Background Analysis on Progress Toward Meeting Goals and Objectives in the National Action Plan for Combating Antibiotic-Resistant Bacteria (2015-2020)

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Introduction

The National Academies of Sciences, Engineering, and Medicine (NASEM) received funding from Congress to examine and quantify the long-term medical and economic impacts of increasing antimicrobial resistance (AMR) in the United States (US). A primary objective of the study was to review progress made on the first National Action Plan for Combating Antibiotic-Resistant Bacteria (2015-2020), herein referred to as the National Action Plan. To complete this aspect of the project, NASEM contracted with the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota in Spring 2021.

The National Action Plan was organized around five goals and contains 22 objectives under those goals, with 230 individual milestones. The goals are as follows:

1. Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections
2. Strengthen National One-Health Surveillance Efforts to Combat Resistance
3. Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
4. Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines
5. Improve International Collaboration and Capacities for Antibiotic-resistance Prevention, Surveillance, Control, and Antibiotic Research and Development

This report contains a summary of progress on each milestone in the first National Action Plan and also highlights key accomplishments for each agency, along with major barriers and challenges and important lessons learned during the 5 years of the National Action Plan.

We would like to thank the federal agency contacts who provided information as part of this report. They are included in the Acknowledgements.

Methods

Each milestone is assigned to one or more of 12 US federal agencies. The federal agencies with responsibilities in the plan are as follows:

- Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response (ASPR), HHS
- Centers for Disease Control and Prevention (CDC), HHS
- Centers for Medicare & Medicaid Services (CMS), HHS
- Department of Defense (DOD)
- Environmental Protection Agency (EPA), Department of the Interior

- Food and Drug Administration (FDA), HHS
- Department of Health and Human Services (HHS)
- National Institutes of Health (NIH), HHS
- Department of State
- US Agency for International Development (USAID), Department of State
- US Department of Agriculture (USDA)
- Department of Veterans Affairs (VA)

Owing to the complexities of tracking the 230 milestones by a range of federal agencies, with a fair amount of overlap, we divided the project into four different phases. Data collection began in early March 2021 and was completed in late June 2021.

Phase 1

The first step of phase 1 was to create agency-specific tables for all of the milestones in the National Action Plan. We created tables for 11 agencies; we did not include a separate table for the Department of State, as HHS was listed in all of the same milestones and HHS was able to speak for them. We then reviewed past progress reports on the 2015-2020 National Action Plan from the Office of the Assistant Secretary for Planning and Evaluation (ASPE) within HHS[1], the 2020 Government Accountability Office (GAO) Report on Antibiotic Resistance, and conducted online searches (primarily involving agency websites but also searched other online resources as appropriate) to identify information about the milestones in the National Action Plan and to find evidence supporting whether or not milestones had been achieved. This information was then entered into each of the agency-specific tables. Phase 1 began in early March and was completed by approximately March 31, 2021.

Phase 2

Although we were able to find information online for many of the milestones during phase 1, important gaps remained. To obtain additional information, we reached out to contacts at each agency (names were provided by NASEM) and we conducted one or more key informant interviews (via Zoom) with agency personnel to clarify questions and fill in gaps in each table. In advance of the interviews, we sent the appropriate table to each agency with embedded questions to facilitate the discussions and to maximize efficient use of time during the calls.

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[1] National Action Plan for Combating Antibiotic Resistant Bacteria: Progress Report for the First 180 Days

National Action Plan for Combating Antibiotic Resistant Bacteria: Progress Report for Years 1 and 2

National Action Plan for Combating Antibiotic Resistant Bacteria: Progress Report for Year 3

National Action Plan for Combating Antibiotic Resistant Bacteria: Progress Report for Year 4

Agency personnel were also asked three additional questions: (1) What do you consider to be the biggest accomplishments of your agency? (2) What were some of the most important barriers and challenges you encountered in terms of completed the milestones? and (3) What were some of the key lessons learned during the process? Agency interviews were conducted between April 1, 2021, and early June 2021. A preliminary analysis of information was presented on May 12, 2021, to the NASEM Committee on Examining the Long-term Health and Economic Effects of Antimicrobial Resistance in the United States. This report reflects updated and finalized information from that presentation.

Phase 3

As we completed the interviews and revised the tables, a number of questions and issues still remained, so we sent each completed table back to agency personnel for additional information and clarification. We asked agency personnel to review the revised content to ensure that we had appropriately characterized what was discussed during the calls. We then revised the tables one or more times (with back-and-forth email communications as necessary) and sent them back to each agency for a final sign off. Again, this was done to ensure that we had accurately captured all of the relevant information and that none of the statements we made were incorrect. This process was performed agency-by-agency as the interviews were completed. The only exception to this general process was NIH. They had previously prepared a summary document of all of the NIH activities in the National Action Plan by goal, objective, and milestone. Once they received internal permission, they shared that document with us and, even though we had completed an agency-specific table for NIH, it was more expeditious to use their content rather than go back and forth with them on the table that we had initially completed. We therefore incorporated the NIH material into a new table for that agency. As with all of the tables, we reviewed all of the content in the NIH material to ensure that the content was applicable to the milestones. Phase 3 began in early April 2021 and ended in late June 2021.

Phase 4

Once all of the agency tables were completed, we examined the status of each milestone by agency to assess agency performance. Some milestones listed multiple agencies as being responsible for completion; such milestones were repeated in each of the agency summary tables as appropriate. If a milestone had multiple activities associated with it, only those activities appropriate for a given agency were included in that agency-specific table. After we examined the status of each milestone by agency, we then consolidated all of the information from the individual tables back into a single overarching table that encompassed all of the goals, objectives, and milestones in the National Action Plan and included information from all agencies for each milestone summary. Phase 4 began in late June 2021 and was completed by mid-July 2021. In the National Action Plan, milestones were slated to be completed within 1, 3,

or 5 years. Obtaining information regarding exactly when a milestone was completed and determining whether or not it was completed in the specified time frame proved not to be feasible; therefore, we did not include information for the timeframes, but rather just noted whether or not the milestone was completed during the 5-year timeframe for the plan. The overarching table is included in the Appendix at the end of this report.

Results

Results are presented for the following areas: (1) a quantitative summary of the status of each milestone by agency and by goal, (2) a summary of milestones that were partially completed, (3) a summary of milestones that are still in progress, (4) a summary of milestones that were not achieved, (5) primary accomplishments for each agency, (6) major barriers and challenges in completing the milestones, and (7) key lessons learned.

Quantitative Summary of Milestone Status

Each milestone was classified according to the following definitions:

- *Completed:* The milestone was fully achieved over the 5-year course of the plan or shortly thereafter.
- *Partially completed:* For a number of the milestones, more than one activity was listed as part of the milestone. In some of those situations, certain activities in the milestone were completed but not all, and plans are not in place to complete the remaining activity or activities for the milestone.
- *In progress:* Work on the milestone is still in progress but the milestone was not completed by the time of data collection for this report. Agency personnel still intend (or aspire) to complete those milestones.
- *Not achieved:* The milestone was not achieved and no plans are in place to complete the milestone.
- *Not applicable:* In one situation involving EPA, CIDRAP determined that a particular milestone was not applicable to that agency, even though that agency had been identified as one of the agencies for that milestone (See Table 1 below).

Table 1. Status of Milestone Completion by Agency for the 2015-2020 National Action Plan

Agency	Total Milestones*	Completed*	Partially Completed	In Progress	Not Achieved	Not Applicable§
BARDA	13	13	--	--	--	--
CDC	92	89	2	--	3	--
CMS	14	11	1	1	1	--
DOD	32	30	1	1	--	--
EPA	2	1	--	--	--	1
FDA	56	54	--	3‡	--	--

HHS	28	26	--	1	1	--
NIH	34	34	--	--	--	--
USAID	10	10	--	--	--	--
USDA	57	53	2	3‡	--	--
VA	4	4	--	--	--	--
TOTAL	--	--	6	6‡	5	1

*Many of the milestones involved participation by more than one agency, so the total number of milestones presented in this table exceeds the 230 milestones in the National Action Plan because of the overlap among agencies; therefore, totals were not included for these two columns.
§This applies to the following milestone under Goal 4, Objective 4.1: "On an annual basis: HHS, NIH, FDA, USDA, CDC, DOD, and EPA will conduct a review to ensure that US government research resources are focused on high-priority antibiotic resistance issues (including basic research on the emergence and spread of resistance genes) and facilitate use of advanced technologies in research on antibiotic resistance (e.g., whole genome sequencing, proteomics, metagenomics, structural biology, bioinformatics)." EPA had a minor role in the 2015-2020 National Action Plan and did not have a research agenda or budget for AMR-related activities; therefore, no annual review was undertaken because no resources were focused on AMR. As a result, CIDRAP decided to classify this milestone as "not applicable" for the EPA. This milestone was completed for all of the other federal agencies listed, so this milestone was categorized as completed in the overall table, which is presented in the Appendix.
‡For milestones that are in progress, the USDA and FDA milestones overlap, so there are only three different milestones for these two agencies, giving a total of six milestones that were in progress at the time of this report.

The table above demonstrates that most of the milestones in the National Action Plan were successfully completed. When duplicates (i.e., multiple agencies being assigned the same milestone) are removed, 213 (93%) of the 230 milestones were fully completed, six (2.5%) were partially completed, six (2.5%) were still in progress, and only five (2%) were not achieved. Details regarding progress on all of the milestones are presented in the overarching table in the Appendix of this report. For some of the completed milestones, it is important to note that while the milestone was met, work in in that area is still ongoing; however, enough progress had been made to consider the milestone as completed. As noted in the methods section, we were unable to accurately determine exactly when milestones were completed, so we listed milestones as completed versus not completed, rather than specifying whether each milestone was completed within the allotted 1-, 3-, or 5-year timeframes.

Table 2 shows milestone status by the five goals in the National Action Plan. Goal 1 had the highest number of milestones that were not completed (11%), with an overall completion rate of 89%. For the other goals, the completion rate was at least 90%; however, no goal stands out as being substantially different than the others in terms of milestone status.

Table 2. Status of Milestone Completion by Goal for the 2015-2020 National Action Plan

2015-2020 NAP Goal	Total Milestones	Completed	Partially Completed	In Progress	Not Achieved

Goal 1: Slow the emergence of resistant bacteria and prevent the spread of resistant infections.	63	56 (89%)	3 (5%)	3 (5%)	1 (1%)
Goal 2: Strengthen national One-Health surveillance efforts to combat resistance.	70	65 (93%)	--	2 (3%)	3 (4%)
Goal 3: Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.	10	9 (90%)	--	--	1 (10%)
Goal 4: Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.	40	39 (98%)	1 (2%)	--	--
Goal 5: Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control, and antibiotic research and development.	47	44 (94%)	2 (4%)	1 (2%)	--
TOTAL	**230**	**213 (93%)**	**6 (2.5%)**	**6 (2.5%)**	**5 (2%)**

Summary for Partially Completed Milestones

For the partially completed milestones, key points are as follows:

- A milestone involving CMS indicated that all acute hospitals governed by the CMS conditions of participation (COP) will implement antibiotic stewardship programs (which was met) and that CMS would expand COP requirements to apply to long-term acute-care hospitals, other post-acute facilities, ambulatory surgery centers, and dialysis centers (which was not met). Therefore, the overall milestone was only partially met. (*Under Goal 1, Objective 1.1, Sub-Objective 1.1.1a*)
- A milestone for CDC called for at least 20 state health departments to develop and maintain *advanced capacity* for rapid response to drug-resistant gonorrhea, including capacity to detect, diagnose, and investigate suspected resistant cases within their state or region and assist healthcare providers in providing appropriate treatment of infected patients. This program is referred to as Strengthening the United States Response to Resistant Gonorrhea (SURRG). It was implemented in nine rather than 20 health departments, owing to limited resources; however, more than 30 states participate in

one or more CDC-supported programs to address capacity to detect, diagnose, and investigate drug-resistant gonorrhea. (*Under Goal 1, Objective 1.1, Sub-Objective 1.1.2*)

- Another milestone for CDC was to conduct two randomized control trials for treatment of multidrug-resistant tuberculosis (MDR-TB); however, only one trial was completed. According to CDC, in the *Combating MDR-TB National Action Plan*, there was a need to develop a stockpile of antibiotics for tuberculosis (TB) treatment. At completion of the first control trial, CDC's TB program requested to utilize available resources to develop a stockpile of antibiotics as opposed to conducting a second trial, given the impact the stockpile would have for public health in the immediate future. Therefore, a second trial was not completed and this milestone was only partially met. (*Under Goal 1, Objective 1.1, Sub-Objective 1.1.4*)
- A milestone for DOD (the Chemical and Biological Defense Program [CBDP] and the Defense Threat Reduction Agency [DTRA]) had two key activities. The first activity called for CBDP/DTRA to submit an Investigational New Drug (IND) application to FDA to initiate the clinical investigation of an antibiotic developed with DOD funding. The IND was expected for Emergent BioSolutions compound GC-072. An IND was not filed for GC-072 because it failed toxicology studies in 2019; therefore, this activity could not be completed. The other activity in the milestone was for CBDP/DTRA to award two new contracts to industry partners to accelerate advancement of novel small-molecule antibiotic therapies that circumvent known resistance mechanisms or potentiate the therapeutic efficacy of existing antibiotics; this activity was completed. Because only one of the two activities was completed, this milestone was partially met. (*Under Goal 4, Objective 4.3*)
- Two partially completed milestones involved USDA. The first stated that, "Within 5 years, USDA will use Veterinary Accreditation training modules—including the Judicious Use Module—to assist countries in at least three [World Health Organization] WHO regions in developing sustainable veterinary service capacity to monitor and slow antibiotic resistance and to report outbreaks of drug resistant disease to WHO, international surveillance networks, collaborative reporting structures, or (when appropriate) to International Health Regulations (IHR) focal points." The modules were only translated into Spanish and were then shared with the USDA Foreign Agricultural Service for use in Latin American countries, so the modules were essentially made available to one WHO region rather than three. The other milestone indicated that the Judicious Use Module would be translated into three other languages; however, it was only translated into Spanish, as noted above. Therefore, both of these milestones were only partially completed. (*Under Goal 5, Objective 5.6*)

Summary for Milestones that Are In Progress

Five milestones were still in progress at the time of this report and the responsible agencies believe that the milestones will be completed. Reasons for these milestones still being in

progress include delays in receiving funding to implement the milestone, delays related to the COVID-19 pandemic, and the fact that some activities are taking longer to implement and complete than anticipated, particularly for complex and challenging issues. The milestones are as follows:

- A milestone for DOD was to establish goals for reducing antibiotic use in DOD facilities that provide outpatient care for military personnel and their families. DOD has established goals for reducing antibiotic use in outpatient care, but has not fully accomplished this milestone because of shifting priorities in response to the COVID-19 pandemic. (*Under Goal 1, Objective 1.1, Sub-Objective 1.1.3*)
- Two milestones for FDA and USDA were: (1) to support drivers-of-change studies to determine which stewardship materials and educational approaches are most effective in improving antibiotic use practices (*Under Goal 1, Objective 1.3, Sub-Objective 1.3.3*) and (2) to collect additional data regarding antibiotic use and resistance in food-producing animals to measure changes in antibiotic stewardship programs and practices over time (*Under Goal 1, Objective 1.3, Sub-Objective 1.3.4*). Completion for both of these milestones involves on-farm survey work through the National Animal Health Monitoring Systems (NAHMS). An initial set of on-farm surveys was completed in 2017, when funding became available (the project was delayed initially because of the delay in funding). A second set of surveys was to be completed in 2020; however, the work was delayed until 2021 because of the COVID-19 pandemic.
- A milestone for CMS was to complete an analysis of standards and terminologies for antibiotic use reporting to ensure alignment between National Healthcare Safety Network (NHSN) reporting and Inpatient Quality Reporting (IQR) and to support local clinical decision-making. CDC and CMS have indicated that this remains a goal and is still being worked on, but other issues have taken priority. (*Under Goal 2, Objective 2.2, Sub-Objective 2.2.2)*
- A milestone for USDA and FDA was to establish an information technology (IT) system that links the National Animal Health Laboratory Network (NAHLN) and Vet-LIRN (Veterinary Laboratory Investigation and Response Network) through a centralized repository. NAHLN and Vet-LIRN are linked via an interactive dashboard hosted through FDA's NARMS website; however, work on an IT system to further link the two networks is not yet in place but is currently being developed by FDA. (*Under Goal 2; Objective 2.3, Sub-Objective 2.3.3*)
- A milestone targeted to US agencies that work with WHO, the Food and Agriculture Organization of the United Nations (FAO), and the World Organisation for Animal Health (OIE) was to support implementation of the *WHO Global Action Plan on Antimicrobial Resistance* through several activities. A number of activities for this milestone have been achieved and a great deal of work has been done; however, one activity was to establish a global database to collect harmonized quantitative data on the use of antibacterial agents in animals. According to HHS personnel, this activity has not been fully

completed owing to lack of dedicated resources; however, work is ongoing and HHS remains interested in moving this database forward. (*Under Goal 5, Objective 5.4, Sub-Objective 5.4.2)*

Summary for Milestones that Were Not Achieved

Five milestones in the National Action Plan were not achieved and plans are not in place at this time to complete them. Table 3 identifies these milestones and provides information on why they were not achieved.

Table 3. Summary of Milestones That Were Not Achieved and Reason for Not Achieving the Milestone

MILESTONE	REASON FOR NOT ACHIEVING
CDC will expand capacity to prevent the importation of cases of multidrug-resistant tuberculosis (MDR-TB) by doubling TB screening among migrants from high-incidence countries from 500,000 to 1 million persons per year. (*Under Goal 1, Objective 1.1, Sub-Objective 1.1.2*)	This activity was stalled because of the COVID-19 pandemic.
Once the analysis has been completed and new [National Quality Forum] NQF measures have been approved, CMS will begin the process of proposing new IQR rules [for requiring hospitals to report AU/AR to NHSN as part of the IQR Program]. (*Under Goal 2, Objective 2, Sub-Objective 2.2.1*)	There is no mandate for hospitals to report antibiotic use/antibiotic resistance (AU/AR) data to the National NHSN; however, voluntary reporting continues to expand. No further progress has been made with the new IQR rules because such rules may not be necessary, if voluntary participation is successful.
CDC will establish up to 10 additional Emerging Infections Program (EIP) sites, including sites in the West and Midwest that will monitor drug-resistant pathogens. CDC will evaluate the contribution of these new sites to collection of data that better represents the incidence and prevalence of drug-resistant disease in the United States. (*Under Goal 2, Objective 2.2, Sub-Objective 2.2.3*)	Owing to limited resources, CDC did not expand the number of EIP sites; however, the number of pathogens being reported by existing EIP sites has been increased.
Milestone for CDC completion: The National Antimicrobial Resistance Monitoring System (NARMS) will partner with NHSN to obtain drug-resistance data from clinical laboratories on bacteria isolated from persons with invasive *Salmonella*, *Campylobacter*, or *Shigella* infections. Analysis of this data will provide much-needed information about the burdens and	CDC explored the benefits of adding enteric pathogens to NHSN as an approach to systematically collect data on the burdens and outcomes of drug-resistant enteric infections. Considerations included the level of effort required to expand these capabilities in NHSN and develop new work flows; the types of risk factor data that would be collected from this high-risk, hospitalized cohort; the burden added with respect to the number of infections that would potentially be

outcomes of drug-resistant enteric infections. (*Under Goal 2, Objective 2.4, Sub-Objective 2.4.1*)	reported through this mechanism; and the incentives that would be needed to report the data into NHSN in a consistent manner to be meaningful. CDC determined that adding enteric pathogens to NHSN reporting was not the most effective way to collect this information; therefore, CDC did not moved forward with this strategy. Alternative approaches linked to other existing surveillance efforts have been discussed and evaluated, and are also being considered in order to identify the most efficient method to collect these important data.
HHS will establish a process that allows product developers to provide data to CMS for use in developing Interpretive Guidelines that facilitate the use of tests for patient treatment, hospital infection control, and reporting of cases of disease during outbreaks. (*Under Goal 3, Objective 3.2*)	HHS determined that CMS does not have the authority to ask for this information in the manner described by this milestone; therefore, this milestone could not be completed.

Primary Accomplishments by Agency

The primary accomplishments for each agency are outlined in the Table 4 below.

Table 4. Primary Accomplishments by Agency for Activities Related to the National Action Plan

Biomedical Advanced Research and Development Authority (BARDA)
Creation and success of the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). • CARB-X is a global non-profit partnership dedicated to accelerating antibacterial research to tackle the global rising threat of AMR. The CARB-X portfolio is the world's largest early development pipeline of new antibiotics, vaccines, rapid diagnostics, and other products to prevent, diagnose, and treat life-threatening bacterial infections. • CARB-X has had remarkable success at obtaining product approval. For example, three products have been FDA-approved, which highlights how well BARDA has worked with non-diluted funding to incentivize companies and ensure products are developed and approved.
Centers for Disease Control and Prevention (CDC)

• The Antibiotic Resistance (AR) Laboratory Network:
  ○ The AR Laboratory Network currently tests tens of thousands of pathogens and performs colonization tests for threats such as carbapenem-resistant Enterobacterales (CRE). It also provides a platform to address unanswered questions and knowledge gaps.
  ○ The AR Laboratory Network is dual purpose (which is true for many public health programs): (1) for regular, day-to-day public health challenges and (2) for pandemic or other public health emergency response needs, where high quality surge capacity is required.
  ○ The use of whole genomic sequencing (WGS) has expanded greatly across the US through this network.

- CDC has been able to increase support to health departments across the nation for domestic infrastructure, both in terms of laboratory capacity and additional response capacity. Through this response capacity, efforts have demonstrated that prevention of resistant pathogens is possible.
- The innovation portfolio for CDC has helped pave the way forward with new tools that are aimed at preventing infections and decreasing the incidence, prevalence, and burden of resistant pathogens.
- The CDC & FDA Antibiotic Resistance (AR) Isolate Bank:
    - CDC obtains resistant bacteria through their response and outbreak surveillance networks.
    - CDC makes the isolates and panels available to researchers, including for diagnostic and drug development. Currently, CDC has 29 different panels and more than 220,000 isolates. These are requested and used from the AR Isolate Bank for activities such as conducting proficiency tests in clinical labs and the development of diagnostics and drugs.
- CDC has been a leader in communications about AMR both domestically and internationally (ranging from policy makers to healthcare providers to the general public).

Centers for Medicare and Medicaid Services (CMS)

- CMS finalized new regulations in 2019 that require US hospitals to develop and implement antibiotic stewardship programs. Under the new CMS COP rule, which was initially proposed in June 2016, all US hospitals and critical-access hospitals are required to have infection prevention and control and antibiotic stewardship programs to receive payments from CMS. The new rule was published in the Federal Register on September 30, 2019.
- CMS published new COPs in November 2016 for Medicare Long-term Care facilities (example: Quality Safety & Oversight - Guidance to Laws & Regulations).

Department of Defense (DOD)

- DOD enhanced coordination across the agency. This included:
    - Establishing a centralized laboratory network.
    - Establishing the Antibiotic Stewardship Working Group (ASPWG), which includes the EpiData Center (EPC), the Multidrug-Resistant Organism Repository & Surveillance Network (MRSN), and the Pharmacovigilance Center (PVC).
- DOD implemented a progressive web application for clinicians, which ensures that information relevant to antimicrobial stewardship is available to clinicians via the mobile app. This has been especially impactful for primary care. The combating antibiotic-resistant bacteria (CARB) effort allowed DOD to apply drug development knowledge to work on identifying antibiotics or alternatives to antibiotics.

Environmental Protection Agency (EPA)

- With the National Aquatic Resource Surveys (NARS) program, EPA has been looking at antimicrobial resistance in service water. On an annual basis, EPA looks at different kinds of waters (e.g., lakes, reservoirs, wetlands) to obtain a national picture of water conditions. This work has allowed EPA to generate national maps on antimicrobial resistance.
- Over the last few years, EPA has entered into a more formal agreement for working with the NARMS group, including the formation of an environmental working group within NARMS. As part of that group, EPA is developing a surface water pilot project called for in the 2020-2025 National Action Plan.

Food and Drug Administration (FDA)

- From the veterinary sector perspective, there were substantial changes in how antimicrobials are used in the agricultural sector during the 2015-2020 timeframe. FDA developed and implemented a strategy with a voluntary approach with relation to the use of medically important pharmaceuticals in food-producing animals for growth promotion. This was a significant shift in how these products are used in agriculture.
- The CDC & FDA AR Isolate Bank is valuable and has shown great progress with advancing device development.
- Several FDA initiatives have helped to streamline FDA's work. Examples: (1) the review of susceptibility devices, which then help in rapid detection of resistance, (2) a website that helps streamline the review criteria, and (3) guidance on coordinated development, which allows sponsors to approach FDA early, so their devices are available when a drug is approved.

Health and Human Services (HHS)

- Many of the key HHS accomplishments are provided under various HHS agencies in this table, including CDC, CMS, FDA, and NIH. For example, CARB-X has been highly successful at stimulating development of new treatment and diagnostic modalities.
- HHS has played a key role in implementing the work outlined in the National Action Plan by coordinating and co-chairing the US government's Task Force for Combating Antibiotic-Resistant Bacteria.
- HHS was able to use the political will of the US government to ensure progress internationally. For example, during this time, HHS participated in the "Alliance of Champions," which was a group of health ministers who met in Geneva, Switzerland, on the margins of WHO work. Because this group decided to prioritize AMR, the AMR topic received high-level attention at the United Nations, which led to the *WHO Global Action Plan on Antimicrobial Resistance*.
- HHS maintained focus on international collaborations and connections, which has been a great success on the global level and has created a foundation for future work.

National Institutes of Health (NIH)

- As part of the National Action Plan, NIH launched several new important programs (two in collaboration with BARDA):
    - The National Database of Antibiotic Resistant Organisms (NDARO): This is an important resource for the scientific community, with the ability to edit, curate, rewrite, and expand on data.
    - The diagnostics prize competition: This led to the development of a new diagnostic for point-of-care diagnosis of sexually transmitted infections, including drug-resistant gonorrhea. NIH has also providing other funding for diagnostics to address antibiotic-resistant bacteria, and has made a number of additional awards in this area.
    - The creation of CARB-X, in coordination with BARDA.
- NIH expanded support of clinical trials through: (1) expanding and strengthening the Antibacterial Resistance Leadership Group (ARLG), which now has enhanced funding and the ability to conduct research at more sites and (2) completing several clinical trials to inform optimal use of existing antibiotics during the course of the first 5-year National Action Plan.
- NIH has also strongly supported the development of non-traditional therapeutics. For example, NIH issued several funding announcements to explore new treatment approaches (e.g., phage therapy, antivirulence inhibitors, monoclonal antibodies, microbiome-based approaches).

US Agency for International Development (USAID)

- Governance

- Support for countries to develop and implement national multi-sectoral AMR strategies or national action plans, and in several countries, national AMR coordination committees.

- Preventing Infections
  - USAID strengthened infection prevention and control (IPC) measures to help prevent healthcare associated infections, including the development and strengthening of national IPC committees, national IPC action plans, and national IPC standards.
  - With USAID support, partners have pioneered the Clean Clinic Approach, a quality improvement strategy to strengthen WASH (water, sanitation, and hygiene) in healthcare facilities.
- Surveillance
  - USAID provided technical assistance, training, and commodities to strengthen laboratory capacity to detect AMR, including in large poultry markets.
- Stewardship and Case Management
  - USAID promoted development of antimicrobial stewardship plans and activities that promote appropriate use by providers, dispensers, and consumers in both human and animal health.
  - USAID supports 25 countries to strengthen the timely diagnosis and appropriate case management of severe bacterial infections, including pneumonia, in newborns and children.
  - USAID supports activities toward correct diagnosis, assessment, and care by trained healthcare workers, according to evidence-based guidelines that underpin the judicious use antimicrobials.

US Department of Agriculture (USDA)

- NAHMS surveys that were conducted in 2017: The surveys provided important information to understand antimicrobial use and practices before the Veterinary Feed Directive (VFD) went into effect.
- The NAHLN AMR Pilot Project (NAHLN AMR pilot project)
  - The project gave a better understanding of resistance in animal pathogens.
  - The project examined both livestock and companion species (horses, cats, and dogs).
- Providing National Veterinary Accreditation Program modules (NVAP Modules) as a resource.
  - The modules are a resource for veterinarians and anyone who wants the information included in the modules.
  - The modules include specific information on the VFD for veterinarians (Module 29).
- Expansion of AMR testing conducted by USDA, such as the inclusion of more commodities (e.g., chicken parts) and starting the cecum sampling program.
- Conducting WGS for the NARMS program.
- In 2015 through 2020, the USDA National Institute of Food and Agriculture (NIFA) funded research, extension. and education activities through the USDA Agriculture and Food Research Initiative (AFRI) Programs and Hatch Multistate projects. Between 2015 and 2018, NIFA made 85 awards totaling $40,097,725 toward AMR. Between 2019 and 2020, NIFA made an additional 49 awards totaling $31,585,383.
- FDA and USDA have been co-leading a US government effort to update and develop international guidance on minimizing and controlling foodborne antimicrobial resistance, as well as developing surveillance guidelines through the Codex Task ad hoc Intergovernmental Task Force on Antimicrobial Resistance since 2016 (Codex Alimentarius Ad hoc Codex Intergovernmental Task Force on Antimicrobial Resistance [TFAMR]).

Veterans Affairs (VA)
• All 140 VA medical centers have implemented antibiotic stewardship programs and are in compliance with Veterans Health Administration (VHA) Directive 1031. • All VA facilities are reporting data on antibiotic use to CDC.

