NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Progress Report for Years 1 and 2

October 2017

Prepared by the United States Task Force for Combating Antibiotic-Resistant Bacteria

Table of Contents

Background

Antibiotic Resistance (AR) is one of the most significant public health threats of our time. Every year, more than two million people in the United States are estimated to get infections that are resistant to antibiotics, and at least 23,000 people die as a result. At least another 15,000 deaths each year in the U.S. are caused by *Clostridium difficile* (*C. difficile*), a bacterium that can cause serious diarrhea and that is often associated with antibiotic use. Many advances in medical treatment—like our ability to effectively treat patients with sepsis, cancer, organ transplants, burns, or trauma— depend on the use of antibiotics to fight infections. If we lose effective antibiotics, the ability to safely offer people many life-saving and life improving modern medical advantages would be lost.

To address this growing threat, the U.S. Government developed a National Strategy for Combating Antibiotic Resistant Bacteria (CARB) and accompanying National Action Plan for Combating Antibiotic-Resistant Bacteria, which provides a five-year road map to guide the Nation toward five goals over five years (2015-2020):

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

Each goal has objectives, sub-objectives, and milestones for Years 1, 3, and 5. The CARB Task Force facilitates implementation of the Action Plan, and is chaired by the Secretaries of the U.S. Departments of Health and Human Services (HHS), Agriculture (USDA), and Defense (DoD).

After two years of activity, the CARB Task Force has developed this report to describe progress to date toward the goals of the Action Plan, highlighting key achievements from Year 1 of the Action Plan, as well as ongoing progress toward Year 3 milestones.

Response to Antibiotic Resistant Threats: The Example of the Emergence of *mcr-1*

U.S. Government agencies continuously collaborate to respond to emerging and ongoing public health threats using effective evidence-based strategies. Many of the activities reported below aim to strengthen detection and tracking of these threats. It is important to note that bacteria will inevitably develop ways to resist antibiotics, and therefore ongoing surveillance is complemented by intensified efforts to slow the spread of resistance through infection control measures that prevent infections in the first place, and by improving how we use antibiotics to ensure that they remain effective.

The emergence of *mcr-1*, a gene that confers resistance to the antibiotic colistin, illustrates the constantly evolving threat of AR and the importance of meticulous and widespread surveillance to detect and track new resistance types. Colistin can cause severe side effects, but is

increasingly used as a "last resort" treatment for infections caused by bacteria that are resistant to other antibiotics, such as carbapenem-resistant enterobacteriaceae (CRE). The *mcr-1* gene was first found in China in 2015 on a plasmid, a small mobile piece of DNA capable of moving from one bacterium to another, meaning that colistin resistance could move to multidrug-resistant CRE bacteria. Indeed, after its initial discovery, retroactive analysis supported by the U.S. National Institutes of Health (NIH) and the National Natural Science Foundation of China found the *mcr-1* gene in several samples of otherwise highly drug resistant bacteria, including CRE strains.[1] Rigorous and constant surveillance for *mcr-1* is therefore imperative to prevent the spread of potentially untreatable infections.

As soon as the *mcr-1* gene was discovered in China, the U.S. Government began conducting surveillance for it here. The Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and USDA, using the National Antimicrobial Resistance Monitoring System (NARMS), began to search for *mcr-1* in the genomes of bacterial isolates taken from humans, retail meats, and food animals. When no *mcr-1* gene was detected, researchers from the USDA Agricultural Research Service (ARS) developed new methods to enhance detection of colistin-resistant bacteria from the intestinal contents of food animals. By screening over 2,000 samples using polymerase chain reaction (PCR), researchers isolated two *E. coli* strains that contained the *mcr-1* gene on a plasmid. ARS scientists determined that one of these specimens was resistant to some, but not all, antibiotics, while the second specimen was susceptible to all tested antibiotics.

In May 2016, DoD scientists from the Multidrug-Resistant Organism Repository and Surveillance Network (MRSN) and Walter Reed National Military Medical Center (WRNMMC) discovered the *mcr-1* gene on a plasmid in an *E. coli*-containing urine sample from a Pennsylvania woman, the first detection in a clinical sample in the United States.[2] This discovery launched a public health investigation led by CDC and the Pennsylvania Department of Health. Federal, state, and local partners collaborated to identify and screen 105 household and healthcare contacts of the Pennsylvania patient, and determined that none carried bacteria containing the *mcr-1* gene. CDC alerted states, hospitals, and clinical laboratories about the discovery of *mcr-1* in the U.S., reiterating recommendations for infection prevention, environmental cleaning, laboratory testing, reporting to public health officials, and preparing food safely. CDC also developed and deployed a rapid laboratory test to help clinical labs find bacteria with the gene. The MRSN modified its screening protocols as well, including educating other clinical laboratories in the military healthcare system. After screening 7,000 isolates by whole genome sequencing, only one additional positive human clinical sample was found after the rigorous response.

Although the isolate was not resistant to all antibiotics, given the *mcr-1* gene's ability to move to other bacteria, including multidrug-resistant bacteria like CRE, the U.S. Government implemented an urgent public health response to contain and slow any potential spread. This targeted response to *mcr-1*, coordinated across multiple agencies and surveillance systems, highlights the dedication of federal agencies to turning back the rising tide of antibiotic resistance through collaboration and innovation. The National Action Plan for Combating

[1] http://www.sciencedirect.com/science/article/pii/S1473309916000566?via%3Dihub
[2] https://www.ncbi.nlm.nih.gov/pubmed/27230792

Antibiotic-Resistant Bacteria is catalyzing transformative improvements across the country that strengthen and expand our ability to prevent, identify, and respond to AR threats.

Progress Report for Years 1 and 2: Highlights

The National Action Plan for Combating Antibiotic Resistant Bacteria provides a road map for implementing five goals over five years:

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

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

The U.S. Government has made progress toward improving antibiotic use in both human and animal health, preventing the spread of resistant infections, and slowing the emergence of resistant bacteria.

Human Health

Human health activities focus on the three key areas: promoting antibiotic stewardship—an organized approach to the responsible use of appropriate antibiotics only when necessary, preventing transmission of resistant bacteria, and preventing healthcare-associated infections in the first place. Progress is already evident**: according to CDC's National Healthcare Safety Network (NHSN), methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in U.S. acute care hospitals declined 13% between 2011 and 2014, and a further 5% by 2016.[3] Meanwhile, *C. difficile* infections declined in U.S. acute care hospitals 8% between 2011 and 2014, and a further 7% by 2016.[4]** Still more progress is needed, as many people are still dying from these infections.

To better understand when antibiotics are needed, and thereby improve their use, CDC worked with The Pew Charitable Trusts and clinical experts to establish metrics for benchmarking in inpatient settings and targets for reducing inappropriate antibiotic use in outpatient settings in support of the 2020 benchmarks outlined in the National Action Plan. **As a result, we now know that at least 1 in 3 antibiotic prescriptions, or 47 million prescriptions per year, prescribed in U.S. doctors' offices and emergency departments are unnecessary.[5,6]** CDC's new report,

[3] Unpublished data, National Healthcare Safety Network, 2016
[4] http://www.cdc.gov/hai/surveillance/progress-report/index.html
[5] http://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html

Antibiotic Use in the United States, 2017: Progress and Opportunities[7] describes not only the current status of antibiotic use across healthcare settings, but also the programs and resources that support antibiotic stewardship.

Antibiotic stewardship ensures that patients get the right antibiotics at the right time for the right duration. However, as of 2014, only 39% of all U.S. hospitals had antibiotic stewardship programs that followed all seven of CDC's Core Elements of Hospital Antibiotic Stewardship.[8] CDC is, therefore, leading a nationwide effort in collaboration with the Centers for Medicare & Medicaid Services (CMS), Agency for Healthcare Research and Quality (AHRQ), NIH, the HHS Office of Disease Prevention and Health Promotion (in the Office of the Assistant Secretary for Health), and the Indian Health Service (IHS) to expand antibiotic stewardship programs. Again, progress is already evident: **based on preliminary CDC data, the percentage of all U.S. hospitals reporting antibiotic stewardship programs that meet all of CDC's Core Elements rose to 46% in 2015 and to 64% in 2016.** The goal is to have antibiotic stewardship programs in 100% of hospitals by 2020.[9]

CDC has also expanded work with The Pew Charitable Trusts to improve antibiotic use in urgent care and retail settings, and to advance measurement of antibiotic use and implementation of antibiotic stewardship in long-term care settings. CDC is collaborating with nursing home partners to improve access to antibiotic prescribing data and facilitate the development of guidance for measuring antibiotic use, and with the American Nurses Association to identify best practices and educational needs for nurses in antibiotic stewardship. CDC is also supporting scale-up of outpatient stewardship interventions in the Department of Veterans Affairs (VA) system.

CDC released guidance for small and critical access hospitals implementing antibiotic stewardship in July 2017, based on a broad collaboration with the Federal Office of Rural Health Policy, American Hospital Association, and The Pew Charitable Trusts.[10] CDC has already created a practical implementation guide for acute care hospitals (downloaded more than 20,000 times), and assisted in developing a new Joint Commission standard for antibiotic stewardship in diverse healthcare settings. CDC also initiated discussions with diagnostic test manufacturers, professional associations, and patient advocates to maximize the impact of diagnostic testing to improve antibiotic use and provide additional tools to further accelerate implementation of stewardship programs nationwide.

CDC released Core Elements of Outpatient Antibiotic Stewardship[11] in November 2016, which provide a framework for implementing stewardship activities in a variety of outpatient settings and complement their existing hospital and nursing home Core Elements. CDC is supporting a large health system to implement and evaluate the Core Elements, and provides subject matter input to assist CMS's quality improvement and patient safety contractors in implementing the Core Elements.

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[6] http://www.pewtrusts.org/en/research-and-analysis/reports/2016/05/antibiotic-use-in-outpatient-settings
[7] https://www.cdc.gov/getsmart/stewardship-report/
[8] http://www.cdc.gov/getsmart/community/pdfs/stewardship_11_13.pdf
[9] http://www.cdc.gov/getsmart/community/pdfs/stewardship_11_13.pdf
[10] https://www.cdc.gov/getsmart/healthcare/implementation/core-elements-small-critical.html
[11] https://www.cdc.gov/getsmart/community/improving-prescribing/core-elements/core-outpatient-stewardship.html

CMS heads the Quality Improvement Organization (QIO) program, which aims to improve the effectiveness, efficiency, economy, and quality of services provided to Medicare beneficiaries. Quality Improvement Network-Quality Improvement Organizations (QIN-QIOs) are a group of health care experts, clinicians, and consumers who work at the local, regional, and state levels to carry out the core functions and contractual aims of the QIO program. CMS and CDC have worked closely to expand technical assistance to health care providers and consumers, supporting improvements in infection prevention and antibiotic stewardship in long-term care and outpatient settings. CMS and CDC also collaborate through the Hospital Improvement Innovation Networks (HIINs), health care improvement and innovation experts contracted through CMS to prevent healthcare-associated infections (HAIs) and promote antibiotic stewardship implementation in hospitals. HIINs develop learning collaboratives to help hospitals achieve goals set by the Partnership for Patients, a nationwide public-private collaboration aimed at reducing preventable hospital-acquired conditions and 30-day hospital readmissions.

