# NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

## Progress Report

**Fiscal Year 2022**

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

# Contents

# The Task Force for Combating Antibiotic-Resistant Bacteria

The Department of Health and Human Services (HHS) and its following components:

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| AHRQ | Agency for Healthcare Research and Quality |
| ASPE | Office of the Assistant Secretary for Planning and Evaluation |
| ASPR | Administration for Strategic Preparedness and Response |
| BARDA | Biomedical Advanced Research and Development Authority (within ASPR) |
| CDC | Centers for Disease Control and Prevention |
| CMS | Centers for Medicare & Medicaid Services |
| FDA | Food and Drug Administration |
| NIH | National Institutes of Health |
| OGA | Office of Global Affairs |

The United States Department of Agriculture (USDA) and its following components:

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| APHIS | Animal and Plant Health Inspection Service |
| ARS | Agricultural Research Service |
| FAS | Foreign Agricultural Service |
| FSIS | Food Safety and Inspection Service |
| NIFA | National Institute of Food and Agriculture |
| OCS | Office of the Chief Scientist |

The Department of Defense (DoD) and its following components:

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| DHA | Defense Health Agency |
| GEIS | Global Emerging Infections Surveillance |
| IDCRP | Infectious Disease Clinical Research Program |
| MIDRP | Military Infectious Diseases Research Program |
| MRSN | Multidrug-Resistant Organism Repository and Surveillance Network |
| PVC | Pharmacovigilance Center |
| WRAIR | Walter Reed Army Institute of Research |

The Department of the Interior (DoI)
The Department of State (DoS)
The Environmental Protection Agency (EPA)
The United States Agency for International Development (USAID)
The Department of Veterans Affairs (VA)

*Links and references to information from non-governmental organizations is provided for informational purposes and is not an HHS endorsement, recommendation, or preference for the non-governmental organizations.*

# Background

Pathogens that have developed resistance to the drugs currently available to treat infections are an ongoing threat to human health and animal health, the environment, food production, and national security. A recent analysis estimated that antimicrobial-resistant (AR)[1] bacteria caused 1.2 million deaths globally in 2019, making this threat a leading cause of death for people of all ages worldwide. Domestically, CDC estimates that more than 3 million Americans suffer from AR infections or *Clostridioides difficile* (an infection that can happen after taking antibiotics) each year and that more than 48,000 people die as a result.

The U.S. government is pursuing a National Strategy for Combating Antibiotic-Resistant Bacteria (CARB), which takes a One Health approach to achieve five goals:

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

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

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

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

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

The National Strategy for CARB is implemented by the federal CARB Task Force, which is co-chaired by DoD, USDA, and HHS. In 2015, the CARB Task Force translated the National Strategy into a five-year National Action Plan for CARB (2015 Plan). The U.S. government reaffirmed its commitment to addressing the threat of antibiotic-resistant bacteria by publishing a National Action Plan for CARB for 2020 through 2025 (2020 Plan). The 2020 Plan maintains the five goals of the National Strategy for CARB and builds on progress since 2015 with new objectives and targets to be met in the next five years.

The National Action Plan for CARB aligns with related U.S. government strategic documents to promote consistency and efficiency and maintain clear roles and responsibilities. This includes Target 1.4.1.1, which aims to meet the targets identified within the Healthcare-Associated Infections (HAI) National Action Plan. The U.S. National Biodefense Strategy and Implementation Plan also includes an action to implement the National

[1] The 2020 CARB National Action Plan follows the framework of CDC's 2019 AR Threats Report and uses the term "antibiotic" to describe antibacterial and antifungal drugs, which kill bacteria and fungi, respectively. CDC has transitioned to use the term "antimicrobial resistance," abbreviated as AR, to describe the phenomenon of resistance among the bacterial and fungal pathogens. In this report, the acronyms AR and AMR are both used to refer to antimicrobial resistance.

Action Plan for CARB, including establishment and support of domestic and global AR detection programs in healthcare, community, animal health, and environment. Relevant targets from the National Biodefense Strategy and Implementation Plan include 3.1.4 ("Strengthen Healthcare-Associated Infections [HAI] and Antibiotic Resistant [AR] Pathogens Capacities") and 1.1.1 ("Develop domestic, and support the development of global, capacities and capabilities to detect and report disease outbreaks in humans, animals, and plants anywhere in the world"). The United States Government Global Health Security Strategy includes AR as a technical priority and contains activities consistent with the National Strategy for CARB. Additionally, while tuberculosis (TB) falls outside the scope of the CARB effort, certain TB activities are reported here because they are critical near-term public health activities that will support progress to reduce the burden of drug-resistant TB in the U.S. Otherwise, U.S. government activities to address drug-resistant TB domestically and internationally are aligned with efforts such as the 2015–2020 National Action Plan for Combating Multidrug-Resistant TB.

The CARB Task Force has developed this report to document progress toward these goals during fiscal year 2022. This report includes highlights of agency activities as well as a comprehensive list of progress toward each target in the 2020 Plan. The report also describes challenges encountered during this period, as well as updates to targets where relevant.

# Spotlight on One Health Surveillance

Surveillance and monitoring are important tools for preparedness and response, and the activities under Goal 2 of the National Strategy for CARB support the role of surveillance for combating AR. The CARB Task Force implements several surveillance systems that monitor different aspects of AR across humans, animals, and the environment. Here we highlight one of those systems, the National Antimicrobial Resistance Monitoring System (NARMS). Established in 1996, NARMS is a collaboration between FDA, CDC, USDA, state and local public health departments, and universities that tracks changes in the antimicrobial susceptibility of certain enteric (gut) bacteria found in sick people (CDC), retail meats (FDA), and food animals (USDA) in the U.S. From its inception, NARMS has operationalized a One Health approach by bringing together multiple sectors and disciplines to develop, run, and collectively understand its data. Most recently, the NARMS initiated a pilot program with EPA to assess antimicrobial-resistant bacteria and genes present in surface waters.

NARMS research and monitoring activities help promote and protect public health by providing information about emerging enteric AR, how enteric antimicrobial-resistant bacteria differ from antimicrobial-susceptible bacteria, and the impact of interventions designed to limit the spread of AR. For example, NARMS partners use NARMS data on a case-by-case basis to inform foodborne illness and outbreak investigations. Further, FDA publishes periodic updates on ongoing, unusual, or concerning AR findings. In addition, FDA also uses NARMS data as part of their review process for approving new antibiotics for use in food animals. Data can be accessed via NARMS Now: Integrated Data, which allows for comparisons of enteric antimicrobial-resistant bacteria from animals, retail meats, and humans. Users can view a tutorial on how to use NARMS Now.

NARMS continues to make program improvements to adapt to the changing landscape of AR risk across time and to help inform the development of science-based policies. These efforts include expanding sampling and developing, adapting, and harmonizing cutting-edge methods for laboratory testing. For example, NARMS expanded sampling to include antimicrobial susceptibility data from clinically ill animals through FDA's Veterinary Laboratory Investigation and Response Network (Vet-LIRN) and APHIS's National Animal Health Laboratory Network (NAHLN) programs. NARMS has also incorporated whole-genome sequencing (WGS) data as part of its reporting to help understand the mechanisms underlying AR.

FDA, in cooperation with CDC, USDA, and other partners, held a public meeting to discuss progress on implementing the NARMS Strategic Plan 2021–2025. The public meeting was preceded by a technical workshop to provide an overview and demonstration of methods, databases, tools, and dashboards used to capture WGS and antimicrobial susceptibility testing (AST) for NARMS bacterial targets. Together, this work highlights how NARMS seeks to inform and gather feedback from a variety of internal and external stakeholders. NARMS will continue to provide a model One Health AR monitoring system into the future.

# Highlights of Progress in Fiscal Year 2022

## COVID-19 and Pandemic Preparedness

The CARB Task Force continued to ensure that AR remained high on the political agenda during the ongoing COVID-19 pandemic and the mpox public health emergency of international concern. During 2022, the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) held public meetings on March 2 and September 12–13. CARB Task Force agencies provided technical support for these meetings and several acted as non-voting regular government employee members of the council. The March meeting centered on One Health retrospectives on past pandemic influenza outbreaks and how they affected AR and antimicrobial use and stewardship to understand and prepare for the role of AR in future viral pandemics. The September meeting was a One Health AR and pandemic preparedness policy workshop, using a hypothetical, large-scale disease outbreak scenario to identify key issues and critical pandemic policy gaps related to AR. A report from the PACCARB reflects its synthesis of these issues and recommendations for future action, and the CARB Task Force is actively considering these recommendations.

## Health Equity

In FY 2022, **CDC** conducted a scoping review of health equity and antibiotic prescribing, which found that certain populations are more likely to receive antibiotics inappropriately. CDC is using this information to incorporate health-equity-driven efforts into its antibiotic stewardship program and research activities. In addition, CDC continued to drive progress to address AR and health equity as a part of its CORE Initiative by working across key agency programs such as Project Firstline to address training gaps for healthcare workers from diverse educational and training backgrounds; CDC's Antimicrobial Resistance Laboratory Network (AR Lab Network) is working to identify ways to include and analyze patient demographic data alongside laboratory test results to be able to provide a more comprehensive picture of AR in certain populations; and the National Healthcare Safety Network (NHSN) to enhance patient demographic data for future analysis and drive improvement in healthcare quality. To assist healthcare facilities and public health entities in collecting information needed to investigate potential inequities related to HAI outbreaks and implement tailored prevention strategies, CDC collaborated with the Council for Outbreak Response: Healthcare-Associated Infections and Antimicrobial-Resistant Pathogens (CORHA) to create a comprehensive list of patient- and facility-level variables that can be collected during or following an HAI outbreak investigation.

## Climate and Environment

In July 2022, the "Managing Climate-Driven Zoonotic Risk Workshop" brought together representatives from **ASPR/BARDA**, **CDC**, **NIH/National Institute of Allergy and Infectious Diseases (NIAID)**, the Department of Homeland Security (DHS), **DoS**, **DoD's Defense Threat Reduction Agency**, **EPA**, the National Aeronautics and Space Administration (NASA), the National Oceanic and Atmospheric Administration (NOAA), the **United States Geological Survey (USGS)**, **USDA**, **FDA**, and the Department of Energy (DoE) National Labs to discuss the increasing risks of zoonotic disease associated with climate change and to discuss and propose strategies for managing these risks.

## Further Highlights

**CMS** hosted a session focused on state Medicaid and the Children's Health Insurance Program (CHIP) activities in antibiotic stewardship, specifically regarding the quality measure "Avoidance of Antibiotic Treatment for Acute Bronchitis/Bronchiolitis (AAB-AD)." CMS collaborated with CDC to host this session and a meeting with state public health departments to promote opportunities for public health programs and Medicaid and CHIP agencies to work together. In October 2022, CMS released guidance in Appendix PP of the *State Operations Manual* to accompany the long-term care requirements related to having an infection preventionist in Nursing Homes at least part-time. On July 6, 2022, CMS released a memo to State Survey Agency Directors, QSO-22-20-Hospitals, regarding the update to the interpretive guidance contained in the *State Operations Manual*, Appendix A for hospitals, which made conforming revisions to the Infection Prevention and Control and Antibiotic Stewardship Program Condition of Participation (CoP) requirements that CMS had finalized previously.

The **AHRQ** Safety Program for Improving Antibiotic Use has adapted the Comprehensive Unit-based Safety Program (CUSP) to promote antibiotic stewardship programs in acute care hospitals, long-term care, and ambulatory care across the country. The project has created the "Four Moments of Antibiotic Decision Making," a significant advance in antibiotic stewardship that provides step-by-step guidance empowering clinicians to serve as stewards of their own antibiotic prescribing, featured in an article in the *Journal of the American Medical Association* to expand the impact of this innovative approach. In February 2022, the program published results of the long-term care cohort of over 400 long-term care facilities in *JAMA Network Open*, showing a significant reduction in antibiotic starts. In July 2022, the program published results of the final cohort of over 350 ambulatory care practices in *JAMA Network Open*, showing a significant reduction in antibiotic prescriptions for visits related to respiratory tract infections for the one-year cohort. An educational toolkit based on the experiences of this cohort was posted on the AHRQ website in October 2022. This toolkit completes the suite of three setting-specific toolkits based on the Four Moments of Antibiotic Decisions Making developed in the project, which resulted in significant reductions in antibiotic use in over 400 acute care hospitals in addition to the improvements demonstrated in long-term care facilities and ambulatory care practices. These accomplishments are a prime example of translating research on improving antimicrobial use into practice.

In June 2021, **FDA's Center for Veterinary Medicine (CVM)** published final Guidance for Industry (GFI) #263, *Recommendations for Sponsors of Medically Important Antimicrobial Drugs Approved for Use in Animals to Voluntarily Bring under Veterinary Oversight All Products That Continue to Be Available Over-the-Counter*, along with a fact sheet to address frequently asked questions for farmers and ranchers. The two-year timeline specified in the guidance contemplates the change from over-the-counter to prescription status occurring between June 2021 and June 2023. CVM has developed a multi-media outreach campaign for stakeholders affected by GFI #263, including 10 online deliverables and targeted outreach to three key states (Texas, Arizona, and Oregon) through social media and radio ads.

In FY 2022, **CDC** awarded approximately $960 million to state, local, and territorial health departments (an average of approximately $15 million per jurisdiction) to prevent and control HAIs, including those that are antimicrobial-resistant, through the Epidemiology and Laboratory Capacity for Prevention and Control of Emerging Infectious Diseases (ELC) cooperative agreement to strengthen the nation's public health infrastructure that prevents, detects, contains, and responds to AR threats, through annual appropriations and

supplemental funding from the American Rescue Plan Act (ARP). Additionally, CDC implemented new AR testing, such as WGS, AST, and colonization screening, for improved detection of AR threats like HAIs, fungi, and *Neisseria gonorrhoeae* (the bacterium that causes gonorrhea), expanding the AR Lab Network across all 50 state health departments and several local health departments, large cities, and territories. With sustained resources, CDC will continue to support states and partner organizations to ensure infectious disease threats are stopped when and where they emerge.

**NIH/NIAID's** Antibacterial Resistance Leadership Group (ARLG) and Vaccine and Treatment Evaluation Units networks collaborated to conduct a clinical trial called Short Course vs. Standard Course Outpatient Therapy of CAP in Children (SCOUT-CAP) to evaluate a shorter course (five days) of treatment strategy for pediatric community-acquired pneumonia (CAP). CAP is a potentially serious lung infection in young children that often leads to hospitalization. The standard treatment for young children is a 10-day course of the antibiotic amoxicillin. The results of the NIH/NIAID-supported trial showed that short course antibiotic treatment is superior to standard treatment in children six months to five years old. Clinical improvement rates were the same, and microbiome analysis demonstrated reduced likelihood of resistance in throat specimens from children in the short course group. These data provide a rationale for shortened treatment courses, reducing the risk of developing bacterial resistance to antibiotics.

This year, **ASPR/BARDA** recommitted to the preclinical development of therapeutic, preventative, and diagnostic candidates by entering into an Other Transaction Agreement with Boston University for the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). Under this agreement BARDA provided $25 million in 2022, with options to provide a total of up to $300 million over the next 10 years to combat antimicrobial-resistant infections. **NIH/NIAID** is providing in-kind services to support product development through CARB-X. This global public-private partnership is dedicated to accelerating the early development of therapeutics, preventatives, and diagnostics for antimicrobial-resistant infections. Since 2016, CARB-X has funded the advancement of 92 innovative projects in 12 countries as part of a scientifically diverse portfolio, and to date 12 CARB-X supported products have progressed into first-in-human clinical trials. In addition to non-dilutive funding, CARB-X provides wrap-around technical, regulatory, and business support to companies for early-stage development. The renewed funding from BARDA and other CARB-X partners will support the existing portfolio and allow for new funding rounds.

In August 2022, **USDA** hosted a virtual public meeting on AR with updates from USDA agencies and federal partners. This meeting recognized 10 years of progress since the first USDA AR workshop, held in 2012 with a look to the future. The meeting highlighted opportunities for collaboration and invited public input to inform future planning on AR activities.

USDA's **ARS** funded 10 one-year-mini-proposals through an internal funding call to address AR and antibiotic alternatives research. These projects include supporting the development of decision support tools for identifying karst topography presence and soil profile AR movement data, vaccines and probiotic interventions to reduce *Salmonella* in chickens, and treating intramammary mastitis through antibiotic alternatives. In addition, ARS hosted a five-part webinar series to highlight ARS research that addresses AR and antibiotic alternatives in agriculture with U.S. and international partners and stakeholders and had 262 registrants from 51 countries. Moreover, ARS scientists published 66 peer-reviewed journal articles relating to AR and

antibiotic alternatives in FY 2022. For example, ARS scientists developed self-neutralizing antibiotics to treat bovine mastitis.

USDA's **FSIS** continued its expanded sampling and analysis under NARMS. In FY 2022 this expansion included the evaluation of AR through sampling and analysis of gut contents from sheep, goats and lambs, and veal for *Salmonella*, *Campylobacter*, *Enterococcus*, and *Escherichia coli*, as well as isolation and characterization of *Enterococcus* and *E. coli* from a subset of Siluriformes fish (e.g., catfish) samples.

USDA's **NIFA** invested more than $5 million to mitigate AR across the food chain in their integrated grant program supporting extramural research, education, and extension. Research approaches being supported include risk assessment, antimicrobial stewardship, understanding mechanisms of resistance, and disease control using antimicrobial alternatives.

# New and Updated Items in the CARB National Action Plan, 2020–2025

| Item | Original | Update | Rationale |
|---|---|---|---|
| Target 1.4.2.1 | Develop and optimize guidance for improving infection control standards across healthcare settings. | Develop and/or strengthen infection control requirements, standards, and associated guidance across healthcare settings. | Revised to broaden the scope of the target to include all steps from the development and promulgation of new requirements and regulations toward regulatory guidance development and optimization. |
| Target 1.4.3.1 | Develop updated biosecurity educational materials by 2022. | Develop updated biosecurity educational materials by 2024. | Implementation delayed due to the COVID-19 response. |
| Target 1.4.4.1 | Report results of biosecurity data from National Animal Health Monitoring System from 2019 (Goats) and 2021 (Feedlot, Swine) by 2022. | Report results of biosecurity data from the National Animal Health Monitoring System from 2021 (feedlot, swine) by 2023. | Implementation delayed due to the COVID-19 response. |
| Target 2.1.3.1 | Establish at least one collaboration through this program to enhance whole-genome sequencing or metagenomics techniques by 2022. | Establish at least one collaboration through this program to enhance whole-genome sequencing or metagenomics techniques by 2023. | Implementation delayed due to the COVID-19 response. |
| Target 2.4.1.3 | Improve timelines of annual outpatient antibiotic use tracking and reporting by 2021. | Improve timelines of annual outpatient antibiotic use tracking and reporting by 2025. | CDC has gained access to data in a more timely manner and continues work on improving the timeliness of analyses. |
| Target 2.4.1.4 | Implement tracking of antibiotic use in all DoD Military Health System facilities, using the Standardized Antimicrobial Administration Ratio (based on observed inpatient antimicrobial days of therapy), by 2021. | Implement tracking of antibiotic use in all DoD Military Health System facilities, using the Standardized Antimicrobial Administration Ratio (based on observed inpatient antimicrobial days of therapy), by 2024. | DoD continues to roll out the new hospital record management system (MHS Genesis) across all facilities, with a completion date of fall 2023. Therefore, we have changed the deadline to 2024 to ensure all hospitals can report through this system. |

| Item | Original | Update | Rationale |
|---|---|---|---|
| Target 4.2.2.1 | Facilitate development of 10 novel potential therapeutics for bacterial infections in humans by 2022. | Facilitate clinical development of 10 novel potential therapeutics for bacterial infections in humans by 2025. | Date changed because this is an ongoing activity. |
| Target 4.2.3.1 | Establish at least two projects supporting the development of new agents and standards by 2021. | Establish at least five projects supporting the development of new agents and standards by 2025. | Date changed because this is an ongoing activity. |
| Target 4.3.1.1 | Award 25 new projects aimed at discovering or developing new preventative products for use in human medicine by 2022. | Award 40 new projects aimed at discovering or developing new preventative products for use in human medicine by 2025. | Date changed because this is an ongoing activity. |
| Target 5.1.2.1 | Support international AR policy efforts to prioritize and coordinate antibiotic resistance efforts within and across international partner organizations (e.g., Global Health Security Agenda [GHSA], World Health Organization [WHO], World Organization for Animal Health [WOAH], the United Nations Environmental Program [UNEP], Food and Agricultural Organization [FAO], G7 and G20, Asia-Pacific Economic Cooperation Forum, Association of Southeast Asian Nations, Pan American Health Organization) by 2022. | Support international AR policy efforts to prioritize and coordinate antibiotic resistance efforts within and across international partner organizations (e.g., Global Health Security Agenda [GHSA], World Health Organization [WHO], World Organization for Animal Health [WOAH], United Nations Environmental Program [UNEP], Food and Agricultural Organization [FAO], G7 and G20, Asia-Pacific Economic Cooperation Forum, Association of Southeast Asian Nations, Pan American Health Organization) by 2025. | Date changed because this is an ongoing activity. |

| Item | Original | Update | Rationale |
|---|---|---|---|
| Target 5.1.2.3 | Complete the Work Plan of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) for 2016–2020 and develop and begin implementation of a new scope of work for TATFAR by 2022. | Complete the Work Plan of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) for 2016–2020, develop and begin implementation of a new workplan for TATFAR by 2022, and continue implementation of the current workplan for 2021–2026. | CARB Task Force members participating in TATFAR are implementing the current workplan, and will continue to report on TATFAR impact and progress. |
| Target 5.2.4.1 | Submit isolates of multidrug-resistant pathogens to the MRSN for advanced characterization and provide reports to the labs that can also inform surveillance of antibiotic resistance, by 2021. | Submit isolates of multidrug-resistant pathogens to the MRSN for advanced characterization and provide reports to the labs that can also inform surveillance of antibiotic resistance, by 2024. | Challenges remain in ensuring all partner sites submit some isolates to MRSN, including partner nation trust in sharing biological and genetic information with entities beyond their borders and related policy/legislation. Therefore, we have changed the date to 2024 to allow more time to address these issues. |
| Sub-objective 5.3.5 | Expand overseas screening of long-term visitors to the U.S. (e.g., international workers and students) from high-risk countries to prevent the importation of cases of multidrug-resistant tuberculosis. | Expand screening of populations migrating to the U.S. from high-risk countries to prevent the importation of cases of multidrug-resistant tuberculosis. | Implementation delayed due to the COVID-19 response. CDC continues to collaborate with DoS to expand TB screening requirements and vaccinations of long-term visitors to the U.S. CDC is also collaborating with DHS to expand this screening to additional migrant communities before they enter the U.S. through the parole process. |
| Target 5.3.5.1 | Pilot screening in five countries by 2021. Expand to 45 countries by 2025. | Pilot expanded screening for populations migrating from five high-risk TB countries by 2025. | Target modified due to delays from the COVID-19 pandemic, expanding screening requirements of migrants entering the U.S., and additional opportunities for screening before they enter the U.S. |

# Common Challenges and Barriers

Combating AR while also addressing concurrent One Health issues continued to create challenges for the CARB Task Force during FY 2022. Many hospitals continued to face extraordinary circumstances due to the COVID-19 pandemic that may have reduced the implementation of standard infection prevention and control (IPC) practices while treating sicker patient populations. In acute care hospitals, the increases seen in some HAIs during 2021 contrast with earlier successes in reducing these infections prior to the pandemic. To address these setbacks, **CDC** continues to invest in IPC activities, training, surveillance, and public health personnel to bolster U.S. and global capacity to fight existing and emerging threats and protect patients.

**CMS** continues its efforts in enhanced enforcement of nursing home infection control compliance by imposing directed plans of correction to improve infection control practices when noncompliance is identified. Additionally, CMS works with Quality Improvement Organizations (QIOs) to support hospitals by providing quality improvement technical assistance, including 1:1 coaching, identification and dissemination of evidence-based best practices, and making resources and tools readily available to help hospitals improve healthcare delivery and patient outcomes. Finally, in November 2022, CMS finalized CoP requirements for a new Medicare provider type (rural emergency hospitals, or REHs), including new IPC and antibiotic stewardship program CoP requirements for REHs that essentially mirror those already established for hospitals and critical access hospitals (CAHs).

Response to other infectious disease outbreaks also affected the CARB Task Force's work. The **USDA/NAHLN** AMR pilot is a voluntary program, and participating laboratories were also responding to highly pathogenic avian influenza (HPAI) as a priority in 2022. HPAI is an extremely infectious disease, mostly fatal to poultry, and can rapidly spread within and between domestic poultry flocks and wild bird (especially waterfowl) populations. To address this challenge, NAHLN increased the number of isolates per category for which laboratories could submit data, and updated reporting standards for laboratories to report when data are available rather than once a quarter.

Limited resources for implementation created several challenges for agencies. To the best of their ability, **USDA/ARS** applies AR yearly intramural funding to address top agricultural AR/antibiotic alternatives priorities to ensure a safe and secure food supply. ARS continues to have trusted partnerships with stakeholders to identify priorities, design solutions, and implement outputs. However, their responsiveness depends on availability of resources and personnel to address emergent antimicrobial and multidrug-resistant (MDR) pathogen issues and to develop sustainable mitigation strategies and antibiotic alternatives.

Likewise, resource limitations have delayed and redirected efforts to define interagency needs and develop options for appointing a Federal Champion for International CARB. In light of the COVID-19 response, agencies felt that their individual representatives could adequately cover needed engagements, particularly given that there are no dedicated resources to support such a position. The CARB Task Force will continue to consider how such a position could be developed.

Data collection challenges persist across the One Health spectrum. Ongoing barriers to collecting data to monitor antimicrobial use in animals include the existence of a diversity of animal production and veterinary settings, lack of a uniform infrastructure to collect data, lack of agreement on metrics, and confidentiality

concerns. To address these barriers, **FDA/CVM** funded two cooperative agreements from 2016 to 2022 to develop methodologies for collecting data on antimicrobial use in food producing animals. Information gathered from these cooperative agreements can be found in the November 2020 special issue of *Zoonoses and Public Health* and FDA/CVM's report *Antimicrobial Use and Resistance in Animal Agriculture in the United States: 2016–2019*. In 2020, FDA funded two cooperative agreements to develop methodologies for collecting data on antimicrobial use in companion animals. Data collected through these cooperative agreements will support efforts to assess potential associations between antimicrobial use practices in dogs and cats and AR. These projects may be funded through 2024. FDA has also funded the Reagan Udall Foundation to explore the feasibility of a public-private partnership for collecting antimicrobial use data in animals.

