaries published in 2019. The information from these studies provides a baseline for how livestock producers used antibiotics prior to implementation of FDA policy changes to the VFD in January 2017. NAHMS will collect similar information in 2021, which will provide information about the impacts of the FDA policy changes and allow trend analyses. NAHMS also collected information about antibiotic use and stewardship on goat and beef cow/calf operations, including collection of fecal samples to evaluate antibiotic susceptibility in select bacterial pathogens, with reports summarizing these results forthcoming. NAHMS collaborated on several projects to improve sampling for antibiotic resistance in animals, including best practices for collecting fecal samples on swine operations and methods for group sampling of feedlot cattle for *Mannheimia haemolytica*, an important respiratory pathogen. These studies will help improve antibiotic resistance monitoring in the future, in addition to supporting the NAHMS mission to gather, analyze, and disseminate data on animal health, management, and productivity across the U.S.

Goal 3
Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria

Improved diagnostic testing for resistant bacteria is essential for healthcare providers to make optimal treatment decisions. Information about susceptibility or resistance at the time when a patient is first diagnosed helps tailor appropriate antibiotic use and avoid unnecessary use of broad-spectrum antibiotics. Diagnostics also provide additional tools for public health officials to detect concerning resistant infections and take action to prevent and control their spread to others. Importantly, the U.S. Government not only supports the development of innovative new diagnostics, but also supports their availability and appropriate use in a wide range of settings.

As described in more detail below, the Office of Assistant Secretary for Preparedness and Response (ASPR)/Biomedical Advanced Research and Development Authority (BARDA), CDC, DoD, and NIH have worked with a variety of product developers to support the development of new diagnostics by providing direct funding, expertise, and technical guidance. These agencies coordinate regularly to ensure that their efforts are complementary and to leverage each agency's strengths toward the pursuit of these objectives. In the past five years, this support has contributed to the development of diagnostics for multiple pathogens designated as urgent threats by the CDC, including *Acinetobacter spp.* (supported by DoD), *Candida auris* (supported by CDC), *N. gonorrhoeae* (supported by NIH and ASPR/BARDA) and *Clostridioides difficile*[5] (supported by ASPR/BARDA). FDA's Center for Devices and Radiological Health (CDRH) has reviewed ongoing premarket submissions from several device manufacturers conducting continuous research and development.

Since 2015, FDA/CDRH has cleared over 100 devices, developed by both government partners and commercial entities, that detect pathogenic organisms and/or determine antimicrobial susceptibility/resistance. These devices include innovative technologies to detect and characterize organisms designated as AR Threat species. FDA's antimicrobial resistance web portal highlights relevant devices that have recently been cleared, and FDA's 510(k) Database contains additional detailed information on these devices. FDA also maintains a list of cleared nucleic-acid based diagnostic tests that detect microbial pathogens and/or resistance markers.

Barriers and Challenges

Technical challenges to the development of diagnostics to detect antibiotic resistance include limitations in

[5] BARDA supported the development of the First Light Diagnostics platform, but the company paid for the *C. difficile* clearance.

the ability to detect a pathogen from a normally sterile site where the amount of pathogen may be low. NIH/NIAID is addressing this challenge by supporting scientists to develop diagnostics for sterile sites, including tools to identify pathogens and determine their antibiotic susceptibility directly from blood samples. Differentiating infection (bacteria causing disease) from colonization (the presence of bacteria on a body surface that does not cause disease) in respiratory tract samples can also pose technical challenges. NIH/NIAID is addressing the question of differentiating infection from colonization in respiratory tract samples by developing rapid diagnostics that discriminate between bacterial and viral respiratory tract infections for optimizing management of antibiotic use for acute respiratory illness. To this end, the NIH/NIAID-supported Antibacterial Resistance Leadership Group's (ARLG's) RADICAL (Rapid Diagnostics in Categorizing Acute Lung Infections) study is evaluating a host-based response assay to distinguish between bacterial and viral infections, which could help reduce inappropriate antimicrobial use. The lack of some bacterial species and the number of isolates from geographically diverse regions may limit the regulatory claims for those organisms. Diagnostic developers also face low potential for clinical use and uptake of new products, due to limited adoption of tests by practitioners and limited reimbursement of certain diagnostic tests.

Objective 3.1

Develop and validate new diagnostics—including tests that rapidly distinguish between viral and bacterial pathogens and tests that detect antibiotic-resistance that can be implemented in a wide range of settings.

Rapid diagnostic tests help inform appropriate antibiotic treatment and facilitate antibiotic stewardship efforts. NIH/NIAID supports a robust portfolio of research projects to develop and evaluate novel diagnostic platforms. In addition to numerous investigator-initiated projects, NIH/NIAID has issued and supported targeted solicitations to foster the development of innovative diagnostic tests for antibiotic-resistant pathogens, including for hospital-associated pathogens and bacteria listed in the CDC's AR Threats Report. Additionally, NIH/NIAID has supported the ARLG since 2013, bringing together more than 50 leading experts to manage a highly productive portfolio of research projects, including several to improve the diagnosis of bacterial infections. These projects have included a collaboration with multiple diagnostics companies to standardize and implement a master diagnostics protocol, which validated multiple diagnostic tests for *N. gonorrhoeae* and *Chlamydia trachomatis (C. trachomatis)* simultaneously using specimens from the same patients and led to the subsequent FDA clearance of two diagnostic tests for new clinical use (diagnosis of extragenital infections); the use of a host biomarker signature to distinguish between viral and bacterial infections in less than one hour with over 80% accuracy; and rapid testing with an already-approved device to more quickly adjust antibiotic prescribing and usage. NIH/NIAID has also supported development of the BIOFIRE FILMARRAY Pneumonia Panel that detects 18 bacteria, eight viruses, and seven genetic markers of resistance in approximately one hour and the BacterioScan 216Dx Urinary Tract Infection detection system that can detect bacteria in urine in three hours.

With technical and regulatory expertise provided by CDC and FDA, NIH and ASPR/BARDA collaborated to launch the AMR Diagnostic Challenge to identify innovative and rapid point-of-need diagnostic tests. With the first phase starting in 2016, the $19 million final prize was awarded in 2020 to Visby Medical, Inc. for their device that detects the bacteria that cause gonorrhea and simultaneously determines susceptibility

to the antibiotic ciprofloxacin in under 30 minutes. With NIH/NIAID support, Visby also developed a point-of-care diagnostic to detect *N. gonorrhoeae*, *C. trachomaits* and *Trichomonas vaginalis*.

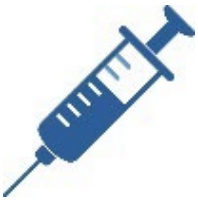
ASPR/BARDA also supports the development of diagnostics through the Combating Antibiotic-Resistant Bacteria Accelerator (CARB-X) program and Advanced Research and Development (ARD) funding. Through CARB-X, ASPR/BARDA is supporting the preclinical development of 11 diagnostics. The effectiveness of this support is illustrated by T2 Biosystems, which was able to advance their diagnostic technology to the point where it was more competitive for financial and technical support from ASPR/BARDA's Detection, Diagnostics, and Devices Infrastructure (DDDI) Division, which it joined in 2019. DDDI is also supporting SeLux, Inc., Inflammatix, Inc., and Tangen Biosciences, Inc. all of which are developing tests to improve patient diagnosis and care. The Antibacterial Branch within ASPR/BARDA is also supporting the development of an IL-6 assay for neonatal sepsis and severe inflammation. The first product in ASPR/BARDA's ARD AMR diagnostics portfolio was cleared by FDA in September 2017, and seven additional products are expected to be submitted for FDA clearance between 2021 and 2024.

Objective 3.2

Expand availability and use of diagnostics to improve treatment of antibiotic-resistant bacteria, enhance infection control, and facilitate outbreak detection and response.

In reviewing available data, CMS has found that Medicare beneficiaries account for the majority of cases of both new diagnoses of drug-resistant infections and resulting deaths in United States hospitals. Drug resistance causes Medicare beneficiaries to spend hundreds of thousands of additional days in hospitals each year, costing taxpayers billions in additional health care costs annually. In recent years CMS has modernized its payment systems to ensure access to medications for Medicare beneficiaries.