In a key action, CMS published final requirements for participation for over 15,000 Medicare and Medicaid-participating long-term care facilities in October 2016 (82 FR 32256). Updated Conditions of Participation (CoPs) are in the rulemaking process for the over 4,900 acute-care hospitals and 1,300 critical access hospitals that participate in the Medicare and Medicaid programs (81 FR 39475). These rules include provisions that address infection prevention and control and antibiotic stewardship programs, with antibiotic use protocols and a system to monitor antibiotic use. CDC has actively partnered with CMS to develop both the requirements and interpretive guidance under these rules.

AHRQ works to combat antibiotic resistance in all three major domains—promoting antibiotic stewardship, preventing transmission of resistant bacteria, and preventing HAIs in the first place. AHRQ is developing and providing key practical guidance to promote implementation of antibiotic stewardship activities in a variety of healthcare settings. In March 2016, AHRQ began adapting its Comprehensive Unit-based Safety Program (CUSP), which has been highly effective in preventing HAIs, to improve antibiotic use and promote antibiotic stewardship across the healthcare system. Launched in September 2016, the AHRQ Safety Program for Improving Antibiotic Use is a 5-year nationwide project to promote and support implementation of antibiotic stewardship in acute care hospitals, long-term care facilities, and ambulatory care settings nationwide (up to 500 of each type of setting). Project interventions are consistent with CDC's Core Elements in applicable settings, are being coordinated with CMS activities, and will produce a publicly available toolkit to promote implementation in all three settings. The project is intended to have a significant impact through the overall increase in antibiotic stewardship it will produce across the country.

AHRQ also developed, field tested, and is now widely disseminating a Guide to Nursing Home Antimicrobial Stewardship, based on the results of four previous AHRQ-funded research studies. The Guide provides four sets of toolkits to help nursing home staff address how to create an antibiotic stewardship program, determine whether to treat with antibiotics, choose the right antibiotic, and engage residents and families.

AHRQ's Toolkit to Reduce CAUTI (Catheter-Associated Urinary Tract Infection) and other HAIs in Long-Term Care Facilities was released in March 2017. The toolkit draws from the

experiences of more than 450 long-term care facilities that participated in the AHRQ Safety Program for Long-Term Care: HAIs/CAUTI, a three-year implementation project that reduced CAUTI rates by approximately 50%. Based on AHRQ's CUSP program, the toolkit provides resources to enhance leadership and staff engagement, teamwork, and safety culture to promote consistent use of evidence-based practices to prevent infections. This toolkit contributes to antibiotic stewardship by preventing CAUTI and other HAIs, thereby preventing the need for antibiotics, and by promoting appropriate use of urine cultures, including avoiding urine cultures for most asymptomatic patients, to help decrease inappropriate use of antibiotics.

AHRQ has also increased its support for research to develop improved methods to combat antibiotic resistance and conduct antibiotic stewardship. This comprehensive portfolio of research addresses promoting antibiotic stewardship, preventing transmission of resistant bacteria, and preventing HAIs within multiple care settings. In June 2016, AHRQ and CDC brought together experts and stakeholders to highlight knowledge gaps for effective prevention of antibiotic-resistant HAIs and to identify potential interventions and targets for research. In late FY 2016 and early FY 2017, AHRQ published four Funding Opportunity Announcements for research on CARB and HAI prevention. Such research strengthens the knowledge base to ensure the effectiveness of the interventions being used today and develop more effective interventions for tomorrow.

CDC is working with diverse public health and healthcare partners to implement CDC's Core Elements of antibiotic stewardship, promote infection prevention and control, and improve antibiotic use across healthcare settings. CDC has made early progress in supporting comprehensive and coordinated implementation of aggressive public health actions at all levels to combat and slow antibiotic resistance, as part of CDC's AR Solutions Initiative.[12] State and local public health partners are fighting antibiotic resistance in healthcare facilities, the community, and food sources, while state programs are implementing tracking, prevention, and antibiotic stewardship activities.

As part of its AR Solutions Initiative, CDC continues to implement prevention networks—where public health and healthcare work together—in all 50 states, six large cities, and Puerto Rico to better prevent infections, stop spread, and improve antibiotic use in healthcare and community settings. CDC is working with 28 states to synchronize prevention strategies across public health, healthcare, and communities. In addition, CDC's AR programs support local expertise, CRE testing, and whole genome sequencing of *Salmonella* in every state to detect and respond to emerging threats. CDC also supports capacity in nine health departments across the country to substantially expand the reach and speed of resistance testing for *Neisseria gonorrheae*, improve local laboratory and epidemiologic capacity, upgrade data systems, and enhance local capacity to prevent the spread of drug-resistant *N. gonorrhoeae*.[13] As part of CDC's AR Solutions Initiative, CDC substantially increased support for applied HAI/AR innovation with academic medical centers, health systems, public health partners, and health departments to identify ways, including through the human microbiome, to better prevent infections, prevent transmission and improve antibiotic use across the spectrum of care.

[12] https://wwwn.cdc.gov/arinvestments
[13] https://www.cdc.gov/mmwr/volumes/65/ss/ss6507a1.htm

Healthcare facilities enrolled in the National Healthcare Safety Network (NHSN) can now use the new risk-adjusted summary measure of antibiotic use, developed by CDC working closely with health system partners and endorsed by the National Quality Forum (NQF No. 2720),[14] to determine where to focus their antibiotic stewardship efforts. Described below under Goal 2, the new risk-adjusted summary measure of antibiotic use, the Standardized Antimicrobial Administration Ratio (SAAR), helps hospitals guide their antibiotic stewardship programs. CDC also issues annual reports describing outpatient antibiotic prescriptions dispensed nationally and by state, and these reports are updated as new data becomes available.[15]

CDC is working with diverse partners to evaluate multiple novel tools to prevent antibiotic resistant infections and stop their spread:

- CDC's Prevention Epicenters conduct applied research, including large multicenter studies, to develop and test innovative approaches for preventing infections. Highlights include a study showing enhanced terminal room disinfection with a UV-light based disinfection protocol, and identification of biomarkers that can reduce unnecessary antibiotic use by predicting risk of post-surgical sepsis. These academic medical partners also use data from patient-sharing networks and mathematical modeling to identify optimal intervention strategies, including predicted economic impact, and then implement and evaluate the intervention's region-wide impact.
- CDC is working with healthcare partners through HAI/AR investments such as Prevention Epicenter expertise, state HAI/AR activities, and CDC's Emerging Infections Program's (EIP) newly awarded 2017-2021 cycle to evaluate innovative HAI/AR prevention efforts, including *C. difficile* prevention bundles, environmental sampling of emergency departments for *C. difficile* contamination, describing CRE transmission networks, and assessing chlorhexidine gluconate resistance.
- CDC is conducting a four-site, randomized controlled trial to compare in-person Directly Observed Therapy (DOT) with electronic communication methods (eDOT), such as video via computer or cellphone, for treatment of tuberculosis (TB). Use of DOT ensures that a TB patient is cured, following a long, uncomfortable treatment regimen, and that drug resistance does not develop. eDOT, if comparable to DOT, could provide flexibility and cost savings to health departments and clinicians.

Based on increased political and public attention,[16,17] CDC's 2015 Get Smart About Antibiotics Week[18] was the largest in the campaign's history with more than 130 partners (a 50% increase in new partners in 2015). The campaign coordinated content with the first World Health Organization (WHO) World Antibiotic Awareness Week, and included a multinational retail corporation's checkout line public service announcement that garnered 120 million views in one week, a provider-focused webinar hosted by a leading healthcare improvement alliance with 1,100 participants, and an educational video with a popular U.S. football quarterback. In 2017 and 2018, CDC plans to launch a national communications effort to raise awareness and motivate behaviors related to reducing inappropriate antibiotic prescribing and use, reaching

[14] http://www.qualityforum.org/QPS/2720
[15] https://www.cdc.gov/getsmart/community/programs-measurement/measuring-antibiotic-prescribing.html
[16] http://www.cdc.gov/drugresistance/federal-engagement-in-ar/stewardship-commitment/index.html
[17] https://www.whitehouse.gov/the-press-office/2015/11/13/presidential-proclamation-get-smart-about-antibiotics-week-2015
[18] http://www.cdc.gov/getsmart/week/index.html

healthcare professionals who prescribe antibiotics, and consumer target audiences.

The VA has a long standing National Veteran's Health Administration (VHA) Stewardship Initiative that is coordinated through the VHA National Antimicrobial Stewardship Taskforce (ASTF). The ASTF, co-chaired by representatives from the VA National Infectious Diseases Service and the National Pharmacy Benefits Management Services, is comprised of a multidisciplinary team of field volunteers that provides national guidance and resources for implementation of stewardship programs at local VHA facilities. VA Central Office leadership confirmed its commitment to stewardship with the publication of VHA Directive 1031: Antimicrobial Stewardship Programs, in January 2014, requiring all VA Medical Centers to establish procedures for the implementation, maintenance and evaluation of Antimicrobial Stewardship Programs. This commitment aligns with subsequent national stewardship efforts including the CDC's Core Elements, published March 2014. Currently, all VHA medical centers have established antimicrobial stewardship programs with identified provider and pharmacy stewardship champions. **The National VHA Stewardship Initiative has had initial success in optimizing antimicrobial use, as evidenced by a significant decline of more than 10% in inpatient antimicrobial use, and has begun to develop example stewardship interventions for outpatient and long-term care.**

In addition, the results of a pilot project by the VA, supported by CDC, exploring antibiotic use for acute respiratory tract infections (ARI) entitled "Variation in Outpatient Antibiotic Prescribing for Acute Respiratory Infections in the Veteran Population" was published in July 2015.[19] Work included an ARI provider support tool kit and antibiotic use dashboard pilot project that was developed in one of the VHA's Veterans Integrated Service Networks, and that resulted in a 13% decline in office visits for ARI resulting in an antibiotic being prescribed in less than one year. This project is projected to expand over the next year to additional VA facilities.

The Department of Defense (DoD) expects to announce the formal approval of its overarching Antimicrobial Stewardship Program policy this year and has remained active in enhancing and implementing existing relevant clinical and research-related initiatives. Through its centralized participation in the CDC's NHSN for both antibiotic use and resistance, the DoD has demonstrated baseline patterns of use upon which interventions can be identified and effectively evaluated. In addition, the DoD plans to participate in the AHRQ Safety Program for Improving Antibiotic Use for both acute care (in 2017) and ambulatory care (2019) settings.