On the human health side, enrolling patients in clinical trials that evaluate strategies and interventions for drug-resistant microbial infections poses significant challenges. These infections typically occur in patients who are critically ill and difficult to enroll. Further, the incidence of the types of resistant infections under study is sporadic, episodic, and difficult to predict, making site selection challenging. Therefore, these clinical trials require many sites and sufficient funding to enroll the number of participants needed to address complex research questions. Established clinical networks like the **NIH/NIAID**-funded ARLG are critical to addressing this challenge, particularly as these networks can be expanded to include additional U.S. and international sites to help reach enrollment targets. Additionally, expanded data authorities for CDC, for example through established tracking systems like NHSN, are essential to better inform prevention, detection, containment, and response activities to address AR threats when and where they emerge.

Other challenges in AR research have emerged as research fields have evolved. For example, the field of microbial genomics is transforming from existing primarily in the academic environment to becoming a key tool in public health. This opens various opportunities in clinical settings, and the volume of data continues to grow, but data quality and analysis capabilities pose a significant challenge. To address this challenge, **NIH/NIAID** has ongoing efforts to improve metadata collection. These new approaches are beginning to be adopted in the field, though the speed of uptake remains limited.

As the burden of the COVID-19 pandemic eases, diagnostic developers are shifting their efforts back to AR diagnostics and anticipate that more gains should be realized in 2023. In light of these shifts, **ASPR/BARDA** plans to review additional broad agency announcement submissions for AR diagnostics in 2023.

# Progress in Fiscal Year 2022

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

### Objective 1.1

**Expand national, regional, and state capacity for detecting, containing, and preventing antibiotic-resistant infections.**

#### Sub-objective 1.1.1

**Reduce the number of infections and deaths from pathogens identified as antibiotic-resistant threats by CDC.**

##### Target 1.1.1.1

**Decrease healthcare-associated antibiotic-resistant infections by 20 percent by 2025 and community-acquired antibiotic-resistant infections by 10 percent by 2025.**

**CDC**'s *2021 National and State HAI Progress Report,* an analysis of CDC's NHSN data, demonstrated that hospital-onset *C. difficile* infection (CDI) continued to fall in 2021, decreasing by 3 percent from 2020. When comparing the 2021 standardized infection ratios (SIRs) to the 2015 national baseline, hospital-onset CDI SIRs have decreased by 50 percent. However, the report also showed that hospital-onset methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections increased by 14 percent from 2020 to 2021 and is now 7 percent higher than the national baseline set in 2015. These results are consistent with changes in antimicrobial-resistant pathogens described in CDC's *COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022*, which also noted increases in hospital-onset infections by 78 percent for carbapenem-resistant *Acinetobacter baumannii* and 35 percent for carbapenem-resistant Enterobacterales (CRE) in 2020. Hospital-onset vancomycin-resistant *Enterococci* and extended-spectrum beta-lactamase (ESBL)–producing Enterobacterales also increased. Among fungal pathogens, antifungal-resistant threats rose in 2020 too, including *Candida auris*—which increased 60 percent overall—and other *Candida* species, with a 26 percent increase in hospital infections. To address these increases, likely due to the challenges maintaining AR prevention programs during COVID-19, CDC updated guidance in 2022 to promote adherence to existing recommendations, including through emphasizing environmental hygiene, for the prevention and containment of antimicrobial-resistant pathogens in healthcare settings.

The CDC Emerging Infections Program's Active Bacterial Core surveillance (EIP-ABCs) collects and utilizes data on invasive bacterial infections including *Streptococcus pneumoniae,* group A *Streptococcus* (GAS) and group B *Streptococcus* (GBS). Surveillance data from EIP-ABCs identified reductions in the rate of infections caused by *S. pneumoniae* and GAS during the COVID-19 pandemic (2020 to 2021). This reduction is likely driven by COVID-19 prevention measures decreasing the transmission of respiratory pathogens.

Despite reductions in the incidence of these infections during 2020 to 2021, the proportion of resistant infections has remained constant (*S. pneumoniae*) or continued to increase (GAS) compared to pre-pandemic (2019) levels. Reductions in the incidence of GAS infections during the COVID-19 pandemic were offset by an increase in the proportion of GAS infections with resistance to erythromycin or clindamycin. Therefore, throughout the COVID-19 pandemic, there has been minimal reduction in the total number of antimicrobial-resistant GAS infections. Transmission of GBS, another pathogen under EIP-ABCs surveillance, was only modestly affected by COVID-19 prevention measures and macrolide

resistance continues to steadily rise among GBS isolates. It is imperative to continue to monitor trends in resistant invasive disease attributable to these pathogens beyond the pandemic period.

Drug-resistant *S. pneumoniae* is one of the only pathogens listed in *CDC's 2019 AR Threats Report* with an effective vaccine to prevent infections, including the pneumococcal conjugate vaccines (PCVs). The EIP-ABCs can be used to evaluate the effectiveness of PCVs to inform the Advisory Committee on Immunization Practices, which promotes use of higher-valency PCVs (PCV15 and PCV20 are now recommended for use in adults and children). These vaccines have helped reduce cases of resistant pneumococcal disease caused by serotypes included in the vaccine formulation.

For other community-acquired antimicrobial-resistant infections, like drug-resistant gonorrhea, CDC has limited data likely due to infections going untreated, decreased screening for asymptomatic infections, inadequate staffing in healthcare facilities, testing/supply shortages in labs and clinics, and decreased access to health insurance from increased unemployment in 2020–2021. However, gonorrhea isolates with elevated minimal inhibitory concentrations (MICs) to ceftriaxone, CDC's recommended treatment, remained under 1 percent during this time, with 99 percent of isolates remaining fully susceptible to the drug.

### Sub-objective 1.1.2

**Support investments in U.S. health departments (including in all states and select tribes, territories, and large cities) to detect, contain, and prevent antibiotic-resistant infections.**

#### Target 1.1.2.1

**Award an average of $2.5 million to Epidemiology and Laboratory Capacity Cooperative Agreement–funded health departments by 2025.**

In FY 2022, **CDC** awarded approximately $960 million to state, local, and territorial health departments (an average of approximately $15 million per jurisdiction) to combat HAIs and address antimicrobial-resistant infections in healthcare settings and the community, through the ELC cooperative agreement. The funding for these awards primarily originated from ARP, which provided temporary supplemental funding to strengthen and equip state, local, and territorial public health departments and other partner organizations with the resources needed to better prevent and fight infections in U.S. healthcare facilities, including COVID-19 and other known and emerging infectious diseases. This supplemental funding is a critical part of CDC's progress in achieving the goals in the 2020 CARB National Action Plan. The FY 2022 awards underscore a sharp contrast to FY 2021 awards provided through annual appropriations, which totaled $85.8 million to state, local, and territorial health departments (a significantly smaller average of $1.34 million per jurisdiction).

This temporary supplemental funding also supported additional awards in FY 2022 for the detection, containment, and response to AR threats. This funding includes expansion of AR Lab Network activities, increasing capacity to rapidly detect emerging and concerning AR threats and inform prevention and response efforts. Additionally, CDC staff trained in fungal disease detection visited six of the seven AR Lab Network sites to assess WGS capacity. CDC also hosted in-person laboratory training for laboratorians from the Tennessee and Maryland AR Lab Network Regional Labs.

### Sub-objective 1.1.3

**Support responses to identify, prevent, and contain antibiotic-resistant pathogens.**

#### Target 1.1.3.1

**Increase capacity nationwide to contain antibiotic-resistant infections and control outbreaks.**

In FY 2022, **CDC** awarded ARP funds to provide support for all 50 state health departments and several local health departments, large cities, and territories to expand or implement new AR testing for improved detection of AR threats, including for HAIs, fungi, and *N. gonorrhoeae* (gonorrhea). More than 25 states will implement local screening for urgent AR threats such as *C. auris*, to inform IPC efforts and support outbreak investigations. More than 40 jurisdictions have used funds to implement WGS for enhanced detection of bacterial HAI/AR threats and to support outbreak response

efforts locally for more than 14,000 isolates sequenced uploaded since the start of FY 2022. Additionally, these jurisdictions tested more than 60,000 samples for carbapenemase-producing organisms (CPOs) and sent approximately 8,000 notifications of resistance in healthcare settings to CDC that required an immediate public health action.

Additionally, ARP funds expanded carbapenem resistance mechanism testing, AST, and WGS through CDC's AR Lab Network. This expansion enabled public health labs to detect a rare strain of extensively drug-resistant *Pseudomonas aeruginosa* from isolates first collected in May 2022. This detection led to an outbreak investigation and response in collaboration with CDC's HAI/AR programs beginning in 2022. Because of CDC's investment in HAI/AR programs in every state, including WGS capabilities, and intensive, quality on-the-ground detective work by our CDC and health departments epidemiologists, we were able to gather evidence, connect the "fingerprints" of each case together through WGS, and work swiftly to contain this outbreak and prevent infections using CDC's IPC training and expertise.

CDC's National Tuberculosis Molecular Surveillance Center, as part of the AR Lab Network, performed WGS on nearly 7,300 *Mycobacterium tuberculosis* isolates. WGS data were used for surveillance purposes to improve the accuracy of outbreak detection systems and to conduct surveillance of mutations associated with drug resistance. On request, 13 state partners were given access to nearly 5,000 WGS data files for their own surveillance or research purposes. Enhancements for the national system are being developed including expanding capacity for WGS in nine public health laboratories with potential use for both outbreak detection as well as clinical laboratory reporting of drug resistance. Additionally, work has been initiated to expand access to bioinformatic tools to help identify resistance and inform response activities. CDC also supported health department response and prevention activities by hosting seven webinars on appropriate laboratory detection and rapid epidemiological response to multidrug-resistant organisms (MDROs).

During the past year, CDC introduced a laboratory-developed nucleic acid amplification test (NAAT) for detecting genetic mutations associated with resistance in gonorrhea.

In 2022, through the ARP funds, CDC provided resources for the capacity-building of Etest® AST for gonorrhea to 16 jurisdictions. This expansion in testing locations quickly identified a gonorrhea isolate of concern (not previously seen in the U.S.) with resistance or decreased susceptibility to multiple antibiotics. CDC personnel also provided the rapid characterization of the isolate of concern including confirmatory AST, WGS, and identification of resistance-determining alleles. CDC provided technical support to the local jurisdiction and performed in-house testing of remnant NAATs specimens from the local jurisdiction for identification of additional occurrences of gonorrhea cases with decreased susceptibility.

CDC provided ongoing technical assistance to partners involved in investigating a CPO in samples taken from dogs living at an animal rescue facility, and in investigating potential zoonotic transmission between people and dogs in veterinary and rescue settings. In early 2022, the Minnesota Integrated Food Safety Center of Excellence (CoE) used CDC-provided funds to outline CPO surveillance definitions and create an algorithm to guide response in the event of CPO detection in a veterinary patient. Detection of a CPO in a dog at the University of Minnesota Veterinary Medical Center presented an opportunity to put the response algorithm into practice. In the summer of 2022, CDC provided additional funding to the Minnesota Integrated Food Safety CoE to perform enhanced AST at the University of Minnesota Veterinary Diagnostic Laboratory, and to further develop, refine, and distribute the CPO response algorithm. The funding included support for development of standard operating procedures for identification of isolates for enhanced phenotypic testing (e.g., reflex testing using the modified carbapenem inactivation method), protocols for isolate handling and transfer to public health laboratories for WGS, processes for data management and analysis, and distribution to other state health departments through state public health veterinarian offices.

In June 2022, CDC also collaborated with states to create and pass a Council for State and Territorial Epidemiologists position statement to update the Nationally Notifiable Diseases Surveillance System (NNDSS) to expand the organisms for CPO to include, but not be limited to, Enterobacterales, *A. baumannii*, and *P. aeruginosa*. The position statement also expands acceptable laboratory criteria and the timeframe for counting new clinical cases. This expansion empowers states to report CPOs, enabling states to investigate CPO isolates and request investigations and tracking trends to

effectively prevent, detect, contain, and respond to CPOs. Jurisdictions will submit NNDSS data under this expanded guidance in 2023.

Additionally, CDC awarded money for epidemiology and laboratory WGS support through ELC mechanisms and through all 10 EIP sites for candidemia tracking and to detect and track *Candida* bloodstream infections.

On July 6, 2022, **CMS** released a memo to State Survey Agency Directors, QSO-22-20-Hospitals, regarding the update to the interpretive guidance contained in the *State Operations Manual*, Appendix A for hospitals, which made conforming revisions to Infection Prevention and Control and Antibiotic Stewardship Program CoP requirements that CMS had finalized previously.

In November 2022, CMS also finalized the CoP requirements for a new Medicare provider type (REHs), including new IPC and antibiotic stewardship program CoP requirements for REHs that essentially mirror those already established for hospitals and CAHs.

As part of the FY 2023 Inpatient Prospective Payment System final rule, CMS is measuring the extent to which hospitals and CAHs participating in the "Promoting Interoperability" program submit both antibiotic use and resistance data to NHSN Antimicrobial Use and Resistance Module in calendar year 2024. CDC worked closely with CMS throughout the rulemaking process.

In 2022, **DoD/MRSN** completed the rollout of near-real-time surveillance for antimicrobial-resistant infections across the Military Health System (MHS). The top 15 hospitals in the network now send all antimicrobial-resistant members of the ESKAPE+ coterie of bacteria (*Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *K. aerogenes*, *A. baumannii*, *P. aeruginosa*, *Enterobacter cloacae*, and *E. coli*) to the MRSN for WGS every week.

### Sub-objective 1.1.4

**Conduct consultations or assessments related to antibiotic-resistant cases, outbreaks, and transmission in healthcare and the community for prevention and containment.**

#### Target 1.1.4.1

**Increase collaborative efforts at national, regional, and/or state levels to assist with antibiotic resistance response and prevention efforts in the general and military populations.**

In FY 2022, **CDC-**funded HAI/AR programs in all 50 state health departments and several local health departments, large cities, and territories continued to engage in public health responses to AR threats. From August 2021 to July 2022, these partners responded to more than 5,000 reports of emerging resistance, including conducting 972 responses involving onsite infection control assessments and/or colonization screening. CDC collaborated with HAI/AR programs by deploying staff for four field investigations for *C. auris* and CRE, including one investigation of a CRE outbreak in an animal rescue facility. Additionally, through ARP funds mentioned above, CDC provided public health departments with support to implement enhanced MDRO prevention programs, which engaged healthcare facilities in sustained, ongoing infection control improvement initiatives and proactive colonization screening, complementing traditional MDRO response activities. Through this funding, HAI/AR programs in 25 health departments are now engaged in enhanced MDRO prevention activities and participate in CDC-led communities of practice for implementation activities.

Additionally, CDC subject matter experts supported the AHRQ Safety Program for MRSA Prevention through active participation in the Technical Expert Panel and support of recruitment efforts. This large national collaborative of healthcare facilities aims to reduce invasive MRSA infections nationwide in three setting-specific cohorts: acute care hospital intensive care units (ICUs) and non-ICUs, acute care hospital surgical services, and long-term care facilities. Evidence-based interventions were tailored to specific settings and based in part on CDC's strategies to prevent hospital-onset *Staphylococcus aureus* bloodstream infections in acute care facilities.

**CMS** hosted a session focused on state Medicaid and CHIP activities in antibiotic stewardship, specifically regarding the quality measure "Avoidance of Antibiotic Treatment for Acute Bronchitis/Bronchiolitis (AAB-AD)." CMS collaborated with

CDC to host both this session and a meeting with state public health departments to promote opportunities for public health programs and Medicaid and CHIP agencies to work together.

In 2022, **DoD/MRSN** responded to 59 outbreaks across the MHS. This included significant collaborative interventions at two large medical facilities involving environmental swabbing that uncovered multiple reservoirs of *P. aeruginosa* in hospital drains that were responsible for infecting patients there. Ongoing mitigation efforts have significantly reduced these reservoirs.

### Sub-objective 1.1.5

**Monitor and report on antibiotic resistance among selected animal pathogens to detect new resistance patterns.**

#### Target 1.1.5.1

**Publish one report on an animal pathogen describing emerging antibiotic resistance by 2021.**

**NARMS partners** published an analysis of genomic data of *E. coli* isolates from five U.S. government organizations to evaluate potential sources of extraintestinal pathogenic *E. coli*, which cause urinary tract and potentially life-threatening invasive infections but whose origins are not always clear.

## Objective 1.2

**Engage the public and other stakeholders to develop, expand, and increase national and state education, training, and communication campaigns focused on using antibiotics responsibly, stopping the spread of antibiotic resistance, and preventing infections and life-threatening conditions like sepsis.**

### Sub-objective 1.2.1

**Expand the scope and reach of CDC's awareness campaigns, including Be Antibiotics Aware and Get Ahead of Sepsis.**

#### Target 1.2.1.1

**Each year, increase clicks, impressions, and earned or paid media.**

From October 1, 2021, to September 30, 2022, **CDC's** Be Antibiotics Aware campaign generated a total of 21.8 million paid media impressions with a total of 111,000+ URL clicks to the website. This is a 45 percent decrease in impressions and a 60 percent decrease in URL clicks, compared to the prior year. The decrease likely happened because the prior fiscal year saw a steady pace of combined messaging on antibiotic use and COVID-19, pushed out the year prior at the height of the COVID-19 pandemic, and this year did not. As well, there were no paid media promotions—a significant driver of impressions and engagements—between May 24 and September 30, 2022.

The Get Ahead of Sepsis campaign generated more than 17 million paid media impressions with a total of 320,000+ URL clicks to the website. This is a 48 percent decrease in impressions and a 42 percent decrease in clicks, compared to the prior year. The decrease likely happened because the prior fiscal year saw more interest in the messaging between sepsis and COVID-19, pushed out at the height of the COVID-19 pandemic. As well, there was no paid media from May 24 to September 30, 2022 (including during September, which was Sepsis Awareness Month).

### Sub-objective 1.2.2

**Develop new or expanded educational training guidelines, outreach, and awareness activities to educate stakeholders, such as consumers, healthcare providers, and industries, on best practices for using antibiotics responsibly, stopping the spread of antibiotic resistance, and preventing infections.**

#### Target 1.2.2.1

**Increase and expand outreach activities each year.**

**CDC's** Office of Antibiotic Stewardship, in collaboration with CDC communications experts, developed new educational resources and content, including a toolkit for healthcare professionals working in nursing homes and materials for community pharmacists. New infographics and materials related to COVID-19 and influenza were developed for the

public, and materials related to common cold and cough illnesses were updated. Updates to six healthcare professional continuing education modules for CDC's Antibiotic Stewardship Training Course have been completed, and additional modules are being updated.

CDC also collaborated with the Association of Public Health Laboratories (APHL) to develop content of a training describing key steps and information on submitting specimens for CPO or *C. auris* screening at the public health laboratories. This training also educates on the importance and need for screening efforts to prevent and contain the spread of CPOs and *C. auris* in healthcare facilities. This course will offer continuing education units.

The **CMS** Quality Innovation Network–Quality Improvement Organizations (QIN-QIOs) are working with their enrolled nursing homes to improve antibiotic stewardship in efforts to improve infection prevention and reduce CDI. The QIN-QIOs are using the CDC Core Elements of Antibiotic Stewardship, the AHRQ Toolkit to Improve Antibiotic Use in Long-Term Care, and the AHRQ Nursing Home Antimicrobial Stewardship Guide, and other toolkits to provide direct education and technical assistance to nursing homes. Additional educational interventions in FY 2022 include providing technical assistance to track antibiotic use, develop data reporting on antibiotics and working with clinicians to address inappropriate antibiotic use, coordinating with the state health department and regional efforts to identify specific needs, and systemic integration of antibiotic stewardship elements in nursing homes. The CMS Hospital Quality Improvement Contractors (HQICs) work to improve antibiotic stewardship in acute care hospitals and CAHs (also based on CDC's Core Elements). They also work on reducing the incidence of MDROs in the hospital setting (e.g., *C. difficile*, MRSA).

**USDA** hosted a virtual public meeting on AR with updates from USDA agencies as well as opportunity for public comment for input on the next USDA AR strategy. Additionally, USDA/APHIS participated in multiple outreach activities, including virtual and in-person events, to provide information about antimicrobial stewardship with different audiences.

### Sub-objective 1.2.3

**Expand the promotion and utility of training guidelines and other communication materials.**

#### Target 1.2.3.1

**Each year, increase the number of individuals trained, continuing education units earned, and reach of efforts.**

As of October 2022, users had registered for participation in 135,995 modules in **CDC's** Antibiotic Stewardship Training Course, and 33,158 unique users had registered for one or more modules, representing an increase in registered users from the previous year. CDC is also developing and updating material for dental professionals to improve antibiotic prescribing for dental patients and working with the Organization for Safety, Asepsis and Prevention, a dental infection and safety association, through a cooperative agreement to develop new materials, website content, and an antibiotic stewardship workshop for dental professionals.

In addition, Strengthening the United States Response to Resistant Gonorrhea (SURRG) jurisdictions continue to establish COEs to share and distribute information about antimicrobial-resistant gonorrhea. CDC has worked with the Minnesota Integrated Food Safety CoE to develop, refine, and evaluate the University of Minnesota's Antimicrobial Resistance Learning Site, a website with numerous antimicrobial stewardship training modules intended for veterinary students and clinicians across multiple veterinary practice settings. CDC also developed online self-guided training modules about *C. auris* and infection control for Latin American audiences, which are available in Spanish.

CDC and USDA/APHIS continued information sharing and educational outreach to major partners, including to the National Institute for Animal Agriculture; the National Institute of Antimicrobial Resistance Research and Education; and Farm2Fork meetings including meetings of the National Cattlemen's Beef Association, National Pork Board, National Turkey Federation, and National Chicken Council. CDC and USDA/APHIS also engaged with the American Veterinary Medical Association's Committee on Antimicrobials to increase education, training, and communication on antibiotic stewardship in veterinary medicine.

CDC began creating an in-depth training for AST of bacteria in 2022. The content of this course was developed in collaboration with 13 subject matter experts from within and outside CDC, including clinical and public health laboratories and industry. The training includes three modules describing methods of AST (disk diffusion, reference broth microdilution, and gradient diffusion), with the final module describing considerations for implementing commercial AST devices. This training is a multicenter collaboration with CDC's National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality and Promotion, and CDC's Center for Surveillance, Epidemiology and Laboratory Services, Division of Laboratory Systems. The interactive, self-paced course will offer continuing education units and will be available on CDC's OneLab Reach training platform in 2024.

**USDA/APHIS** trained approximately 7,000 people on antimicrobial stewardship through two online modules offered by the National Veterinary Accreditation Program, which is consistent with participation in the previous year.

## Objective 1.3

**Develop and implement policies and practices to promote the responsible use of antibiotics.**

### Sub-objective 1.3.1

**Improve national outpatient antibiotic use.**

#### Target 1.3.1.1

**Lower the annual rate of outpatient antibiotic dispensing per 1,000 U.S. population, overall and among specified subpopulations.**

**CDC** found that the annual rate of outpatient antibiotic dispensing was 709 prescriptions per 1,000 persons in 2022. Prescribing decreased substantially starting in 2020, at the beginning of the pandemic, and remains lower than during the pre-pandemic period.

**DoD** is measuring the annual rate of antibiotic prescribing across all facilities and has completed the outpatient antibiotic usage report for calendar year 2021. The rate of outpatient prescribing in the DoD population decreased from 225.0 prescriptions per 1,000 enrollees in 2019 to 148.8 prescriptions per 1,000 enrollees in 2020 and 133.7 prescriptions per 1,000 enrollees in 2021, though the rates may be artificially low due to the COVID pandemic.

#### Target 1.3.1.2

**Lower the annual proportion and rate of antibiotic prescriptions for outpatient visits where antibiotics are not needed (according to evidence-based guidelines) and provide descriptive statistics for trends in unnecessary prescribing patterns.**

**CDC** is working to update its analysis, *Measuring Outpatient Prescribing*, with more recent prescribing data to understand the impact of the COVID-19 pandemic on unnecessary prescribing patterns. In 2018, the most recent year for which outpatient appropriateness data are available, CDC found 15.5 percent of visits for which antibiotics are never appropriate nevertheless resulted in antibiotic prescriptions. Unnecessary antibiotic prescribing occurred in 60.1 percent of bronchitis visits and 23.6 percent of viral upper respiratory infection visits. Children received fewer unnecessary antibiotics than adults: overall, 10.3 percent versus 18 percent; for bronchitis, 41.1 percent versus 65.6 percent; and for viral upper respiratory infections, 10.4 percent versus 33.1 percent.

Additionally, although antibiotics do not work against viruses like SARS-CoV-2, antibiotics have been frequently prescribed for patients with COVID-19 during the pandemic. During the first year of the COVID-19 pandemic, historic gains made on antibiotic stewardship were reversed as antibiotics were often the first option given to treat those who presented with pneumonia-like symptoms of fever and shortness of breath—even though this often represented the viral illness of COVID-19, for which antibiotics are not effective. CDC also reported that, during this time, 30 percent of outpatient visits for COVID-19 among Medicare beneficiaries were linked to antibiotic prescriptions.

**CMS's** Medicaid and CHIP Child and Adult Core Sets are measures that, taken together, can be used to estimate the overall national quality of healthcare for Medicaid and CHIP beneficiaries with the purpose of monitoring performance at the state level and improving the quality of healthcare. CMS added a measure of antimicrobial stewardship, "Avoidance of Antibiotic Treatment for Acute Bronchitis/Bronchiolitis," to the 2022 Adult Core Set in FY 2021; in FY 2022, CMS added the same measure to the 2023 Child Core Set. These decisions came out of a rigorous stakeholder engagement process to ensure that CMS adds only measures to the Core Sets that are appropriate for use at the state level, provide useful and actionable results to drive improvement in care delivery and health outcomes, address a strategic performance measurement priority, and are likely to be reported by states to CMS. In recommending this measure, members of the Child and Adult Core Set Annual Review Workgroup indicated the importance of having a measure that encourages avoidance of unnecessary antibiotics. States have used this measure to promote appropriate antibiotic dispensing and found significant room for improvement. Reporting on Core Set measures is voluntary for states until 2024, when reporting will become mandatory for the Child Core Set and behavioral health measures in the Adult Core Set. During FY 2022, CMS collaborated with CDC to host a Quality Technical Advisory Group meeting on this measure to highlight opportunities for state public health departments and Medicaid programs to work together.

**DoD** is creating a dashboard to assess inappropriate prescribing for specific conditions. This dashboard is expected to be complete and available to DoD facilities in FY 2023.

### Sub-objective 1.3.2

**Help healthcare providers adopt recommended antibiotic use practices.**

#### Target 1.3.2.1

**Each year, increase the number of facilities and providers that implement CDC's best practices.**

In 2021, 95 percent of acute care hospitals reported that they had antibiotic stewardship programs in place that incorporate all seven of **CDC's** Core Elements of Antibiotic Stewardship, a slight increase compared with 2020. Given the high implementation of stewardship programs, in 2021, CDC launched priority implementation approaches for hospital stewardship programs to advance stewardship efforts and improve the quality of hospital antibiotic stewardship programs.