CMS and FDA have also worked together to share information in an effort to increase quality of patient health care by facilitating earlier access to innovative treatments for Medicare beneficiaries. This allows both agencies to give faster and more informative feedback to companies developing these products. CDC has supported the AR Lab Network in implementing testing to identify antibiotic-resistant infections, filling critical gaps in hospital laboratory capacity to allow hospitals to make well-informed decisions about infection prevention and control. CDC has also implemented a new antibiotic susceptibility testing capability in regional laboratories, Expanded Antimicrobial Susceptibility Testing for Hard-to-Treat Infections (ExAST), to guide decisions on the use of new antibiotic drugs for antibiotic-resistant infections. DoD's MRSN also conducts next generation sequencing, polymerase chain reaction testing, and rapid testing of submitted isolates from suspected outbreak investigations.



Goal 4
Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines

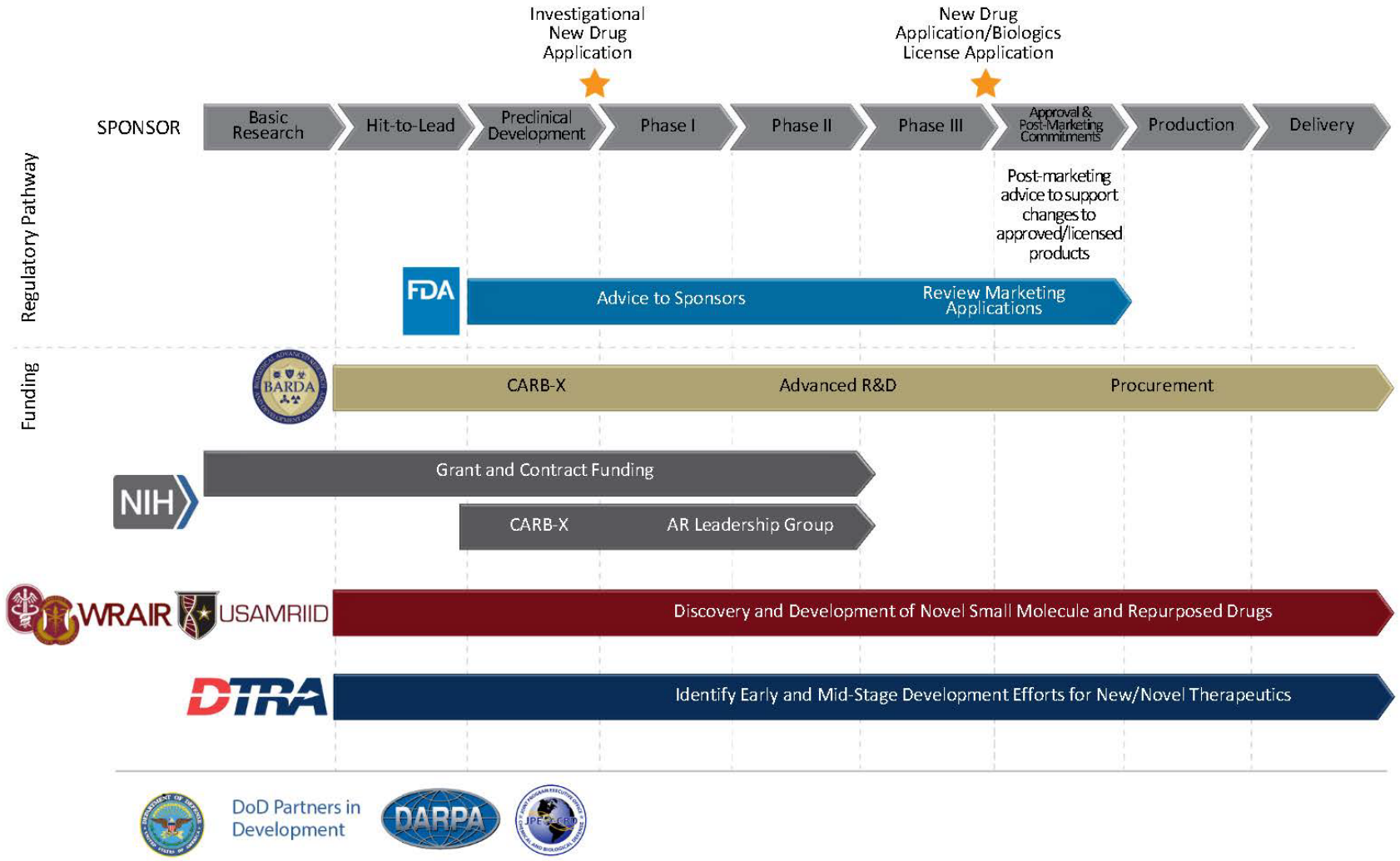
Support for basic and applied research is a critical part of implementing a comprehensive One Health strategy as the effectiveness of existing antibiotics continues to wane. Research support feeds into a multipronged approach to promote innovative treatments by de-risking products for further investment and facilitating clinical trials of new antibiotics, other therapeutics, and relevant vaccines. While the pipeline of new antibiotics must be continually renewed through discovery and development research, the effectiveness of existing antibiotics can be prolonged by determining optimal doses, durations, regimens, and drug combinations. In addition, alternatives to antibiotics – including bacteriophages, microbiome-based products, vaccines, and other products – can help prevent and treat infections in humans and animals without promoting antibiotic resistance. The activities within this Goal require extensive collaborative work between the U.S. Government, private companies and organizations, and global partners to promote economic sustainability for products that combat antibiotic resistance.

Barriers and Challenges

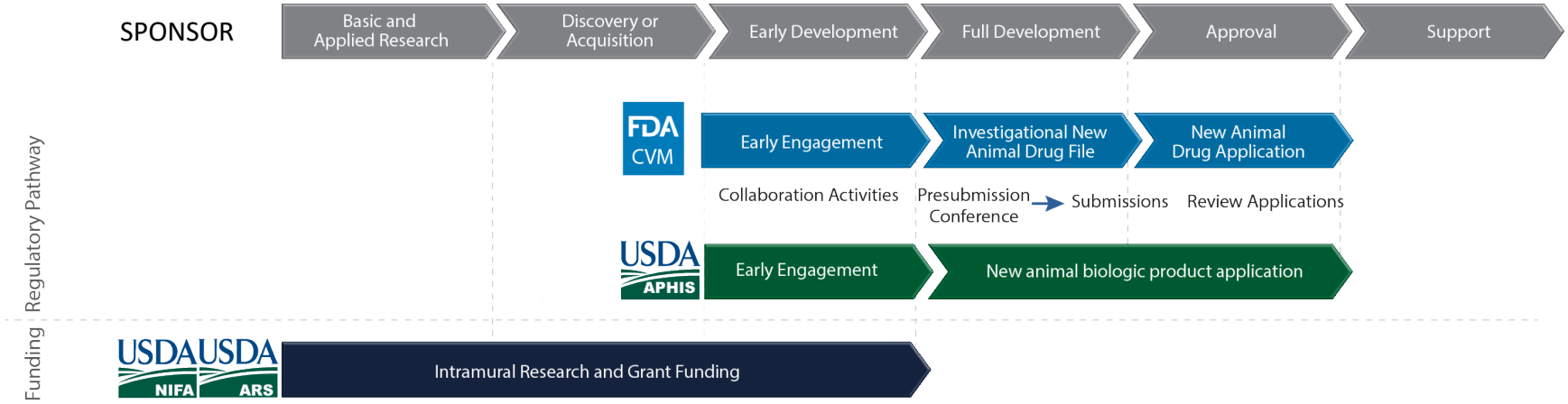
Discovery of new classes of antibiotics with activity against gram-negative bacteria and the development of vaccines for multi-serotype and commensal bacteria have both proven very challenging. Additionally, the lag time between completing and publishing the results of basic and applied research studies can delay their real-world impact. The development of new antibiotics, therapeutics, and vaccines typically requires a multi-year process with a high-level of uncertainty. Key prevention tools such as vaccines and alternatives to traditional antibiotics are also critical to the overarching fight against resistant infections and these products face similar if not greater challenges to development and availability. Clinical evidence of the effectiveness of new products can take many years and be extremely difficult and costly to generate for key treatment scenarios, including resistant infections, bloodstream infections, and hospital-associated or ventilator-acquired pneumonia and special populations. The pipeline for all of these tools is fragile and product developers find it difficult to sustain new antibiotic therapeutics on the commercial market because of low volume of sales (which may be driven by both appropriate stewardship and potentially inappropriate use of alternative products) and commensurately low revenue. The CARB Task Force continually monitors the pipeline of products and options to combat resistant infections and evaluates further options to strengthen the pipeline.