Animal Health

The U.S. Government is promoting the judicious use of antibiotics and ensuring that the uses of medically important antimicrobial drugs in food-producing animals are limited to those necessary for assuring animal health and include veterinary oversight.

In December 2013, the U.S. Food & Drug Administration (FDA) took a significant step forward in addressing antibiotic resistance by publishing Guidance for Industry No. 213.[20] This document

[19] http://annals.org/article.aspx?articleid=2397690
[20] http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf

outlines a three-year plan calling on animal drug sponsors of approved, medically important antimicrobials administered to food-producing animals through medicated feed or water to remove from their product labels indications for use related to growth promotion, and to bring the remaining therapeutic uses of these products under the oversight of licensed veterinarians by switching their marketing status from over-the-counter (OTC) to either prescription or Veterinary Feed Directive (VFD). On January 1, 2017, FDA announced that it had completed implementation of the Guidance; all affected animal drug sponsors voluntarily worked in cooperation with FDA to align their products with the FDA guidance. Of the 292 new animal drug applications initially affected by the Guidance, 84 were completely withdrawn. Of the remaining 208 applications, 93 applications for oral dosage form products intended for use in water were converted from OTC to prescription status, 115 applications for products intended for use in feed were converted from OTC to VFD status, and production (e.g., growth promotion) indications were withdrawn from all 31 applications authorizing them.

To complement this Guidance, in June 2015, FDA updated existing VFD regulations that provide veterinarians with a framework for authorizing the use of medically important antimicrobials in feed. The updates to these regulations are intended to improve the efficiency of the VFD process, a critical step to facilitate transitioning medically important antimicrobial drugs used in feed from OTC status to VFD marketing status. FDA also issued two guidance documents in 2015 to support implementation of the VFD regulation.

To educate veterinarians in private practice about regulations and responsibilities, the USDA's Animal and Plant Health Inspection Service (APHIS) works with States' licensing boards through the National Veterinary Accreditation Program, which includes a Use of Antibiotics in Animals module. Since 2012, over 10,000 hours of training have been logged for accredited veterinarians, and the online module has been completed 20,857 times. The module has now been updated to include information for compliance with FDA policies. Module 29 addresses requirements for issuing a VFD, and has been completed by 2,888 veterinarians since January 2017. The module is in demand beyond accredited veterinarians and now has the capability of issuing a Certificate of Completion for other stakeholders. These policies set the groundwork for important efforts to address antibiotic stewardship in agriculture.

USDA's National Institute of Food and Agriculture (NIFA) funded an integrated project in FY 2015 that focuses specifically on Voluntary Compliance in Antimicrobial Stewardship. The project team, including scientists from Texas, New York, and the United Kingdom, is concentrating efforts on beef and dairy production systems, and aims to increase voluntary adoption to maximize antimicrobial stewardship. In 2016, NIFA expanded funding to include five projects in the Agriculture and Food Research Initiative (AFRI) integrated program, and three basic research projects in Understanding Antimicrobial Resistance and Animal Health and Well-Being programs. These projects include mitigating risk of antibiotic resistance in beef cattle manure management, mitigating fluoroquinolone-resistant *Campylobacter* in cattle, mitigating transmission of antimicrobial-resistant pathogens and genes by reducing behavioral pathways of exposure, targeting pathogen altruism to prevent infections, and co-sponsoring an International Symposium on Environmental Dimensions of Antibiotic Resistance in August 2017. Scientists funded through the integrated program have been conducting Extension and Outreach workshops across their States, or when studies are conducted on-site, hosting Field Days allowing audiences to see side-by-side comparisons of demonstrations. For example, a

Washington State awardee worked with cattle producers and their workers on nine farms, communicating in Spanish and English, to evaluate the effect of reward systems on influencing adoption of management practices to reduce unnecessary use of antibiotics. Two new projects on alternatives to antimicrobials will focus on vaccine and other preventative measures for diseases that contribute to the use of antibiotics.

As of April 2017, APHIS has begun conducting antibiotic use monitoring and antimicrobial resistance surveillance, including surveys of two major commodity groups: beef feedlots and swine. As part of the National Animal Health Monitoring System 2017 antimicrobial use surveys in swine and beef cattle, producers are being surveyed about stewardship practices on farms.

GOAL 2: Strengthen national one-health surveillance efforts to combat resistance.

The One Health concept recognizes that the health of humans, animals, and the environment are strongly connected, and that detecting and responding to antibiotic resistance requires broad data collection and surveillance across these settings. The U.S. has strengthened existing surveillance systems and expanded access to antibiotic resistant bacterial isolates and data from those systems. Critical antibiotic resistance surveillance systems include those that monitor resistance in healthcare, such as CDC's NHSN,[21] and in agricultural settings, such as NARMS.[22,23,24] Enhanced data sharing and coordination of surveillance and lab systems will ensure public health, healthcare, veterinary health, and lab partners can better detect resistance and respond to outbreaks faster.

Human Health

CDC's NHSN is the nation's most widely used system to track HAIs, including bloodstream infections, MRSA, and *C. difficile*, and antibiotic use and resistance. Beginning decades ago with 300 hospitals, NHSN now serves over 21,000 medical facilities—including acute care hospitals, long-term acute care hospitals, rehabilitation hospitals, outpatient dialysis centers, and nursing homes. Facilities use NHSN to fulfill federal and state reporting requirements, and act on their own NHSN data to monitor and prevent infections.

CDC has worked with hospitals across the nation to increase antibiotic use data reporting to NHSN. **As of July 2017, 330 hospitals have reported antibiotic use data. In addition, CDC and VA worked closely to implement reporting in VA hospitals, leading to well over half of all VA hospitals reporting antibiotic use data to NHSN. CMS also invited public comment on the possibility of future inclusion of the NHSN Antimicrobial Use measure (NQF No. 2720) in the CMS Hospital Inpatient Quality Reporting (IQR) Program (81 FR 25197).** As more hospitals report antibiotic use data to NHSN, our ability to assess hospital antibiotic use

[21] http://www.cdc.gov/nhsn/
[22] https://www.cdc.gov/narms/
[23] http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/
[24] http://www.ars.usda.gov/Main/docs.htm?docid=6750

and associated stewardship programs across the nation increases.

CDC developed the Standardized Antimicrobial Administration Ratio (SAAR)—now endorsed by the National Quality Forum as a metric for hospitals to benchmark antibiotic use—as part of the NHSN Antimicrobial Use Option to help participating hospitals assess antibiotic use in their facilities and guide interventions to improve antibiotic use. CDC is improving the SAAR metric by working with hospital systems to explore more detailed risk adjustment of antibiotic use data and assess how improvements in hospital stewardship programs impact the SAAR metric.

In addition to the Hospital Inpatient Quality Reporting (Hospital IQR) program, both the Hospital Value-Based Purchasing and Hospital-Acquired Conditions (HAC) Reduction Programs use payment incentives for Medicare-participating hospitals to report multi-drug resistant organisms, as well as infections associated with antibiotic misuse or overuse. Several appropriate use of antibiotic quality measures have also been approved for reporting and payment under the Merit-based Incentive Program (MIPs).

CDC made early progress on the AR Regional Lab Network (ARLN), part of CDC's AR Solutions Initiative. CDC is working with all 50 states and five major cities to build lab capacity to test for CRE and carbapenem-resistant *Pseudomonas aeruginosa*. CDC also supports seven regional labs to detect and respond to resistant organisms recovered from human samples, including CRE testing, CRE colonization screening, and targeted surveillance of emerging threats, such as antifungal resistance in *Candida auris* (*C. auris*)[25] and *mcr-1*-mediated colistin resistance.[26] Select regional labs are building capacity to conduct antimicrobial susceptibility testing for *Streptococcus pneumoniae* and Candida species, as well as conduct *C. difficile* special projects. In addition, select labs are building capacity to conduct antimicrobial susceptibility testing and whole genome sequencing for *Neisseria gonorrhoeae* to support CDC's ongoing gonorrhea surveillance and local rapid response efforts. In Year 2 of CDC's AR Solutions Initiative, the ARLN will continue building this capacity, add tuberculosis testing, and expand *Candida* testing to all seven regional labs. These efforts will generate more robust data for stronger infection control to contain current threats and prevent future resistance threats.

Federal agencies released several new open antibiotic resistance data tools, including interactive and customizable maps and tables showing antibiotic resistance patterns, to make it easier and faster for the public to find out how antibiotic resistance has changed over time.

- CDC's *Antibiotic Resistance Patient Safety Atlas* provides interactive data on antibiotic use and healthcare-associated infections caused by AR bacteria.[27]
- CDC's *NARMS Now: Human Data* provides interactive AR data on bacteria transmitted commonly through food, and will soon include multi-drug resistant combinations.[28]
- FDA, USDA, and CDC's *NARMS Now: Integrated Data* provides enteric bacterial isolate-level data from humans, retail meats, and food animals.[29]

[25] http://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-alert.html
[26] http://www.hhs.gov/blog/2016/05/26/early-detection-new-antibiotic-resistance.html
[27] http://www.cdc.gov/hai/surveillance/ar-patient-safety-atlas.html
[28] http://wwwn.cdc.gov/narmsnow/
[29] http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm458213.htm
http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm458213.htm

CDC and FDA launched the CDC/FDA Antibiotic Resistance Isolate Bank, a centralized, curated repository of nearly 500 unique isolates pulled from CDC's repository of AR isolates; this repository includes more than 450,000 AR isolates and more than 18,000 characterized genomes.[30] The bacterial pathogens in the isolate bank are associated with known or emerging resistance mechanisms, such as colistin resistance. Since the June 2015 launch, when the isolates were first made available, the AR Isolate Bank has processed 563 orders and shipped nearly 52,000 aliquots to 536 institutions throughout the U.S., including orders from diagnostic test manufacturers, academic researchers, and pharmaceutical companies. The 14 panels currently available include *mcr-1* bacteria, *N. gonorrheae,* and a specific *C. auris* panel, and can be used to design the next generation of clinical tests and therapeutic agents.

CDC, FDA, and NIH also partnered to genetically sequence high-priority reference strains from the AR Isolate Bank and other collections to populate the NIH National Database of Resistant Pathogens,[31] an open-access forum that allows users to compare an outbreak strain to those already in the database. As of April 2017, the National Database of Resistant Pathogens contains more than 130,000 pathogen isolates collected from publicly accessible information, and includes a web interface to search isolates and explore their genetic relatedness. In addition, CDC, NIH, and academic partners are collaborating to sequence CRE strains to determine national laboratory standards for molecular diagnostics. NIH completed 66 high quality reference genomes as of April 2017; genome sequences were submitted to the public database GenBank,[32] published at the National Library of Medicine's National Center for Biotechnology Information (NLM/NCBI) at NIH. NIH is planning to sequence 89 additional reference genomes as well as 16 bacterial strains from human clinical isolates from the NIH Clinical Center.

