

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Progress Report: Year 3

October 2018

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

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Background

Antibiotics are among the most commonly prescribed drugs used in human and veterinary medicine and they save lives every day. However, as genetically-adapted pathogens survive exposure to these drugs, antibiotic resistance (AR) results in infections that are difficult or even impossible to treat. Some bacteria can also directly transfer their drug-resistance to other bacteria, further spreading resistance and threatening the effectiveness of existing antibiotics. The Centers for Disease Control and Prevention (CDC) [estimate](#) that every year, more than two million people in the United States acquire resistant infections, and at least 23,000 people die as a result. Antibiotic use can also [lead to](#) illness from *Clostridium difficile* (*C. difficile*), a bacterium that can cause serious diarrhea and results in at least another 15,000 deaths each year in the U.S.

To address this public health threat, the U.S. Government developed a National Strategy and accompanying [National Action Plan for Combating Antibiotic-Resistant Bacteria](#) (CARB), which provides a 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 to be completed within one, three, and five years of the plan's launch. The CARB Task Force facilitates implementation of the plan, and is chaired by the Secretaries of the U.S. Departments of Health and Human Services (HHS), Agriculture (USDA), and Defense (DoD).

In 2017, the CARB Task Force released a [Progress Report for Years 1 and 2](#), which highlighted key achievements under the National Action Plan. Now, after three years of activity, the CARB Task Force has developed this report to describe further progress toward these goals. The report does not enumerate each Year 3 milestone of the plan, but rather provides a narrative description of high-impact activities, generally organized in order of the level of activity by each agency within each goal. This report refers to the period between spring 2017 and spring 2018. Many of these activities rely on continuous collaboration among multiple agencies; these activities include:

- Continuing efforts to prevent healthcare-associated infections (HAIs) as an important strategy to reduce antibiotic resistance;
- Testing and translating innovations in infection control, prevention, and stewardship strategies, and developing policies and tools to ensure that these new practices are implemented across healthcare settings;
- Fostering discovery and development of new rapid point-of-care diagnostics, antibiotics, non-traditional therapeutics, and vaccines;

- Continuous monitoring of resistance in the U.S. and in military populations to sound the alarm when threats emerge;
- Improving identification of resistance through federal support of increased laboratory capacity in all 50 states, five large cities, and Puerto Rico, including seven regional labs and a national tuberculosis lab for specialty testing;
- Federal support for prevention programs nationwide to prevent spread of resistance and improve antibiotic use, and to provide data and recommendations for local prevention and response; and
- Federal support for multiple extensive data and isolate resources, including whole genome sequences from outbreak response, research, and isolates, so that researchers can publicly access the data needed to inform innovation in diagnostics and drug development.

The activities described in this report highlight the continued efforts of the U.S. Government to collaborate, innovate, and adopt early, aggressive action across multiple agencies, public health services, healthcare settings, and laboratories to slow the emergence of new resistance. The National Action Plan for CARB continues to support these capacities across the country to strengthen and expand our ability to prevent, identify, and respond to AR threats.

Progress Report for Year 3

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

The U.S. Government continues to make progress toward preventing infections, slowing the spread of resistant pathogens, improving antibiotic use, and identifying and responding to unusual antibiotic resistance with early, aggressive action to stop spread. Federal agencies use data and evidence to pinpoint areas for further improvement, and work together to develop tools, recommendations, and programs that offer strategies to help protect patients.

Infection Prevention

According to CDC's National Healthcare Safety Network (NHSN) and other CDC data sources, the nation has seen [major progress](#) since 2005 in preventing methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, but these declines are slowing.¹ The Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP) data suggest that healthcare-associated *C. difficile* infections (CDI) are remaining relatively stable, but community-associated CDI may be increasing. These data and the transmissible nature of MRSA and CDI underscore the need for comprehensive and innovative public health approaches to prevent infections, including central line-associated bloodstream infections (CLABSI) and catheter-associated urinary tract infections (CAUTI), and to improve antibiotic use across the continuum of healthcare and the community.

CDC supports capacity in 50 states, Puerto Rico, and six major cities to detect, respond to, and contain emerging AR threats, as well as to improve methods and timeliness of carbapenem-resistant Enterobacteriaceae (CRE) laboratory testing in all 50 states and specialized testing in the seven regional laboratories. Health departments continue to use data from NHSN, outbreak investigations, and the AR Laboratory Network to target their response and prevention actions. Prevention across healthcare continues in over 30 state and local health departments to not only stop transmission of antibiotic resistant pathogens and *C. difficile* between healthcare settings, but also to build and strengthen partnerships to improve antibiotic prescribing in acute care, including critical access hospitals, nursing homes, and in outpatient settings.

Health departments continue to work with the Centers for Medicare & Medicaid (CMS)-funded Hospital Improvement Innovation Networks (HIINs) and Quality Innovation Network/Quality Improvement Organizations (QIN/QIOs) to prevent device and procedure-associated infections and *C. difficile* in hospitals and nursing homes. CDC works closely with CMS and the HIINs to provide prevention tools and expertise to target HAIs and antibiotic resistant infections in acute care and critical access hospitals. *As of March 2018, more than 3,000 or 21 percent of CMS-certified nursing homes are actively enrolled and eligible to report C. difficile infections into NHSN, and CMS-supported HIINs have recruited more than 4,000 hospitals to benefit from CDC's expertise in improving patient safety, preventing hospital-acquired conditions including C. difficile, and implementing antibiotic stewardship programs.* Each hospital receives technical assistance around implementing Antibiotic Stewardship Programs based upon the Core Elements

¹ Healthcare-associated Infections in the United States, 2006-2016: A Story of Progress
<https://www.cdc.gov/hai/surveillance/data-reports/data-summary-assessing-progress.html>.

for acute care settings defined by the CDC, and to reduce antibiotic misuse or overuse and HAIs like *C. difficile* and other multi-drug resistant organisms (MDROs).

CDC also supports capacity in states and cities to track, investigate, and prevent foodborne disease. As of March 2018, 49 laboratories in 44 states have established capacity to perform whole genome sequencing on all *Salmonella* isolates. CDC is working with partners to validate these data for reliability and accuracy, and is developing computer algorithms to automate and improve detection of new resistance patterns for faster identification and response to foodborne outbreaks with known markers of antibiotic resistance.

To address the emerging threat of resistant gonorrhea in the United States, CDC also supports capacity in nine health departments to establish rapid detection and response through local laboratory testing for gonorrhea and resistant *Neisseria* at their local sexually transmitted disease (STD) clinics and public health labs. Between February and December 2017, these nine sites collected nearly 14,000 specimens; of the more than 3,200 specimens testing positive for gonorrhea, 242 (7.6 percent) had less than optimal responses in the laboratory to recommended antibiotics and triggered rapid local response to prevent spread. Other CDC data are showing a growing proportion of pathogens with less than optimal response in the lab to recommended treatment, which include a concerning cluster of gonorrhea in Hawaii (2016). The United Kingdom also recently described a multi-drug resistant infection in the (2018) that did not respond to first line therapy. These examples underscore the need for local capacity to slow the emergence of antibiotic-resistant gonorrhea.

CDC's Prevention Epicenters conduct applied research, including large multicenter studies, to develop and test innovative approaches for preventing infections and improve antibiotic use. Preliminary Prevention Epicenter study results have found that skilled nursing facilities that provided care to ventilated patients are an important reservoir of MDROs, and so will be a key target for ongoing infection prevention and control efforts. Further, results demonstrate that clinical outcomes are not negatively impacted by adding predefined criteria to the electronic health record to reduce inappropriate *C. difficile* testing. CDC is supporting the Modelling Infectious Diseases in Healthcare (MIND-Healthcare) network, working in close collaboration with the Prevention Epicenters, to develop mathematical models of potential interventions that will help develop tools that most effectively reduce AR pathogen transmission by identifying promising combinations of interventions.

CDC's Emerging Infections Program (EIP) and Prevention Epicenters are working together to combine state/local public health and academic medical center expertise and test interventions in the field. These strategies include genomic analysis of CRE transmission networks to better define true transmission events; testing an antimicrobial stewardship intervention package on CDI reduction; testing a CDI intervention package in multiple acute care facilities and using EIP surveillance data to measure community-wide intervention impact; and testing for chlorhexidine gluconate resistance among carbapenem-resistant gram negative isolates.

Ahead of the Year 5 milestone on analyzing the resistance of bacteria in the human gut, CDC is investing in research to discover and develop new ways to prevent AR infections and their spread, as well as the public health impact of microbiome disruption. Since October 2016, CDC has awarded more than \$32.5 million to pilot innovative solutions and explore knowledge gaps

about how antibiotic resistance spreads to and between humans, including research on how the human microbiome can be used to predict and prevent infections caused by drug-resistant microorganisms.

The Agency for Healthcare Research and Quality (AHRQ) supports a comprehensive portfolio of research that supports the development and implementation of tools to prevent HAIs, slow transmission of resistant bacteria, and promote antibiotic stewardship in acute care, long-term care, and ambulatory care settings. In May 2017, AHRQ released the final report of the AHRQ Safety Program for Long-Term Care: Preventing CAUTI and Other HAIs. This three-year implementation project, which included more than 400 nursing homes nationwide, significantly reduced CAUTI rates by approximately 50 percent.² There was also a notable 15 percent decrease in urine culture orders during the project, which had encouraged appropriate use of urine cultures, including avoiding urine cultures for most asymptomatic patients, to help decrease inappropriate use of antibiotics for asymptomatic bacteriuria. The program used principles and methods from AHRQ's Comprehensive Unit-based Safety Program (CUSP) to enhance leadership and staff engagement, teamwork, and safety culture. The project also provided insights about factors affecting how infection prevention is conducted in nursing homes based on interviews with eight regional/state project leads and eight facility leads.³ AHRQ continues to disseminate the [Toolkit to Reduce CAUTI and Other HAIs in Long Term Care Facilities](#), an extensive toolkit that was developed in the project and is available on the AHRQ website. This AHRQ national project and toolkit contribute to CARB in two ways. First, every CAUTI prevented means a course of antibiotics avoided, thereby avoiding an exposure that promotes antibiotic resistance. Second, avoiding urine cultures for most asymptomatic patients helps decrease inappropriate use of antibiotics for asymptomatic bacteriuria.

Up-to-date antimicrobial susceptibility testing (AST) device results, which are used to identify patients who have certain types of resistant bacteria, are essential to infection control practices and patient care. In December 2017, the Food and Drug Administration (FDA) launched the susceptibility test interpretive criteria (breakpoints) [webpage](#) to streamline the updating of breakpoint information for drugs and devices, as required by the 21st Century Cures Act.

Antibiotic Stewardship in Human Healthcare

CDC works with hospitals, health systems, nursing homes, and clinical providers in outpatient settings to identify ways to improve antibiotic use and facilitate antibiotic stewardship—ensuring patients get the right antibiotics at the right time for the right duration—aligned with CDC's Core Elements of antibiotic stewardship. CDC is also working to incorporate antifungal stewardship into existing efforts. CDC also assesses antibiotic use across healthcare settings to better understand how to target action to improve use. For example, recent studies show that some antibiotics are inappropriately selected for children, and that fluoroquinolones are frequently overprescribed and misused in adults, pointing to key areas for targeted antibiotic

² Mody L, Greene MT, Meddings J, Krein SL, McNamara SE, Trautner BW, Ratz D, Stone ND, Min L, Schweon SJ, Rolle AJ, Olmsted RN, Burwen DR, Battles J, Edson B, Saint S. A National Implementation Project to Prevent Catheter-Associated Urinary Tract Infection in Nursing Home Residents. *JAMA Intern Med.* 2017;177(8):1154-1162. Published online May 19, 2017.

³ Krein SL, Harrod M, Collier S, Davis KK, Rolle AJ, Fowler KE, Mody L. A national collaborative approach to reduce catheter-associated urinary tract infections in nursing homes: A qualitative assessment. *American Journal of Infection Control.* 2017;45(12):1342-1348.

stewardship.

CDC recently launched two major, national health educational initiatives that were separate yet mindfully integrated. First, during U.S. Antibiotic Awareness Week in November 2017, CDC unveiled *Be Antibiotics Aware: Smart Use, Best Care*, which focused on improving antibiotic use across the spectrum of human health care, with new branding, resources, and educational materials targeting healthcare providers and the general public. The *Be Antibiotics Aware* public service announcement had more than 35 million media impressions, and more than 86,000 materials were downloaded in the subsequent four months. Second, on August 31, 2017, and in conjunction with Sepsis Awareness Month, CDC launched *Get Ahead of Sepsis*, an educational initiative to protect Americans from the devastating effects of sepsis. This initiative emphasized the importance of recognizing sepsis early and acting quickly if sepsis is suspected, balancing messages about the importance of proper antibiotic treatment and reassessment, as well as infection prevention, as infections lead to sepsis in the first place. Between November 2017 and April 2018, the educational effort received about 245 million total estimated impressions⁴, more than 90,000 materials were downloaded, public service announcements generated more than 39 million impressions, and CDC sepsis web traffic increased by 78 percent (year over year). CDC conducted a survey to measure the effectiveness of the *Get Ahead of Sepsis* educational initiative among target audiences. According to the survey of 1,616 consumers conducted from February 26, 2018 to March 30, 2018, 71 percent of respondents who saw CDC's messaging said they searched for more information about sepsis and over half of the respondents who saw CDC's messaging said they asked a healthcare professional for more information about sepsis.