Federal Agencies and the Antibiotic R&D Pathway

Human Drug Approval Process



Animal Product Approval Process



Objective 4.1

Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic-resistance and the spread of resistance genes that are common to animals and humans.

The need to better understand factors within the environment (e.g., water, soil) that facilitate antibiotic resistance has instigated a major cross-agency collaboration: the Genomics for Food Safety (Gen-FS) consortium. Gen-FS coordinates, strengthens, and leads WGS efforts among federal and state partners to further improve public health, and includes USDA/Food Safety and Inspection Service (FSIS) in partnership with FDA, CDC, USDA/Agricultural Research Service (ARS), USDA/APHIS, and NIH/NLM/NCBI. The Gen-FS consortium focuses on crosscutting priorities for molecular sequencing of foodborne and other zoonotic pathogens causing human illness, including the emergence and spread of the genetic determinants of antibiotic resistance, and using this information to support surveillance and outbreak investigation activities. In addition to this consortium, several federal agencies individually conduct and support research to better understand the genetics of antibiotic resistance. NIH/NIAID continues to support programs in systems biology, genomics, structural biology, and bioinformatics. USDA/ARS scientists continue to conduct research on the development of antibiotic resistance and the remediation of antibiotic resistance in animal settings, including the quantification of antibiotic-resistant bacteria and their genes in food animal production systems and in surface and ground waters (in collaboration with EPA), and refining measurement to support future monitoring of specific types of antibiotic resistance. In addition, the CDC Prevention Epicenters Program has supported academic investigators in exploring the role of the environment in transmission of antibiotic-resistant organisms in healthcare settings, such as the role of premise plumbing as a reservoir of transmission of certain resistant gram-negative pathogens. The U.S. Government regularly and systematically reviews these research activities to ensure that resources are focused on high priority antibiotic resistance issues.

Objective 4.2

Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.

Microbial communities within humans, animals, and the environment can include a vast array of organisms, and understanding their interactions can shed light on the development of antibiotic resistance and provide ideas for new treatments. CDC has invested in hundreds of research partners since 2016 to pilot innovative solutions and explore knowledge gaps about how antibiotic resistance spreads to and between humans, including research on how the human microbiome can be used to predict and prevent infections caused by antibiotic-resistant microorganisms. For example, CDC Prevention Epicenter investigators have increased our understanding of the relationship between disruption of the gut microbiota and risk of antibiotic-resistant infections and spread in acute and long-term healthcare settings. NIH continues to invest in research on the impact of antibiotics on the microbiome of humans. NIH/National Human Genome Research Institute (NHGRI) and NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) collaborated to investigate alterations in human-associated

microbial communities following introduction of systemic antibiotics to healthy human volunteers. NIH-supported research has also made critical advances in the understanding and use of fecal microbiota transplants, including efforts to identify protective bacterial strains and formulate them into products and to characterize the stability and resilience of the human gut microbiome over time and after perturbations such as antibiotic use. To support this effort, NIH/NIAID and the American Gastroenterological Association have launched a Fecal Microbiota Transplant (FMT) national registry, which collects clinical data from FMT donors and recipients to assess the short- and long-term safety and effectiveness of this intervention. Initial results showed that 90% of patients with *C. difficile* infection recovered within one month of FMT administration. FDA's Center for Biologics Evaluation and Research (CBER) is assessing regulatory measures regarding the safety, manufacturing, efficacy, and potency of transplant products.

U.S. agencies also continue to support research on the microbiome in priority animal species and agricultural settings. USDA/ARS has worked to define background and baseline levels of antibiotic-resistant bacteria and antibiotic resistance genes in agricultural systems, and these definitions provide a foundation for quantitative evaluation of control measures and management strategies on animal gut microbiomes. USDA/ARS scientists are also providing insight into the ecology of antibiotic resistance in food animal production systems by conducting research to characterize the normal gut flora for food animals and how it is impacted by antibiotic use. Further research is uncovering the underlying mechanisms driving the spread of resistant bacteria and resistance genes between zoonotic pathogens and commensal microbiota in food animal gastrointestinal systems and to humans and the environment; results from these studies have been published in over 60 peer-reviewed research articles spanning swine, beef, dairy, poultry, and aquaculture settings.

Objective 4.3

Intensify research and development of new therapeutics and new and improved vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.

Overall, the U.S. Government has provided significant support for research into new types of antibiotic candidates over the past five years. These include NIH/NIAID-supported projects that leveraged systems biology, sequencing, and structural genomics to identify, quantify, model, and predict the dynamics of the molecular interactions of antibiotic-resistant pathogens and their hosts during disease initiation. When the results of this research are incorporated into the antibiotic drug development process, the development of resistance should be less likely. Similarly, USDA/ARS scientists work to understand and harness microbial communities to promote animal health, including evaluation of microbial-derived products as potential new therapies. NIH/NIAID continues to provide critical early support for discovery and development of promising antibacterial candidates, and has funded hundreds of new basic, translational, and clinical research projects since 2015. NIH/NIAID has also supported the development of novel predictive assays, models, and research tools aimed at facilitating therapeutic discovery for carbapenem-resistant

Enterobacterales, MDR *Acinetobacter,* and MDR *Pseudomonas aeruginosa*. Several companies have built on NIAID-supported preclinical development and have advanced potential new drugs from the conceptual stage through early clinical testing to enter license agreements to further develop and commercialize their products. For example, NIH/NIAID has supported preclinical development, investigational new drug (IND) submissions, and four Phase 1 clinical trials for a novel tetracycline and two Phase 1 clinical trials for Taniborbactam, a beta-lactamase inhibitor. With support for the next stage of the development pipeline from ASPR/BARDA and the Global Antibiotic Research and Development Partnership (GARDP), Taniborbactam is currently in a global Phase 3 trial for treatment of complicated urinary tract infections. This hand-off of support from one CARB agency to another represents a commitment to translating research into promising new products. NIH/NIAID has also supported two Phase 1 clinical trials and an ongoing Phase 2 clinical trial for an oral first-in-class antibiotic intended to treat *C. difficile*.

To support medical countermeasure development against CDC's 2013 Urgent or Serious Threats List, ASPR/BARDA has successfully spurred innovation and early-stage development of products globally through CARB-X as described elsewhere in this report. In addition to CARB-X, ASPR/BARDA is actively supporting the development of five first-in-class candidates, including two non-traditional candidates in clinical development (all noted in Objective 4.4), and a diagnostic for sepsis through its ARD program. In addition to these active programs, BARDA has funded the development of three novel antibiotics, VABOMERE®, ZEMDRI®, and XERAVA™, that received FDA approval in 2017, 2018, and 2018, respectively. ASPR/BARDA held a workshop to review the development pipeline of vaccines against AMR bacterial threats, which drew over 170 participants from across industry and academia and provided ASPR/BARDA a better understanding of the AMR vaccine landscape and vital feedback from industry on key development hurdles in this space.

Objective 4.4

Develop non-traditional therapeutics, vaccines, and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.

Non-traditional therapeutics have the potential to circumvent existing mechanisms of resistance, reduce side effects by minimizing collateral damage to the host microbiome, extend the useful lifespan of existing drugs, enable more sustainable treatment approaches, and leverage technologies from other medical fields. NIH/NIAID funding for non-traditional therapeutics includes advancing research for live microbiome-based products, bacteriophages, and other novel treatment options as alternatives to antibiotics, including a placebo-controlled Phase 1/2 clinical trial assessing the safety and efficacy of fecal transplants in individuals with one or more recurrence of *C. difficile* infection. NIH/NIAID researchers revealed that the probiotic bacterial species *Bacillus* secretes compounds that block communication between *Staphylococcus aureus (S. aureus)* and inhibit intestinal colonization by *S. aureus*. This result suggests that *Bacillus*-containing probiotics could be used for simple and safe *S. aureus* decolonization strategies. NIH/NIAID also continues to support development of novel small molecule candidates called mannosides, which instead of killing bacteria, prevent infection by preventing bacteria from sticking to the walls of the bladder. In 2020, an NIH-supported mannoside product advanced to become part of the CARB-X portfolio. DoD has also funded programs that support discovery and development of therapeutic modules using a

range of nontraditional approaches. Importantly, non-traditional therapeutic approaches require appropriate regulatory consideration, so NIH/NIAID and FDA have worked together to address key regulatory considerations related to using bacteriophages for decolonization of vancomycin-resistant enterococci and MRSA, and for live biotherapeutics, as well as safety and efficacy considerations related to fecal microbiota transplantation (FMT) and FMT-based products.