CDC's Emerging Infections Program (EIP), which monitors antibiotic resistance across a population of about 44 million people, and measures risk by population and community, expanded in 2016 to include more sites conducting active surveillance for invasive *Staphylococcus aureus* infections, candidemia, CRE, and carbapenem-resistant *Pseudomonas* and *Acinetobacter*. Expanded work in 2017 includes sepsis epidemiology in multiple sites and surveillance for extended-spectrum beta-lactamase producing gram-negative bacteria. EIP also completed a survey of HAIs and antibiotic use in nearly 200 acute care hospitals with more than 10,000 patients, and began a similar survey in nursing homes.

CDC is actively supporting the implementation of whole genome sequencing in all states, including tools that will predict whether an isolate will be resistant to any antibiotics. Beginning in summer 2017, resistance characterization will begin to be completed as states upload sequencing data into the national PulseNet surveillance system, including sequencing of *Salmonella*, Shiga toxin-producing *E. coli*, and *Campylobacter*. By the end of 2017, all states will have the ability to sequence isolates in a timely manner.

Animal Health and Agricultural Settings

To improve our understanding of antibiotic use and resistance in agricultural settings, USDA,

[30] http://www.cdc.gov/drugresistance/resistance-bank/index.html
[31] https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/
[32] https://www.ncbi.nlm.nih.gov/genbank/

FDA, and CDC held a public meeting on September 30, 2015, to obtain input on the collection of on-farm antimicrobial drug use and resistance data. On-farm data, combined with existing data on antibiotics sold for use in food-producing animals and data from the NARMS, will help provide a more comprehensive, data-driven approach to judicious use of antimicrobials.

In May 2016, FDA issued a final rule revising the annual reporting requirements for drug sponsors of antimicrobials sold or distributed for use in food-producing animals. This additional data will improve understanding of how antimicrobials are sold or distributed for use in major food-producing species and will help further target efforts to ensure judicious use of medically important antimicrobials.

As of April 2017, APHIS has begun conducting antibiotic use monitoring, antibiotic resistance surveillance, and antimicrobial use surveys of beef feedlots and swine through the National Animal Health Monitoring System (NAHMS). Such data is needed to monitor implementation of FDA policy changes and to understand the relationships between antibiotic use and resistance.

NARMS has enhanced surveillance by expanding testing, which in turn will improve the statistical bases for determining resistance trends in food products and strengthen the scientific foundation for strategies to limit resistance. To improve the representativeness of surveillance data on bacterial contamination of meat products, **FDA doubled annual retail meat testing from 6,700 food samples in 2015 to about 17,280 in 2017. Similarly, testing of chicken parts at USDA's Food Safety and Inspection Service (FSIS) regulated establishments increased from 3,850 in 2015 to 8,000 in 2016, and FSIS began exploratory sampling of raw pork products at regulated establishments in 2015**. In addition, as of January 2017, NARMS increased the number of sites conducting tests to identify *Enterococcus* and *E. coli* from four sites to 11 and 9 sites, respectively. All *Salmonella* and *Campylobacter* strains, select strains of *Enterococcus*, and multi-drug resistant *E. coli* are now subjected to whole genome sequencing (WGS), and results are made publically available at NLM/NCBI.

NARMS has continued to expand the use of WGS technology into the surveillance framework for target bacteria at all three NARMS agencies (FDA, CDC, and USDA). WGS allows state labs to rapidly uncover foodborne bacteria with known resistance genes and find outbreaks faster. It also allows FDA to better understand the sources of resistance genes and their movement through the food production chain. To date, more than 10,000 NARMS isolate sequences have been uploaded to NCBI. WGS also makes it possible to screen genetic data again as new resistance genes are discovered.

FSIS conducted real-time WGS on all ready-to-eat product isolates and all isolates from foodborne investigation samples, increasing the pace of WGS on NARMS isolates from 600 in 2015 to 2,400 in 2016. In addition to conducting antimicrobial susceptibility testing on all FSIS NARMS and regulatory isolates, FSIS has subjected 3,291 isolates to WGS and uploaded the data to NCBI (*Salmonella*, Shigatoxigenic *E. coli* [STEC], *Campylobacter*, and *Listeria monocytogenes*).

In keeping with the principles of the principles of open data, the three NARMS agencies continue to publish the entire historical database of NARMS surveillance isolates through NARMS. It now consists of an integrated data web portal comprising antimicrobial resistance

(AMR) data on more than 200,000 bacterial isolates tested since NARMS began in 1996.[33] Making national surveillance data publicly available enables public health experts to explore these data in new ways and provides a large set of data for innovators in antibiotic drug development. For example, scientists are currently using these data to explore machine learning algorithms to predict antibiotic resistance accurately from the DNA sequence data.

To continue enhancing the NARMS Integrated Report, FDA has developed four publicly available interactive data dashboards that allow stakeholders to interactively investigate resistance by bacterium, resistance by sample source and place, resistance genes in *Salmonella*, and resistance to multiple antimicrobial agents.[34]

The architecture and availability of the Antimicrobial Resistance Monitoring and Research Database (ARMoR-D) and isolate panels was published in an open access journal in May 2016 (PLoS One). An initial version of the ARMoR-D was electronically released locally in April 2016. This database contains over 3 million results from 47,000 isolates representing more than 33,000 patients from 120 locations worldwide. Of those gram-negative organisms archived, more than 10% demonstrated carbapenem resistance. The DoD and VA are actively coordinating on the timely electronic exchange and sharing of relevant antibiotic resistance data. In addition, the MRSN and CDC's ARLN have been working together to share best practices for U.S.-based resistance gene identification. Over 950 genomes of MRSN strains have been uploaded to the NLM/NCBI Pathogen Tracker to date, and curated panels are available for dissemination to facilitate diagnostic and therapeutic developmental efforts.

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

The U.S. Government has provided significant support to research and development (R&D) efforts that could lead to new diagnostic tests. With these tests, clinicians will be able to more accurately diagnose whether infections are viral or bacterial, or detect resistance at the point of patient care, reducing unnecessary prescriptions for antibiotics and helping to inform clinical decision-making.

In the past two years, FDA approved or cleared for marketing several new diagnostic devices that may significantly enhance detection or prevention of antibiotic resistance, including molecular devices to rapidly detect bacteria with carbapenemase genes from stool specimens, significantly faster devices to assess phenotypic resistance in bacteria, and serum tests to identify likely bacterial respiratory infection, thereby reducing use of unnecessary antibiotics for this common illness.

In September 2016, NIH and the Biomedical Advanced Research and Development Authority (BARDA) within the HHS Office of the Assistant Secretary for Preparedness and Response

[33] https://wwwn.cdc.gov/narmsnow/
[34] https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm059103.htm

announced the Antimicrobial Resistance Diagnostic Challenge,[35] which seeks diagnostic tests that identify and characterize antibiotic-resistant bacteria or that distinguish between viral and bacterial infections to reduce unnecessary use of antibiotics. This 3-Step competition was developed with technical and regulatory expertise from CDC and FDA, as well as public input. In March 2017, ten semi-finalists for Step 1 of this competition were announced; each will receive $50,000 to develop concepts into prototypes.[36,37] NIH supported earlier related work for three of these semi-finalists. NIH and BARDA are each contributing $10 million to the challenge.

NIH supports a robust portfolio of diagnostics research projects, many focused on the development of new tools that would allow clinicians to rapidly determine appropriate treatments for infected individuals, and that facilitate antibiotic stewardship by reducing the use of broad-spectrum drugs. NIH supports targeted research solicitations to foster development of novel diagnostic approaches to benefit public health. In April 2015, NIH awarded more than $11 million in first-year funding to support enhanced diagnostics to rapidly detect antimicrobial-resistant bacteria, including pathogens that frequently cause healthcare-associated infections.[38,39] In June 2017, NIH released RFA-AI-17-014, Partnerships for Development of Clinically Useful Diagnostics for Antimicrobial-Resistant Bacteria,[40] which will support development of diagnostic platforms that detect bacterial pathogens listed in CDC's 2013 report *Antibiotic Resistance Threats in the United States*,[41] and determine associated antimicrobial sensitivity and/or resistance. In addition, NIH supports research to develop tests that rapidly determine the antibiotic-resistance profiles of bacterial threats.

Researchers at the NIH-supported Antibacterial Resistance Leadership Group (ARLG)[42] are developing and testing diagnostic tools to help inform treatment options, including a simple blood test that analyzes patterns of gene expression to determine if a patient's respiratory symptoms stem from a bacterial infection, viral infection, or no infection at all.[43] The ARLG investigator leading this project was selected as a semi-finalist in the first stage of the Antimicrobial Resistance Diagnostic Challenge to expand on this work and adapt a Biofire technology for gene expression analysis. ARLG investigators demonstrated that two rapid diagnostic candidates could accurately predict whether *Acinetobacter* isolates were susceptible or resistant to carbapenems.[44] To further accelerate the development of new diagnostic tools, the ARLG is collaborating with multiple diagnostics companies to implement a master diagnostics protocol, through which multiple diagnostics tests can be validated simultaneously using specimens from the same patients. Additional NIH-supported researchers are seeking to determine if a molecular bacterial DNA can reliably identify gonorrhea infections that may be

[35] https://www.nih.gov/news-events/news-releases/federal-prize-competition-seeks-innovative-ideas-combat-antimicrobial-resistance
[36] https://dpcpsi.nih.gov/AMRChallengeSemifinalists
[37] https://www.cccinnovationcenter.com/challenges/antimicrobial-resistance-diagnostic-challenge/
[38] https://www.niaid.nih.gov/news-events/nih-funds-nine-antimicrobial-resistance-diagnostics-projects
[39] https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-14-019.html
[40] https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-17-014.html
[41] https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf
[42] https://www.arlg.org
[43] https://directorsblog.nih.gov/2016/02/02/gene-expression-test-aims-to-reduce-antibiotic-overuse/
[44] http://jcm.asm.org/content/55/1/134.long

successfully treated with a single dose of an older antibiotic, ciprofloxacin. This could potentially allow healthcare providers to reintroduce ciprofloxacin as an oral treatment for gonorrhea instead of antibiotics delivered by injection. The NIH-supported Sexually Transmitted Infections Clinical Trials Group launched a clinical study to evaluate this test in November 2016.[45]

CDC convened public heath scientists, diagnostic test manufacturers, representatives from professional societies, patient advocates, and federal partners (FDA and NIH) in December 2015 to discuss how to maximize the impact of diagnostics to address the resistance problem, including opportunities not only to help with innovation and uptake of diagnostics to improve patient care and public health, but also to ensure proper implementation of available tests and of new tests coming to market.