Preliminary 2017 data show that 76 percent of all U.S. hospitals report having antibiotic stewardship programs that meet all of CDC's Core Elements, compared to 64 percent in 2016. The goal is to have programs meeting CDC Core Elements of Hospital Antibiotic Stewardship Programs in 100 percent of hospitals by 2020. CDC is working directly with multiple large health systems, professional organizations, The Joint Commission, and the Federal Office of Rural Health Policy to implement CDC's Core Elements of Hospital Antibiotic Stewardship and CDC's Implementation of Antibiotic Stewardship Core Elements at Small and Critical Access Hospitals (released in July 2017), promote infection prevention and control, and improve antibiotic use, including having antibiotic use and resistance data to target actions. CDC works with hospitals to evaluate the impact of CDC's Core Elements on antibiotic use through NHSN antibiotic use data and CDC's Emerging Infections Program. CDC uses these findings to identify patient-level and facility-level risk factors to both target action and to improve the quality and usability of the data for hospital leaders and staff.

To disseminate best practices for implementation of antibiotic stewardship across outpatient settings and clinical provider specialties (e.g., physicians, nurses, dentists, pharmacists), CDC developed an antibiotic stewardship training course that allows healthcare professionals to earn continuing medical education credits, which was released in February 2018 and is linked to the CMS Quality Payment Program (QPP)-Merit-Based Incentive Payment System (MIPS) Improvement Activities. CDC has also started working with the National Committee for Quality Assurance and clinical experts to expand three existing quality measures for tracking outpatient antibiotic use.

⁴ Total estimated impressions = estimate of the number of people reached by a particular advertisement

CDC has expanded work to improve antibiotic use in nursing homes through data, tools, and partnerships for implementation of CDC's Core Elements of Antibiotic Stewardship for Nursing Homes. CDC is currently conducting the first comprehensive analysis of nursing home antibiotic use to guide action. With partners including CMS, CDC is developing an Infection Prevention in Post-Acute and Long-Term Care Certificate Course for long-term care facilities, and convened nursing home systems, provider organizations, electronic health record vendors, and pharmacy vendors to discuss ways to report antibiotic use and implement antibiotic stewardship. CDC is also working with the National Quality Forum to create a practical guide to implement antibiotic stewardship activities, similar to the tool created for hospitals.

CDC also works closely with federal partners to support improved use of antibiotics. CDC is supporting the scale-up of stewardship interventions in the Department of Veterans Affairs' (VA) outpatient and acute care settings and is collaborating with the VA to refine methods for measuring hospital antibiotic use in NHSN. CDC is also providing technical support and subject matter expertise to the Federal Office of Rural Health Policy within the Health Resources and Services Administration (HRSA), CMS, and the QIN-QIOs to enroll nursing homes and outpatient settings to implement antibiotic stewardship using CDC's Core Elements. *As of April 2018, QIN-QIOs have recruited over 7,500 outpatient settings, including physician practices, hospital emergency departments, urgent care centers, and others.*

In the three years since the launch of the National Action Plan for CARB, AHRQ has significantly increased its support for research to develop improved methods to combat antibiotic resistance and promote antibiotic stewardship, including grants for investigator-initiated research that will total more than \$37 million. In this period, new Funding Opportunity Announcements for research on CARB and HAI prevention have been issued and increased the volume of grant applications submitted to AHRQ. The Agency conducted a webinar in March 2018 for members of the Society for Healthcare Epidemiology of America (SHEA) to inform them of the areas of AHRQ's scientific interest and the availability of research funding and to stimulate additional interest in applying for AHRQ grants to combat antibiotic resistance.

AHRQ is also developing and providing key practical guidance to promote implementation of antibiotic stewardship activities in a variety of healthcare settings. The AHRQ Safety Program for Improving Antibiotic Use has made significant progress in adapting AHRQ's Comprehensive Unit-based Safety Program (CUSP), which has been highly effective in preventing HAIs, to improve antibiotic use and promote antibiotic stewardship in multiple healthcare settings. In December 2017, the project began implementation in a one-year acute care cohort of over 425 hospitals, which currently includes six DoD facilities and more than 80 critical access hospitals. In March 2018, a one-year pilot phase was completed in three integrated health care delivery systems, each of which comprises all three care settings that will be addressed in this five-year nationwide effort. In total, the project will promote and support implementation of antibiotic stewardship in 250-500 acute care hospitals, 250-500 long-term care facilities, and 250-500 ambulatory care settings across the country. The project team is developing an educational and technical assistance toolkit, consistent with CDC's Core Elements for antibiotic stewardship, to promote implementation of stewardship in all three settings, which will be made publicly available at the end of the project.

AHRQ has also increased its wide dissemination of the Guide to Nursing Home Antimicrobial Stewardship, which is based on the results of four previous AHRQ-funded research studies. For example, the Guide was featured during a workshop at the American Medical Directors Association Annual Conference in March 2018, as part of a presentation from a large initiative in Pennsylvania that included implementation of the SBAR (Situation, Background, Assessment, Recommendation) forms for suspected urinary tract infection and family engagement materials. CMS state surveyors now offer the Guide to nursing homes to support their antibiotic stewardship activities, and CMS also added the Guide to their quality assurance and performance improvement (QAPI) website to offer this resource to nursing homes to support antibiotic stewardship programs. 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.

As noted in the prior Annual Report, CMS published final requirements for participation for over 15,000 Medicare and Medicaid-participating long-term care (LTC) facilities in October 2016 (81 FR 68688). This rule included provisions that address infection prevention and control, antibiotic use protocols, and a system to monitor antibiotic use, for phased-in implementation. By November 2016 and November 2017, respectively, LTC facilities were required to have a more robust infection control and prevention program, and an antibiotic stewardship program in place. Updated Conditions of Participation (CoPs) remain 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 39447).

CMS completed and released new Interpretive Guidance (IG) on June 30, 2017, which included how to survey for antibiotic stewardship in nursing homes. As the LTC IGs have been finalized, training webinars for CMS surveyors have been updated to include information on antibiotic utilization in nursing homes. Additional evidence-based tools produced from an on-going three-year pilot will be geared to enhance surveyor assessment of adherence to infection control and prevention guidance as well as assess efficacy and compliance with CDC's Core Elements for antibiotic stewardship in this setting. CMS and CDC are also collaborating on new LTC infection prevention/antibiotic stewardship training materials. To share best practices for antibiotic stewardship and CDI prevention guidance, *CMS has implemented intensive trainings, technical assistance, and collaborative learning opportunities that have reached over 4,000 hospitals, 2,400 nursing homes and 7,600 outpatient settings based on CDC and AHRQ stewardship protocols.*

CMS 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 24945). This measure was included in CMS' Measures Under Consideration List and will be ready to consider for proposed rule-making, in consultation with CDC, at a future time. Further, under the QPP-MIPS, CMS has included an Improvement Activity regarding implementation of an antibiotic stewardship program that measures the appropriate use of antibiotics as well as two Improvement Activities regarding the initiation and completion of CDC Training on Antibiotic Stewardship. As measures appropriate for the out-patient setting are developed, CMS will work with CDC and others to consider proposals for inclusion in appropriate CMS programs in future rules.

The VA has implemented antimicrobial stewardship programs in all Veterans Health Administration (VHA) medical centers. The VA has an ongoing initiative dedicated to enrollment in the National Healthcare Safety Network's (NHSN) Antimicrobial Use (AU) Option. *To date, nearly eighty percent of VHA acute care facilities have enrolled and submitted data to CDC's NHSN's AU Option and VHA is developing an action plan to complete enrollment of all facilities.* VA has also launched a national outpatient antimicrobial stewardship intervention aimed at improved prescribing for acute respiratory tract infections for elective implementation at any VHA facility.

DoD has recently implemented centralized reporting to NHSN AU and AR modules. In an important collaboration, DoD has enrolled six facilities in AHRQ's Safety Program for Improving Antibiotic Use, which is adapting the CUSP effort to antibiotic stewardship. DoD is in the process of reviewing the formal Implementation Guidance document that will accompany the DoD-Instruction creating its Antimicrobial Stewardship Program, which was approved in 2017. The Multidrug-resistant organism Repository and Surveillance Network (MRSN) is actively collaborating with DoD Infectious Disease Clinical Research Program (IDCRP) efforts and with the VA regarding wound infection surveillance and pathogen characterization. The MRSN also maintains an active external collaboration with CDC's Antimicrobial Resistance Laboratory Network.

Throughout 2017 and 2018, The Navy Marine Corps Epi Data Center (EDC) designed, developed and launched several data visualization platforms which allow for centralization of antimicrobial resistance (AMR) data as well as improved access and efficiency for key stakeholders in the antimicrobial stewardship community. The Antibiotic Susceptibility and Prescribing Practices (ASPP) Tool is an interactive, web-based data visualization tool that displays trends of antibiotic susceptibility and consumption throughout the Military Health System. In ASPP, the user can customize the display of data points to investigate trends related to the population or region of interest. Data for ASPP is available from 2006 through present and can be queried by age groups.

Antibiotic Stewardship in Animal Health

Significant progress was also made in animal health stewardship activities this year. Working through public-private partnerships, FDA has incorporated strategies for judicious use of medically important antimicrobial drugs in animal health, which is essential to combating resistance and thereby preserving the therapeutic effectiveness of antibiotics for humans and animals.

To further support implementation of [Guidance for Industry \(GFI\) #213](#), FDA sought public input on establishing appropriately targeted durations of use for medically important antimicrobial drugs in food-producing animals. FDA has evaluated the comments received and is currently developing a specific strategy to ensure that all of these drugs have specifically defined durations of use. FDA will consider the approved use conditions of these drugs on a product-by-product basis. Any changes to their use conditions will need to be based on sound science and available evidence. FDA also published two Question and Answer documents to clarify materials related to Veterinary Feed Directive (VFD) drugs, for [The Use of Medically Important Antimicrobials in Bees](#) and [Free-Choice Medicated Feeds for Controlling Anaplasmosis in](#)

Cattle.

FDA's Center for Veterinary Medicine (CVM) provided technical input to USDA's Animal and Plant Health Inspection Service (APHIS) National Veterinary Accreditation Program (NVAP), which works with states' veterinary licensing boards to educate veterinarians in private practice. The NVAP has delivered over a half-million training modules to veterinarians, veterinary technicians, and veterinary students in Web, classroom, and printed formats since 2011. *In August 2017, NVAP vastly expanded its educational outreach by enhancing all 29 modules to provide professional continuing education credit for the nation's 100,000-plus veterinarians and 100,000-plus licensed veterinary technicians.* Two NVAP modules play key roles in USDA's AR global education and outreach efforts, and these modules have been updated to include information to foster compliance with FDA policies:

- NVAP Module 23: *Use of Antibiotics in Animals* has been completed by 26,050 accredited veterinarians since its launch in 2012. The module is the product of the collective efforts of academic, livestock, and companion animal veterinarians, as well as officials from FDA, CDC, DoD, and USDA-National Institute of Food and Agriculture (NIFA). At the Group of Seven (G7) meeting in Germany in 2015, NVAP Module 23 was recognized as one of the world's "Best Practices of Combating Antimicrobial Resistance".
- NVAP Module 29: *Veterinary Feed Directive* launched in January 2017 to coincide with the transition of medically important antimicrobials used in the feed of food producing animals from over-the-counter to Veterinary Feed Directive marketing status in January 2017, as part of FDA's strategy to promote the judicious use of medically important antimicrobials in animal agriculture. Food animal producers must now obtain a VFD from a licensed veterinarian to obtain and use in animal feed antibiotics that are medically important in human medicine. Module 29 has already been completed 7,176 times by accredited veterinarians, and Google Analytics data indicates that the module's usage extends to "agriculturalist" users (feed manufacturers, feed mill owners/operators, feedlot personnel, and livestock producers), far exceeding NVAP's traditional accredited veterinarian audience.

To evaluate the impacts of FDA policy and provide a more comprehensive, science-based approach to assessing FDA's judicious use strategy, FDA supports efforts to monitor antimicrobial drug use in food-producing animals through periodic collection of nationally representative on-farm data on antimicrobial-use practices and resistance.

Since 2016, FDA has funded two grants for antimicrobial use data collection. These collection efforts intend to provide critical information on antimicrobial use practices in the four major food-producing animal species (cattle, pigs, chickens, and turkeys), which can help inform assessment of the overall impact of FDA's judicious use strategy and help optimize long-term strategies to collect and report such antimicrobial use data. FDA has also provided input to the USDA APHIS Center for Epidemiology and Animal Health on surveys conducted on antimicrobial use in swine operations and cattle feedlots.

CDC is working with Integrated Food Safety Centers of Excellence across the country to assess veterinary prescribing practices for food-producing animals, update veterinary training with current antibiotic stewardship principles, and support coordination and sharing of antimicrobial susceptibility testing and One Health surveillance among veterinary diagnostic laboratories and

public health laboratories.

USDA, FDA's CVM and CDC serve as Advisors to the American Veterinary Medical Association (AVMA) Committee on Antimicrobials, whose members represent affiliated veterinary practice organizations. The AVMA-CoA developed principles for antimicrobial stewardship in veterinary settings in 2017 that were unanimously approved in January 2018 by the [AVMA House of Delegates](#).

USDA-NIFA funded nearly \$15M in FY2017 in research to decrease the need for antibiotic use in agriculture. These projects include alternative treatment regimens to control bovine anaplasmosis; developing a communication framework for conveying AR science and mitigation opportunities; mitigation of antibiotic resistance in poultry through resensitization, vaccination and microbial restoration; methods to reduce the perceived need for critically important antimicrobial uses on dairy farms; educational approaches to improve cattle health and reduce the need for antibiotic use; examining Berberine as an alternative to antibiotics in nursery pig diets; investigating properties of mesenchymal stromal cells as a biological alternative to conventional antibiotics in veterinary medicine; use of macrophages and endothelial cells for cell-based therapy; and building strain libraries as alternatives to antibiotic growth promoters in broiler chickens.

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

Enhanced data sharing and coordination of surveillance and laboratory systems will enable public health, healthcare, veterinary health, and laboratory partners to better detect resistance and more quickly respond to outbreaks, containing spread and reducing resistant infections.