Primary Barriers and Challenges for Completing Milestones

During interviews with agency personnel, they identified a number of important barriers and challenges to completing work on the National Action Plan. Several key themes that emerged from these conversations include the following: (1) many of the milestones in the National Action Plan were considered aspirational without adequate resources to fully implement them; (2) new drug development to combat AMR is a major challenge; (3) the COVID-19 pandemic had an impact on completing AMR-related work; (4) addressing AMR through a One Health lens adds to complexities; (5) political issues can pose barriers; (6) lack of standardization or alignment of concepts among different countries is an important barrier to global efforts, and (7) other agency-specific issues. Highlights on these themes are outlined in the bullets below.

Resource Constraints

- CDC indicated that they were only been able to provide about half of the funding that states requested as part of the National Action Plan; therefore, states' ability and interest in implementing AMR programs outpaced CDC's ability to provide funding. CDC also indicated that funding often has been provided in large boluses, with mandates to spend the money quickly, which is not always the most effective way to utilize resources. Stable, consistent funding would be a more effective approach for this effort.
- HHS noted that, while the US government could help promote the development of national action plans in other countries, resources to implement the plans were limited, which created a barrier to moving AMR-related work forward around the globe. For example, if a country has no mechanism to determine the burden of disease, the Minister of Health has no data to justify acquisition of resources to address AMR-related issues. Implementing surveillance systems to identify the major AMR pathogens is an initial step, and is one of the things that Global Health Security Agenda (GHSA) is supporting in low-income countries. If that cycle (of not having data to identify problem areas that require funding) isn't broken, the resources will never be made available. Furthermore, low-income countries have a number of other competing health priorities, which can also impede action on AMR-related issues.
- Several agencies noted disparity of resources between different agency sectors.
- Despite resource constraints, US government agencies were still highly successful in accomplishing activities laid out in the first National Action Plan.

New Drug Development

- CDC noted that there are 18 different pathogens in the most recent CDC 2019 report on Antimicrobial Resistance Threats in the United States, which dramatically increases the complexities of creating new treatments and prevention/control strategies for AMR.
- The pipeline of AMR drugs is limited and creating new antibacterial drugs is very challenging, with few companies actively working on the field. Although steps have been taken to improve the pipeline, this remains a challenge and significant market failures have occurred.
- Incentivizing industry to invest in the development of new drugs can be challenging. The uncertainty that antibiotic companies (and to a certain extent, non-traditional companies) face is a challenge for the entire field.
- Companies are less willing to invest in new products if they don't know whether a market will exist or not. Market pull is critical, and the lack of proof of principle or known market is a challenge. Changing management reimbursement for products will be necessary for development of new antibiotics. Both push and pull incentives are needed.
- It is important to de-risk companies and provide companies the needed support to advance products. For example, NIH has moved earlier in the development pipeline to stimulate and support early stages of discovery and development, because they have found this stage to be a critical bottleneck, especially for therapeutics targeted to Gram-negative organisms.
- The regulatory pathway for non-traditional therapeutics is not clear and this needs to be addressed (including creation of new standards and assays to support product development).

The COVID-19 Pandemic

- The COVID-19 pandemic was cited as an important barrier, since resources were diverted away from AMR activities to pandemic response.
- USDA noted that NIFA was impacted by COVID-19 by not being able to meet in-person with funded awardees to learn about outcomes, accomplishments, and achievements, which delayed progress.

AMR Through the One Health Lens

- While essential to AMR work, the One Health lens makes issues more complicated.
- Implementing a One Health approach involves extensive collaboration across multiple agencies.

- It can be challenging for agriculture departments from around the world to come together and find solutions that are protective of human health while not destructive to the animal/agricultural economy.

Political Issues

- Leadership changes can result in priority and policy changes. There was an administration change in the middle of the timeframe for the National Action Plan, and certain priorities under one administration were not necessarily priorities under the next administration.

Lack of Standardization or Alignment Across Countries

- Data reconciliation is needed for data collected through different surveillance systems. Different countries measure benchmarks based on different standards (e.g., consumption vs. prescription for antibiotic use, different definitions of "antimicrobial", etc.); this creates challenges in aligning best practices and standards.
- NIH has worked to align clinical trial strategies between the US and in Europe to improve efficiencies for enrolling patients across different countries.
- Differences in terminology, disease conditions, methodologies, regulatory structures, antimicrobial resistance patterns, antimicrobial access, priorities, and resources in different countries can make it challenging to communicate and find a common path forward.

Other Issues

- For DOD, a major challenge was transitioning and modernizing the I system (e.g., shifting to electronic medical records). Another major challenge was creating standardization and centralization across an extremely large organization.
- The USDA faced important challenges in gaining producer trust and garnering support of industry groups to conduct AMR-related research, since producers have been very sensitive on the topic of antimicrobial use (particularly around the time that the VFD was introduced). USDA has worked to build trust by stressing voluntary cooperation, ensuring producer confidentiality, working with industry groups, crafting communications messages, and gathering data that are useful to the producers.
- The EPA noted a lack of authority to conduct certain types of research. For example, the Clean Water Act provides EPA broad authority to conduct research on emerging areas, but the Act does not specifically authorize EPA to conduct wastewater surveillance.

Key Lessons Learned

Similar to barriers and challenges, a number of important themes for lessons learned emerged from the key informant interviews with agency personnel. These include the following:

- The capabilities built through the National Action Plan are dual use (such as pandemic or emergency response capabilities). These additional capabilities support the value of expending national resources to prevent AMR and can contribute to additional critical public health infrastructure needs.
- Prevention of AMR is possible through concerted public health efforts (human and animal).
- The One Health aspect of AMR prevention and control has been validated and expanded. For example, the environment (clean water, the need for sanitation, etc.) wasn't really discussed in relation to the 2015-2020 National Action Plan. This has fundamentally shifted, and the environment has been incorporated to a greater degree in the 2020-2025 plan. To address AMR from a One Health perspective, an interdisciplinary approach is necessary. The US government's collaborative efforts to find common, workable solutions through the CARB Task Force and soliciting external expert advice through the Presidential Advisory Council for Combating Antibiotic Resistant Bacteria have shown how a truly One Health approach is actionable at the national level.
- Collaboration across agencies was a critical factor in the success of the first National Action Plan. Such collaboration was essential owing to the complexities of AMR-related issues. Federal agencies also worked together to ensure that work being done was synergistic and was not duplicative. Without the relationships and trust that have been built over the last few years, it would have been very difficult to accomplish all that has been done.
- The importance of political will is a key lesson learned; without political will behind the National Action Plan, funding and other resources critical for success would not have been available.
- Basing discussions in science and risk and soliciting the experience of experts, especially those that understand issues at a practical, on the ground local level, is key to bridging understanding and achieving practical solutions that are globally achievable.
- The first National Action Plan had too many milestones and not enough focus on outcomes. The focus for the second National Action Plan was changed as a result.
- On the international level, common, measurable targets, tools to assess capacity, guidance, and standards are needed to allow meaningful comparisons, address gaps, and strengthen capacity.

Comments

Limitations

This study has several important limitations. First, many of the milestones in the National Action Plan were more process-oriented rather than outcome-oriented and could not be adequately assessed for completion without input from federal agency personnel. Similarly, for a number of milestones, we were unable to identify publicly available information to determine if the milestone had been achieved. Therefore, we needed to rely on input from federal agency personnel to provide information on whether or not certain milestones were adequately

completed. Even after speaking with agency personnel, because of the complexity of the discussions, we requested their review of our findings to ensure that we had accurately captured the discussions. While this level of agency involvement in the process was essential to ensure that we accurately captured the information, it potentially introduced bias in the findings and also left us unable to externally validate all of the data in the overarching data table in the Appendix. Second, the scope of this project was to focus on whether or not milestones were operationally achieved. The project scope did not focus on trying to capture all of the scientific contributions made during the 5 years of the first National Action Plan. For example, we are aware that activities completed for the National Action Plan resulted in a many scientific publications; however, we did not capture that information as it was out of scope for the project. While this report details a tremendous number of accomplishments, it underestimates the true progress that was made. Finally, many of the accomplishments by federal agencies are dual use, meaning that they benefit the public's health more broadly than just achieving the goal of combating antibiotic-resistant bacteria. Such benefits are not fully captured in this report, again underestimating the true value of the work by US federal agencies in meeting the milestones in the National Action Plan.

Conclusions

Based on our findings, we conclude that US federal agencies were remarkably successful in completing the milestones in the first National Action Plan, with a 93% overall completion rate, particularly since many of the milestones were intended to be aspirational. This success can be attributed to several key factors. The first was political will on the part of the US government, which led to substantial funding and resources being allocated to this issue (although even with this support, the agencies still cited resource constraints as an important barrier in fully achieving all of the activities outlined in the National Action Plan). The second key to success was a foundation of highly dedicated agency personnel who are deeply committed to their work and who formed a strong collaborative network aimed at achieving the milestones in the National Action Plan. The third important factor was extensive international outreach by US government personnel to elevate the awareness about and the status of AMR at the global level. This advocacy by US government personnel helped to ensure the success of Goal 5 in the National Action Plan, which was aimed developing international coordination and capacity to combat antibiotic resistant bacteria.

Acronyms

AFRI	Agriculture and Food Research Initiative
AMR	Antimicrobial resistance
AR	Antibiotic resistance
ARLG	Antibacterial Resistance Leadership Group
ASPWG	Antibiotic Stewardship Working Group
ASPE	Office of the Assistant Secretary for Preparedness and Response
ASPR	Office of the Assistant Secretary for Planning and Evaluation
AU	Antibiotic use
BARDA	Biomedical Advanced Research and Development Authority
CARB	Combating Antibiotic Resistant Bacteria
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CBDP	Chemical and Biological Defense Program
CDC	Centers for Disease Control and Prevention
CIDRAP	Center for Infectious Disease Research and Policy
CMS	Centers for Medicare & Medicaid Services
COP	Conditions of participation
CRE	Carbapenem-resistant Enterobacterales
DOD	Department of Defense
DTRA	Defense Threat Reduction Agency
EIP	Emerging Infections Program
EPA	The Environmental Protection Agency, Department of the Interior
EPC	EpiData Center
FDA	Food and Drug Administration
GAO	Government Accountability Office
GHSA	Global Health Security Agenda
HHS	Department of Health and Human Services
IHR	International Health Regulations
IND	Investigational New Drug
IPC	Infection prevention and control
IQR	Inpatient quality reporting
IT	Information technology
MDR-TB	Multidrug-resistant tuberculosis
MRSN	Multidrug-Resistant Organism Repository & Surveillance Network
NAHLN	National Animal Health Laboratory Network
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
NARS	National Aquatic Resource Surveys
NASEM	National Academies of Sciences, Engineering, and Medicine
NDARO	National Database of Antibiotic Resistant Organisms
NHSN	National Healthcare Safety Network

NIFA	National Institute of Food and Agriculture
NIH	National Institutes of Health
NQF	National Quality Forum
NVAP	National Veterinary Accreditation Program
PVC	Pharmacovigilance Center
SURRG	Strengthening the United States Response to Resistant Gonorrhea
TB	Tuberculosis
TFAMR	Task Force on Antimicrobial Resistance
US	United States
USDA	US Department of Agriculture
USAID	US Agency for International Development
VA	Department of Veterans Affairs
Vet-LIRN	Veterinary Laboratory Investigation and Response Network
VHA	Veterans Health Administration
VFD	Veterinary Feed Directive
WASH	Water, sanitation, and hygiene
WGS	Whole genomic sequencing
WHO	World Health Organization

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Appendix

The following pages provide a detailed table that outlines progress to date on each of the 230 milestones in the 2015-2020 National Action Plan for Combating Antibiotic Resistant Bacteria. The milestones are organized as they are in the National Action Plan. If a milestone included participation by more than one agency, the summary of progress includes input from each involved agency.

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA, 2015-2020: Progress Report July 2021

GOAL 1: SLOW THE EMERGENCE OF RESISTANT BACTERIA AND PREVENT THE SPREAD OF INFECTIONS.		
Objective 1.1*:** Implement public health programs and reporting policies that advance antibiotic resistance prevention and foster antibiotic stewardship in healthcare settings and the community. ***Sub-Objective 1.1.1A: Strengthen antibiotic stewardship in inpatient, outpatient, and long-term care settings by expanding existing programs, developing new ones, and monitoring progress and efficacy.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: The Departments of Health and Human Services (HHS), Defense (DOD), and Veterans Affairs (VA) will review existing regulations and propose new ones, as needed, requiring hospitals, ambulatory surgery centers, dialysis facilities, and other inpatient facilities to implement robust antibiotic stewardship programs that align with the Centers for Disease Control and Prevention (CDC) Core Elements. HHS, DOD, and VA will also work together to optimize standardization of stewardship programs and activities, including monitoring activities and reporting criteria.	Yes	Department of Health and Human Services (HHS): • In October 2016, the Centers for Medicare & Medicaid Services (CMS) published final requirements for >15,000 Medicare and Medicaid-participating long-term care (LTC) facilities. The rule included provisions that address infection prevention and control, antibiotic use protocols, and a system to monitor antibiotic use, with phased-in implementation. By November 2016 and November 2017, respectively, LTC facilities were required to have a more robust infection control and prevention program, and an antibiotic stewardship program in place (NAP Progress Report: Year 3). • In September 2019, CMS finalized new regulations that require US hospitals to develop and implement antibiotic stewardship programs. Under the new CMS conditions of participation (COP) rule, which was initially proposed in June 2016, all United States (US) hospitals and critical access hospitals will be required to have infection prevention and control and stewardship programs in order to receive payments from CMS. The new rule (Medicare and Medicaid Programs: Regulatory Provisions To Promote Program Efficiency, Transparency, and Burden Reduction; Fire Safety Requirements for Certain Dialysis Facilities; Hospital and Critical Access Hospital [CA]) Changes To Promote Innovation, Flexibility, and Improvement in Patient Care) was published in the Federal Register on September 30, 2019. Department of Defense (DOD): • Per the NAP First 180 Days Report, as of November 2015, DOD was working with CDC, VA, and others to standardize reporting language/terms. • As reported in 2017, DOD also planned to participate in the Agency for Healthcare Research and Quality (AHRQ) Safety Program for Improving Antibiotic Use for both acute-care (in 2017) and ambulatory care (2019) settings (NAP Progress Report: Years 1 and 2). • As of September 2019, DOD had published its Antimicrobial Stewardship Program Implementation Guidance, Defense Health Agency Procedural Instruction 6025.09, aligned with

		the Antimicrobial Stewardship Program Policy, DOD-I 6025.26, which was published in October 2017 (NAP Progress Report: Year 4). • The Government Accountability Office (GAO) Report (2020) noted that the policy above required antibiotic stewardship programs to be established within military medical treatment facilities. The policy specified that facilities' antibiotic stewardship programs include components such as: (1) leadership commitment by each facility; (2) accountability; (3) pharmacy expertise; (4) implementation of action for change that would demonstrate commitment to the program; and (5) training for clinicians regarding antibiotic resistance (AR) and prescribing practices. Department of Veterans Affairs (VA): • Per the National Action Plan (NAP) Progress Report for years 1-2, the VA has a long standing National Veteran's Health Administration (VHA) Stewardship Initiative that is coordinated through the VHA National Antimicrobial Stewardship Taskforce (ASTF). In January 2014, the VA Central Office leadership published VHA Directive 1031: Antimicrobial Stewardship Programs, requiring all VA Medical Centers to establish procedures for the implementation, maintenance, and evaluation of antimicrobial stewardship programs (NAP Progress Report: Years 1 and 2). • In 2018, the Multidrug-resistant organism Repository and Surveillance Network (MRSN) reported working with the VA regarding wound infection surveillance and pathogen characterization (NAP Progress Report: Year 3). • In January 2019, VA updated its 2014 policy directive (detailed above). This policy directive includes requirements for its facilities to develop a written policy, conduct an annual evaluation of stewardship activities, ensure that adequate staff and resources are in place, and identify medical and pharmacy personnel as stewardship "champions" (GAO Report, NAP Progress Report: Year 4). • The VA has successfully implemented antibiotic stewardship programs in all of its healthcare facilities (GAO Report, NAP Progress Report: Year 3). • Per the 2020 GAO Report, the VA offers antibiotic stewardship training to its healthcare facilities through webinars, workshops, or briefings (GAO Report).
Within 1 year: The National Healthcare Safety Network (NHSN) will begin tracking the number of healthcare facilities with stewardship policies and programs in place.	Yes	• In 2014, CDC began tracking the number of hospitals that have implemented all seven of the core elements for antimicrobial stewardship through the CDC NHSN Annual Hospital Survey. Based on CDC data, the percentage of all US hospitals reporting antibiotic stewardship programs that meet all of CDC's Core Elements rose to 46% in 2015 and to 64% in 2016. In 2020, 88.9% of hospitals have implemented CDC's Core Elements (see Antibiotic Use in the United States, 2020 Update: Progress and Opportunities).

Within 1 year: DOD will establish a multidisciplinary group, under the purview of the Asst. Sec. of Defense for Health Affairs, to support and coordinate stewardship across DOD.	Yes	• Per the NAP First 180 Days Report, as of November 2015, DOD, using the 2014 Combating Antibiotic-Resistant Bacteria (CARB) Executive Order and the 2015 National Defense Authorization Act as authorizing documents, was formalizing the stewardship working group and policy. The group first met on September 16, 2015. • The Antimicrobial Stewardship Program Policy, DOD-I 6025.26 (2017) outlines responsibilities across DOD to support stewardship activities.
Within 3 years: All hospitals that participate in Medicare and Medicaid programs must comply with Conditions of Participation (COP). The Centers for Medicare & Medicaid Services (CMS) will issue new COPs or revise current COP Interpretive Guidelines to advance compliance with recommendations in CDC's Core Elements of Hospital Antibiotic Stewardship Programs. HHS, DOD, and VA will also implement policies that: (1) encourage implementation of stewardship programs as a condition for receiving federal grants for health care delivery and (2) require health facilities operated by the USG (US government) to develop and implement antibiotic stewardship programs and participate in NHSN reporting (related to Objective 2.2).	Yes	• In September 2019, CMS finalized new regulations that require US hospitals to develop and implement antibiotic stewardship programs. Under the new CMS COP rule, which was initially proposed in June 2016, all US hospitals and critical access hospitals will be required to have infection prevention and control and stewardship programs in order to receive payments from CMS. The new rule (Medicare and Medicaid Programs: Regulatory Provisions To Promote Program Efficiency, Transparency, and Burden Reduction; Fire Safety Requirements for Certain Dialysis Facilities; Hospital and Critical Access Hospital [CAH]) Changes To Promote Innovation, Flexibility, and Improvement in Patient Care) was published in the Federal Register on September 30, 2019. • The Omnibus Burden Reduction (Conditions of Participation) Final Rule was also published in 2019. The Final Rule removes Medicare regulations identified as unnecessary, obsolete, or excessively burdensome on hospitals and other healthcare providers to reduce inefficiencies. <u>Encourage implementation of stewardship programs as a condition for receiving federal grants for healthcare delivery.</u> • Per HHS personnel in May 2021, this milestone has been accomplished. HHS activities relevant to this milestone focused on conditions of participation and not grants, whereas agencies within HHS may encourage implementation of stewardship programs as a condition for receiving federal grants for healthcare delivery. • This milestone is not applicable for DOD or VA (per VA and DOD personnel in March and April 2021, respectively). <u>Require health facilities operated by the US government to develop and implement antibiotic stewardship programs and participate in NHSN reporting</u>. • The Antimicrobial Stewardship Program Policy, DOD-I 6025.26 (2017) notes the Director, Defense Health Agency (DHA), is tasked with ensuring that the DOD CARB program includes "antibiotic resistance monitoring and reporting procedures for all military medical treatment facilities."

		• The GAO Report (2020) noted that the policy above required antibiotic stewardship programs to be established within military medical treatment facilities. The GAO Report also noted that DOD requires their hospitals to report antibiotic use data to the NHSN Antimicrobial Use (AU) Option, and 44 of 48 DOD hospitals were reporting such data as of September 2019.
		• Per DOD personnel in April 2021, all applicable DOD health facilities participate in NHSN reporting.
		• The National VHA Stewardship Initiative had, as of 2017, initial success in optimizing antimicrobial use, as evidenced by a significant decline of >10% in inpatient antimicrobial use, and has begun to develop example stewardship interventions for outpatient and long-term care.
		• In 2019, VA updated its 2014 policy directive to require all VA facilities with 30 or more acute-care beds to report their antibiotic use data to CDC's NHSN AU Option by January 30, 2020 (GAO Report).
		  ○ In 2018, VA reported that nearly 80% of VHA acute-care facilities had enrolled in and submitted data to CDC's NHSN AU Option (NAP Progress Report: Year 3).
		  ○ In 2018, VA reported that they were developing an action plan to complete enrollment of all facilities (NAP Progress Report: Year 3).
		  ○ As of January 1, 2020, 97% (113 of 116) VA hospitals with more than 30 or more acute-care beds were reporting their antibiotic use data to CDC (GAO Report). Per VA personnel in March 2021, all facilities were reporting data on antibiotic use to CDC.
		• Per the 2020 GAO Report, CDC, VA, and DOD are collaborating to report antibiotic resistance data to CDC via NHSN (GAO Report).

Within 3 years:
All acute-care hospitals governed by the CMS COP will implement antibiotic stewardship programs. CMS will expand COP requirements to apply to long-term acute care hospitals, other post-acute facilities, ambulatory surgery centers, and dialysis centers.
	Partially	• Per CMS personnel in May and June 2021:
		  ○ New COPs were published in November 2016 for Medicare Long-term Care facilities. For example: Quality Safety & Oversight - Guidance to Laws & Regulations
		  ○ Hospital COPs were updated in September 2019.
		  ○ Hospitals and critical access hospitals were required to implement the regulations involving hospital antibiotic stewardship programs by March 30, 2020.
		• COPs for dialysis centers, ambulatory surgery centers, and other sites have not been expanded, so this milestone is only partially complete. The last set of fully implemented Conditions for Coverage (CfCs)/COPs in dialysis facilities occurred in 2008 (CMS End-Stage Renal Disease Facilities).

Within 3 years: CMS will revise existing Interpretive Guidelines (IGs), as	Yes	• Per CMS personnel in May 2021, IGs were updated to include Antibiotic Stewardship Programs can be found in the State Operations Manual Appendix A - Survey Protocol, Regulations and Interpretive Guidelines for Hospitals (revised February 2020).

needed, to include antimicrobial stewardship improvements. For example, IGs on Quality Assurance and Performance Improvement for hospitals may incorporate antibiotic-stewardship performance measures developed by the CDC, the Agency for Healthcare Research and Quality (AHRQ), and other professional organizations.		
Within 3 years: Training webinars for CMS surveyors will be updated to include information on antibiotic utilization in nursing homes, in accordance with existing IGs in the Infection Control Nursing Home regulations.	Yes	• In October 2016, CMS published a final rule, "Medicare and Medicaid Programs: Reform of Requirements for Long-Term Care Facilities" (81 FR 68688). Training webinars for CMS surveyors were created and are available on the requirements for infection prevention and control and antibiotic stewardship (NAP Progress Report: Year 4).
Within 3 years: CDC, CMS, AHRQ, and other partners will issue guidance on antibiotic stewardship and best practices for ambulatory surgery centers, dialysis centers, nursing homes and other long-term care facilities, doctors' offices and other outpatient settings, pharmacies, emergency departments, and medical departments at correctional facilities.	Yes	• In October 2016, CMS published a final rule, "Medicare and Medicaid Programs: Reform of Requirements for Long-Term Care Facilities" (81 FR 68688). • Per CDC personnel in April 2021: ○ By 2018, CDC worked directly with multiple large health systems, professional organizations, The Joint Commission, and the Federal Office of Rural Health Policy to implement CDC's Core Elements of Hospital Antibiotic Stewardship and CDC's Implementation of Antibiotic Stewardship Core Elements at Small and Critical Access Hospitals (released in July 2017), promote infection prevention and control, and improve antibiotic use, including having antibiotic use and resistance data to target actions. ○ CDC works with hospitals to evaluate the impact of CDC's Core Elements on antibiotic use through NHSN antibiotic use data and CDC's Emerging Infections Program (EIP). CDC uses these findings to identify patient-level and facility-level risk factors to both target action and to improve the quality and usability of the data for hospital leaders and staff. CDC has developed Core Elements of Antibiotic Stewardship for a variety of settings include

		acute-care, small and critical access hospitals, outpatient settings, nursing homes, and resource-limited settings (CDC Core Elements of Antibiotic Stewardship). ○ CDC has expanded work to improve antibiotic use in nursing homes through data, tools, and partnerships for implementation of CDC's Core Elements of Antibiotic Stewardship for Nursing Homes. CDC conducted the first comprehensive analysis of nursing home antibiotic use to guide action. With partners including CMS, CDC is developing an Infection Prevention in Post-Acute and Long-Term Care Certificate Course for long-term care facilities, and convened nursing home systems, provider organizations, electronic health record vendors, and pharmacy vendors to discuss ways to report antibiotic use and implement antibiotic stewardship. CDC is also working with the National Quality Forum (NQF) to create a practical guide to implement antibiotic stewardship activities, similar to the tool created for hospitals. ○ CDC also works closely with federal partners to support improved use of antibiotics. CDC is supporting the scale-up of stewardship interventions in the VA's outpatient and acute-care settings and has worked with the VA to refine methods for measuring hospital antibiotic use in NHSN. CDC is also providing technical support and subject matter expertise to the Federal Office of Rural Health Policy within the Health Resources and Services Administration (HRSA), CMS, and the Quality Innovation Network-Quality Improvement Organizations (QIN-QIOs) to enroll nursing homes and outpatient settings to implement antibiotic stewardship using CDC's Core Elements. As of April 2018, QIN-QIOs have recruited over 7,500 outpatient settings, including physician practices, hospital emergency departments, urgent care centers, and others. ○ CMS and CDC are also collaborating on new LTC infection prevention/antibiotic stewardship training materials. To share best practices for antibiotic stewardship and *Clostridioides difficile* infection (CDI) prevention guidance, CMS has implemented intensive trainings, technical assistance, and collaborative learning opportunities that have reached over 4,000 hospitals, 2,400 nursing homes, and 7,600 outpatient settings based on CDC and AHRQ stewardship protocols. ○ CDC has collaborated with the VA and provided expertise and financial resources to help support accomplishment of mutual goals related to antibiotic stewardship. The VA has an ongoing initiative dedicated to enrollment in the NHSN's AU Option. To date, nearly all required VHA acute-care facilities have enrolled and submitted data to CDC's NHSN's AU Option. The VA has also launched a national outpatient antimicrobial stewardship

		intervention aimed at improved prescribing for acute respiratory tract infections for elective implementation at any VHA facility. • To disseminate best practices for implementation of antibiotic stewardship across outpatient settings and clinical provider specialties (e.g., physicians, nurses, dentists, pharmacists), CDC developed an antibiotic stewardship training course (CDC Antibiotic Stewardship Training Series) that allows healthcare professionals to earn continuing medical education credits, which was released in February 2018 and is linked to the CMS Quality Payment Program (QPP)-Merit-Based Incentive Payment System (MIPS) Improvement Activities. CDC has also started working with the National Committee for Quality Assurance and clinical experts to expand three existing quality measures for tracking outpatient antibiotic use. • The various stewardship guidelines that have been published by CDC cover all of the settings identified in the milestones, except for prisons. In July 2019, the Federal Bureau of Prisons published: Antimicrobial Stewardship: Federal Bureau of Prisons Guidance, which is based on the CDC Core Elements of Antibiotic Stewardship and covers this setting, so this milestone has been met.
Within 3 years: At least 25 states, the District of Columbia, and Puerto Rico will establish or enhance antibiotic stewardship activities in inpatient healthcare delivery settings, in accordance with the CDC Core Elements. CDC will support these efforts via State AR Prevention (Protect) Programs for Healthcare ("AR Protect Programs; related to sub-objective 1.1.2).	Yes	• Per CDC personnel in April 2021: CDC supports capacity in 50 states, Puerto Rico, and six major cities to detect, respond to, and contain emerging AR threats, as well as to improve methods and timeliness of carbapenem-resistant Enterobacterales (CRE) laboratory testing in all 50 states and specialized testing in the seven regional laboratories. Health departments continue to use data from NHSN, outbreak investigations, and the AR Laboratory Network to target their response and prevention actions. Prevention across healthcare continues in over 30 state and local health departments to not only stop transmission of antibiotic resistant pathogens and *C. difficile* between healthcare settings, but also to build and strengthen partnerships to improve antibiotic prescribing in acute-care, including critical access hospitals, nursing homes, and in outpatient settings. This work is being supported through CDC's AR Solutions Initiative, which provides support to all 50 states, some local health departments, Puerto Rico, and the US Virgin Islands.
Within 5 years: DOD will support antibiotic stewardship programs and interventions critical for maintaining quality health care throughout the Military Healthcare System (MHS).	Yes	• The Antimicrobial Stewardship Program Policy, DOD-I 6025.26 (2017) notes the Director, DHA, is tasked with ensuring that the DOD CARB program includes "antibiotic resistance monitoring and reporting procedures for all military medical treatment facilities." • The GAO Report (2020) noted that the policy above required antibiotic stewardship programs to be established within military medical treatment facilities. ○ The policy specified that facilities' antibiotic stewardship programs include components such as: (1) leadership commitment by each facility; (2) accountability; (3) pharmacy

		expertise; (4) implementation of action for change that would demonstrate commitment to the program; and (5) training for clinicians regarding AR and prescribing practices. ○ As of 2020, DOD officials noted that facilities (inpatient and outpatient) were at different stages of implementing the antibiotic stewardship policy. • The GAO Report (2020) also noted that DOD has offered antibiotic stewardship training to their healthcare facilities through webinars, workshops, or briefings. • Per DOD personnel in April 2021: All applicable MHS facilities have some form of an antibiotic stewardship program.
Within 5 years: CDC will work with select hospital systems to expand antibiotic use reporting and stewardship implementation, and will partner with nursing organizations to develop and implement stewardship programs and interventions in a set of nursing homes.	Yes	• CDC works closely with CMS and the Hospital Improvement Innovation Networks (HIINs) to provide prevention tools and expertise to target healthcare-associated infections (HAIs) and antibiotic-resistant infections in acute-care and critical access hospitals. As of March 2018, more than 3,000 or 21% of CMS-certified nursing homes are actively enrolled and eligible to report *C. difficile* infections into NHSN, and CMS-supported HIINs have recruited more than 4,000 hospitals to benefit from CDC's expertise in improving patient safety, preventing hospital-acquired conditions including *C. difficile*, and implementing antibiotic stewardship programs. Each hospital receives technical assistance around implementing Antibiotic Stewardship Programs based on the Core Elements for acute-care settings defined by CDC, and to reduce antibiotic misuse or overuse and HAIs like *C. difficile* and other multi-drug resistant organisms (NAP NAP Progress Report: Year 3). • In 2019, CDC updated the hospital core elements to reflect evidence and best practices that were published/presented since the initial core elements were released in 2014. One of the major updates was to recommend the implementation of prospective audit with feedback and/or preauthorization as priority actions for stewardship programs. • Implementation of the Core Elements of Antibiotic Stewardship in Nursing Homes Enrolled in the National Healthcare Safety Network was published in 2019 and an updated analysis of core element implementation was completed. Abstracts of the analyses of long-term care pharmacy and electronic health record data were presented at a national infectious disease conference. Potential utility of pharmacy data to measure antibiotic use in nursing homes was published in 2019. Antibiotic use variability in nursing homes, 2016 has been completed and published.
Within 5 years: All states will establish or enhance antibiotic stewardship activities in healthcare delivery settings.	Yes	• CDC leads the AR Solutions Initiative, which provides support to all 50 states, some local health departments, Puerto Rico, and the US Virgin Islands. Between 2016-2020, CDC's Epidemiology and Laboratory Capacity (ELC) funded more than $550 million to all states and several other jurisdictions, which included antibiotic resistance and stewardship activities (including proposed activities/interventions in acute-care, nursing homes, and ambulatory settings).