The U.S. Army Medical Research Institute for Infectious Disease (USAMRIID) and the Defense Threat Reduction Agency Joint Science and Technology Office (DTRA-JSTO) are leveraging diagnostic capabilities for rapid identification of targeted clinically relevant antimicrobial-resistant bacterial pathogens.

The MRSN at the Walter Reed Army Institute of Research (WRAIR) offers an almost unprecedented 48-hour turn-around time to all DoD hospitals for next generation sequencing to support outbreak investigations and has similar services available to non-DoD institutions. Scientists from the MRSN published the processes and impact of this capability as well as practical application with *mcr-1* identification in *Diagnostics in Microbiology and Infectious Diseases* (McGann, 2016) and in *Antimicrobial Agents of Chemotherapy* (McGann, 2016).

The MRSN also has a validated *mcr-1* gene screen that operates in less than 45 minutes, and that will enable rapid awareness of gene presence throughout its clinical laboratories. WRAIR has published results using its rapid PCR diagnostic for a virulent extensive drug resistant (XDR) *Acinetobacter* strain with the propensity to develop colistin resistance after only minimal drug exposure.[46,47] By using a novel combination of in-house developed PCR assays, culture, and swabbing protocols, MRSN was the first to report that environmental levels of bacterial DNA correlated with HAI of same species, and that intensity of cleaning does not correlate with effective bioburden removal.[48,49]

GOAL 4: Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.

The U.S. Government works collaboratively on strategies to advance research through public and

[45] https://www.niaid.nih.gov/news-events/niaid-supported-study-examines-vulnerability-gonorrhea-older-antibiotic-drug
[46] https://academic.oup.com/jid/article/208/7/1142/2192696/Emergence-of-Colistin-Resistance-in-Extremely-Drug
[47] https://academic.oup.com/cid/article/61/2/145/328660/Fatal-Outbreak-of-an-Emerging-Clone-of-Extensively
[48] https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/relationships-among-cleaning-environmental-dna-and-healthcareassociated-infections-in-a-new-evidencebased-design-hospital/9B6387232FA273F3E4C2C03F68C20029
[49] http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0155779

private sector engagement. Cross-agency collaborations are complemented by agencies' work within their respective missions to conduct intramural and extramural research, and to identify priorities that advance discovery and innovative solutions to the threat of antibiotic resistance.

Human Health

To spur innovation in human health solutions, BARDA has awarded public private partnerships for the development of new antibacterial drugs and diagnostics, including portfolio partnerships awarded to Roche, the Medicines Company, and Pfizer for the clinical stage development of candidate antibiotics and diagnostics. **In July of 2016, BARDA launched CARB-X, a five-year $450 million public private partnership between BARDA, NIH, and the Wellcome Trust aimed at bolstering innovation in antibacterial product development**. In March 2017, CARB-X announced awards to eleven biotech companies and research teams for drug discovery and development projects to tackle antibiotic resistance.[50] NIH provided previous funding to seven of the eleven CARB-X awardees.

NIH has supported numerous targeted research solicitations over the past decade to advance the development of promising therapeutic products against a number of high priority pathogens. An important backdrop to these targeted efforts is NIH's long-standing support of basic research, fundamental studies that help spur new translational and applied discoveries. Indeed, many of the projects supported through these targeted efforts were first identified through basic research. For example, NIH basic research support has enabled the chemical synthesis of over 2,000 novel tetracyclines, some of which represent potential new tools for the treatment of multidrug-resistant bacterial infections. With NIH support, one of these products (known as TP-271) advanced to two early-stage clinical trials in 2016 and 2017; enrollment is complete for both studies.[51,52] In 2016, NIH awarded six multi-disciplinary systems biology projects to identify, quantify, model, and predict the molecular interactions between antibiotic-resistant pathogens and hosts during disease initiation, progression, or in response to treatment.[53]

NIH-supported clinical research provides insight on the safety, effectiveness, and use of novel antibiotic candidates as well as existing antibiotics. For example, NIH has supported clinical trials for investigational oral antibiotics to treat gonorrhea,[54,55] as well as products with broad-spectrum activity, including an ongoing early stage clinical trial of a novel beta-lactamase inhibitor (VNRX-5133) to be paired with a licensed beta-lactam antibiotic.[56] In addition, the ARLG and other NIH-supported investigators are conducting clinical trials to determine optimal use of licensed antibiotics (e.g., duration, dosage, whether antibiotic treatment is required at all) for bacterial infections, including pediatric community-acquired pneumonia,[57] urinary tract infections,[58,59] and gram-negative infections.[60] NIH-supported scientists recently found that, in

[50] http://www.carb-x.org/press_march_30_2017
[51] https://www.clinicaltrials.gov/ct2/show/NCT02724085?term=NCT02724085&rank=1
[52] https://www.clinicaltrials.gov/ct2/show/NCT03024034?term=NCT03024034&rank=1
[53] http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-14-064.html
[54] https://clinicaltrials.gov/ct2/show/NCT02257918
[55] https://clinicaltrials.gov/ct2/show/NCT02348424
[56] https://www.clinicaltrials.gov/ct2/show/NCT02955459?term=NCT02955459&rank=1
[57] https://www.clinicaltrials.gov/ct2/show/NCT02891915?term=NCT02891915&rank=1
[58] https://www.clinicaltrials.gov/ct2/show/NCT02570074?term=NCT02570074&rank=1

young children, shortened treatment for middle ear infection is less effective than the standard course,[61] and that in adults and children, two off-patent antibiotic treatments (clindamycin and trimethoprim–sulfamethoxazole) work very well against bacterial skin infections caused by community-associated MRSA.[62,63,64]

NIH continues to invest in research exploring novel approaches to address AMR, including host-targeted therapeutics, microbiome-based therapeutics, bacteriophage, phage lysins, biofilm inhibitors, anti-virulence strategies, immune-based therapies, among other areas. NIH scientists and their colleagues report that complement-based therapy approach may be useful against the CRE organism, *K. pneumoniae* sequence type 258 (ST258) bacteria.[65] Through the Centers of Excellence for Translational Research (CETR) program, NIH is supporting research on discovery and development of new therapeutic approaches against bacterial pathogens, including drug-resistant organisms.[66] Projects include identifying potential drug targets, discovering novel antimicrobial compounds effective against resistant bacteria, evaluating new classes of antibacterial agents, and harnessing the microbiota to target antibiotic-resistant infections. As a result of work conducted through the CETR program and other NIH grants, one CETR investigator holds a provisional patent and notice of invention for a new chemical scaffold that may hold promise for future drug design.

FDA is participating fully in the Federal Interagency Microbiome Working Group and has initiated an FDA-NIH Microbiome Working Group as well as an internal FDA Microbiome Working Group. Together, these activities will strengthen inter-FDA Center and interagency discussions about scientific and regulatory issues surrounding the microbiome and microbiome-based medical products, and will support translation of microbiome research into novel medical products and approaches to combat antibiotic resistance.

The Walter Reed Army Institute of Research (WRAIR) has established an industry-based approach to efficiently screen and evaluate new antibiotic candidate compounds, and to help government, academic, and industry partners further develop candidates and progress faster toward Investigational New Drug (IND) submissions to the FDA. Specific highlights for the initial phase of this effort include:

- Establishing WRAIR-based high-throughput screening capability for antimicrobial compounds;
- Validating WRAIR-based *in vitro* and *in vivo* assays for initial drug safety and efficacy testing; and
- Creating cooperative R&D agreements with researchers at Vanderbilt University, Calvin College, Entasis Therapeutics, and the U.S. Department of Veterans Affairs. Each group possesses later-stage antibiotic candidates and will partner with WRAIR for safety/efficacy testing and compound optimization. Together, this consortium is a fully functional antibiotic

[59] https://clinicaltrials.gov/ct2/show/NCT01595529?term=NCT01595529&rank=1
[60] https://clinicaltrials.gov/ct2/show/NCT01597973?term=NCT01597973&rank=1
[61] http://www.nejm.org/doi/full/10.1056/NEJMoa1606043
[62] http://www.nejm.org/doi/full/10.1056/NEJMoa1403789
[63] http://www.nejm.org/doi/full/10.1056/NEJMoa1507476
[64] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4885652
[65] http://aac.asm.org/content/61/4/e02533-16.full.pdf+html
[66] https://www.niaid.nih.gov/research/translational-research

discovery team with the requisite skill sets.

The Military Infectious Diseases Research Program (MIDRP) has collaborations to develop a multiplexed automated digital microscopy system to quantify and identify target pathogens within two hours, with additional phenotypic characterization within six hours. This program continues to identify early and mid-stage development efforts for new/novel therapeutics. USAMRIID and DTRA-JSTO are also working to leverage capabilities toward development of therapies to target clinically relevant antimicrobial-resistant bacterial pathogens.

DoD's Defense Health Program Military Infectious Disease Research Program (MIDRP) continues to fund novel therapeutics and delivery technology efforts, specifically those looking at inhibiting and dispersing of biofilms of infected wounds. Phage cocktails also remain under development, with a recent successful clinical use by U.S. Navy researchers in a resistant gram-negative infection. Vaccines, human skin substitutes, monoclonal antibodies, and peptides represent some of the focus areas in discovery.

Animal Health

U.S. Government agencies work collaboratively to advance research on animal health by expanding public and private sector engagement. For example, USDA, FDA and private sector partners participated in a National Academy of Sciences Food Forum workshop in April 2016, to discuss when, where, and how antibiotics enter the food supply, how antibiotic resistance transfers from animals to humans, and alternatives to antibiotics. In July 2016, NIH hosted a roundtable discussion with academic, private sectors, and other Federal experts (including CDC, DoD, FDA, and USDA) to assess steps that can be taken to address resistance. Also in July 2016, USDA hosted a stakeholder webinar with FDA, NIH, and private sector partners to discuss, prioritize, and develop strategies to help meet the most pressing animal health research education and extension needs related to antibiotic resistance. ARS, in collaboration with NIH and FDA and with the support of the World Organization for Animal Health (OIE), organized the Second International Symposium on Alternatives to Antibiotics in Animal Production in December 2016. The symposium was structured to promote public-private partnerships to enable the development of innovative alternatives to medically important antibiotics.

ARS is actively implementing alternatives-to-antibiotics R&D projects, including products that could reduce the use of medically important antibiotics through vaccines, bacterial-derived products, immune-related products, phytochemicals, and other chemicals and enzymes. For example, a vaccine for respiratory disease of poultry, and antibodies for use in poultry feed to prevent disease, are under development with commercial partners under Cooperative Research and Development Agreements (CRADAs). ARS researchers are also exploring on-farm manure management strategies to reduce antibiotic use, resistant bacteria, and resistance genes in the environment. Strategies include evaluation of composting, land application strategies, hydrothermal processing, biochar, and constructed wetlands. ARS is characterizing mobile genetic elements in manure and environmental samples, to inform future efforts to assess risk of transferring antibiotic resistance through agroecosystems.