Surveillance of Human Pathogens

As of April 1, 2018, 776 out of the over 5,500 U.S. hospitals have voluntarily reported antibiotic use data and 317 hospitals have reported antibiotic resistance data to NHSN's Antibiotic Use and Resistance (AUR) module, which began accepting AU data in July 2011 and AR data in July 2014. Through a CDC partnership with the VA and DOD designed to facilitate AUR reporting, 84 VA hospitals and 24 DoD hospitals have reported antibiotic use data, and 18 DoD hospitals have reported antibiotic resistance data. CDC is also working with partners in Missouri, the first state to pass legislation requiring all hospitals to report antibiotic use and resistance data through the NHSN AUR module and establish antibiotic stewardship programs. As more hospitals report antibiotic use and resistance data to NHSN's AUR module, our ability to assess hospital antibiotic use and resistance and to direct associated antibiotic stewardship programs and prevention actions across the nation will increase.

CDC is working with public health, healthcare, and informatics partners to improve the NHSN's Antimicrobial Use Measure, develop implementation tools, and promote reporting at the state and local levels. *In January 2018, CDC added a way for hospitals to visualize their NHSN antibiotic use data in detail so that they can identify specific gaps and direct stewardship solutions.* CDC is also working with the Vermont Oxford Network to develop antibiotic use measures for neonatal patient care locations, which would update the Antimicrobial Use Measure

already endorsed by the National Quality Forum. In early 2017, CDC worked with the HHS Office of the National Coordinator for Health Information Technology (ONC) to finalize an online tool that software developers can use to validate their files to meet the ONC Health IT Certification Program for NHSN Antimicrobial Use and Resistance reporting. In March 2018, CDC began work on updating pediatric and adult antibiotic use measures in a collaboration with a variety of experts.

Federal agencies continue to collaborate on improving open data access tools and reports:

- CDC released three HAI/AR data reports to assess prevention progress while strategizing about the best way to move forward nationally:
 - Healthcare-associated Infections in the United States, 2006-2016: A Story of Progress uses NHSN, EIP, and HAI prevalence survey data to examine the nation's progress over 10 years preventing five of the most common infections and next steps.
 - Additional technical reports describe surveillance protocol changes, and HAI/AR data following those changes.
- The 2015 National Antimicrobial Resistance Monitoring System (NARMS) Integrated Report, released by CDC, FDA, and USDA in October 2017, highlights antimicrobial resistance patterns in foodborne bacteria isolated from people, meats purchased from grocery stores, and animals at slaughter. The report includes information about resistance genes for *Salmonella* and some *Campylobacter* isolates using whole genome sequence data.
- *CDC's NARMS Now: Human Data makes NARMS data publicly available within three months from time of submission and testing, a significant improvement from the original reporting time of 18 months.*
- CDC's Antibiotic Resistance Patient Safety Atlas now includes data on outpatient antibiotic prescriptions, 2011–2015, and hospital antibiotic stewardship programs meeting all CDC Core Elements, 2014–2016. The 2016 State HAI Progress Reports will be posted in summer 2018. CDC also plans a major facelift of the Atlas in 2018 to improve user experience.
- CDC's Antibiotic Resistance Investment Map is updated with CDC's activities in FY 2017 to meet national goals to prevent drug-resistant infections through CDC's AR Solutions Initiative.

Through the AR Lab Network (ARLN), CDC supports seven regional laboratories with specialized capabilities to rapidly detect and identify emerging antibiotic resistant threats. This capacity includes CRE testing, CRE colonization screening, and targeted surveillance of emerging threats, such as antifungal resistance in *Candida auris*, *mcr-1*-mediated colistin resistance, and carbapenem-resistant *Acinetobacter*. 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 2017, CDC added an additional regional lab to serve as a national center for molecular surveillance of *Mycobacterium tuberculosis*. CDC and DoD are also working to include the MRSN/Antibiotic Resistance Monitoring and Research Program (ARMoR) program as an ARLN regional hub. DoD has provided written guidance for how military healthcare facilities, MRSN, regional laboratories, and CDC will interact when emerging AR threats or trends are identified. In addition to this regional lab detection capacity, every state public health lab is now able to test for CRE.

As of February 2018, the ARLN has tested 6,690 isolates of CRE or carbapenem-resistant Pseudomonas aeruginosa; 1,142 specimens for CRE colonization; 9,083 isolates of Neisseria

gonorrhoeae, an average monthly increase of 148 percent when compared to 2016; 518 isolates of *Candida* species; 189 specimens for *C. auris* colonization; and 510 isolates of *C. difficile*. These data have led to response activities where state and local health departments worked with facilities to stop the spread of resistance, and further enhance surveillance of resistant strains, monitor emerging resistance, and validate molecular detection methods. CDC also shares whole genome sequences in the National Library of Medicine's National Center for Biotechnology Information (NLM/NCBI) at the National Institutes of Health (NIH) for public access. CDC and ARLN share test results with states and submitting hospitals and nursing homes to direct infection prevention, control, and treatment measures. CDC has worked with the Association of Public Health Laboratories (APHL) to implement an informatics solution to ensure that CDC and labs can securely transfer lab test data and results.

As detection and data tracking methods improve, CDC identifies emerging resistance that must be contained through rapid response. CDC is working with health departments, hospitals, and healthcare societies to stop the spread of organisms with "unusual resistance" in the United States. Examples of recent emerging or unusual antibiotic resistance include the following:

- *C. auris* is a new and emerging "fungal superbug" that is resistant to many antifungal medications and can spread between patients in hospitals and nursing homes. Approximately 30 percent of patients with *C. auris* infections have died within 30 days. *C. auris* has already become a major problem globally and, by February 2018, had gained a foothold in the U.S. with 233 confirmed clinical cases in 10 states. CDC continues to provide guidance, public education, and laboratory and investigative support to prevent this fungus from becoming widespread in U.S. healthcare facilities as it has in other countries.
- In its first nine months of testing, CDC's AR Lab Network identified more than 220 instances of unusual resistance genes in "nightmare bacteria" CRE and carbapenem-resistant *Pseudomonas aeruginosa*. These germs are especially concerning because they carry genes that are rare but can make them resistant to all antibiotics, or have a special gene that allows them to easily spread their resistance to other bacteria.
- Cases and clusters of antibiotic-resistant *Shigella* have been identified among men who have sex with men, highlighting the need for more data to inform prevention and control strategies. New CDC data, expected by the end of 2018, will describe shigellosis in this community and will be used to guide the development of focused health communication messaging to reach those at risk.

The CDC and FDA Antibiotic Resistance Isolate Bank now contains 580 unique isolates and 16 panels curated from CDC's collection of more than 450,000 isolates, representing bacterial pathogens associated with known or emerging resistance mechanisms, such as colistin resistance. CDC has received and filled 1,018 isolate orders with nearly 96,000 shipped to U.S. institutions including diagnostic test manufacturers, academic researchers, and pharmaceutical companies. In March 2018, CDC launched a redesigned website to simplify isolate ordering and order processing. These isolates can be used for research and development efforts directed toward understanding, preventing, and combating AMR.

CDC is supporting capacity in 44 states to implement whole genome sequencing of Salmonella and other enteric pathogens, and all states are on track to have this testing capacity by summer 2018. States are increasingly submitting representative isolates from foodborne outbreaks to CDC-NARMS, now supporting investigations of more than 150 foodborne disease clusters per

year. When PulseNet identifies a multistate outbreak, these sequences allow CDC to quickly analyze isolates and report on susceptibility. These foundational tools will ensure progress towards decreasing the time to detect and characterize resistant pathogens. CDC itself has sequenced over 40,000 isolates, including resistant pathogens causing healthcare-associated infections and resistant enteric pathogens *Salmonella*, *Shigella*, *Campylobacter* and *Escherichia coli* O157, and deposited those whole genome sequences in NLM/NCBI for public access.

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 2018 to include more sites conducting surveillance for invasive *Staphylococcus aureus* infections, candidemia, CRE, carbapenem-resistant *Pseudomonas*, extended-spectrum beta-lactamase producing gram-negative bacteria, and sepsis. EIP completed a point prevalence survey of healthcare associated infections and antibiotic use in 200 acute care hospitals with more than 10,000 patients, and preliminary results indicate that the percentage of patients in acute care hospitals with an HAI has decreased approximately 20 percent overall compared to a similar survey in 2011. EIP also completed a large HAI and antibiotic use survey in more than 160 nursing homes with 15,000 residents. Data from these surveys will be publicly available by the end of 2018.

CDC is working with state health department, academic, and public health partners to examine risk factors related to resistant *Salmonella*, *Shigella*, and *Campylobacter* infections, such as prior antibiotic use, time spent in healthcare settings, and recent food intake, to improve routine surveillance for enteric pathogens. Notable shifts in susceptibility values and emergence of resistance mechanisms that are identified from CDC NARMS isolates and surveillance are shared with Clinical and Laboratory Standards Institute (CLSI) to help support their decisions on clinical breakpoint settings and cutoff values for emerging resistance.

As part of the NARMS program, FDA increased the number of retail meats tested from 6,700 per year in 2015 to 18,240 samples in 2018. The 2018 expansion includes addition of two new testing sites in North Carolina and Los Angeles. All *Salmonella* and *Campylobacter* isolates and every other *E. coli* isolate collected from the retail meat program are now subjected to whole genome sequencing (WGS), with results published in NLM/NCBI. Furthermore, as of January 2018, NARMS increased the number of sites conducting tests to identify *Enterococcus* and *E. coli* from 4 to 13 and 4 to 11 sites, respectively. Since 2016, geographic representation increased from 14 to 21 states. In addition, NARMS is working with state laboratories to assume the WGS testing to help achieve more real-time testing of the bacteria under surveillance.

A subcommittee of the FDA Science Board reviewed the NARMS program in June 2017, and several recommendations were presented as guidance for future enhancements to the program. These recommendations served as the basis of a NARMS public meeting held in October 2017 to examine the scientific and logistical challenges associated with broadening the scope of NARMS within the One Health framework.

FDA published the 2015 NARMS Integrated Report in October 2017. The new report was simplified by streamlining the narrative and enhanced by adding a second suite of interactive data displays, called [NARMS Now: Integrated Data](#), to convey WGS results for *Salmonella*. Stakeholders can explore: (a) changes in resistance genes among retail meat isolates, (b)

distribution of resistance genes among isolates from all NARMS sources, (c) distribution of resistance genes by serotype, and (d) comparison of resistance genes by serotype and source. FDA will produce additional interactive interfaces with the next release of the Integrated Report to convey WGS for *Campylobacter* and *E. coli* and other resistance trend information.

In November 2017, FDA announced the release of [Resistome Tracker](#), a tool that can be used to monitor antibiotic resistance alleles present in the genomes of microorganisms submitted to NLM/NCBI from around the world. While the first iteration of Resistome Tracker contains only *Salmonella* genomes, future iterations will include other foodborne and non-foodborne bacteria.

NIH in partnership with FDA and CDC, is expanding the NIH [National Database of Resistant Pathogens](#). The web-based open-access database, developed by NLM/NCBI, contains genomic data for more than 205,000 pathogen isolates collected from publicly available information. The database includes information on high priority bacterial threats such as *Acinetobacter*, *Klebsiella*, *Pseudomonas*, and isolates containing genes known to confer antibiotic resistance (e.g., mobile colistin resistance [*mcr*] and *Klebsiella pneumoniae* carbapenemase [KPC]) and can be searched by resistance genotypes, and, when available, antibiotic susceptibility phenotype. In addition, NIH and CDC continue to sequence high priority reference strains, as identified by CDC and FDA, to inform the development of new diagnostic tests and drugs. NIH's National Institute of Allergy and Infectious Diseases (NIAID) and National Human Genome Research Institute (NHGRI) completed 100 high quality reference genomes over two years (as of March 2018). By June 2019, NIH/NIAID and NIH/NHGRI will complete sequencing of at least 150 additional high quality reference genomes. Genome sequence data are rapidly released to the public through the database [GenBank](#) (published by NLM/NCBI) and the NIH/NIAID-funded Bioinformatics Resource Center, PATRIC ([Pathosystems Resource Integration Center](#)). PATRIC contains data for more than 136,000 bacterial genomes and more than 120 different antibiotics. NLM/NCBI has developed the Bacterial Antimicrobial Resistance Reference Gene Database, which is a comprehensive, highly curated, reference set of over 4,500 resistance genes, and which serves as an authoritative gene nomenclature reference for several important classes of key resistance genes (e.g., mobile colistin resistance, *mcr*). This database serves as the basis of NLM/NCBI's AMRFinder, a publicly available software tool that identifies resistance genes in genomic sequence, and which also is used to identify resistance genes in genomes submitted to NLM/NCBI. Scientists from all over the world can access and leverage these databases to foster understanding of resistance mechanisms and inform development of improved diagnostics, therapeutics, vaccines, and antimicrobial strategies.

DoD has made available multiple characterized pathogen panels for use in the development of diagnostics and therapeutics. *As of June 2018, the DoD repository houses nearly 56,000 characterized pathogen panels, with this number roughly increasing by 1000 per month.* Of that 56,000 isolate repository, 100-isolate pathogen panels exist for *Pseudomonas*, *Acinetobacter*, and *Klebsiella* isolates with the remainder of ESKAPE pathogen panels complete within the year. Over 1.3 million tests have been performed on these isolates as of May, 2018. Examples of the utility of these panels include an analysis that characterized 49 *C. difficile* isolates from one healthcare facility, which suggested that a low likelihood of nosocomial transmission followed by a diagnostic stewardship intervention resulted in a sustained decrease in the facility onset *C. difficile* rate for 12 months.

The VA has an ongoing initiative dedicated to enrollment in the National Healthcare Safety Network's (NHSN) Antimicrobial Use (AU) Option. To date, nearly eighty percent of VHA acute care facilities have enrolled and submitted data to the NHSN's AU Option and VHA is developing an action plan to complete enrollment of all facilities.