Given the need and potential utility of new, innovative products to overcome the increasing challenge of antibiotic-resistant bacteria, ASPR/BARDA has expanded its portfolio to include two non-traditional candidates and three first-in-class candidates. The non-traditional candidates include an engineered phage cocktail carrying a CRISPR-Cas3 cassette for the treatment of recurrent urinary tract infections caused by *E. coli*, and human microbiome bacterial consortia for the prevention of recurrent *C. difficile* infection. The first-in-class candidates include a direct acting lytic agent against MRSA, a LepB inhibitor for the treatment of Enterobacteriaceae infections, and a narrow spectrum treatment for *C. difficile* infection that is in Phase 3 clinical development. The inclusion of these types of products is a new frontier for ASPR/BARDA, and these investments highlight the growing attractiveness of innovative non-traditional candidates to clinical stage funding through the efforts of other U.S. Government agencies and CARB-X.

While new therapeutic options will be essential as resistant pathogens continue to evolve, the U.S. Government has also continued to build an understanding of how to optimize the use and preserve the effectiveness of currently available antibiotics for as long as possible. DoD has explored the revitalization of failed antibiotics through combinations with other therapeutics or through novel delivery methods. NIH/NIAID supports research on the optimization of dosing levels, duration, route of administration, and use of combination drug therapy to suppress emergence of resistance and minimize toxicity. For example, the ARLG's Short-Course Therapy in Pediatric Community-Acquired Pneumonia randomized controlled trial showed that short course (five day) antibiotic treatment is superior to standard (10 day) treatment of community-acquired pneumonia in children six months to five years of age, reducing the number of days of antibiotic exposure.

Vaccines and immunoprophylactics (products that harness the immune system to prevent disease) represent potential tools to help hospitalized patients avoid resistant infections altogether, with the added benefit of reduced spread of resistant strains and genes. NIH/NIAID-funded projects are targeting antibiotic-resistant gram-negative bacteria, including a collaboration with Walter Reed Army Institute of Research aimed at evaluating a promising vaccine candidate for the prevention of *Shigella sonnei*. Additionally, NIH/NIAID has established six STIs Cooperative Research Centers focused on developing vaccines to prevent syphilis, gonorrhea, and chlamydia. NIH/NIAID investigators have also developed a non-human primate model of *Klebsiella pneumoniae* sequence type 258 pneumonia and successfully used a vaccine to moderate disease severity in these animals, suggesting a path toward a vaccine to prevent bacterial pneumonia in humans.

Significant progress has been made in designing and implementing alternative strategies, including bacteriophages, viruses that target bacteria, for treating necrotic enteritis in poultry, the most economically important enteric disease affecting the poultry industry worldwide. USDA/ARS has also supported its aquaculture scientists in publishing on the use of natural compounds from sycamore trees

and the use of bacteriophage to treat the four major bacterial infections in fish. USDA/ARS researchers continue to optimize the use of novel methods to inactivate antibiotic-resistant bacteria, including irradiation of pathogens present on lettuce leaves, identification of bacteriophage that might be used for biocontrol of foodborne pathogens, and evaluating the efficacy of plant products (e.g., black cumin) as substitutes for conventional antibiotics.

Objective 4.5

Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates and promising vaccines that can reduce the need to treat bacterial infections.

Providing data and materials help support the development of novel therapeutics. NIH/NIAID, CDC, and DoD continue to release antibiotic resistance data sets into publicly accessible and searchable databases developed by NIH/NLM/NCBI (e.g., GenBank, BioSample, and the National Database of Antibiotic-Resistant Organisms) and the NIH/NIAID-funded Bioinformatics Research Center, PATRIC. As part of this effort, CDC has sequenced and deposited over 40,000 isolates, including resistant pathogens causing HAIs and resistant enteric pathogens.

NIH/NIAID lowers the risk and fills gaps for new entries into discovery and development efforts by providing preclinical service support to foster antibacterial product development. These preclinical services have supported novel antibiotic candidates, vaccine candidates for antibiotic-resistant infections, non-traditional antibiotic products such as bacteriophage, and compounds to be used in conjunction with existing antibiotics to restore their effectiveness. CDC fills gaps in epidemiologic evidence that can be useful in guiding discovery and development efforts. For example, through the Modeling Infectious Diseases Healthcare program, mathematical modeling studies have shown that agents that decolonize carriers of drug-resistant organisms can be highly cost-effective when considering indirect benefits within populations vulnerable to outbreaks (e.g., hospitals), and that finding ways to incentivize development of such agents may have as much or more impact than development of agents designed solely to treat infections. NIH/NIAID also tests new candidate therapeutics in standard mouse models of bacterial thigh and lung infections, which can provide initial *in vivo* indications of efficacy, as well as in more detailed models of bacterial infection, which can provide additional data on a drug candidate's performance. The CARB-X initiative has also provided data and material support for promising candidates (see Objective 4.7).

Objective 4.6

Enhance opportunities for public-private partnerships to accelerate research on new antibiotics and other tools to combat resistant bacteria.

Partnerships between federal agencies and private entities can leverage the strengths of both sectors toward accelerated innovation. ASPR/BARDA has been a driver of public-private partnerships for antibiotic development, investing $1.5 billion through CARB-X, the ARD portfolio, and Project BioShield. In the 2015 Plan, ASPR/BARDA proposed to establish one additional portfolio partnership with a pharmaceutical or

biotechnology company to accelerate development of new antibacterial drugs within one year. ASPR/BARDA exceeded this target in 2016 when it entered into three partnerships. Since 2016, BARDA has established a total of 14 public-private partnerships and established an ARD portfolio of 17 promising antibacterial drug candidates across all phases of development, with seven currently in Phase 3 development. These candidates target a majority of the drug-resistant pathogens identified by CDC as "urgent" and "serious" threats. Using a new partnership strategy, ASPR/BARDA recently awarded a Project BioShield contract to Paratek Pharmaceuticals to support advanced clinical development and procurement. This contract provides funding during capital-intensive stages of commercializing a newly approved antibiotic, including pediatric studies and post-marketing commitments. CARB-X, which is supported by ASPR/BARDA and NIH/NIAID and is described in more detail under the following objective, has become a fundamental example of the benefit of and success that can come from these types of partnerships. In addition to supporting CARB-X, NIH/NIAID supports studies that generate data required for IND submissions to FDA and has facilitated applications for multiple antibiotic candidates, including products with broad gram-negative antibacterial activity and novel first-in-class products to treat *C. difficile* infection.

Objective 4.7

Create a biopharmaceutical incubator—a consortium of academic, biotechnology, and pharmaceutical industry partners—to promote innovation and increase the number of antibiotics in the drug-development pipeline.

In 2016, in collaboration with NIH/NIAID and the Wellcome Trust, ASPR/BARDA launched CARB-X, a global public-private partnership dedicated to accelerating antibacterial innovation to enhance the preclinical antibacterial product pipeline. This partnership expanded in 2018 to include support from the Gates Foundation, the United Kingdom Government, and the German Government. As of 2020, CARB-X received $303 million from funders and $180 million from ASPR/BARDA for a total of $483M, and supported 75 projects, including 9 new classes of antibiotics, 16 non-traditional therapies, eight AMR vaccine candidates and six rapid diagnostics. Through 2020, NIH/NIAID provided technical support and preclinical drug development services to approximately half of CARB-X awardees to further advance the development of new antibacterial products. These services fill critical gaps for researchers working toward product development.

Goal 5
Improve International Collaboration and Capacities for Antibiotic-Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development

Domestic action alone is insufficient to protect the nation's public and agricultural health and security. The U.S. Government works domestically and internationally to address the emergence, spread, and impact of AMR[6]. Internationally, these efforts include direct investments and collaboration with multilateral organizations, partner nations, private donors, and civil society to promote the development and implementation of policies, capabilities, standards, systems, and networks to address AMR. The U.S. Government's efforts[7] under the 2015 Plan focused on securing a strong national and international commitment to addressing AMR, strengthening capacities through direct investment and catalytic leadership, by contributing to the development of assessment tools and supporting assessments, and promoting research and evidence-informed decision making.