ARS has initiated two public-private partnerships under CRADAs to enable the development, registration, and commercialization of alternatives to antibiotics. ARS collaborated with

university and public health partners on the Comprehensive Antibiotic Resistance Database (CARD), and on the development of a One Health antimicrobial stewardship program in Washington State. ARS scientists have formed an Agricultural Antibiotic Resistance (AgAR) Network that focuses on issues related to environmental dimensions of antibiotic resistance and that is developing a database that will allow intra- and inter-agency and public sharing of ARS antibiotic resistance data sets.

USDA awarded $3.4 million in FY 2015 through its Agricultural and Food Research Initiative competitive grants program. In May 2016, USDA awarded an additional $5.7 million for projects to develop novel systems approaches to investigate the ecology of antibiotic resistance; for alternative practices that mitigate emergence, spread, or persistence of resistant pathogens within the agricultural ecosystems; to identify critical control points for mitigating antimicrobial resistance pre- and post-harvest; to design innovative training, education, and outreach resources for users across the food chain; and to design studies to evaluate impacts. In FY 2016, NIFA funded six projects that addressed alternatives to antibiotics, including infection prevention and immune modulation in animals. In 2016 and 2017, ARS funded eleven alternative to antibiotic intramural research proposals.

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

The U.S. Government implements a coordinated, strategic, and innovative approach to enable immediate and lasting action globally to combat antibiotic and antimicrobial resistance (AMR, a broader term used internationally), working with diverse stakeholders and partners at home and abroad. The cornerstones of this approach are:

- **Garnering political support**: Lead by the State Department (DoS), HHS, and USDA, the U.S. Government advanced a multi-year strategic approach to build political support through incremental and increasing commitments specific to sectors (e.g., through the World Health Organization (WHO), Food and Agriculture Organization (FAO), and World Organization for Animal Health (OIE)) or countries (e.g. through G7, G20, and GHSA).
- **Enabling individual, community, and country ownership**: The U.S. Government successfully engaged in multiple international activities to enhance local capacity to address antibiotic resistance. Engagement with international bodies includes efforts to promote the adoption of equivalent standards to help sustain the usefulness of antibiotics for human medical and veterinary use throughout the world. **Through the Global Health Security Agenda, U.S. agencies have enhanced efforts to combat antibiotic resistance in over 30 countries**.

These efforts are led by HHS's Office of Global Affairs (OGA), DoS, and USDA, with participation from DoD, VA, the Department of Homeland Security, the White House Office of Science and Technology Policy, the National Safety Council, the U.S. Agency for International Development (USAID), the Environmental Protection Agency, and HHS's CDC, FDA, NIH, CMS, AHRQ, BARDA, and the Health Resources and Services Administration (HRSA).

Key recent achievements include:

- World leaders at the 71st United Nations General Assembly (UNGA) High-Level Meeting

(HLM) on AMR affirmed AMR as a grave threat to human health and adopted a UN Resolution calling for specific global multi-sectoral actions to combat AMR, including the U.S. priority position of universal high-level commitment by all nations across sectors. The U.S. Delegation, led by the Secretary of HHS, announced the United States' commitment and actions to combat AMR, and called for global cooperation on this issue;

- The 68th World Health Assembly ratified the WHO Global Action Plan (GAP) on AMR;
- The FAO passed resolutions to address AMR;
- The OIE passed resolutions on AMR and began a process to collect antibiotic use data across nations;
- G7 Leaders committed to increasingly comprehensive action to address AMR starting with Germany's chairmanship in 2015, through Italy's chairmanship in 2017;
- The G20, under Germany's presidency in 2017, placed an unprecedented emphasis on heath including a significant commitment to address drug-resistant disease;
- Along with Global Health Security Agenda (GHSA) partners, the U.S. began implementing the GHSA AMR Action Package in 2015, which assists in developing national action plans and surveillance capacity guided by the WHO GAP on AMR and the WHO Global Antibiotic Resistance Surveillance System (GLASS). The U.S. underwent Joint External Evaluation in March, 2016;
- Members of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) began work to fill technical gaps in addressing AMR in agriculture including surveillance;
- The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) published *Ranking of Antimicrobials According to Their Importance in Human Medicine: A Critical Step for Developing Risk Management Strategies to Control Antimicrobial Resistance From Food Animal Production* in August 2016, and *Critically important antimicrobials for human medicine, 5th revision*; and
- The WHO held the first World Antibiotic Awareness Week in November 2015, where countries across the world, including the United States, developed educational and outreach campaigns to promote awareness and understanding of AMR, including best practices related to antibiotic stewardship.

To align with the 71st UNGA High Level Meeting, OGA organized and led a side event entitled "Prevention: Antibiotic Stewardship, Infection Prevention and Control" with participation from ministers of health, global health advocacy organizations, academic research institutions, physician and patient-safety societies, and private-sector companies. Presenters and panelists included representatives from the health ministries of Japan, Thailand, and the United Kingdom, along with the CDC Director. NIH and CDC participated in a side-event entitled "Public-Private Sector Collaboration to Address Antimicrobial Resistance." This meeting addressed the need for collaborative engagement on a variety of AMR-related topics including diagnostic testing to support treatment decisions, and surveillance and reporting on appropriate use of antimicrobials.

Held in September 2016, the G7 continued to accelerate political commitments to promote effective action, and to reinforce urgency in the global cooperation to combat AMR. Communiques prioritized G7 efforts to fully implement the WHO Global Action Plan on AMR, including G7 countries' own national action plans, support to other countries on their national plans, and the importance of improving infection prevention and control measures, as well as integrated and aligned surveillance, in both humans and animals.

In a rare discussion of health issues at the G20, at the September 2016 meeting, leaders adopted a communique emphasizing AMR as a serious threat to public health, growth, and global economic stability. The leaders affirmed the need to explore how to fight AMR through evidence-based prevention and mitigation strategies and how to unlock R&D around new and existing antimicrobials from a G20 value-added perspective. Leaders called on the WHO, FAO, OIE, and the Organisation for Economic Co-operation and Development (OECD) to collectively report back in 2017 on these options, including economic implications. They committed to promoting prudent use of antibiotics and considering the huge challenges of affordability and access of antimicrobials and their impact on public health. Under China's chairmanship, the 2016 G20 committed to combating AMR, including diseases such as multidrug-resistant tuberculosis, by examining what economic incentives G20 countries could leverage to address commercial markets for antibiotics.

In 2017, leaders decided to add an official health track to the G20 platform. The Berlin Declaration of the G20 Health Ministers prioritized AMR and committed all G20 countries to developing national action plans by 2018, strengthening domestic and international surveillance and focusing on infection, prevention, and control and stewardship. The G20 also decided to strive to reinvigorate R&D in science and industry for antimicrobials.

At the request of Member States, in February 2017 the WHO published a global Pathogen Priority List (PPL) of antibiotic-resistant bacteria to help prioritize R&D of new and effective antibiotic treatments. Many U.S. Government departments and agencies helped to develop the PPL methodology, data collection, and analysis of results. The global PPL aims to guide the prioritization of incentives and funding, to help align R&D priorities with public health needs, and to support global coordination in the fight against antibiotic-resistant bacteria. The WHO PPL targets policy initiatives to incentivize basic science and advanced R&D by both public funding agencies and the private sector investing in new antibiotics.

In addition to the multilateral policy fora work, DoS launched two innovative efforts to convert political commitment to action on the ground, specifically targeting important yet neglected areas in the global effort to address antimicrobial resistance:

- In September 2016, DoS, Bureau of Oceans, International Environmental and Scientific Affairs (OES) hosted, in collaboration with the U.S Geological Survey and the Society of Environmental Toxicology and Chemistry, a workshop on "Mapping the Lifecycle of Antibiotics in Southeast Asia", the outcomes of which will chart the way toward integration of environmental interventions into a multipronged strategy for combatting AMR. The workshop covered chemical lifecycle assessment strategies to map and model the environmental fate of antibiotics, to identify hotspots and prevent the rise of resistance; methods development for low-resource, low-infrastructure settings to conduct antibiotic lifecycle mapping and modeling; and community-based participatory strategies for data collection, organization, and integration regarding antibiotic use and disposal.
- In December 2016, in Rome, Italy, DoS co-hosted the first forum for faith-based organizations (FBOs) to self-assess their roles and responsibilities in addressing drug-resistant disease, entitled "Combating the Emergence and Spread of Antimicrobial Resistance: A Workshop to Strengthen Faith-Based Engagement". DoS (OES's Health Office and the Secretary's Office of Religion and Global Affairs) partnered with Caritas Internationalis and Georgetown University's Berkley Center for Religion, Peace, and World

Affairs to host the workshop. Participants included over 35 senior professionals from Catholic orders, Islamic and Lutheran health service networks, the WHO and other global health and migration agencies, programs in the Caribbean, Africa, South Asia and Southeast Asia, funding agencies and the diagnostics industry, and communications and logistics experts. Participants committed to individual and collaborative actions and issued the first global "Call to Action" on addressing drug-resistant disease. The workshop delivered a starting point to address the complex emergency of drug-resistant disease, and a method for donor or stakeholder groups to mobilize action. Faith communities, both at institutional and local levels, are well positioned to encourage ongoing high-level support, mobilize individual and community action, and advance social and medical practices to combat the emergence and spread of AMR.

Through the GHSA AMR Action Package, self-assessments of laboratory networks and antimicrobial resistance surveillance have been completed in all 17 GHSA Phase One countries, and country-specific work plans have been generated to assist the implementation of surveillance. Through multi-lateral collaboration, including global health security work, CDC assisted ministry of health partners with the development, initiation, or implementation of national action plans and surveillance networks in India, Vietnam, Thailand, Senegal, Georgia, Tanzania, Ethiopia, and Kenya. Based on laboratory assessments completed during FY 2016, additional support for laboratory strengthening in these countries and additional GHSA countries will provide health ministries with improved antimicrobial resistance data to inform policy.

CDC is working with the WHO to develop a Global Emerging AMR reporting portal. This portal will facilitate global communication of new or emerging resistance threats. In 2017, CDC and WHO developed a draft document, "Emerging AMR reporting framework and risk assessment" which defines the framework, rules, and protocols for early reporting of new antimicrobial resistance. WHO has solicited feedback from member countries, and in the next year, will pilot test the framework and develop the IT portal.