Surveillance of Animal Pathogens

In 2017, APHIS' Center for Epidemiology and Animal Health (CEAH) conducted antimicrobial-use studies on swine operations and cattle feedlots, during which producers and operators completed questionnaires on stewardship practices, operation inventory, and antimicrobials used in 2016. Survey results will be released in 2018. CEAH is also collecting data on antimicrobial use and resistance in cow-calf operations as a component of the National Animal Health Monitoring System (NAHMS) 2017 national cow-calf study. CEAH continues to work with stakeholders in planning for on-farm longitudinal studies of antimicrobial use and resistance on swine operations and cattle feedlots.

USDA APHIS launched an AR pilot project in FY 2018, with the primary goals of monitoring AR profiles in animal pathogens from veterinary diagnostic laboratories across the U.S. using standard test methods, and developing standardized antimicrobial data transmission and sharing processes. Nineteen veterinary diagnostic laboratories from across the U.S. are enrolled in the initial year of the project, which is focused on gathering antimicrobial susceptibility testing data from six animal species (cattle, swine, poultry, horses, dogs and cats) and four bacterial pathogens (*E. coli*, *Salmonella*, *Mannheimia haemolytica* and *Staphylococcus pseudintermedius*). *As of June 2018, data from approximately 1200 isolates have been submitted to USDA APHIS since the project began in January 2018.* USDA APHIS is developing a standardized electronic messaging format for sharing antimicrobial susceptibility data, based on the Health Level 7 (HL7) standards.

USDA APHIS developed a pilot proficiency test (PT) for antimicrobial susceptibility testing (AST) in FY2018. This pilot proficiency test seeks to assess the consistency and improve the standardization of AST reporting and interpretations in veterinary diagnostic laboratories. USDA APHIS personnel will evaluate the results of this pilot PT, report summary data, and work with the 39 participating laboratories to achieve more consistent results and improve testing as necessary. The isolates used in the 2018 pilot PT were obtained from the FDA through a material transfer agreement; subsequent graded AST PTs will be developed using clinical isolates from the National Veterinary Services Laboratories (NVSL) AR bacterial repositories.

In FY2018, work began to leverage the *Salmonella* samples in the NVSL clinical isolate repository to further evaluate the prevalence of AR, pairing phenotypic AST via broth microdilution with genotypic AST via WGS. The samples originated from common domesticated species (cats, cattle, chickens, dogs, ducks, goats, horses, pigs, sheep, and turkeys) and *Salmonella* serotypes of particular interest as both zoonotic pathogens and pathogens of economic importance to animal industry. *Testing of the isolates began in February 2018; over 800 isolates have completed phenotypic AST and approximately 300 of those isolates have undergone paired WGS.* The data are being collated and analyzed for trends as well as to further validate the use of WGS as the primary surveillance tool for AR in *Salmonella* isolates.

CY 2017 USDA's Food Safety and Inspection Service (FSIS) continued to expand the species and commodities to test for regulated pathogens and subject 100 percent of pathogen isolates, including *Salmonella*, *Campylobacter* and Shiga toxin-producing *Escherichia coli* (STEC) originating from regulatory samples to WGS and further characterization. In addition, all the *Salmonella*, *Campylobacter*, *E. coli* and *Enterococcus* isolated from the regulatory and NARMS cecal surveillance programs were subject to phenotypic AST. FSIS also started conducting WGS on a small fraction of *E. coli* and *Enterococcus* spp. FSIS included AR as one of the harmful traits for considering expanded investigation and/or testing (*Federal Register* Notice 81 FR 7285) under certain circumstances.

USDA-FSIS continued to partner with FDA, CDC, USDA-Agricultural Research Service (ARS), APHIS, and NLM/NCBI, under the umbrella of the "Gen-FS" consortium. The primary function of Gen-FS is to coordinate, strengthen, and lead U.S. WGS efforts among Federal and State partners and further improve public health. This interagency group is steered by agency leaders to focus on crosscutting priorities for molecular sequencing of foodborne and other zoonotic pathogens causing human illness, for data collection and analysis including AR, and to use this information to support surveillance and outbreak investigation activities. One of the focus areas under Gen-FS is genetic determinants of AR and their spread.

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

NIH and the Biomedical Advanced Research and Development Authority (BARDA), within the HHS Office of the Assistant Secretary for Preparedness and Response, continue progress on the [Antimicrobial Resistance Diagnostic Challenge](#), which launched in September 2016. The goal of this Challenge competition is to incentivize the development of rapid, point-of-need in vitro diagnostics that detect and distinguish antibiotic resistant bacteria and improve antibiotic stewardship. This 3-Step competition was developed with technical and regulatory expertise from CDC and FDA, as well as public input. *In 2017, [ten semi-finalists](#) for Step 1 of this competition received \$50,000 each to develop concepts into prototypes.* Letters of intent for submission to Step 2 are due no later than August 3, 2018, and submissions must be made by September 4, 2018. NIH and BARDA have each contributed \$10 million to support the Diagnostic Challenge. In addition, CARB-X is currently supporting the development of six rapid and innovative diagnostics to identify resistant bacteria. CARB-X is a five-year \$500 million public private partnership between BARDA, NIH/NIAID, Wellcome Trust, the UK Government, and the Bill & Melinda Gates Foundation, tasked with accelerating global antibacterial innovation and transition antibacterial products into clinical development. The full CARB-X portfolio is available [online](#).

BARDA continues to invest in its AMR diagnostics portfolio, adding additional awardees. An effort by Roche Molecular Systems to develop *C. difficile* and MRSA assays for use on the Liat point of care instrument platform is partially funded by BARDA through its Other Transactions Authority. Roche has launched these products in the European Economic area and other CE-markets. On September 12, 2017, Roche received FDA 510K clearance for their *C. difficile* assay on the Liat platform.

NIH continues to support an extensive portfolio of research projects to improve the diagnosis of bacterial infections. With NIH/NIAID support, scientists are developing and testing new tools to rapidly detect bacteria and determine their sensitivity and/or resistance to antibiotics at the patient point-of-care. In addition to ongoing grant opportunities and Small Business Innovation Research awards, NIH/NIAID has issued and supported numerous [targeted solicitations](#) to foster the development of innovative diagnostic tests for AMR pathogens. *In 2015, NIH/NIAID funded [nine projects](#) to develop tools to detect hospital-associated pathogens ([RFA-AI-14-019](#)). Among these ongoing projects, one team is exploring whether diagnostic tests can rapidly detect Enterobacteriaceae directly from blood samples. To rapidly determine antibiotic susceptibility, another research team is developing a [platform](#) that reduces the time needed to detect bacterial growth. As of June 2018, NIH/NIAID awarded three projects to support development of new diagnostic platforms for bacterial pathogens listed in the [CDC's Antibiotic Resistance Threats in the United States, 2013 report](#) ([RFA-AI-17-014](#)).*

The NIH/NIAID-supported Antibacterial Resistance Leadership Group (ARLG) is pioneering a robust clinical research agenda on antibacterial resistance, including novel diagnostics. In collaboration with industry and the NIH/NIAID-supported Vaccine and Treatment Evaluation Units, the ARLG is conducting a [clinical trial](#) assessing whether blood levels of the protein, procalcitonin, could help inform appropriate treatment for patients with lower respiratory tract infections. The ARLG is also [collaborating](#) with multiple diagnostics companies to implement a master diagnostics protocol, through which multiple diagnostic tests for *N. gonorrhoeae* and *Chlamydia trachomatis* can be validated simultaneously using specimens from the same patients.

Since October 2016, CDC has awarded more than \$32.5 million to pilot innovative solutions and explore knowledge gaps about how antibiotic resistance spreads to and between humans, including research on how the human microbiome can be used to predict and prevent infections caused by drug-resistant organisms and antibiotic resistance in the environment. CDC also continues to work with federal partners to consider the risk of using antibiotics, typically used in human medicine as pesticides in agriculture. CDC and FDA provided consultation to the Environmental Protection Agency (EPA) on the use of streptomycin and oxytetracycline to treat huanglongbing disease in citrus crops. CDC shared ideas with the U.S. Geological Survey on antibiotics and resistance genes for environmental monitoring and explored ways to share information on existing sampling and surveillance. CDC continues to provide isolates from the CDC and FDA AR Isolate Bank to test for cross-resistance between antibiotics commonly used in human medicine and antibiotics approved for use as pesticides.

In April 2018, the CDC, UK government, and the Wellcome Trust organized a meeting to discuss the impact of antibiotic resistant bacteria and antibiotics in the environment on human health. One topic at this meeting was the impact of using antibiotics as pesticides and outlining what is known and what investigations are still needed. EPA has an ongoing process that includes both CDC and FDA to evaluate the potential impact of antibiotic agricultural plant pesticides on resistance. EPA works with both CDC and FDA on the conclusions of the analysis, and determines whether any mitigation measures could reduce the potential to develop resistance or whether monitoring is needed to detect any resistance that may be developing. EPA expects to continue these discussions during the upcoming registration review of existing antibiotic pesticide registrations. During this review, which includes multiple opportunities for public

comment, EPA will evaluate streptomycin and oxytetracycline pesticides registered as of October 1, 2007. These interagency discussions and collaborations help to reduce the risk of resistance to human antibiotic drugs from the use of antibiotics to control bacterial pests on agricultural crops.

DoD's Austere environments Consortium for Enhanced Sepsis Outcomes (ACESO) investigates the pathogenesis and management of sepsis in operationally relevant environments. ACESO has established a platform with the ability to conduct clinical research at multiple sites in Southeast Asia and Africa. With support from the CARB program, ACESO has enrolled 204 severely ill patients in Ghana and 422 patients in Cambodia to date. A central component of ACESO's research involves the discovery and subsequent validation of host-based biomarkers that can be translated to point-of-care diagnostic devices for early characterization of severe infections. To achieve this, ACESO incorporates novel next-generation nucleic acid sequencing and analysis approaches to provide data on both the pathogen identity and the host-response. Sequencing from patient samples has directly promoted the identification of pathogens including Dengue and *Orientia tsutsugamushi* (Scrub typhus) through increased sensitivity or when appropriate serological samples are unavailable.

Results obtained using the Empowering the Development of Genomics Expertise (EDGE) platform are used to complement results from clinical adjudication to provide additional insight into the infecting pathogen. The analysis of RNAseq data to discriminate patients with bacterial infections from patients with other infectious etiologies as well as to predict treatment failure is ongoing, and will be complete in 2018.

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

BARDA is currently supporting the research, development and/or progress toward regulatory approval of 45 promising antibacterial products, eight of which have advanced into Phase 3 clinical development addressing the most urgent and serious threats to public health due to antimicrobial resistance as determined in 2013 by the CDC. In August 2017, Vabomere, which was developed by the Medicines Company with demonstrated activity against some types of CRE, became the first BARDA-supported antibiotic to be approved for use by the FDA for the treatment of complicated urinary tract infections. In September 2017, BARDA entered into two new public-private partnerships: with Achaogen for the research and development of C-scape, a combination of two previously approved oral antibiotics for treatment of complicated urinary tract infections; and with Summit Therapeutics to develop a novel oral antibiotic to prevent and treat infection due to *C. difficile*. In December 2017, a New Drug Application for Eravacycline, developed by Cubrc/Tetraphase for the treatment of complicated intra-abdominal infections was submitted to the FDA with decision expected in August 2018. In June 2018, the FDA approved ZEMRI (Plazomicin) developed by Achaogen and supported by BARDA since 2010. ZEMRI was approved to treat complicated urinary tract infections due to drug-resistant bacteria. The company has also generated significant data to support the potential use of ZEMRI for treatment of blood stream infections but this indication is not on the label. ZEMRI is the second BARDA-supported antimicrobial product to achieve FDA approval.

Support continues for CARB-X, established by NIH/NIAID and BARDA in 2016 through a cooperative agreement with Boston University. CARB-X expanded in 2018, when the UK Government and Bill & Melinda Gates Foundation joined the effort with a combined \$50 million commitment. CARB-X is now a \$500 million five-year public private partnership funded by BARDA, NIH/NIAID, Wellcome Trust, the UK Government, and Bill & Melinda Gates Foundation. *In less than 2 years, the CARB-X portfolio has expanded to include 33 antibacterial products, including antibacterial drugs, vaccines, diagnostics and non-traditional products, including 10 new antibiotics classes.* For every \$1 CARB-X has invested in early development and Phase 1 clinical trials, follow-on private capital has invested \$7, for a total of \$548M. *Since the inception of the program, NIH/NIAID has provided technical support and [preclinical drug development services](#) to more than half of CARB-X awardees to further advance the development of new products. NIH/NIAID provided previous support to ~50 percent of companies that have now received a CARB-X award (as of April 2018). NIH/NIAID's historical support has helped small companies strengthen their product development skills, including growing and advancing their portfolios of antibacterial products.* The full CARB-X portfolio is available [online](#).

As part of its long-term investment in AMR research, NIH continues to make significant progress through a robust portfolio spanning basic, translational, and clinical research. Investigators in NIH/NIAID's Centers of Excellence for Translational Research (CETR) program are helping to discover novel antimicrobial compounds, including a [new class of antibiotics](#) (known as malacidins) found in soil. NIH/NIAID also supports research on innovative alternatives to antibiotics, including bacteriophages (viruses that can attack and destroy harmful bacteria) and microbiome-based approaches. NIH/NIAID-supported scientists are working to identify protective bacterial strains and formulate them into products to prevent and treat *C. difficile* infection. In March 2018, NIH/NIAID issued two funding opportunities ([PA-18-724](#) and [PA-18-725](#)) to advance research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease, as well as research exploring combination antibiotic therapies to address the emergence of resistance.