Objective 1.1: Implement public health programs and reporting policies that advance antibiotic resistance prevention and foster antibiotic stewardship in healthcare settings and the community. ***Sub-Objective 1.1.1B:*** Strengthen educational programs that inform physicians, veterinarians, members of the agricultural industry, and the public about good antibiotic stewardship.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: CDC and VA will apply lessons learned from the CDC and VA pilot project to provide clinicians with support for making prescribing decisions based on judicious use of antibiotics and will submit a manuscript for publication describing initial research findings from this effort.	Yes	Apply lessons learned from the CDC and VA pilot project. • The VA's pilot project, supported by CDC, included an acute respiratory infection (ARI) provider support tool kit and antibiotic use dashboard was developed in one of the VHA's Veterans Integrated Services Networks. In less than one year, it resulted in a 13% decline in office visits for ARI resulting in an antibiotic being prescribed. The project is projected to expand over the next year to additional VA facilities (NAP Progress Report: Years 1 and 2). • In 2018, VA reported having launched a national outpatient antimicrobial stewardship intervention aimed at improving prescribing for acute respiratory tract infections (NAP Progress Report: Year 3). Submit a manuscript for publication describing initial research findings. • In July 2015, the results of the VA pilot project were published: *Variation in Outpatient Antibiotic Prescribing for Acute Respiratory Infections in the Veteran Population* (Jones 2015, NAP Progress Report: Years 1 and 2).
Within 3 years: CDC will support public health departments in establishing statewide programs for antibiotic stewardship and appropriate antibiotic use. These programs will identify healthcare facilities with high antibiotic-prescribing rates and use lessons learned from the CDC and VA pilot project (see above) and other best practices to improve antibiotic prescribing in these facilities. The success of these efforts will be assessed by measuring changes in	Yes	• CDC leads the AR Solutions Initiative, which provides support to all 50 states, some local health departments, Puerto Rico, and the US Virgin Islands. • CDC has ongoing systems in place for tracking antibiotic use in the US over time. Reports on tracking antibiotic use have been published in 2017, 2018, and 2020 and are available on the CDC website: Antibiotic Prescribing and Use. • Per CDC personnel in April 2021: ○ CDC supports capacity in 50 states, Puerto Rico, and six major cities to detect, respond to, and contain emerging AR threats, as well as to improve methods and timeliness of CRE laboratory testing in all 50 states and specialized testing in the seven regional laboratories. Health departments continue to use data from NHSN, outbreak investigations, and the AR Laboratory Network to target their response and prevention actions. Prevention across healthcare continues in over 30 state and local health departments to not only stop transmission of antibiotic resistant pathogens and *C. difficile* between healthcare settings, but also to build and strengthen partnerships to

prescribing rates and in clinicians' understanding of antibiotic stewardship activities and programs.		improve antibiotic prescribing in acute-care(including critical access hospitals), nursing homes, and outpatient settings. ○ CDC also supports capacity in states and cities to track, investigate, and prevent foodborne disease. As of March 2018, 49 laboratories in 44 states have established capacity to perform whole genome sequencing (WGS) on all *Salmonella* isolates. CDC is working with partners to validate these data for reliability and accuracy and is developing computer algorithms to automate and improve detection of new resistance patterns for faster identification and response to foodborne outbreaks with known markers of antibiotic resistance. ○ To address the emerging threat of antibiotic-resistant gonorrhea (ARGC) in the US, CDC also supports capacity in nine health departments to establish rapid detection and response through local laboratory testing for gonorrhea (GC) and resistant *Neisseria gonorrhoeae* at their local sexually transmitted disease (STD) clinics and public health labs. Between February and December 2017, these nine sites collected nearly 14,000 specimens; of the more than 3,200 specimens testing positive for GC, 242 (7.6%) had less than optimal responses in the laboratory to recommended antibiotics and triggered rapid local response to prevent spread. Other CDC data are showing a growing proportion of pathogens with less than optimal response in the lab to recommended treatment, which include a concerning cluster of GC cases in Hawaii (2016).
Within 3 years: CDC will provide technical assistance to Federal facilities (e.g., those operated by DOD, the VA, and the Indian Health Service [IHS]) and other large health systems in scaling up implementation and assessment of interventions to improve outpatient antibiotic prescribing, extending effective interventions to long-term care settings, and ensuring long-term sustainability of antibiotic stewardship efforts.	Yes	• Per CDC personnel in April 2021: CDC also works closely with federal partners to support improved use of antibiotics. CDC is supporting the scale-up of stewardship interventions in the VA's outpatient and acute-care settings and is collaborating with the VA to refine methods for measuring hospital antibiotic use in NHSN. CDC is also providing technical support and subject matter expertise to the Federal Office of Rural Health Policy within HRSA, CMS, and the QIN-QIOs to enroll nursing homes and outpatient settings to implement antibiotic stewardship using CDC's Core Elements. As of April 2018, QIN-QIOs have recruited over 7,500 outpatient settings, including physician practices, hospital emergency departments, urgent care centers, and others.
Within 3 years:	Yes	• Per DOD personnel in April 2021:

DOD will initiate the planning and approval process to modify clinical decision-support interventions in DOD facilities in targeted regions.		○ DOD uses clinical decision support tools. For example, facilities use an antimicrobial stewardship mobile application (DOD DHA's new app assists providers with treating infectious diseases). ○ DHA's Antimicrobial Stewardship Working Group (ASWG) reviews stewardship activities and processes (e.g., process for updating clinical guidelines).
Within 3 years: CDC, CMS, and partners will propose expanded quality measures for antibiotic prescribing.	Yes	• CDC developed the Standardized Antimicrobial Administration Ratio (SAAR)—now endorsed by the NQF as a metric for hospitals to benchmark antibiotic use—as part of the NHSN AU Option to help participating hospitals assess antibiotic use in their facilities and guide interventions to improve antibiotic use. CDC is improving the SAAR metric by working with hospital systems to explore more detailed risk adjustment of antibiotic use data and assess how improvements in hospital stewardship programs impact the SAAR metric (NAP Progress Report: Years 1 and 2). • In addition to the Hospital Inpatient Quality Reporting (Hospital IQR) program, both the Hospital Value-Based Purchasing and Hospital-Acquired Condition (HAC) Reduction Programs use payment incentives for Medicare-participating hospitals to report multi-drug resistant organisms, as well as infections associated with antibiotic misuse or overuse. Several appropriate use of antibiotic quality measures have also been approved for reporting and payment under the MIPs (NAP Progress Report: Years 1 and 2). • CDC has also started worked with the National Committee for Quality Assurance (NCQA) and clinical experts to expand three existing quality measures for tracking outpatient antibiotic use (NAP Progress Report: Year 3). • Per CDC personnel in April 2021: ○ CDC has example letters for providing feedback on quality measure performance for 2019 and 2020 Healthcare Effectiveness Data and Information Set (HEDIS®) measure performance available for tracking and reporting. ○ In 2020, NCQA was awarded a contract for development of a new HEDIS® measure that would combine multiple potential respiratory measures for prescribing into one. CDC provided recommendations regarding experts for the panel, and an expert panel convened in 2020 to discuss the components of the new measure. Measure development will continue into 2021. ○ CDC continues to fund and collaborate with external partners to explore ways the SAAR metric can help inform efforts to assess and improve antibiotic use. CDC is currently exploring methods to perform electronic assessments of the appropriateness of hospital antibiotic use.

		• Per CMS personnel in May 2021: The 12th Scope of Work as part of the Quality Improvement Organization (QIO) is underway. Patient Safety efforts including infection control and prevention and antibiotic stewardship are part of the quality improvement-innovation work that is ongoing in rural and small hospitals and outpatient settings that serve low-access populations.
Within 3 years: CMS will expand the Physician Quality Reporting System (PQRS) to include quality measures that discourage inappropriate antibiotic use to treat non-bacterial infections, such as respiratory tract infections.	Yes	• In 2019, CMS published Quality ID #116 (NQF 0058): Avoidance of Antibiotic Treatment in Adults With Acute Bronchitis. This measure includes the percentage of adults 18–64 years of age with a diagnosis of acute bronchitis who were not prescribed or dispensed an antibiotic prescription. • Per CMS personnel in May 2021: PQRS was replaced nearly four years ago in the QPP developed under the Medicare Access and CHIP Reauthorization Act (MACRA). Two programs under QPP are the MIPS and alternative payment models (APMs). Quality measures and improvement activities for eligible clinicians are developed through annual rulemaking. See Quality Measures: Traditional MIPS Requirements for additional details.
Within 3 years: CDC will expand training and support to acute-care facilities and nursing homes to improve antibiotic stewardship, as part of the *Get Smart for Healthcare* project.	Yes	• Per CDC personnel in April 2021: CDC launched two major, national health educational initiatives that were separate yet mindfully integrated. ○ First, during US Antibiotic Awareness Week in November 2017, CDC unveiled Be Antibiotics Aware: Smart Use, Best Care, which focused on improving antibiotic use across the spectrum of human healthcare, with new branding, resources, and educational materials targeting healthcare providers and the general public. The Be Antibiotics Aware public service announcement had more than 35 million media impressions, and more than 86,000 materials were downloaded in the subsequent four months. ○ Second, on August 31, 2017, and in conjunction with Sepsis Awareness Month, CDC launched Get Ahead of Sepsis, an educational initiative to protect Americans from the devastating effects of sepsis. This initiative emphasized the importance of recognizing sepsis early and acting quickly if sepsis is suspected, balancing messages about the importance of proper antibiotic treatment and reassessment, as well as infection prevention, as infections lead to sepsis in the first place. Between November 2017 and April 2018, the educational effort received about 245 million total estimated impressions, more than 90,000 materials were downloaded, public service announcements generated more than 39 million impressions, and CDC sepsis web traffic increased by 78% (year over year). CDC conducted a survey to measure the effectiveness of the Get Ahead of Sepsis educational initiative among target audiences. According to the survey of 1,616 consumers (conducted from February 26, 2018 to March 30, 2018) 71% of respondents who saw CDC's messaging said they searched for more information about sepsis and over

		half of the respondents who saw CDC's messaging said they asked a healthcare professional for more information about sepsis.
Within 5 years: CDC will evaluate the impact of quality measures on antibiotic use and provide feedback to healthcare partners. Additionally, CDC will continue to host a *Get Smart About Antibiotics Week* observance each November to raise public awareness about antibiotic-resistance and the importance of appropriate antibiotic prescribing.	Yes	• Per CDC personnel in April 2021: The NQF renewed its endorsement of the NHSN Antimicrobial Use Measure (NQF #2720) on October 23, 2019, for 3 years. The updated measure includes new versions of NHSN's SAARs, and the new SAARs were developed using 2017 AU data from hospitals participating in NHSN's AU surveillance. CDC published a summary report of 2019 antibiotic use data reported into NHSN. This endorsement, coupled with NHSN's collaboration with antibiotic stewardships and other partners, has prompted an increase in voluntary AU reporting to NHSN. As of December 1, 2019, 1,496 facilities had reported at least one month of data to the AU Option. • Facilities reporting data into both NHSN AU Option and the AR Option can get credit for the Public Health Registry Reporting measure under the Public Health and Clinical Data Exchange objective of the Promoting Interoperability Program (PIP) (Medicare promoting interoperability program eligible hospitals, critical access hospitals, and dual eligible hospitals attesting to CMS objectives and measures for 2020). • CDC hosts the US Antibiotics Awareness Week annually in November.
Objective 1.1: Implement public health programs and reporting policies that advance antibiotic resistance prevention and foster antibiotic stewardship in healthcare settings and the community. ***Sub-Objective 1.1.2***: Expand collaborative efforts by groups of healthcare facilities that focus on preventing the spread of antibiotic-resistant bacteria that pose a serious threat to public health (Table 3).		
Milestone	**Accomplished?**	**Comments**

Within 1 year:
The DOD Multidrug-Resistant Organism Repository & Surveillance Network (MRSN) will expand its detection and reporting capabilities to include *C. difficile* and other high-risk drug-resistant pathogens.
	Yes	• The MRSN is a department within the Walter Reed Army Institute of Research's (WRAIR's) Bacterial Diseases Branch (MRSN website).
		  ○ The MRSN serves as the primary surveillance organization for antibiotic-resistant bacteria across the Army, Navy, and Air Force.
		  ○ The MRSN focuses on the "ESKAPE-E" pathogens: *Enterococcus faecium* (vancomycin-resistant), *Staphylococcus aureus* (methicillin-resistant), *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp., and *Escherichia coli.*
		• DOD/MRSN's expanded its collection parameters to include standardized means for collecting and testing *C. difficile* isolates (NAP First 180 Days Report).
		• The MRSN maintains an active external collaboration with CDC's AR Laboratory Network (NAP Progress Report: Year 3).

		• As of 2018, MRSN was collaborating with DOD Infectious Disease Clinical Research Program efforts and with the VA regarding wound infection surveillance and pathogen characterization (NAP Progress Report: Year 3).
		• In May 2016, scientists from MRSN and Walter Reed National Military Medical Center (WRNMMC) discovered the *mcr-1* gene on a plasmid in an *E. coli*-containing urine sample, the first detection in a clinical sample in the US (NAP Progress Report: Years 1 and 2).
		  ○ The emergence of *mcr-1*, a gene on a plasmid that confers resistance to the antibiotic colistin, was first identified in China in 2015. The US government began conducting surveillance for *mcr-1* in the US after its identification (NAP Progress Report: Years 1 and 2).
		  ○ In response to the discovery, CDC developed and deployed a rapid laboratory test to help clinical labs find bacteria with the gene. The MRSN modified its screening protocols as well, including educating other clinical laboratories in the military healthcare system (NAP Progress Report: Years 1 and 2).

Within 3 years: At least 25 states, the District of Columbia, and Puerto Rico will establish or enhance State AR Prevention (Protect) Programs to improve antibiotic use and reduce transmission of resistant pathogens. Activities will include measuring the incidence of at least one regionally important multidrug-resistant organism (MDRO), providing healthcare facilities with feedback on local and regional MDRO rates, and providing healthcare facilities with technical assistance to advance MDRO prevention. CDC and CMS Quality Improvement Networks (QINs) will work with state and large local health departments to	Yes	• CDC leads the AR Solutions Initiative, which provides support to all 50 states, some local health departments, Puerto Rico, and the US Virgin Islands. In fiscal year 2016, Congress appropriated $160 million of new investments for CDC to fight AR across the country. • Health departments continue to work with the CMS-funded HIINs and QIN-QIOs to prevent device and procedure-associated infections and *C. difficile* in hospitals and nursing homes (NAP Progress Report: Year 3). • CDC works closely with CMS and the HIINs to provide prevention tools and expertise to target HAIs and antibiotic resistant infections in acute-care and critical access hospitals. As of March 2018, CMS-supported HIINs have recruited more than 4,000 hospitals to benefit from CDC's expertise in improving patient safety, preventing hospital-acquired conditions including *C. difficile*, and implementing antibiotic stewardship programs (NAP Progress Report: Year 3).

advance these efforts. QINs are groups of health quality experts, clinicians, and consumers who help improve the care delivered to people with Medicare.		
Within 3 years: At least 20 state health departments will maintain advanced capacity for rapid response to drug-resistant gonorrhea, including capacity to detect, diagnose, and investigate suspected resistant cases within their state or region and assist healthcare providers in providing appropriate treatment of infected patients.	Partially	• More than 30 states participate in one or more CDC-supported programs to address capacity to detect, diagnose, and investigate drug-resistant gonorrhea (CDC: Combating the Threat of Antibiotic-Resistant Gonorrhea). These programs include the Gonococcal Isolate Surveillance Project (GISP), the enhanced Gonococcal Isolate Surveillance Project (eGISP), the STD Surveillance Network (SSuN), the Antibiotic Resistance Laboratory Network (AR Laboratory Network), and Strengthening the United States Response to Resistant Gonorrhea (SURRG). • Per CDC personnel in April 2021: ○ To address the emerging threat of ARGC in the US, by 2018, CDC also supported capacity in nine health departments to establish rapid detection and response through local laboratory testing for GC and resistant *Neisseria gonorrhoeae* at their local STD clinics and public health labs as part of the SURRG program. Because of less than initially anticipated funding, CDC was not able to issue this funding to the full 20 state health departments to meet this milestone (CDC CARB Sites Map). ○ Between February and December 2017, these nine sites collected nearly 14,000 specimens; of the more than 3,200 specimens testing positive for GC, 242 (7.6%) had less than optimal responses in the laboratory to recommended antibiotics and triggered rapid local response to prevent spread. Other CDC data are showing a growing proportion of pathogens with less than optimal response in the lab to recommended treatment, which include a concerning cluster of gonorrhea cases in Hawaii (2016). The United Kingdom (UK) also recently described a multi-drug resistant infection (2018) that did not respond to first line therapy. These examples underscore the need for local capacity to slow the emergence of ARGC. ○ Between 2016-2020, CDC awarded between $5.6 to $6.5 million per year across eight health departments (nine were funded in 2016 and 2017) to establish rapid detection and response activities designed to quickly identify and respond to the threat of ARGC in the US. ○ The program has hired epidemiologists, microbiologists, disease investigators and others to focus on ARGC. Local clinical staff were trained on collecting specimens for culture, laboratory staff were trained on performing GC culture and resistance testing, and

		disease investigators staff were trained on conducting rapid response investigations. All grantees developed protocols, enhanced information systems, and implemented testing. This capacity was previously limited or unavailable. This activity is even more critical with CDC's September 2018 publication of new data showing increasing resistance to azithromycin (reduced susceptibility increased to 4.6%), part of the recommended combination GC treatment. Molecular studies provide details of concerning strains associated with reduced susceptibility to azithromycin in Indiana (Sept 2017- Sept 2019) (Pham et al.: Emergence of Neisseria gonorrhoeae strains harboring a novel combination of azithromycin-attenuating mutations), in Hawaii (May 2016), and a predominant, persistent and expanding GC strain in the US (Gernert et al.: Azithromycin susceptibility of Neisseria gonorrhoeae in the USA in 2017: a genomic analysis of surveillance data). ○ Between inception of specimen collection (February 2017) and June 2020, SURRG grantees collected 83,248 genital and extragenital specimens for GC culture from 38 participating health centers, with 16,071 (19%) testing positive for GC. Through local rapid antibiotic resistance testing, 1,760 (11.0% of all GC-positive cultures) were determined to have reduced susceptibility to at least one of the two antibiotics in the current recommended GC treatment, which in each case led grantees to initiate patient follow-up and other rapid response activities. In addition, WGS capacity was established within the AR Laboratory Network, resulting in over 5,840 SURRG isolates being sequenced, including ~1,970 male urethral specimens, ~2,380 male extragenital specimens, and ~1,140 female genital and extragenital specimens. 4,300 sequences are publicly available through National Center for Biotechnology Information (NCBI)/Sequence Read Archive (SRA) data archive.
Within 5 years: CDC will expand capacity to prevent the importation of cases of multidrug-resistant tuberculosis (TB) (MDR-TB) by doubling TB screening among migrants from high-incidence countries from 500,000 to 1 million persons per year.	No	• Per CDC personnel in April 2021: ○ CDC has continued to work with Department of State to address the regulatory framework necessary to implement screening of long-term visitors (i.e., international workers and students that would reside in the US for at least 12 months) from 45 high-incidence TB countries. Screening efforts were stalled in 2020 due to the COVID-19 response. ○ Additionally, CDC has rolled out eMedical (an electronic medical record system for panel physicians conducting screening) to all countries. This system will improve efficiencies in tracking TB cases among immigrants and long-term visitors to the US.
Within 5 years:	Yes	• CDC leads the AR Solutions Initiative, which provides support to all 50 states, some local health departments, Puerto Rico, and the US Virgin Islands. Between 2016-2020, CDC ELC has funded

State AR Prevention (Protect) Programs will be in place in all 50 states, as well as the District of Columbia and Puerto Rico.		more than $550 million to all states and several other jurisdictions, which have included antibiotic resistance and stewardship activities—including proposed activities/interventions in acute-care, nursing homes, and ambulatory settings.
Objective 1.1*:** Implement public health programs and reporting policies that advance antibiotic resistance prevention and foster antibiotic stewardship in healthcare settings and the community. ***Sub-Objective 1.1.3: Implement annual reporting of antibiotic use in inpatient and outpatient settings and identify geographic variations and/or variations at the provider and/or patient level that can help guide interventions.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: CDC will finalize arrangements for the purchase of proprietary data on inpatient antibiotic use to supplement NHSN data until a larger number of hospitals begin to utilize the NHSN module for antibiotic use reporting.	Yes	• CDC purchased proprietary data on inpatient antibiotic use to supplement the NHSN. The data helped CDC explore antibiotic use across hospitals in the US and the potential factors that might explain that variability (NAP First 180 Days Report).
Within 1 year: CDC will work with healthcare and public health partners to propose new healthcare-facility antibiotic use measures to the National Quality Forum (NQF; see also Sub-Objective 2.2.1).	Yes	• CDC worked closely with health system partners and developed SAAR, which has been endorsed by the NQF (NQF No. 2720). This measure allows healthcare facilities to use the new risk-adjusted summary measure of antibiotic use to determine where to focus their antibiotic stewardship efforts (NAP Progress Report: Years 1 and 2). • Per CDC personnel in April 2021: ○ As of August 31, 2020, CDC had collected AU data from 1,843 hospitals in 49 states and AR data from 731 hospitals in 48 states; 718 of these hospitals have reported both AU and AR data to CDC. ○ CDC continues to work with partners on this effort. For example, CDC works with Tennessee to support the implementation of their state requirement for hospitals to report AU data into NHSN. In Tennessee, 48 hospitals reported at least one month of AU data in 2020. ○ The NQF renewed its endorsement of the NHSN Antimicrobial Use Measure (NQF #2720) on October 23, 2019, for 3 years. The updated measure includes new versions of NHSN's SAARs, and the new SAARs were developed using 2017 AU data from hospitals participating in NHSN's AU surveillance. CDC is working on a summary report of 2019 antibiotic use data reported into NHSN.

		○ Facilities reporting data into both NHSN AU Option and the AR Option can get credit for the Public Health Registry Reporting measure under the Public Health and Clinical Data Exchange objective of PIP (Medicare promoting interoperability program eligible hospitals, critical access hospitals, and dual eligible hospitals attesting to CMS objectives and measures for 2020).
Within 3 years: CDC will use data collected through the NHSN AU module to provide annual national estimates of aggregated inpatient antibiotic use and feedback to healthcare facilities on antibiotic use, indicating whether antibiotic use rates are above or below the national average.	Yes	• Nearly 2,000 acute-care hospitals across the US submitted at least one month of data to the AU Option as of October 2020. CDC began reporting data on antibiotic use collected through NHSN AU in its 2020 report: Antibiotic Use in the United States, 2020 Update: Progress and Opportunities.
Within 3 years: CDC will establish routine reporting of antibiotic use and resistance data from select hospital systems via the NHSN AU and AR modules (see Objective 2.2).	Yes	• Per CDC personnel in April 2021: ○ CDC has worked with multiple hospital systems to establish routine reporting of antibiotic use via the antibiotic use and resistance (AUR) module, and CDC is working with additional hospital systems to establish their reporting. AMR reporting to the AUR module has begun, but only from a single hospital. ○ CDC also supported the CMS QIN-QIO 11th Scope of Work by recruiting a group of nursing homes to track and report *C. difficile* infections (CDIs) into NHSN. The CMS CDI reporting and reduction project officially began May 2016. CDC provided a series of training sessions on NHSN enrollment and CDI reporting (Jan/Feb 2016) for QIN-QIO staff supporting nursing homes in this nationwide collaborative effort. ○ CDC is working with the two largest hospital systems in the country, the Hospital Corporation of America (HCA) and Ascension, to enroll their member hospitals in the NHSN AU option. CDC is also funding a large health system/hospital stewardship network to implement the CDC Core Elements and enroll hospitals in the NHSN AU option. ○ All hospitals reporting data into NHSN AU are now able to view risk-adjusted, benchmarking data on their antibiotic use for a variety of groups of antibiotics and hospital locations. ○ HCA is working on a phased implementation of antimicrobial use and AMR reporting in all of its hospitals and CDC is supporting that effort. Premier is also making antibiotic use

		reporting available to many of its members and CDC is supporting the roll out of that effort. In fiscal year (FY) 2017, the pace of hospital participation in the NHSN AUR Module increased. ○ CDC is having monthly calls with partners in Missouri, including the health department and hospital association to support enrollment of all Missouri hospitals in AU and AR in accordance with their state reporting mandate. As of February 2019, 1,189 hospitals had submitted at least one month of AU data to NHSN, and 502 hospitals had submitted at least one month of AR data to NHSN. The VA system is requiring reporting to NHSN AU across their hospitals.
Within 3 years: DOD will centralize its reporting of inpatient antibiotic use to NHSN.	Yes	• As of June 2015, DOD planned to use FY2015 funds to develop algorithms for the collection of antibiotic use data, and inpatient data collection would precede outpatient data collection) by the Pharmacovigilance Center (Antimicrobial Stewardship Program Plan, Medical Facilities, DOD). • As reported in 2018, DOD had recently implemented centralized reporting to NHSN AU and AR modules (NAP Progress Report: Year 3).
Within 5 years: CDC will provide estimates of inappropriate inpatient antibiotic prescribing rates by state and region and use this data to target and prioritize intervention efforts.	Yes	• Per CDC personnel in April 2021: CDC published Assessment of the Appropriateness of Antimicrobial Use in Hospitals in 2020 estimating that more than half of antibiotic prescribed for select events in hospitals was not consistent with recommended prescribing practices. Researchers found that among patients treated for community-acquired pneumonia, prescribing was unsupported in 79.5% of cases, while for urinary tract infections, prescribing was unsupported for 76.8% of cases. Prescribing was considered unsupported for many reasons, including long durations, antibiotic selection that did not follow guidelines, no documented infection signs or symptoms, or no lab results confirming the presence of an infection. Based on CDC's finding, the Pew Charitable Trust released a report setting new benchmarks for prescribing of these selected events.
Within 1 year: CDC will report outpatient prescribing rates for 2011 and 2012 and use this data to target and prioritize intervention efforts.	Yes	• This information has been published and can be accessed on the CDC website: Antibiotic Prescribing and Use in Doctor's Offices. The summaries capture outpatient antibiotic prescriptions by year, age, antibiotic, antibiotic class, and provider specialty from IQVIA data and US Census files. • A study, Changes in Outpatient Antibiotic Prescriptions from 2011-2016 was published in 2020. The Antibiotic Resistance & Patient Safety Portal has been enhanced and includes updated outpatient antibiotic use data.
Within 1 year: CDC will establish a benchmark (in terms of prescriptions per	Yes	• To better understand when antibiotics are needed, and thereby improve their use, CDC worked with The Pew Charitable Trusts and clinical experts to establish metrics for benchmarking in inpatient settings and targets for reducing inappropriate antibiotic use in outpatient settings in

population) for reduction in antibiotic use.		support of the 2020 benchmarks outlined in the National Action Plan. As a result, we now know that at least 1 in 3 antibiotic prescriptions, or 47 million prescriptions per year, prescribed in US doctors' offices and emergency departments are unnecessary (Pew Charitable Trusts: Antibiotic Use in Outpatient Settings). • CDC published Assessment of the Appropriateness of Antimicrobial Use in Hospitals in 2020 estimating that more than half of antibiotic prescribed for select events in hospitals were not consistent with recommended prescribing practices. Researchers found that among patients treated for community-acquired pneumonia, prescribing was unsupported in 79.5% of cases, while for urinary tract infections, prescribing was unsupported for 76.8% of cases. Prescribing was considered unsupported for many reasons, including long durations, antibiotic selection that did not follow guidelines, no documented infection signs or symptoms, or no lab results confirming the presence of an infection. Based on CDC's finding, the Pew Charitable Trust released a report setting new benchmarks for prescribing of these selected events.
Within 3 years: Starting in 2016, CDC will issue yearly reports on progress in meeting the national target of 50% reduction in inappropriate use of antibiotics in outpatient settings (see above), as well as on overall trends in antibiotic prescribing.	Yes	• Per CDC personnel in April 2021: ○ CDC works with hospitals, health systems, nursing homes, and clinical providers in outpatient settings to identify ways to improve antibiotic use and facilitate antibiotic stewardship—ensuring patients get the right antibiotics at the right time for the right duration—aligned with CDC's Core Elements of Antibiotic Stewardship. CDC is also working to incorporate antifungal stewardship into existing efforts. ○ CDC also assesses antibiotic use across healthcare settings to better understand how to target action to improve use. For example, recent studies show that some antibiotics are inappropriately selected for children, and that fluoroquinolones are frequently overprescribed and misused in adults, pointing to key areas for targeted antibiotic stewardship. ○ In 2019, CDC published Antibiotic Use in the United States, 2020 Update: Progress and Opportunities, describing outpatient prescribing data.
Within 3 years: DOD will establish goals for reducing antibiotic use in DOD facilities that provide outpatient care for military personnel and their families.	In progress	• As of June 2015, DOD planned to establish goals for reducing antibiotic use in inpatient facilities during FY2016 (Antimicrobial Stewardship Program Plan, Medical Facilities, DOD). • Per DOD personnel in April 2021: DOD has established goals for reducing antibiotic use, but has not fully accomplished this milestone because of shifting priorities in response to the COVID-19 pandemic. DOD personnel noted this milestone is being addressed as part of a phased approach; goals have been set, but the threshold/metric that will be used for evaluating reduction has not been firmly established.