The MRSN at the WRAIR remains the central focus for international DoD surveillance efforts, in collaboration with Armed Forces Health Surveillance Branch-Global Emerging Infections Surveillance (AFHSB-GEIS). The GEIS network includes Peru, Egypt, Kenya, Uganda, Ghana, Liberia, Philippines, Cambodia, Nepal, and Europe. Additional collaborations exist with the Israeli Defense Force (working with serious MRSA outbreaks), Kenya (MRSA and fatal *Acinetobacter* infections), Thailand (AFRIMS and Royal Thai Army analyzing carbapenemase-resistant gram-negatives), and Honduras (military and civilian). The MRSN also collaborates with the JMI laboratories/SENTRY Program that receives isolates from more than 50 countries. The MRSN partners with the Army Pharmacovigilance Center and Navy/Marine Corps Epi-data Center as members of the chartered Antimicrobial Stewardship Program Working Group, the coordinating body for implementation of the DoD antimicrobial stewardship program.

Through TATFAR, CDC and DoD have worked with the European Union (E.U.), Canada, and Norway to harmonize surveillance practices. The U.S. and E.U. have made significant progress toward harmonizing lab definitions for detecting AMR, including colistin definitions for resistant gram-negative bacteria like *E. coli*. These efforts will help the U.S. and E.U. determine when bacteria are resistant to antibiotics, thus providing opportunities to enhance infection prevention and control to prevent the spread of resistant infections.

USDA, OGA, and the State Department worked together to coordinate messaging during the 2016 World Antibiotic Awareness Week in order to amplify their messages to both domestic and international audiences. #CombatingAMR, launched by the United States for the UNGA High Level Meeting on AMR in September 2016, received over 10 million interactions in the first four days.

USAID has sponsored a myriad of activities in many dozens of low- and middle-income countries to contain antibiotic resistance, including by developing national strategies and implementation plans on antibiotic resistance, conducting antimicrobial stewardship and mobile health interventions, and strengthening the medicines registration processes to assure the market entry of quality-assured drugs and combat sub-standard and counterfeit products. Examples include:

- Under the GHSA, USAID has assisted 10 countries to train health providers on how to reduce healthcare associated infections. For example, in 200 health facilities in Sierra Leone, USAID funded improvements in water and sanitation, and trained staff on infection prevention and control;
- Working with Systems for Improved Access to Pharmaceuticals and Services (SIAPS), USAID developed a two-part on-line course on AMR that has trained hundreds of people from 73 countries;
- USAID also supported Ministries of Health to develop and revise national essential medicine lists in Angola, Guinea, Mozambique, Namibia, South Africa, and Ukraine;
- USAID supported strengthening of regulatory capacity and improving processes for registering medicines in Angola, Bangladesh, the Democratic Republic of the Congo (DRC), Ethiopia, Mozambique, and Namibia. With USAID support, Bangladesh, Mozambique and Namibia are implementing the registration module of a web-based regulatory information system (Pharmadex) to make their processes more efficient and transparent;
- In Swaziland, USAID assisted the Ministry of Health to develop and finalize a draft of the *National Antimicrobial Resistance Containment Strategic Plan 2017 – 2021 of the Kingdom of Swaziland*, and in Ethiopia supported the National AMR Advisory Committee in developing a plan of action to guide interventions described in the *Strategy for the Prevention and Containment of Antimicrobial Resistance for Ethiopia, 2015 to 2020*;
- USAID supported 40 National Quality Control Laboratories (NQCLs) to ensure the reliable and accurate testing for quality of medicines, including antibiotics;
- USAID continued efforts to build regulatory and laboratory capacity in low- and middle-income countries and, in FY2016, facilitated the training of more than 1,100 individuals from 19 countries on topics concerning the quality-assurance of medicines, to include inspection, Good Manufacturing Practices, post-marketing surveillance, quality control, and registration;
- With Promoting the Quality of Medicines (PQM), USAID is working to strengthen regulatory systems to protect populations against poor-quality medicines and build capacity to ensure the quality of medicines both produced locally and imported in low- and middle-income countries. PQM supported national regulatory authorities in developing countries to establish more than 520 new regulatory procedures or guidelines aimed at assuring the quality of medicines, and worked with 51 manufacturers across nine countries to improve the supply of quality-assured essential medicines, including antibiotics used for tuberculosis (TB) and maternal, newborn, and child health; and
- In Bangladesh, the Philippines, and Senegal, USAID supported the development of national

strategic plans for the health sector that support these countries to strengthen regulatory capacity, establish efficient medicine registration systems, and reduce backlogs and wait times for registration.

NIH and BARDA are collaborating with international partners to identify incentives and best practices to stimulate R&D of new drugs and drug alternatives, along with affordable, rapidly deployable, point-of-need diagnostics. These partnerships include research in TATFAR, participation in ReAct, collaboration with the Innovative Medicines Initiative (IMI), and providing technical advice to the newly established Drugs for Neglected Diseases Initiative (DNDi) Global Antibiotic Research and Development Partnership. TATFAR has enabled alignment of NIH and E.U. clinical trial networks for access to patients. For example, NIH is supporting a Phase 3 trial to determine how best to use an older antibiotic (colistin), alone or in combination with a carbapenem, in patients with multi-drug resistant gram-negative infections.[67] NIH plans to add sites from European clinical trials networks to the current U.S. sites.

FDA and USDA continue to collaborate with international organizations on the development of vaccines, antimicrobial drugs, and diagnostic tests for use in agriculture. FSIS and CDC representatives participate actively in international organizations whose goals are to optimize antibiotic use in animals, reduce AMR, build consensus, and harmonize methods. FSIS collaborates with the Pan American Health Organization (PAHO) and the International Network of Food Analysis Laboratories to document regional capability for AMR work. NIFA's Agriculture and Food Research Initiative programs are funding projects targeting antimicrobial resistance ecology, an important knowledge gap. In August 2017, NIFA will co-sponsor a meeting on International Symposium on Environmental Dimensions of Antibiotic Resistance. Other ongoing projects address interventions to prevent emergence and dissemination of antimicrobial resistance at the population, animal and microbial levels, understanding antimicrobial resistance ecology through whole genome analysis of microbial communities, and understanding antimicrobial resistance mitigation strategies in cattle.

On behalf of the U.S., FDA co-chaired the Codex Physical Working Group on AMR, and USDA and FDA co-led the US Delegation to the PWG, which took into consideration ongoing work of the FAO, WHO, OIE, and the International Plant Protection Convention to define the scope of work for a three-year Codex Task Force on AMR to commence work in November 2017. The Task Force will update Codes of Practice to Minimize and Contain AMR, and develop guidance for integrated AMR surveillance.

FDA has also met with regulatory counterparts from the European Medicines Agency and Japan's Pharmaceuticals and Medical Devices Agency to discuss approaches for evaluating antibacterial drugs in clinical trials. These meetings have identified several areas for potential convergence on clinical trial criteria for studying antibacterial drugs. Convergence on clinical trial recommendations should facilitate antibacterial drug development for certain conditions by allowing for trials of the same design to be used to support applications for approval of such drugs in different jurisdictions.

[67] https://clinicaltrials.gov/ct2/show/NCT01597973?term=NCT01597973&rank=1

APPENDIX A: HIGHLIGHTS OF ADDITIONAL ACTIVITIES

In addition to the specific goals and objectives of the National Action Plan, CARB Task Force agencies engage in additional activities that support efforts to combat antibiotic resistance.

MEETINGS, WORKGROUPS, and ADVISORY COUNCILS

CDC worked with local, state, and national public health and academic partners and federal partners in 2016 and 2017 to establish the Council for Outbreak Response: HAIs and Antibiotic Resistance (CORHA) and the CDC/Council of State and Territorial Epidemiologists (CSTE)/Association of Public Health Laboratories (APHL) Antimicrobial Resistance Surveillance Task Force to strategically advance public health priorities to combat AR in the United States. Multi-agency participation in the two groups includes FDA and CMS, and DOD and VA, respectively.

In July 2015, NIH organized a workshop on "Bacteriophage Therapy: An Alternative Strategy to Combat Drug Resistance. FDA and NIH co-sponsored a subsequent workshop in July 2017, entitled, "Bacteriophage Therapy: Scientific and Regulatory Issues."[68] These workshops explored phage therapy as an alternative strategy to combat drug resistance.

In February 2017, NIH and The Pew Charitable Trusts Antibiotics Innovation Program co-sponsored a meeting, "Challenges in the Discovery of Gram-negative Antibacterials: The Entry & Efflux Problem."[69] Workshop participants identified action items to advance the field, including a platform to enable the scientific community to better access, share, and use information, an antibiotic discovery "society" or virtual consortium, and tackling key research priorities in a systematic way. Related to this topic, in November 2016, NIH released a funding opportunity seeking to advance discovery of antibacterials for gram-negative bacteria: CRE, MDR *Acinetobacter*, and/or MDR *Pseudomonas aeruginosa*.[70]

In February 2017 in Seoul, Korea, NIH participated in the U.S.-Japan Cooperative Medical Sciences Program 19th International Conference on Emerging Infectious Diseases in the Pacific Rim. NIH shared an overview of CARB activities, including CARB-X.

DoD presented seven posters and two podium presentations at the American Society of Microbiology meeting in Spring 2017, on isolates, the composite transposon for transferable colistin resistance, protracted outbreak of Klebsiella pneumoniae Carbepenemase-containing *Klebsiella* isolates, assigning pulsed-field gel electrophoresis types to *S. aureus* using WGS, its integrated bioinformatics pipeline for microbial sequencing, and its SpaTyper for gene typing, and in silico identification of novel Acinetobacter beta-lactamase genes and ID of hidden AmpC beta-lactamases in the Military Health System.

The Agricultural Antibiotic Resistance (AgAR) Network, a group of ARS scientists working on

[68] https://www.niaid.nih.gov/news-events/bacteriophage-therapy-scientific-and-regulatory-issues-public-workshop
[69] http://www.pewtrusts.org/en/research-and-analysis/analysis/2017/03/08/the-importance-of-better-drug-design-for-antibiotic-innovation
[70] https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-16-081.html

issues related to environmental dimensions of antibiotic resistance, has coordinated and recently started cross-location, multi-year studies to characterize and quantify antibiotic resistant bacteria and antibiotic resistance genes in applied food-animal production environments, and has been working over the past year to develop a database that will allow intra- and inter-agency and public sharing of ARS antibiotic resistance data sets.

RESEARCH

CDC is investing in applied innovative work with universities and healthcare partners to discover and develop new ways to prevent antibiotic resistant infections and their spread across diverse healthcare settings and in the community, as well as assess the role of the microbiome in the prevention of infections. New funding opportunities in 2016 and 2017 include the creation of a Healthcare-Associated Infectious Disease Modeling Network to Improve Prevention Research and Healthcare Delivery, CDC Prevention Epicenters Program, the Safe Healthcare, Epidemiology, and Prevention Research Development (SHEPheRD) Program, and Broad Agency Announcement awards.