All **DoD** inpatient military treatment facilities assess compliance with CDC's Core Elements of Hospital Antibiotic Stewardship on a yearly basis. The percent of inpatient facilities meeting all seven Core Elements has increased from 78.3 percent in 2020 to 95.5 percent in 2021. Outpatient military treatment facilities' implementation of relevant core elements is not assessed at this time.

### Sub-objective 1.3.3

**Support national and state policies that improve the use of antibiotics across healthcare settings and communities.**

#### Target 1.3.3.1

**Develop and optimize interpretative guidance for the antibiotic stewardship requirements within the conditions of participation for Medicare and Medicaid programs.**

On July 6, 2022, **CMS** released a memo to State Survey Agency Directors, QSO-22-20-Hospitals, regarding the update to the interpretive guidance contained in the *State Operations Manual*, Appendix A for hospitals, which made conforming revisions to the Infection Prevention and Control and Antibiotic Stewardship Program CoP requirements that CMS had finalized previously.

### Sub-objective 1.3.4

**Partner with clinical societies to consider options for improving the development, speed, and harmonization of antibiotic use and diagnostic guidelines that reflect clinical and public health needs for major syndromes.**

### Target 1.3.4.1

**Initiate at least one coordinated effort to improve antibiotic or diagnostic guidelines by 2021.**

During FY 2022, **CDC** collaborated with the Infectious Disease Society of America (IDSA) to develop a framework to incorporate stewardship principles into guideline development. This framework will be incorporated in the update of guidelines for management of urinary tract infections (UTIs). Stewardship principles and a clinical pathway for implementation of IDSA's community-acquired pneumonia guidelines are drafted and will be published.

Additionally, CDC, in collaboration with the APHL, seven of the AR Lab Network Labs, and two university labs, established a gentamicin quality control range for gonorrhea disk diffusion AST. In June 2022, the data were presented to the Clinical and Laboratory Standards Institute (CLSI) and approved. This new range will be published in *M100: Performance Standards for Antimicrobial Susceptibility Testing* in January 2023.

In collaboration with CLSI, CDC began developing a guidance document titled *Methods for Active Surveillance of Multidrug Resistant Organisms* (proposed as M66). The document development committee includes 26 subject matter experts, of whom two are representing CDC. This document will provide much-needed guidance for clinical and public health laboratories on importance, implementation, methodology, considerations, and result reporting when performing active surveillance of MDROs. This guidance is scheduled for publication in 2024.

In collaboration with CLSI, CDC is an active contributor to the revision of the CLSI M52 guidance document *Verification of Commercial Microbial Identification and Antimicrobial Susceptibility Testing Systems*. This document describes CLSI's recommendations on necessary steps for verifying a commercial FDA-cleared AST/microbial identification device. The proposed revisions include a less burdensome pathway for verification so that laboratories can implement new AST devices or update devices to report current breakpoints faster to ensure the best information is available for patient care and public health surveillance. The revision is scheduled for publication in 2024.

In collaboration with CLSI, CDC is an active voting member for the revision of CLSI guidelines M02 (Performance Standards for Antimicrobial Disk Susceptibility Tests, 13th edition) and M07 (Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 11th edition), which describe the disk diffusion and dilution methods, respectively, of AST. CDC is considered a "super user" of reference broth microdilution panels and is one of the few laboratories in the U.S. with the capability, capacity, and knowledge to make these panels. Thus, CDC is an important stakeholder in the revision of these documents. These FDA-recognized standards documents serve as a valuable resource for clinical and public health laboratories, diagnostic device manufacturers, and academic centers. Both are receiving important revisions, and CDC has proposed that a new reading guide be developed for broth microdilution testing (one already exists for disk diffusion). The documents are in review and are scheduled for publication in early 2024, alongside the M100 publications.

## Sub-objective 1.3.5

**Support research to improve the responsible use of antibiotics across settings and translate important findings into practice.**

### Target 1.3.5.1

**Increase research on the responsible use of antibiotics and translate significant findings into practice.**

In FY 2022, **AHRQ** committed additional funds totaling $12.1 million, including the out-years of projects initially funded in FY 2022, to research on improving antibiotic use. Meritorious antibiotic-use-related grant applications funded in 2022 focused largely on improving antibiotic prescribing as well as improving diagnostic stewardship to prevent overdiagnosis of infection and subsequent overprescribing of antibiotics. AHRQ's support for research on improving antibiotic use is ongoing.

**CDC** examined antibiotic prescribing and factors that influence prescribing practices such as provider type, geographic location, setting, and patient age to inform targets for antibiotic stewardship. A *Mortality and Morbidity Weekly Report*

published in February 2022 evaluated publicly available data to better understand how antibiotics were prescribed for adults over 65 in 2019. The highest 10 percent of antibiotic prescribers prescribed 41 percent of total antibiotic prescriptions. Publicly available data can be used by public health organizations and healthcare systems to guide antibiotic stewardship interventions and optimize antibiotic prescribing.

Additionally, a CDC study using machine-learning modeling examined drivers of inappropriate antibiotic prescribing for acute respiratory illnesses (based on IQVIA Medical Claims Data [Dx] and the IQVIA Longitudinal Prescription Data [LRx]). The analysis showed antibiotics were prescribed in 11 percent of 42 million visits; outpatient setting type, particularly urgent care, older patient age mix, and state location in the South, were identified as top drivers of inappropriate prescribing. These findings give antibiotic stewards an opportunity to target education and resources to places where they are likely to have the most impact.

CDC continues to support the Prevention Epicenters Program, a collaborative network of academic partners, to perform innovative studies to improve antimicrobial use and decrease AR. As an example, Duke University led a multicenter, randomized controlled trial to evaluate a protocol to de-escalate or stop antibiotics in patients with suspected sepsis. The protocol was associated with less antibiotic use (32 percent lower odds of antibiotic continuation) and no evidence of harm. These findings give stewards an evidence-based tool to decrease antibiotic use in hospitalized patients.

The **DoD/DHA** Antimicrobial Stewardship Program is supporting an ongoing research project to evaluate antimicrobial stewardship programs at DoD facilities.

### Sub-objective 1.3.6

**Evaluate data on antibiotic use and stewardship practices in production animal species, including cattle, swine, poultry, goats, and sheep.**

#### Target 1.3.6.1

**Publish information on relevant practices by 2021.**

**USDA/APHIS** published antibiotic stewardship information in the descriptive report *Goat 2019 Part I: Reference of Goat Management Practices in the United States, 2019* and in the information brief *Antibiotic Use and the VCPR on Goat Operations*. More detailed information on antibiotic use in goats, including use of specific antimicrobials in feed, water, injection, bolus, drench, or intramammary infusion, will appear in the second Goat descriptive report, which will be published in 2024. Information on antibiotic use and stewardship on U.S. feedlots and swine operations will be published in 2023 and 2024. Information on antibiotic stewardship and some limited information on antibiotic use in bison will be available in 2024; however, antibiotics are not commonly used on U.S. bison operations.

### Sub-objective 1.3.7

**Engage the animal health community, crop protection community, and other relevant stakeholders to advance strategies intended to foster the responsible use of medically important antibiotics in plants and animals.**

#### Target 1.3.7.1

**Develop and implement strategies by 2025.**

Preserving the effectiveness of antibacterial and antifungal drugs is essential to protecting the health of humans, animals, and plants. However, the use of antibacterial or antifungal compounds, including certain pesticides, in any setting can contribute to the emergence of antimicrobial-resistant organisms, and possibly result in future infections in humans, animals, and plants becoming more difficult to treat. Certain pesticides, including antibacterials and some antifungals used in agriculture as well as some pesticides used in other settings, are similar to medically important antimicrobial drugs used in human and veterinary medicine. Recent evidence indicates that the use of some antifungal pesticides can select for resistant organisms that pose a potential risk to human and animal health. The U.S. government has recognized the potential impact of this on the development and spread of AR and has initiated an interagency process, involving **HHS**, **EPA**, and **USDA**, to consider available evidence and develop an approach to improve

assessments of potential risks to human and animal health where the use of certain pesticides could result in AR that compromises the effectiveness of medically important antibacterial and antifungal drugs.

To promote judicious use of antimicrobial drugs in animals, **FDA/CVM** published a concept paper to obtain early input from the public on a potential framework for how animal drug sponsors could voluntarily make changes to the approved conditions of use for certain medically important antimicrobial drugs to establish a defined duration of use for those indications that currently lack a defined duration of use. This concept paper received over 30,000 comments. CVM is reviewing the feedback received.

In 2021, CVM also finalized GFI #263, which outlines the process for animal drug sponsors to voluntarily change the approved marketing status of certain medically important antimicrobial drugs from over-the-counter to prescription. Once this change is made, these important drugs may only be used in animals under the supervision of a licensed veterinarian. This GFI outlines a two-year timeframe to implement this change. In the interim, FDA plans to work with affected stakeholders and state partners to answer questions about the voluntary transition process and provide assistance where possible. CVM has developed a multi-media outreach campaign for stakeholders affected by GFI #263, including 10 online deliverable, and targeted outreach to three key states (Texas, Arizona, and Oregon) through social media and radio ads.

**CDC** has developed epidemiology and laboratory infrastructure and expertise to investigate antimicrobial-resistant infections that are defined as caused by reoccurring, emerging, or persisting strains. During FY 2022, CDC partnered with the National Institute for Animal Agriculture to hold the Antibiotic Symposium, during which antibiotic stewardship was presented as a key issue when it comes to agriculture sustainability.

CDC also funded Food Safety CoEs to engage with stakeholders and foster responsible use of medically important antibiotics in animals. The Colorado CoE assessed antimicrobial drug prescribing by companion animal veterinarians during telehealth visits, documented barriers to judicious antimicrobial drug prescribing, and described pet owner use and satisfaction with telemedicine visits. The Minnesota CoE piloted veterinary MDRO and hospital-associated case definition to quantify transmission in companion animal patients; expanded veterinary laboratory capacity for detection, characterization, and public health response communication of carbapenem-resistant organisms; and created educational and outreach materials for MDRO discussions with clients.

The New York CoE worked to quantify use of World Health Organization Critically Important Antimicrobials (WHO-CIA) in horses and document the effect of veterinary teaching hospital antimicrobial stewardship guidelines on clinician prescribing of WHO-CIA in small animal patients. Antimicrobial-resistant infections have been associated with contact with animals purchased from pet stores and feedstores. Therefore, the Tennessee CoE used CDC funding to assess pet store and feedstore employees' knowledge, attitudes, and practices involving the prevention and transmission of enteric pathogens from contact with animals. These survey results will inform the development of educational interventions and materials.

## Objective 1.4

**Develop and implement evidence-based policies and practices to prevent infections and stop the spread of antibiotic resistance across One Health.**

### Sub-objective 1.4.1

**Support further prevention of healthcare-associated infections (HAIs) prioritized in the National HAI Action Plan.**

#### Target 1.4.1.1

**Meet the targets identified in the National HAI Action Plan.**

The **CMS** HQICs target reduction in numerous HAIs in critical access, rural, and lower-performing Inpatient Prospective Payment System hospitals, as well as tribally run American Indian/Alaska Native facilities. CMS also supports the Indian Health Service facilities to support improved outcomes and decreased HAIs. The CMS HQICs work with state hospital

associations and health departments in addition to accessing tools and resources from numerous specialty organizations such as CDC, the Society for Healthcare Epidemiology of America (SHEA), IDSA, and Institute for Healthcare Improvement (IHI) on instituting best practices for infection control in the hospitals they support.

Through the QIN-QIOs, CMS targets reduction of HAIs in enrolled nursing homes. The QIN-QIOs use the CDC Core Elements of Antibiotic Stewardship, the AHRQ antibiotic stewardship toolkit, and other toolkits to provide direct education and technical assistance to nursing homes. Additional coordination takes place with the state health department and regional efforts to identify specific needs, and systemic integration of antibiotic stewardship elements in nursing homes.

In FY 2022, **CDC** worked to develop targets for the next HAI National Action Plan for key HAIs, including MRSA bloodstream infections, central-line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), and CDI. Data for 2021 from acute care hospitals suggested increases in SIRs for most HAI types compared to 2020. Compared to the 2015 baseline, ventilator-associated pneumonia and MRSA bloodstream SIRs were both higher. Both HAIs, as well as most other HAI types, were likely substantially affected by issues related to the COVID-19 pandemic including surges in patient volumes, shortages of supplies, and limitations on dedicated time for support of IPC activities.

HAI targets (i.e., CLABSI, CAUTI, and CDI) are tracked by DHA Patient Safety Program and the EpiData Center and reported routinely. **DoD** is currently unable to track CDI data for facilities that have transitioned to the new electronic health record system.

### Sub-objective 1.4.2

**Support national and state policies to help prevent HAIs and stop the spread of antibiotic resistance within and between settings and communities.**

#### Target 1.4.2.1

**Develop and/or strengthen infection control requirements, standards, and associated guidance across healthcare settings.**

**CDC** continued to update guidance related to healthcare infection control practices for the COVID-19 pandemic. CDC also began to expand lessons learned during the pandemic to broader guidance documents, including updates to the *Infection Prevention and Control Core Practices*. As well, CDC worked to update its antimicrobial-resistant pathogen containment guidance and developed additional antimicrobial-resistant infection prevention guidance designed to address ongoing increases in antimicrobial-resistant pathogens. CDC worked with the Healthcare Infection Control Practices Advisory Committee to provide guidance on a new strategy for controlling antimicrobial-resistant pathogens in nursing homes. Called Enhanced Barrier Precautions, this strategy is designed to target infection control practices to the highest-impact situations while maintaining resident quality of life. CDC continued to update its healthcare occupational health guidance and has started on a revision of healthcare HIV post-exposure guidance.

The **CMS** HQICs work with state hospital associations and health departments in addition to accessing tools and resources from numerous specialty organizations—such as CDC, AHRQ, SHEA, IDSA, and IHI—on instituting best practices for infection control in the hospitals they support, with particular attention to ensuring the use of evidence-based protocols and interventions to the hospitals that may include, but shall not be limited to, preventing and reducing the misuse of antibiotics, early detection of *C. difficile* and prevention of transmission in ICU and non-ICU settings, promoting best practices in hand-washing, and decontamination strategies, among others.

#### Target 1.4.2.2

**Promote equity across public health by incorporating efforts to understand and address health disparities in antibiotic resistance, including through CDC's CORE Health Equity Science and Intervention Strategy, an agency-wide strategy that includes tailored prevention efforts and materials.**

In FY 2022, **CDC** conducted a scoping review of health equity and antibiotic prescribing. The review found that certain populations are more likely to receive inappropriate antibiotics. CDC is using this information to incorporate health-equity-driven efforts into its antibiotic stewardship program and research activities. In addition, CDC continued to drive progress to address AR and health equity as a part of CDC's CORE Initiative by working across key agency programs such as Project Firstline (to address training gaps for healthcare workers from diverse educational and training backgrounds), the AR Lab Network (working to identify ways to include and analyze patient demographic data alongside laboratory test results to provide a more comprehensive picture of AR in certain populations), and the NHSN (to enhance patient demographic data for future analysis and drive improvement in healthcare quality). While racial and ethnic minority patients and those from lower socioeconomic levels are known to be disproportionately affected by HAIs, further research is needed to better understand which patient- and facility-level factors can affect outbreak risks. To assist healthcare facilities and public health entities in collecting information needed to investigate potential inequities related to HAI outbreaks and implement tailored prevention strategies, CDC collaborated with CORHA to create a comprehensive list of patient- and facility-level variables that can be collected during or following an HAI outbreak investigation.

### Sub-objective 1.4.3

**Promote biosecurity practices on farms and other animal care facilities to reduce the risk from antibiotic-resistant pathogens.**

#### Target 1.4.3.1

**Develop updated biosecurity educational materials by 2024.**

**USDA/APHIS**'s pursuit of this target is delayed due to challenges in data collection.

### Sub-objective 1.4.4

**Collect information about biosecurity practices on farms to optimize educational materials about biosecurity for different industries.**

#### Target 1.4.4.1

**Report results of biosecurity data from the National Animal Health Monitoring System from 2021 (feedlot, swine) by 2023.**

**USDA/APHIS** published information on biosecurity practices used on U.S. goat operations in *Goat 2019 Part I: Reference of Goat Management Practices in the United States, 2019*. *Goat 2019 Part II: Reference of Goat Health and Management Practices in the United States, 2019* will provide a more in-depth examination of biosecurity practices on U.S. goat operations and will be published in 2024. Information on biosecurity practices used at U.S. feedlots and swine operations will be published in 2023 and 2024. Information on biosecurity practices used at U.S. bison operations will be published in 2024.

### Sub-objective 1.4.5

**Increase research on infection prevention and the emergence and spread of antibiotic resistance and use this research to prevent infections and the spread of antibiotic resistance.**

#### Target 1.4.5.1

**Increase research in this area and translate significant findings into practice.**

In FY 2022, **AHRQ** committed additional funds totaling $8.2 million, including the out-years of projects initially funded in FY 2022, to research projects on HAI prevention. Meritorious grants in FY 2022 included several focusing on various aspects of surgical site infections and a project studying appropriate infection prevention staffing. AHRQ's support for research on HAI prevention is ongoing.

Preventing HAIs reduces the need for antibiotics, thereby slowing the development of AR. Preventing HAIs also prevents the transmission of antimicrobial-resistant bacteria, further reducing the risks of patients developing resistant HAIs. **AHRQ** collaborated with NIH to further these aims, while also supporting the goal of translating the results of clinical trials into practical materials for clinical use. AHRQ has completed the development of a toolkit based on the NIH-supported ABATE Infection Trial, which indicated that targeted decolonization to remove bacteria from adult non-ICU patients who have indwelling medical devices produced a significant reduction in bloodstream infections. The toolkit provides hospital infection prevention programs with videos and written materials on how to implement best practices for performing targeted decolonization in these patients. The project also completed a usability assessment of draft toolkit materials which informed revisions of the toolkit materials. The final toolkit materials were posted on the AHRQ website in March of 2022.

In 2022, the AHRQ Safety Program on preventing CLABSI and CAUTI in ICUs completed its multi-year quality improvement program, consisting of a series of six cohorts participating in 12-month intervention periods. This large-scale implementation program assisted over 650 ICUs nationwide with preventing and reducing their elevated CLABSI and/or CAUTI rates using the AHRQ-developed CUSP. CUSP combines techniques to improve safety culture, teamwork, and communication, together with technical practices that have shown success in preventing and reducing CLABSI and CAUTI. An educational toolkit developed based on the experiences of the participating units, including videos, webinars, and tip sheets, is available for public use. The toolkit was posted in March 2022 and was highlighted by subject matter experts in a virtual session at the Society of Critical Care Medicine's 2022 Critical Care Congress.

The AHRQ Safety Program for improving surgical care and recovery has adapted CUSP to promote hospitals' use of standardized, evidence-based clinical care practices designed to improve pre-, peri- and post-operative care and to enhance patient recovery after surgery. Over six years (September 2016 through September 2022), roughly 350 hospitals participated in the program. A toolkit is being developed consisting of evidence-based components of enhanced recovery for surgical patients undergoing elective colorectal, gynecologic, or hip or knee replacement procedures, or more urgent hip fracture or emergency general surgery procedures, including components designed to optimize antibiotic use and to prevent postoperative infections. The toolkit is being refined based on hospitals' and patients' experience with the program. AHRQ anticipates finalizing and posting toolkit materials in the spring of 2023.

The AHRQ Safety Program for MRSA prevention is a nationwide implementation project targeting ICUs/non-ICUs, surgical services, and long-term care facilities with the goal of reducing the burden of MRSA infections, surgical site infections, and other HAIs caused by antimicrobial-resistant bacteria. The program provides educational materials and technical assistance for the implementation of evidence-based infection practices. The program also strengthens the culture of safety and improves teamwork by adapting the CUSP method to each setting. A toolkit based on the content shared in the project and refined by participants' experience in the project will be made available on the AHRQ website after the program is completed. The ICU/non-ICU cohort is well into the implementation phase, which started in May 2022. Surgical service recruitment is ongoing with implementation scheduled to begin in January 2023. Long-term care recruitment is scheduled to begin early 2023. Each cohort's implementation phase will last 18 months.

**CDC** is conducting applied research to better understand molecular mechanisms of resistance in TB. In this research, WGS data are combined with phenotypic susceptibility testing, primarily through the determination of MIC, to identify and characterize different genetic determinants of resistance for new and repurposed anti-TB drugs. This work includes an evaluation of the contribution of phylogenetic lineage to different MIC values. A new bioinformatic pipeline has been developed for sharing with state public health laboratory partners to expand capacity and advance their ability to detect drug resistance and potentially predict susceptibility for some drugs. Work is also being conducted as part of a global surveillance study to evaluate MIC values in multidrug-resistant TB isolates to the newest anti-TB drug, pretomanid. This applied research helps to support the Molecular Detection of Drug Resistance clinical testing service as scientific data are shared to aid results interpretation.

Additionally, CDC evaluated national and international gonorrhea genomic sequences collected through multiple programs, including CDC's SURRG program to study resistance development within the U.S. This method also helps researchers identify the acquisition of resistance markers via recombination within gonorrhea lineages.

CDC has also partnered with The Ohio State University to conduct sampling of animal feed and pet food to evaluate the presence of antimicrobial-resistant bacteria and resistance genes and elucidate potential mechanisms of antimicrobial-resistant bacteria transmission from feed to animals. Data collection is complete; manuscript and educational materials for feed mills are in development. During 2021–2022, CDC shared data with partners at the American Veterinary Medical Association, and other relevant animal health organizations, to discuss antibiotic use practices and barriers to implementing stewardship activities among dog breeders and pet owners. Additionally, CDC collaborated with Texas Tech University to assess the emergence and spread of MCR-1—which can make bacteria resistant to colistin, a last-resort drug for some antimicrobial-resistant infections—in the Dominican Republic; a manuscript has been submitted for publication.

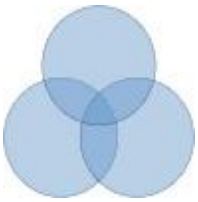
CDC also continues to fund 11 academic centers through the Prevention Epicenters Program to conduct collaborative research that leads to the prevention of HAIs and AR. The Prevention Epicenters Program is a collaborative network of public health experts in relevant fields of HAI and AR that responds to research priorities to protect patients. The network conducts research to support the translation of innovative IPC strategies for preventing HAIs, AR, and other adverse events in all healthcare settings.

CDC continues to support more than two dozen organizations to participate in the Safety and Healthcare Epidemiology Prevention Research Development (SHEPheRD) Program to develop and conduct research and innovative prevention projects related to HAIs and AR across the healthcare spectrum.

CDC's Modeling Infectious Diseases in Healthcare Network (MInD-Healthcare) responds to evolving public health needs in healthcare settings by conducting transmission modeling research and assessing high-impact intervention strategies.

Projects conducted by several **DoD** components have been initiated to look at predictors for MDROs.

# Goal 2: Strengthen National One Health Surveillance Efforts to Combat Resistance



## Objective 2.1

**Strengthen testing and training capacities and capabilities, enhance integration and harmonization of testing data, and expand the reach of federal antibiotic resistance laboratory networks across One Health.**

### Sub-objective 2.1.1

**Expand surveillance through existing systems to monitor antibiotic resistance from multiple sources across One Health.**

#### Target 2.1.1.1

**Increase the amount of laboratory testing for antibiotic resistance, the number of isolates accompanied by test results and available data, and the number of different specimen sources and specimen types collected.**

Through the AR Lab Network, **CDC** supports all 50 states, several large cities, and some territories in expanding or implementing new AR testing for improved detection of AR threats, including for HAIs, fungi, and gonorrhea. More than 25 states have implemented local screening for urgent AR threats such as *C. auris* to inform IPC efforts and support outbreak investigations. Additionally, more than 40 jurisdictions were funded to implement WGS for enhanced detection of AR threats and to support outbreak response efforts (14,000 isolates sequenced and uploaded since the start of FY 2022). Since 2016, the AR Lab Network has performed more than 650,000 different tests, including more than 160,000 isolate characterizations, 160,000 colonization screenings, and 320,000 whole-genome sequences—including approximately 8,000 TB isolates annually through the National TB Molecular Surveillance Center to identify resistance and control outbreaks as soon as they emerge.

The WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) country assessment was completed for 2021. CDC's 2020 gonorrhea data were submitted for the 2021 data call. Additional data are not yet available during the WHO timeframe because of delays due to the COVID-19 pandemic. Teams continue to collect data as available, but delays continue. In 2022, CDC participated in the pilot of the GLASS-FUNGI module, which focuses on fungal bloodstream infections caused by *Candida* spp. Data from 2018 were successfully uploaded.

Through CDC's AR Lab Network, CDC continued to provide AST testing of more than 3,600 gonorrhea isolates and WGS of more than 1,700 of gonorrhea isolates collected through the Gonococcal Isolate Surveillance Project (GISP), enhanced GISP (eGISP) and SURRG programs in 2022. In 2021–2022, CDC improved the processing of WGS, through quality programs and timeliness, and provided over 2,500 sequences to public databases for study. The genomic analysis of surveillance-based *N. gonorrhoeae* isolates from the U.S. in 2019 was submitted for publication in September 2022 and is pending publication. Additionally, CDC's eGISP (Part B) was added to the overall GISP project in 2021 to develop methods for conducting molecular surveillance of markers associated with gonococcal resistance. In addition to collecting samples for culture, this component of eGISP continues to collect remnant NAAT samples to develop assays for identifying known resistance associated mutations.

Through NARMS, CDC coordinated with the PulseNet Network to perform WGS analysis to detect resistance on more than 100,000 enteric isolates. Among these isolates, more than 80,000 were clinical isolates from state public health labs and more than 20,000 were food/animal/environmental isolates sequenced by USDA/FSIS. CDC also tracks the number

of resistant enteric infections (typically "community-acquired") through the NARMS Now platform. Due to the reporting lag caused by the COVID-19 pandemic, AST data for 2020–2022 are currently preliminary but analysis is in progress. Resistance data predicted by WGS are up to date and available in near real time.

CDC also improved monitoring of known AR reoccurring, emerging, or persisting in strains from human, food, and animal sources and collaborated with state partners to perform enhanced surveillance for extensively drug-resistant Typhi, MDR *Salmonella* Kentucky, and MDR *Salmonella* Newport. CDC also funded the Washington Food Safety CoE to evaluate and improve the Washington Integrated Surveillance for Antibiotic Resistance (WISAR) surveillance database. WISAR is a database maintained by the University of Washington that combines clinical and public health bacterial isolate antibiotic susceptibility test results for humans, animals, and the environment from NARMS (data on humans, animals, and food), the Washington Department of Health Public Health Laboratory, and medical facilities (including a large medical laboratory database), as well as veterinary clinical data from a regional veterinary diagnostic laboratory called the Washington Animal Disease Diagnostic Laboratory. The database is used to generate community antibiograms for human and veterinary antibiotic stewardship and surveillance. A periodic summary is distributed between human, animal, and environmental health agencies; stakeholders; and professionals.