Within 3 years: DOD will centralize reporting of outpatient antibiotic use and issue annual summary reports.	Yes	• As of June 2015, DOD planned to use FY2015 funds to develop algorithms for the collection of antibiotic use data (and inpatient data collection would precede outpatient data collection) by the Pharmacovigilance Center (Antimicrobial Stewardship Program Plan, Medical Facilities, DOD). • Per DOD personnel in April 2021: ○ DOD has centralized reporting for both inpatient and outpatient antibiotic use via the Pharmacovigilance Center. ○ Annual summary reports are completed; these reports are available in a variety of locations, depending on which component completed the report.
Objective 1.1*:** Implement public health programs and reporting policies that advance antibiotic resistance prevention and foster antibiotic stewardship in healthcare settings and the community. ***Sub-Objective 1.1.4: Develop and pilot new interventions to address geographic, sociocultural, policy, economic, and clinical drivers of the emergency and spread of antibiotic-resistance and misuse or overuse of antibiotics.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: The Agency for Healthcare Research and Quality (AHRQ) and CDC will host a meeting of experts and stakeholders to consider knowledge gaps for prevention of antibiotic-resistant, healthcare-associated infections and identify potential interventions for development, field testing, and eventual widespread implementation.	Yes	• In June 2016, AHRQ and CDC brought together experts and stakeholders to highlight knowledge gaps for effective prevention of antibiotic-resistant HAIs and to identify potential interventions and targets for research. In late FY2016 and early FY2017, AHRQ published four Funding Opportunity Announcements for research on CARB and HAI prevention (NAP Progress Report: Years 1 and 2).
Within 1 year: CDC Emerging Infections Program (EIP) sites will perform assessments of antibiotic use and resistance to allow updating of national estimates of antibiotic-resistant, healthcare-associated infections and of antibiotic-resistance threats in the US.	Yes	• Per CDC personnel in April 2021: ○ CDC's EIP, which monitors antibiotic resistance across a population of about 44 million people and measures risk by population and community expanded in 2016 to include more sites conducting active surveillance for invasive *S. aureus* infections, candidemia, CRE, and carbapenem-resistant *Pseudomonas* and *Acinetobacter*. Expanded work in 2017 includes sepsis epidemiology in multiple sites and surveillance for extended-spectrum beta-lactamase producing Gram-negative bacteria. The EIP also completed a survey of HAIs and antibiotic use in nearly 200 acute-care hospitals with more than 10,000 patients, and began a similar survey in nursing homes.

		○ Assessments of antibiotic use in hospitals and nursing homes as part of HAI prevalence surveys in 2015 and 2017, respectively, quantified the extent to which several common HAIs drive inappropriate antibiotic use (treatment of pneumonia among hospitalized patients, and urinary tract infections [UTIs] among nursing home residents were identified as prominent targets for antibiotic stewardship coordinated by state programs). ○ In 2020, genomic analyses are underway as part of the investigation of CRE transmission networks in collaboration with Epicenters-affiliated investigators. ○ In 2020, a multisite assessment of chlorhexidine gluconate resistance and antimicrobial cross-resistance in hospitals implementing chlorhexidine decolonization interventions demonstrated that chlorhexidine minimum inhibitory concentrations (MICs) remain stable among isolates during 2005-2019, which supports efforts by state HAI programs to increase appropriate use of chlorhexidine. ○ Innovative techniques to link EIP surveillance data with CMS healthcare encounter, NHSN, or hospital discharge data, which exploits existing data streams to inform and measure impact of new interventions, have been launched in three EIP sites with three more coming online in 2021. ○ EIP data analyses were critical for development of the 2019 Threat Report, supplying the estimates of CDIs among hospitalized patients and defining epidemiology of many other HAI pathogens, particularly among community-acquired infections.
Within 1 year: CDC EIP sites will solicit applications for funding large-scale interventions to reduce *C. difficile* infections through enhanced antibiotic stewardship programs.	Yes	• CDC in partnership with state partners in the EIP sites and clinical partners in the CDC Prevention Epicenters submitted an application for funding a large-scale intervention to reduce CDIs through enhanced inpatient stewardship programs (NAP First 180 Days Report).
Within 3 years: The CDC Prevention Epicenters Program will evaluate one or more novel antibiotic-resistance prevention tools for use in diverse healthcare settings.	Yes	• In 2016, CDC expanded the Epicenters Program, enhancing capacity to find innovative strategies to protect patients by stopping spread of antibiotic-resistant bacteria, Ebola virus, and other dangerous organisms (Preventing Transmission of Antibiotic-Resistant Organisms and Other Infectious Threats in Healthcare: Selected Research Topics). Prevention Epicenter investigators' activities include: ○ Testing regional, versus single-facility strategies to prevent infections, identify and track transmission of antibiotic-resistant bacteria including CRE.

		○ Researching new approaches to help slow the development of antibiotic-resistant bacteria and prevent spread. ○ Testing regional versus single-facility strategies to prevent infections, and identify and track transmission antibiotic-resistant bacteria including CRE. ○ Studying new approaches that minimize the role of the healthcare environment (e.g., surfaces such as bed rails or equipment) in the spread of pathogens. • Per CDC personnel in April 2021: In 2020, the University of Maryland Epicenter is testing a CDI computerized clinical decision support tool for reducing CDI acquired in hospital and is now testing this in multiple hospitals to see if overall community rates decrease in the surrounding community.
Within 3 years: CDC EIP sites will initiate large-scale demonstration projects to field-test AR interventions developed by the Prevention Epicenters Program.	Yes	• Per CDC personnel in April 2021: The EIP Cooperative Agreement has been awarded, and projects for the 2017-2021 cycle are underway in the 10 selected sites. The University of Maryland Epicenter is testing a CDI intervention package in multiple acute-care facilities that makes use of EIP CDI surveillance data to measure community-wide intervention impact. Several projects that combine EIP and Prevention Epicenter expertise and resources were funded in 2018, including an investigation of CRE transmission networks that includes genomic analyses that will better define true transmission events, and an assessment of chlorhexidine gluconate (CHG) resistance among pathogens in hospitals implementing CHG decontamination. With sufficient resources, one or more additional Prevention Epicenter-EIP projects could be among the selected projects in the planned new Prevention Epicenter cooperative agreement.
Within 3 years: AHRQ will sponsor research to develop improved methods and approaches for combating antibiotic-resistance and conducting antibiotic stewardship activities in multiple healthcare settings, with a focus on long-term and ambulatory care centers, as well as acute care hospitals. AHRQ will support translation of research findings into antibiotic-resistance prevention tools that can be	Yes	• As reported in 2018, AHRQ supports a comprehensive portfolio of research that supports the development and implementation of tools to prevent HAIs, slow transmission of resistant bacteria, and promote antibiotic stewardship in acute-care, long-term care, and ambulatory-care settings (NAP Progress Report: Year 3). • In May 2017, AHRQ released the final report of the AHRQ Safety Program for Long-Term Care: Preventing CAUTI and Other HAIs. This three-year implementation project, which included more than 400 nursing homes nationwide, significantly reduced catheter-associated urinary tract infections (CAUTI) rates by approximately 50%. There was also a 15% decrease in urine culture orders during the project, which had encouraged appropriate use of urine cultures to help decrease inappropriate use of antibiotics for asymptomatic bacteriuria. The program used principles and methods from AHRQ's Comprehensive Unit-based Safety Program (CUSP) to enhance leadership and staff engagement, teamwork, and safety culture. The project also provided insights about factors affecting how infection prevention is conducted in nursing homes

implemented by healthcare providers in long-term and ambulatory care settings, as well as in hospitals.		based on interviews with eight regional/state project leads and eight facility leads (NAP Progress Report: Year 3). • As reported in 2018, AHRQ continued to disseminate the Toolkit to Reduce CAUTI and Other HAIs in Long Term Care Facilities (NAP Progress Report: Year 3).
Within 3 years: CDC will perform two randomized control trials to test improved treatment methods to prevent the spread of MDR-TB.	Partially	• CDC completed a two-year randomized controlled trial comparing electronic directly observed therapy (eDOT) with traditional, in-person directly observed therapy (DOT). The trial was conducted in four New York City TB clinics with funding from CDC's Antibiotic Solutions Initiative. Results demonstrated eDOT was as effective as traditional in-person DOT for ensuring high adherence to treatment while enabling patient-centered care for TB disease. Results were presented during the 51st Union World Conference on Lung Health in October 2020 and the Union's North American Region Conference in February 2021. A manuscript reporting the trial's primary objective has been completed and is undergoing clearance at this time. Work is underway on additional manuscripts reporting on secondary objectives. In addition, an economic evaluation linked to this trial determined that eDOT is associated with lower costs from a societal perspective, and with lower or similar costs from a program perspective. CDC will consider results of both studies to improve TB treatment methods and programs for providing better patient care and preventing the spread of drug-susceptible and drug-resistant TB in the US and globally. • Per CDC personnel in July 2021: The Combating MDR-TB National Action Plan, noted a need to develop a stockpile of antibiotics for TB treatment. At completion of the first control trial, CDC's TB program requested to utilize available resources to develop a stockpile of antibiotics as opposed to conducting a second trial given the impact the stockpile would have for public health in the immediate future. Therefore, only one trial was completed. • Per CDC personnel in April 2021: Additionally, CDC has made significant progress in advancing lab capabilities for detection of drug resistance. Over 1,000 isolates of *M. tuberculosis* have undergone WGS to evaluate mechanisms of drug resistance and microevolution of drug resistance during treatment. CDC has identified new mutations that confer resistance to isoniazid that will improve the accuracy of rapid molecular tests for the identification of resistance. Databases to capture the data generated from different methods are being developed to aid analysis. Additionally, CDC has optimized growth-based methods. The clinical service is being transitioned from conventional to next generation sequencing methods and work is ongoing to optimize a multiplex assay for performance in different matrices. In FY2017, CDC added an additional laboratory to the AR Laboratory Network. This laboratory will serve as a national center for molecular surveillance of *M. tuberculosis*. The US domestic TB surveillance system is being upgraded to be able to collect and report the results of these new methods. The molecular

		drug susceptibility testing reporting (MDSTR) form has been successfully developed and tested within the National TB Surveillance System Case Reporting (NTSSCR) system. CDC is in the beginning stages of adding pilot users to the system for beta testing the MDSTR form. CDC is in the beginning stages of developing and implementing HL7 standardized coding for electronic laboratory reporting (ELR) into state surveillance systems as well as standardized coding for electronic transmission from state surveillance systems and CDC labs into the NTSSCR MDSTR data collection system. The TB Emergency Drug Stockpile is now established and is stocked with the initial drug orders to assure continuity of TB therapy should the drug supply be disrupted. These activities support strategies and goals under the National Action Plan for Combating MDR-TB.
Within 5 years: CDC will finalize data collection to validate new antibiotic-resistance prevention tools tested by the EIP sites and transition validated interventions to ongoing State AR Prevention (Protect) Programs.	Yes	• Per CDC personnel in April 2021: o Assessments of antibiotic use in hospitals and nursing homes as part of HAI prevalence surveys in 2015 and 2017, respectively, quantified the extent to which several common HAIs drive inappropriate antibiotic use (treatment of pneumonia among hospitalized patients, and UTIs among nursing home residents were identified as prominent targets for antibiotic stewardship coordinated by state programs). o In 2020, the University of Maryland Epicenter is testing a CDI computerized clinical decision support tool for reducing CDI acquired in hospital and is now testing this in multiple hospitals to see if overall community rates decrease in surrounding community. o Genomic analyses are underway as part of the investigation of CRE transmission networks in collaboration with Epicenters-affiliated investigators. o A multisite assessment of CHG resistance and antimicrobial cross-resistance in hospitals implementing CHG decolonization interventions demonstrated that CHG MICs remained stable among isolates collected between 2005 and 2019, which supports efforts by state HAI programs to increase appropriate use of CHG. o Innovative techniques to link EIP surveillance data with CMS healthcare encounter, NHSN, or hospital discharge data, which exploits existing data streams to inform and measure impact of new interventions, have been launched in three EIP sites with three more coming online in 2021. o EIP data analyses were critical for development of the 2019 Threat Report, supplying the estimates of CDIs among hospitalized patients and defining epidemiology of many other HAI pathogens particularly among community-acquired infections.
***Objective 1.1*:** Implement public health programs and reporting policies that advance antibiotic resistance prevention and foster antibiotic stewardship in healthcare settings and the community.		

***Sub-Objective 1.1.5**:* Streamline regulatory processes for updating and approving or clearing antibiotic susceptibility testing devices, as appropriate, so that clinicians receive up-to-date interpretive criteria to guide antibacterial drug selection.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: The US Food and Drug Administration (FDA) will provide technical assistance, as appropriate, on legislative proposals being considered to streamline updating of interpretive criteria for antibiotic susceptibility testing (AST) devices.	Yes	• The FDA's Antimicrobial Susceptibility Test (AST) Systems - Class II Special Controls Guidance for Industry and FDA is available on their website; content is noted current as of February 2018. • Per the NAP First 180 Days Report (November 2015), FDA had provided and continues to provide technical assistance on legislative proposals being considered to streamline updating interpretive criteria for AST devices. • Per FDA personnel in May 2021: ○ To provide a flexible mechanism to support streamlined review of drugs and AST devices, FDA (Center for Devices and Radiological Health [CDRH]/Center for Drug Evaluation and Research [CDER]) held a joint workshop and published draft guidance in September 2016, entitled *Coordinated Development of Antimicrobial Susceptibility Test Devices*. ○ The guidance was finalized and FDA held a public webinar with stakeholders in February 2019 (FDA 2019). ○ The program has shown tremendous success, resulting in availability of AST devices for drugs soon after drug approval.
Within 5 years: FDA will update AST interpretive criteria more efficiently and rapidly (e.g., by adopting criteria developed by standards developing organizations (SDOs) rather than including interpretive guidelines on labels).	Yes	• The 21st Century Cures Act, which was signed into law in December 2016, requires FDA to post information online about FDA's recognition, or withdrawal from recognition, in whole or in part, of AST interpretive criteria (aka "breakpoints") and provide up-to-date information to the healthcare community in a more streamlined manner (FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria). ○ FDA updates this information at least every six months through notifications on their website. Annually, FDA publishes a compilation of the notices on the Federal Register for public comment. • Per FDA personnel in May 2021: To streamline adoption of revised breakpoints if changes occur in the future, CDRH initiated a new approach to encouraging AST device manufacturers to develop and submit a drug-specific "breakpoint change protocol" to CDRH for review. Once accepted, this protocol, which is described in the Decision Summary upon clearance, outlines the steps necessary and whether a new 510(k) is or is not required.
Objective 1.2: Eliminate the use of medically important antibiotics for growth promotion in food-producing animals and bring under veterinary oversight other in-feed and in-water uses of antibiotics that are medically important for treatment, control, and prevention of disease. ***Sub-Objective 1.2.1**:* Implement FDA GFI #213 to eliminate the use of medically important antibiotics for growth promotion in animals and bring other in-feed and in-water uses of medically important antibiotics under veterinary oversight. FDA should evaluate the adoption of the		

proposed changes under GFI #213 after the three-year implementation period and take further action as appropriate.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: FDA will finalize changes to the Veterinary Feed Directive (VFD) regulation to encourage manufacturers to transition the dispensing status of in-feed antibiotics covered by Guidance for Industry (GFI) #213 from over-the-counter (OTC) to VFD status, which requires veterinary oversight. FDA will publish an enhanced summary report of antibiotics sold or distributed for use in food-producing animals from 2009 to 2013. This report will support the effort to monitor the antibiotic usage aspects of Guidance #213 (see also Objective 2.2.4).	Yes	• On June 3, 2015, the FDA published in the Federal Register the final rule revising the VFD regulations in 21 Code of Federal Regulations (CFR) Part 558. The final rule became effective on October 1, 2015 (FDA VFD, NAP Progress Report: Years 1 and 2). • On January 3, 2017, the FDA announced that it had completed the implementation of GFI #213 (FDA Announces Implementation of GFI #213, Progress Report: Years 1 and 2). • As of January 2017, all affected drug applications had either aligned with the GFI #213 recommendations or their approvals had been voluntarily withdrawn (FDA Announces Implementation of GFI #213). • In March 2019, FDA published a draft revised GFI #120 that enhances and expands upon the previous version released in September 2014. The updated version was made in response to stakeholder feedback and comments submitted to FDA's Center for Veterinary Medicine (CVM) since the VFD final rule went into effect and the implementation of GFI #213 (FDA VFD). • In April 2015, FDA published the 2013 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals, which includes information on antimicrobial drugs for the 2013 calendar year and observations on changes in sales/distribution from 2019-2013 and 2012-2013.
Within 3 years: FDA, in partnership with animal drug sponsors, will complete all changes recommended by GFI #213 and GFI #209. Once these changes are complete, growth promotion uses of medically important antibiotics will no longer be permitted, and the use of medically important antibiotics in the feed or water of food-producing animals will require veterinary oversight.	Yes	• On January 3, 2017, the FDA announced that it had completed the implementation of GFI #213 (FDA Announces Implementation of GFI #213, NAP Progress Report: Years 1 and 2). GFI #213 provides sponsors "with specific recommendations on how to voluntarily modify the use conditions of their medically important antimicrobial drug products to align" with two of the recommended principles of GFI #209 (FDA GFI #213). Specifically: (1) limit medically important antimicrobial drugs to uses in animals that are considered necessary for assuring animal health, and (2) limit medically important antimicrobial drugs to uses in animals that include veterinary oversight or consultation (FDA GFI #213, FDA GFI #209). • As of January 2017, all affected drug applications had either aligned with the GFI #213 recommendations or their approvals had been voluntarily withdrawn (FDA Announces Implementation of GFI #213).

***Objective 1.2*: Eliminate the use of medically important antibiotics for growth promotion in food-producing animals and bring under veterinary oversight other in-feed and in-water uses of antibiotics that are medically important for treatment, control, and prevention of disease. *Sub-Objective 1.2.2:* Assess progress toward eliminating the use of medically important antibiotics for growth promotion in food-producing animals through enhanced data collection of antibiotic sales and use.**		
Milestone	**Accomplished?**	**Comments**
Within 5 years: FDA, in partnership with the US Department of Agriculture (USDA) and the animal agricultural industry, will evaluate and report on the impact of GFI #213 by analyzing data on antibiotic use, including total sales of antibiotics in animal agriculture and types and prevalence of antibiotic-resistance among selected foodborne pathogens and commensals isolated from retail meat and farm animals.	Yes	• In August 2019, FDA published a summary assessment for VFD compliance activities during fiscal years 2016-2018. The VFD Compliance Assessment summarizes inspections carried out by FDA's Office of Regulatory Affairs (ORA) and participating state feed regulatory programs. It indicates that affected parties (e.g., producers, veterinarians, feed mills, and retail establishments) are generally in compliance with the VFD final rule, which provides the pathway for veterinarians to authorize the use of VFD drugs in food-producing emails. • FDA's 2017 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals includes additional years of data (i.e., 2008-2017) and highlights changes in sales/distribution from 2016 through 2017, which allow insights into changes related to GFI #213. • FDA's 2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals presents the sales and distribution data for actively marketed antimicrobial drugs approved for use in food-producing animals by drug class, medical importance, route of administration, indication, and dispensing status, as well as species-specific estimates, of sales and distribution from 2010 through 2019.
***Objective 1.2*: Eliminate the use of medically important antibiotics for growth promotion in food-producing animals and bring under veterinary oversight other in-feed and in-water uses of antibiotics that are medically important for treatment, control, and prevention of disease. *Sub-Objective 1.2.3:* Develop and implement educational outreach efforts to ensure that veterinarians and animal producers receive information and training to support implementation of these changes.**		
Milestone	**Accomplished?**	**Comments**
Within 3 years: FDA will collaborate with veterinary organizations, animal producer organizations, the animal feed industry, and others to develop and implement educational outreach efforts to ensure that veterinarians and animal producers receive the necessary information and	Yes	• As described in FDA's Summary Assessment of Veterinary Feed Directive Compliance Activities Conducted in Fiscal Years 2016-2018: ○ FDA's CVM developed a framework for inspections of distributors, veterinarians, and producers involved in the VFD process. Inspection activities were carried out by FDA's ORA and under contract by participating state feed regulatory programs. ○ During FY2016 and FY2017, inspections focused primarily on providing education to producers, veterinarians, and VFD medicated feed distributors as part of the phased-in compliance strategy. ○ In FY2018, FDA transitioned toward inspections focused on compliance with VFD requirements.

training to support implementation of GFI #213 (see also: Sub-Objective 1.3.1).		○ The inspections allowed FDA to respond to additional stakeholder questions about VFD implementation, gain understanding of industry practices related to the VFD final rule, and shape a broader inspection strategy to ensure ongoing compliance with the VFD regulation. • The FDA's VFD webpage includes a number of educational materials related to GFI #213 (e.g., fact sheet, informational videos, etc.) (FDA VFD). • The USDA Animal and Plant Health Inspection Service's (APHIS's) online training modules have been updated to include information for compliance with FDA policies (NAP Progress Report: Years 1 and 2).
***Objective 1.2*:** Eliminate the use of medically important antibiotics for growth promotion in food-producing animals and bring under veterinary oversight other in-feed and in-water uses of antibiotics that are medically important for treatment, control, and prevention of disease. ***Sub-Objective 1.2.4**:* Optimize public awareness about progress toward eliminating the use of medically important antibiotics for animal-growth promotion.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: FDA will publish and maintain a public web listing of products affected by GFI #213.	Yes	• The FDA website has a page dedicated to Drugs with Veterinary Feed Directive (VFD) Marketing Status that lists the medically important antimicrobials approved for use in or on animal feed that require a VFD, including those that are transitioned from over-the-counter (OTC) to VFD marketing status upon completion of the implementation of GFI #213. The webpage is current as of February 11, 2021. • FDA also has a webpage dedicated to a List of Medically Important Antimicrobial Drugs Affected by GFI #213.
Within 1 year: FDA will begin publishing periodic updates summarizing progress in adoption of the changes proposed in GFI #213.	Yes	• Since 2008, FDA has been developing annual summary reports of approved/conditionally approved animal drugs with antimicrobial ingredients that are sold/distributed for use in food-producing animals. • For 2016 through 2019, FDA developed annual reports on antimicrobial animal drug distribution: ○ 2016 Summary Report ○ 2017 - The 2017 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals includes additional years of data (i.e., 2008-2017) and highlights changes in sales/distribution from 2016 through 2017, which allow insights into changes related to GFI #213. ○ 2018 Summary Report ○ 2019 - The 2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals presents the sales and distribution data for actively marketed antimicrobial drugs approved for use in food-producing animals by drug class, medical

		importance, route of administration, indication, and dispensing status, as well as species-specific estimates, of sales and distribution from 2010 through 2019.
Within 3 years: FDA will publish a final assessment of the progress of GFI #213 on eliminating the use of medically important antibiotics for animal-growth promotion.	Yes	• See FDA's Summary Assessment of Veterinary Feed Directive Compliance Activities Conducted in Fiscal Years 2016-2018.
***Objective 1.3*:** Identify and implement measures to foster stewardship of antibiotics in animals. ***Sub-Objective 1.3.1**:* Develop, implement, and measure the effectiveness of evidence-based educational outreach to veterinarians and animal producers to advance antibiotic stewardship and judicious use of antibiotics in agricultural settings.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: FDA and USDA will consult with livestock and veterinary organizations on the development of educational outreach materials on judicious use of antibiotics and antibiotic stewardship, and will meet with the American Veterinary Medical Association (AVMA) and the American Association of Veterinary Medical Colleges (AAVMC) to consider the incorporation of additional material on antibiotic resistance and antibiotic stewardship into the curricula of US veterinary colleges.	Yes	• Per the NAP First 180 Days Report, as of November 2015, an educational outreach plan was under development. FDA and USDA were participating in a task force that the (AAVMC and Association of Public and Land-grant Universities had formed to identify education and research needs. Also, USDA was working with specie- specialty veterinary organizations and producer organizations to help with the development of stewardship programs and metrics. • In 2012, USDA APHIS developed a training module on Use of Antibiotics in Animals (Module 23) (NAP Progress Report: Years 1 and 2, USDA APHIS NVAP Training Module 23). • Another module launched in January 2017 includes requirements for issuing a VFD (Module 29) (USDA APHIS NVAP Training Module 29, NAP Progress Report: Years 1 and 2). • Both modules 23 and 29 have been updated to include information about compliance with current FDA policies (NAP Progress Report: Years 1 and 2, NAP Progress Report: Year 3). • In 2015, Module 23 was recognized at a Group of Seven (G7) meeting as one of the world's "Best Practices of Combating Antimicrobial Resistance." (NAP Progress Report: Year 3) • In 2017, USDA APHIS's National Veterinary Accreditation Program (NVAP) expanded its educational outreach by enhancing all 29 modules to provide continuing education for 100,000+ veterinarians and 100,000+ licensed veterinary technicians in the US (NAP Progress Report: Year 3). • In January 2018, the AVMA Committee on Antimicrobials (which includes USDA, FDA CVM, and CDC representatives) approved principles for antimicrobial stewardship in veterinary settings (NAP Progress Report: Year 3).

		• Both USDA APHIS training modules 23 and 29 have been updated to include information about compliance with current FDA policies (NAP Progress Report: Years 1 and 2, NAP Progress Report: Year 3).
Within 1 year: USDA will conduct assessments in various animal production and veterinary settings to identify priority areas in which research is needed to support the development and validation of stewardship activities to assure judicious antibiotic use.	Yes	• Per the NAP First 180 Days Report, as of November 2015, stakeholder discussions were underway. Meetings had been conducted with participants representing beef, swine, and poultry sectors of agriculture production. USDA APHIS continued to meet with industry representatives to identify feasible surveillance streams and begin study design and development. The NAP First 180 Days Report noted that assessments would be conducted based on funding availability. • USDA's National Institute of Food and Agriculture (NIFA) funded an integrated project in FY2015 that focuses on Voluntary Compliance in Antimicrobial Stewardship. The project team focused on beef and dairy production systems to increase voluntary adoption of stewardship practices (NAP Progress Report: Years 1 and 2).
Within 1 year: USDA will solicit applications to the USDA Antimicrobial Resistance Initiative Program, which aims to advance development and use of antibiotic stewardship practices that assure judicious use of antibiotics in agriculture. Applicants may propose a combination of activities, including research studies and development of educational and outreach materials. Projected outcomes of the educational and outreach activities include better preparation of the next generation of veterinarians and laboratory scientists Projected outcomes of the research activities include development of	Yes	• The USDA's NIFA project (above) was expanded in 2016 to include five projects in the Agriculture and Food Research Initiative (AFRI) integrated program and three basic research projects in Understanding Antimicrobial Resistance and Animal Health and Well-Being (NAP Progress Report: Years 1 and 2). • In FY2017, USDA NIFA funded nearly $15 million in research to decrease the need for antibiotic use in agriculture (NAP Progress Report: Year 3). Projects included: ○ Alternative treatment regimens to control bovine anaplasmosis ○ Developing a communication framework for conveying AR science and mitigation opportunities ○ Mitigation of antibiotic resistance in poultry ○ Methods to reduce the perceived need for critically important antimicrobial uses on dairy farms ○ Educational approaches to improve cattle health and reduce the need for antibiotics ○ Examining Berberine as an alternative to antibiotics for nursery pigs ○ Investigating properties of mesenchymal stromal cells as a biological alternative to conventional antibiotics ○ Use of macrophages and endothelial cells for cell-based therapy ○ Building strain libraries as alternatives to antibiotic growth promoters in broiler chickens

sustainable strategies to mitigate antibiotic resistance (see Objective 4).		