NIH support also helps investigators advance potential new drugs from the conceptual stage through early clinical testing. For example, NIH/NIAID has supported preclinical development, investigational new drug submissions, and six Phase 1 clinical trials for the novel tetracycline [TP-271](#) and beta-lactamase inhibitor [VNRX-5133](#). Both of these products have broad-spectrum activity against multiple bacteria, including difficult-to-treat gram-negative strains. To address additional AMR threats, NIH/NIAID-supported scientists conducted Phase 1 clinical testing for a new class of antibiotics ([clinical trials; publication](#)) intended to treat *C. difficile* and completed enrollment for a Phase 1 trial evaluating a novel oral antibiotic ([zoliflodacin](#)) intended to treat gonorrhea. Zoliflodacin is progressing to a global Phase 3 clinical trial sponsored by the Global Antibiotic Research and Development Partnership/Drugs for Neglected Diseases initiative.

In addition to evaluating new antibiotic candidates, NIH/NIAID's clinical research portfolio includes clinical trials assessing novel formulations and combinations of existing antibiotics. NIH/NIAID is supporting research on the intravenous formulation of the broad-spectrum antibiotic fosfomycin (also known as ZOLYD™), which is not currently available in the U.S. NIH/NIAID's investment in preclinical and [early clinical testing of this drug](#) enabled a small company to complete a successful Phase 2/3 clinical trial. This study assessed ZOLYD's™ effectiveness as a treatment for hospitalized patients with complicated urinary tract infections or

acute pyelonephritis. In addition, the ARLG is exploring novel treatment regimens comprised of licensed antibiotics. In January 2017, the ARLG [reported](#) that ceftazidime-avibactam may be a reasonable alternative to colistin to treat KPC-producing CRE infections.

Preventive strategies, such as vaccines, are important tools to complement therapeutic approaches and keep pace with the increasing threat of AMR. NIH/NIAID is supporting early development of several vaccine candidates for *C. difficile* and *N. gonorrhoeae*. In 2018, NIH/NIAID funded three projects for vaccine and immunoprophylactics (products that harness the immune system to prevent disease) targeting AMR gram-negative bacteria in healthcare settings ([RFA-AI-17-017](#)). NIH/NIAID is also supporting research exploring monoclonal antibodies for prevention of bacterial infections.

CDC, in collaboration with the New Vaccine Surveillance Network, is evaluating the lower intestinal microbiome of 200-300 healthy children to address sources and prevention of antibiotic resistance genes. As part of its continued efforts to protect patients, CDC is using new metagenomics tools to identify resistance within the full stool resistome. CDC surveillance data and analyses are also being used by private companies to assist vaccine development and support trial design. Vaccines against *Staphylococcus aureus* and *C. difficile* are now in Phase 3 trials.

To support development of bacteriophage therapies, FDA and NIH/NIAID co-hosted a workshop on July 10-11, 2017, [Bacteriophage Therapy: Scientific and Regulatory Issues Public Workshop](#). With NIH/NIAID support, FDA scientists have developed mouse models for assessment of bacteriophage-based approaches towards decolonization of vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus aureus*, and for assessment of mechanisms of action of fecal microbial transplantation against *C. difficile*. To support safety evaluation of fecal microbiota transplantation, FDA scientists have completed an assessment of sensitivity of *C. difficile* screening assays. Starting in 2015, NIH/NIAID entered an Interagency Agreement with FDA to address key regulatory considerations related to using bacteriophages for decolonization of vancomycin-resistant enterococci and MRSA. FDA scientists have also identified that a MAIT knock-out mouse model has a microbiota structure that is highly resistant to *C. difficile* colonization, independent of all antibiotic treatments tested to date. Ongoing studies are using this model to identify specific families that appear to contribute to the phenotype.

FDA continues to advance the science of animal models of infection to support development of new antibacterial drugs. In fiscal year 2017, FDA [awarded contracts](#) through a [Broad Agency Announcement](#) (FDABAA-17-00123N) to advance the development of animal models of serious infections caused by *Acinetobacter baumannii* or *Pseudomonas aeruginosa*.

In June 2018, FDA issued the [draft guidance](#), “Limited Population Pathway for Antibacterial and Antifungal Drugs,” describing the criteria, processes and other general considerations for drugs seeking approval under the limited population antibacterial drug (LPAD) pathway, which was established by the 21st Century Cures Act. LPAD is designed to facilitate the development and approval of antibacterial and antifungal drugs intended to treat serious and life-threatening infections in a limited population of patients with unmet needs.

Walter Reed Army Institute of Research (WRAIR) has created a 15-project portfolio with academic, federal, and pharmaceutical partners to advance candidates. Notably, the WRAIR

partnership with the NIH National Center for Advancing Translational Sciences (NCATS) identified a promising lead against *Klebsiella pneumoniae* as well as providing knowledge to train physicians for a new combination therapy approach.

USDA-ARS continues to implement alternatives-to-antibiotics R&D projects, including products that could reduce the need for agricultural use of medically important antibiotics through vaccines, bacterial-derived products, immune-related products, phytochemicals, and other chemicals and enzymes. ARS researchers are also continuing to explore the impact of different cattle production methods on [occurrence of AR](#), and on-farm manure management strategies to reduce the need for antibiotic use, and reduce the occurrence of resistant bacteria and genes in the environment. Strategies include evaluation of composting, land application strategies, hydrothermal processing, biochar, and constructed wetlands. ARS researchers in Peoria, IL have discovered a way to modify tunicamycin to minimize its toxicity to human and animal cells, but retain its ability as an antibiotic, and have also enhanced the effectiveness of other penicillins by using [tunicamycin in concert](#).

The USDA APHIS Center for Veterinary Biologics continues to develop fast track conditional licenses that have full purity, identity, and safety requirements, but lack definitive efficacy data for full licensure, through the use of platform technologies and prescription products (which are a derivative of platform technologies). In 2018, draft memos for comment were published that further define both platform products and prescription products.

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

In Year Three, the United States built upon the initial approach established in Years One and Two to garner sustained political support and efforts by working with G7 partner countries under Italy's leadership to prioritize AMR in the Health Track and to harmonize definitions of use by the Chief Veterinary Officers in the Agriculture track. The United States is a founding member of the Global AMR Research & Development (R&D) Hub, which was called for in the 2017 G20 Leader's statement to coordinate and collaborate with fellow donor countries and foundations on AMR R&D. The HHS Office of Global Affairs (OGA) holds a seat on the board and continues to advocate for the U.S. Government (USG) approach to R&D and economic incentives.

To fulfill the commitment to establish an International Stakeholders group, members of the USG participated in multiple fora and conferences with international partners including: the Global Health Security Agenda (GHSA) AMR Action Package, Transatlantic Task Force on Antimicrobial Resistance (TATFAR), the UK- and Wellcome Trust-sponsored Call to Action meeting, Prince Mahidol Award Conference, Center for Strategic and International Studies sponsored meetings on "Winning the Fight Against Drug Resistance" and Protecting Health Security, World Health Summit, and United Nations General Assembly side events on Spurious and Falsified medicines and Stewardship. In addition, OGA facilitated bilateral meetings where AMR was a priority topic of discussion between HHS and the Ministries of Health from the European Union (E.U.), Netherlands, Japan, Canada, and Argentina. In July 2017, OGA hosted leaders from the World Health Organization (WHO) for a discussion on policy and efforts with the CARB Task Force members. A second visit with WHO principals was hosted in March 2018

to introduce new WHO leadership on AMR to HHS and USDA principals.

TATFAR continued its efforts to advance action to combat AMR and coordinate among the United States, the E.U., Canada, and Norway by hosting its second in-person open meeting in Atlanta, GA in March 2018. The meeting included government agency representatives along with other leading experts on AMR. The meeting's keynote opening speakers were Xavier Prats-Monné, Director General for Health and Food Safety within the European Commission, and Anne Schuchat, Acting Director for U.S. CDC, and Acting Administrator of the Agency for Toxic Substances and Disease Registry, U.S. CDC. In Year Three, TATFAR also hosted its first policy dialog videoconference where members compared and contrasted their national action plans in order to learn from each other and share best practices.

Through TATFAR, CDC, FDA, and DoD have worked with the E.U., Canada, and Norway to develop guidance for assessing appropriateness of human antibiotic use and a review of antibiotic reduction goals in TATFAR countries, provide consultation and collaborate on point-prevalence surveys, and harmonize surveillance practices. The USDA became a TATFAR Member in 2017. The U.S. and E.U. have harmonized breakpoint definitions for colistin and gram-negative bacteria (*Enterobacteriaceae*, *Acinetobacter* spp. and *Pseudomonas aeruginosa*) and identified priority areas for harmonization moving forward. In 2018, the Clinical and Laboratory Standards Institute (CLSI) will review data for *Neisseria gonorrhoeae* breakpoints, finalize the *Enterobacteriaceae* fluoroquinolone breakpoint decision, consider harmonization of test methods for *Streptococcus pneumoniae*, and establish a process for prospective harmonization of disk diffusion test methods of antimicrobial susceptibility testing. CDC, in collaboration with TATFAR partners, WHO, and non-TATFAR countries, also coordinates the U.S. Antibiotic Awareness Week, that coincides with other international observances.

NIH's engagement with TATFAR has facilitated alignment of U.S. and E.U. AMR research activities and greater access to critically important patient populations. NIH/NIAID is supporting a [Phase 3 clinical trial](#) evaluating the optimal use of an older antibiotic (colistin), alone or in combination with a carbapenem, in patients with multidrug-resistant (MDR) gram-negative infections. In 2017 and 2018, European clinical trials networks joined this trial. In addition, the ARLG is adding U.S. sites to ongoing international efforts supported by industry and the Brussels-based Innovative Medicines Initiative Joint Undertaking and the Combatting Antimicrobial Resistance in Europe (COMBACTE) consortium. This includes a [Phase 2 trial](#) evaluating an investigational monoclonal antibody to prevent pneumonia caused by *Pseudomonas aeruginosa*. NIH continues to engage new international partners and increase global research collaborations. For example, the ARLG is conducting an observational clinical study on CRE at sites in the U.S., Australia, South America, China, and Singapore.

As a part of TATFAR, USDA shared information related to regulatory, research and technical issues for addressing AMR in animal agriculture. Specifically, USDA APHIS VS Center for Veterinary Biologics explained US processes for veterinary vaccine approvals, USDA ARS held a panel session on alternatives to antibiotics at the 2018 TATFAR physical meeting, and USDA Office of the Chief Scientist initiated sharing information on antibiotic stewardship initiatives amongst TATFAR members.

In addition, NIH/NIAID is supporting several AMR sequencing and bioinformatics projects in Thailand and India to better understand molecular mechanisms of AMR and patterns of resistance. NIH/NIAID and the Indian Council of Medical Research are collaborating on a pilot project using genomics, bioinformatics and systems biology to compare MDR *Acinetobacter* strains from neonatal intensive care units in India and the U.S.

BARDA has continued to participate in an international collaboration with Pfizer and the Innovative Medicines Initiative focused on development toward regulatory approval of Aztreonam-Avibactam (ATM-AVI) for the treatment of bacterial infections caused by gram-negative pathogens, including MBL expressing multi-drug resistant bacteria. In May 2018, Pfizer initiated a Phase 3 registrational study (ReVisit) for the evaluation of ATM-AVI for the treatment of serious infections due to susceptible gram-negative bacteria, including MBL expressing multi-drug resistant bacteria.

CDC, both through engagement with the Global Health Security Agenda (GHSA) and through the Antibiotic Resistance Solutions Initiative (ARSI) aligned with the World Health Organization (WHO) Global Action Plan, supports the 17 Phase I countries and Thailand, Georgia, and CARICOM (Caribbean community) by providing technical assistance to ministries of health on national plans and policies for antibiotic resistance surveillance and infection prevention and control in healthcare facilities. CDC has worked with public health, laboratory, and global partners like the WHO to:

- Develop and deploy a laboratory assessment tool for AMR surveillance;
- Pilot tele-mentoring and training between U.S. and international clinical labs;
- Develop training resources for resource-limited settings;
- Provide tools to contain CRE in resource-limited settings, including a field guide for implementation of WHO core components for infection prevention and control, both released in 2017; and
- Support response to outbreaks of antibiotic resistant organisms.

In collaboration with a WHO working group, CDC has developed and tested an information sharing protocol and developed a WHO alert portal website that will go live in 2018. The protocol was shared with WHO member state consultation in April 2017 and tabletop-exercised in November 2017, resulting in positive feedback about the ease of communicating new resistance and sharing of technical expertise.

In addition, USAID supports infection prevention and control in selected at-risk health facilities in Guinea and Sierra Leone with GHSA and other Ebola funding to help prevent health care associated infections and the emergence of AMR. USAID also implements a pilot AMR stewardship program targeting the animal health sector in Senegal to promote the rational use of antibiotics in the livestock sector.

The Naval Medical Research Center (NMRC) supports the development of clinical and laboratory operations in strategically important locations in West Africa and Southeast Asia through ACESO. The ACESO protocol has implemented blood culture and antimicrobial susceptibility testing as standard practice for all enrolled patients to promote informed clinical interventions and to support global surveillance. For example, in Cambodia, ACESO works in collaboration with the Naval Medical Research Unit No. 2 (NAMRU-2) and Takeo Provincial

Referral Hospital to implement the observational protocol. Through this partnership, ACESO has improved identification, treatment and management of sepsis at Takeo through protocol specific training in clinical management of sepsis and microbiology in clinical practice. ACESO has facilitated advanced molecular and biological confirmatory testing of microbiological isolates from Takeo by leveraging NAMRU-2 capabilities.

In Ghana, ACESO has promoted microbiology infrastructure and capacity by supporting the maintenance and purchase of equipment including BACTEC blood culture systems, a microscope, centrifuges and biosafety cabinets. Additional onsite specimen laboratory testing protocols including rapid diagnostic assays have been trained-on and deployed in Ghana. ACESO also supports a collaboration between the American Society for Microbiology (ASM) and West African partners to validate chromogenic media approaches for bacterial identification that eliminates the need for sheep's blood, streamlines the identification process, and reduces overall cost. Implementation of these protocols will enhance antimicrobial stewardship by yielding earlier identification and sensitivity testing results for targeted therapy. As a result of these efforts, WHO pathogens of concern including methicillin resistant *Staphylococcus aureus* and *Escherichia coli* resistant to 3rd generation cephalosporins and to fluoroquinolones continue to be identified. Current ongoing efforts include the generation of genotypic data to complement AMR phenotypes as well as continued capacity building towards improved antibiotic stewardship.