Barriers and Challenges

Internationally, competing priorities remain one of the greatest barriers to sustained attention and action on AMR. Particularly for low- and middle-income countries, existing limitations in infrastructure, governance, and health systems (human and animal), as well as broader economic and development challenges, place significant demands on limited political, financial, technical, and personnel resources. While significant progress was made between 2015 and 2020 in the number of countries with national AMR action plans, converting those plans into action faced significant challenges. Initial AMR capacity levels were low in many countries and the availability and implementation of AMR-related capacity assessments at the national and facility level (not associated with specific diseases such as TB, human immunodeficiency virus [HIV], and malaria) were limited. Recognizing these diverse challenges, the U.S. Government strengthened the foundation for sustainable capacity at facility, community, and national levels. These efforts include assessments to inform tailored action; development and adoption of relevant policies, guidance, and tools; and establishment or strengthening of local capacity to manage progress and sustain action. For example, DoD expanded AMR surveillance capacity through international laboratories (e.g., Georgia), resulting in better AMR-related capacity by utilizing the MRSN sequencing capability. In implementing the activities below, aligning resources to establish a well-functioning international network

[6] While the original U.S. National Strategy for Combating Antibiotic-Resistant Bacteria focused on antibiotic resistance, the international community frequently combines work on various forms of resistance under the term antimicrobial resistance. This report therefore refers to AMR in this section unless a specific activity focused solely on antibiotic resistance.

[7] For disease-specific AMR issues, U.S. Government investments between 2015 and 2020 were managed through complementary efforts including the U.S. Action Plan for Combating Multidrug Resistant Tuberculosis, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and the U.S. President's Malaria Initiative. This work is ongoing.

was a significant challenge, including supporting laboratory proficiency assessment efforts and supporting partner countries in accurately identifying the emergence and spread of AMR. Variations in approach regarding antimicrobial use, surveillance, and practices posed another major challenge, particularly to efforts that required harmonization across regions.

Objective 5.1

Promote laboratory capability to identify at least three of the seven WHO priority AMR pathogens using standardized, reliable detection assays.

With funding for the Global Health Security Agenda (GHSA) and guided by the World Health Organization (WHO) Global Action Plan, CDC and USAID worked with national governments and laboratory facilities to effectively detect and report AMR and supported laboratory proficiency assessments to inform interventions in more than 17 countries. To strengthen the laboratory ecosystem and promote sustainability of in-lab investments, USAID supported incorporating necessary microbiology commodities into national supply chains and strengthened microbiology commodity procurement and management capacities. USAID also supported knowledge management, integration, and reporting of AMR data including utilization of the WHONET system and assessments to identify potential opportunities for integrating human and animal health disease reporting systems. To ensure standardization and reliability throughout laboratory capacity building and AMR surveillance networks, CDC developed the Lab Assessment of Antibiotic Resistance Testing Capacity tool, which has been deployed to assess and improve lab capacity in at least six countries and it is available on the CDC website in four languages. Laboratory capacity was also improved through training and mentorship in a collaboration between CDC, the American Society for Microbiology, and the Association of Public Health Laboratories. CDC also conducted lab strengthening activities in seven countries that involved some baseline assessments and targeted technical assistance. Follow up assessments have not been comprehensive due in large part to the COVID-19 pandemic.

Objective 5.2

Collaborate with WHO, the World Organization for Animal Health (OIE), and international efforts focused on development of lab surveillance to detect/monitor antibiotic-resistant bacteria in animal/human foodborne pathogens.

The U.S. Government collaborates with international partners such as the Transatlantic Task Force on Antimicrobial Resistance (TATFAR), WHO, Food and Agriculture Organization (FAO), OIE, United Nations Environment Programme (UNEP) and the World Bank to strengthen global capacity for AMR surveillance in animal and foodborne pathogens. These partner organizations strive to optimize antimicrobial use in animals, reduce AMR, build consensus, and harmonize methods. These international collaborations have also advanced the WHO Global Action Plan and mentored projects developed by U.S. agencies that support regional capacity-building of AMR surveillance.

FDA/CVM and USDA co-led the U.S. delegation to the Codex Alimentarius *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance, which updated a Code of Practice to Minimize and Contain Antimicrobial Resistance and developed international guidelines on integrated surveillance for antimicrobial resistance in the food chain. USDA/FSIS collaborates with the Pan American Health Organization and the International Network of Food Analysis Laboratories to document regional capability for AMR work.

USAID partners supported 12 FAO Assessment Tool for Laboratories and Antimicrobial Resistance Surveillance Systems (FAO-ATLASS) missions to improve national AMR surveillance systems in the food and agriculture sectors in West, Central, and East Africa and in South Asia, encompassing 43 laboratories in Africa and 17 laboratories in Asia. Through its partnership with FAO, USAID has improved animal laboratory testing capacities and surveillance to detect prioritized antimicrobial-resistant pathogens in seven countries (Bangladesh, Burkina Faso, Cambodia, Cameroon, Indonesia, Liberia, Tanzania), informed by the USAID-supported FAO-ATLASS assessments.

CDC drafted minimum technical requirements for Antimicrobial Resistance National Reference Laboratories in support of the WHO recommendation that all countries establish a National Reference Laboratory, a key component of implementing the Global Action Plan for Antimicrobial Resistance. Additional CDC technical training and mentorship programs provided information related to foodborne disease surveillance across One Health, microbiological methods of pathogen analysis, and whole-genome sequencing and analysis. Examples of these activities include CDC's extensive participation in providing training to build capacity for regional PulseNet International laboratories and for analyzing WGS data. CDC also developed educational materials, offered technical assistance, and provided mentorship for integrated AMR surveillance programs both through the Antimicrobial Resistance Collaborating Centers Network and with the Advisory Group on Integrated Surveillance of Antimicrobial (AGISAR).

The USDA agencies and FDA also engaged in training and mentorship projects for One Health surveillance and AMR testing.

From 2015 to 2020, the DoD/GEIS-funded Gonococcal Reference Laboratory and Repository continued work with its international laboratory network and received and tested nearly 700 specimens from seven locations for *N. gonorrhoeae* as well as another ~ 5,000 ESKAPE-E (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacter species, *Esherichia coli*) pathogens.

Objective 5.3

Develop a mechanism for international communication of critical events that may signify new resistance trends with global public and animal health implications.

CDC was integral in developing and promoting the WHO Global Antimicrobial Resistance Surveillance System (GLASS) and the Emerging Antimicrobial Resistance Reporting (EAR) portal, which is a functional component within the GLASS IT platform for early warning information regarding potential EAR events.

This system collects and disseminates reports of new or emerging resistant pathogens globally. Since the completion of GLASS in 2018, CDC continues to contribute data on an annual basis for several priority pathogens and provides input on newly drafted WHO guidance documents. More than 3 million laboratory-confirmed infections have been reported by more than 24,000 surveillance sites in 70 countries through GLASS. CDC has also continued its work with the WHO as it develops guidance for Antimicrobial Resistance National Reference Laboratories, which will include the detection of new resistant pathogens and global communication.