Within 3 years:
USDA will support the distribution of educational and outreach materials on antibiotic stewardship and judicious use of antibiotics that target veterinarians, producers, educators, and consumers. These activities will be accomplished through the Antimicrobial Resistance Initiative awardees whose integrated projects are linked to the Cooperative Extension System for education and extension/outreach activities.
	Yes	• As reported in 2017, scientists funded through the AFRI integrated program had conducted Extension and Outreach workshops across states; when studies were conducted on-site, they hosted Field Days to allow audiences to see side-by-side comparisons of demonstrations (NAP Progress Report: Years 1 and 2).
		  ○ For example, a Washington state awardee worked with cattle producers and their workers on nine farms, communicating in Spanish and English, to evaluate the effect of reward systems on influencing adoption of management practices to reduce unnecessary use of antibiotics (NAP Progress Report: Years 1 and 2).
		  ○ Two new projects on alternatives to antimicrobials will focus on vaccine and other preventive measures for diseases that contribute to the use of antibiotics (NAP Progress Report: Years 1 and 2).
		• Per USDA personnel in April 2021: In 2019, USDA NIFA shifted to an integrated approach in the AFRI Foundational and Applied Science Program titled, "Mitigating AMR Across the Food Chain" (A1366), which requires projects to address two of the three components of NIFA's research, education, and extension mission. This ensures that antimicrobial use, stewardship, and resistance initiatives conducted by researchers, educators, and others supported by NIFA incorporate outreach activities.

Objective 1.3: Identify and implement measures to foster stewardship of antibiotics in animals. ***Sub-Objective 1.3.2****:* Foster collaborations and public-private partnerships with public health, pharmaceutical, and agricultural stakeholders to facilitate identification and implementation of interventions (e.g., good husbandry practices) to reduce the spread of antibiotic-resistance.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: FDA and USDA will identify priority areas for research to develop and validate stewardship activities to reduce the spread of antibiotic-resistance.	Yes	• USDA Agricultural Research Service (ARS) research priorities related to AMR are: population-based studies on microbial communities, monitoring emerging pathogens, identifying novel organisms and resistances in ecological communities and determining reservoirs and amplifiers of resistance, and identification of factors that enhance or reduce fitness characteristics of resistant and multidrug-resistant microbial populations (USDA ARS World Antibiotic Awareness Week 2020). • In September 2018, FDA released an agency-wide strategic approach for combating AMR and published a 5-year plan for Supporting Antimicrobial Stewardship in Veterinary Settings. The strategic approach goals were as follows:

		○ Facilitating efficient development of new antibiotics, vaccines for humans, nontraditional antimicrobial products, and diagnostic devices ○ Promoting appropriate and responsible use of antimicrobials and disseminating information to promote interventions that help slow development of resistance ○ Supporting the development and enhancement of tools for conducting surveillance of antimicrobial use and resistance ○ Advancing regulatory science to develop tools, standards, and approaches to facilitate the translation of breakthrough discoveries in science and technology into innovative, safe, and effective medical products (NAP Progress Report: Year 4, FDA's Strategic Approach for Combating AMR - Remarks from FDA Commissioner Gottlieb).
Within 1 year: FDA and USDA will work with livestock and veterinary organizations to consider ways to develop, update, and incorporate assessments of antibiotic stewardship activities into quality assurance programs.	Yes	• From Putting Antibiotic Stewardship into Action (February 2017) on the USDA website: ○ Animal feed industry organizations and livestock and poultry farmers are educating producers and ranchers about FDA labeling changes that will bring all feed uses of medically important antibiotics under the oversight of licensed veterinarians. These educational campaigns are helping to make farmers aware of antimicrobial stewardship programs and keeping them updated on best practices for antimicrobial use and policy. ○ Livestock and poultry farmers are conducting education and outreach campaigns to make farmers aware of antibiotic stewardship programs and keeping them updated on best practices for antibiotic use and policy. ○ Veterinary, animal agriculture, and meat associations are developing and updating species-specific judicious use guidelines, conducting education campaigns on judicious use, and encouraging data collection efforts. The organizations are committed to magnifying education outreach efforts through their vast networks by distributing educational material, holding symposiums to bring those in public health and agriculture together, and conducting regional workshops on new antibiotic use and veterinary oversight policies. • From FDA's Strategy on AMR - Questions and Answers webpage (current as of July 2018): ○ FDA has been working closely with the AVMA, other veterinary associations, and animal producer organizations, as well as holding listening sessions around the country to hear concerns from both producers and veterinarians. Based on this outreach, we are confident that animal producers and veterinarians understand the role that they play in ensuring that these important drugs are used appropriately and judiciously. ○ FDA currently collects data on AMR among foodborne pathogens as part of the National Antimicrobial Resistance Monitoring System (NARMS). FDA is currently working in

		collaboration with other agencies including USDA and CDC to explore approaches for enhancing current data collection efforts.
Within 3 years: FDA and USDA will support applied research in field settings to demonstrate the feasibility and effectiveness of stewardship programs and test and validate alternatives to traditional uses of antibiotics in agriculture.	Yes	• In 2016, FDA began funding two grants for antimicrobial use data collection. The collection efforts intended to provide information on antimicrobial use practices in the four major food-producing animal species (cattle, pigs, chickens, and turkeys), which can help inform assessment of the overall impact of FDA's judicious use strategy and help optimize long-term strategies to collect and report such antimicrobial use data (NAP Progress Report: Year 3, RFA-FD-16-046). The pilot data collection efforts are expected to be funded for up to 5 years and will help provide part of the baseline information about on-farm antimicrobial use practices. FDA also expects the pilot projects to assist in the development of long-term functional and efficient systems for collecting antimicrobial use data in food animal production settings (FDA CVM Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019-2023). • Per FDA personnel in April 2021: FDA does not direct many resources towards applied research. The work noted above is relevant to this milestone in that it is focused on data collection, which helps ensure capabilities to assess progress made or effectiveness of stewardship programs. • Per USDA personnel in April 2021: ○ USDA APHIS Center for Epidemiology & Animal Health (CEAH) was involved with the work described above. CEAH participated in periodic meetings with cooperators regarding methodology, data analytics, etc. as part of an audit process. Although FDA funded the work, USDA APHIS played a role. ○ USDA APHIS National Animal Health Monitoring System (NAHMS) studies typically collect information about stewardship, and that information is then used to guide and improve educational efforts (USDA APHIS NAHMS).
Within 5 years: FDA and USDA will identify validated interventions to reduce the spread of antibiotic resistance and work with public and private sector partners to incorporate them into veterinary practice.	Yes	• The AVMA website has information on antimicrobial stewardship and judicious use for veterinary professionals and client education (AVMA Antimicrobial Use in Veterinary Practice). This includes a link to the June 2020 Clinical and Laboratory Standards Institute (CLSI) report on understanding susceptibility test data as a component of antimicrobial stewardship in veterinary editions (CLSI VET09). • FDA maintains a publically available education and outreach page focused on Judicious Use of Antimicrobials. • FDA CVM developed a multi-pronged, multi-year strategy designed to slow the emergence of resistance arising from the use of antibiotics in animals, while continuing to ensure the availability of safe and effective antibiotics for use in animals and humans. Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019-2023 serves as

		CVM's action plan for guiding its activities over 2019-2023 to combat AMR and help preserve the effectiveness of medically important drugs. The three overarching goals in the plan are: (1) align antimicrobial drug product use with the principles of antimicrobial stewardship; (2) foster stewardship of antimicrobials in veterinary settings; and (3) enhance monitoring of AMR and antimicrobial drug use in animals. • Per USDA personnel in April 2021: USDA APHIS participates on the AVMA Committee on Antimicrobials. Additionally, USDA APHIS is working on developing materials to share regarding results of NAHMS studies on antimicrobial stewardship, specifically the 2017 antimicrobial use studies on feedlot cattle and swine. USDA APHIS is repackaging previously published data in formats that are more accessible to various audiences (e.g., one page documents and info sheets).
***Objective 1.3*:** Identify and implement measures to foster stewardship of antibiotics in animals. ***Sub-Objective 1.3.3**:* Identify, develop, and revise key agricultural practices that allow timely and effective implementation of interventions that improve animal health and efficient production.		
Milestone	**Accomplished?**	**Comments**
Within 3 years: FDA and USDA will support drivers-of-change studies to determine which stewardship materials and educational approaches are most effective in improving antibiotic use practices.	In progress	• Per USDA personnel in April 2021: ○ This is a good example of an aspirational goal. When the National Action Plan was drafted in 2014/2015, the vision was that USDA APHIS would be conducting on-farm surveys and that there would be continuous information on how antibiotics were being used. That, in turn, would allow USDA to perform hypothesis testing on alternatives to antibiotics and other pertinent aspects, management practices that could be adjusted, etc. However, the resources to bring this work to fruition were not immediately available; instead, resources to conduct on-farm studies were not available until 2017. ○ Activity related to this milestone is ongoing/in-progress. Once funding became available in 2017, USDA APHIS began on-farm survey work through NAHMS. In 2017, surveys focused on on-farm practices in 2016 for feedlot cattle and swine (i.e., before FDA's VFD was fully implemented [which occurred in January 2017]). While USDA APHIS planned to repeat the surveys in 2020, the work was delayed until 2021 because of the COVID-19 pandemic. USDA APHIS will be conducting these surveys again in 2021, which will provide information about how on-farm practices related to antimicrobial use and stewardship changed after the VFD was put in place. Also, USDA APHIS has updated the surveys to gather a broad look at swine and cattle health—not only antibiotic use—in recognition of the breadth of animal disease challenges that producers face.

		○ USDA APHIS personnel noted that these studies provide information applicable to identifying drivers of change. For example, the NAHMS study provided information about bovine respiratory disease (BRD), which is one of the primary drivers of antibiotic use in cattle. If USDA APHIS can better understand this disease, risk factors, and other ways to prevent BRD on feedlots through these studies, this will help reduce the overall need for antibiotics.
***Objective 1.3*:** Identify and implement measures to foster stewardship of antibiotics in animals. ***Sub-Objective 1.3.4**:* Develop appropriate metrics to gauge the success of stewardship efforts and guide their continued evolution and optimization.		
Milestone	**Accomplished?**	**Comments**
Within 3 years: FDA and USDA will: • Collect additional data regarding antibiotic use and resistance in food-producing animals. These data will supplement existing surveillance data used to evaluate the impact of GFI #213 on use practices and resistance trends over time. • Measure changes in antibiotic stewardship programs and practices as part of quality assurance programs in cattle operations and swine and broiler chicken production. • Use baseline data from the National Animal Health Monitoring System (NAHMS), where available, to evaluate changes over a 5-year time horizon.	In progress	Collect additional data regarding antibiotic use and resistance in food-producing animals. • As of April 2017, USDA APHIS had begun conducting antibiotic use monitoring and AMR surveillance, including surveys of two major commodity groups: feedlot cattle and swine (NAP Progress Report: Years 1 and 2). • As part of the NAHMS 2017 antimicrobial use surveys in swine and beef cattle, producers were being surveyed about stewardship practices on farms (NAP Progress Report: Years 1 and 2). • Key Initiative #3 of FDA's CVM Key Initiatives for Antimicrobial Stewardship is to assess the impact of strategies intended to curb the emergence of AMR associated with the use of antimicrobial drugs in veterinary settings. This is to be assessed by enhancing the collection of antimicrobial drug use data in veterinary settings, enhancing the collection of data on AMR patterns, and increasing the exchange of information among stakeholders to aid in the monitoring of antimicrobial drug use practices and resistance. Measure changes in antibiotic stewardship programs and practices as part of quality assurance programs in cattle operations and swine and broiler chicken production. • Per USDA personnel in April 2021: ○ Activity related to this milestone is ongoing/in-progress. Once funding become available in 2017, USDA APHIS began on-farm survey work through NAHMS. In 2017, surveys focused on on-farm practices in 2016 for feedlot cattle and swine (i.e., before FDA's VFD was fully implemented). While USDA APHIS planned to repeat surveys in 2020, the work was delayed until 2021 because of the COVID-19 pandemic. USDA APHIS will be conducting these surveys in 2021, which will give information about how on-farm practices related to antimicrobial use and stewardship changed after the VFD was put in place. Also, USDA APHIS updated the surveys to gather a broad look at swine and cattle

		health—not only antibiotic use—in recognition of the breadth of animal disease challenges that producers face. ○ NAHMS also supports a cooperative agreement with the University of Minnesota to collect antimicrobial use data in poultry. <u>Use baseline data from the NAHMS, where available, to evaluate changes over a 5-year time horizon.</u> • Per USDA personnel in April 2021: ○ Activity related to this milestone is ongoing/in-progress. Once funding become available in 2017, USDA APHIS began on-farm survey work through NAHMS. In 2017, surveys focused on on-farm practices in 2016 for feedlot cattle and swine (i.e., before FDA's VFD was fully implemented). While USDA APHIS planned to repeat surveys in 2020, the work was delayed until 2021 because of the COVID-19 pandemic. USDA APHIS will be conducting these surveys in 2021, which will give information about how on-farm practices related to antimicrobial use and stewardship changed after the VFD was put in place. Also, USDA APHIS updated the surveys to gather a broad look at swine and cattle health—not only antibiotic use—in recognition of the breadth of animal disease challenges that producers face. ○ NAHMS also supports a cooperative agreement with the University of Minnesota to collect antimicrobial use data in poultry.

GOAL 2: STRENGTHEN NATIONAL ONE HEALTH SURVEILLANCE EFFORTST TO COMBAT RESISTANCE.		
Objective 2.1: Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains, and create a specimen repository to facilitate development and evaluation of diagnostic tests and treatments. ***Sub-Objective 2.1.1:*** Create a regional public health laboratory network that uses standardized testing platforms to expand the availability of reference testing services, characterize emerging resistance patterns and bacterial strains from outbreaks and other sources, and facilitate rapid data analysis and dissemination of information.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: CDC will develop an implementation plan for the Detect Network of AR Regional Laboratories that considers all aspects of operation, including	Yes	• The AR Laboratory Network was established in 2016. It includes labs in 50 states, four cities, and Puerto Rico, and seven regional labs. The seven regional labs coordinate and complement activities performed at the local and state level (The Antibiotic Resistance [AR] Lab Network and About the AR LRN Lab Network).

specimen transport, testing, reporting, and data-sharing.		

Within 1 year:
Multidrug-resistant Organism Repository & Surveillance Network (MRSN) will be formally recognized as a reference laboratory network with responsibility for reporting data on antibiotic resistance and antibiotic use in military treatment facilities. It will expand its mission to include rapid characterization of emerging resistance patterns, laboratory support during outbreak investigations, and reporting of clinically relevant bacterial pathogens for facilities that serve military service members and their families.
	Yes	• Per the NAP First 180 Days Report, as of November 2015:
		  ○ DOD/MRSN announced the first release of a relational database in May 2015 and was planning expanded access to authorized users.
		  ○ DOD/MRSN held ~30,000 characterized isolates and 1,500 genomes within its repository and database.
		  ○ DOD continued to support MRSN for enterprise use and collaboration with other US government agencies.
		  ○ DOD was in the process of establishing policy to formalize the status of the MRSN as a reference laboratory for all three services.
		• As reported in 2017, the MRSN and CDC's AR Laboratory Network had been working together to share best practices for US-based resistance gene identification. Over 950 genomes of MRSN strains had been uploaded to the National Library of Medicine (NLM)/NCBI Pathogen Tracker as of November 2017, and curated panels were available for dissemination to facilitate diagnostic and therapeutic developmental efforts (NAP Progress Report: Years 1 and 2).
		• As of 2018, CDC and DOD were working to include the MRSN/Antibiotic Resistance Monitoring and Research Program (ARMoR) as an AR Laboratory Network regional hub. DOD had provided written guidance for how military healthcare facilities, MRSN, regional laboratories, and CDC would interact when emerging AR threats or trends were identified (NAP Progress Report: Year 3).
		• Per DOD personnel in April 2021: MRSN/ARMoR is a reference laboratory network with a collaborative relationship with the AR Laboratory Network, although not officially part of the AR Laboratory Network.

Within 3 years: CDC will designate at least five public health laboratories as part of the Detect Network of Regional AR Laboratories, which is charged with rapid detection of outbreaks caused by drug-resistant pathogens, characterization of resistance mechanisms, and tracking resistance trends and	Yes	• CDC has designated seven labs as part of the Detect Network of Regional AR Laboratories; they are located in Maryland, Minnesota, New York, Tennessee, Utah, Washington, and Wisconsin (The Antibiotic Resistance [AR] Lab Network). • Per CDC personnel in April 2021: By 2018, CDC supports capacity in 50 states, Puerto Rico, and six major cities to detect, respond to, and contain emerging AR threats, as well as to improve methods and timeliness of CRE laboratory testing in all 50 states and specialized testing in the seven regional laboratories. Health departments continue to use data from NHSN, outbreak investigations, and the AR Laboratory Network to target their response and prevention actions. Prevention across healthcare continues in over 30 state and local health departments to not only stop transmission of antibiotic resistant pathogens and *C. difficile* between healthcare settings,

identifying emerging forms of resistance. CDC will work with DOD and USDA to share resistance detection strategies and protocols.		but also to build and strengthen partnerships to improve antibiotic prescribing in acute-care (including critical-access hospitals), nursing homes, and outpatient settings. • CDC has worked with DOD to share best practices for US-based resistance gene identification (NAP Progress Report: Years 1 and 2) and with USDA through NARMS.
Within 3 years: CDC will work with the Association of Public Health Laboratories (APHL), state and local health laboratories, and other partners to provide technical assistance and guidance to the Regional AR Laboratories, as needed.	Yes	• Per CDC personnel in April 2021: ○ CDC has worked with APHL to implement an informatics solution to ensure that CDC and labs can securely transfer lab test data and results. As detection and data tracking methods improve, CDC identifies emerging resistance that must be contained through rapid response. CDC is working with health departments, hospitals, and healthcare societies to stop the spread of organisms with "unusual resistance" in the US. Examples of recent emerging or unusual antibiotic resistance include the following: ▪ *C. auris* is a new and emerging "fungal superbug" that is resistant to many antifungal medications and can spread between patients in hospitals and nursing homes. Approximately 30% of patients with *C. auris* infections have died within 30 days. *C. auris* has already become a major problem globally and, by February 2018, had gained a foothold in the US with 233 confirmed clinical cases in 10 states. CDC continues to provide guidance, public education, and laboratory and investigative support to prevent this fungus from becoming widespread in US healthcare facilities as it has in other countries. ▪ In its first nine months of testing, CDC's AR Laboratory Network identified more than 220 instances of unusual resistance genes in "nightmare bacteria" CRE and carbapenem-resistant *P. aeruginosa*. These bacteria are especially concerning because they carry genes that are rare but can make them resistant to all antibiotics, or have a special gene that allows them to easily spread their resistance to other bacteria. ▪ Cases and clusters of antibiotic-resistant *Shigella* have been identified among men who have sex with men, highlighting the need for more data to inform prevention and control strategies. In March 2021, CDC released a new toolkit—*Shigella* Prevention and Control Toolkit—intended to help state and local health departments respond to suspected or confirmed cases, clusters, or outbreaks of *Shigella* infection including information on: data collection, responding to an outbreak of *Shigella* infection, sanitation, hygiene, and cleaning, and fact sheets,

		palm cards, and letter templates to aid communications with the public, including materials specific to key populations. ○ CDC awarded $55.1 million in 2019 and $56.5 million in 2020 to support healthcare-associated infection/antibiotic resistance programs in all 50 states, DC, five large cities, Puerto Rico, US Virgin Islands, and Guam. These funds support expertise in local and state health departments to detect and contain the spread of emerging resistant pathogens including support for specialized healthcare-associated infection and antibiotic resistance expertise in 50 states, the District of Columbia (DC), four large cities, and Puerto Rico. ○ In the FY2019 and FY2020, CDC provided direct technical assistance for response and prevention activities, including evaluation of program priorities. In addition, CDC provided large webinars, twice annually, to guide healthcare-associated infection/antibiotic resistance programs in setting overall goals and standards. CDC convened one to two in-person meetings with program staff annually, including one hosted in through partnership with the Council of State and Territorial Epidemiologists (CSTE). Additional technical assistance included monthly calls with members of the CSTE HAI Subcommittee, quarterly NHSN guidance calls, and in-depth individual discussions with programs in all 50 states, DC, five large cities, Puerto Rico, US Virgin Islands, and Guam. ○ The above efforts created a robust infrastructure for AR response. This provided capability for ongoing AR testing and response throughout the COVID-19 pandemic, when supply and staff shortages required redirection of specimens and support. During the peak of the COVID-19 pandemic, this infrastructure was leveraged to support the COVID-19 laboratory response. The ability of this system to rapidly pivot to COVID-19 public health efforts, with guidance and support from CDC, is a testament to the critical role that such infrastructure can play during public health emergencies. • Program highlights, best practices, and lessons learned have been shared at national and international conferences, and more than 18 scientific papers related to these ARGC rapid detection and response activities have been published or are in development. Genomic analyses are being used to monitor the distribution of GC strains, and in combination with partner services data, to improve our understanding of sexual network connectivity and to inform local programmatic action. In 2019, CDC also worked with state and local health departments in two states to develop ARGC outbreak response plans and test those plans through simulated

		emergency "tabletop" exercises, and we are in the process of developing a toolkit of ARGC preparedness materials for other jurisdictions based on this pilot project.
Objective 2.1: Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains, and create a specimen repository to facilitate development and evaluation of diagnostic tests and treatments. ***Sub-Objective 2.1.2:*** Link data generated by the regional public health laboratory network to existing public health surveillance networks so that antibiotic susceptibility testing data are immediately available to local, state, and Federal public health authorities as they detect and investigate outbreaks, as well as to veterinary diagnostic and food safety laboratory databases and/or surveillance systems, as needed.		
Milestone	**Accomplished?**	**Comments**
Within 3 years: The five designated Detect Network Regional AR Laboratories (Sub-Objective 2.1.1) will be integrated into an AR communications network that posts early warning alerts and reports urgent results and trends.	Yes	• The AR Laboratory Network is an integrated communications network. CDC has an alert system in place for each pathogen.
Within 3 years: The AR communication network will establish linkages with DOD and VA clinical, veterinary, and food safety laboratories.	Yes	• Per CDC personnel in April 2021: DOD has provided written guidance for how military healthcare facilities, MRSN, regional laboratories, and CDC will interact when emerging AR threats or trends are identified. CDC and DOD are also working to include the MRSN/ ARMoR program as an AR Laboratory Network regional hub.
Objective 2.1: Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains, and create a specimen repository to facilitate development and evaluation of diagnostic tests and treatments. ***Sub-Objective 2.1.3:*** Create a repository of resistant bacterial strains (an "isolate bank") and maintain a well-curated reference database that describes the characteristics of these strains. The repository will aid biotechnology and pharmaceutical companies that develop new antibiotics and therapeutics and/or design next-generation tests, diagnostic test developers and regulatory agencies who evaluate these tests, government facilities, academic labs, and pharmaceutical companies that test antibiotics for clinical effectiveness and researchers, regulators, and others who assess the effectiveness of interventions to prevent resistance.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: CDC and FDA will develop a defined set of microorganisms to be included in a repository of resistant bacterial strains,	Yes	• In June 2015, CDC and FDA launched the CDC & FDA Antibiotic Resistance Isolate Bank, a centralized, curated repository of ~500 unique isolates pulled from CDC's repository of AR isolates. The bacterial pathogens in the isolate bank are associated with known or emerging resistance mechanisms (e.g., colistin resistance) (NAP Progress Report: Years 1 and 2, CDC & FDA AR Isolate Bank).

including the urgent and serious threats listed in Table 1, and a bioinformatics database to maintain detailed information on the drug susceptibilities and resistance mechanisms of each repository strain.		• As of October 2017, 14 panels were available, which could be used to design the next generation of clinical tests and therapeutic agents (NAP Progress Report: Years 1 and 2). As of October 2018, 580 unique isolates and 16 panels were available from the isolate bank (NAP Progress Report: Year 3). As of February 2021, 29 panels and 952 isolates were available (CDC & FDA AR Isolate Bank). As of October 2018, CDC had filed 1,018 isolate orders with nearly 96,000 shipped to US institutions, including diagnostic test manufacturers, academic researchers, and pharmaceutical companies (NAP Progress Report: Year 3). As of January 2021, the AR Isolate Bank had shipped more than 5,000 isolate panels (CDC & FDA AR Isolate Bank).
Within 1 year: The DOD will post data on a representative sample of characterized isolates on a website that can be accessed by authenticated users.	Yes	• DOD released its relational database in May 2015, to provide access to authorized users for facility antibiotic-resistance data. At the outset, access was limited to DOD, although expansion was planned once Information Assurance measures were accepted (NAP First 180 Days Report).
Within 3 years: CDC and FDA will create the repository and database for resistant bacterial strains and, in conjunction with DOD, will provide isolates to diagnostic test manufacturers and research laboratories, as needed.	Yes	• In June 2015, CDC and FDA launched the CDC/FDA Antibiotic Resistance (AR) Isolate Bank, a centralized, curated repository of ~500 unique isolates pulled from CDC's repository of AR isolates. The bacterial pathogens in the isolate bank are associated with known or emerging resistance mechanisms (e.g., colistin resistance) (NAP Progress Report: Years 1 and 2, CDC & FDA AR Isolate Bank). • As of October 2017, 14 panels were available, which could be used to design the next generation of clinical tests and therapeutic agents (NAP Progress Report: Years 1 and 2). • As reported in 2018, DOD had made available multiple characterized pathogen panels for use in diagnostics and therapeutics development (NAP Progress Report: Year 3). • As of June 2018, the DOD repository housed nearly 56,000 characterized pathogen panels, with the number increasing by 1,000 per month (NAP Progress Report: Year 3). • As of October 2018, 580 unique isolates and 16 panels were available from the isolate bank (NAP Progress Report: Year 3). • As of October 2018, CDC had filed 1,018 isolate orders with nearly 96,000 shipped to US institutions, including diagnostic test manufacturers, academic researchers, and pharmaceutical companies (NAP Progress Report: Year 3). • The AR Isolate Bank has 29 panels and 952 isolates as of February 2021. As of January 2021, the AR Isolate Bank had shipped more than 5,000 isolate panels. The AR Isolate Bank helps: ○ Strengthen diagnostics by validating lab tests.

		○ Inform research and development to develop drugs such as antibiotics and antifungals; develop diagnostic devices, tests, or assays; and satisfy a request or support an application to FDA. ○ Perform testing to ensure drug effectiveness. ○ Study biology and pathogenic mechanisms. ○ Detect new and unusual public health resistance threats.
Within 3 years: DOD will continue to maintain its repository of resistant bacterial strains within the MRSN, update procedures for specimen collection, storage, and data-sharing, and share information, as appropriate, with industry, academic, non-profit, and government stakeholders.	Yes	• As reported in 2018, DOD had made available multiple characterized pathogen panels for use in diagnostics and therapeutics development (NAP Progress Report: Year 3). • As of June 2018, the DOD repository housed nearly 56,000 characterized pathogen panels, with the number increasing by 1,000 per month (NAP Progress Report: Year 3). • In early FY2020, MRSN and the Uniformed Services University Gonococcal Reference Laboratory & Repository both released handbooks outlining submission and laboratory procedures. Per the AFHSB 2019 Annual Report, these handbooks will help the AMR Focus Area to improve harmonization and standardization of laboratory procedures for OCONUS (outside of the continental US) labs submitting isolates.
Annually thereafter: CDC and FDA will update the repository of bacterial strains, incorporating isolates with new resistance mechanisms or emerging resistance patterns identified by the national infectious disease surveillance system.	Yes	• Per CDC personnel in April 2021: ○ CDC regularly reviews and updates information, isolates, and panels available on the CDC & FDA AR Isolate Bank web application related to emerging resistance threats as needed. ○ CDC has developed a work plan to add new panels over the next year, which will increase the diversity of resistant bacterial and fungal pathogens. For example, panels of recent clinical isolates from CDC surveillance programs will be included in the bank. A set of *C. difficile* from the CDC EIP has been added in 2020 and a set from the Multi-site Gram-negative Surveillance Initiative (MuGSI) will be included in the AR Isolate Bank collection in2021. ○ Since 2016, AR Isolate Bank panels have been tested to newly approved drugs to provide an updated susceptibility profile. CDC updates its priorities and targets with regard to concerning types of AMR requiring a public health response and the types of testing that should be done to confirm resistance.
Annually thereafter: CDC, FDA, and DOD will update procedures for strain collection, storage, and data-sharing.	Yes	• Per CDC personnel in April 2021: ○ The CDC & FDA Antibiotic Resistance (AR) Isolate Bank continues to expand, now encompassing 29 unique panels, with seven panels added in 2019 and one added during 2020. As of October 2020, the CDC & FDA AR Isolate Bank has 29 panels, 952 isolates, has processed 2,800 orders, and has shipped 202,752 isolates. FDA has observed that an

		increasing number of developers cite the AR Isolate Bank as a valuable resource that has expedited development and validation of new devices to measure antimicrobial susceptibility/resistance. • Per FDA personnel in April 2021: This milestone was initially completed in that procedures were assessed and determined efficient. Thereafter, procedures have been assessed and updated as needed. • Per DOD personnel in April 2021: Regular review and updating of procedures (as necessary) is conducted.
Objective 2.1: Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains, and create a specimen repository to facilitate development and evaluation of diagnostic tests and treatments. ***Sub-Objective 2.1.4:*** Develop and maintain a national sequence database of resistant pathogens.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: FDA and the National Institutes of Health (NIH) and pilot-test a sequence database containing more than 550 drug-resistant bacterial strains, with accompanying clinical and demographic data ("metadata"). The entries will cover a range of organisms selected by CDC to assist in diagnostic development.	Yes	• Per NIH personnel in April 2021: NIH worked with other US government agencies to launch and pilot a sequence database initially populated with a representative dataset of about 300 strains including both genomic and associated meta/clinical data. Data were submitted to NIH/NCBI in April 2015 and the pilot phase is complete. • As reported in 2018, NIH, FDA, and CDC expanded the NIH National Database of Resistant Pathogens. The database is web-based and open-access. It was developed by NLM/NCBI, and as of 2018 contained genomic data for >205,000 pathogen isolates collected from publically available information. This includes information on high-priority bacterial threats (e.g., *Acinetobacter, Klebsiella*) and can be searched by resistance genotype and, when available, antibiotic susceptibility phenotype (Progress Report: Year 3). • As of March 2021, the database was available online as the National Database of Antibiotic Resistant Organisms (NDARO). NDARO is described online as a collaborative, cross-agency, centralized hub for researchers to access AMR data to facilitate real-time surveillance of pathogenic organisms.
Within 1 year: NIH and partners will sequence additional high-priority, drug-resistant strains to add to the database.	Yes	• Per NIH personnel in April 2021: ○ NIH and CDC continued to sequence high-priority reference strains, as identified by CDC and FDA, to inform the development of new diagnostic tests and drugs (*April 2021 Update*: This activity is no longer ongoing for NIH.) NIH's National Institute of Allergy and Infectious Diseases (NIAID) and National Human Genome Research Institute (NHGRI) completed 164 high quality genomes for reference strains in the AR Isolate Bank (CDC & FDA AR Isolate Bank).