The Global Emerging Infections Surveillance section of the Armed Forces Health Surveillance Branch-funded Global Mapping of Antimicrobial Resistance work by Georgetown University finalized WHO results for the Africa region. Country maps were created for each country in Africa. Strategy refinement is ongoing for 26 countries in Asia with a focus on SE Asian nations with data gaps.

FDA, USDA, and CDC continue to work with public health and international partners (APHL, TATFAR, WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance [AGISAR], The Food and Agriculture Organization of the United Nations [FAO], The World Organisation for Animal Health [OIE], International Health Regulations-Joint External Evaluation [IHR-JEE], and the World Bank) to optimize antibiotic use in animals, reduce antibiotic resistance, build consensus, harmonize methods, and improve surveillance. CDC NARMS, through WHO AGISAR, also supports work in Argentina to implement integrated antibiotic resistance surveillance in humans and poultry. CDC is also working with partners to collect data from international travelers on healthcare-associated and enteric disease infections, including risk factors and resistance characteristics.

FDA-CVM has collaborated with the Public Health Agency of Canada, USDA APHIS, and U.S. and Canadian representatives on the OIE Global Harmonized Database ad hoc group, regarding biomass correction, normalization denominators, antimicrobial sales and use data collection and reporting, and the OIE Global Harmonized Database reporting methods and formats. An interoffice working group conducted a case study of a U.S.-specific approach to applying a biomass correction to antimicrobial sales data to help identify challenges to harmonizing global AMR requirements. While this method will not produce values directly comparable to the EMA ESVAC method, it will be a biomass correction representing new animal drug approvals and animal population and weights in the U.S. FDA published the proposed biomass denominator

method in a Federal Register Notice in August of 2017 and is in the process of evaluating public comments received.

FDA-CVM supports regional capacity building of AR surveillance by supporting the WHO Global Action Plan (GAP) and is mentoring a project in Argentina to help implement an integrated surveillance program on AMR along the food chain. FDA is also contributing to the GAP through development and implementation of global integrated surveillance for ESBL-producing *E. coli* using a 'ONE Health' approach (role of environment, animals, and people). Further, FDA-CVM also supports the GAP by contributing to the WHO's Critically Important List of Antimicrobials for Human Medicine, a guideline used globally to encourage the prudent use of antimicrobials in both human and veterinary medicine.

In December 2016, ARS, in collaboration with NIH/NIAID and FDA and with the support of the World Organisation for Animal Health (OIE), organized the Second International Symposium on Alternatives to Antibiotics (ATA) Challenges and Solutions in Animal Production. So far, this meeting has led to one [publication](#) with authors from FDA and EMA, which highlights the regulatory pathways needed to enable licensing of alternatives to antibiotics.

In June 2017, the Codex Alimentarius Commission approved work for the Codex *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance within three to four years to develop international guidance on AR by: 1) updating the 2005 Code of Practice to Minimize and Contain AR; 2) drafting guidelines for integrated surveillance. The FDA and USDA led the U.S. Delegation to the Task Force chaired by the Republic of Korea, which met in November-December 2017 to [develop products](#). The USG provided leadership as Chair of the electronic working group (EWG) responsible for drafting revisions to the Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005) in preparation for the session and is continuing in that role in 2018 to further develop products for the next Task Force meeting in December 2018.

In December 2017, the U.S. Department of State worked with HHS, USDA, U.S. Department of the Interior, and other agencies to secure language regarding antibiotic pollution in the environment at the Third U.N. Environment Assembly in Nairobi. The language calls on the U.N. Environment Program Secretariat to work with other U.N. system agencies to support the strengthening of the evidence base regarding antibiotics in the environment, while also calling on member states to consider evidence-based policy measures.

From September 2017 to April 2018, the U.S. Department of State leveraged its "Diplomacy Lab" program to engage U.S.-based academic teams investigating 1) technologies for better sampling of antibiotic pollution in the environment and 2) awareness raising materials produced by WHO and others, to study their efficacy in conveying clear and accurate AMR information to non-scientific audiences.

USAID has worked to promote access to safe and effective medicines by strengthening pharmaceutical quality assurance and regulatory systems in several low- and middle-income countries. Notably, USAID, through the Promoting the Quality of Medicines (PQM) program has developed or updated 745 new quality assurance policies, procedures, or guidelines in Nigeria, Indonesia, Mozambique, and Ethiopia. USAID, working in Ethiopia, supported the

regulatory authority to expedite the review of dossiers, eliminate the backlog of new medicine applications, and reduce the registration lead time for fast-track medicines (medicines, including antibiotics, for public health priorities) from an average of 24 months to 4.5 months.

At Addis Ababa University, USAID supported a new Master's of Regulatory Affairs program to which 35 students have already been admitted. USAID also supported 66 national quality control laboratories (NQCLs) in low- and middle-income countries to work toward increasing compliance with international quality standards. Fifteen of these NCQLs achieved or maintained ISO 17025 or WHO Prequalification, or both.

USAID's PQM program worked with 62 manufacturers to improve the supply of quality-assured essential medicines, including antibiotics for tuberculosis (TB) and maternal, newborn, and child health. USAID support resulted in WHO Prequalification of manufacturers for seven products, including amoxicillin, cycloserine, streptomycin, and capreomycin.

In addition, USAID is working through a One Health approach with the Food and Agriculture Organization of the United Nations, and WHO in Asia and Africa, to develop a more comprehensive understanding of current patterns of antibiotic use and regulatory practices within the livestock and aquaculture industries. Through this One Health partnership, USAID is also promoting best practices and prudent use of antibiotics across the animal-health value chains. Presently USAID is working in 10 countries in Asia and 14 countries in Africa to strengthen One Health national AMR plans.

HIGHLIGHTS OF ADDITIONAL ACTIVITIES

MEETINGS, WORKGROUPS, and ADVISORY COUNCILS

The [Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria](#) (PACCARB) advises the HHS Secretary regarding programs and policies intended to support and evaluate the implementation of the CARB National Action Plan. To date, the PACCARB has held nine public meetings and hosted presentations from subject matter experts ranging from academia, industry, food, agricultural, and health associations, to international health organizations. PACCARB issued its second report on incentivizing the development of vaccines, diagnostics, and therapeutics to combat antibiotic-resistance in September 2017. In 2018, the PACCARB transmitted two letters with recommendations to the Secretary surrounding issues related to: the inclusion of AMR as part of a comprehensive national security strategy, and the need for sustained funding for federal research dedicated to antibiotic stewardship for both human and animal health. The PACCARB has since established a working group on Infection Prevention and Stewardship which has been tasked to identify best practices, the strategies for implementing those practices, and a path to augmenting the current and future workforce needed to sustain infection prevention and stewardship of antibiotics for human and animal health.

In September 2018, during the United Nations General Assembly (UNGA) week, OGA is planning, co-sponsoring and recruiting international governments, non-government organizations, and private sector partners for the AMR side event: "The AMR Challenge: Launch Event and One Health Solutions Showcase."

In May 2018, OGA supported Secretary Azar, Germany, and CARB-X at the World Health Assembly (WHA) for the Global AMR R&D Coordination Hub event, an initiative to promote research into combating AMR and inform and collaborate, on a global level, to promote investments into identified AMR R&D gaps. Finally, in collaboration with G20, OGA finalized the draft G20 Health Ministers' Declaration section on AMR, which was initiated at the G20 Health Ministers' meeting in Berlin 19th – 20th May 2017.

In March 2018, NIH/NIAID, the Bill & Melinda Gates Foundation and World Health Organization, organized the 2018 [Global Vaccine and Immunization Research Forum \(GVIRF\)](#), during which leading experts and diverse stakeholders discussed obstacles, gaps, and opportunities related to vaccine discovery, development, and delivery, including the role of vaccines in combating AMR.

In March 2017, FDA sponsored a workshop on “[Current State and Further Development of Animal Models of Serious Infections Caused by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*](#).” This workshop included an overview of the challenges with development of a new antibacterial drug targeting a single species, approaches to animal model development, and discussion of next steps and research priorities.

In September 2017, NIH/NIAID officials participated in a joint workshop with the Chinese Academy of Medical Sciences (CAMS) on the current state of knowledge and key bottlenecks to the development of new medical countermeasures to address AMR, and attended CAMS' 2017 International Forum on Gonococcal Infections and Resistance, which addressed research challenges, practice and policy, the epidemiology of drug-resistant *N. gonorrhoeae*, among other areas.

RESEARCH

CDC, in collaboration with the VA, has funded the CDC/VA Infection Control Research Network to evaluate high priority HAI/AR prevention focus areas in 15 VA medical centers and their affiliated skilled nursing facilities. Areas include the impact of antibiotic stewardship practices on CDI, diagnostic stewardship related to urinary tract infections, impact of UV-light systems for terminal room disinfection on CDI rates, and the impact of a human factors engineering approach to improve cleaning and disinfection by environmental service workers.

USDA-ARS is developing a high-throughput assay to determine susceptibility of *Salmonella* to 17 biocides. This method will be made publicly available for use by animal production facilities and for scientific inquiries. Biocide testing coupled with investigation of the genetics leading to AR will give a better understanding of the role of biocides in bacterial contamination of meat and development of antimicrobial resistance.

To date outcomes and potential impacts of USDA NIFA-funded AR projects include:

- Florida scientists working on cattle have discovered bacterial isolates exhibiting AR to the antibiotic cefotaxime that also exhibit AR to multiple other drugs. Most of the bacteria are neither primary human nor animal pathogens. They are of soil, commensal and environmental origin. So there is potential for carriage of cefotaxime resistance by food

animals having no history of cefotaxime exposure. This has implications in understanding how AR determinants move through agricultural production systems even in the absence of antibiotic use on farms.

- In calves, researchers found that colonization by the AR shiga-toxin positive *E. coli* is age-dependent. With these results, the scientists are now developing models to reduce transmission of the drug-resistant pathogen. These models will be important for identifying specific critical control points for the spread of drug-resistant pathogens in feedlots and calving operations.
- The scientists have also found that chitosan, a natural fiber product derived from crab shell waste, can mitigate antibiotic resistance, and can be used as an alternative to antimicrobials to sequester pathogens.

To date outcomes and potential impacts of FDA NARMS-funded AR projects include:

- FDA scientists have discovered resistance to linezolid, a critically important drug in human medicine, in three isolates of *Enterococcus* from swine and cattle sources. Subsequent work identified each resistance as plasmid-mediated, resulting in potential concern that resistance can spread to foods and humans, where resistance to this drug is rare.
- Recent work has identified plasmid-mediated quinolone resistance in *Salmonella* from swine and retail pork isolated in nearly 20 states within the U.S. This has the potential to cause resistant infections in people, which is of concern because fluoroquinolones such as ciprofloxacin are used to treat serious cases of salmonellosis in humans.
- In strains of *Salmonella* Dublin from sick cattle and retail meats, scientists have identified large plasmids containing a combination of multiple antimicrobial resistance genes and virulence genes, potentially contributing to severe human infections associated with infection by *Salmonella* with this serotype. The potential transmissibility of these plasmids could increase virulence and resistance in recipient strains.
- Using large-scale WGS of *Campylobacter* (589 isolates) and *Enterococcus* (197 isolates), FDA scientists demonstrated, for most of the drugs tested, that the resistance genotypes highly correlated with phenotypic resistance. This shows the utility of WGS for predicting antimicrobial resistance.
- Shotgun metagenomics analysis of 449 cecal samples collected from food-producing animals (113 cattle, 122 swine, 120 chicken, and 94 turkey) revealed over 180 antimicrobial resistance genes, representing 11 different antibiotic resistance classes. The distribution and relative abundance of antimicrobial resistance genes observed varied by animals. This research provides a baseline resistome and serves as a reference point for monitoring antimicrobial resistance in food-producing animals and for measuring the impact of intervention efforts.

In California, a research team has for the first time identified a chicken gene that controls resistance to *Campylobacter*, making it potentially possible to incorporate this gene into chicken breeding programs to reduce the load of *Campylobacter* in birds. Scientists in New York found that expression of virulence genes in *Salmonella* can be controlled by fatty acids. The approach does not use antibiotics (and therefore does not put pathogens under the selective pressure to evolve resistance and also does not negatively impact native microbiome) but specifically inhibits problematic behaviors in pathogens. A team of Wisconsin and Michigan scientists is targeting AR mitigation strategies on large eight dairy farms across Wisconsin, and will test whether transmission of potentially resistant pathogens from dairy cattle to farm workers

depends on human behavior. Mississippi scientists are targeting the next generation of antibiotic stewards by providing training to 4-H youth and veterinary medicine students. This education and outreach project will also prepare a veterinary workforce to help livestock producers in rural communities improve animal health and well-being while using fewer antibiotics.

In June 2017, NIH/NIAID awarded six projects for preclinical development of therapeutics and vaccines addressing AMR threats ([RFA-AI-16-034](#)). These projects include immune-based therapeutics (for *C. difficile* and MDR *N. gonorrhoeae*), novel antibiotics (for MDR *N. gonorrhoeae*, gram-negative bacteria, and broad-spectrum antibacterials), and a vaccine candidate (for Shigella/enterotoxigenic *E. coli*).

To help understand and prevent HAIs caused by MDR bacteria, NIH/NHGRI intramural scientists are using whole genome and whole plasmid sequencing and analysis. These researchers are investigating mechanisms of AMR and developing methods for prompt detection and recognition of common, emerging, and novel strains of resistant bacteria. Under this initiative, the NIH team has sequenced 45 clinical and 69 environmental CRE isolates collected at the NIH Clinical Center.