Objective 5.4

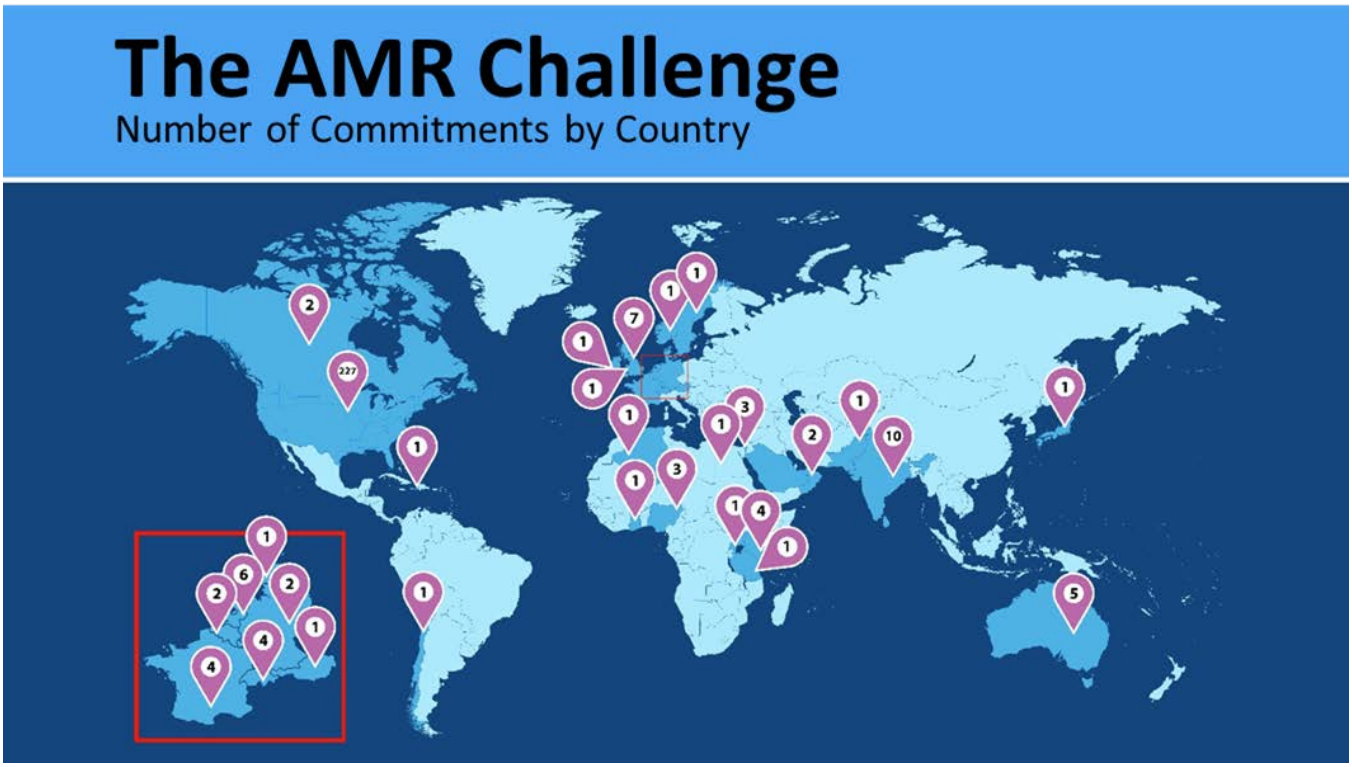
Promote the generation and dissemination of information needed to effectively address antibiotic resistance.

Coordinated efforts by the U.S. Government have elevated the awareness of AMR among global policymakers. The State Department incorporates AMR issues into engagements with foreign entities, including in bilateral science and technology dialogues. State, HHS/Office of Global Affairs (OGA), and USDA co-lead U.S. Government efforts to actively promote AMR topics internationally at the G7, G20, WHO-led consultations, and United Nations General Assembly meetings on AMR. Several of these organizations aim to enhance a One Health approach to AMR globally. HHS/OGA advances U.S. Government equities related to AMR within the Tripartite, which is the coordinated effort of FAO, WHO, and OIE, with UNEP, to ensure that human, animal, and environmental health are considered in AMR work within each of these organizations. Created in 2009 to address the global threat of antibiotic resistance, TATFAR includes Canada, the European Union (E.U.), the U.S., and Norway and is co-chaired by HHS and the European Commission. Members collaborate and share best practices to strengthen domestic and global efforts in improving appropriate antimicrobial drug use in human and animal health settings, preventing healthcare and community-associated drug-resistant infections, and developing strategies for improving the pipeline of new antimicrobial drugs. Through TATFAR, HHS/OGA, CDC, NIH, FDA, ASPR/BARDA, USDA, and DoD have worked to develop guidance for assessing the appropriateness of human antibiotic use, review antibiotic reduction goals, provide consultation and collaboration on point-prevalence surveys, and harmonize surveillance practices. CDC has served as TATFAR Secretariat since 2014.

HHS/OGA leads U.S. engagement with WHO on all global health issues, including adoption of the WHO Global Action Plan on AMR, which was endorsed by the World Health Assembly in 2015, and aims to reduce the global burden of AMR. HHS/OGA also led the negotiations for the 2019 WHO resolution on AMR. In 2014, the United States in partnership with nearly 30 countries launched the GHSA to achieve the vision of a world safe and secure from global health threats posed by infectious diseases, including AMR. The Antimicrobial Resistance Action Package under GHSA continues to be a useful forum to encourage international collaboration and coordination on AMR. HHS/OGA, FDA, USDA, USAID, and CDC continue to work with public health and international partners (Association of Public Health Laboratories, TATFAR, FAO, OIE, International Health Regulations-Joint External Evaluation [IHR-JEE], and the World Bank) to optimize antibiotic use in animals, reduce antibiotic resistance, build consensus, harmonize methods, and improve surveillance.

The U.S. Government also amplifies dissemination of information on AMR research, education, and stewardship during World Antimicrobial Awareness Week and U.S. Antibiotic Awareness Week, which is held annually in November. For example, USAID implementing partners conducted activities to promote awareness during World Antimicrobial Resistance Week, publish on their activities, and promote information sharing among USAID-assisted facilities and countries. CDC coordinated an HHS wide twitter storm, publish leadership videos and op-eds to raise awareness and share information on antimicrobial resistance. To spur dedicated and comprehensive actions worldwide to combat AMR, CDC and HHS/OGA launched the Antimicrobial Resistance Challenge, a yearlong effort by the U.S. Government to accelerate the fight against this global threat. Kicked off in 2018 by the U.S. Secretary of Health and Human Services, the Challenge resulted in more than 350 organizations across the globe committing to slow AMR using a One Health approach.

In 2015, the Obama Administration convened the White House Forum on Antibiotic Stewardship, which brought together more than 150 animal and health stakeholders and government and private sector leaders, including from multinational organizations, securing commitments to address antibiotic resistance. This forum provided the foundation upon which additional international activities were modeled, such as the AMR Challenge.



Standardization of data is a key strategy to promote the flow of information needed to combat AMR globally. Varying definitions for resistance between both countries and surveillance networks have limited the interoperability of international surveillance data. To address this limitation, the U.S.-based Clinical and Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the WHO AMR Collaborating Centres (which include CDC), identified priority areas for harmonization, including fluoroquinolone breakpoints for Enterobacterales and carbapenem breakpoints

for gram-negative bacteria. Currently, DoD provides technological packages for surveillance and reporting purposes to its international partners. Under the Chemical, Biological, and Radiological (CBR) Memorandum of Understanding between the U.S., United Kingdom, Canada, and Australia, DoD has proposed the Biosurveillance Ecosystem as a potential platform for surveillance data and technology sharing that will facilitate real-time biosurveillance for early warning and course-of-action analysis. CDC has provided technical expertise on the development of surveillance plans, policies, or sentinel programs for infection prevention and control in more than 17 countries and have assisted at least 10 countries with initiating, strengthening, or implementing national surveillance systems. USAID's Infectious Disease Detection and Surveillance project supports countries to detect priority diseases and AMR through building national and subnational capacities to improve diagnostic networks and surveillance systems that implement and promote a One Health approach.

USAID and CDC have collaborated to evaluate third-party water, sanitation, and hygiene in healthcare facilities interventions in ten countries. As of September 2020, with USAID support, 111 facilities have undergone an Infection Prevention and Control Assessment Framework assessment; re-assessments of some facilities indicated that they have improved infection prevention and control, including the establishment of infection prevention and control committees. USAID also supported rapid assessments in the agriculture sector, including infection prevention, control, and hygiene assessment at 67 veterinary clinics, slaughterhouses, and poultry farms.

Objective 5.5

Establish and promote international collaboration and public-private partnerships to incentivize development of new therapeutics to counter antibiotic-resistance, including new, next-generation, and other alternatives to antibiotics, vaccines, and affordable, rapidly deployable, point-of-need diagnostics.

International collaboration can harness global knowledge and expertise to facilitate research and development of new therapeutics. To guide the overall global AMR research agenda and promote alignment across countries and funders, CDC and HHS/OGA facilitated and convened a meeting of TATFAR in 2018 to review current lines of work and discuss improved and expanded communication among Member States. USDA and OIE co-sponsored, with NIH/NIAID assistance, the Third International Symposium on Alternatives to Antibiotics in Agriculture, which featured strong interaction and exchange across One Health fields. USDA actively contributed to OIE ad hoc work prioritizing animal diseases for vaccine research to help inform groups such as the STAR-IDAZ International Research Consortium, a forum of public and private research and development program owners/managers aiming to coordinate research on animal health at a global level.