CDC funding will be used for surveillance database evaluation and resulting publications (antibiograms and spatial analyses of resistance) to increase usability, acceptability, and timeliness, and to determine ways to increase the volume of human and veterinary clinical laboratory database submissions. The Washington CoE aims to disseminate the pilot project and lessons learned with other states and universities.

AST data from over 5,000 isolates and WGS data from over 500 isolates were collected through **USDA/APHIS'** NAHLN AMR pilot. APHIS's Wildlife Services National Wildlife Research Center (WS NWRC) has ongoing work on antimicrobial-resistant bacteria in feral pigs frequenting landfills, with isolates being stored.

To further understand AR in bacteria from food animal species, **USDA/FSIS'** NARMS expansion program continued additional sampling and AR analysis. The usual NARMS bacterial targets (*Salmonella*, *Campylobacter, Enterococcus*, *E. coli*) were isolated and characterized from the cecal contents of minor animal species—sheep, goats, and veal. The same targets except *Campylobacter* were isolated from Siluriformes. Additional isolates were also characterized from the microbial diversity and carbapenem resistance projects. During FY 2022, under the traditional NARMS cecal sampling and the expansion sampling, over 5,000, and 1,000 isolates were retrieved respectively and characterized further for AR.

### Target 2.1.1.2

**Submit all identified multidrug-resistant bacterial and fungal isolates of concern (e.g., antibiotic-resistant pathogens identified in the CDC 2019 AR Threats Report) from DoD Defense Health Agency Medical Centers for centralized and standardized genetic characterization at the Multidrug-Resistant Organism Repository and Surveillance Network (MRSN) by 2023.**

**DoD** has completed this target ahead of schedule. All major hospitals across the MHS now submit all antimicrobial-resistant bacterial and fungal isolates of concern to the MRSN on a weekly basis, where they undergo centralized storage and standardized genetic characterization.

### Target 2.1.1.3

**Increase laboratory capacity for colonization screening in state and local health departments to detect and respond to existing and emerging threats that can be exacerbated by COVID-19, such as CRE and *C. auris*, by 2025.**

In FY 2022, **CDC's** AR Lab Network expanded colonization screening from seven regional laboratories to 26 labs nationwide with "Strengthening HAI/AR Program Capacity" supplemental funding supported by ARP funding. This expansion includes doubling *C. auris* screening by the AR Lab Network between 2020 and 2021. The AR Lab Network also started screening of *Aspergillus fumigatus* isolates for azole resistance in August 2021 and has already found three isolates with confirmed azole resistance and two with a genetic mutation associated with agriculture fungicide use. CDC

also published an article detailing a case of fatal *A. fumigatus* infection in Pennsylvania. Since 2016, the AR Lab Network has performed more than 650,000 different tests, including more than 160,000 colonization screenings.

### Sub-objective 2.1.2

**Increase whole-genome sequencing and antibiotic resistance phenotypic and genotypic testing in laboratory networks for antibiotic-resistant pathogens listed in CDC's 2019 AR Threats Report and upload sequenced data to the National Institutes of Health (NIH) National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) or to other approved, secure, and widely accessible databases.**

#### Target 2.1.2.1

**Increase numbers of isolates each year with test results and uploaded sequence data.**

ARP funds awarded this year to **CDC's** AR Lab Network support new or expanded WGS activities of bacterial and/or fungal pathogens at more than 40 state or local public health laboratories. CDC updated guidance to enhance timeliness of NIH/NLM/NCBI sequence uploads. There are currently more than 21,000 bacterial HAI sequence files uploaded to the CDC HAISeq Umbrella BioProject, including nearly 16,000 posted in the past two years (compared to 2,000 uploaded during 2014–2020).

CDC increased the bioinformatic tools available for WGS data analyses, developing and releasing new HAI (PHoeNIx) and fungal (MycoSNP) pipelines and working with states to improve their capacity for local analysis, tracking resistance, and response activities. CDC has worked directly and individually with more than 40 groups to support the local implementation of PHoeNIx.

AST data from over 5,000 isolates and WGS data from over 500 isolates were collected through **USDA/APHIS'** NAHLN AMR pilot.

### Sub-objective 2.1.3

**Establish an accelerator program to advance implementation of whole-genome sequencing, metagenomics, and other molecular testing for antibiotic-resistant pathogens in humans, animals, plants, and the environment and to coordinate training guidance across agencies and among public and private organizations.**

#### Target 2.1.3.1

**Establish at least one collaboration through this program to enhance whole-genome sequencing or metagenomics techniques by 2023.**

In FY 2022, **CDC**, in collaboration with the AR Lab Network, continued to roll out *C. auris* WGS as a part of a larger effort to launch FungiNet, a global network to advance pathogen genomics in fungal disease surveillance and epidemiology. As a part of these efforts, CDC, the State Public Health Bioinformatics Group, and other ELC partners developed and launched a new bioinformatics pipeline, MycoSNP, that analyzes WGS data of fungal pathogens. This tool helps improve the operability of state public health lab infrastructure while improving the tracking of fungal pathogens and outbreak investigations. CDC hosts a monthly "MycoSNP Discussions Group" to encourage further community development of the pipeline.

CDC also hosted a series of onboarding workshops to enhance laboratory and bioinformatics capacity to perform *C. auris* WGS for earlier detection and more effective investigation of clusters and outbreaks of fungal pathogens. More than 60 partners attended the workshops, which brought together regional and non-regional labs in the AR Lab Network. Additionally, CDC provided technical support to the 10 public health labs implementing *C. auris* WGS through AR Lab Network and activities funded through ARP. CDC continues to validate *C. auris* sequences generated by participating laboratories to ensure sufficient quality and the correct isolate classification. Finally, CDC staff conducted site visits to the seven regional laboratories to get a better sense of each lab's sequencing and analysis workflow, share the national vision and strategy of FungiNet, and identify any gaps or issues. As a result of these efforts, there are more than 700

isolates with sequence data available through NIH/NLM/NCBI's GenBank and Sequence Read Archive (SRA) within the first full year of the rollout (compared to the approximately 1,000 isolates uploaded between 2017 and 2021).

CDC continued the collaboration and advancement of sequencing for HAI/AR pathogens through the APHL, CDC, and state public health laboratory HAI/AR sequencing workgroup and through the AR Lab Network. In 2022, CDC rapidly built and deployed a bioinformatic pipeline, PHoeNIx, for analyses of HAI/AR sequencing data. PHoeNIx is a free, publicly available pipeline that enables states to perform their own bioinformatic analyses on bacterial pathogens, instead of sending to a private company or CDC. To our knowledge, this is the only free, readily available pipeline that has been tailored for HAI/AR bacterial pathogens. CDC worked to ensure PHoeNIx could be accessed through a variety of platforms, which enables states with a range of bioinformatic capacity to be able to run PHoeNIx. Additionally, through the collaboration of the HAI/AR sequencing workgroup and other ELC state public health lab partners, CDC completed multiple rounds of beta and pilot testing of the PHoeNIx pipeline before launch, which significantly improved the pipeline and rollout. Furthermore, CDC has provided a critical database for running PHoeNIx to approximately 50 partners, further improving the data generated by states using PHoeNIx. PHoeNIx has a Git issues tracker that enables any group using the pipeline to provide feedback; CDC follows up on each issue raised. The HAI/AR Sequencing workgroup, held monthly, provides an alternative route for state public health laboratories to provide feedback.

Through the AR Lab Network, CDC enhanced local capacity through both funding (including support by ARP) and technical support from CDC to more than 40 public health labs sequencing and analyzing HAI/AR bacterial pathogens. As a result of the efforts to accelerate sequencing, there are now more than 21,000 bacterial HAI isolates with sequence data available through NIH/NLM/NCBI's GenBank and SRA (compared to approximately 2,000 isolates uploaded between 2014 and 2020). CDC has established concrete workflows to connect these sequencing data with other relevant laboratory testing data to identify putative novel carbapenemase genes for rapid response, known carbapenemase genes that may be escaping detection by traditional methods, or other laboratory improvements that are needed. Finally, CDC revamped and overhauled guidance and priorities for HAI/AR bacterial sequencing to enhance their capacity and standardize sequencing nationally; this information was distributed in fall 2022 and promoted through multiple seminars and calls with states, the AR Lab Network, APHL, and other partners. CDC continues to provide technical assistance to states to increase capacity for interpretation of sequencing data.

In 2021, CDC established a gonorrhea WGS external quality assessment (EQA) program for AR Lab Network labs that test gonorrhea isolates. The EQA program has been valuable in identifying sequence quality concerns and any sample issues. The CDC EQA technical team supports these AR Lab Network labs to troubleshoot issues and develop corrective and preventative actions to optimize real-time WGS for surveillance and public health action. CDC also continued to enhance eGISP Part B, started in 2021. These eGISP sites provide NAAT samples to CDC, which aids CDC in providing real-time polymerase chain reaction, or PCR, test for future surveillance for the detection of DNA sequences at five gonorrhea-resistance-determining alleles. This process helps detect AR variants in remnant NAAT specimens in settings without culture capacity.

The COVID-19 pandemic prevented multiple collaborations from commencing, but as restrictions are lifted collaborations are starting to proceed. Currently, **DoD/MRSN** is in preliminary talks with scientists at the CDC to collaborate on a project to compare and enhance WGS of bacteria at both agencies.

## Objective 2.2

**Continue expanding and improving access to specimen and data repositories for research and innovation.**

### Sub-objective 2.2.1

**Expand the contents of current repositories across One Health of bacterial and fungal strains and their associated genotypic, phenotypic, and descriptive data and, where possible, improve and increase the accessibility, transparency, interoperability, security, storage, and utility of these data.**

### Target 2.2.1.1

**Increase the number of isolates, panels, and data available and relevant publications in the scientific literature.**

**CDC** and **FDA** continue their collaboration with a new interagency agreement to enhance the number of isolates in the CDC &FDA AR Isolate Bank, as well as the information available on the isolates, including WGS data. The AR Isolate Bank isolates continue to be distributed to researchers' clinical laboratories, as well as to diagnostic device manufacturers who request the isolates for verification, validation testing, research and development, and studies to prepare for regulatory submissions to FDA.

Since 2021, CDC has also added several isolates to the AR Isolate Bank: ESBL bacterial isolates collected as part of the EIP Healthcare-Associated Infections—Community Interface (HAIC) Multi-Site Gram-Negative Surveillance Initiative (MuGSI); one *Pseudomonas aeruginosa* isolate harboring blaSIM (a gene conferring resistance to carbapenems); a positive *Pseudomonas aeruginosa* isolate; and cefiderocol susceptibility data for 37 AR Isolate Bank isolates. In addition, the AR Isolate Bank website now contains a dedicated section listing publications that reference AR Isolate Bank isolates. The AR Bank website has also been enhanced to display drug/isolate updates made over time (e.g., MICs to new antibiotics).

During 2021, CDC began adding to a set of *Shigella* isolates from NARMS, with a target goal of 30 isolates in 2022, that represent different mechanisms of resistance to fluroquinolones and a range of susceptibility to fluroquinolones and azithromycin. This activity has now been completed.

In 2022, isolates harboring IMP-type metallo-beta-lactamases, a type of carbapenemase detected in Enterobacterales, collected through CDC's AR Lab Network were added to the CDC & FDA AR Isolate Bank collection to detect IMP variants. Furthermore, WGS raw data are being reanalyzed with newly in-house-developed AR gene detection tools based on amino acid similarity for assembled genes to address potential redundant/missed gene calls of closely related multiple copy genes. To date, two panels have been reanalyzed and updated gene information has been published on the AR Isolate Bank website. Detection tools like these help researchers and laboratorians detect new and unusual resistance mechanisms more efficiently and build innovative solutions to combat AR threats.

**CDC** published several manuscripts including a manuscript describing national surveillance of *E. faecalis* and *E. faecium* and a manuscript describing the molecular epidemiology of carbapenem-resistant *A. baumannii* in the U.S., a manuscript unpacking the molecular epidemiology of CRE as well a manuscript focused on WGS of carbapenem-resistant *P. aeruginosa*.

**FDA's** Vet-LIRN laboratories conducted AST on over 4,000 isolates across nine different organism groups in the past year. Collections were from a variety of animal sources, including sick companion and food animals. FDA NARMS conducted both AST and WGS on over 5,000 isolates from retail meat and seafood.

**NIH's** National Database of Antibiotic Resistant Organisms (NDARO) is a centralized hub for researchers to access AR data to facilitate real-time surveillance of pathogenic organisms. The project aims to make AR-related data more widely available by collecting genetic and antibiotic susceptibility data in a centralized website hosted by the NIH/NLM/NCBI. To increase standardization, NIH/NLM/NCBI developed and maintains a curated reference database of AR, virulence, and stress response genes. NIH/NLM/NCBI developed the AMRFinderPlus algorithm to identify these genes in bacterial genomes using the reference database. NIH/NLM/NCBI also developed the Isolates Browser, which (as of September 30, 2022) provides information for more than 1 million isolates on clonality and allows researchers to identify bacterial genomes with AR, virulence, and stress response genes, along with associated metadata. The NIH/NIAID-supported Bacterial and Viral Bioinformatics Resource Center (BV-BRC) is a public knowledge base that provides open-source bioinformatics tools and a platform to analyze integrated data. It houses more than 640,000 bacterial genomes and more than 37 million annotated AR genes. The BV-BRC also continued the development of machine learning and artificial intelligence models to predict AR directly from genomic sequences.

**USDA/APHIS** shared AST data from the NAHLN AMR Pilot in its Tableau dashboard in near real time.

During FY 2022, **USDA/FSIS** conducted AST analysis on over 6,100 cecal and other NARMS isolates, and over 8,000 food product Pathogen Reduction/Hazard Analysis and Critical Control Point isolates. All the pathogens (over 5,300 *Salmonella* and over 5,600 *Campylobacter*) from food product, cecal, and other samples were subject to WGS analysis, as were a subset of indicator bacteria (over 1,000 *E. coli*, over 500 *Enterococcus*). All the sequences from FSIS WGS analysis were uploaded into NIH/NLM/NCBI's GenBank and SRA in real time. FSIS also continued to publish quarterly aggregate AMR tables for FSIS commodities (product and cecal content samples) on its website.

The FSIS NARMS team contributed to several publications focused on WGS and/or AR:

- "Use of Whole Genome Sequencing by the Federal Interagency Collaboration for Genomics for Food and Feed Safety in the United States"
- "Assessing the Effectiveness of Performance Standards for *Salmonella* Contamination of Chicken Parts"
- "Long-Read Sequencing Reveals Evolution and Acquisition of Antimicrobial Resistance and Virulence Genes in *Salmonella enterica*"
- "Use of Large-Scale Genomics to Identify the Role of Animals and Foods as Potential Sources of Extraintestinal Pathogenic *Escherichia coli* That Cause Human Illness"

In 2022, **DoD/MRSN** provided a diverse panel of 100 *K. pneumoniae* to the research community for use in antimicrobial development and published six peer-reviewed papers in scientific journals, an increase of two over 2021.

**EPA** published a manuscript describing a national survey of AR genes in U.S. rivers and streams.

### Sub-objective 2.2.2

**Support and expand efforts to provide rapid, accurate, and comprehensive access to antibiotic-resistant isolates, integrated data sources (including genomic, phenotypic, and functional data), and up-to-date computational analysis tools, and improve adherence to the "FAIR" (findability, accessibility, interoperability, and reusability) principles for scientific data management and stewardship.**

#### Target 2.2.2.1

**Award new grants that support access to data and computational tools focused on antibiotic resistance.**

**NIH/NLM/NCBI's** AMRFinderPlus is a tool developed to identify AR genes and point mutations, virulence, and stress response genes in bacterial genomes. The reference set of genes and point mutations is curated and includes allele submissions. Curation includes collaborative efforts with other AR databases and occurs directly from the literature when new genes and point mutations are discovered. There is an ongoing collaboration with the Public Health Alliance for Genomic Epidemiology to standardize results. As of September 30, 2022, the software has been downloaded more than 75,000 times, and three publications about the tool in *Antimicrobial Agents and Chemotherapy*, *Scientific Reports*, and *Microbial Genomics* have been cited more than 340 times.

Additionally, the **NIH/NIAID**-funded Strain Genome Explorer (StrainGE) is a toolkit that analyzes same-species, strain-level diversity in metagenomic sample mixtures. Distinguishing at the strain level is important because organisms of the same species, such as *E. coli*, can cause distinct diseases including diarrhea and UTIs, or be benign. The tool uses short-read metagenomic sequencing and is more sensitive and has a higher resolution than other available tools.

**CDC** funding supported implementation of PHoeNIx by states funded through ELC to complete sequencing and analyses of HAI/antimicrobial-resistant bacterial pathogens. This tool provides a comprehensive solution for genomic characterization of HAI/antimicrobial-resistant bacterial pathogens to inform the national landscape, including identifying the species and strain type, as well as what resistance genes are present. This work expands states' capabilities to identify and track resistance, helping inform response efforts.

### Target 2.2.2.2

**Offer training opportunities and outreach for FAIR principles.**

In FY 2022, the **NIH/Fogarty International Center (FIC)** made multiple awards to support global research training in areas such as genomic and molecular epidemiology for AR pathogens in Peru and Africa. NIH/FIC also continues to support the Combatting Antimicrobial Resistance in Africa Using Data Science project to study the clinical and molecular epidemiology of AR and MDROs in Nigeria and Rwanda. These opportunities build international research capacity and support efforts to understand and monitor the spread of AR, control healthcare- and community-associated outbreaks, and to evaluate transmission dynamics in low- and middle-income countries (LMICs). For example, researchers funded by NIH/FIC conducted a comprehensive analysis in Bangladesh of the genetic mechanisms inducing azithromycin resistance in *Shigella*. NIH/FIC-supported trainees also presented a data science approach for the precision diagnosis of sepsis in infants and children living in LMICs.

As part of the NDARO, **NIH/NLM/NCBI** is analyzing unassembled sequence data submitted to the SRA to generate assembled and annotated sequences in standard formats and then submitting these annotated microbial genomes to GenBank to make the data easily findable, accessible, interoperable, and reusable. In addition, the Microbial Browser for Genetic and Genomic Elements (MicroBIGG-E) interface contains the detailed sequence information, including location, of the AR genes and point mutations, stress response, and virulence genes identified using AMRFinderPlus for pathogen genomes in the NDARO that have been submitted to GenBank. As of September 30, 2022, more than 760,000 genomes have been submitted to GenBank as part of the analysis pipeline and are available in the MicroBIGG-E. As of September 30, 2022, the total number of genetic elements in the MicroBIGG-E is more than 17.5 million, including point mutations, acquired resistance genes, virulence, and stress response genes.

The NIH/NIAID-supported BV-BRC offers multiple training opportunities, ranging from webinars, online tutorials, onsite workshops, workshops at conferences, and a massively open online course. The BV-BRC implemented hybrid outreach activities to accommodate the exponentially increased demand for online training and resources during the COVID-19 pandemic while rebooting in-person BV-BRC training, which was paused and has been critical for developing the bioinformatics workforce. Over the course of FY 2022, NIH/NLM/NCBI and NIH/NIAID resources offered multiple virtual and in-person training opportunities, including at major domestic and international meetings such as American Society for Microbiology (ASM) Microbe, the International Association for Food Protection annual meeting, the International Conference on Emerging Infectious Diseases, the NARMS technical workshop, and CDC's Technical Outreach and Assistance for States Team 2022 meeting. These are in addition to online tutorials, videos, and analysis support.

## Sub-objective 2.2.3

**Through the National Antimicrobial Resistance Monitoring System (NARMS) and the Veterinary Laboratory Investigation and Response Network (Vet-LIRN), contribute antibiotic-resistant isolates from food and animals to the existing CDC & FDA AR Isolate Bank.**

### Target 2.2.3.1

**Establish mechanisms for sharing food and animal isolates by 2021.**

**FDA's** Vet-LIRN isolates from AR monitoring are being kept indefinitely at sequencing labs and are available upon request to NARMS. NARMS retail food isolates are stored on site and available upon request to stakeholders.

The **USDA/FSIS** cecal content and other AR sampling operates under the FDA-FSIS NARMS Interagency Agreement, which includes a formal agreement and mechanism to store and routinely share bacterial AR cultures with FDA as need arises.

## Sub-objective 2.2.4

**Migrate DoD's bacterial and fungal genome sequencing data and associated phenotypic data to a secure, cloud-based or equivalent environment, to allow authorized federal users to access pathogen data.**

### Target 2.2.4.1

**Identify suitable storage solutions that will satisfy access requirements by 2022.**

This target is complete. **DoD/MRSN** has identified two possible storage solutions that will satisfy data access requirements. Both allow for secure cloud-based access to genomic data that can be accessed by authorized federal users across the U.S. government. Discussions continue to determine what system will be selected as the final solution.

## Objective 2.3

**Strengthen the national infrastructure for antibiotic resistance surveillance data across One Health, by improving capacity, utility, timeliness, and the use of harmonized terminology.**

### Sub-objective 2.3.1

**Expand the number of sources for and quantity of antibiotic resistance surveillance data collected from inpatient healthcare facilities.**

### Target 2.3.1.1

**Explore interagency collaborations to examine options for increased reporting to the CDC National Healthcare Safety Network (NHSN) Antibiotic Resistance Option.**

In the FY 2023 Inpatient Prospective Payment System final rule, **CMS** adopted in its Medicare Promoting Interoperability Program for eligible participating hospitals and CAHs a new Antimicrobial Use and Resistance Surveillance Reporting measure under the Public Health and Clinical Data Exchange Objective, beginning with the CY 2024 electronic health record reporting period. This measure will require eligible hospitals and CAHs to be in active engagement with CDC's NHSN and to submit antimicrobial use and resistance data. **CDC** will onboard facilities and partner with other state, local, and federal government agencies to help them meet this new mandatory reporting requirement in NHSN.

While **VA** has experienced some delays in implementing an updated electronic health record, efforts continue to prepare the necessary technological infrastructure to syndicate appropriate data for submission to NHSN's antibiotic use and AR options.

### Target 2.3.1.2

**75 percent of acute care hospitals, 100 percent of DoD hospitals, 100 percent of applicable VA hospitals that have transitioned to the VA's updated electronic health record, and 25 percent of critical access hospitals, reporting to the NHSN Antibiotic Resistance Option.**

Approximately 91 percent of **DoD** hospitals (39 out of 43) are reporting to the NHSN Antibiotic Resistance Option. Most hospitals that are not reporting to the NHSN AR option are not reporting due to data availability and quality issues for antibiotic susceptibility data with DoD's new electronic medical record, MHS GENESIS.

As of October 1, 2022, **CDC** reported that 28 percent of general acute care hospitals and 7 percent of CAHs had submitted data to the NHSN AR Option. Compared to large hospitals, CAHs usually have relatively limited recourses to implement AR option reporting. CDC also reported that zero VA hospitals have submitted data as facilities are still transitioning to a new electronic health record.

### Target 2.3.1.3

**Expand DoD and VA collaborations to increase the number of VA medical centers submitting multidrug resistance data or isolates from multidrug-resistant pathogens to the MRSN.**

In 2022, **DoD/MRSN** placed an employee at the Baltimore VA Medical Center and weekly shipments of multidrug-resistant pathogens and their associated resistance data are provided to the MRSN for further characterization using WGS. The MRSN continues to engage with additional VA centers, including at San Antonio and Washington, D.C., to increase DoD/VA collaborations further.

### Sub-objective 2.3.2

**Expand the number of sources for and quantity of community-transmitted antibiotic resistance surveillance data from humans including sexually transmitted infections, enteric diseases, respiratory illness, and other diseases caused by antibiotic-resistant pathogens.**

#### Target 2.3.2.1

**Each year, increase the number of human isolates collected and analyzed.**

In FY 2022, **CDC's** AR Lab Network conducted isolate testing on over 55,000 samples, colonization screening on over 114,000 samples, and WGS on over 68,000 samples, including resistant HAIs, fungal infections, gonorrhea, *S. pneumoniae*, TB, and enteric infections.

CDC's SURRG continues to collect and analyze isolates across community-associated pathogens (such as gonorrhea), perform AR testing across specimen sources, and respond to emerging resistance. However, isolate numbers were lower than in prior years due to the COVID-19 pandemic and 2022 mpox outbreak. GISP continues to collect and analyze gonococcal isolates for AR in sexually transmitted infection (STI) clinics as a way to monitor antimicrobial susceptibility patterns in the U.S. During the first half of 2022, CDC has received roughly 4,158 samples of gonorrhea cultures that are archived at the CDC Biorepository. Recently, CDC established a gonorrhea ciprofloxacin panel of isolate resistance within the CDC & FDA AR Isolate bank. Additionally, CDC collaborated with the American Type Culture Collection (ATCC) to develop a curated, international, antibiotic-resistant Gonorrhea Isolate Panel. Currently, 49 international isolates have been phenotypically characterized and sequenced.

CDC also continues to support population-based surveillance for antimicrobial-resistant pathogens through the EIP HAIC, including collecting and submitting specimens and isolates for further testing. In FY 2022, CDC received 575 CRE, 109 carbapenem-resistant *A. baumannii*, 327 ESBL-producing bacteria, 1,017 invasive *S. aureus*, 89 nontuberculous mycobacteria, more than 1,264 *Candida*, and 970 *C. difficile* isolates for testing through EIP HAIC surveillance.

Additionally, CDC added 30 *Shigella* isolates to the CDC & FDA AR Isolate Bank. Isolates are now available for request by laboratories that want to perform verification studies needed to implement the new Clinical Laboratory Standards Institute azithromycin breakpoints.

Through NARMS, CDC has performed WGS analysis enabling predicted resistance assessment for more than 100,000 isolate sequences in year two, compared to more than 46,000 collected in year one. CDC will add Puerto Rico as an additional surveillance site in NARMS for AST surveillance for *Salmonella* for 2022.

Additionally, EIP-ABCs conducts surveillance for invasive bacterial disease caused by five key bacterial pathogens (GAS, GBS, *Haemophilus influenzae*, *Neisseria meningitidis*, and *S. pneumoniae*) at 10 sites representing approximately 14 percent of the U.S. population; EIP-ABCs collects isolates from the majority of cases, which are sent to CDC for WGS. These data are used to estimate serotype/serogroup distribution and AR data.

### Sub-objective 2.3.3

**Expand the number of sources for and quantity of antibiotic resistance surveillance data from animals, farms, and production facilities.**

#### Target 2.3.3.1

**Increase the number of animal, feed, or food isolates collected, analyzed, and used for prevention and response efforts.**

**FDA** has an ongoing human food and animal food testing program. FDA field laboratories do the testing, and the data are continuously mined for AR findings. In 2021, FDA curated a Microsoft Access database on over 8,000 *Salmonella* isolates and made a presentation at the International Association for Food Protection 2021 Annual Meeting. In 2022, FDA leveraged animal food testing efforts at state partner laboratories for isolate-level AR data and metagenomics data.