The NIH/NIAID-supported [Genomic Centers for Infectious Diseases](#) has sequenced multiple strains and human clinical isolates, including over 8,000 AMR bacterial genomes (e.g., *Enterococcus*, *Klebsiella*, *Acinetobacter*, CRE, and MRSA) from different parts of the world. Sequence data are rapidly released into the public databases GenBank (NLM/NCBI) and the NIH/NIAID-funded Bioinformatics Resource Centers, and contribute to the development of improved diagnosis, therapeutic interventions, and understanding of the complexity and evolution of drug resistance. The NIH/NIAID-supported [Structural Genomics Centers](#) have generated more than 340 structures of proteins from pathogens associated with AMR, including *C. difficile*, *A. baumannii*, *P. aeruginosa*, *Klebsiella*, *Enterobacter*, *Streptococcus pneumoniae*, *S. aureus* and *N. gonorrhoeae*. By determining the structures of unique proteins related to antibiotic resistance mechanisms and vaccine candidates, researchers are providing new insights about the mechanisms and evolution of resistance. The structures are deposited and available in [Protein Data Bank](#).

REPORTS & PUBLICATIONS

In April 2018, CDC released a [Vital Signs](#) report on stopping the spread of antibiotic-resistant germs with “unusual resistance” by using the Containment Strategy. The report’s scientific article showed that in its first nine months of testing, the AR Lab Network identified more than 220 instances of unusual resistance genes in “nightmare bacteria.” The report calls on public health departments nationwide to coordinate the Containment Strategy within their area at the first sign of unusual resistance, every time. The report garnered media interest nationwide and CDC is preparing further partner engagement to ensure maximum implementation and stop spread of new or rare forms of resistance.

In February 2018, NIH scientists from NHGRI and the NIH Clinical Center [reported](#) that genomic analysis of hospital plumbing revealed a diverse reservoir of bacterial plasmids conferring carbapenem resistance. Data from a five-year period showed that despite a very low prevalence of patients infected with these organisms, all samples from the intensive care unit

pipe wastewater and external manholes contained carbapenemase-producing organisms, suggesting a vast, resilient reservoir that may contribute to the spread of resistance genes. These findings may help inform infection control strategies.

Some types of bacteria, including *S. aureus*, have the ability to persist despite exposure to antibiotics. These persisters make it difficult to treat *S. aureus*, and contribute to chronic and recurrent infections. To help address this challenge, NIH/NIAID is [supporting](#) preclinical development of a new class of synthetic retinoid antibiotics effective against bacterial persisters.

In January 2018, NIH/NIAID-supported researchers reported that the sugar substitute, trehalose, increases the virulence of epidemic strains of *C. difficile*. They found that two epidemic types of *C. difficile* have the special ability to metabolize low levels of trehalose, and they hypothesize that the widespread use of this compound as a dietary additive may have contributed to the spread of these strains. This project is supported through NIH/NIAID grants and the NIH/NIAID-funded AMR Systems Biology Centers.

In September 2017, NIH/NIAID-supported researchers [described](#) a new class of precision antimicrobials to specifically target *C. difficile* without harming other bacteria in the gut microbiome, making them potential candidates to treat and/or prevent *C. difficile* infection.

NIH/NIAID scientists have advanced an [immunotherapy approach](#) for treating bacteria. Use of an antibody that recognizes ST258 capsule polysaccharide type 2 (CPS2) has been identified as a way to boost killing of *K. pneumoniae* bacteria by neutrophils in human blood *in vitro*. In addition, findings [suggest](#) the ST258 capsule polysaccharide is a viable vaccine target antigen.

Publications by NIH-supported researchers and NIH/NIAID scientists include:

- Caballero S, Kim S, Carter RA, Leiner IM, Sušac B, Miller L, Kim GJ, Ling L, Pamer EG. Cooperating Commensals Restore Colonization Resistance to Vancomycin-Resistant *Enterococcus faecium*. *Cell Host Microbe*. 2017 May 10;21(5):592-602.e4. doi: 10.1016/j.chom.2017.04.002.
- Daum RS, Miller LG, Immergluck L, Fritz S, Creech CB, Young D, Kumar N, Downing M, Pettibone S, Hoagland R, Eells SJ, Boyle MG, Parker TC, Chambers HF; DMID 07-0051 Team. A Placebo-controlled trial of antibiotics for smaller skin abscesses. *N Engl J Med*. 2017 Jun;376(26):2545-2555. doi: 10.1056/NEJMoa1607033.
- Larsen J, Petersen A, Larsen AR, Sieber RN, Stegger M, Koch A, Aarestrup FM, Price LB, Skov RL; Danish MRSA Study Group. Emergence of livestock-associated methicillin-resistant *Staphylococcus aureus* bloodstream infections in Denmark. *Clin Infect Dis*. 2017 May 30. doi: 10.1093/cid/cix504.
- Lebreton F, Manson AL, Saavedra JT, Straub TJ, Earl AM, Gilmore MS. Tracing the Enterococci from Paleozoic Origins to the Hospital. *Cell*. 2017 May 18;169(5):849-861.e13. doi: 10.1016/j.cell.2017.04.027. Epub 2017 May 11.
- Lee YJ, Arguello ES, Jenq RR, Littmann E, Kim GJ, Miller LC, Ling L, Figueroa C, Robiloti E, Perales MA, Barker JN, Giralt S, van den Brink MRM, Pamer EG, Taur Y. Protective Factors in the Intestinal Microbiome Against *Clostridium difficile* Infection in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation. *J Infect Dis*. 2017 Apr 1;215(7):1117-1123. doi: 10.1093/infdis/jix011.

- Maffioli SI, Zhang Y, Degen D, Carzaniga T, Del Gatto G, Serina S, Monciardini P, Mazzetti C, Gugliera P, Candiani G, Chiriac AI, Facchetti G, Kaltofen P, Sahl HG, Dehò G, Donadio S, Ebricht RH. Antibacterial Nucleoside-Analog Inhibitor of Bacterial RNA Polymerase. *Cell*. 2017 Jun 15;169(7):1240-1248.e23. doi: 10.1016/j.cell.2017.05.042.
- Moran GJ, Krishnadasan A, Mower WR, Abrahamian FM, LoVecchio F, Steele MT, Rothman RE, Karras DJ, Hoagland R, Pettibone S, Talan DA. Effect of Cephalexin Plus Trimethoprim-Sulfamethoxazole vs Cephalexin Alone on Clinical Cure of Uncomplicated Cellulitis: A Randomized Clinical Trial. *JAMA*. 2017 May 23;317(20):2088-2096. doi: 10.1001/jama.2017.5653.
- Panigrahi P, Parida S, Nanda NC, Satpathy R, Pradhan L, Chandel DS, Baccaglini L, Mohapatra A, Mohapatra SS, Misra PR, Chaudhry R, Chen HH, Johnson JA, Morris JG, Paneth N, Gewolb IH. A randomized synbiotic trial to prevent sepsis among infants in rural India. *Nature*. 2017 Aug 24;548(7668):407-412. doi: 10.1038/nature23480. Epub 2017 Aug 16.
- van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, Watkins RR, Doi Y, Kaye KS, Fowler VG Jr, Paterson DL, Bonomo RA, Evans S; Antibacterial Resistance Leadership Group. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. *Clin Infect Dis*. 2018 Jan 6;66(2):163-171. doi: 10.1093/cid/cix783.
- Vila-Farres X, Chu J, Ternei MA, Lemetre C, Park S, Perlin DS, Brady SF. An Optimized Synthetic-Bioinformatic Natural Product Antibiotic Sterilizes Multidrug-Resistant *Acinetobacter baumannii*-Infected Wounds. *mSphere*. 2018 Jan 24;3(1). pii: e00528-17. doi: 10.1128/mSphere.00528-17. eCollection 2018 Jan-Feb.
- Zheng Y, Joo HS, Nair V, Le KY, Otto M. Do amyloid structures formed by *Staphylococcus aureus* phenol-soluble modulins have a biological function? *Int J Med Microbiol*. 2017 Sep 1. pii: S1438-4221(17)30308-9. doi: 10.1016/j.ijmm.2017.08.010.

DoD scientists generated several relevant publications, including:

- Lesho EP, Snesrud E, Bronstein M, Pettis M, Ong A, Maybank R, Kwak Y, Jones A, Vore K, McGann P, Hinkle M. Got GAS? Ease the Bloat with Real-Time Whole-Genome Sequencing. *Infect Control Hosp Epidemiol*. 2018 Apr 2:1-2. doi:10.1017/ice.2018.73. [Epub ahead of print] PubMed PMID: 29606173.
- Srijan A, Margulieux KR, Ruekit S, Snesrud E, Maybank R, Serichantalergs O, Kormanee R, Sukhchat P, Sriyabhaya J, Hinkle M, Crawford JM, McGann P, Swierczewski BE. Genomic Characterization of Nonclonal mcr-1-Positive Multidrug-Resistant *Klebsiella pneumoniae* from Clinical Samples in Thailand. *Microb Drug Resist*. 2018 Apr 24. doi: 10.1089/mdr.2017.0400. [Epub ahead of print] PubMed PMID: 29688801.
- Snesrud E, McGann P, Chandler M. The Birth and Demise of the ISAp11-mcr-1-ISAp11 Composite Transposon: the Vehicle for Transferable Colistin Resistance. *MBio*. 2018 Feb 13;9(1). pii: e02381-17. doi: 10.1128/mBio.02381-17. PubMed PMID: 29440577.
- Lesho EP, Bronstein MZ, McGann P, Stam J, Kwak Y, Maybank R, McNamara J, Callahan M, Campbell J, Hinkle MK, Walsh EE. Importation, Mitigation, and Genomic Epidemiology of *Candida auris* at a Large Teaching Hospital. *Infect Control Hosp Epidemiol*. 2018 Jan;39(1):53-57. doi: 10.1017/ice.2017.231. Epub 2017 Dec 6. PubMed PMID: 29208056.
- Lesho E, Snesrud E, Kwak Y, Ong A, Maybank R, Laguio-Vila M, Falsey AR, Hinkle M. *Pseudomonas* Endocarditis with an unstable phenotype: the challenges of isolate characterization and Carbapenem stewardship with a partial review of the literature.

Antimicrob Resist Infect Control. 2017 Aug 29;6:87. doi: 10.1186/s13756-017-0245-5. eCollection 2017. PubMed PMID: 28855980;

- Morgan M, McGann P, Gierhart S, Chukwuma U, Richesson D, Hinkle M, Lesho E. Consumption of Chlorhexidine and Mupirocin Across the Health System of the US Department of Defense (DOD) and the Incidence of the *qacA/B* and *mupA* Genes in the DOD Facilities of the National Capital Region. Clin Infect Dis. 2017 Jun 15;64(12):1801-1802. doi: 0.1093/cid/cix276. PubMed PMID: 28369328.
- Snesrud E, Ong AC, Corey B, Kwak YI, Clifford R, Gleeson, T, Wood S, Whitman TJ, Lesho EP, Hinkle M, McGann P. Analysis of Serial Isolates of mcr-1-Positive Escherichia coli Reveals a Highly Active ISAp11 Transposon. Antimicrob Agents Chemother. 2017 Apr 24;61(5). pii: e00056-17 doi: 10.1128/AEM doi: 10.1128/AAC.00056-17. Print 2017 May. PubMed PMID: 28223389.
- Jones CL, Singh SS, Alamneh Y, Casella LG, Ernst RK, Lesho EP, Waterman PE, Zurawski DV. In Vivo Fitness Adaptations of Colistin-Resistant Acinetobacter baumannii Isolates to Oxidative Stress. Antimicrob Agents Chemother. 2017 Feb 23;61(3). pii: e00598-16. doi: 10.1128/AAC.00598-16. Print 2017 Mar. PubMed PMID: 27993849.
- Perkins MJ, Snesrud E, McGann P, Duplessis CA. Clostridium sphenoides Chronic Osteomyelitis Diagnosed Via Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry, Conflicting With 16S rRNA Sequencing but Confirmed by Whole Genome Sequencing. Mil Med. 2017 Jan;182(1):e1669-e1672. doi: 10.7205/MILMED-D-15-00535. PubMed PMID: 28051992.

USDA-ARS continues to perform research and develop methods to examine antibiotics and AR in the environment and the agricultural landscape. In 2017, ARS scientists authored 95 publications related to Antimicrobial Resistance and [Alternatives to Antibiotics](#).

In 2017, USDA-FSIS collaborated with its partners in outward-facing communications about the NARMS partnership and findings. This included web-publications, publications in peer reviewed journals and presentations/representation at national and international meetings and hosting two public meetings on NARMS and WGS.

- [FSIS NARMS Webpage to Communicate FSIS Findings and Publications](#)
- [Public Meeting on the National Antimicrobial Resistance Monitoring System](#)
- [Use of Whole Genome Sequence \(WGS\) Analysis to Improve Food Safety and Public Health](#)

USDA-FSIS and collaborators generated several relevant publications:

- [Comparative Analysis of Extended-Spectrum- \$\beta\$ -Lactamase CTX-M-65-Producing Salmonella enterica Serovar Infantis Isolates from Humans, Food Animals, and Retail Chickens in the United States](#)
- [Review Article National Antimicrobial Resistance Monitoring System: Two Decades of Advancing Public Health Through Integrated Surveillance of Antimicrobial Resistance](#)
- [Identification of Plasmid-Mediated Quinolone Resistance in Salmonella Isolated from Swine Ceca and Retail Pork Chops in the United States](#)

USDA-APHIS [published results](#) from a survey that was administered to U.S. veterinary clinics and diagnostic laboratories in 2015. This survey assessed current practices with respect to antimicrobial susceptibility testing and corresponding data sharing, providing an understanding of how AR data is being shared within the veterinary diagnostic community, and with whom.