International collaborations have also enabled connections among clinical trial networks and facilitated communication and cooperation between research sites. NIH/NIAID's engagement with TATFAR has facilitated alignment of U.S. and E.U. AMR research activities and enabled greater access to critically important patient populations. NIH/NIAID has also worked with the WHO, GARDP, and the Foundation for

Innovative New Diagnostics (FIND) to create Target Product Profiles for point-of-care diagnostics to distinguish chlamydia and gonorrhea infections and determine antibiotic sensitivity for *N. gonorrhoeae*, resulting in FIND and WHO funding for several projects. The ARLG also collaborates with the Innovative Medicines Initiative's Combatting Antimicrobial Resistance in Europe (COMBACTE) consortium to select optimal U.S. and E.U. sites for COMBACTE and ARLG trials. International collaborations have contributed to the progress of several new therapeutic candidates to global Phase 3 clinical trials, including three products supported by NIH/NIAID, ASPR/BARDA, and GARDP. In addition, European clinical trial networks joined an NIH/NIAID-supported Phase 3 clinical trial evaluation on the optimal use of an older antibiotic (colistin), alone or in combination with a carbapenem, in patients with MDR gram-negative infections. Given the potential for vaccines to prevent infections and thereby mitigate the impact and spread of resistance. USAID supports the Coalition for Epidemic Preparedness Innovations' (CEPI) mission to stimulate and accelerate the development of vaccines against high consequence pathogens and emerging infectious diseases and enable access to these vaccines during outbreaks.

Objective 5.6

Support countries to develop and implement national plans to combat antibiotic resistance and strategies to enhance antimicrobial stewardship.

Sustainably financed, multisectoral national action plans, adaptable to evolving national contexts, are the cornerstone of national capacity to effectively address AMR. Given the importance of public accountability, HHS/OGA negotiated language in the G7 declaration that called for making all AMR national strategies and other national implementation guidance publicly accessible. USAID and CDC have supported the development of National Action Plans, technical assistance to strengthen country systems to accelerate and monitor, of their implementation, in at least 15 countries.

To support multisectoral coordination in implementation of AMR national action plans, USAID's Medicines Technologies and Pharmaceutical Services (MTaPS) program worked in 11 target countries to bring together organizations involved in the countries' One Health activities. Support included establishing multisectoral coordination bodies; conducting landscape analyses that provided lessons learned for how to institutionalize and strengthen a country's multisectoral coordination across sectors and between departments in countries; and contributing to multisectoral AMR communication strategies.

U.S. Government investments also strengthened implementation of national action plans. For example, USAID, through support provided by the MTaPS program, trained healthcare providers in 10 countries on how to reduce HAIs and led updates to the Global Health eLearning Course on AMR. CDC has assisted in the development of operational strategies for five countries with the initiation of antimicrobial-resistant containment programs. CDC has also developed and is finalizing a global tool for antibiotic stewardship in resource-limited settings, a tool to assess readiness of laboratories to conduct AMR surveillance, protocols for HAI surveillance in resource limited settings, and infection prevention and control guidelines and training materials for resource-limited settings. In addition to tool development, CDC has assisted with the implementation of infection prevention and control programs in over 40 facilities in nine countries. USAID advances rational drug use and antimicrobial stewardship through its support of integrated case management guidelines and training materials. For example, USAID funded the Systems for Improved

Access to Pharmaceuticals and Services (SIAPS) program, which promotes self-evaluation among therapeutics committees in Namibia to improve rational use of medicines.

Preventing infections, early, correct diagnosis, and appropriate care are critical elements of effective national approaches to addressing AMR. Through USAID's support to Gavi, the Vaccine Alliance, more than 60 countries have introduced pneumococcal conjugate vaccine, which has the potential to significantly lower antibiotic use through infection prevention. USAID supports 25 countries to strengthen the timely diagnosis and appropriate case management of possible severe bacterial infections, including pneumonia, in newborns and children. Further, USAID supports local governments and stakeholders to strengthen crucial water, sanitation, and hygiene systems at the household, community, and institutional levels.

Fellows in USDA's Faculty Exchange Program (FEP) on African Veterinary Science Education built capacities for teaching AMR concepts, detection, and mitigation at their respective veterinary colleges in Africa. For example, one FEP fellow with Iowa State University conducted and published their research on AMR in *Staphylococci* among Kenyan dairy cows. Their work contributed to the "baseline" of AMR evidence in Kenya and demonstrated the value of these fellowships in strengthening partner countries' capacities (e.g., evidence, expertise) to combat AMR at international, national or subnational levels. In addition, through USDA's Scientific Cooperation Exchange Program and in collaboration with China's Ministry of Agriculture, a U.S. multi-disciplinary team, led by Michigan State University, visited Nanjing University, the China Agricultural University, and Chinese Academy of Sciences facilities in 2017 to promote cooperation on methods for molecular genetic surveillance of AMR bacteria in livestock, crops, and farmland.

Objective 5.7

Partner with other nations to promote quality, safety, and efficacy of antibiotics and strengthen their pharmaceutical supply chains.

To help ensure the availability of high-quality medicines, including antibiotics, USAID has supported 40 National Quality Control Laboratories, and supported Ministries of Health to develop and revise national essential medicine lists in six countries. USAID funds the Promoting the Quality of Medicines (PQM, 2009-2020) and follow-on PQM+ (2019-2024) programs, both administered by U.S. Pharmacopia, to further strengthen regulatory systems to protect populations against poor-quality medicines produced in or imported to low- and middle-income countries, including the development of more than 2000 new regulatory procedures or guidelines to ensure the quality of medicines. USAID with SIAPS has also supported the strengthening of regulatory capacity and improving processes for medicine registration in six countries, three of which adopted the Common Technical Document format and specifications to standardize the medicines' registration application process. With USAID support, these countries are implementing the registration module of a web-based regulatory information system to make their processes more efficient and transparent.

Objective 5.8

Coordinate approaches with international organizations to harmonize international data submission requirements, risk guidelines related to licensure, and/or approval of veterinary products.

Both USDA and FDA have coordinated with international organizations to further harmonize the antimicrobial product development and approval process for veterinary products. USDA has implemented a reporting structure for adverse events for the Pharmacovigilance program that is consistent with international guidelines set out in the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). To facilitate the timely approval and availability of veterinary products, FDA/CVM is working with the Regulatory Cooperation Council to perform simultaneous approvals with the Veterinary Drug Directorate in Canada and is pursuing the use of parallel scientific advice to engage drug sponsors who are seeking approvals in both the U.S. and the E.U. FDA/CVM also continues to report data on U.S. antimicrobial sales for animals to OIE. USDA/APHIS expanded its Global Outreach Forum through continued sponsorship of the annual Veterinary Biologics Training Program, which gives participants an overview of the scientific principles of vaccines and vaccination as well as the USDA regulatory process for assuring the purity, safety, potency, and efficacy of veterinary biologics.

Objective 5.9

Coordinate multilateral organizations to advance and prioritize international AMR objectives.

NOTE: While this objective was not part of the CARB National Action Plan as published in 2015, the CARB Task Force began tracking these activities in 2016 in response to the rapidly expanding global landscape to address AMR.

The U.S. Government maintains a strong presence in global multilateral organizations and continues to advance awareness and action on a breadth of AMR issues. The U.S. worked actively to support the development and adoption of the Global Action Plan on Antimicrobial Resistance at the 2015 World Health Assembly, and the adoption of related FAO, OIE, and UNEP resolutions.

USDA/Foreign Agricultural Service (FAS) has coordinated the drafting of compromise language with other federal agencies and other delegations for the G20 Agricultural Minister's Communique and Action Plan and the G7 Agricultural Minister's statement. As described in several objectives above, USDA continues its interactions within the OIE, FAO, and the Organisation for Economic Co-operation and Development (OECD).

On behalf of the U.S. Government, HHS/OGA led an AMR resolution calling for the reinvigoration of WHO commitment to addressing AMR through the Tripartite, meaningful Member State engagement on the ad hoc Interagency Coordination Group recommendations and UN Secretary-General’s report, and the accelerated development and implementation of context-specific national action plans on AMR.

The State Department has shaped how the international community understands and will address the environmental component of drug-resistant disease through effective negotiation of and technical input on the third UN Environment Assembly processes. The United Nations Environmental Assembly-3 (UNEA-3) resolutions on environment and health and on water monitoring call for greater UNEP and Member-State action, particularly to address the lack of data and the limited availability of tools for understanding and addressing the impacts of antimicrobial pollution on the development and spread of drug-resistant disease as well as on biodiversity, ecosystems, and the environment and to prepare a report on the environmental impacts of AMR.