During FY 2022, over 40,000 pathogen genomes of a food, environmental, animal, or feed isolate have been submitted and made available in **NIH/NLM/NCBI's** NDARO, the vast majority from U.S. surveillance efforts. However, the COVID-19 pandemic has affected foodborne surveillance efforts in multiple ways, including a decrease in the number of sequenced and submitted foodborne pathogens.

**USDA/APHIS**'s WS NWRC has ongoing work on antimicrobial-resistant bacteria in feral pigs frequenting landfills, with isolates being stored. AST data from over 5,000 isolates and WGS data from over 500 isolates were collected through APHIS's NAHLN AMR pilot. With over 14,100 isolates retrieved from over 58,000 FSIS samples (food product, NARMS cecal, and other), **UDSA/FSIS** is well poised to detect potential changes in AR in food animals. These changes can involve novel or emerging resistance, resistance to critically important antimicrobials, or multidrug resistance. During FY 2022, FSIS recorded multidrug resistance of concern in *Salmonella* serotypes Infantis, Senftenberg, and Newport. Although these findings were not related to known outbreaks, in order to understand and possibly contain or prevent these multidrug-resistant strains/serotypes from entering/spreading through our food supply, FSIS took prompt actions to engage with NARMS partners and stakeholders.

Additionally, **NARMS** and the Public Health Agency of Canada established the Emerging Antimicrobial Resistance Alert System, which provides real-time monitoring and response to emerging and concerning mechanisms of resistance, plasmids, and resistant strains among enteric pathogens in the U.S. and Canada. Monthly updates are provided to leadership and communicated to partners.

### Sub-objective 2.3.4

**Establish new capacities for collecting antibiotic resistance data from the environment, including water and soil.**

#### Target 2.3.4.1

**Establish at least two projects to expand antibiotic resistance data collection from the environment, including national-scale testing of surface waters as part of NARMS by 2022.**

**EPA** led a NARMS watershed-scale project to collect AR data in October 2022. EPA also planned another national-scale survey of AR determinants in U.S. rivers and streams, set to begin late spring 2023. **FDA** is conducting metagenomic analysis of samples collected from the watershed. NARMS has also established a pilot expansion of the EPA National Rivers and Stream Assessment to include additional analytes and molecular targets relevant to AR. Analyses will commence in quarter two of 2023. FDA will perform metagenomic analysis of water samples. **CDC** did not have resources for surface water testing projects for 2021, and staff leads for environmental AR work were diverted to COVID-19 response activities. However, CDC partners began sample collection in Ohio in summer 2022. Plans for analyzing these data are in development.

Additionally, CDC's National Wastewater Surveillance System (NWSS) began optimizing and validating assays in 2022 to detect and quantify AR genes in wastewater. Assays in development target emerging resistance threats including carbapenemases, ESBLs, mobile colistin resistance, and vancomycin resistance.

#### Target 2.3.4.2

**Pilot collection of antibiotic resistance data from wastewater surveillance by 2023.**

**CDC**'s NWSS was established in 2020 to provide data on trends in SARS-CoV-2 infections through PCR-based analysis of community wastewater. As of December 2022, CDC has provided support to 50 states, five cities, seven tribes, and three territories for COVID-19 wastewater surveillance. In 2022, NWSS began efforts to expand the system to include additional targets, including *C. auris* and AR genes. Nine genes associated with emerging AR threats have been selected for development. The assays are currently being optimized and validated for use in wastewater.

In 2022, as part of the NWSS, **CDC** established the Healthcare–Wastewater Antimicrobial Resistance Network (Healthcare-WARN) to build capacity for the detection of AR threats in U.S. healthcare facilities through collaborations with academic, healthcare, and public health partners. In addition to the wastewater surveillance at local-Atlanta

metropolitan nursing home facilities by CDC, Healthcare-WARN has funded two partners in the western and central regions of the U.S. to conduct wastewater surveillance in long-term care facilities and skilled nursing homes through 2027. These regional efforts began in September 2022 and will assess the feasibility of wastewater surveillance for AR at long-term care facilities, optimize wastewater surveillance methodologies, and align epidemiological and case data with AR detection in the facility wastewater.

Additionally, a new CDC partner is leading development of a global community of practice for wastewater surveillance as part of the Global AR Laboratory and Response Network. These efforts expand on innovative wastewater surveillance strategies, such as NWSS, which provides community-level data on COVID-19 infection trends by looking for markers in wastewater that tell scientists when SARS-CoV-2 is present.

### Sub-objective 2.3.5

**Establish a platform for more comprehensive understanding of the carriage of antibiotic resistance genes (also known as the resistome) present across One Health.**

#### Target 2.3.5.1

**Establish a pilot sampling strategy to collect healthy human, animal, plant, and environmental specimens and epidemiological data by 2023.**

**CDC** launched its microbial ecology webpage in 2022, which features prevention tools and messages about connections between AR and microbiomes. The content underscores that efforts to better understand the role of microbial ecology in human health can be leveraged to develop and implement life-saving tools. However, any other progress in meeting this target has been delayed due to challenges resulting from the public health response to the COVID-19 pandemic.

## Objective 2.4

**Strengthen the national infrastructure for antibiotic use surveillance data across One Health, by improving capacity, utility, timeliness, and the use of harmonized terminology.**

### Sub-objective 2.4.1

**Expand the number of sources for and quantity of surveillance data on the use of antibiotics from inpatient and outpatient healthcare facilities to improve understanding and implementation of the optimal use of antibiotics.**

#### Target 2.4.1.1

**Explore interagency collaborations to examine options for increased reporting to CDC's National Healthcare Safety Network (NHSN) Antimicrobial Use Option.**

In the FY 2023 Inpatient Prospective Payment System final rule, **CMS** adopted a new Antimicrobial Use and Resistance Surveillance measure for eligible participating hospitals and CAHs as part of the Medicare Promoting Interoperability Program. The measure will require reporting under the Public Health and Clinical Data Exchange Objective, beginning with the CY 2024 electronic health record reporting period.

#### Target 2.4.1.2

**100 percent of acute care and 50 percent of critical access hospitals reporting to the CDC NHSN Antibiotic Use Option.**

As of October 1, 2022, **CDC** reported that 55 percent of general acute care and 18 percent of CAHs had reported data to the NHSN Antimicrobial Use Option.

**CDC** and **CMS** anticipate that these numbers will significantly increase over the next two years, as eligible hospitals and CAHs take steps to come into compliance with the new antimicrobial use and resistance reporting requirement in the CY 2024 Medicare Promoting Interoperability Program.

Although all **DoD** hospitals are enrolled in the NHSN antibiotic use option, only 19 facilities (41 percent) are reporting to the NHSN antibiotic use option. Facilities that have transitioned to the new electronic health record are unable to report to the antibiotic use option due to data availability issues. These facilities are expected to resume reporting in FY 2023.

### Target 2.4.1.3

**Improve timelines of annual outpatient antibiotic use tracking and reporting by 2025.**

While this target was met in 2021, **CDC**'s Office of Antibiotic Stewardship has gained access to several data sources for more timely tracking of outpatient antibiotic use and appropriateness, including the CMS Virtual Research Data Center (for Medicare data), the IQVIA National Prescription Audit, the Total Patient Tracker, longitudinal prescription and medical claims, and MarketScan data. CDC encountered challenges with staffing to support analysis of these data due to the ongoing COVID-19 response.

### Target 2.4.1.4

**Implement tracking of antibiotic use in all DoD Military Health System facilities, using the Standardized Antimicrobial Administration Ratio (based on observed inpatient antimicrobial days of therapy), by 2024.**

**CDC's** NHSN continues to provide analytic tools, technical assistance, user support, and education materials to assist NHSN users, including all DoD facilities, using the Standardized Antimicrobial Administration Ratio (SAAR).

**DoD** has created a dashboard for DoD facilities to track SAARs; however, facilities that have transitioned to the new electronic health record are unable to report to the NHSN antibiotic use option and track the SAAR metric due to data availability issues. These facilities are expected to resume tracking of SAAR values in FY 2023.

### Target 2.4.1.5

**Increase the percentage of optimal antibiotic prescriptions in the DoD Military Health System.**

**DoD** is creating an outpatient dashboard to assess inappropriate prescribing for specific conditions. This dashboard is expected to be complete and available to DoD facilities in FY 2023.

## Sub-objective 2.4.2

**Develop new or expand the number of sources for and quantity of surveillance data on the use of antibiotics collected from animals, farms, and production facilities to improve understanding and implementation of responsible use of antibiotics.**

### Target 2.4.2.1

**Increase published reports and dashboards on antibiotic use in animals.**

**FDA** published a report titled *Antimicrobial Use and Resistance in Animal Agriculture in the United States: 2016–2019* to describe current U.S. government monitoring and surveillance systems for antimicrobial sales, use, and resistance in animal agriculture and the related food chain. It cites publicly available data from 2016 to 2019 on medically important antimicrobial sales (including sales adjusted by a biomass denominator), use, and resistance as tracked by existing federal programs for each of the four major food-producing species (cattle, swine, chickens, turkeys).

**USDA/APHIS** published antibiotic stewardship information in the descriptive report *Goat 2019 Part I: Reference of Goat Management Practices in the United States, 2019* and in the information brief *Antibiotic Use and the VCPR on Goat Operations*. More detailed information on antibiotic use in goats, including use of specific antimicrobials in feed, water, injection, bolus, drench, or intramammary infusion, will appear in the second *Goat* descriptive report, which will be published in 2024. Information on antibiotic use and stewardship on U.S. feedlots and swine operations will be published in 2023 and 2024. Information on antibiotic stewardship and some limited information on antibiotic use in bison will be available in 2024; however, antibiotics are not commonly used on U.S. bison operations.

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

## Objective 3.1

**Develop and validate new diagnostics.**

### Sub-objective 3.1.1

**Develop new or enhance existing diagnostics that use isolates and primary samples to determine the presence, severity, or antimicrobial susceptibility or resistance of bacterial or fungal infections and to identify appropriate treatment.**

#### Target 3.1.1.1

**Support 10 new antibiotic-resistance-related diagnostics projects across the U.S. government annually through 2025, through funding or scientific or technical support.**

In FY 2022, **ASPR/BARDA** awarded one new contract for antibiotic-resistance-related diagnostics. The current full portfolio includes five companies supporting diagnostic projects for bacterial identification and phenotypic AST results, bacterial versus viral infections, sequencing, and/or molecular markers of resistance, and three companies developing diagnostics to detect anthrax infections. In CY 2022, two companies filed their 510(k) applications with FDA. BARDA is also currently evaluating broad agency announcement white paper and full proposal submissions from additional companies developing bacterial versus viral infections, sequencing, or phenotypic AST diagnostics.

Also during the reporting period, two BARDA-supported CARB-X diagnostic projects graduated from the portfolio and are preparing to commence clinical trials. Through 2030, **NIH/NIAID** is providing in-kind product development support through its preclinical services programs to CARB-X diagnostic contract awardees.

In FY 2022, **NIH/NIAID** supported 15 new projects on AR-related diagnostics to inform treatment options for bacterial infections and improve antibiotic stewardship. These projects include rapid point-of-care diagnostics for antimicrobial-resistant pathogens as well as novel platforms to detect STIs, sepsis, AR genes in bloodstream infections, among other areas. For example, NIH/NIAID is funding development of a rapid diagnostic to identify bacterial pathogens and characterize AR in hours instead of days directly from patient blood samples. NIH/NIAID-supported researchers are also developing a clinical algorithm to inform diagnosis and treatment of lower respiratory tract infections in resource-limited settings.

The **USDA/ARS** Infectious Bacterial Diseases Research team initiated the research project "Diagnostic and Mitigation Strategies to Control Tuberculosis in Cattle and Wildlife." This project will develop vaccines, improve current and develop novel diagnostics, and enable the rational-design of intervention strategies. Additionally, ARS researchers and colleagues published an analysis of metaphylactic antimicrobial effects on AR in high-risk beef cattle.

**CDC's** eGISP Part A continues to collect gonococcal isolates to detect AR in gonococcal infections in the pharynx and rectum for men and women and at the genital site in women. Beginning in 2021, eGISP Part B began to utilize remnant NAAT samples to identify known resistance-associated genetic mutations to expand AR surveillance in a culture-independent manner.

CDC has completed and submitted a validation packet for transition of the Clinical Laboratory Improvement Amendments–compliant Molecular Detection of Drug Resistance clinical service to a next-generation sequencing platform. This new targeted next-generation sequencing assay includes testing across 18 different genetic loci for 11 first and second-line anti-TB drugs including the newer drug bedaquiline as well as the repurposed drugs clofazimine and linezolid. Implementation is anticipated for early 2023 for all U.S. TB Programs. Additionally, CDC is working to build out electronic reporting capacity for results from this new assay to aid efficient reporting to laboratory submitters. Planning has also been initiated to develop a new molecular identification assay and for validation of drug susceptibility testing for the new anti-TB drugs pretomanid and delaminid. Validation of phenotypic testing for these newer drugs will aid efforts to correlate genotypic and phenotypic results to better understand resistance.

## Objective 3.2

**Support research to determine the appropriate use of diagnostics.**

### Sub-objective 3.2.1

**Stimulate research to better understand the appropriate use of diagnostics to determine the presence, severity, or antimicrobial susceptibility or resistance of bacterial or fungal infections in human and veterinary care.**

#### Target 3.2.1.1

**Invite research applications and support research on the appropriate use of CARB-related diagnostics in human clinical and veterinary care.**

**AHRQ** continues to invite research applications investigating the role of new and existing diagnostics, including rapid diagnostics, in improving antibiotic use, including how diagnostics should be integrated into clinical care, through its Notice of Funding Opportunity for Large Research Projects for Combating Antibiotic-Resistant Bacteria and its Notice of Funding Opportunity for Large Health Services Research Demonstration and Dissemination Projects for CARB. In 2022, AHRQ funded two new large research grants aimed at diagnostic stewardship—one aimed at reducing unnecessary respiratory cultures in pediatric critical care patients and one aimed at improved implementation of an intervention to reduce unnecessary urinary cultures in acute care hospital and long-term care patients. In addition, AHRQ funded a mentored grant supporting an investigator studying appropriate integration into care of multiplex testing for common infectious syndromes to improve antibiotic use.

**CDC** continues to analyze electronic health data to assess trends in hospital utilization of blood and urine cultures and variability between hospitals. CDC has also funded projects through the Prevention Epicenters Program and SHEPheRD Program to improve respiratory diagnostics (culture and viral testing) to decrease inappropriate antibiotic use.

The **NIH/NIAID**-supported ARLG continues to build upon initial clinical research to inform the appropriate use of CARB-related diagnostics for patient care. For example, the ARLG is preparing to conduct the Fast Antibiotic Susceptibility Testing for Gram-Negative Bacteremia Trial (FAST) trial. Additional ARLG studies in development include Rapid Diagnostic in Categorizing Acute Lung Infections (RADICAL-3), a prospective, randomized, pilot study evaluating a host gene expression test that discriminates between bacterial and viral infections among patients with acute, febrile respiratory infection in an emergency room setting, and MASTERMIND-BSI to evaluate multiple diagnostics for rapid detection of bloodstream infection directly from blood samples.

## Objective 3.3

**Stimulate the appropriate adoption and use of diagnostics.**

### Sub-objective 3.3.1

**Develop evidence-based guidance to promote the appropriate use of new diagnostics and to improve the use of existing diagnostics that determine the presence, severity, or antimicrobial susceptibility or resistance of bacterial or fungal infections in human clinical care.**

### Target 3.3.1.1

**Support the development of evidence-based guidelines for the use of new and existing antibiotic and antifungal resistance-related diagnostics.**

In collaboration with CLSI, ASM, the College of American Pathologists, and APHL, **CDC** worked to develop a toolkit for streamlined verification and/or validation of AST devices to implement updated breakpoints. In response to two new College of American Pathologists checklist items (MIC.11380 and MIC.11385), this small working group of AST leaders (two CDC members, one public health representative, three clinical lab representatives [one of them on the College of American Pathologists microbiology committee], and three industry representatives) was formed in 2022 and tasked to provide guidance and expert consensus on best practices and streamline recommendations for updating breakpoints. This toolkit will be published in June 2023; the deliverables include an introductory narrative describing breakpoints and device clearance, a form to record breakpoints used to satisfy MIC.11380, a spreadsheet comparing 2023 CLSI breakpoints to FDA interpretive criteria, refereed (tested by others in the work group) CDC & FDA AR Isolate Bank isolate sets specifically curated to address gram-negative breakpoints updated since 2009, an Excel workbook that automatically calculates performance characteristics of an AST validation or verification study (the user only has to enter their raw results), and validation/verification protocol templates. This toolkit will also include video tutorials and a webinar to orient users. The use of obsolete breakpoints can compromise AR surveillance efforts and endanger patients; a 2016 paper surveying NHSN data reveals that more than 25 percent of clinical laboratories were using outdated carbapenem breakpoints. By using this toolkit, laboratories will be able to update breakpoints to improve patient care and the accuracy of data used in AR surveillance across CDC programs.

In FY 2022, CDC worked with public health partners in the AR Lab Network to validate and deploy a new commercially available broth microdilution panel that contains 24 antibiotics, including key antimicrobial agents relevant to the AR Lab Network for gram-negative bacteria such as carbapenems, cephalosporins, monobactams, and newer beta-lactam/beta-lactamase inhibitor combination agents. These newer beta-lactam/beta-lactam inhibitor agents, like ceftazidime/avibactam and ceftolozane/tazobactam, remain active against CPOs deemed as serious healthcare threats by CDC in its 2019 AR Threats Report.

GISP and SURRG data collected by CDC were used to guide updates to the gonorrhea section of CDC's STI Treatment Guidelines, 2021 published in the *Morbidity and Mortality Weekly Report*. These data were used in determining recommended treatment regimens and for test-of-cure testing recommendations.

On October 24, 2022, **FDA's Center for Devices and Radiological Health** sent a letter to AST device stakeholders that have marketed devices in the U.S. informing them of the importance of using up-to-date breakpoints for appropriate patient management and in addressing global AR. To ensure availability of devices that use up-to-date AST breakpoints, the letter contained a request that sponsors provide FDA with listing information on the currently used breakpoints in cleared devices within 60 days.

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

## Objective 4.1

**Expand basic and applied interdisciplinary research to better understand the emergence, spread, and persistence of antibiotic resistance, and develop mitigation strategies for antibiotic resistance in human, animal, agricultural, and environmental settings.**

### Sub-objective 4.1.1

**Advance our understanding of the emergence, spread, and persistence of antibiotic resistance.**

#### Target 4.1.1.1

**Report success stories to disseminate new knowledge about antibiotic resistance and inform mitigation strategies in human health (at least two stories) and agriculture (at least one story) annually through 2025.**

**NIH/NIAID** is advancing research to better understand diversity and genomic evolution of HAIs to inform outbreak detection and prevention efforts. In an analysis of more than 3,000 bacterial isolates from hospitalized patients, NIH/NIAID-supported researchers identified nearly 100 bacterial species and found that different species were likely evolving at varying rates. In another study, NIH/NIAID-funded researchers examined clinical isolates of *C. auris* and determined that antimicrobial drug resistance is relatively stable and certain strains of *C. auris* appear primed to develop antimicrobial drug resistance.

**NIH/NIAID** established the CARB Interdisciplinary Research Units (CARBIRUs) in 2021 to support discovery to early development research activities, with a focus on combating CDC-designated antibiotic resistance threats. In FY 2022, two new centers were added to the program, expanding the scope of activities to include more studies on mechanisms of resistance as well as studies focused on identification and validation of novel cell envelope targets for antibiotic intervention in gram-negative and gram-positive bacteria. CARBIRU investigators studying poorly understood mechanisms of antibiotic resistance identified cefiderocol heteroresistance among carbapenem-resistant bacteria. Heteroresistance is a phenomenon in which only a minor subpopulation of cells is resistant to a given antibiotic. The results suggested that there could be a link between heteroresistance and antibiotic treatment failure. CARBIRU study findings are further described in a paper published in October 2021.

**NIH/NIAID** supported a study called INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection (INSPIRE-ASP), which is a set of two 92-hospital cluster randomized trials in non-critically-ill adults hospitalized with abdominal and skin/soft tissue infections. Currently, over half of non-critically-ill patients with one of these infections receive extended-spectrum antibiotics, which are used to treat antibiotic-resistant infections, but less than 5 percent are infected with an antibiotic-resistant pathogen. This trial will test the use of real-time computerized physician order entry smart prompts providing the probability that a patient is infected with a resistant pathogen. The goal of this trial is to limit the use of broad-spectrum antibiotics to situations in which the patient is likely to require them, while maintaining excellent patient outcomes. If successful, these trials could establish best practices for antimicrobial stewardship in patients with abdominal and skin and soft tissue infections.

Researchers at the **NIH/National Human Genome Research Institute**, **NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases**, **NIH/National Cancer Institute**, and the **NIH/National Institute of Dental and**

**Craniofacial Research** collaborated with external scientists to evaluate how commonly prescribed antibiotics affected the human skin microbiome. The team randomized healthy volunteers to one of four oral antibiotic regimens and collected skin microbiota samples over the course of a year. They found that participants who received two of the regimens exhibited greater changes to their skin microbiomes, including the emergence and persistence of antibiotic-resistant staphylococci. Researchers also detected an increase of genes involved in gene mobilization, indicating a stress response of microbes to antibiotics. These findings highlight the skin microbiome as a site for the development and persistence of antibiotic resistance.

**NIH/NIAID** intramural researchers showed the immune system recognizes phenol-soluble modulins, a type of staphylococcal toxin, as an early signal specifically for an *S. aureus* invasion. Researchers found that neutrophils enter from the bloodstream to destroy the invading bacteria. They further identified the internal signaling mechanism behind this neutrophil response to phenol-soluble modulins.

**USDA/ARS** organized and hosted a five-part webinar series to highlight ARS research that addresses AR and antibiotic alternatives in agriculture with U.S. and international partners and stakeholders.

In July 2022, **CDC** released *COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022*—the most comprehensive analysis to date of the effects of the COVID-19 pandemic on antimicrobial-resistant infections in the U.S. This analysis found significant surges in antibiotic use and antimicrobial-resistant infections in U.S. hospitals during the first year of the pandemic, including an alarming 15 percent increase in both resistant hospital-onset infections and deaths. These surges reflect a reversal of progress noted in the 2019 AR Threats Report, which previously showed a reduction of AR deaths by 18 percent overall from 2012 to 2017.

Although these setbacks are alarming, the report also demonstrates that CDC's foundational investments to combat AR are working, but more work is needed. The U.S. must continue to invest in preparing public health systems across One Health to address threats from multiple angles simultaneously.

Additionally, CDC described new and emerging epidemiology of MDROs with reports on community-associated CRE identified through EIP, reduced trimethoprim-sulfamethoxazole susceptibility among methicillin-resistant *S. aureus* clinical isolates, transmission of highly resistant *P. aeruginosa* from a contaminated faucet, and a multistate outbreak of extensively drug-resistant *P. aeruginosa* linked to bariatric surgery medical tourism.

CDC also supported state and local health departments to implement measures to prevent and respond to emerging AR threats, including to pursue innovative approaches for the early detection of AR genes.

CDC released a new document, *Public Health Strategies to Prevent the Spread of Novel and Targeted MDROs*, to guide health department implementation of these measures. An abstract highlighting prevention and response measures was presented at IDWeek 2022 by the California Department of Public Health and described response to a regional outbreak of highly resistant *A. baumannii*, in which the health department performed colonization screening through the AR Lab Network, conducted 71 infection control assessments, and launched a prevention collaborative, leading to sustained reductions in clinical cases. Additionally, CDC provided ARP funding for a Utah Public Health Laboratory project to develop culture-based methods to detect both carbapenemase-producing-CRE and *C. auris* from wastewater and demonstrated the relatedness of a subset of isolates from municipal wastewater treatment plant influent to isolates identified from clinical cultures of Utahans. These findings were shared at the 2022 ASM meeting.

In addition, the 2020 GISP Profiles, published in 2022, provided the overall and site-specific AST and epidemiological data for all participating eGISP Part A sites for 2018–2020.

## Objective 4.2

**Intensify basic, translational, and clinical research to support the discovery and development of new treatments, including antibiotics, non-traditional therapeutics, and optimized treatment regimens.**

### Sub-objective 4.2.1

**Support the discovery and preclinical development of new therapeutics.**

#### Target 4.2.1.1

**Award 100 new projects (e.g., grants, contracts, CARB-X awards) aimed at therapeutic discovery or development by 2024.**

During FY 2022, **ASPR/BARDA** added two assets to the Roche other transaction portfolio agreement. These assets represent novel classes of antibiotics targeting MDR gram-negative bacteria. Both will be developed as potential treatments for patients with severe MDR infections caused by MDR gram-negative bacteria that do not respond to any other antibiotic.

Also in FY 2022, seven BARDA-supported CARB-X therapeutic projects completed their initial development activities and advanced to the next stage in their respective development.

In FY 2022, **NIH/NIAID** supported over 100 new projects through grants, contracts, and preclinical services aimed at therapeutic discovery or preclinical development. The projects included research covering a range of products to treat antibiotic-resistant infections, such as small molecules, peptides, and phage therapies.

NIH/NIAID provides preclinical services to fill gaps in the product development pathway. These services include *in vitro* and *in vivo* studies, and pharmacokinetic (PK) and toxicology evaluation. In FY 2022, NIH/NIAID supported numerous products through preclinical services programs. These include novel antibiotic candidates, vaccine candidates for antimicrobial-resistant infections, non-antibiotic products such as bacteriophage and monoclonal antibodies, and compounds to be used in conjunction with existing antibiotics to restore or augment their effectiveness. NIH/NIAID preclinical services also supported novel platforms for manufacturing bacteriophage preparations and PK studies of bacteriophage in mouse models. NIH/NIAID tests new candidate therapeutics in standard mouse models of bacterial thigh and lung infections, which can provide initial *in vivo* indications of efficacy, as well as in more detailed models of bacterial infection, which can provide additional data on a candidate's performance. These projects complement numerous relevant projects that were begun in previous fiscal years. NIH/NIAID also is supporting development of new animal models through preclinical services, including models for chronic infections.

NIH/NIAID is providing preclinical and technical support to 50 percent of CARB-X projects, with a total of more than 290 studies performed since 2017. As of November 2022, a total of 92 projects have been funded through the CARB-X program. Of them, 39 are active (25 therapeutics, seven preventatives, seven diagnostics).

The NIH/NIAID Structural Genomics Centers determine 3-D structures of proteins from priority human pathogens to address key research gaps and help identify targets and strategies for therapeutic development. They have solved over 700 structures from different target proteins related to antimicrobial organisms or AR and include ESKAPE pathogens (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* species) as well as *C. difficile, Chlamydia* and *Neisseria*, of which 99 were solved in the past year. The 3-D structure information and reagents are made publicly available.