Publication resulting from USDA-NIFA AR-funded projects include:

- Afema JA, Ahmed S, Besser T, Jones L, Sicho WM, Davis M. Molecular epidemiology of dairy cattle-associated *Escherichia coli* carrying bla CTX-M genes in Washington State. *Applied Env Micro*. 2018; XX doi: 10.1128/AEM doi: 10.1128/AEM.02430-17
- R. Noyes, Maggie E. Weinroth, Jennifer K. Parker, Chris J. Dean, Steven M. Lakin, Robert A. Raymond, Pablo Rovira, Enrique Doster, Zaid Abdo, Jennifer N. Martin, Kenneth L. Jones, Jaime Ruiz, Christina A. Boucher, Keith E. Belk, and Paul S. Morley. Enrichment allows identification of diverse, rare elements in metagenomic resistome-virulome sequencing. *Microbiome*. 2017; 5: 142
- Martin D. Muggli, Alexander Bowe, Noelle R. Noyes, Paul S. Morley, Keith E. Belk, Robert Raymond, Travis Gagie, Simon J. Puglisi, Christina Boucher. Succinct colored de Bruijn graphs. *Bioinformatics*. 2017 Oct 15;33 (20):3181-3187.
- Cazer, C.L., Ducrot, L., Volkova, V.V., Grohn Y.T.: Monte Carlo Simulations Suggest Current Chlortetracycline Drug-Residue Based Withdrawal Periods Would Not Control Antimicrobial Resistance Dissemination from Feedlot to Slaughterhouse. *Frontiers*. 2017 Sep 20;8:1753. doi: 10.3389/fmicb.2017.01753. eCollection 2017
- Poole TL, Callaway TR, Norman KN, Scott HM, Loneragan GH, Ison SA, Beier RC, Harhay DM, Norby B, Nisbet DJ. Transferability of antimicrobial resistance from multidrug-resistant *Escherichia coli* isolated from cattle in the USA to *E coli* and *Salmonella* Newport recipients. *J Glob Antimicrob Resist*. 2017 Dec;11:123-132. PubMed PMID: 28801276.
- Ohta N, Norman KN, Norby B, Lawhon SD, Vinasco J, den Bakker H, Loneragan GH, Scott HM. Population dynamics of enteric *Salmonella* in response to antimicrobial use in beef feedlot cattle. *Sci Rep*. 2017 Oct 30;7(1):14310. PubMed PMID: 29085049; PubMed Central PMCID: PMC5662634
- Collignon, P. C., Conly, J. M., Andreumont, A., McEwen, S.A., Aidara-Kane, A., Agero, Y., Ninh, T.D., Donado-Godoy, P., Fedorka-Cray, P., Fernandez, H., Galas, M. Irwin, R., Karp, B., Matar, G., McDermott, P., McEwen, S., Mitema, E., Reid-Smith, R., Scott, H. M., Singh, R., Smith DeWaal, C., Stelling, S., Toleman, M., Watanabe, H., Woo, G-J. (2017) World Health Organization 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. *Clinical Infectious Diseases*. 63,1087-1093
- Cummings, K.J., Rodriguez-Rivera, L.D., Norman, K.N., Ohta, N., Scott, H.M. (2017) Identification of a plasmid-mediated quinolone resistance gene in *Salmonella* isolates from Texas dairy farm environmental samples. *Zoonoses and Public Health*. 64, 305-307

USDA-NIFA AR-funded projects resulted in several conference papers and presentations:

- Cazer, L. C., Grohn, Y.T.: Applying Behavior Pattern Sensitivity Analysis to a System Dynamics Model of Resistant Enteric Bacteria in Beef Steers Fed Chlortetracycline. The Biological & Biomedical Sciences Symposium, Cornell, Ithaca, NY, Aug 18, 2017
- Cazer, L. C., Volkova, V. V., Grohn, Y.T.: Behavior pattern sensitivity analysis identifies interventions to reduce enteric antimicrobial resistance in beef steers fed chlortetracycline. CRWAD. Chicago, December 3-5, 2017.

OTHER ACTIVITIES

Starting in April 2018, CDC established and stocked the Tuberculosis (TB) Emergency Drug Stockpile with initial drug orders to assure continuity of rifapentine therapy should the drug supply be disrupted. Patients who have already started latent TB infection treatment and risk interruption are first priority for receiving rifapentine from the stockpile. This activity supports strategies and goals under both the CARB National Action Plan and the [National Action Plan for Combating Multidrug-Resistant Tuberculosis \(MDR-TB\)](#).

CDC has also made significant progress updating the U.S. domestic TB surveillance system with molecular drug susceptibility testing reporting and developing electronic reporting between state surveillance systems and CDC labs. Clinical service is being transitioned from conventional to next generation sequencing methods. More than 1,200 isolates of *M. tuberculosis* have undergone whole genome sequencing to evaluate resistance mechanisms and microevolution during TB treatment. CDC has identified new mutations that confer resistance to isoniazid that will improve the accuracy of rapid molecular tests for the identification of resistance. These activities support strategies and goals under both the CARB National Action Plan and the National Action Plan for Combating MDR-TB.

Additional USG activity to address TB can be found in progress reports for the National Action Plan for Combating MDR-TB.

Starting in 2015, NIH entered an Interagency Agreement with FDA to address key regulatory considerations related to using bacteriophages for decolonization of vancomycin-resistant enterococci (VRE) and MRSA. FDA scientists have developed a robust model for VRE colonization and transmission. Using this model, FDA scientists have: (1) tested bacteriophage efficacy for clearance of VRE and shown that clearance is nearly to the limit of detection; (2) demonstrated an apparent association between phage success and microbiota damage; and (3) identified a single point mutation between two phages that dramatically alters host range. Further, FDA scientists have established a mouse MRSA colonization model in the upper respiratory tract that they used to demonstrate that Staphylococcal phage can decrease the bacterial load. They are additionally investigating the genetic mechanisms of MRSA resistance to Staphylococcal phage K and related phages (at least three novel and unexpected mechanisms of resistance have been identified). The results of these studies have been presented at various national and international meetings, including the European Molecular Biology Organization of Viruses of Microbes.

In 2017, NIH/NIAID established an additional Interagency Agreement with FDA to address key regulatory questions regarding the manufacture of fecal microbiota transplant (FMT) products, as well as to assess the effectiveness of current donor screening recommendations by determining specificity and sensitivity of commonly used molecular diagnostic tests. In addition, NIH/NIAID and the American Gastroenterological Association have launched an [FMT national registry](#) for *C. difficile* infection. The registry is designed to collect clinical data from FMT donors and recipients to assess the safety, effectiveness, and best practices of this intervention.

The NMRC's ACESO program presented a poster at the American Society of Tropical Medicine and Hygiene (ASTMH) annual meeting in Baltimore (November 2017) describing infectious etiologies of patients enrolled in an observational sepsis study in Kumasi, Ghana. In addition, an award-winning poster describing antimicrobial sensitivities from this study was also presented

by an in-country physician on the ACESO study team at the African Association for research and control of AntiMicrobial Resistance in Bamako, Mali (February 2018).

The Navy and Marine Corps Public Health Center developed the Antibiotic Susceptibility and Prescribing Practices (ASPP) Tool, which can display antibiotic prescription rates by state and year, and identify when prescription rates reach alter thresholds within each state.

Examples of outputs of USDA-NIFA-funded AR projects:

- Pruden, A. <http://www.hort.vt.edu/args/index.html>
- Sischo, W. <http://vetextension.wsu.edu/research-projects/ARcap/>
- Scott, H.M. <http://www.asi.k-state.edu/research-and-extension/antibiotics/index.html>

Appendix B

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 <i>Clostridium difficile</i> 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 <i>Neisseria gonorrhoeae</i> below 2% compared to estimates from 2013. | |
| For CDC Recognized Serious Threats: | |
| Reduce by 35% multidrug-resistant <i>Pseudomonas spp.</i> infections acquired during hospitalization compared to estimates from 2011. | |
| Reduce by at least 50% overall methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) bloodstream infections by 2020 as compared to 2011.* | |
| Reduce by 25% multidrug-resistant non-typhoidal <i>Salmonella</i> 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

| | |
|----------|---|
| ACESO | Austere Environments Consortium for Enhanced Sepsis Outcomes |
| AGISAR | Advisory Group on Integrated Surveillance of Antimicrobial Resistance |
| AHRQ | Agency for Healthcare Research and Quality |
| AMR | antimicrobial resistance |
| AMT-AVI | Aztreonam – Avibactam |
| APHIS | Animal and Plant Health Inspection Service |
| APHL | Association of Public Health Laboratories |
| AR | antibiotic resistance |
| ARLG | Antibacterial Resistance Leadership Group |
| ARLN | Antimicrobial Resistance Laboratory Network |
| ARMoR | Antibiotic Resistance Monitoring and Research Program |
| ARS | Agricultural Research Service |
| ARSI | Antibiotic Resistance Solutions Initiative |
| ASPP | Antibiotic Susceptibility and Prescribing Practices |
| ASM | American Society for Microbiology |
| AST | Antimicrobial Susceptibility Test |
| ASTMH | American Society of Tropical Medicine and Hygiene |
| ATA | Alternatives to Antibiotics |
| AU | antibiotic use |
| AUR | antibiotic use and resistance |
| AVMA | American Veterinary Medical Association |
| BARDA | Biomedical Advanced Research and Development Authority |
| CAMS | Chinese Academy of Medical Sciences |
| CARB | Combating Antibiotic-Resistant Bacteria |
| CARICOM | Caribbean community |
| CAUTI | catheter-associated urinary tract infections |
| CDC | Centers for Disease Control and Prevention |
| CDI | <i>Clostridium difficile</i> infection |
| CEAH | Center for Epidemiology and Animal Health |
| CETR | Centers of Excellence for Translational Research |
| CLABSI | central line-associated bloodstream infections |
| CLSI | Clinical and Laboratory Standards Institute |
| CMS | Centers for Medicare and Medicaid Services |
| COMBACTE | Combating Antimicrobial Resistance in Europe |
| CoPs | Conditions of Participation |
| CPS2 | capsule polysaccharide type 2 |
| CRE | carbapenem-resistant Enterobacteriaceae |
| CUSP | Comprehensive Unit-based Safety Program |
| CVM | Center for Veterinary Medicine |
| DoD | Department of Defense |
| EDC | Epidemiology Data Center |
| EDGE | Empowering the Development of Genomics Expertise |
| EIP | Emerging Infections Program |
| EPA | Environmental Protection Agency |
| ERS | Economic Research Service |

| | |
|-----------------|---|
| EU | European Union |
| EWG | Electronic Working Group |
| FAO | Food and Agriculture Organization |
| FDA | Food and Drug Administration |
| FMT | fecal microbiota transplant |
| FSIS | Food Safety and Inspection Service |
| G7 | Group of Seven |
| GAP | Global Action Plan |
| GFI | Guidance For Industry |
| GHSA | Global Health Security Agenda |
| GVIRF | Global Vaccine and Immunization Research Forum |
| HAI | healthcare-associated infections |
| HCUP | Healthcare Cost and Utilization Project |
| HHS | Department of Health and Human Services |
| HIIN | Hospital Improvement Innovation Networks |
| HL7 | Health Level 7 |
| HRSA | Health resources and Services Administration |
| IDCRP | Infectious Disease Clinical Research Program |
| IG | Interpretive Guidance |
| IHR-JEE | International Health Regulations – Joint Extension Evaluation |
| IPT | Integrated Product Team |
| IQR | Inpatient Quality Reporting |
| KPC | <i>Klebsiella pneumoniae</i> carbapenemase |
| LPAD | limited population antibacterial drug |
| LTC | long-term care |
| MCR | mobile colistin resistance |
| MDR | multi-drug resistant |
| MDRO | multi-drug resistant organism |
| MInD-Healthcare | Modelling Infectious Diseases in Healthcare |
| MIPS | Merit-based Incentives Program |
| MRSA | methicillin-resistant <i>Staphylococcus aureus</i> |
| MRSN | Multidrug-resistant organism Repository and Surveillance Network |
| NAHMS | National Animal Health Monitoring System |
| NAMRU-2 | Naval Medical Research Unit No. 2 |
| NARMS | National Antimicrobial Resistance Monitoring System |
| NCATS | National Center for Advancing Translational Sciences |
| NLM/NCBI | National Center for Biotechnology Information, National Library of Medicine |
| 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 |
| NQF | National Quality Forum |
| NMRC | Naval Medical Research Center |
| NVAP | National Veterinary Accreditation Program |
| NVSL | National Veterinary Services Laboratories |
| OGA | Office of Global Affairs |

| | |
|---------|---|
| OIE | World Organization for Animal Health |
| ONC | Office of the National Coordinator for Health Information Technology |
| PACCARB | Presidential Advisor Council on Combating Antibiotic-Resistant Bacteria |
| PATRIC | Pathosystems Resource Integration Center |
| PT | proficiency test |
| QAPI | Quality assurance and performance improvement |
| QIN/QIO | Quality Innovation Network/Quality Improvement Organizations |
| QPP | Quality Payment Program |
| R&D | Research & Development |
| RFA | Request for Applications |
| SBAR | Situation, Background, Assessment, Recommendation |
| SHEA | Society for Healthcare Epidemiology of America |
| STD | sexually transmitted diseases |
| STEC | Shiga toxin-producing Escherichia coli |
| TATFAR | Transatlantic Taskforce on Antimicrobial Resistance |
| TB | tuberculosis |
| UNGA | United Nations General Assembly |
| USDA | United States Department of Agriculture |
| USG | United States Government |
| VA | Department of Veterans Affairs |
| VFD | Veterinary Feed Directive |
| VHA | Veterans Health Administration |
| VRE | vancomycin-resistant enterococci |
| WGS | whole genome sequencing |
| WHA | World Health Assembly |
| WHO | World Health Organization |
| WRAIR | Walter Reed Army Institute of Research |