		○ NIH/NHGRI completed sequencing of 53 additional genomes. Genome sequences are rapidly released to the public through the database GenBank (GenBank Overview; published by NIH/NCBI) and the NIH/NIAID-funded Bioinformatics Resource Center, PATRIC (PATRIC). PATRIC contains data for more than 360,000 bacterial genomes and resistance phenotypes for more than 120 different antibiotics. Scientists from all over the world can access and leverage these databases to foster understanding of resistance mechanisms and inform development of improved diagnostics, therapeutics, vaccines, and antimicrobial strategies. ○ The NIH/NIAID-supported Genomic Centers for Infectious Diseases (NIAID GCID) have sequenced multiple strains and human clinical isolates, including over 8,800 AMR bacterial genomes (e.g., *Enterococcus*, *Klebsiella*, *Acinetobacter*, carbapenem-resistant CRE, methicillin-resistant *S. aureus* [MRSA], and *C. difficile*) from different parts of the world. Sequence data are rapidly released in the public databases (GenBank/NCBI) and to the NIH/NIAID-funded Bioinformatics Resource Centers, and contribute to the development of improved diagnosis, therapeutic interventions, and understanding of the complexity and evolution of drug resistance.
Within 1 year: DOD will stand up its diagnostic sequence database, inclusive of genomic information (including raw reads and interpretations/annotations) and relevant phenotypic metadata for access by authenticated users.	Yes	• DOD released its relational database in May 2015, to provide access to authorized users for facility antibiotic-resistance data. At the outset, access was limited to DOD, although expansion was planned once Information Assurance measures were accepted (NAP First 180 Days Report). • As of November 2015, DOD was contributing data to the NDARO database, maintained by NCBI (NAP First 180 Days Report).
Within 3 years: FDA and NIH will review the pilot project to address challenges and identify lessons learned concerning data standards, analysis tools, and data-sharing (see also Objective 4.2).	Yes	• Per FDA personnel in April 2021: The project has built-in tools and resources. Specifically, the "Isolates Browser" on the NDARO database is now updated to provide one location for pathogen information with AMR-related repertoire and AMR genotypes and phenotypes. It allows users to browse and search by multiple filters. Specific to the FDA & CDC AR Isolate Bank, the isolates with sequence and AMR information are included in this database (see milestone below) and allows access and searches. There is a specific example search for retrieving information from all available isolates of the AR Bank. • Per NIH personnel in April 2021: ○ NIH has a long-standing commitment to establish and implement data standards, develop analysis tools, and rapidly releasing genomic and other data sets in the public

		domain. NIH has reviewed the pilot phase of the NDARO and identified areas for expansion, including data-sharing, data access, and analysis of genomic data related to AMR. ○ Multiple tools were added to the database over the course of 2015 to 2020. As described in the website: ▪ To increase standardization, NIH/NCBI has developed and maintains a curated database of AMR genes. ▪ To make AMR-related data more widely available, NIH/NCBI is collecting genetic and antibiotic susceptibility data. ▪ To make more effective use of bacterial genomic data, NIH/NCBI has developed AMRFinderPlus to identify AMR genes in bacterial genomes. ▪ To assist researchers and public health officials, NIH/NCBI has developed the Isolate Browser to allow researchers to identify bacterial genomes with AMR genes.
Within 3 years: As new strains are added to the repository of resistant strains described in Sub-Objective 2.1.3, NIH, FDA, and CDC will work with public and private sector partners to add the genomic sequences of each isolate to the database.	Yes	• The National Database of Antibiotic Resistant Organisms (NDARO), which was developed in 2015 and is maintained by NCBI, is a collaborative, cross-agency, centralized hub for researchers to access AMR genomic data to facilitate real-time surveillance of pathogenic organisms. CDC uploads its data to NCBI. • Per CDC personnel in April 2021: ○ The CDC & FDA AR Isolate Bank now contains 580 unique isolates and 16 panels curated from CDC's collection of more than 450,000 isolates, representing bacterial pathogens associated with known or emerging resistance mechanisms, such as colistin resistance. ○ CDC has received and filled 1,018 isolate orders with nearly 96,000 shipped to US institutions including diagnostic test manufacturers, academic researchers, and pharmaceutical companies. • Per FDA personnel in April 2021: ○ Phenotypic and genotypic data are available on CDC's webpage (CDC & FDA AR Isolate Bank; aka FDA & CDC AR Bank, since initial funding and project initiation came from FDA). ○ The AR Isolate Bank website was improved and is now searchable by multiple filters, whereas initially it was searchable by panel. ○ In addition, all isolates with sequence and AMR gene information are provided through NCBI for all sequences genomes (~350). This information is incorporated into the NDARO database and is searchable. For example, in the "Tools and Resources" section, the filters and searches allow access to all the information on those isolates in the AR Bank or a

		specific isolate or gene of interest. This information is linked through the biosample number, assembly, and other information. (Example: Search for AR0003 and links to all the AMR genotype, sequence, and AST phenotype information here.)
		• Per NIH personnel in April 2021:
		  ○ NIH and CDC continued to sequence high-priority reference strains, as identified by CDC and FDA, to inform the development of new diagnostic tests and drugs (*April 2021 Update*: This activity is no longer ongoing for NIH.)
		  ○ NIH's NIAID and NHGRI completed 164 high quality genomes for reference strains in the AR Isolate Bank (CDC & FDA AR Isolate Bank).
		  ○ NIH/NHGRI completed sequencing of 53 additional genomes. Genome sequences are rapidly released to the public through the database GenBank (GenBank Overview; published by NIH/NCBI) and the NIH/NIAID-funded Bioinformatics Resource Center, PATRIC (PATRIC). PATRIC contains data for more than 360,000 bacterial genomes and resistance phenotypes for more than 120 different antibiotics. Scientists from all over the world can access and leverage these databases to foster understanding of resistance mechanisms and inform development of improved diagnostics, therapeutics, vaccines, and antimicrobial strategies.

Within 3 years: NIH will expand the pilot project database into a National Database of Resistant Pathogens that will continue to incorporate information on newly identified bacterial strains. The database entries will be cross-referenced with entries in the bioinformatics database described in Sub-Objective 2.1.3.	Yes	• Per NIH personnel in April 2021: NIH, in partnership with FDA and CDC, is expanding the NIH National Database of Antibiotic Resistant Organisms (NCBI NDARO). The web-based open-access database, developed by NIH/NCBI, contains genomic data for more than 674,000 pathogen isolates collected from publicly available information. The database includes information on high-priority bacterial threats such as *Acinetobacter*, *Klebsiella*, *Pseudomonas*, and isolates containing genes known to confer antibiotic resistance (e.g., mobile colistin resistance [mcr] and *K. pneumoniae* carbapenemase [KPC]). NIH/NCBI is integrating both antimicrobial susceptibility phenotypic data and AMR genotypic data from pathogen isolates. An additional interface was released, the Microbial Browser for Identification of Genetic and Genomic Elements (Microbial Browser for Identification of Genetic and Genomic Elements), which contains detailed information on the sequences encoding resistance genes found in these isolates.
Objective 2.2: Expand and strengthen the national infrastructure for public health surveillance and data reporting, and provide incentives for timely reporting of antibiotic-resistance and antibiotic use in all healthcare settings. ***Sub-Objective 2.2.1:*** Enhance reporting infrastructure and provide incentives for reporting (e.g., require reporting of antibiotic-resistance data to NHSN as part of the CMS Hospital Inpatient Quality Reporting Program).		
Milestone	**Accomplished?**	**Comments**

Within 1 year: CDC will submit proposals for new measures for hospital reporting of data on antibiotic use to the National Quality Forum (NQF).	Yes	• CDC worked closely with health system partners and developed the SAAR, which has been endorsed by the NQF (NQF No. 2720). This measure allows healthcare facilities to use the new risk-adjusted summary measure of antibiotic use to determine where to focus their antibiotic stewardship efforts (NAP Progress Report: Years 1 and 2). • Per CDC personnel in April 2021: ○ The NQF renewed its endorsement of the NHSN Antimicrobial Use Measure (NQF #2720) on October 23, 2019, for 3 years. The updated measure includes new versions of NHSN's SAARs, and the new SAARS were developed using 2017 AU data from hospitals participating in NHSN's AU surveillance. CDC is working on a summary report of 2019 antibiotic use data reported into NHSN. ○ Facilities reporting data into both NHSN AU Option and the AR Option can get credit for the Public Health Registry Reporting measure under the Public Health and Clinical Data Exchange objective of PIP (Medicare promoting interoperability program eligible hospitals, critical access hospitals, and dual eligible hospitals attesting to CMS objectives and measures for 2020).
Within 1 year: CDC will create a user-friendly electronic portal that makes aggregated NHSN data publicly available and facilitates integrated analyses of state and regional trends and practices.	Yes	• The NHSN Portal can be found on the CDC website. NHSN data are publicly available in the Antibiotic Resistance and Patient Safety Portal and include state-level data.
Within 3 years: CDC will submit proposals for new measures for hospital reporting of data on antibiotic resistance to NQF.	Yes	• Per CDC personnel in April 2021: The NHSN Antimicrobial Use measure was successfully renewed by NQF in 2019 and includes new versions of the NHSN's SAARs.
Within 3 years: CDC will work with CMS and public health partners to minimize the regulatory burden and maximize the health utility of requiring hospitals to report antibiotic use and resistance to NHSN as part of	Yes	• CMS invited public comment on the possibility of future inclusion of the NHSN Antimicrobial Use measure (NQF No. 2720) in the CMS Hospital IQR Program (81 FR 24945). This measure was included in CMS's Measures Under Consideration List and will be ready to consider for proposed rule-making, in consultation with CDC, at a future time (NAP Progress Report: Year 3). • Per CDC personnel in April 2021: ○ CDC has worked with CMS to minimize the regulatory burden of having hospitals report antibiotic use and resistance data to NHSN. Currently, there is no mandate for hospitals

the CMS Hospital Inpatient Quality Reporting (IQR) Program. Data will be reported through the NHSN AU and AR modules.		to report AU/AR data; however, voluntary reporting has been increasing. As of March 2021, CDC has collected at least one month of AU data from 2,051 hospitals in all states, DC, Puerto Rico, and Armed Forces Europe (AE) and Pacific (AP), and at least one month of AR data from 879 hospitals all states, DC, Puerto Rico, and AE and AP. Of these hospitals, 816 have reported both AU and AR data to CDC through NHSN. ○ CDC continues to work with partners on this effort. For example, CDC works with Tennessee to support the implementation of their state requirement for hospitals to report AU data into NHSN. In Tennessee, 48 hospitals reported at least one month of AU data in 2020. The NQF endorsed the NHSN Antimicrobial Use measure was successfully renewed in 2019 and includes new versions of the NHSN's SAARs.
Within 3 years: Once the analysis has been completed and new NQF measures have been approved, CMS will begin the process of proposing new IQR rules.	No	• There is no mandate for hospitals to report antibiotic use/antibiotic resistance (AU/AR) data to the National Healthcare Safety Network (NHSN); however, voluntary reporting continues to expand. No further progress has been made with the new IQR rules because such rules may not be necessary, if voluntary participation is successful.
Within 3 years: CDC will work with DOD and VA to define steps and resource needs to support NHSN data submission by DOD and VHA facilities and ensure timely analysis of trends in antibiotic use and antibiotic resistance.	Yes	• As reported in 2017 and 2018, CDC and VA reported working closely to implement reporting in VA hospitals to NHSN (NAP Progress Report: Years 1 and 2, NAP Progress Report: Year 3). • In 2017, DOD and VA were actively coordinating on the timely electronic exchange and sharing of relevant antibiotic resistance data (NAP Progress Report: Years 1 and 2). • As of April 2018, 84 VA hospitals had reported antibiotic use data (NAP Progress Report: Year 3). • In 2018, VA noted the ongoing initiative dedicated to enrollment in the NHSN Antimicrobial Use (AU) Option (NAP Progress Report: Year 3). • In 2018, VA reported that nearly 80% of VHA acute-care facilities had enrolled in and submitted data to CDC's NHSN AU Option (NAP Progress Report: Year 3). • By October 2018, DOD had implemented centralized reporting to NHSN AU and AR modules (NAP Progress Report: Year 3). • As of 2018, through a CDC partnership to facilitate AUR reporting, 24 DOD hospitals had reported antibiotic use data and 18 DOD hospitals had reported antibiotic resistance data (NAP Progress Report: Year 3). • By January 2020, all VA hospitals were required to participate in the NHSN AU option (NAP Progress Report: Year 4). • Per CDC personnel in April 2021: Through a CDC partnership with the VA and DOD designed to facilitate AUR reporting, 84 VA hospitals and 24 DOD hospitals have reported antibiotic use data,

		and 18 DOD hospitals have reported antibiotic resistance data. The VA has an ongoing initiative dedicated to enrollment in the NHSN's AU Option. To date, nearly 80% of VA acute-care facilities have enrolled and submitted data to CDC's NHSN's AU Option and the VA is developing an action plan to complete enrollment of all facilities.
Within 3 years: CDC will expand user-support and validation programs to accommodate expected increases in hospital reporting through the NHSN AU and AR modules during 2017-2019.	Yes	• CDC has worked with public health, healthcare, and informatics partners to improve the NHSN's AU Measure, develop implementation tools, and promote reporting at the state and local levels. In January 2018, CDC added a way for hospitals to visualize their NHSN antibiotic use data in detail so that they can identify specific gaps and direct stewardship solutions. (NAP Progress Report: Year 3). • Per CDC personnel in April 2021: ○ CDC is also working with the Vermont Oxford Network to develop antibiotic use measures for neonatal patient care locations, which would update the Antimicrobial Use Measure Progress Report. ○ In early 2017, CDC worked with the HHS Office of the National Coordinator for Health Information Technology (ONC) to finalize an online tool that software developers can use to validate their files to meet the ONC Health Information Technology (IT) Certification Program for NHSN Antimicrobial Use and Resistance reporting. ○ In March 2018, CDC began work on updating pediatric and adult antibiotic use measures in a collaboration with a variety of experts.
Within 5 years: CDC will work with hospital consortiums and state-based hospital networks to determine whether additional reporting incentives are needed in place of (or in addition to) reporting required by CMS.	Yes	• Per CDC personnel in April 2021: ○ CDC continues to work with partners on this effort. For example, CDC works with Tennessee to support the implementation of their state requirement for hospitals to report AU data into NHSN. In Tennessee, 48 hospitals reported at least one month of AU data in 2020. The NQF endorsed the NHSN Antimicrobial Use measure was successfully renewed in 2019 and includes new versions of the NHSN's SAARs. ○ Not all hospitals have the infrastructure in place to incorporate these measures. Hospitals are developing this infrastructure over time as they can and they are linking into NHSN once they have that capability. This effort could be enhanced by additional funding for supporting electronic reporting systems in hospitals to build reporting systems.
Objective 2.2*:* Expand and strengthen the national infrastructure for public health surveillance and data reporting, and provide incentives for timely reporting of antibiotic-resistance and antibiotic use in all healthcare settings. ***Sub-Objective 2.2.2:*** Add electronic reporting of antibiotic use and resistance data in a standard file format to the Stage 3 Meaningful Use certification program for electronic health record systems.		

Milestone	Accomplished?	Comments
Within 1 year: CDC will provide technical assistance to hospitals across the nation that report drug-resistance data to NHSN via the NHSN AU and AR modules.	Yes	• The CDC NHSN website offers a user support help desk option. According to the website, "The NHSN User Support Help Desk is operated by support specialists primarily responsible for the enrollment and integration of users into the NHSN application. Support specialists provide such assistance as facility contact reassignments, enrollment and consent form processing, and first time User access, among other types of User assistance." • Per CDC personnel in April 2021: ○ CDC's NHSN is the nation's most widely used system to track HAIs, including bloodstream infections, MRSA, and *C. difficile*, and antibiotic use and resistance. Beginning decades ago with 300 hospitals, NHSN now serves over 21,000 medical facilities—including acute-care hospitals, long-term acute-care hospitals (LTACHs), rehabilitation hospitals, outpatient dialysis centers, and nursing homes. Facilities use NHSN to fulfill federal and state reporting requirements, and act on their own NHSN data to monitor and prevent infections. ○ CDC has worked with hospitals across the nation to increase antibiotic use data reporting to NHSN. As of July 2017, 330 hospitals have reported antibiotic use data. ○ In addition, CDC and VA worked closely to implement reporting in VA hospitals, leading to well over half of all VA hospitals reporting antibiotic use data to NHSN. ○ CMS also invited public comment on the possibility of future inclusion of the NHSN Antimicrobial Use measure (NQF No. 2720) in the CMS Hospital IQR Program (81 FR 25197). CDC developed the SAAR—now endorsed by the NQF as a metric for hospitals to benchmark antibiotic use—as part of the NHSN AU Option to help participating hospitals assess antibiotic use in their facilities and guide interventions to improve antibiotic use. CDC is improving the SAAR metric by working with hospital systems to explore more detailed risk adjustment of antibiotic use data and assess how improvements in hospital stewardship programs impact the SAAR metric.
Within 3 years: CMS will finalize a tool to help software developers certify electronic health records and other health IT software, as appropriate, for recording and submitting AU data.	Yes	• In early 2017, CDC worked with ONC to finalize an online tool that software developers can use to validate their Antimicrobial Use and Antimicrobial Resistance files before submitting those files to the ONC Health IT Certification Program for NHSN Antimicrobial Use and Resistance reporting. More information about the tool is available online at NHSN CDA Submission Support Portal. • In FY2018, the online tool developed for certification purposes remains ready for use.

Within 3 years: CMS will complete an analysis of standards and terminologies for AU reporting to ensure alignment between NHSN reporting and IQR reporting and to support local clinical decision-making.	In progress	• No quality measure for NHSN reporting of AU has been introduced into IQR at this time, although NQF 2720 (antimicrobial use tracking in NHSN) was included on CMS's measures under consideration list. This step by CMS would clear the way for NQF 2720 to be proposed in future IQR rules. CMS subject matter experts will follow CDC progress on this measure and work with CDC at the appropriate time. (NAP Progress Report: Year 3). • Per CDC personnel in April 2021, this remains a goal and is still being worked on.
Within 5 years: CDC and partners will develop an AU electronic clinical-quality NHSN-reporting measure in a standard file format that hospitals can use to achieve the Stage 3 Meaningful Use objective and accelerate reporting. The timing of this activity will depend on the timeframe of the CMS Meaningful Use certification program.	Yes	• CDC has developed an AU electronic clinical-quality NHSN-reporting measure in a standard file format that achieves the Meaningful Use objective and reporting is ongoing. • Per CDC personnel in April 2021: As of August 31, 2020, CDC has collected AU data from 1,843 hospitals in 49 states and AR data from 731 hospitals in 48 states; 718 of these hospitals have reported both AU and AR data to CDC.
Within 5 years: Once an AU electronic clinical-quality NHSN-reporting measure has been developed, it will be submitted to NQF for review and endorsement and to CMS for consideration as a reporting requirement of the CMS Hospital Inpatient Quality Reporting Program.	Yes	• The NQF renewed its endorsement of the NHSN Antimicrobial Use Measure (NQF #2720) on October 23, 2019 for 3 years. The updated measure includes new versions of NHSN's SAARs, and the new SAARS were developed using 2017 AU data from hospitals participating in NHSN's AU surveillance. CDC published a summary report of 2019 antibiotic use data reported into NHSN. • Facilities reporting data into both NHSN AU Option and the AR Option can get credit for the Public Health Registry Reporting measure under the Public Health and Clinical Data Exchange objective of PIP (CMS Promoting Interoperability).
Objective 2.2: Expand and strengthen the national infrastructure for public health surveillance and data reporting, and provide incentives for timely reporting of antibiotic-resistance and antibiotic use in all healthcare settings. ***Sub-Objective 2.2.3:*** Expand the activities and scope of the Emerging Infections Program (EIP) to include monitoring of additional urgent and serious bacterial threats (see Table 3) and evaluating populations at risk across community and healthcare settings.		
Milestone	**Accomplished?**	**Comments**

Within 1 year: CDC will host a meeting of EIP Principal Investigators to consider ways to improve EIP surveillance for drug-resistant threats. The outcomes of this meeting will include refined protocols and standard operating procedures to enable EIP surveillance of additional threats in additional EIP sites.	Yes	• CDC hosted a face-to-face meeting of EIP Principal Investigators to consider ways to improve EIP surveillance for drug-resistant threats. Subsequent teleconferences have allowed production of prioritized enhancements to the program, but additional funding is needed to refine protocols and standard operating procedures to enable EIP surveillance of additional threats in additional or expanded EIP sites (NAP First 180 Days Report).
Within 1 year: CDC EIP sites will pilot methodology to incorporate at least one additional urgent or serious threat into surveillance activities.	Yes	• CDC piloted methodology to incorporate at least one additional urgent or serious threat into surveillance activities, and analysis is underway. Expansion of the pilot is subject to availability of funding (NAP First 180 Days Report).
Within 3 years: CDC will establish up to 10 additional EIP sites, including sites in the West and Midwest that will monitor drug-resistant pathogens. CDC will evaluate the contribution of these new sites to collection of data that better represents the incidence and prevalence of drug-resistant disease in the US.	No	• Owing to limited resources, CDC has not expanded the number of EIP sites; however, the number of pathogens being reported by existing EIP sites has been increased (GAO Report: Antibiotic Resistance: Additional Federal Actions to Better Determine Magnitude and Reduce Impact). • Per CDC, the reason for not expanding EIP sites was limited resources.
Within 3 years: CDC EIP sites will initiate a study to evaluate populations at risk for CRE.	Yes	• The Multi-site Gram-negative Surveillance Initiative (MuGSI) is a part of the CDC's EIP Healthcare-Associated Infections Community Interface (HAIC) activity. Through MuGSI, CDC is conducting active population- and laboratory-based surveillance in a defined surveillance catchment for seven carbapenem-resistant organisms: *E. coli, Enterobacter cloacae, Enterobacter aerogenes, K. pneumoniae, Klebsiella oxytoca*, *A. baumannii* and *P. aeruginosa.* The EIP MuGSI surveillance project will:

		○ Determine the extent of CRE, carbapenem-resistant *Acinetobacter* and carbapenem-resistant *P. aeruginosa* disease in the US. ○ Identify people most at risk for illness from these organisms. ○ Measure trends of disease over time. • Per CDC personnel in April 2021: CDC's EIP and Prevention Epicenters are working together to combine state/local public health and academic medical center expertise and test interventions in the field. These strategies include genomic analysis of CRE transmission networks to better define true transmission events.
Within 3 years: CDC will work with research partners and EIP sites to validate molecular assays to support surveillance for drug-resistant gonorrhea.	Yes	• Per CDC personnel in April 2021: ○ Between 2016-2020, CDC awarded between $5.6 to $6.5 million per year across eight health departments (nine were funded in 2016 and 2017) to establish rapid detection and response activities designed to quickly identify and respond to the threat of ARGC in the US. ○ Health departments funded through this initiative, which is named Strengthening the US Response to Resistant Gonorrhea, or SURRG, hired epidemiologists, microbiologists, disease investigators, and others to focus on ARGC. Local clinical staff were trained on collecting specimens for culture, laboratory staff were trained on performing GC culture and resistance testing, and disease investigators staff were trained on conducting rapid response investigations. All grantees developed protocols, enhanced information systems, and implemented testing. As part of this process, the necessary molecular assays were validated. This capacity was previously limited or unavailable. In 2020 CDC began to e-test through the ELC.
Within 5 years: CDC will expand EIP activities to include surveillance for additional urgent and serious AR threats.	Yes	• Per CDC personnel in April 2021: ○ CDC and EIP sites provided key data and analyses for the 2019 Threat Report for organisms listed in Table 3, including drug-resistant Candida species, *C. difficile*, MRSA, extended spectrum beta-lactamase-resistant or carbapenem-resistant Enterobacterales, and *A. baumanii*. Annual estimates of burden and detailed risk factor analyses have shown the importance of community-associated transmission for several key pathogens driving overall increases or slowed decreases in incidence, despite considerable decreases for hospital onset infection. EIP-led analyses of *C. difficile*, invasive MRSA, extended spectrum beta-lactamase (ESBL) infections have informed additional prevention and containment strategies aimed at community transmission, and monitored impact of existing interventions and programs in healthcare settings.

		○ Data from the established EIP sites are reported on an annual basis, with identification of successful decreases in AR threats, as well as opportunities for further needed improvements. This work through active, laboratory-confirmed population-based surveillance for infections caused by multiple threat organisms will continue through the next 5 years of the National Action Plan for 2020-2025, as the tracking of these AR concerns and monitoring for new AR emergence remains vital to CDC ongoing CARB efforts.
Within 5 years: EIP will help coordinate a public health surveillance study to explore the impact of bacterial populations within the human microbiome on attack rates of drug-resistant pathogens (e g , *C. difficile*, CRE, MRSA, *Candida, Salmonella, Shigella, Campylobacter,* and *S. pneumoniae*).	Yes	• Since October 2016, CDC has awarded more than $32.5 million to pilot innovative solutions and explore knowledge gaps about how antibiotic resistance spreads to and between humans, including research on how the human microbiome can be used to predict and prevent infections caused by drug-resistant microorganisms. (NAP Progress Report: Year 3). • Per CDC personnel in April 2021: CDC has supported microbiome studies through both intramural and extramural mechanisms. These studies have examined the impacts of antibiotics on the microbiome and correlations between antibiotic use and *C. difficile* infection and acquisition and transmission of multidrug-resistant organisms. Findings of note include: 1) levofloxacin disrupted the gut microbiome less than broad spectrum beta lactams when used for infection prophylaxis among patients with hematologic malignancy; 2) among LTACH patients, receipt of carbapenems was associated with increased risk of carriage and infection with carbapenem-resistant *Klebsiella*, and 3) identified microbiota and clinical features that distinguished *K. pneumoniae* carbapenemase-producing *K. pneumoniae* KPC-KP gut colonization in LTACH patients. CDC has also funded projects to develop human, animal, and in vitro models to characterize the microbiome disruption potential of individual antibiotics.
Within 5 years: CDC will analyze the resistance of bacteria in the intestines of healthy people with a variety of diets, lifestyles, and antibiotic-use histories.	Yes	• Per CDC personnel in April 2021: ○ CDC performed metagenomic and amplicon sequencing on 100 stool samples—methods that allow researchers to sample all genes in all organisms present in a sample and to analyze genetic variations in specific genomic regions. ○ CDC is also developing a positive control approach for this assaying of the resistome and a bioinformatics pipeline to analyze results from the sequencing. ○ CDC is also supporting: ▪ Funded Broad Agency Announcement (BAA) which identified a specific metabolomic feature of stool that could improve diagnosis of CDI. A project to fold these findings into an applied in vitro model to characterize microbiome disruption (specifically of antibiotics) was funded in late 2019.