#### Target 4.2.1.2

**Identify one candidate therapeutic for bacterial infections in human medicine for further research and development by 2022.**

This target is complete. The **DoD** CARB Working Group is collaborating with an academic partner on progressing a first-in-class small molecule antibiotic (targeting the bacterial fatty acid biosynthesis pathway) toward an Investigational New Drug (IND) application to FDA with data to date reported in a peer-reviewed journal.

#### Target 4.2.1.3

**Identify one candidate therapeutic for bacterial infections in agriculture for further research and development by 2021.**

**USDA/ARS** researchers developed a novel "reversible antibiotic," or biocide, derived from natural products that has demonstrated excellent efficacy against pathogens that cause mastitis. When formulated in a mastitis balm, this reversible biocide dramatically reversed the onset of mastitis. Further research showed that the diluted biocide reverted to benign, farm-safe ingredients, which minimizes the development of antibiotic resistance associated with a residual accumulation of unwanted chemicals.

### Target 4.2.1.4

**Report success stories about additional therapeutic options for human health (at least five stories) and agriculture (at least one story) annually through 2025.**

*S. aureus* infection of bone (osteomyelitis) is difficult to treat due to its ability to colonize the osteocyte-lacuno-canalicular network, which existing antibiotics have trouble penetrating. To overcome this, **NIH/NIAID**-supported investigators proposed two bone-targeted bisphosphonate-conjugated antibiotics (BCAs). In this study, the investigators demonstrate the *in vivo* efficacy of the BCAs in mice with implant-associated osteomyelitis. The findings show clear evidence of BCA-induced killing of *S. aureus* within the osteocyte-lacuno-canalicular network of infected bone, superior to controls. If additional preclinical studies also yield promising results, these novel drugs for osteomyelitis may move forward into clinical trials to continue the development process.

Next-generation sequencing methods have revealed a large number of previously unidentified biosynthetic gene clusters in a diverse collection of bacteria. These biosynthetic gene clusters hold promise to reveal new mechanisms of action and inform discovery of novel antibiotic candidates. Leveraging a bioinformatics analysis of biosynthetic gene clusters, **NIH/NIAID**-supported researchers synthesized a novel peptide antibiotic that evades resistance. This compound, known as cilagicin BP, demonstrated activity against several ESKAPE pathogens in preclinical studies.

**NIH/NIAID** scientists evaluated cochleated amphotericin B, a new oral amphotericin B formulation, in mouse models of oropharyngeal candidiasis and vulvovaginal candidiasis and in patients with azole-resistant chronic mucocutaneous candidiasis. Oral cochleated amphotericin B reduced tongue and vaginal fungal burdens during murine candidiasis. A proof-of-concept clinical trial in human chronic mucocutaneous candidiasis showed efficacy with good tolerability and safety.

With rising antibiotic resistance among difficult-to-treat bacterial infections, scientists are exploring bacteriophage therapy as an alternative to traditional antibiotics. Through the **NIH/NIAID**-supported CARBIRU program, researchers evaluated bacteriophage activity against clinical isolates for uropathogenic *E. coli*, a leading cause of UTIs. They reported that phage resistance emerged rapidly *in vitro*; however, the phage-resistant bacteria were more susceptible to antibiotics in urine and less likely to colonize the bladder in a mouse model. Another NIH/NIAID-supported research team examined a bacteriophage-polymyxin combination in multidrug-resistant *K. pneumoniae*, demonstrating synergistic bacterial killing and minimal phage resistance among a polymyxin-resistant clinical isolate.

Live biotherapeutic products offer a promising alternative to antibiotics for the prevention and treatment of multidrug-resistant infections. **NIH/NIAID**-funded researchers considered the emerging field of live biotherapeutic products and found several new opportunities to control infectious disease and reduce the reliance on antibiotics. They also identified some novel challenges related to unprecedented levels of biological complexity, relevant preclinical models, manufacturing, and commercial viability. NIH/NIAID is actively supporting preclinical studies to advance live biotherapeutic product research. For example, NIH/NIAID-funded investigators found that fecal microbial communities with reduced complexity can restore colonization resistance to *C. difficile* and help prevent infection.

**USDA/ARS** researchers published a characterization of a T4-like bacteriophage as a potential biocontrol agent for Shiga-toxin-producing *E. coli* O45 contaminated on mung bean seeds.

**USDA/NIFA** funded research that has identified a best management practice for metaphylactic antimicrobial use in cattle at high risk for bovine respiratory disease and is continuing to analyze data to implement a novel intervention

strategy to reduce the spread of AR in the beef cattle industry. In addition, **NIFA** has funded research to study trans-cinnamaldehyde as an antimicrobial feed additive to control and prevent enteric septicemia of catfish.

The **DoD** CARB Working Group is partnering with industry (Bugworks Research, Inc.) to evaluate a broad-spectrum novel antibacterial lead molecule, BWC0977, currently progressing through Phase 1 clinical studies, for a potential future indication as a new treatment for MDR bacterial wound infections. Another pharma collaboration (Juvabis) resulted in preclinical evaluations of apramycin, a next-generation aminoglycoside in clinical development with improved safety over antibiotics of the same class and engineered to overcome aminoglycoside drug-resistance mechanisms, for potency against MDR gram-negative bacterial infections.

### Sub-objective 4.2.2

**Support clinical research into and development of new treatments, including antibiotics, non-traditional therapeutics, and optimized treatment regimens.**

#### Target 4.2.2.1

**Facilitate clinical development of 10 novel potential therapeutics for bacterial infections in humans by 2025.**

During FY 2022, **ASPR/BARDA** supported two assets to advance clinical trials. Locus Biosciences progressed to a Phase 2/3 clinical trial for LBP-EC01, a bacteriophage-based therapy developed to treat acute and recurring UTIs caused by *E. coli*, the bacterium that causes most UTIs. This therapeutic could become the first genetically engineered phage treatment approved by FDA and represents the first bacteriophage therapy supported by BARDA. Genentech began a Phase 1 clinical trial for GDC-5780, an IV therapeutic being development to treat complicated UTIs caused by Enterobacteriaceae species.

During FY 2022, three **ASPR/BARDA**-supported CARB-X therapeutic projects (Bugworks, Peptilogics, and Clarametyx Biosciences) and two prevention projects (SNIPR Biome and GSK Vaccines Institute for Global Health) received approval from FDA or the equivalent in-country regulatory body to begin clinical trials. Bugworks, Peptilogics, SNIPR Biome, and the GSK Vaccines Institute for Global Health also commenced first-in-human clinical trial enrollment during the period. GSK commenced a Phase 1b clinical trial with an oral small-molecule anti-virulence inhibitor that graduated from CARB-X. Seres Therapeutics also commenced first-in-human studies with the decolonization program (SER-155) that CARB-X had brought through IND. These studies are designed to evaluate safety in healthy volunteers.

**NIH/NIAID** supported 10 clinical trials, at various stages of development, for seven novel potential therapeutics for CARB pathogens in FY 2022. Select trials include an early stage ARLG trial evaluating bacteriophage therapy in adults with cystic fibrosis who carry *P. aeruginosa* in their lungs; a Phase 2 clinical trial of an oral first-in-class antibiotic, CRS3123, for the treatment of *C. difficile*; and four Phase 1 clinical trials of VNRX-7145, a novel oral beta-lactamase inhibitor for the treatment of MDR gram-negative pathogens, to evaluate a single ascending dose and multiple ascending dose of VNRX-7145 in healthy adults, drug-drug interaction with ceftibuten in healthy adults, the safety and PK of VNRX-7145 with ceftibuten in people with renal impairment, and the effect of food on the PK and safety and VNRX-7145 with ceftibuten in healthy adults. The ARLG's Phage Task Force also published a review to inform clinicians considering the use of experimental phage therapy for their patients.

The **DoD** CARB Working Group this past year established multiple new collaborations with external partners that facilitated tech inserts into the CARB small molecule drug development pipeline with promising "first-in-class" candidates and potential "re-purposed" approved drugs for evaluation as possible future wound infection or sepsis therapies.

#### Target 4.2.2.2

**Provide guidance on regulatory requirements, including clinical trial designs and other relevant topics.**

**FDA's Center for Drug Evaluation and Research (CDER)** published guidance documents titled *Nontuberculous Mycobacterial Pulmonary Disease Caused by* Mycobacterium avium *Complex: Development Drugs for Treatment*,

*Development of Anti-Infective Drug Products for the Pediatric Population*, and *Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases*, as well as several additional guidance documents on clinical trial design considerations for anti-infective drug development.

FDA/CDER's Division of Anti-Infectives, Office of Infectious Diseases, published five draft guidances for industry: *Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases—Questions and Answers (Revision 1)*, Clostridioides difficile *Infection: Developing Drugs for Treatment, Reduction of Recurrence, and Prevention*, *Early Lyme Disease as Manifested by Erythema Migrans: Developing Drugs for Treatment*, *Pulmonary Tuberculosis: Developing Drugs for Treatment*, and *Diabetic Foot Infections: Developing Drugs for Treatment*.

**The FDA Center for Biologics Evaluation and Research's** Vaccines and Related Biological Products Advisory Committee met to review data supporting the BLA for the live fecal microbiota biotherapeutic Rebyota, which was developed to reduce recurrent CDI after antibiotic usage.

#### Target 4.2.2.3

**Support New Drug Application (NDA) filings for three new therapeutics to treat bacterial infections in humans by 2025.**

During FY 2022, **ASPR/BARDA** provided support to Spero Therapeutics for development of tebipenem HBr oral tablets, including Spero's submission of an NDA for treatment of adult patients with complicated UTIs, including pyelonephritis.

### Sub-objective 4.2.3

**Provide specimens, testing, data, and evaluations to collaborations aimed at developing new agents or older agents for new uses and to support establishment or revision of antibiotic-susceptibility testing standards.**

#### Target 4.2.3.1

**Establish at least five projects supporting the development of new agents and standards by 2025.**

**CDC** is evaluating novel host-directed therapies (HDTs) and new drug combinations for the treatment of susceptible and drug-resistant *M. tuberculosis* infections. To achieve this goal, CDC developed a novel 3-D tuberculoma bioplatform (i.e., a cell culture model) to screen potential HDT compounds and identify new targets for HDT. Key features of human TB granulomas are achieved in this model, and the bioplatform was used to screen large compound libraries. Thirty-three potential HDT compounds are invested in the mouse model of *M. tuberculosis* aerosol challenge to validate findings observed in the 3-D bioplatform. To date, these investigations have identified five novel HDT candidates with efficacy for additional evaluation including immunology and transcriptomic studies in the mouse model of *M. tuberculosis* infection and disease.

The **DoD** CARB Working Group is conducting preclinical studies to explore expanding clinical utility of the approved fourth generation tetracycline drug (omadacycline) as a potential treatment for gram-negative bacterial wound infections.

## Objective 4.3

**Intensify basic, translational, and clinical research to support the discovery and development of new preventative products or strategies.**

### Sub-objective 4.3.1

**Support the discovery and development of new preventative strategies.**

#### Target 4.3.1.1

**Award 40 new projects aimed at discovering or developing new preventative products for use in human medicine by 2025.**

During FY 2022, three **ASPR/BARDA**-supported CARB-X prevention projects (a CRISPR-engineered precision product for cancer patients, a vaccine for salmonella and typhoid fever, and an immunotherapy antibiotic-alternative biologic) completed their initial development activities and advanced to the next stage in their respective development.

In FY 2022, **NIH/NIAID** awarded more than 45 new projects through grants and contracts aimed at discovering or developing new preventative products against infections caused by antimicrobial-resistant bacteria such as *S. aureus*, *P. aeruginosa,* and *K. pneumoniae*. These projects study various options such as bioconjugation, viral vectors, new adjuvants, new formulation, and mucosal delivery, and aim to develop effective vaccines to prevent these difficult-to-treat infections.

### Target 4.3.1.2

**Support two candidate preventative agents for agricultural uses by 2021.**

**USDA/ARS** scientists and collaborators published two analyses of potential alternatives to using antibiotics, one which evaluated the effects of *Saccharomyces cervisiae* fermentation products on dairy calves' immune status, and one which evaluated the effect of protected organic acids and essential oils on the intestinal health of broiler chickens raised under field conditions.

**USDA/NIFA** supported a grant to explore the potential strategy of using phage endolysins as alternative antibiotics to control clostridia in poultry.

### Target 4.3.1.3

**Report success stories about improved preventative strategies for human health at least two stories) and agriculture (at least one story) by 2023.**

**CDC's** Antimicrobial Resistance Coordination and Strategy Unit published four partnership stories, highlighting the collaboration between CDC and partners to combat AR. These success stories highlight work to address health disparities, pilot drug-resistant gonorrhea testing in emergency departments, expand AR wastewater surveillance to detect SARS-CoV-2, and enhance global detection and response in healthcare and community settings.

CDC's *AMR Exchange Series* is a global webinar series to engage a broad group of partners, practitioners, veterinarians, and policy-makers on AR topics across One Health. Since the launch of the *AMR Exchange Series* in 2021, CDC has hosted five webinars in the series, attracting more than 17,000 registrants globally. CDC will continue the *AMR Exchange Series* in 2023. During FY 2022, CDC hosted two webinars in the *AMR Exchange Series*. "Antifungal Resistance: Understanding This Growing Global Threat" was held in June 2022, focusing on ways of addressing resistance in fungal infections, like *C. auris*, to protect people, animals, and the environment. "Addressing Health Inequities through Strengthening Antibiotic Stewardship," held in October 2022, discussed disparities in antibiotic prescribing and use and where opportunities exist to ensure equity across healthcare settings and communities.

Through the **NIH/NIAID**-supported DoxyPEP study, researchers are evaluating whether a dose of oral doxycycline after unprotected sex can reduce the risk of bacterial STIs among men who have sex with men and transgender women. The trial is assessing the effectiveness of doxycycline post-exposure prophylaxis on the incidence of STIs as well as on the risk of antibiotic resistance in bacterial STIs and commensal bacteria (e.g., that live on the body or in the gut). Researchers shared initial results at the 2022 International AIDS Conference, reporting that a significant portion of bacterial STIs (gonorrhea, chlamydia or syphilis) were prevented with a dose of doxycycline after unprotected sex.

With **NIH/NIAID** support, scientists developed an investigational multivalent GBS bioconjugate vaccine against several of the most common GBS serotypes. GBS is a gram-positive bacterium that can cause severe illness and may be passed from mothers to their infants. Currently, there are no licensed vaccines to prevent GBS. The research team demonstrated that this multivalent GBS bioconjugate vaccine candidate induced functional antibodies against GBS in mice.

**NIH/NIAID** scientists examined *E. faecalis* translocation from the gut to the bloodstream. *E. faecalis* is an opportunistic pathogen that causes systemic infection after translocation through the intestinal epithelium, particularly in hospitalized and immune-depleted patients receiving antibiotic therapy. The researchers found the translocation was mediated by the fecal streptococci regulator quorum-sensing system and commercially available orally administered probiotic *Bacillus subtilis* spores blocked subsequent systemic infection in mice by inhibiting fecal streptococci regulator activity.

**USDA/ARS** researchers and collaborators published an investigation of whether inducing endogenous host defense peptides could protect chickens from necrotic enteritis, thus preventing disease and reducing the need for antibiotics. The results suggest that butyrate and forskolin, two natural products, could be developed as novel antibiotic alternatives in poultry and other animals.

**USDA/NIFA** supported researchers at the University of Pennsylvania to develop and understand novel immunobiotics and their protective effects against fish mucosal pathogens.

### Sub-objective 4.3.2

**Clarify pathways for new pharmaceutical preventatives by defining appropriate clinical trial designs, including end points.**

#### Target 4.3.2.1

**Convene two meetings to discuss developmental pathways and regulatory considerations, including clinical trial designs, by 2025.**

On August 30, 2022, **CDC** and **FDA** collaborated on a public workshop titled "Drug Development Considerations for the Prevention of Healthcare-Associated Infections" to discuss new developmental and regulatory approval pathways for novel pharmaceutical agents that can prevent antimicrobial-resistant infections.

**FDA/CDER** convened a public workshop on June 3, 2022, titled "Development Considerations of Antimicrobial Drugs for the Treatment of Uncomplicated Urinary Tract Infections (UTI)."

The **DoD** CARB Working Group meets regularly (at least monthly) and also holds project team meetings with external partners.

### Sub-objective 4.3.3

**Facilitate development of vaccines that prevent bacterial and fungal infections with known rates of resistance, and augment existing post-licensure evaluation systems to evaluate vaccination rates and antibiotic or antifungal use and resistant infections over time.**

#### Target 4.3.3.1

**Establish at least two antibiotic-resistant pathogen-related projects to further vaccine development or uptake by 2022.**

**CDC** continues to support EIP sites to conduct population-based surveillance for antimicrobial-resistant pathogens and infections due to these pathogens. Data gathered through these surveillance activities can be used to inform development of or evaluate the effect of new AR prevention interventions, such as vaccines. CDC is currently in the process of sharing 300 gonorrhea isolates obtained from GISP sites with a pharmaceutical company to produce a vaccine.

Additionally, **CDC** has developed plans to expand the EIP HAIC MuGSI to include resistant and susceptible invasive *E. coli* infections. Isolates will be collected and submitted for characterization, including serotype identification through sequencing and bioinformatic analyses. This surveillance platform will support work to inform development and evaluation of vaccines against extraintestinal pathogenic *E. coli*.

### Target 4.3.3.2

**Further support existing active, laboratory, population-based bacterial and fungal monitoring activities to provide vital serotype distribution and resistance data to inform development of vaccine candidates for bacteria or fungi with known resistance.**

**CDC** continues to support EIP sites to conduct population-based surveillance for antimicrobial-resistant pathogens and infections due to these pathogens through the HAIC and ABCs program. Streptococcal isolates collected through routine surveillance are whole-genome-sequenced at CDC, which provides serotype and AR data. These data are used to inform development of or evaluate the effect of new AR prevention interventions, such as vaccines. ABCs is currently exploring how CDC can increase isolate retentions and submission and streamline surveillance methodology to allow for faster reporting of resistance data.

## Objective 4.4

**Enhance efforts to promote sustainability of the commercial market for new antibiotic products.**

### Sub-objective 4.4.1

**Leverage an existing mechanism to reduce barriers to research and establish a comprehensive understanding of safety and effectiveness of new antibiotic agents in challenging clinical settings and indications.**

### Target 4.4.1.1

**Provide scientific and technical support, including recommendations on platform trial design and other regulatory considerations.**

**FDA/CDER's** Office of Infectious Diseases provides scientific and regulatory advice to developers of antibacterial drugs to treat resistant infections and funds research activities in this area. Studies awarded funding between October 2021 and September 2022 include "Advancing Methods to Optimize Antimicrobial Dosing in Patients with Obesity," "Ex Vivo Modeling, Simulation, and In Vivo Pharmacokinetic Validation to Guide Antimicrobial Dosing Recommendations for Patients on Continuous Renal Replacement Therapy," and "Development and Validation of CRRT-Specific Beta-Lactam Population Pharmacokinetic Models to Guide Treatment for Patients with Hospital-Acquired Pneumonia." Five articles related to CARB activities were published in peer-reviewed journals between October 8, 2021, and October 8, 2022, including publications focused on cefiderocol dosing for patients receiving continuous renal replacement therapy, considerations for the development of antifungal drugs, and trends in antibacterial drug development.

### Target 4.4.1.2

**Support at least one special population clinical trial by 2025.**

**ASPR/BARDA** is targeting a possible contract award to a company for the development of pediatric antibiotics in FY 2023.

### Sub-objective 4.4.2

**Examine changes in new technology add-on payments (NTAPs) under the CMS Inpatient Prospective Payment System (IPPS) final rules, starting with the FY 2020 IPPS/long-term care hospital prospective payment system final rule, to inform potential additional actions.**

### Target 4.4.2.1

**Report the number of applications, approvals, and renewals for new technology add-on payments and the estimated amount of those payments.**

Per **CMS** regulation, novel antimicrobials designated under certain approval pathways by FDA are considered new and not substantially similar to an existing technology, and do not need to meet the substantial clinical improvement criterion. Medicare pays 75 percent of the cost of the antimicrobial (or 75 percent of the portion of the cost exceeding

the MS-DRG payment, whichever is lower). In comparison, other NTAP products receive payment of 65 percent of such costs, respectively.

There was one application for DefenCath under the Qualified Infectious Disease Product pathway in 2022 for the FY 2023 NTAP cycle. It was granted conditional approval because the product was not yet approved by FDA. NTAP payments for Recarbrio and Fetroja were continued in 2022 for FY 2023.

### Sub-objective 4.4.3

**Strengthen commercial markets for antibiotic products through direct Public Health and National Security purchases.**

#### Target 4.4.3.1

**Acquire antibiotics to ensure national security and to provide revenue to encourage commercialization.**

On September 30, 2022, **ASPR/BARDA** awarded its second antibiotic Project BioShield contract. This award was made to Venatorx Pharmaceuticals for the development and potential procurement of cefepime-taniborbactam as a potential therapeutic option for melioidosis and pathogens classified as urgent drug-resistant public health threats by CDC. Under this contract Venatorx will seek approval of cefepime-taniborbactam for the treatment of hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and melioidosis.

### Sub-objective 4.4.4

**Support efforts to secure U.S.-based manufacturing infrastructure.**

#### Target 4.4.4.1

**Work with innovator companies to generate domestic production of critically needed products and expand U.S.-based manufacturing capabilities.**

**ASPR/BARDA**-supported Paratek Pharmaceuticals added Patheon Pharmaceuticals, located in Cincinnati, Ohio, as an alternate manufacturing and analytical testing site for NUZYRA tablets. This onshoring of the tablet drug product manufacturing process is the first completed step in transferring the manufacturing supply chain to domestic facilities. Manufacturing of active pharmaceutical ingredient for NUZYRA tablets and NUZYRA vials scheduled to complete in 2023 and 2024, respectively.

## Objective 4.5 [Activity 1]

**Enhance basic research on antibiotic resistance mechanisms, as well as translational and clinical research on therapeutics, vaccines, and diagnostics.**

### Sub-objective 4.5.1 [Activity 1 Target]

**Support at least 1,000 publications focused on basic, translational, and clinical research to combat antibiotic resistance annually through 2025.**

In FY 2022, **NIH/NIAID** supported over 925 peer-reviewed publications spanning a range of basic, translational, and clinical research topics around combating antibiotic resistance. Select topics include the development of a mouse model for studying occult colonization and outgrowth of CRE; the discovery of broad-spectrum metallo-beta-lactamase inhibitors; bacterial superinfection in patients ventilated for COVID-19 pneumonia; comparison of antibiotic regimens for patients with hospital-acquired or ventilator-associated bacterial pneumonia; a study demonstrating a small molecule's activity against staphylococcal bacterial persister cells and biofilms; skin models for *C. auris* colonization; and the development of a genome-wide atlas of drug susceptibility determinants for *S. pneumoniae*.

**NIH/FIC** has supported over 10 publications on AR in FY 2022, on topics such as resistance-guided therapy for *N. gonorrhoeae*, loss of novel diversity in human gut microbiota associated with ongoing urbanization in China, and the occurrence of antibiotic-resistant *Staphylococcus* in orange orchards in Thailand.

In FY 2022, **USDA/ARS** scientists published 66 articles relating to AR and antibiotic alternatives.

**USDA/NIFA** supported a project resulting in two publications on dissemination and risk of anthropogenically induced antibiotic resistance in the agricultural environment.

**ASPR/BARDA** staff published scientific articles on the impact of bacterial infections and antibiotic use on hospitalized COVID-19 patients using a survey administered through the Emerging Infections Network Survey, and proposing a model for evaluating antimicrobial therapy to prevent life-threatening bacterial infections following exposure to a medically significant radiation dose.

## Objective 4.6 [Activity 2]

**Support the training of new investigators and new entrants in the field to improve research capacity on antibiotic resistance.**

### Sub-objective 4.6.1 [Activity 2 Target]

**Provide support to at least 60 new or early-career investigators annually through 2025.**

**NIH/NIAID** is committed to supporting a diverse cohort of new and early-career investigators to improve research capacity on antibiotic resistance. In FY 2022, NIH/NIAID supported over 60 new or early-career investigators in CARB-related pathogen research through several different grant mechanisms. For example, since the ARLG mentoring program began, it has supported a total of 10 Early-Stage Investigator grants, nine ARLG Fellowships, and eight Trialists in Training. The ARLG also awarded the first Early Faculty Seedling Award in FY 2022.

In addition, NIH/NIAID actively promotes workforce diversity in early-career investigators and has published two program announcements in this area in FY 2022: PAR-22-241, "NIAID Research Opportunities for New and 'At-Risk' Investigators to Promote Workforce Diversity," and PAR-21-258, "NIAID Research Education Program Advancing the Careers of a Diverse Research Workforce."

New NIH/NIAID-funded investigators are studying diverse areas including equity and AR; wastewater-based surveillance of multidrug-resistant bacteria; bacteriophages; development of novel antimicrobial agents, vaccines, and immunotherapeutic strategies; persistent and drug-resistant bloodstream infections; and live biotherapeutics for *C. difficile*. Examples of select new investigator projects include "Community-Onset Urinary Tract Infections Caused by ESBL-Producing *Escherichia coli* in Women of Diverse Backgrounds," "Operationalizing Wastewater-Based Surveillance of Multidrug-Resistant Bacteria," and "Bacteriophages as Modulators of Bacterial Colonization."

In FY 2022, **USDA/ARS** has supported six new/early-career investigators.

**USDA/NIFA** funded an early-career investigator in a project that includes both career development and research on pharmaceutical contamination from human and agricultural sources using stable water isotope analysis.

**CDC** awarded the Infectious Diseases Society of America to direct the Leadership in Epidemiology, Antimicrobial Stewardship, and Public Health (LEAP) fellowship that provides a one-year training award to up to six competitively selected early career infectious disease physicians. The LEAP fellowship aims to foster the next generation of promising leaders, bridging the disciplines of hospital epidemiology and public health. Fellows will gain experiential training in public health work, hospital epidemiology, and antimicrobial stewardship. They will also take part in collaborative learning with each other, as well as didactic lectures from some of the U.S.'s premier infectious diseases experts. Each Fellow will be required to propose and engage in a year-long Fellowship project, to eventually be presented at IDWeek 2024.

Additionally, **CDC** and public health laboratories in New York, Tennessee, Minnesota, Wisconsin, Utah, and Washington state hosted 10 APHL-funded fellows.

## Objective 4.7 [Activity 3]

**Enhance interagency collaborations to accelerate basic and applied research for developing new antibiotics, therapeutics, and vaccines.**

### Sub-objective 4.7.1 [Activity 3 Target]

**Establish at least two new collaborations for human health and one for agriculture by 2023, through interagency agreements, collaborative programs, and/or interdisciplinary workshops.**

In May 2022, **ASPR/BARDA**, **NIH**, and **DoD** held an Interagency Joint Anti-infective Annual Meeting to facilitate information sharing of respective portfolios.