NIH investigators have identified a Staphylococcus epidermidis toxin (PSM-mec) that is released into the bloodstream and contributes to sepsis. Previously, scientists thought that S. epidermidis sepsis resulted from an overwhelming immune response to unchanging surface structures on the invading bacteria. This is the first time a toxin from S. epidermidis or closely related bacteria has been linked to sepsis.[71]

The Pathosystems Resource Integration Center (PATRIC), an NIH-supported Bioinformatics Resource Center, provides open access to diverse data sets, including a repository on antibiotic susceptibility and resistance for more than 12,000 bacterial genomes and 68 different antibiotics.[72] PATRIC investigators developed a machine learning based computational tool to predict antimicrobial resistance-related genomic features and phenotypes in *Acinetobacter*, *Mycobacterium*, *Staphylococcus* and *Streptococcus*.[73]

The NIH-supported Genomic Centers for Infectious Diseases (GCID) has sequenced over 8,000 AMR bacterial genomes (e.g., *Enterococcus*, *Klebsiella*, *Acinetobacter*, CRE, and MRSA). These data, which are rapidly released into GenBank and NIH-funded Bioinformatics Resource Centers, contribute to the development of improved diagnosis, therapeutic interventions, and understanding of the complexity and evolution of drug resistance.[74]

NLM/NCBI publicly released a pathogen isolate browser, which is being used to aid outbreak and traceback investigations of foodborne illnesses. This browser can rapidly identify genomes containing AR genes with particular phenotypes or specific AR genes of interest, and display them in the context of known outbreaks or other highly related genomes.

ARS base research programs have measured the efficacy of pilot scale and on-farm strategies to

[71] http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006153
[72] https://www.patricbrc.org/
[73] https://www.nature.com/articles/srep27930
[74] https://www.niaid.nih.gov/research/genomic-centers-infectious-diseases

reduce resistance in soils, surface waters, and ground waters, tracked distribution AR on farms and in fields, examined uptake of AR into plants, and measured baseline resistance in agricultural soils. ARS is actively involved in the development of improved methods for reliable and reproducible detection of antibiotic drugs, resistant bacteria, and resistance genes in complex environmental samples, and has expanded capacity in this area over the last two years.

REPORTS & PUBLICATIONS

Since 2015, CDC has made critical contributions to the knowledge base and field of public health by supporting antimicrobial resistance work reflected in more than 300 peer-reviewed publications, moving the nation forward in detecting and responding to resistance threats, preventing infections, stopping spread, and improving antibiotic use in healthcare and community settings.

In recent years, CDC has responded to several forms of emerging resistance—such as *mcr*-1 and *Candida auris* (*C. auris*)—which arm already tough-to-treat pathogens with better, stronger defenses. CDC believes that one case of novel resistance justifies mobilization to contain the threat. In early 2017, CDC published general guidance to state and local health departments and healthcare facilities for initial response to contain novel or targeted multidrug-resistant organisms.

CDC is actively working with partners to better contain and prevent spread of *C. auris*, an emerging multidrug-resistant yeast that can cause invasive infection and death. Following a CDC clinical alert in June 2016 asking labs and healthcare workers to be on the lookout for *C. auris* in patients, healthcare facilities quickly reported several *C. auris* cases, and CDC began investigating with state and local public health partners. CDC has described the first reported U.S. cases in CDC's *Morbidity and Mortality Weekly Report* (MMWR) and developed *C. auris* guidance for clinicians and infection control personnel.

CDC has leveraged its Vital Signs series to raise awareness among clinicians, public health practitioners, and the public. "CDC Vital Signs: Stop the Spread of Antibiotic Resistance" was released in 2015 to increase awareness around AR and provide new CDC scientific information to stop spread of resistant infections and *C. difficile* by implementing public health-healthcare prevention networks, which have the potential to more completely address the emergence and spread of AR threats than independent facility-based efforts. In 2016, CDC released "CDC Vital Signs: Protect Patients from Antibiotic Resistance", which urged healthcare personnel to always follow infection control recommendations and stewardship to better protect patients from healthcare-associated infections caused by AR bacteria. In addition, CDC released an MMWR Surveillance Supplement on *N. gonorrhoeae* resistance in 2016, which raised awareness among clinicians, public health practitioners, and the public.

In March 2017, NIH's ARLG published an extensive summary of its activities, describing progress, ongoing efforts, and future directions.[75] Many of the ARLG's studies have involved innovative approaches, such as novel trial designs that optimize enrollment in therapeutic trials and increase clinical trial efficiencies.

[75] https://academic.oup.com/cid/issue/64/suppl_1

ARS led the generation and publication of "Antibiotics in Agroecosystems: State of the Science" special issue of the Journal of Environmental Quality, including co-authoring four of five core review papers, four of 19 technical papers, and a glossary of commonly used environmental antibiotic resistance terms.

OTHER ACTIVITIES

As part of their mission and charter,[76] the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) issued its first report[77] in March 2016 assessing the U.S. Government's (USG) progress toward the goals of the CARB National Action Plan after its first 180 days. One of the recommendations included the exploration of incentives for the development of novel products, including vaccines, diagnostics, and therapeutics for both humans and animals to counter antibiotic resistance. As such, the PACCARB's working groups have developed a draft report to address this specific issue, which was presented to the full council for deliberation and subsequently unanimously accepted at their September 2017 public meeting. To date, the PACCARB has held six public meetings and hosted presentations from subject matter experts from academia, industry, food, agricultural, and health associations, as well as international health organizations. Topics discussed have included infection prevention and control, antibiotic stewardship for both human and animal health, and utilization of One Health as a comprehensive USG approach to combating antibiotic resistance.

DoD continues to be represented as an ex officio member of PACCARB, as a moderator at the 2017 Global Health Engagement Summit in June 2017, planner for the National Academies of Sciences, Engineering, and Medicine Forum on Microbial Threats AMR symposium in June 2017, speaker at the Association of the United States Army Army Medical Symposium and Exposition in July 2017, co-coordinator of antimicrobial stewardship in the DoD webinars, and in providing quarterly webinars for Military Healthcare System on MRSN activities/capabilities/educational opportunities for those federal healthcare professionals working with AMR pathogens.

USDA's Foreign Agriculture Service (FAS) has coordinated drafting of compromise language with other federal agencies and other delegations for multiple international venues including G-20 Agricultural Minister's Communique and Action Plan, the G-7 Agricultural Minister's statement, and USDA continues interactions within the OIE, FAO, and the Organisation for Economic Co-operation and Development (OECD). Bilaterally, the USDA has also provided background documents and negotiating support for the US-Brazil Consultative Committee on Agriculture, and technical advice to Vietnam in drafting its domestic policies to address antimicrobial resistance.

[76] https://www.hhs.gov/ash/advisory-committees/paccarb/about-paccarb/charter/index.html
[77] https://www.hhs.gov/sites/default/files/paccarb-final-report-03312016.pdf

APPENDIX B: NATIONAL TARGETS FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

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

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

APPENDIX C: ACRONYMS

AAVLD	American Association of Veterinary Laboratory Diagnosticians
AAVMC	Association of American Veterinary Medical Colleges
AFRI	Agriculture and Food Research Initiative
AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AHRQ	Agency for Healthcare Research and Quality
AMR	antimicrobial resistance
AMS	Agricultural Marketing Service
APHIS	Animal and Plant Health Inspection Service
AR	Antibiotic resistance
ARIP	Antimicrobial Resistance Initiative Program
ARLG	Antibacterial Resistance Leadership Group
ARLN	Antibacterial Resistance Regional Laboratory Network
ARS	Agricultural Research Service
AS	Antibiotic Stewardship
AST	Antimicrobial Susceptibility Test
AU	antibiotic use
AUR	antibiotic use and resistance
AVMA	American Veterinary Medical Association
BARDA	Biomedical Advanced Research and Development Authority
C. difficile	*Clostridium difficile*
CARB	Combating Antibiotic-Resistant Bacteria
CAUTI	Catheter-associated urinary tract infection
CDC	Centers for Disease Control and Prevention
CETR	Centers of Excellence for Translational Research
CMS	Centers for Medicare and Medicaid Services
CRE	carbapenem-resistant Enterobacteriaceae
cSMRT	Consortium for Structure-guided Microbial Resistance Targets
CUSP	Comprehensive Unit-based Safety Program
CVM	Center for Veterinary Medicine
DBL	Diagnostic Bacteriology Laboratory
DoD	Department of Defense
ECDC	European Centre for Disease Prevention Control
EIP	Emerging Infections Program
EPA	Environmental Protection Agency
ERS	Economic Research Service
E.U.	European Union
FAO	Food and Agriculture Organization
FAS	Foreign Agricultural Service
FDA	Food and Drug Administration
FOA	Funding Opportunity Announcement
FMT	Fecal Microbiome Transplant
FSIS	Food Safety and Inspection Service
GC	Gonorrhea
GCID	Genomic Centers for Infectious Diseases

GFI	Guidance For Industry
GHSA	Global Health Security Agenda
HAI	healthcare-associated infections
HIIN	Hospital Improvement Innovation Network
HHS	Department of Health and Human Services
IICAB	Institute for International Cooperation in Animal Biologics
IMDRF	International Medical Device Regulators Forum
IMI	Innovative Medicines Initiative
IND	Investigational New Drug
IPT	Integrated Product Team
IV	Intravenous
JSTO	Joint Science and Technology Office
LTC	long-term care
MBL	metallo-β-lactamase
MDR	multi-drug resistant
MMWR	Morbidity and Mortality Weekly Report
MOU	Memorandum of Understanding
MRSN	Multidrug-resistant organism Repository and Surveillance Network
NAHLN	National Animal Health Laboratory Network
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
NCBI	National Center for Biotechnology Information
ND4BB	New Drugs for Bad Bugs
NHGRI	National Human Genome Research Institute
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIFA	National Institute of Food and Agriculture
NIH	National Institutes of Health
NLM	National Library of Medicine
NQF	National Quality Forum
NVSL	National Veterinary Services Laboratories
OGA	Office of Global Affairs
OIE	World Organization for Animal Health
OSTP	Office of Science and Technology Policy
PAHO	Pan American Health Organization
PATRIC	Pathosystems Resource Integration Center
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
POC	point-of-care
PR/HACCP	Pathogen Reduction/Hazard Analysis and Critical Control Point
QIN-QIO	Quality Innovation Network-Quality Improvement Organizations
QIDP	Qualified Infectious Disease Product
RFA	Request for Applications
SAAR	Standardized Antibiotic Administration Ratio
SGCID	Structural Genomics Centers for Infectious Diseases
STI CTG	Sexually Transmitted Infections Clinical Trials Group
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance

TB	Tuberculosis
USDA	United States Department of Agriculture
USG	United States Government
UTI	Urinary Tract Infection
VA	Department of Veterans Affairs
Vet-LIRN	Veterinary Laboratory Investigation and Response Network
VTEU	Vaccine and Treatment Evaluation Unit
VFD	Veterinary Feed Directive
VHA	Veterans Health Administration
VICH	International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal Products
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research