		▪ CDC completed a pilot study to assess microbiome/stool as a method for surveillance of new and emerging AR threats from returning travelers. ▪ A study in microbiomes of healthy individuals and stem cell transplant patients demonstrated horizontal spread of AR genes across both pathogenic and non-pathogenic species within individuals and highlighted there may be an associated increased risk of MDR pathogens consequently. In addition, this highlights the importance of developing capacity to characterize the resistome (i.e., resistome diagnostics) to inform antibiotic selection and stewardship. ▪ Using microbiome data and mathematical models of the Cystic Fibrosis lung microbiome, CDC supported research, which could enable ways to make and test predictions that will improve antibiotic selection. These efforts also resulted in improvements in public health informatics, with data linking across variety of sources including clinical, demographic, clinical laboratory, and microbiome data.
Over the following years: The EIP network will continue to conduct active surveillance for drug-resistant bacteria, provide data to inform CDC's AR threat reports, identify populations at special risk, and test interventions to reduce the emergence and spread of AR threats.	Yes	• The EIP network has been expanded to include Healthcare Associated Infections –Community Interface, which focuses on AR threats. • Per CDC personnel in April 2021: ○ CDC and EIP sites provided key data and analyses for the 2019 Threat Report for organisms listed in Table 3, including drug-resistant Candida species, *C. difficile*, MRSA, extended spectrum beta-lactamase-resistant or carbapenem-resistant Enterobacteriaceae, and *A. baumanii*. Annual estimates of burden and detailed risk factor analyses have shown the importance of community-associated transmission for several key pathogens driving overall increases or slowed decreases in incidence, despite considerable decreases for hospital onset infections, EIP-led analyses of *C. difficile*, invasive MRSA, ESBL infections have inform additional prevention and containment strategies aimed at community transmission, and monitored impact of existing interventions and programs in healthcare settings. ○ Data from the established EIP sites are reported on an annual basis, with identification of successful decreases in AR threats, as well as opportunities for further needed improvements. This work through active, laboratory-confirmed population-based surveillance for infections caused by multiple threat organisms will continue through the next 5 years of the National Action Plan for 2020-2025, as the tracking of these AR concerns and monitoring for new AR emergence remains vital to CDC ongoing CARB efforts.

***Objective 2.3**:* Develop, expand, and maintain capacity in veterinary and food safety laboratories to conduct standardized antibiotic susceptibility testing and characterize select zoonotic and animal pathogens.

Sub-Objective 2.3.1: Expand and maintain veterinary and food safety laboratory infrastructure for the identification of select zoonotic and animal health pathogens through implementation of new diagnostic technologies (see also Goal 3).

Milestone	Accomplished?	Comments
Within 1 year: USDA and FDA will assess current capacities and protocols within the National Animal Health Laboratory Network (NAHLN) and the Veterinary Laboratory Investigation and Response Network (Vet-LIRN) member laboratories and identify capacity development needs to support nationwide AR surveillance for zoonotic pathogens and pathogens of importance to animal health.	Yes	• In 2015, APHIS-Veterinary Services (VS) engaged the American Association of Veterinary Laboratory Diagnosticians (AAVLD) to participate in a joint working group comprised of representatives from veterinary diagnostic laboratories belonging to AAVLD, the CLSI, the FDA CVM's Vet-LIRN, USDA APHIS's VS CEAH, USDA APHIS's National Veterinary Services Laboratories (NVSL), and NAHLN. This working group developed recommendations for an implementation plan to monitor AMR in bacteria from sick animals, which included standardized antimicrobial testing and data collection, and identifying concerns or gaps that could impede the implementation of this plan (NAP Progress Report: Year 4). • Per the NAP First 180 Days Report (November 2015), with funding requested for FY2016, FDA's Vet-LIRN would begin to develop the funding opportunity for laboratories to obtain the needed equipment, staffing, and infrastructure to participate in the testing. • USDA APHIS published results from a survey that was administered to US veterinary clinics and diagnostic laboratories in 2015. The survey collected information about AST from the US veterinary diagnostic laboratory community, assessing current practices and technologies and determining how AST information is shared (NAP Progress Report: Year 3, NAP Progress Report: Year 4, Dargatz 2017). • Per FDA personnel in April 2021, this milestone was completed as part of expanding capacity for Vet-LIRN laboratories.

Within 3 years:
USDA and FDA will support capacity development in ten selected NAHLN and Vet-LIRN member laboratories by providing training in standardized methodologies for antibiotic-susceptibility testing.
	Yes	• During 2017-2018, the Vet-LIRN Program Office coordinated a 2-year pilot project to evaluate the feasibility of using Vet-LIRN diagnostic laboratories to monitor the antimicrobial susceptibility of three veterinary pathogens: *E. coli* and *Staphyloccocus pseudintermedius* in dogs and *Salmonella enterica* in any host. In 2018-2019, additional labs began collecting and sequencing isolates (FDA Veterinary Laboratory Investigation and Response Network). Additional details:
		  ○ Twenty Vet-LIRN source diagnostic laboratories collected isolates and tested the susceptibility using CLSI methods.
		  ○ Each source lab was partnered with one of four WGS laboratories. WGS laboratories sequenced a subset of the isolates submitted by their source labs and uploaded all sequences to NCBI through the GenomeTrakr program.
		  ○ Vet-LIRN is partnering with the NARMS to make the data public.

		• Per USDA personnel in April 2021: All laboratories participating in the NAHLN AMR pilot project (30 labs in 2020) are expected to successfully participate in an AMR proficiency panel provided by the NVSL. Furthermore, all laboratories are provided with work instructions outlining quality control steps for antimicrobial susceptibility testing and are expected to conform with the parameters outlined in the document for participation in the pilot project.

Within 3 years:
USDA and FDA will provide support to five or more NAHLN and/or Vet-LIRN member laboratories for next-generation sequencing equipment and training on the use of whole-genome sequencing techniques and bioinformatics.
	Yes	• During 2017-2018, the Vet-LIRN Program Office coordinated a 2-year pilot project to evaluate the feasibility of using Vet-LIRN diagnostic laboratories to monitor the antimicrobial susceptibility of three veterinary pathogens: *E. coli* and *S. pseudintermedius* in dogs and *S. enterica* in any host. In 2018-2019, additional labs began collecting and sequencing isolates (FDA Veterinary Laboratory Investigation and Response Network). Additional details:
		  ○ Twenty Vet-LIRN Source diagnostic laboratories collected isolates and tested the susceptibility using CLSI methods.
		  ○ Each source lab was partnered with one of four WGS laboratories. WGS laboratories sequenced a subset of the isolates submitted by their Source labs and uploaded all sequences to NCBI through the GenomeTrakr program.
		  ○ Vet-LIRN is partnering with the NARMS to make the data public.
		• As reported in 2018, NARMS has been working with state laboratories to assume the WGS testing to help achieve more real-time testing of bacteria under surveillance (NAP Progress Report: Year 3).
		• WGS technology has become a routine part of NARMS surveillance to screen for resistance genes in enteric bacteria. Use of WGS can provide better isolate resolution including resistance genes and mobile elements and help link human and non-human resistance data (NARMS USDA website).
		• Per USDA personnel in April 2021:
		  ○ Participation in WGS was made available to all NAHLN laboratories in 2020, with 13 laboratories providing sequencing data during Year 3 of the project.
		  ○ For 2021, 20 NAHLN laboratories have established capacity for WGS and have agreed to sequence selected isolates from their laboratories as part of the NAHLN AMR pilot project.

Within 5 years: Ten to twenty NAHLN and Vet-LIRN member laboratories will establish capacity and infrastructure for antibiotic	Yes	• During 2017-2018, the Vet-LIRN Program Office coordinated a 2-year pilot project to evaluate the feasibility of using Vet-LIRN diagnostic laboratories to monitor the antimicrobial susceptibility of three veterinary pathogens: *E. coli* and *S. pseudintermedius* in dogs and *S. enterica* in any host. In 2018-2019, additional labs began collecting and sequencing isolates (FDA Veterinary Laboratory Investigation and Response Network). Additional details:

susceptibility testing of bacterial isolates using standardized testing methods (involving WGS or other techniques) and data-sharing mechanisms.		○ Twenty Vet-LIRN Source diagnostic laboratories collected isolates and tested the susceptibility using CLSI methods. ○ Each source lab was partnered with one of four WGS laboratories. WGS laboratories sequenced a subset of the isolates submitted by their Source labs and uploaded all sequences to NCBI through the GenomeTrakr program. ○ Vet-LIRN is partnering with the NARMS to make the data public. • As reported in 2018, NARMS was working with state laboratories to assume the WGS testing to help achieve more real-time testing of bacteria under surveillance (NAP Progress Report: Year 3). • Per USDA personnel in April 2021: ○ Participation in WGS was made available to all NAHLN laboratories in 2020, with 13 laboratories providing sequencing data during year 3 of the project. ○ For 2021, 20 NAHLN laboratories have established capacity for WGS and have agreed to sequence selected isolates from their laboratories as part of the NAHLN AMR pilot project.
***Objective 2.3**:* Develop, expand, and maintain capacity in veterinary and food safety laboratories to conduct standardized antibiotic susceptibility testing and characterize select zoonotic and animal pathogens. ***Sub-Objective 2.3.2**:* Accelerate and standardize antibiotic susceptibility testing and bacterial characterization for select zoonotic and animal health pathogens, coordinating with appropriate stakeholder groups.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: USDA and FDA will develop standardized protocols for assessing proficiency in susceptibility testing.	Yes	• Per the NAP First 180 Days Report (November 2015), FDA CVM and USDA were discussing coordinating efforts to meet this milestone, and that as resources became available, a project plan would be developed and implemented. • The isolates used in the 2018 pilot proficiency test (described below) were obtained from the FDA through a material transfer agreement. Subsequent graded antimicrobial susceptibility testing proficiency tests will be developed using clinical isolates from the USDA's NVSL AR bacterial repositories (NAP Progress Report: Year 3). • Per FDA personnel in April 2021, this milestone was accomplished when sufficient funding was available. • Per USDA personnel in April 2021: ○ As part of USDA APHIS's responsibilities for the National Action Plan, the NVSL agreed to develop an AST proficiency test for veterinary laboratories. ○ The first proficiency test panel was distributed as a trial in 2018 and was well-received. The most recent proficiency panel was distributed to 39 participants at 36 laboratories in the US. USDA APHIS expects to distribute the 2021 proficiency panel in summer 2021;

		the proficiency test was scheduled to release earlier this year, but was postponed because of COVID-19 deployments. ○ This is the only AST proficiency panel specifically focused on veterinary testing. The purpose of proficiency panels is to allow participants to judge how their results compare with those from other veterinary diagnostic laboratories and thus promote consistency in testing among participating laboratories. ○ The NVSL uses two major methods (Sensititre and BIOMIC) for AST and has the expertise to advise veterinary laboratory personnel on testing when requested.
Within 3 years: USDA and FDA will launch pilot projects in three to five NAHLN and/or Vet-LIRN laboratories to establish proficiency in conducting standardized antibiotic susceptibility testing.	Yes	• In FY2018, USDA APHIS developed a pilot proficiency test (PT) for AST. The focus was to assess the consistency and improve the standardization of AST reporting and interpretations in veterinary diagnostic laboratories (NAP Progress Report: Year 3). ○ USDA APHIS personnel planned to evaluate the results of the pilot PT, report summary data, and work with the 39 participating laboratories to achieve more consistent results and improve testing as necessary (NAP Progress Report: Year 3). • During 2017-18, the Vet-LIRN Program Office coordinated a 2-year pilot project to evaluate the feasibility of using Vet-LIRN diagnostic laboratories to monitor the antimicrobial susceptibility of three veterinary pathogens: *E. coli* and *S. pseudintermedius* in dogs and *S. enterica* in any host. Twenty Vet-LIRN Source diagnostic laboratories collected isolates and tested the susceptibility using CLSI methods (FDA Veterinary Laboratory Investigation and Response Network).
Within 5 years: Ten to twenty NAHLN and/or Vet-LIRN member laboratories will actively conduct antibiotic susceptibility testing using standardized methodologies.	Yes	• As of 2017 and 2018 (respectively), Vet-LIRN and NAHLN were collecting data on antimicrobial susceptibility of clinically relevant bacterial isolates from different animal hosts, including companion animal species (FDA 2018 NARMS Update). • During 2017-2018, the Vet-LIRN Program Office coordinated a 2-year pilot project to evaluate the feasibility of using Vet-LIRN diagnostic laboratories to monitor the antimicrobial susceptibility of 3 veterinary pathogens: *E. coli* and *S. pseudintermedius* in dogs and *S. enterica* in any host. In 2018-2019, additional labs began collecting and sequencing isolates. Twenty Vet-LIRN Source diagnostic laboratories collected isolates and tested the susceptibility using CLSI methods (FDA Veterinary Laboratory Investigation and Response Network). • A 2017 article in the *Journal of Veterinary Diagnostic Investigation* detailed a survey conducted among US veterinary diagnostic laboratories (Dargatz 2017). The survey "results… confirm that disk diffusion and broth microdilution methods remain the preferred AST methods employed by most laboratories. These methods are generally considered interchangeable…" Also, the "survey indicates that veterinary laboratories generally use standardized interpretive criteria for

		evaluating AST results. Laboratories reported either using CLSI standards directly, or relying on automated software for interpreting AST data." • In September 2017, USDA APHIS launched an AR pilot project with the primary goals of monitoring AR profiles in animal pathogens from veterinary diagnostic labs across the US using standardized antimicrobial data transmission and sharing processes (NAP Progress Report: Year 3, Progress Report: Year 4, USDA APHIS AMR Pilot Project). ○ In 2018, 19 veterinary diagnostic laboratories (18 from the NAHLN and one from outside NAHLN, associated with a US college of vet medicine) from across the US were enrolled in the initial year of the project (NAP Progress Report: Year 3, Progress Report: Year 4). ○ In 2019, 24 laboratories participated (23 were NAHLN member and one from outside NAHLN) (USDA APHIS VS NAHLN AMR Pilot Project Year 2 Report).
***Objective 2.3**:* Develop, expand, and maintain capacity in veterinary and food safety laboratories to conduct standardized antibiotic susceptibility testing and characterize select zoonotic and animal pathogens. ***Sub-Objective 2.3.3**:* Enhance communications and identify mechanisms for sharing and reporting antibiotic-susceptibility data on select zoonotic and animal health pathogens collected by veterinary diagnostic and food safety laboratories. These data should be stored in a centralized repository that can be linked with relevant public health databases, as appropriate, while maintaining source confidentiality.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: USDA and FDA will initiate discussions with veterinary diagnostic and food safety laboratories to identify opportunities and incentives to share antibiotic-susceptibility data and consider barriers such as confidentiality concerns that would prevent or incentives that would encourage this type of data sharing among NAHLN and Vet-LIRN laboratories.	Yes	• Per the NAP First 180 Days Report, as of November 2015, FDA's Vet-LIRN had begun discussions with the USDA's NAHLN. USDA APHIS was collaborating with the AAVLD to determine the methods used to assess AMR among animal pathogens and the extent of the data that would be available to a centralized surveillance system for AMR in animal pathogens. • Per FDA personnel in April 2021, this milestone was accomplished when sufficient funding was available.
Within 3 years: USDA and FDA will identify requirements for a system to facilitate national collection,	Yes	• Per FDA personnel in April 2021: The NAHLN and Vet-LIRN laboratories have successfully been linked in a manner that allows for data to be captured and funneled into other data systems (e.g., NARMS). For example, in 2017, the Vet-LIRN laboratories conducted susceptibility testing on

analysis, and reporting of antibiotic-susceptibility testing data by NAHLN and/or Vet-LIRN laboratories, develop guidelines for data collection and for sharing metadata, and generate mechanisms and criteria for linking veterinary data to public health data (e.g., by entering veterinary data into the NARMS database).		~3,000 isolates and conducted WGS on ~1,000 of those isolates. The data were then uploaded into the NCBI and were incorporated into the 2017 and 2018 NARMS reports. • Per USDA personnel in April 2021: ○ NAHLN and Vet-LIRN have collaborated to combine AMR results collected from companion animals and report AST results via an interactive dashboard hosted through FDA's NARMS website (FDA Animal Pathogen AMR Data). ○ A separate interactive dashboard is publicly available for AST data collected through the NAHLN AMR pilot project (USDA APHIS AMR Pilot Project).
Within 3 years: USDA and FDA will launch pilot projects in three to five NAHLN and/or Vet-LIRN laboratories for data collection and sharing.	Yes	• In September 2017, USDA APHIS launched an AR pilot project with the primary goals of monitoring AR profiles in animal pathogens from veterinary diagnostic labs across the US using standardized antimicrobial data transmission and sharing processes (NAP Progress Report: Year 3, NAP Progress Report: Year 4, USDA AHIS AMR Pilot Project). ○ In 2018, 19 veterinary diagnostic laboratories (18 from the NAHLN and one from outside NAHLN, associated with a US college of vet medicine) from across the US were enrolled in the initial year of the project (NAP Progress Report: Year 3, NAP Progress Report: Year 4). ○ In 2019, 24 laboratories participated (23 were NAHLN member and one from outside NAHLN) (USDA APHIS VS NAHLN AMR Pilot Project Year 2 Report). ○ The project gathers antimicrobial susceptibility testing data from six animal species (cattle, swine, poultry, horses, dogs, and cats) and four bacterial pathogens (E. *coli, Salmonella, Mannheimia haemolytica,* and *S. pseudintermedius*). ○ Evaluation of antibiotic resistance was confounded by the fact that veterinary clinical breakpoints had not been established for the majority of antibiotic/bacterial combinations in most animal species (NAP Progress Report: Year 4). ○ Reports describing the first and second years of the project are available online. • During 2017-18, the Vet-LIRN Program Office coordinated a 2-year pilot project to evaluate the feasibility of using Vet-LIRN diagnostic laboratories to monitor the antimicrobial susceptibility of three veterinary pathogens: *E. coli* and *S. pseudintermedius* in dogs and *S. enterica* in any host. In 2018-2019, additional labs began collecting and sequencing isolates (FDA Veterinary Laboratory Investigation and Response Network). Additional details:

		○ Twenty Vet-LIRN Source diagnostic laboratories collected isolates and tested the susceptibility using CLSI methods. ○ Each source lab was partnered with one of four WGS laboratories. WGS laboratories sequenced a subset of the isolates submitted by their Source labs and uploaded all sequences to NCBI through the GenomeTrakr program. ○ Vet-LIRN is partnering with the NARMS to make the data public.
Within 5 years: USDA and FDA will establish an IT system that links NAHLN and Vet-LIRN laboratories that conduct antibiotic susceptibility testing and facilitates sharing, analysis, and reporting of veterinary AR data through a centralized repository.	In progress	• USDA APHIS developed a standardized electronic messaging format for sharing antimicrobial susceptibility data, based on the Health Level 7 (HL7) standards. This format was successfully used to upload data from laboratory reporting spreadsheets (from the AR pilot project described above) into an APHIS database (NAP Progress Report: Year 3, NAP Progress Report: Year 4). • Per FDA personnel in April 2021, the IT system to link the two networks is not yet in place but is currently being developed and is in progress. • Per USDA personnel in April 2021: NAHLN and Vet-LIRN have collaborated to combine AMR results collected from companion animals and report AST results via an interactive dashboard hosted through FDA's NARMS website (FDA Animal Pathogen AMR Data).
Objective 2.4: Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain for food animals and retail meat. ***Sub-Objective 2.4.1:*** Enhance surveillance of antibiotic resistance in animal and zoonotic pathogens and commensal organisms by strengthening the National Antimicrobial Resistance Monitoring System (NARMS) and leveraging other field- and laboratory-based surveillance systems.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: USDA will develop a plan to enhance efforts to monitor the occurrence of drug-resistant zoonotic pathogens in food animals on farms and at slaughter.	Yes	• Per USDA personnel in April 2021: ○ The USDA Food Safety Inspection Service (FSIS) has a systematic approach for strategic planning. For example, USDA FSIS will develop a strategic plan that broadly lays out what will occur in the next five years; an annual plan accompanies the five-year plan, and the annual plan highlights what will be accomplished during the year as part of the bigger (i.e., five year plan) picture. USDA FSIS's strategic plans, annual plans, and year in review documents are available online (USDA FSIS Strategic Planning). ○ USDA FSIS also develops annual sampling plans, which detail USDA FSIS's sampling plans for each fiscal year; for an example, see FSIS Annual Sampling Program Plan Fiscal Year 2020. ○ USDA APHIS's work with the on-farm NAHMS surveys (described above) is relevant to this milestone. While not all studies include biological sampling (because of budget limitations), the next iteration of this work will include testing biological samples from swine for AMR.

		○ USDA APHIS has recently (i.e., within the last 5 years) looked at the cow/calf and goat industries and will be getting results of AMR in those industries as well. ○ USDA APHIS participates with other federal partners on foodborne disease outbreaks to provide on-farm expertise. ○ NVSL analyzed sequences of selected salmonellae isolates from multiple species submitted in 2014-2017, using analysis tools and public databases to search for resistance genes in the sequences. This work was presented at several meetings and has been developed into a manuscript. The study results provide baseline information against which future studies can be compared. • In 2014, a Memorandum of Understanding (MOU) between USDA APHIS and USDA FSIS was developed for slaughter plant and on-farm investigations. Although the MOU was created before the 2015-2020 time period of the National Action Plan, it details how APHIS and FSIS work together in such circumstances.
Within 3 years: CDC will decrease by 50% the time required to detect and characterize drug-resistant enteric pathogens through NARMS surveillance, and communicate results to stakeholders.	Yes	• CDC's NARMS Now: Human Data makes NARMS data publicly available within 3 months from time of submission and testing, a significant improvement from the original reporting time of 18 months (NAP Progress Report: Year 3).
Within 3 years: CDC will improve the detection, investigation, and mitigation of multistate outbreaks caused by resistant enteric bacteria through a 25% reduction in time from the initial notification to NARMS to reporting of susceptibility testing results.	Yes	• Per CDC personnel in April 2021: ○ CDC found a 25% reduction in turnaround time for traditional testing (not including WGS, which likely shortened this further). CDC is supporting capacity in 44 states to implement WGS of *Salmonella* and other enteric pathogens, and all states had this testing capacity by summer 2018. ○ States are increasingly submitting representative isolates from foodborne outbreaks to CDC-NARMS, now supporting investigations of more than 150 foodborne disease clusters per year. States are routinely sequencing surveillance and multistate outbreak isolates, resistance genes are submitted to NARMS through PulseNet, and the predicted resistance and MIC data are now available to the states in their secure NARMS web user interface as soon as results are approved. Results are also posted routinely in the outbreak web postings. Sustaining this progress depends on states having resources toobtain isolates, ship them, and sequence them.

		○ When PulseNet identifies a multistate outbreak, these sequences allow CDC to quickly analyze isolates and report on susceptibility. These foundational tools will ensure progress towards decreasing the time to detect and characterize resistant pathogens. CDC has sequenced over 40,000 isolates, including resistant pathogens causing healthcare-associated infections and resistant enteric pathogens *Salmonella*, *Shigella*, *Campylobacter,* and *E. coli* O157, and deposited those whole genome sequences in NLM/NCBI for public access.
Within 3 years: CDC will gather risk factor information, including data on recent antibiotic use, foreign travel, medical conditions, non-food exposures, and health outcomes for patients with drug-resistant infections. This data (including information about sources of infection) will be used to help improve antibiotic prescribing practices, reduce invasive infections, and decrease hospitalization rates.	Yes	• CDC is working with state health department, academic, and public health partners to examine risk factors related to resistant *Salmonella*, *Shigella*, and *Campylobacter* infections, such as prior antibiotic use, time spent in healthcare settings, and recent food intake, to improve routine surveillance for enteric pathogens (NAP Progress Report: Year 3). Notable shifts in susceptibility values and emergence of resistance mechanisms that are identified from CDC NARMS isolates and surveillance are shared with CLSI to help support their decisions on clinical breakpoint settings and cutoff values for emerging resistance. • Per CDC personnel in April 2021: ○ CDC completed a pilot study to assess microbiome/stool as a method for surveillance of new and emerging AR threats from returning travelers. ○ Implementation of the Core Elements of Antibiotic Stewardship in Nursing Homes Enrolled in the National Healthcare Safety Network was published and an updated analysis of core element implementation was completed. Abstracts of the analyses of long-term care pharmacy and electronic health record data were presented at a national infectious disease conference, a Potential utility of pharmacy data to measure antibiotic use in nursing homes was published in 2019. Antibiotic use variability in nursing homes, 2016 has been completed and published. ○ CDC published Assessment of the Appropriateness of Antimicrobial Use in Hospitals estimating that more than half of antibiotic prescribed for select events in hospitals was not consistent with recommended prescribing practices. Researchers found that among patients treated for community-acquired pneumonia, prescribing was unsupported in 79.5% of cases, while for urinary tract infections, prescribing was unsupported for 76.8% of cases. Prescribing was considered unsupported for many reasons, including long durations, antibiotic selection that did not follow guidelines, no documented infection signs or symptoms, or no lab results confirming the presence of an infection. Based on CDC's finding, the Pew Charitable Trust released a report setting new benchmarks for prescribing of these selected events.

		○ Assessments of antibiotic use in hospitals and nursing homes as part of HAI prevalence surveys in 2015 and 2017, respectively, quantified the extent to which several common HAIs drive inappropriate antibiotic use (treatment of pneumonia among hospitalized patients and UTIs among nursing home residents were identified as prominent targets for antibiotic stewardship coordinated by state programs). ○ CDC and EIP sites provided key data and analyses for the 2019 Threat Report for organisms listed in Table 3, including drug-resistant Candida species, *C. difficile*, MRSA, extended spectrum beta-lactamase-resistant or carbapenem-resistant Enterobacterales, and *A. baumanii*. Annual estimates of burden and detailed risk factor analyses have shown the importance of community-associated transmission for several key pathogens driving overall increases or slowed decreases in incidence, despite considerable decreases for hospital onset infections. EIP-led analyses of *C. difficile*, invasive MRSA, ESBL infections have informed additional prevention and containment strategies aimed at community transmission, and monitored impact of existing interventions and programs in healthcare settings. Data from the established EIP sites are reported on an annual basis, with identification of successful decreases in AR threats, as well as opportunities for further needed improvements. This work through active, laboratory-confirmed population-based surveillance for infections caused by multiple threat organisms will continue through the next 5 years of the National Action Plan for 2020-2025, as the tracking of these AR concerns and monitoring for new AR emergence remains vital to CDC ongoing CARB efforts.
Within 3 years: CDC will identify resistance patterns for *Salmonella* by analyzing near-real-time data from all *Salmonella* isolates sent to public health laboratories. This activity will help detect outbreaks earlier and faster, improve health outcomes, and avert large food recalls.	Yes	• CDC conducts systematic resistance testing for *Salmonella* through NARMS. All state public health laboratories submit every 20th non-typhoidal *Salmonella, Shigella*, and *E. coli* O157 isolate received at their laboratories to CDC NARMS for antibiotic susceptibility testing. They also submit every *Salmonella* serotype Typhi, serotype Paratyphi A, serotype Paratyphi C, and *Vibrio* (other than *V. cholerae)* isolate received at their laboratories (National Antimicrobial Resistance Monitoring System for Enteric Bacteria [NARMS]). • A brief summary of resistance in non-typhoidal *Salmonella* is included in the 2019 CDC report: Antibiotic Resistance Threats in the United States, 2019. Also, CDC has published a number of scientific reports on non-typhoidal *Salmonella*, using surveillance data. Examples can be found on the CDC NARMS website: Selected CDC NARMS Publications 2013-Present. • NARMS Now is an interactive tool that was launched in 2015 from CDC that contains antibiotic resistance data from bacteria isolated from humans as part of the NARMS. The system includes *Campylobacter*, *E.coli* O157:H7, *Salmonella*, and *Shigella*.

		• Per CDC personnel in April 2021:
		  ○ By 2018, CDC was supporting capacity in 44 states to implement WGS of *Salmonella* and other enteric pathogens, and all states had this testing capacity by summer 2018. States are increasingly submitting representative isolates from foodborne outbreaks to CDC-NARMS, now supporting investigations of more than 150 foodborne disease clusters per the Year 3 CARB Progress Report.
		  ○ When PulseNet identifies a multistate outbreak, these sequences allow CDC to quickly analyze isolates and report on susceptibility. These foundational tools will ensure progress towards decreasing the time to detect and characterize resistant pathogens.
		  ○ CDC has sequenced over 40,000 isolates, including resistant pathogens causing HAIs and resistant enteric pathogens (*Salmonella, Shigella, Campylobacter,* and *E. coli* O157), and deposited those whole genome sequences in NLM/NCBI for public access.