**CDC** and **FDA** established an interagency agreement (FY 2022: 75F40122S30012) to conduct a study titled "Identify Metabolomic Features Shared by In Vitro and In Vivo Human Intestinal Microbiome Disruption." The goal of this study is to create an experimental culture system that characterizes the intestinal microbiome disruption potential of antibiotic, probiotic, pharmacologic, and dietary agents. In addition, the study will identify metabolomic features that can be used to evaluate intestinal microbiome health, which may be a good predictor of risk of acquiring/becoming sick with an MDRO.

An **FDA**-funded cooperative agreement was awarded in June 2022 to help identify potential alternative practices for reducing the reliance on antimicrobial drugs for addressing the health needs of food-producing animals.

FDA and **NIH** established an interagency agreement (FY 2022: 75F40122S30009) to conduct a study titled "Assessment of the Impact of the IDSA Guidance for the Treatment of Gram-Negative Infection on Use of New Antibiotics in U.S. Healthcare Facilities." Relevant FDA activities are also described under Target 4.3.2.1.

**USDA/ARS** established an interagency agreement with FDA for FY 2022 on a project titled "Antimicrobial Resistance in Surface Waters: Pilot Environmental Monitoring Effort," which includes method development to standardize analytical approaches and culture methods for analyzing *Salmonella* and *E. coli* with AR in environmental surface water samples, conducting a field assessment to test the methods, and helping finalize the design of the watershed-scale study.

Released in November 2021, the **HHS** *Sexually Transmitted Infections National Strategic Plan* is a groundbreaking, first-ever, five-year plan that aims to reverse the recent dramatic rise in STIs in the U.S. The STI Plan sets a vision as well as goals, objectives, and strategies to respond to this STI epidemic. The plan was developed by a steering committee composed of subject-matter experts from many different federal departments, agencies, and programs including DoD, the Department of Education, and HHS (CDC, FDA, NIH, CMS, the Health Resources and Services Administration, and others). Goal 3 of the plan is to accelerate progress in STI research, technology, and innovation; this includes developing new STI treatment options and diagnostic tests in order to address and identify AR.

In June 2022, **NIH/NIAID** organized a workshop called "Strategies for Early-Stage Programs Developing Novel Antibacterial and Antifungal Drugs." The focus of the workshop was to describe and discuss the early phases of product development for antibacterial and antifungal agents, starting after discovery phase when lead series have been identified. Speakers from FDA as well as BARDA/CARB-X participated in this virtual workshop.

The **DoD** CARB Working Group accomplished artificial intelligence (AI)–accelerated antibacterial drug discovery via a Defense Advanced Research Projects Agency (DARPA)–funded effort through which the WRAIR Experimental Therapeutics Branch accomplished independent verification and validation using novel AI algorithms developed by academia for discovery of novel small molecules with activity MDR gram-negative bacteria. The DoD CARB team also has an ongoing new collaboration (a CRADA) to facilitate tech inserts from the Defense Threat Reduction Agency's portfolio (in clinical development for biothreat purposes) into the CARB small molecule pipeline to evaluate for broadening utility against MDR bacterial infections in combat wounds.

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

## Objective 5.1

**Enhance U.S. leadership in the global fight against antibiotic resistance.**

### Sub-objective 5.1.1

**Examine mechanisms for appointing a U.S. Federal Champion for International CARB, who would support the Secretaries of HHS, USDA, and DoS and the Administrator of USAID by advocating for U.S. policy positions on antibiotic resistance at international fora and organizations using a One Health approach, and who would report to the CARB Task Force to inform international engagements.**

#### Target 5.1.1.1

**Convene a working group of the CARB Task Force to define interagency needs and develop options for appointing a Federal Champion for International CARB by 2021.**

Since the Federal Champion Working Group convened virtually in March 2021, there have not been additional meetings. A draft options paper was developed but due to lack of resources, no additional progress has been made toward a mechanism for appointing a Federal Champion.

### Sub-objective 5.1.2

**Enhance engagements with multilateral organizations to support progress on U.S. priorities to combat antibiotic resistance.**

#### Target 5.1.2.1

**Support international AR policy efforts to prioritize and coordinate antibiotic resistance efforts within and across international partner organizations (e.g., Global Health Security Agenda [GHSA], World Health Organization [WHO], World Organization for Animal Health [WOAH], United Nations Environmental Program [UNEP], Food and Agricultural Organization [FAO], G7 and G20, Asia-Pacific Economic Cooperation Forum, Association of Southeast Asian Nations, Pan American Health Organization) by 2025.**

**OGA** assisted with the U.S.'s Asia-Pacific Economic Cooperation (APEC) project proposal, which was officially endorsed by the APEC economies and began in October 2022. The project focuses on identifying incentives to bring new antibiotics to APEC markets and will consist of a gap analysis of barriers to access and market entry in APEC economies, a workshop following intercessional work, and an options paper with potential best practices by APEC economies to address the triad of economic incentives, equitable access, and stewardship. The project is being co-sponsored by Canada, Malaysia, and Thailand.

OGA attended the Third AMR Ministerial in Muscat, Oman, with the Principal Deputy Assistant Secretary for Health (PDAS) and provided support for the PDAS for a panel on key challenges to the AR response. OGA also attended the virtual consultation on the Muscat Manifesto, which aims to pave the way for bold and specific political commitments at the 2024 United Nations General Assembly High Level Meeting on AMR. Additionally, there has been ongoing

engagement with the G20 for AMR on the priorities for 2022 and for the coming year, 2023. OGA assisted in negotiations for the G20 One Health Policy Brief and the TB Call to Action.

**USDA** participated in World Organization for Animal Health activities throughout 2022 and contributed to U.S. government work in the other international fora.

**OGA** and **CDC** conduct regular calls with the WHO AMR team to collaborate on efforts such as GLASS and Laboratory diagnostic initiatives. OGA serves as co-chair of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) on behalf of the U.S. Together with partners from CDC, NIH, FDA, BARDA, and USDA, they share best practices to strengthen domestic and global efforts for stewardship, surveillance, prevention, and research and development. CDC serves as the TATFAR secretariat.

CDC engages with international partners at all levels to provide U.S. government expertise to address AR. This includes engagement through the WHO Strategic and Technical Advisory Group for Antimicrobial Resistance, the WHO AMR Surveillance and Quality Assessment Collaborating Centres Network, the Surveillance and Epidemiology of Drug-Resistant Infections Consortium Board, the G7 AR Surveillance Meeting, and other international partnerships, as well as input on all G7 and G20 AR documents. CDC collaborates with the ASEAN-U.S. IPC Task Force, the Pan American Health Organization (PAHO), and Africa CDC to strengthen regional approaches to IPC, AR, and healthcare worker safety. CDC's partnership with PAHO resulted in the publication and rollout of IPC monitoring and evaluation indicators in Central and South America. CDC also supported Africa CDC in developing the first IPC Legal Framework endorsed by the African Union in 2022 to help member states identify legal instruments that monitor, evaluate, and enforce IPC standards while authorizing budgets and directing financial resources to national and healthcare facility IPC programs.

**USAID** partner FAO supported AR control planning efforts in India and Indonesia that were highlighted at a 2022 G20 side event. Also in India, and through partnership with USAID, WHO provided strategy and technical advice to the Ministry of Health and Family Welfare on the G20 call to action on AMR.

### Target 5.1.2.2

**Chair the Global Health Security Agenda AMR Action Package by 2022.**

The U.S. successfully chaired the GHSA AMR Action Package (APP1) from November 2020 to December 2021. As chair, the U.S. led monthly meetings with presentations from key players in the global AR space, which provided a forum for members to connect, communicate, and collaborate on pressing AR issues through a One Health lens and provided tools, resources, and information to improve national action plans and facilitate connections among members. The U.S. also increased participation among members by giving them the floor to share their progress and successes in monthly meetings and highlighting their work in the workplan and webpage. As chair, the U.S. drafted the AR Action Package (AP) workplan, which includes AP goals and member commitments; drafted language and design of a new AR AP webpage for the GHSA website; oversaw the addition of Asia-Europe Foundation's Mekong Basin Disease Surveillance group as an APP1 member; started discussions with UNEP to join the AP; and encouraged International Health Regulation benchmark library participation to help countries improve their Joint External Evaluation scores. This AP was featured in the GHSA newsletter published on June 28, 2021, which highlighted key stories of AP members' impact and success. Finally, the U.S. is leading efforts to create a landscape analysis of major players in the global AR space through this AP.

### Target 5.1.2.3

**Complete the Work Plan of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) for 2016–2020, develop and begin implementation of a new workplan for TATFAR by 2022, and continue implementation of the current workplan for 2021–2026.**

TATFAR continued to serve as a forum for collaboration on AR for TATFAR partners throughout the first year of its most recent work period (2021–2026). Activities are spread across four key areas: appropriate antimicrobial use in human and veterinary medicine; surveillance and prevention of AR; strategies to improve financial incentives, access, research, and

development of antimicrobial drugs, diagnostics, and alternatives; and cross-cutting actions to improve awareness and disseminate information from TATFAR. The updated TATFAR workplan was officially adopted in February 2022.

As the TATFAR secretariat, **CDC** continues to host monthly calls with TATFAR coordinators to discuss pending issues and to plan various activities, work with TATFAR coordinators to plan semi-annual full group video conference calls where members share ideas and discuss successes and challenges, facilitate communications between TATFAR member countries, and manage calls for the working groups. For the 2022 World AMR Awareness Week (WAAW), CDC worked with partners to host a new webpage to raise awareness and understanding of AR by highlighting country activities. As of 2022, two working groups have been merged to better align with the TATFAR goals and objectives. As a result, an updated workplan will soon be published to reflect such changes. CDC is also working with TATFAR partners to plan an in-person meeting in 2023.

### Target 5.1.2.4

**Work with international partners through the Codex Alimentarius Commission's Task Force on Antimicrobial Resistance to develop global, science- and risk-based guidance on managing foodborne antimicrobial resistance and surveillance, including revising the Codex *Code of Practice to Minimize and Contain Foodborne Antibiotic Resistance* and developing new guidelines for integrated surveillance of antimicrobial resistance.**

**FDA** and **USDA** led the U.S delegation to the four-year Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance (2017–2021), which revised and updated the *Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance* and drafted *Guidelines on Integrated Monitoring and Surveillance for Foodborne Antimicrobial Resistance*. The U.S. chaired the working group on revising the *Code of Practice*. Both documents were adopted for final publication at the 44th session of the Codex Alimentarius Commission in November 2021. This task is now complete.

### Target 5.1.2.5

**Continue to support member governments' sharing of antibiotic-resistant pathogen information to the relevant collaborating centers, including to the WHO Global Antimicrobial Resistance Surveillance System (GLASS).**

In FY 2022, **CDC** worked with funded partners in five countries to enhance reporting of antimicrobial-resistant gonorrhea through GLASS, with part of this work happening through the Global AR Lab & Response Network. This included the maintenance of data uploading and validation capacity and expansion of the Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP) module in GLASS to ensure data are accessible to national focal points, WHO Collaborating Centers, and WHO/U.S. CDC.

AST and epidemiologic data are transmitted to the GLASS-IT platform and are subsequently validated, analyzed, and disseminated in reports from WHO, WHO Collaborating Center Laboratories, CDC, and individual EGASP countries. WHO will continue to support development of international IT solutions to support provision of EGASP data into the GLASS-IT platform. Additional countries as well as sentinel clinics and reference laboratories will be selected through this collaboration.

CDC also helped develop, and established the U.S. as a pilot site for, the expanded GLASS-FUNGI module, which focuses on surveillance of invasive fungal infections such as *C. auris.* CDC plans to promote reporting to this new module by other countries as part of Global AR Lab & Response Network activities once the module is available broadly.

Through the Global AR Lab & Response Network, CDC and FIOTEC worked with 15 sentinel hospital sites, five regional reference laboratories, and two national AR reference laboratories in Brazil to enhance laboratory capacity for detection of antimicrobial-resistant pathogens and increase reporting to the National Antimicrobial Resistance Monitoring System of Brazil (BR-GLASS). This work includes training 180 participants at 42 laboratories located at local, state, or regional levels and conducting WGS training for five participants at national reference labs. As lab capacity grows, results reported to BR-GLASS will inform AR prevention activities and antimicrobial stewardship practices and will enhance reporting to WHO GLASS.

CDC also supported country-level work in at least 19 countries to strengthen surveillance for emerging diseases, including infections caused by antimicrobial-resistant pathogens in healthcare settings. This includes work supported through the Global Action in Healthcare Network (GAIHN).

**USAID's** Infectious Disease Detection and Surveillance (IDDS) program and partner WHO provided technical assistance in Cameroon, Guinea, Liberia, Kenya, India, and Tanzania to improve the quality and consistency of reporting of antimicrobial surveillance and susceptibility data to GLASS.

### Sub-objective 5.1.3

**Provide additional financial or technical support to public and private organizations to further U.S. priorities to combat antibiotic resistance.**

#### Target 5.1.3.1

**Support international policy efforts to reduce antibiotic resistance beyond the current mandates of U.S. government departments and agencies by 2022.**

**OGA** met with TATFAR member countries and the TATFAR secretariat to discuss inviting Mexico to join. The inclusion of Mexico is also being considered as a deliverable for the North American Leaders' Summit 2023, as there is interest in incorporating AR topics. OGA's AMR team began working with the OGA Americas team on developing a potential memorandum of understanding between Canada and the U.S., which would include AR topics. OGA has also facilitated meetings between the Global Antibiotic Research and Development Partnership (GARDP), SECURE, and CDC to identify potential areas for collaboration, and shared messaging and priorities of the Global Hygiene Council through social media for WAAW.

**USDA/APHIS** chaired the Animal Health Quads Alliance Antimicrobial Resistance Network, leading discussions on addressing antimicrobial use and resistance in animals with technical experts from the Quads countries, including Australia, Canada, New Zealand, and the United Kingdom.

### Sub-objective 5.1.4

**Increase the U.S. government's presence in international organizations and other multilateral efforts to combat antibiotic resistance.**

#### Target 5.1.4.1

**Provide at least one AMR expert either by secondment or appointment to a multilateral organization to enhance the U.S. government's programmatic collaborations and provide high-level technical and policy guidance by 2022.**

A **CDC** IPC expert began a two-year detail in FY 2022 to support AR-related activities at the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

### Sub-objective 5.1.5

**Enhance domestic and international communications about the U.S. government's activities to combat antibiotic resistance and increase the coordination of federal departments and agencies on the CARB Task Force around large-scale efforts and announcements.**

#### Target 5.1.5.1

**Increase coordination among the CARB Task Force on communication strategies by instituting regular calls by 2021.**

The **CARB Task Force** completed regular calls in FY 2022 including discussion of relevant communication strategies.

#### Target 5.1.5.2

**Increase high-level social-media promotion of antibiotic resistance activities among the departments and agencies on the CARB Task Force.**

**CARB Task Force** agencies, including HHS and USDA, participated in WAAW 2021 by sharing and amplifying each other's social media posts to promote awareness of antimicrobial stewardship and activities. **OGA, NIH/NIAID, USDA, ASPR/BARDA,** and **CDC** shared key messages and visuals on AR on Twitter (now X) during the TATFAR Global Twitter Relay for WAAW 2021. The theme was "Spread Awareness, Stop Resistance." OGA shared messages on U.S. government international efforts to combat AR, and OGA's work through TATFAR and the importance of combating AR with a multisectoral, multilateral One Health approach. Additionally, OGA promoted and attended the Third Global High-Level Ministerial Conference on AR in Oman and shared tweets of the meeting and the U.S. government's representation through OGA's Twitter.

Throughout the 2022 fiscal year, **CDC** posted AR content—including text, videos, graphics, and hyperlinks designed to increase awareness and education about AR—to its @CDC_AR Twitter handle and increased consistent posts to the main CDC social media channels (Twitter, Facebook, Instagram, LinkedIn). CDC participated in WAAW/U.S. Antibiotic Awareness Week 2022 by promoting agency key messages, materials, and visuals that covered AR, antibiotic use, and antibiotic stewardship through the @CDC_AR Twitter handle and the main CDC social media channels. CDC also participated in the TATFAR Global Twitter Relay and a Twitter chat with partner organizations. Throughout the year, CDC participated in other observance weeks, including, *C. diff* Awareness Week, STI Awareness Week, World TB Day, Fungal Disease Awareness Week, and One Health Day by sharing and amplifying social media posts that focus on AR.

## Objective 5.2

**Promote increased awareness and capacity in countries to address the emergence and slow the spread of antibiotic resistance.**

### Sub-objective 5.2.1

**Improve capacity in partner countries to implement effective practices to combat AR, including preventing and controlling infection through the availability and proper use of water, sanitation, and hygiene (WASH).**

#### Target 5.2.1.1

**Assist governments, civil society, and the private sector in a total of 10–15 low- or middle-income countries to develop and implement national plans consistent with the Global Action Plan, establish and implement antibiotic-resistance-focused collaborations and activities, and/or build capacity for preventing and controlling infections in both animals and humans annually.**

The Global AR Lab & Response Network is a comprehensive, One Health network that spans nearly 50 countries and works with nearly 20 organizations worldwide to build laboratory capacity that detects antimicrobial-resistant organisms, prevent infections in healthcare and the community through proven infection control practices, and apply new and innovative ways to respond to AR threats. In 2022, **CDC** supported the expansion of laboratory network systems through Global AR Lab & Response Network–funded projects. This included supporting the expansion of sentinel sites screening and referring isolates within national systems and supporting the investigation and response to the emergence of *C. auris* in healthcare systems.

Additionally, through the Global AR Lab & Response Network, CDC worked with the PulseNet Asia Pacific region to strengthen program capabilities, including creating quarterly meetings for this region, performing assessments for capacity, and launching a pilot project for four countries. One of these recipients has worked to build capacity for monitoring water quality and performing environmental testing. In this first year of funding, the recipient worked to identify laboratories, develop standard operating procedures, train personnel, and build a system that can link environmental and laboratory data. In Year 2, laboratory partners will be trained to perform enteric WGS within their countries.

In FY 2022, CDC began collaborating with Family Health International 360, Washington State University, and APHL to implement environmental monitoring in Kenya to address antimicrobial-resistant enteric pathogen transmission as a part of CDC's Global AR Lab & Response Network efforts. Experts work with local laboratories in Kenya to develop

environmental monitoring of antimicrobial-resistant enteric pathogens in household water, water sources, and environmental samples and work to assess risk factors for exposure to those pathogens to understand and improve prevention measures. The CDC team is concurrently working to establish Kenya as a wastewater/environmental surveillance training platform for epidemiology, laboratory, and bioinformatics capacity.

CDC improved patient and healthcare personnel safety with an emphasis on IPC in four continents through numerous initiatives, programs, and implementing partners to improve healthcare safety from infectious disease threats both locally and regionally. Several examples are provided below.

Through GAIHN, a part of CDC's Global AR Lab & Response Network, CDC and partners conducted IPC, informatics, and laboratory capacity assessments at national and hospital levels across six countries to investigate gaps and resources needed to improve prevention of, detection of, and response to AR threats in healthcare.

CDC also worked with the Liberia Ministry of Health and Jhpiego (formerly known as Johns Hopkins Program for International Education in Gynecology and Obstetrics) to develop an IPC certificate course and a national IPC action plan. CDC also supported the development of a national IPC monitoring and evaluation plan in Ethiopia and continued to support the Sierra Leone Ministry of Health and Sanitation with its IPC certification course. The course was evaluated this year so it could be refined to meet participant needs, and a new cohort began in September 2022.

CDC also supported partners in expanding the East Africa Infection Prevention and Control Network, which aimed to build healthcare worker capacity to improve adherence to IPC standards. This network, established in 2020, includes 22 hospitals across four countries: Ethiopia, Kenya, Tanzania, and Uganda. As of September 2022, network activities have included over 60 case-based learning sessions, two collaborative quality improvement projects to improve IPC practices, five facility assessments to assess adherence to COVID-19 IPC standards, and tailored professional development for facility IPC focal points and team members.

In India, CDC has supported partners in developing the first standardized HAI surveillance network in the country, which has succeeded in implementing locally adapted and context-appropriate protocols consistently in more than 40 hospitals. The implementation of this surveillance system allows better understanding of HAI prevalence and identification of which hospital units are most affected, providing crucial information for targeting interventions and measuring progress toward HAI prevention, including resistant infections.

Additionally, CDC collaborated with partners at ICAP (formerly the International Center for AIDS Care and Treatment Programs) at Columbia University and the Georgia National Center for Disease Control and Public Health to implement environmental (wastewater) surveillance for SARS-CoV-2 in Tbilisi, with plans to expand to AR targets in FY 2024. To date, protocols have been cleared and sites selected for surveillance. Within GAIHN, the CDC & **FDA** AR Isolate Bank successfully shipped isolates to the national laboratories in Argentina, Chile, and Ethiopia to support verification and validation of laboratory methods for rapid detection of mobile AR genes at the national and hospital levels to inform IPC actions. Isolates were also sent to Brazil for optimization of immunochromatographic tests used for carbapenemase detection from rectal swabs without the need to perform culture. The goal is to improve timeliness for detection of colonized patients and implementation of IPC actions in healthcare settings.

CDC and the Ministry of Public Health in Thailand also worked to implement environmental (wastewater and septic-system-based) surveillance for AR targets as part of a One Health Framework. The CDC team is working to establish Thailand as a wastewater/environmental surveillance training platform for epidemiological, laboratory, and bioinformatics capacity.

**USDA/FAS'** Faculty Exchange Program (FEP) pairs instructors from veterinary colleges in priority countries with mentors at host U.S. universities to improve veterinary curricula and instruction in their home countries. With COVID-19 restrictions on international travel lessening, FEP activities resumed in 2022 with 17 Fellows representing Ghana, Kenya, Tanzania, and Uganda participating in FEP from August to December 2022.

**USAID,** through its Medicines, Technologies, and Pharmaceutical Services (MTaPS) and IDDS programs and in partnership with FAO, supported efforts in 16 LMICs countries to develop, approve, assess, review, and/or update evaluate National Action Plans on AR and/or costed operational plans for those National Action Plans. These efforts included expanding the sectors and communities engaged in the National Action Plan processes. In addition, USAID helped support countries' participation in the annual Tripartite AMR Country Self-Assessment Survey for 2022, which is used to monitor country progress on implementing AR action plans. USAID, in partnership with FAO, MTaPS, and WHO, supported efforts in 16 LMICs to establish, strengthen and/or operationalize multisectoral coordination bodies and technical groups, including supporting the participation by diverse stakeholders in these bodies and/or working groups at the national, sub-national, and/or district levels. These efforts resulted in outcomes and products that helped advance action on AR in-country.

USAID partners supported diverse efforts to directly strengthen local and national infectious disease prevention and control capacities in human and animal health in at least seven LMICs. USAID, in a partnership with FAO, MTaPS, and WHO, continues to support the ongoing development of IPC action plans, policies, and guidance documents at both state and national levels in 12 LMICs. USAID, in a partnership with MTaPS, FAO, IDDS, and TRANSFORM, supported efforts to strengthen IPC capacity in public and animal health settings in 12 LMICs. Activities included formation and operation of IPC committees, training (including train-the-trainer exercises, as well as efforts to strengthen and expand the use of e-learning platform and virtual training), strengthening communities of practice, and strengthening IPC practices in public health and on-farm settings. By the end of FY 2022, 135 out of 141 MTaPS-supported facilities across 12 countries maintained functional IPC committees and 125 MTaPS-supported facilities across 11 countries implemented continuous quality improvement to improve IPC. USAID, through its MTaPS program and in partnership with FAO, supported efforts in seven LMICs to increase the use of assessments to inform and improve IPC plans. By the end of FY 2022, 100 percent of MTaPS-supported facilities across 12 countries used standardized tools for monitoring IPC and informing programmatic improvement. In animal health settings, appraisals of IPC measures in poultry, dairy, and swine value chains were used to inform strategic FAO interventions issues at the community level.

To raise awareness and promote action on AR, USAID partners Breakthrough ACTION, FAO, IDDS, MTaPS, and WHO supported a variety of efforts in 13 countries during the 2020 WAAW. These efforts include One Health and sector-specific advocacy and awareness-raising events involving diverse sectors from finance ministries to journalists to farmers; they also include the development of information and communication materials to use for advocacy and events (including supporting the translation of AR materials to enable the public to understand and comprehend AR issues at the community level). Additional public outreach efforts include activities such as FAO presenting a live educational program on antimicrobial use and AR to the public during the Ethiopian Broadcasting Corporation's national Nutrition and Health radio show. USAID partners also supported the production and distribution of AR newsletters, guidelines, curricula, and general education materials including leaflets, street banners, and digital media, which helped to educate the general public, farmers, sectoral experts, and policy-makers on AR and antimicrobial use.

USAID, in a partnership with FAO, IDDS, MTaPS, One Health Workforce–Next Generation, and TRANSFORM, supported efforts on stakeholder training and professional education on AR (including One Health) in six LMICs. Activities included supporting continuing professional development and education, a train-the-trainer effort, updating and disseminating training materials, and encouraging greater access to and support for training. These efforts were directed at diverse sectors from university deans to community agro-vet entrepreneurs. For example, the Africa One Health University Network supported Cameroon in developing a post-graduate course on AR adapted from the in-service training curriculum. To institutionalize training of this course, AFROHUN Cameroon organized meetings with key stakeholders, resulting in the Senate of the University of Buea approving the university's health sciences faculty to host and launch the program as a two-year master's program. IDDS collaborated with USAID's University of Nairobi Health IT project to conduct a virtual refresher training for course managers from the ministry of health, department of veterinary services, research academia, and IDDS. Enrollment in the course increased from 670 to 922 students after e-course flier was

circulated. IDDS also worked to improve the course materials and user interface following feedback from the learners and course managers.

### Target 5.2.1.2

**Assist governments, civil society, and the private sector in 10 to 15 low- or middle-income countries to improve the monitoring of WASH in healthcare facilities or to create and/or implement standards for environmental health in healthcare settings.**

**CDC** is working with Washington State University in Kenya and Guatemala; the Infectious Diseases Institute in Uganda; Baylor College of Medicine in Belize and El Salvador; Brigham and Women's Hospital in the Dominican Republic; Universidad del Valle de Guatemala in Guatemala; the Hilton Foundation in Niger, Mali, Uganda, Ghana, and Ethiopia; as well as other partners to improve WASH practices in healthcare facilities. Initiatives include trainings and assistance with evaluations using WASH FIT and other WHO evaluation modalities; initiatives to improve local production of alcohol-based hand rub at district scale; assessments of novel management structures, including for sanitation facilities; and behavioral assessments of drivers of hand hygiene behavior among healthcare workers and staff. Accomplishments include development of an online course to train producers on local production of alcohol-based hand rub using WHO formulations, which was evaluated among producers in East Africa; development of novel guidance on cleaning, disinfecting, and managing supplies within local alcohol-based hand rub production frameworks; evaluations in each country of interventions to improve access to and use of hand hygiene in healthcare locations, including behavioral messaging; and the publication of the first manuscript on local production of alcohol-based hand rub at district scale. CDC is also collaborating with WHO on the development of a hand hygiene global agenda.