HHS/OGA represented the United States priority AMR issues at the 2nd Call to Action to Combat Antimicrobial Resistance in Ghana and the Grand Challenges meeting in Berlin, both held in 2018 and effectively advanced U.S. AMR priorities.

Next Steps

The U.S. Government is committed to continuing the fight against antibiotic resistance. Building on the abovementioned efforts set in motion in 2015, the CARB Task Force has drawn from lessons learned since 2015 to develop a new National Action Plan to be implemented between 2020 and 2025.

Maintaining the five goals established by the National Strategy for CARB, the 2020 Plan builds upon established and successful activities, addresses ongoing and emerging issues, and outlines aspirational targets (to be updated and/or added to annually) that the U.S. Government will undertake to further reduce the spread and impact of antibiotic resistance and improve antibiotic stewardship. These targeted actions of the new 2020 Plan will equip the United States to continue its One Health response to antibiotic resistance threats of today and prepare for new resistance that might emerge tomorrow. The 2020 Plan also describes barriers and challenges that the CARB Task Force has proactively identified as relevant for the next five years of work, and those were considered in the development of objectives and targets.

Many of the activities outlined in the 2020 Plan have become achievable because of the work accomplished over the past five years. The CARB Task Force will continue to report annually on progress toward the 2020 Plan.

Appendix A: Key Documents and Links

AHRQ	Association of a Safety Program for Improving Antibiotic Use With Antibiotic Use and Hospital-Onset Clostridioides difficile Infection Rates Among US Hospitals
	Toolkit to Improve Antibiotic Use in: Acute Care Hospitals; Long-Term Care
CDC	Antibiotic Resistance Threats in the United States (2013; 2019)
	Antibiotic Use in the United States: Progress and Opportunities (2017; 2018; 2020)
	AR Isolate Bank Reports
	AR Investment Map
	Frequency of First-line Antibiotic Selection Among US Ambulatory Care Visits for Otitis Media, Sinusitis, and Pharyngitis
	Implementation of Antibiotic Stewardship Core Elements at Small and Hospital Levels
	The Core Elements of Antibiotic Stewardship for Nursing Homes
	The Core Elements of Hospital Antibiotic Stewardship Programs
	The Core Elements of Human Antibiotic Stewardship Programs in Resource-Limited Settings: National and Hospital Levels
CMS	Regulatory Provisions on Infection Prevention and Control as part of Hospital and Critical Access Hospital Changes to Promote Innovation, Flexibility, and Improvement in Patient Care
DoD	The Challenges of Implementing Next Generation Sequencing Across a Large Healthcare System, and the Molecular Epidemiology and Antibiotic Susceptibilities of Carbapenemase-Producing Bacteria in the Healthcare System of the U.S. Department of Defense
FDA	Supporting Antimicrobial Stewardship in Veterinary Settings
NIH/NIAID	NIH/NIAID's Antibiotic Resistance Research Framework: Current Status and Future Directions 2019
USAID	Improving Medication Adherence through Systems Strengthening Approaches
USDA	Alternatives to Antibiotics Conference: Programmes and Abstracts
	National Animal Health Laboratory Network AMR Pilot Project Dashboard
	National Animal Health Monitoring System Antimicrobial Use 2017
	USDA's Role in Addressing Antimicrobial Resistance
USDA/ARS	Antimicrobial Resistance (AMR) and Alternatives to Antibiotics (ATA) Accomplishment Summary
VA	VHA Directive 1031, Antimicrobial Stewardship Programs (ASP)

Appendix B: Acronyms

AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial
AHRQ	Agency for Healthcare Research and Quality
AMR	Antimicrobial Resistance
APHIS	USDA/Animal and Plant Health Inspection Service
AR	Antibiotic Resistance
AR Lab Network	Antibiotic Resistance Laboratory Network
AR&PSP	Antibiotic Resistance & Patient Safety Portal
ARD	Advanced Research and Development
ARLG	Antibacterial Resistance Leadership Group
ARMoR-D	Antimicrobial Resistance Monitoring and Research Database
ARS	USDA/Agricultural Research Service
ASPR	Assistant Secretary for Preparedness and Response
AST	Antimicrobial Susceptibility Testing
AUR	Antibiotic Use and Resistance
BARDA	ASPR/Biomedical Advanced Research and Development Authority
C. difficile	Clostridioides difficile
C. trachomatis	Chlamydia trachomatis
CARB	Combating Antibiotic-Resistant Bacteria
CARB Strategy	National Strategy for Combating Antibiotic-Resistant Bacteria
CARB-X	Combating Antibiotic-Resistant Bacteria Accelerator Program
CBR	Chemical, Biological, and Radiological
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CEPI	Coalition for Epidemic Preparedness Innovations
CLSI	Clinical and Laboratory Standards Institute
COMBACTE	Combatting Antimicrobial Resistance in Europe
CoP	Conditions of Participation
COVID-19	Coronavirus Disease 2019
CUSP	Comprehensive Unit-based Safety Program
CVM	Center for Veterinary Medicine
DDDI	Detection, Diagnostics, and Devices Infrastructure
DHS	Department of Homeland Security
DoD	Department of Defense
DoI	Department of Interior
E. coli	Escherichia coli
E.U.	European Union
EAR	Emerging Antimicrobial Resistance Reporting
EIP	Emerging Infection Program
EPA	Environmental Protection Agency

ESKAPE-E	*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacter species, *Escherichia coli*
EUCAST	European Committee on Antimicrobial Susceptibility Testing
ExAST	Expanded Antimicrobial Susceptibility Testing for Hard-to-Treat Infections
FAO	Food and Agriculture Organization
FAO-ATLASS	FAO Assessment Tool for Laboratories and Antimicrobial Resistance Surveillance Systems
FAS	USDA/Foreign Agricultural Service
FDA	Food and Drug Administration
FEP	Faculty Exchange Program
FIND	Foundation for Innovative New Diagnostics
FMT	Fecal Microbiota Transplant
FSIS	USDA/Food Safety and Inspection Service
G7	Group of Seven
GAO	U.S. Government Accountability Office
GARDP	Global Antibiotic Research and Development Partnership
GEIS	Global Emerging Infections Surveillance
Gen-FS	Genomics for Food Safety
GFI	Guidance for Industry
GHSA	Global Health Security Agenda
GISP	Gonococcal Isolate Surveillance Project
GLASS	Global Antimicrobial Resistance Surveillance System
HAI	Healthcare-associated infection
HAI/AR	Healthcare-associated infection and antibiotic-resistant
HHS	Department of Health and Human Services
HIV	Human Immunodeficiency Virus
IHR-JEE	International Health Regulations-Joint External Evaluation
IND	Investigational New Drug
MDR	Multidrug-resistant
MRSA	Methicillin-resistant Staphylococcus aureus
MRSN	Multidrug-Resistant Organism Repository and Surveillance Network
MTaPS	Medicines Technologies and Pharmaceutical Services
N. gonorrhoeae	Neisseria gonorrhoeae
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
NASEM	National Academies of Science, Engineering, and Medicine
NCBI	NIH/National Center for Biotechnology Information
NDARO	NCBI National Database of Antibiotic-Resistant Organisms
NHGRI	NIH/National Human Genome Research Institute
NHSN	National Healthcare Safety Network
NIAID	NIH/National Institute of Allergy and Infectious Diseases
NIAMS	NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIFA	National Institute of Food and Agriculture
NIH	National Institutes of Health
NLM	NIH/National Library of Medicine

NQF	National Quality Forum
NVAP	National Veterinary Accreditation Program
OECD	Organisation for Economic Co-operation and Development
OGA	HHS/Office of Global Affairs
OIE	World Organisation for Animal Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PATRIC	Pathosystems Resource Integration Center
PHE	Public Health England
PQM	Promoting the Quality of Medicines
S. aureus	Staphylococcus aureus
SAAR	Standardized Antimicrobial Administration Ratio
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
State	Department of State
SURRG	Strengthening the U.S. Response to Resistant Gonorrhea
TATFAR	Transatlantic Task Force on Antimicrobial Resistance
TB	Tuberculosis
UNEA-3	United Nations Environmental Assembly-3
UNEP	United Nations Environment Programme
USAID	U.S. Agency for International Development
USDA	Department of Agriculture
VA	Department of Veterans Affairs
Vet-LIRN	Veterinary Laboratory Investigation and Response Network
VFD	Veterinary Feed Directive
VICH	Veterinary Medicinal Products
WGS	Whole-Genome Sequencing
WHO	World Health Organization