CDC also completed a package of environmental cleaning guidance for resource-limited settings, conducted a pilot of the implementation toolkit for its *Best Practices for Environmental Cleaning in Resource-Limited Settings* document in Nigeria and Vietnam, and published the *Environmental Cleaning in Global Healthcare Settings* guidance on the CDC website.

**USAID**, through its MTaPS program, supported the implementation, monitoring, and improvement of environmental health and WASH activities in facilities across Cameroon, Kenya, and Uganda. In addition, in Uganda, MTaPS worked with the USAID Uganda Mission to conduct two workshops on IPC/WASH for other implementing partners in the country, including John Snow International, the Elizabeth Glaser Pediatric AIDS Foundation, University Research Co., IntraHealth, and the Joint Clinical Research Center.

## Sub-objective 5.2.2

**Optimize the use of antibiotics in humans, animals, and agriculture outside the U.S.**

### Target 5.2.2.1

**Assist governments, civil society, and the private sector in at least four low- or middle-income countries with capacity-building for antibiotic stewardship and regulation to address the appropriate use and availability of quality-assured antibiotics in humans and animals by 2022.**

**CDC** continued to support appropriate antibiotic use and stewardship efforts across public and private healthcare settings. This includes a study done in collaboration with Jhpiego and Health Security Partners that found that the use of intravenous antibiotics for respiratory infections during the COVID-19 pandemic increased in more than half of the hospitals studied, with increases of up to 160 percent in South America and up to 63 percent in Southeast Asia. Use of at least one broad-spectrum antibiotic also increased during the pandemic in more than half of the hospitals, with increases of up to 82 percent in South America and up to 212 percent in Southeast Asia. Preliminary analyses of AR data in South America show that there were up to five times more infections with MDROs during the pandemic compared to before the pandemic. Results from these analyses will provide the participating countries with a better understanding of the pandemic's immediate and long-term impacts, strategies to decrease antibiotic use and resistance, and ways to avoid similar impacts in future pandemics.

CDC is working with Johns Hopkins University, the University of Oxford/Duke University, the University of Pennsylvania, and their international partners to develop an antibiotic stewardship assessment tool for use by healthcare facilities worldwide. This tool, which helps facilities identify opportunities to improve antibiotic stewardship programs and monitor progress of antibiotic stewardship actions over time, will be implemented in 90 hospitals across 12 countries in Latin America, Southeast Asia, and Southern Africa. Implementation began in October 2022 and will continue through early 2023.

CDC is also collaborating with CDC Bangladesh and icddr,b (formerly the International Center for Diarrhoeal Disease Research, Bangladesh) as they develop a network of hospitals focused on improving IPC and antimicrobial stewardship programs in metropolitan Dhaka. The network currently has 11 participating hospitals.

CDC also supported partners across 12 countries to conduct antibiotic stewardship national and healthcare facility assessments based on the WHO policy guidance on integrated antibiotic and antifungal stewardship in 90 healthcare facilities. These assessments help identify gaps and needs to establish or improve antimicrobial stewardship programs which is part of many LMIC national action plans on AR.

**USAID** partners supported countries in developing, adopting, and reviewing, updating, and validating standard treatment and other guidelines in human and/or animal health (terrestrial, aquatic, and companion animals) in at least 10 countries to include the integration of the WHO Access, Watch, Reserve (AWaRe) categorization in essential medicines lists and standard treatment guidelines. In at least 12 countries, USAID (through FAO, MTaPS, and host governments) supported assessments to strengthen antimicrobial use and stewardship capacities. USAID also worked in partnership with FAO to support the development of tools to facilitate antimicrobial stewardship practices.

USAID's Promoting the Quality of Medicines Plus (PQM+) program is working with partner countries to improve the availability, quality, and safe use of antimicrobials. PQM+ supported the medicine regulatory authorities of Liberia and Kenya in conducting risk-based post-marketing surveillance of the quality of specific antimicrobials; PQM+ also helped the medicine regulatory authority of Uzbekistan operationalize the Collaborative Procedure for Accelerated Registration to facilitate more timely review and approval of medicines from suppliers that have been prequalified (i.e., already thoroughly reviewed and approved) by WHO. PQM+ supported the Drug Regulatory Authority of Pakistan in developing a regulatory framework for risk-based decisions on AR based on the AWaRe list for antimicrobial medicines. The regulatory framework provides guidance on appropriate regulatory interventions to take based on medicines' AWaRe classification. PQM+ also supported development of an online antimicrobial consumption monitoring dashboard in the Pakistan Integrated Regulatory Information Management System portal that provides information on the quantity of antimicrobial material imported, the quantity of products manufactured, and the number of registered manufacturers.

### Sub-objective 5.2.3

**Promote the use of existing and new vaccines, including pneumococcal and typhoid-conjugate vaccines, to reduce the unnecessary use of antibiotics.**

#### Target 5.2.3.1

**Promote prevention and vaccine use in low- and middle-income countries, including through the U.S. government's partnership with Gavi, the Vaccine Alliance, supported by funding and technical assistance from USAID and CDC worldwide.**

**CDC**'s work on this target has been delayed due to the COVID-19 pandemic response.

**USAID** partner FAO supported work in Tanzania and Indonesia that aims to reduce overall antibiotic use, and therefore AR, by implementing routine livestock vaccination campaigns.

### Sub-objective 5.2.4

**Conduct surveillance that identifies the presence and movement of antibiotic resistance genes of concern within partner nations as part of DoD/GEIS-funded surveillance to protect military force health.**

### Target 5.2.4.1

**Submit isolates of multidrug-resistant pathogens to the MRSN for advanced characterization and provide reports to the labs that can also inform surveillance of antibiotic resistance, by 2024.**

**DoD/GEIS**-funded surveillance sites continue to submit isolates to MRSN for genomic characterization. GEIS continues to standardize submission of isolates from all surveillance site locations and additional partners have committed to begin submitting isolates in FY 2022/23. Challenges remain in ensuring all partner sites submit some isolates to MRSN, including partner nation trust in sharing biological and genetic information with entities beyond their border and related policy/legislation.

## Objective 5.3

**Generate consistent and actionable global data on antibiotic resistance, including by extending CDC's AR Lab Network to global sites to address the identification, emergence, spread, and effects of antibiotic resistance.**

### Sub-objective 5.3.1

**Expand the AR Lab Network and other networks (e.g., PulseNet International) internationally to implement networks for detection and containment that can rapidly test and respond to high-threat antibiotic-resistant pathogens in key regions.**

### Target 5.3.1.1

**Launch at least one international AR Lab Network project and make operational at least one international AR Lab Network laboratory by 2022. Incorporate five additional laboratories by 2026.**

In FY 2022, the Global AR Lab & Response Network recipients worked across 111 laboratories throughout nearly 50 countries. **CDC** also expanded the number of funded partners for its Global AR Lab & Response Network, launching three new projects for *C. auris* capacity and response activities in new target countries, and one new project to improve surveillance and response for typhoid. CDC also funded a project to work with several partners to develop and pilot a strategic framework for a community of practice for wastewater and environmental surveillance in low-resource settings. Through GAIHN's AR Module, a part of the Global AR Lab & Response Network, CDC also supported a project in Brazil to evaluate culture-free tests for detection of mobile resistance genes (carbapenemases) from rectal swabs to improve the timeliness of detection of colonized patients and implementation of IPC actions in healthcare settings.

### Sub-objective 5.3.2

**Charge the global AR Lab Network with detecting and containing new and critical antibiotic resistance threats.**

### Target 5.3.2.1

**Establish the capacity of the global AR Lab Network to receive and test isolates and deploy rapid responses to control and contain infections.**

During FY 2022, **CDC** funded 10 recipients to build laboratory capacity to detect fungal pathogens, including *C. auris*, and bacterial pathogens including foodborne enterics, *N. gonorrhoeae*, and invasive respiratory pathogens (*S. pneumoniae*, *B. pertussis, N. meningitidis*) through the Global AR Lab & Response Network. Four recipients worked in three countries (up to 10 identified laboratories per country) to build laboratory capacity for *Candida*, including performing assessments within country, providing network trainings for culture, identification, antifungal susceptibility testing and WGS, and building reporting systems for sharing laboratory results. Recipients worked to identify target sites, conducted site visits, performed gap analyses, and procured equipment and supplies for testing. Three recipients covering the invasive respiratory bacterial pathogens trained laboratory personnel on techniques to collect, transport, and process samples as well as to culture and detect AR pathogens, for *S. pneumoniae*, *B. pertussis*, and *N. meningitis*. Implementation of EGASP has been ongoing in Cambodia, Philippines, and Thailand. During year 1, the program expanded to additional sites, including two countries (South Africa and Uganda).

Through the Global AR Lab & Response Network, GAIHN has expanded into Greece, Ethiopia, India, and Belize. Capacity assessments were conducted for eight hospitals and two national laboratories in Greece, Ethiopia, and Belize. In addition, in Ethiopia, seven staff received hands-on training with use of fluorescent markers for assessment of environmental cleaning and 13 clinical informatics management staff were trained on how to conduct mCIM testing. An implementation road map has been developed for the country. In India, capacity assessments and training are ongoing. Additionally, CDC and PAHO performed an in-depth IPC and laboratory assessment across four hospitals to inform implementation of AR prevention and response. CDC is developing a data system to monitor progress and impact of the GAIHN AR network and to support rapid communication and response to emerging AR threats. Elements of this data system are being integrated into national-level informatics platforms in Argentina and Chile and will be deployed to the hospitals to facilitate rapid communication between laboratory and IPC teams.

In 2022, **DoD/MRSN** completed the implementation of near-real-time surveillance in the 15 largest hospitals in the MHS. All hospitals now house an MRSN employee that ensures all MDRO are shipped to the MRSN on a weekly basis, allowing for rapid responses to control and contain infections. In 2022, the MRSN identified and responded to 48 potential nosocomial transmission across eight hospitals. This target is completed for DoD.

### Sub-objective 5.3.3

**Identify innovative and effective strategies for stopping the spread of antibiotic-resistant pathogens in low- and middle-income countries.**

#### Target 5.3.3.1

**Establish "learning laboratories" through the AR Lab Network to develop or test innovative, cost-effective solutions for containing critical-threat antibiotic-resistant pathogens by 2021.**

**CDC** continues to work with funded partners to conduct trainings of lab personnel in various countries. During FY 2022, Global Scientific Solutions for Health conducted a workshop in Togo to assist with developing and updating laboratories' standard operating procedures, specifically for meningitis technical procedures. In Burkina Faso, CDC's partner worked in-country to develop a collaborative workplan. Other planned activities include a simulation sample exercise in both countries to better understand challenges with transporting specimens. Through another project, CDC will work with funded partners in Indonesia to train staff members at six hospitals and assist laboratory staff members in conducting quality control for *S. pneumoniae*.

### Sub-objective 5.3.4

**Improve laboratory capacity for antibiotic resistance surveillance including the standardization of laboratory methodologies and data collection to improve the quality, reliability, and utility of data to facilitate global comparisons of antibiotic resistance.**

#### Target 5.3.4.1

**Implement standardized or harmonized laboratory methods and data collection in AR Lab Network facilities and, with partner countries, strengthen laboratory capacity for antibiotic resistance surveillance and comparison of antibiotic resistance trends when appropriate. Initiate data-reporting efforts with trusted partner nations by 2021. Support operations through training and funding annually.**

**CDC** continues to work through the Global AR Lab & Response Network to build regional and national networks for laboratory testing and surveillance for AR threats. In addition to the work noted in Target 5.1.2.5, CDC also piloted clinical tracking system for 12 sentinel healthcare facilities, which includes laboratory data for *C. auris* developed by NIH Pakistan.

Additionally, the Antibiotic Resistance in Communities and Healthcare (ARCH) research consortium, a part of CDC's Global AR Lab & Response Network, continues to track the amount and spread of colonization in hospitals and communities in six countries and to study predictors and outcomes of colonization. ARCH partners are currently

conducting analyses of risk factors for MDRO colonization at all six participating sites, and they have initiated WGS of colonizing MDRO isolates in four countries. Enrollment for follow-up studies evaluating health outcomes among colonized individuals has begun in two countries. ARCH partners also set up the first Vitek machine in Botswana to perform bacterial identification and antibiotic susceptibility testing.

CDC has supported mentoring networks for basic bacteriology capacity building via the ECHO model in Kenya and Ethiopia. Beginning in 2020, interactive webinars have been offered bi-weekly for the past three years. In Ethiopia, more than 49 sessions have been given with five participating laboratories. In Kenya, more than 68 sessions have been given with more than 27 participating laboratories.

CDC is supporting ministries of health in multiple countries and partners as they build national AR surveillance networks. For example, in India, CDC works with the National Centre for Disease Control to implement a network of over 50 hospitals in 23 states conducting lab-based AR surveillance using standardized laboratory testing protocols.

**USAID** supported assessments to strengthen national AR surveillance systems. USAID, in partnership with FAO, worked with seven countries in Africa to assess AR surveillance infrastructure in the human health and agriculture sectors using the FAO Assessment Tool for Laboratories and Antimicrobial Resistance Surveillance Systems (FAO-ATLASS). These evaluations identify critical gaps that need to be addressed to strengthen AR surveillance capacity across the continent. In Cameroon, Senegal, Tanzania, and Kenya, USAID program IDDS supported national, regional, and local assessments of AR surveillance capacities in both the veterinary and human health sectors.

USAID partners FAO, MTaPS, and IDDS supported the development and implementation of appropriate protocols, guidelines, standard operating procedures, data management tools, and surveillance strategies in seven countries including strengthening capacities in specimen collection, AST, harmonization of pathogen identification, and surveillance of hospital-acquired infections at health facilities. For example, IDDS in Kenya, after extensive consultations with experts, provided technical inputs to the development of the national AR surveillance dashboard.

USAID partners facilitated a wide variety of training for laboratory, healthcare, and veterinary personnel to appropriately conduct AR surveillance in 12 countries across Africa and Asia. Through FAO, MTaPS, and IDDS, USAID supported a wide variety of workshops, train-the-trainer exercises, coordination meetings, site visits, conferences, and other avenues of technical assistance that prioritizes sustainable capacity gains through empowering individuals to contribute to national, and global, efforts to address AR. For example, in Indonesia, so much progress has been made that national AR surveillance activities are performed according to national standards, with a functional national AR reference laboratory that participates in external quality assurance and conducts confirmatory or additional testing on a regular basis.

USAID partners FAO and IDDS supported labs across 10 countries by facilitating the procurement of equipment, microbiology reagents, laboratory supplies, and other consumables. These commodities are critical to strengthen the AR detection capacity in these countries. In addition, IDDS enabled the Cameroon Laboratories Network to provide maintenance and certification of 18 biosafety cabinets in six human and two animal laboratories nationwide, drastically increasing the national capacity to conduct AR surveillance.

USAID supported regular AR surveillance, susceptibility testing, and reporting in eight countries across Africa and Asia. For example, through partnerships with FAO and IDDS, four countries (Cameroon, Bangladesh, India, and Indonesia) have continued to conduct national-scale genomic analysis for AR surveillance across the human, livestock, poultry, and fishery sectors. Key successes in India include AR testing in 21 designated laboratories, implementation of an AR surveillance strategy in animal health, identification of priority AR pathogens, and external quality assurance through a national service provider. Additionally, USAID partners FAO and IDDS supported laboratories in Vietnam and Kenya, respectively, to submit their antimicrobial susceptibility and surveillance data to WHONET. WHO India and IDDS Guinea also facilitated AR data sharing from state surveillance networks to national databases, which then furthered international AR data sharing.

The EpiData Center at Defense Centers for Public Health-Portsmouth developed the capacity for near-real-time surveillance of infectious diseases using systematic, sophisticated algorithms on electronic auxiliary health data. The Center publishes these data on a web-based dashboard for use by **DoD** antimicrobial stewardship and infection prevention work groups. The EpiData Center collaborates with GEIS, MRSN, PVC, and others to establish comprehensive antimicrobial use and resistance surveillance.

### Sub-objective 5.3.5

**Expand screening of populations migrating to the U.S. from high-risk countries to prevent the importation of cases of multidrug-resistant tuberculosis.**

#### Target 5.3.5.1

**Pilot expanded screening for populations migrating from five high-risk TB countries by 2025.**

**CDC** will continue to engage DoS to discuss next steps on expanding TB screening requirements for long-term visitors. CDC will also work with DHS to incorporate TB screening into requirements for migrants coming to the U.S. through newly expanded lawful pathways.

## Objective 5.4

**Increase international collaborations to facilitate basic, translational, and clinical research into understanding the causes of antibiotic resistance and developing countermeasures.**

### Sub-objective 5.4.1

**Collaborate with international scientists and organizations to better understand and address the development, spread, and health risks of antibiotic resistance and resistance sources present in animals, the environment, the community, and healthcare settings.**

#### Target 5.4.1.1

**Conduct research and/or surveillance projects to evaluate sources of antibiotic resistance, mechanisms of persistence, and impact of sociological factors, with a focus on animal and environmental systems by 2023.**

As a part of CDC's Global AR Lab & Response Network, and as highlighted in Target 5.2.1.1, **CDC** is working with Family Health International 360 to develop environmental monitoring of antimicrobial-resistant enteric pathogens in household water, water sources, and environmental samples and work to assess risk factors for exposure to those pathogens to understand and improve prevention measures.

**DoD/GEIS** introduced a "One Health" surveillance category into the FY 2022 strategic guidance and request for proposals. The program office received six proposals to conduct AR surveillance with a focus on human, environmental, and/or animal systems. Of these studies, three were selected for FY 2022 funding: two environmentally focused, one companion animal focused. GEIS continues to highlight the desire for more One Health proposal submissions and evaluate DoD priorities in establishing comprehensive One Health surveillance and/or non-human-domain-focused surveillance.

### Sub-objective 5.4.2

**Promote and enhance the alignment of U.S. and international translational and clinical research activities to facilitate the development of new products to better diagnose, prevent, and treat infections or to provide data on the best use of existing products.**

#### Target 5.4.2.1

**Report one success story about products or regimens undergoing preclinical or clinical testing annually through 2025.**

This year, **ASPR/BARDA** awarded a new award to Boston University for continued support of the CARB-X program, a global public-private partnership that supports the early-stage development of novel products to treat, prevent, and

diagnose drug-resistant infections. BARDA provided $25 million this year and has options to provide a total of up to $300 million over the next 10 years to combat antimicrobial-resistant infections through CARB-X.

During the reporting period, **ASPR/BARDA** produced three ASPR blog posts: "Addressing Antimicrobial Resistance" (June 2022), "To Save Lives in Public Health Emergencies, Healthcare Providers Must Curb Antibiotic Resistant Infections" (May 2022), and "Partnering to Protect: Public & Private Sectors Unite Against Antimicrobial Resistance" (November 2021). CARB-X also published five Spotlight on Science stories, which highlight projects undergoing preclinical development within the portfolio.

**NIH/NIAID** continues to collaborate with global partners and facilitate dialogue to advance AR research efforts, including the development of novel antibacterial products. In FY 2022, NIH/NIAID awarded a contract to a Netherlands company to support advanced development of an intranasal vaccine candidate to prevent gonorrhea. This contract may include manufacture of vaccine batches under Good Manufacturing Practices and nonclinical toxicology testing, with the goal of advancing to an IND submission and Phase 1 clinical trial to evaluate the safety and immunogenicity of the investigational vaccine.

In FY 2022, NIH/NIAID was heavily involved in international conferences and activities highlighting NIH/NIAID AR priorities and research opportunities, including a conference in Switzerland with outreach to non-governmental AR stakeholders, coalitions, and EU drug development companies; an STI conference in Zimbabwe with a presentation on STI vaccines; and visits to the Korean National Institute of Infectious Diseases and Korean CDC to discuss AR opportunities. NIH/NIAID also represents the U.S. as a board member in the Global AMR R&D Hub to improve coordination and address challenges in global AR research and development.

### Target 5.4.2.2

**Convene a meeting with international regulators to seek alignment on clinical trial designs for new products by 2023.**

**FDA**, the European Medicines Agency and the Pharmaceuticals and Medical Devices Agency of Japan participated in a joint workshop on trial designs pertaining to developing drugs for treatment of gonorrhea in April 2021. FDA's Division of Anti-Infectives (within the Office of Infectious Diseases, which is part of the Office of New Drugs, which in turn is part of CDER) conducts quarterly meetings with the European Medicines Agency, Health Canada, and the Pharmaceuticals and Medical Devices Agency to discuss elements of clinical trial design and other aspects of the development of antibacterial and antifungal drugs to treat resistant infections.

# Appendix A: Abbreviations

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|---|---|
| AHRQ | Agency for Healthcare Research and Quality |
| AMR | antimicrobial resistance |
| AP | Action Package |
| APEC | Asia-Pacific Economic Cooperation |
| APHIS | Animal and Plant Health Inspection Service |
| APHL | Association of Public Health Laboratories |
| AR | antimicrobial resistance |
| ARCH | Antibiotic Resistance in Communities and Healthcare |
| ARLG | Antibacterial Resistance Leadership Group |
| ARS | Agricultural Research Service |
| ASEAN | Association of Southeast Asian Nations |
| ASM | American Society for Microbiology |
| ASPR | Administration for Strategic Preparedness and Response |
| AST | antimicrobial susceptibility testing |
| AWaRe | WHO Access, Watch, Reserve categorization of antibiotics |
| BARDA | Biomedical Advanced Research and Development Authority |
| BV-BRC | Bacterial and Viral Bioinformatics Resource Center |
| CAH | critical access hospital |
| CAP | community-acquired pneumonia |
| CARB | Combating Antibiotic-Resistant Bacteria |
| CARBIRU | CARB Interdisciplinary Research Unit |
| CAUTI | catheter-associated urinary tract infection |
| CDC | Centers for Disease Control and Prevention |
| CDER | Center for Drug Evaluation and Research |
| CDI | *Clostridioides difficile* infection |
| CHIP | Children's Health Insurance Program |
| CLABSI | central-line-associated bloodstream infection |
| CLSI | Clinical and Laboratory Standards Institute |
| CMS | Centers for Medicare & Medicaid Services |
| CoE | Center of Excellence |
| CoP | condition of participation |
| CORHA | Council for Outbreak Response: Healthcare-Associated Infections and Antimicrobial-Resistant Pathogens |
| CPO | carbapenemase-producing organism |
| CRADA | Cooperative Research and Development Agreement |
| CRE | carbapenem-resistant Enterobacteriales |
| CUSP | Comprehensive Unit-based Safety Program |
| CVM | Center for Veterinary Medicine |
| DoD | Department of Defense |
| EGASP | Enhanced Gonococcal Antimicrobial Surveillance Program |
| eGISP | enhanced Gonococcal Isolate Surveillance Project |

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|---|---|
| EIP | Emerging Infections Program |
| EIP-ABCs | Emerging Infections Program's Active Bacterial Core surveillance |
| ELC | Epidemiology and Laboratory Capacity for Prevention and Control of Emerging Infectious Diseases |
| EPA | Environmental Protection Agency |
| EQA | external quality assessment |
| ESBL | extended-spectrum beta-lactamase |
| FAO | Food and Agriculture Organization |
| FAS | Foreign Agricultural Service |
| FDA | Food and Drug Administration |
| FEP | Faculty Exchange Program |
| FSIS | Food Safety and Inspection Service |
| FY | fiscal year |
| GAIHN | Global Action in Healthcare Network |
| GAS | group A *Streptococcus* |
| GBS | group B *Streptococcus* |
| GFI | Guidance for Industry |
| GHSA | Global Health Security Agenda |
| GISP | Gonococcal Isolate Surveillance Project |
| GLASS | Global Antimicrobial Resistance Surveillance System |
| HAI | healthcare-associated infections |
| HAIC | Healthcare-Associated Infections—Community Interface |
| HDT | host-directed therapy |
| HHS | Department of Health and Human Services |
| HPAI | highly pathogenic avian influenza |
| HQIC | Hospital Quality Improvement Contractor |
| ICU | intensive care unit |
| IDDS | Infectious Disease Detection and Surveillance |
| IDSA | Infectious Disease Society of America |
| IHI | Institute for Healthcare Improvement |
| IND | Investigational New Drug |
| IPC | infection prevention and control |
| LEAP | Leadership in Epidemiology, Antimicrobial Stewardship, and Public Health |
| LMICs | low- and middle-income countries |
| MDR | multidrug-resistant |
| MDRO | multidrug-resistant organism |
| MHS | Military Health System |
| MIC | minimum inhibitory concentration |
| MicroBIGG-E | Microbial Browser for Genetic and Genomic Elements |
| MRSA | methicillin-resistant *Staphylococcus aureus* |
| MRSN | Multidrug-resistant organism Repository and Surveillance Network |
| MTaPS | Medicines, Technologies, and Pharmaceutical Services |
| NAAT | nucleic acid amplification test |
| NAHLN | National Animal Health Laboratory Network |

| | |
|---|---|
| NARMS | National Antimicrobial Resistance Monitoring System |
| NCBI | National Center for Biotechnology Information |
| NDARO | National Database of Antibiotic Resistant Organisms |
| NHSN | National Healthcare Safety Network |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIFA | National Institute of Food and Agriculture |
| NIH | National Institutes of Health |
| NLM | National Library of Medicine |
| NNDSS | Nationally Notifiable Diseases Surveillance System |
| NWSS | National Wastewater Surveillance System |
| OGA | Office of Global Affairs |
| PAHO | Pan American Health Organization |
| PCV | pneumococcal conjugate vaccines |
| PK | pharmacokinetic |
| PQM+ | Promoting the Quality of Medicines Plus |
| QIN-QIOs | Quality Innovation Network–Quality Improvement Organizations |
| REH | rural emergency hospital |
| SAAR | Standardized Antimicrobial Administration Ratio |
| SHEA | Society for Healthcare Epidemiology of America |
| SHEPheRD | Safety and Healthcare Epidemiology Prevention Research Development |
| SIR | standardized infection ratio |
| SRA | Sequence Read Archive |
| STI | sexually transmitted infection |
| SURRG | Strengthening the United States Response to Resistant Gonorrhea |
| TATFAR | Transatlantic Taskforce on Antimicrobial Resistance |
| USDA | United States Department of Agriculture |
| UTI | urinary tract infection |
| VA | Department of Veterans Affairs |
| Vet-LIRN | Veterinary Laboratory Investigation and Response Network |
| WAAW | World AMR Awareness Week |
| WASH | water, sanitation, and hygiene |
| WGS | whole-genome sequencing |
| WHO | World Health Organization |
| WHO-CIA | World Health Organization Critically Important Antimicrobials |
| WOAH | World Organization for Animal Health |
| WRAIR | Walter Reed Army Institute of Research |
| WS NWRC | Wildlife Services National Wildlife Research Center |