Within 3 years:
CDC will conduct susceptibility testing on an increased proportion of *Campylobacter* isolates to help identify outbreaks and determine the sources of drug-resistant *Campylobacter* infections.
	Yes	• Public health laboratories of the 10 state health departments that participate in CDC's Foodborne Diseases Active Surveillance Network (FoodNet) also forward a sample of *Campylobacter* isolates to CDC for susceptibility testing. The FoodNet sites are Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, Tennessee, and selected counties in California, Colorado, and New York.
		• A brief summary of resistance in *Campylobacter* is included in the 2019 CDC report: Antibiotic Resistance Threats in the United States, 2019. Also, CDC has published a number of scientific reports on resistant *Campylobacter*, using surveillance data. Examples can be found on the CDC NARMS website: Selected CDC NARMS Publications 2013-Present.
		• NARMS Now is an interactive tool that was launched in 2015 from CDC that contains antibiotic resistance data from bacteria isolated from humans as part of the NARMS. The system includes *Campylobacter*, *E.coli* O157:H7, *Salmonella*, and *Shigella*.
		• Per CDC personnel in April 2021:
		  ○ CDC is supporting capacity in 44 states to implement WGS of *Salmonella* and other enteric pathogens, and all states had testing capacity by summer 2018. States are increasingly submitting representative isolates from foodborne outbreaks to CDC-NARMS, now supporting investigations of more than 150 foodborne disease clusters per the Year 3 Progress Report.
		  ○ When PulseNet identifies a multistate outbreak, these sequences allow CDC to quickly analyze isolates and report on susceptibility. These foundational tools will ensure progress towards decreasing the time to detect and characterize resistant pathogens. CDC itself has sequenced over 40,000 isolates, including resistant pathogens causing HAIs

		and resistant enteric pathogens *Salmonella, Shigella, Campylobacter,* and *E. coli* O157, and deposited those whole genome sequences in NLM/NCBI for public access. ○ CDC is working with state health department, academic, and public health partners to examine risk factors related to resistant *Salmonella, Shigella,* and *Campylobacter* infections, such as prior antibiotic use, time spent in healthcare settings, and recent food intake, to improve routine surveillance for enteric pathogens. Notable shifts in susceptibility values and emergence of resistance mechanisms that are identified from CDC NARMS isolates and surveillance are shared with CLSI to help support their decisions on clinical breakpoint settings and cutoff values for emerging resistance
Within 3 years: USDA will implement routine susceptibility testing of veterinary diagnostic isolates and report its findings.	Yes	• In FY2018, work began to leverage the *Salmonella* samples in the NVSL clinical isolate repository to further evaluate the prevalence of AR. The samples originated from common domesticated species and *Salmonella* serotypes of particular interest as both zoonotic pathogens and pathogens of economic importance. Data were collected/analyzed for trends and to further validate the use of WGS as the primary surveillance tool for AR in *Salmonella* isolates (NAP Progress Report: Year 3). • Per USDA personnel in April 2021: The work conducted as part of the NAHLN AMR pilot project (described above) meets this milestone (USDA APHIS NAHLN AMR Pilot Project).
Within 3 years: USDA-FSIS will expand its meat sample and cecal sample surveillance for antibiotic resistance, in collaboration with FDA, NARMS, and other USDA offices.	Yes	• As reported in 2017, NARMS enhanced surveillance by expanding testing, which in turn will improve the statistical bases for determining resistance trends in food products and strengthen the scientific foundation for strategies to limit resistance (NAP Progress Report: Years 1 and 2). • Between 2015 and 2016, USDA FSIS increased testing of chicken parts (NAP Progress Report: Years 1 and 2). • In 2015, USDA FSIS began exploratory sampling of raw pork products (NAP Progress Report: Years 1 and 2). • As of January 2017, NARMS increased the number of testing sites for *Enterococcus* and *E. coli* from four to 11 and 9, respectively (NAP Progress Report: Years 1 and 2). • As reported in 2018, all the *Salmonella, Campylobacter, E. coli*, and *Enterococcus* isolated from the regulatory and NARMS cecal surveillance programs were subject to phenotypic AST (NAP Progress Report: Year 3).
Within 3 years: FDA will expand retail meat sampling to improve the representativeness of surveillance	Yes	• The FDA, USDA, and CDC's *NARMS Now: Integrated Data* tool provides enteric bacterial isolate-level data from humans, retail meats, and food animals (NAP Progress Report: Years 1 and 2). • FDA doubled annual retail meat testing from 6,700 food samples in 2015 to ~17,280 in 2017. In 2018, FDA tested 18,240 samples; the 2018 expansion included additions of two new testing sites

data on bacterial contamination of meat products.		in North Carolina and Los Angeles, CA (NAP Progress Report: Years 1 and 2, NAP Progress Report: Year 3). • As of 2018, all *Salmonella* and *Campylobacter* isolates and every other *E. coli* isolate collected from the retail meat program were subjected to WGS and results were published in NLM/NCBI (NAP Progress Report: Year 3).
Within 5 years: NARMS will partner with NHSN to obtain drug-resistance data from clinical laboratories on bacteria isolated from persons with invasive *Salmonella*, *Campylobacter*, or *Shigella* infections. Analysis of this data will provide much-needed information about the burdens and outcomes of drug-resistant enteric infections.	No	• Per CDC personnel in April 2021: ○ The CDC intention of this objective was to explore the potential benefits and costs of adding enteric pathogens to NHSN reporting. CDC has explored the benefits of adding enteric pathogens to NHSN as an approach to systematically collect data on the burdens and outcomes of drug-resistant enteric infections. ○ Considerations included the level of effort required to expand these capabilities in NHSN and develop new work flows; the types of risk factor data that would be collected from this high-risk, hospitalized cohort; the burden added with respect to the number of infections that would potentially be reported through this mechanism; and the incentives that would be needed to get the data reported into NHSN in a consistent manner to be meaningful. ○ CDC has determined that adding enteric pathogens to NHSN reporting at this time is not the most effective way to collect this information; therefore, CDC has not moved forward with this strategy. ○ Alternative approaches linked to other existing surveillance efforts have been discussed and evaluated, and are also being considered in order to identify the most efficient method to collect these important data.
Within 5 years: CDC will begin a pilot project to evaluate the association between antibiotic-resistant urinary tract infections and foodborne bacteria.	Yes	• CDC funded a report published in 2018: A population-based surveillance study of shared genotypes of *Escherichia coli* isolates from retail meat and suspected cases of urinary tract infections. • Per CDC personnel in April 2021: ○ CDC has developed an annual process to identity priority areas to address research needs. This process allows CDC to work with external partners to fill data gaps. ○ Using this approach, CDC supported a pilot project to evaluate the association between antibiotic-resistant UTIs and foodborne bacteria; data have been collected and final results are being evaluated; two manuscripts have already been published from the results and findings of this work.
Objective 2.4*:* Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain for food animals and retail meat.		

***Sub-Objective 2.4.2**:* Enhance collection and reporting of data regarding antibiotic drugs sold and distributed for use in food-producing animals.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: FDA will publish enhanced annual summary reports on the sale and distribution of antibiotics approved for use in food-producing animals. An FDA summary report for 2009-2013 will provide baseline information regarding antibiotic sales for the period preceding the implementation of FDA Guidance for Industry #213.	Yes	• FDA's annual reports on antimicrobials sold or distributed for use in food-producing animals can be found on the FDA website at: ADUFA Reports. • In April 2015, FDA published the 2013 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals, which includes information on antimicrobial drugs for the 2013 calendar year as well as observations on changes in sales/distribution from 2009-2013 and 2012-2013.
Within 1 year: FDA will publish a proposed regulation that includes additional proposed reporting requirements for sponsors of antibiotics approved for use in food-producing animals.	Yes	• In May 2015, FDA published a proposed regulation that included additional proposed reporting requirements for sponsors of antibiotics approved for use in food-producing animals (NAP First 180 Days Report). • In May 2016, FDA issued a final rule revising the annual reporting requirements for drug sponsors of antimicrobials sold or distributed for use in food-producing animals (Progress Report: Years 1 and 2, Federal Register 11 May 2016).
Objective 2.4: Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain for food animals and retail meat. ***Sub-Objective 2.4.3:*** Implement voluntary monitoring of antibiotic use and resistance in pre-harvest settings to provide nationally representative data while maintaining producer confidentiality.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: USDA and FDA will seek public input on a plan for collecting drug use and resistance data on farms.	Yes	• On September 30, 2015, USDA, FDA, and CDC held a public meeting to obtain input on the collection of on-farm antimicrobial drug use and resistance data (NAP Progress Report: Years 1 and 2). ○ On-farm data, combined with existing data on antibiotics sold for use in food-producing animals and data from the NARMS, will help provide a more comprehensive, data-driven approach to judicious use of antimicrobials (NAP Progress Report: Years 1 and 2).
Within 3 years:	Yes	• From NAP Progress Report: Year 3:

CDC and FDA will work with the Environmental Protection Agency (EPA) to evaluate the risk of environmental uses of antibiotics on human health.		○ CDC and FDA provided consultation to the EPA on the use of streptomycin and oxytetracycline to treat huanglongbing disease in citrus crops. CDC shared ideas with the US Geological Survey on antibiotics and resistance genes for environmental monitoring and explored ways to share information on existing sampling and surveillance. CDC continues to provide isolates from the CDC and FDA AR Isolate Bank to test for cross-resistance between antibiotics commonly used in human medicine and antibiotics approved for use as pesticides. ○ In April 2018, CDC, the UK government, and the Wellcome Trust organized a meeting to discuss the impact of antibiotic-resistant bacteria and antibiotics in the environment on human health. One topic at this meeting was the impact of using antibiotics as pesticides and outlining what is known and what investigations are still needed. ○ EPA has an ongoing process that includes both CDC and FDA to evaluate the potential impact of antibiotic agricultural plant pesticides on resistance. EPA works with both CDC and FDA on the conclusions of the analysis, and determines whether any mitigation measures could reduce the potential to develop resistance or whether monitoring is needed to detect any resistance that may be developing. EPA expects to continue these discussions during the upcoming registration review of existing antibiotic pesticide registrations. During this review, which includes multiple opportunities for public comment, EPA will evaluate streptomycin and oxytetracycline pesticides registered as of October 1, 2007. These interagency discussions and collaborations help to reduce the risk of resistance to human antibiotic drugs from the use of antibiotics to control bacterial pests on agricultural crops. • There are numerous papers and presentations on the EPA website on the topic AMR (found via the EPA Science Inventory).
Within 3 years: USDA and FDA will initiate collection of drug use and resistance data on farms. This information will be used to determine baselines and trends in drug use and resistance.	Yes	• In 2017, USDA APHIS collected antibiotic use monitoring, antibiotic resistance surveillance, and antimicrobial use surveys of beef feedlots and swine operations through the NAHMS. Producers and operators completed questionnaires on stewardship practices, operation inventory, and antimicrobials used in 2016 (NAP Progress Report: Years 1 and 2, NAP Progress Report: Year 3). ○ Such data are needed to monitor implementation of FDA policy changes and to understand the relationships between antibiotic use and resistance (NAP Progress Report: Years 1 and 2). ○ Survey results were expected in 2018 (NAP Progress Report: Year 3). These reports were published in 2019 and 2020 and can be found on the NAHMS website.

		• In 2018, APHIS's CEAH was also collecting data on antimicrobial use and resistance in cow-calf operations as a component of the NAHMS 2017 national cow-calf study (NAP Progress Report: Year 3). Information about these studies can be found on the NAHMS website. • As reported in 2018, CEAH was working with stakeholders in planning for on-farm longitudinal studies of antimicrobial use and resistance on swine operations and cattle feedlots (NAP Progress Report: Year 3). • In 2016, FDA began funding two grants for antimicrobial use data collection. The collection efforts intended to provide information on antimicrobial use practices in the four major food-producing animal species (cattle, pigs, chickens, and turkeys), which can help inform assessment of the overall impact of FDA's judicious use strategy and help optimize long-term strategies to collect and report such antimicrobial use data (NAP Progress Report: Year 3, RFA-FD-16-046). The pilot data collection efforts are expected to be funded for up to 5 years and will help provide part of the baseline information about on-farm antimicrobial use practices. FDA also expects the pilot projects to assist in the development of long-term functional and efficient systems for collecting antimicrobial use data in food animal production settings (FDA CVM Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019-2023).
Objective 2.4: Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain for food animals and retail meat. ***Sub-Objective 2.4.4****:* Collect quantitative data on antibiotic-resistance and management practices along various points at pre-harvest, harvest, and processing stages, in collaboration with producers and other stakeholders, and disseminate information as appropriate.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: USDA will develop a plan for expanded monitoring of resistant bacteria throughout the food production continuum (e.g., pre-harvest, harvest, and processing of food products). On-farm sampling will be voluntary.	Yes	• Per the NAP First 180 Days Report (November 2015), as part of the NARMS program, USDA FSIS planned to expand AMR susceptibility and WGS analysis on isolates derived from its Pathogen Reduction/Hazard Analysis Critical Control Point program to include pork and chicken parts on a routine basis in FY2016. • As reported in 2019, a team of dairy scientists are working to mitigate transmission of AMR on farms by reducing behavioral pathways of exposure to resistant bacteria. They plan to identify farm-worker behaviors associated with increased risk of carriage of selected pathogens and AMR genes (ARGs) on farms having cows with varying exposure to antimicrobials, and subsequently develop interventions to change worker behaviors that are associated with exposure to pathogens and ARGs (NAP Progress Report: Year 4). • Per USDA personnel in April 2021:

		○ Work relevant to this milestone is detailed in the annual sampling plans (e.g., FSIS Annual Sampling Program Plan Fiscal Year 2020). As one example of expanded monitoring, USDA FSIS began a Raw Pork Products Exploratory Sampling Program in April 2015. ○ USDA APHIS began on-farm survey work through NAHMS in 2017. In 2017, surveys focused on on-farm practices in 2016 for feedlot cattle and swine (i.e., before FDA's VFD was fully implemented). Results of these surveys are available on the NAHMS website. While USDA APHIS planned to repeat surveys in 2020, the work was delayed until 2021 because of the COVID-19 pandemic. USDA APHIS will be conducting these surveys in 2021, which will give information about how on-farm practices related to antimicrobial use and stewardship changed after the VFD was put in place. While not all studies include biological sampling (because of budget limitations), the next iteration of this work will include testing biological samples from swine for AMR.
Within 3 years: USDA will implement collection of data on antibiotic-resistance and management practices during pre-harvest, harvest, and processing of food products. On-farm sampling will be voluntary. This information will be used to monitor trends in drug-resistant bacteria and identify potential mitigation strategies for further investigation.	Yes	• As reported in 2019, a team of dairy scientists are working to mitigate transmission of AMR on farms by reducing behavioral pathways of exposure to resistant bacteria. They plan to identify farm-worker behaviors associated with increased risk of carriage of selected pathogens and ARGs on farms having cows with varying exposure to antimicrobials, and subsequently develop interventions to change worker behaviors that are associated with exposure to pathogens and ARGs (NAP Progress Report: Year 4). ○ Ultimately, the scientists will transfer the knowledge to end-users through extension networks and multimedia interactive materials (NAP Progress Report: Year 4). • Per USDA personnel in April 2021: USDA APHIS began on-farm survey work through NAHMS in 2017. In 2017, surveys focused on on-farm practices in 2016 for feedlot cattle and swine (i.e., before FDA's VFD was fully implemented). Results of these surveys are available on the NAHMS website. While USDA APHIS planned to repeat surveys in 2020, the work was delayed until 2021 because of the COVID-19 pandemic. USDA APHIS will be conducting these surveys in 2021, which will give information about how on-farm practices related to antimicrobial use and stewardship changed after the VFD was put in place. While not all studies include biological sampling (because of budget limitations), the next iteration of this work will include testing biological samples from swine for AMR.
Within 3 years: USDA will begin coordinated investigations of emerging zoonotic antibiotic resistant	Yes	• In 2014, an MOU between USDA APHIS and USDA FSIS was developed for slaughter plant and on-farm investigations. Although the MOU was created before the 2015-2020 time period of the National Action Plan, it details how APHIS and FSIS work together in such circumstances.

pathogens on the farm and at slaughter.		• Per USDA personnel in April 2021: An example of a coordinated investigation was when, in 2016, USDA APHIS worked with state partners to investigate an outbreak of *Salmonella* Heidelberg in Wisconsin in dairy calves (APHIS CEAH Info Sheet).

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 – including tests that rapidly distinguish between viral and bacterial pathogens and tests that detect antibiotic resistance – that can be implemented in a wide range of settings.		
Milestone	**Accomplished?**	**Comments**
Within 3 years: NIH will fund at least five new projects aimed at the development of rapid diagnostics, including: • Point-of-need diagnostic tests that rapidly distinguish between bacterial and viral infections. • Tests that can rapidly determine the antibiotic-resistance profiles of resistant bacterial threats of high importance to public health, including CRE, MRSA, and ceftriaxone-resistant *N. gonorrhoeae.*	Yes	• Per NIH personnel in April 2021: ○ NIH Funding Opportunity Announcements: ▪ NIH continues to support an extensive portfolio of research projects to improve the diagnosis of bacterial infections. With NIH/NIAID support, scientists are developing and testing new tools to rapidly detect bacteria and determine their sensitivity and/or resistance to antibiotics at the patient point-of-care. In addition to numerous investigator-initiated grant opportunities and Small Business Innovation Research awards, NIH/NIAID has issued and supported targeted solicitations to foster the development of innovative diagnostic tests for AMR pathogens (Recent NIAID Research Initiatives on Antimicrobial Resistance). ▪ In 2015, NIH/NIAID funded nine projects to develop tools to detect hospital-associated pathogens (RFA-AI-14-019, NIH Funds Nine Antimicrobial Resistance Diagnostics Projects). For example, one team has developed a novel rapid antibiotic susceptibility test that detects bacterial ribonucleic acid (RNA) transcriptional changes induced by initial exposure to antibiotics. This strategy allows antibiotic susceptibility to be assessed directly from blood cultures in less than 4 hours, which is more than 24 hours faster than standard antibiotic susceptibility tests (Bhattacharyya 2019). A different team is exploring whether diagnostic tests can rapidly detect Enterobacteriaceae directly from blood samples. To rapidly determine antibiotic susceptibility, another research team is developing a platform that reduces the time needed to detect bacterial growth (Kaushik 2017).

		▪ In 2018, NIH/NIAID awarded an additional five solicited projects to support development of new diagnostic platforms for bacterial pathogens listed in the CDC's Antibiotic Resistance Threats in the United States, 2013 report (RFA-AI-17-014). These projects include: • Rapid diagnostic platform to identify pathogens and determine their antibiotic susceptibility and resistance directly from blood • Diagnostic technology that can rapidly detect and determine antibiotic susceptibility of Gram-negative pathogens in uncomplicated urinary tract infections directly from urine • Rapid point-of-care diagnostic test to identify *N. gonorrhoeae* and antimicrobial susceptibility directly from swab samples • Noninvasive, rapid breath test for the diagnosis of ventilator-associated pneumonia • Rapid point-of-care pathogen identification and antimicrobial susceptibility testing technology for UTIs using large-image-volume microscopy of single bacterial cells in urine samples and machine learning ○ NIH-supported Antibacterial Resistance Leadership Group (ARLG): ▪ The NIH/NIAID-supported ARLG is pioneering a robust clinical research agenda on antibacterial resistance, including novel diagnostics. In collaboration with bioMerieux and the NIH/NIAID-supported Vaccine and Treatment Evaluation Units, the ARLG completed a clinical trial assessing whether blood levels of the protein, procalcitonin, could help inform appropriate treatment for patients with lower respiratory tract infections (NCT03341273); analysis is underway. The ARLG also collaborated with multiple diagnostics companies to implement a master diagnostics protocol, through which multiple diagnostic tests for *N. gonorrhoeae* and *Chlamydia trachomatis* were validated simultaneously using specimens from the same patients. This study provided data for FDA clearance of both tests (NCT02870101, Doernberg 2020). ▪ Additionally, ARLG researchers are developing and testing diagnostic tools to help inform treatment options, including a simple blood test that analyzes patterns of gene expression to determine if a patient's respiratory symptoms stem from a bacterial infection, viral infection, or no infection at all (NIH Gene Expression Test Aims to Reduce Antibiotic Overuse). This study, known as the

		ARLG RADICAL study, has developed a host biomarker signature to distinguish between viral, bacterial, and non-infectious respiratory diseases. The study, which also utilized the NIH/NIAID supported BIOFIRE® FILMARRAY® device, found that diagnostic determination of the biomarker signature was able to determine the cause of infection in less than 1 hour with about 80% accuracy, which is superior to other available tests (NCT03192072, Liu 2020). ▪ The ARLG RAPIDS-GN study used an FDA-approved device to examine the impact of rapid bacterial identification and phenotypic susceptibility testing on antimicrobial prescribing/usage and clinical outcomes compared to the standard of care culture-based methods. The study found that the rapid diagnostic led to a significantly quicker adjustment of antibiotics when compared to the standard of care methods (NCT03218397, Banerjee 2020). ○ NIH-supported Sexually Transmitted Infections Clinical Trials Group: ▪ NIH/NIAID-supported researchers are also seeking to determine if a molecular test can reliably identify GC infections that may be successfully treated with a single dose of an older antibiotic, ciprofloxacin. This could potentially allow healthcare providers to reintroduce ciprofloxacin as an oral treatment for GC instead of antibiotics delivered by injection. The NIH/NIAID-supported Sexually Transmitted Infections Clinical Trials Group launched a clinical study (NCT02961751) to evaluate this test in November 2016 (NIAID-Supported Study Examines Vulnerability of Gonorrhea to Older Antibiotic Drug). The trial ended in January 2019 and found 100% successful ciprofloxacin treatment in patients determined to have ciprofloxacin-susceptible GC infections (Klausner 2020). ○ Selected NIH-funded Investigator-Initiated Projects: ▪ NIH/NIAID-funded Small Business Innovation Research (SBIR) projects of note include the development and commercialization of a rapid low cost phenotypic antibiotic susceptibility test, development of a tool to rapidly detect bloodstream infection using laser light scattering, and a system for rapid pathogen identification/quantification, antimicrobial susceptibility testing for suspected urinary tract infections, and a rapid (< 20-minute) antibiotic susceptibility test using a surface-resonance technology. ▪ Through an NIH Director's New Innovator Award, NIH is supporting research to develop a rapid diagnostic test featuring freeze-dried biosensors on strips of paper. The system is designed to determine whether an infection is viral or

		bacterial, as well as its antibiotic susceptibility. It works by sequencing transcriptomes of bacterial strains to analyze their genomic response to various antibiotics. Another research team (funded by NIH/NIAID) published a paper in *Science* in April 2017 describing a CRISPR-based tool that can distinguish pathogenic bacteria and detect resistance genes (Gootenberg 2017). This platform, called SHERLOCK (Specific High Sensitivity Enzymatic Reporter UnLOCKing), includes components that can be freeze-dried and reconstituted on paper for field applications, opening the door to many practical uses.
Within 3 years: The Assistant Secretary for Preparedness and Response (ASPR)/Biomedical Advanced Research and Development Authority (BARDA) will fund at least three new diagnostic development projects that involve next-generation sequencing, multiplex molecular assays, or other new technologies that shorten the time needed for reliable and accurate detection of drug resistance.	Yes	• BARDA and NIH are participating in the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), which is a $500 million public-private partnership between BARDA, NIH, Wellcome Trust, the UK Government, the Bill & Melinda Gates Foundation (BMGF), and others to support the development of seven rapid and innovative diagnostics to identify antimicrobial resistant bacteria. The portfolio for the seven diagnostics can be found on the CARB-X website. • The goal of CARB-X is as follows: "In addition to non-dilutive funding, CARB-X provides scientific and business support to accelerate the development of products focused on the most serious drug-resistant bacteria identified by the World Health Organization (WHO) and CDC. The goal is to support them through the early stages of product development and Phase 1 so they can attract private or public investment for further clinical stage development." (CARB-X Overview) • According to the CARB-X website in May 2021, "CARB-X is in the fifth year of a five-year mandate to invest $480 million to support the early development of innovative products to prevent, diagnose and treat drug-resistant bacterial infections. . . . Remaining funds will continue to support projects in the portfolio and new projects that are currently under negotiation." CARB-X is in discussions with potential funders; at the time of this report, no new funding rounds are scheduled until additional funding for the program is secured.

Within 3 years:
NIH and ASPR/BARDA will establish a prize for development of a rapid diagnostic test that can improve treatment of drug-resistant infections and facilitate antibiotic stewardship.
	Yes	• NIH and BARDA launched the Antimicrobial Resistance Diagnostic Challenge in September 2016.
		• Per NIH personnel in April 2021:
		  ○ The goal of this challenge competition is to incentivize the development of rapid, point-of-need in vitro diagnostics that detect and distinguish antibiotic resistant bacteria and improve antibiotic stewardship. This 3-Step competition was developed with technical and regulatory expertise from CDC and FDA, as well as public input.
		  ○ In 2017, ten semi-finalists for Step 1 of this competition received $50,000 each to develop concepts into prototypes (AMR Diagnostic Challenge Finalists). NIH/NIAID supported earlier related work for three of the Step 1 semi-finalists.

		○ Step 2 submissions were due in September 2018 (Antimicrobial Resistance Diagnostic Challenge). Step 2 semi-finalists were announced in December 2018. Each Step 2 semi-finalist received $100K (Antimicrobial Resistance Diagnostic Challenge Names Five Finalists). NIH/NIAID supported earlier related work for three of the Step 2 semi-finalists. ○ NIH and BARDA have each contributed $10 million to support the Diagnostic Challenge. • In August 2020, Visby Medical, Inc., received $19 million as a prize for its winning diagnostic. The company's diagnostic, known as Patient-side, Disposable, Molecular PCR [polymerase chain reaction] Diagnostic Device for *Neisseria gonorrhoeae* and Drug Resistance Markers, is a palm-size, single-use, disposable device for the detection of *Neisseria gonorrhoeae*, the microorganism that causes GC (Antimicrobial Resistance Diagnostic Challenge, Rapid diagnostic for gonorrhea wins $19 million federal prize competition to combat antibiotic resistance).
Within 3 years: DOD will fund projects to develop: • A functional (phenotypic) antibiotic susceptibility test that provides results more quickly than conventional susceptibility tests. This project will be conducted in collaboration with CDC. • A set of assays that can characterize the drug-resistance profile of any bacterial isolate. • An innovative method for AST aimed at eliminating the need to perform AST in centralized microbiology laboratories and enabling rapid AST in non-traditional healthcare settings.	Yes	• In 2020, the GAO Report noted that HHS and DOD have awarded grants and contracts for the development of new FDA-authorized tests for diagnosing antibiotic-resistant infections. <u>A functional (phenotypic) antibiotic susceptibility test.</u> • As reported in 2017, DOD's Defense Health Program Military Infectious Disease Research Program (MIDRP) had collaborations to develop a multiplexed automated digital microscopy system to quantify and identify target pathogens within 2 hours, with additional phenotypic characterization within 6 hours (NAP Progress Report: Years 1 and 2). <u>A set of assays that characterize the drug-resistance profile of any bacterial isolate.</u> • Per DOD personnel in April 2021, work related to this milestone has been funded by DOD. <u>An innovative method for AST.</u> • Per DOD personnel in April 2021, work related to this milestone has been funded by DOD.
Within 3 years: DOD will also fund at least one project involving next-generation sequencing technologies or	Yes	• The Defense Advanced Research Projects Agency (DARPA) used FY2015 funding on contracts for the development of rapid molecular tests for resistant GC and to distinguish between viral and bacterial infections (GAO Report).

bioinformatics platforms or tools that can be leveraged to improve diagnostics for drug-resistant or multidrug resistant pathogens.		• As reported in 2018, DOD's Austere environments Consortium for Enhanced Sepsis Outcomes (ACESO) investigates the pathogenesis and management of sepsis in operationally relevant environments. With support from the CARB program, ACESO had enrolled patients in Ghana and Cambodia. A central component of ACESO's research involves the discovery and subsequent validation of host-based biomarkers that can be translated to point-of-care diagnostic devices for early characterization of severe infections. To achieve this, ACESO incorporates novel next-generation nucleic acid sequencing and analysis approaches to provide data on both the pathogen identity and the host-response. Sequencing from patient samples has directly promoted the identification of pathogens including dengue and scrub typhus through increased sensitivity or when appropriate serological samples are unavailable (NAP Progress Report: Year 3). • As of 2020, DARPA was funding three projects using Other Transaction Authority or direct funding to a DOD service laboratory for developing tests (GAO Report).
Within 5 years: At least one new diagnostic product, the development of which was facilitated by NIH or ASPR/BARDA, will be submitted for FDA approval or clearance.	Yes	• Per NIH personnel in April 2021: ○ NIH/NIAID has supported development of five new FDA-cleared diagnostic products, including: ▪ The BacterioScan 216Dx UTI detection system that detects bacteria in urine in 3 hours. The company utilized bacterial strains provided by the NIH/NIAID-supported ARLG to evaluate this tool. In addition, NIH/NIAID is funding the company to explore expanding this tool for rapid detection of bloodstream infections. ▪ The BIOFIRE® FILMARRAY® Pneumonia Panel that detects 18 bacteria, eight viruses as well as seven genetic markers of AMR in approximately an hour. NIH/NIAID also funded the company to expand this platform for the detection of pathogens directly from blood. ▪ The NIH/NIAID funded ARLG MASTER-GC study that created a standardized master protocol to test the detection of extra-genital chlamydia and GC from both throat and rectal samples using two different diagnostic devices. Researchers found that the devices—the Aptima Combo 2 Assay from Hologic Inc. and the Xpert CT/NG diagnostic from Cepheid Inc.—were able to accurately identify extra-genital chlamydia and GC infections. These findings provided the critical data needed for FDA approval of both devices for extra-genital detection of chlamydia and GC (New Study Supports Expanded Testing for Gonorrhea and Chlamydia, NCT02870101).

		▪ Binx Health has obtained FDA clearance for a device capable of detecting *C. trachomatis* and *N. gonorrhoeae* in 30 minutes from either vaginal swab specimens or male urine samples. The development of this device was supported by a partnership with the National Institute for Biomedical Imaging and Bioengineering through the Point of Care Technology Research Network. ○ Since 2017, NIH/NIAID has supported the development of a rapid point-of-care diagnostic for *N. gonorrhoeae*, *C. trachomatis* and *Trichomonas vaginalis* by Visby Medical. A clinical study testing this device at the point-of-care found good agreement with three FDA-approved laboratory assays. Study results were published in November 2020 (Morris 2021). This work was supported through the NIH/NIAID Sexually Transmitted Infections Clinical Trials Group as well as a SBIR grant (NCT03596151, NCT03852316, Commercialization of low cost, disposable, point-of-care molecular diagnostic device for sexually transmitted infections). ○ In March 2020, Visby Medical submitted the diagnostic device for FDA clearance.
Within 5 years: NIH and ASPR/BARDA will manage and administer a prize contest (see above) for development of a rapid diagnostic test that can improve treatment of drug-resistant infections and facilitate antibiotic stewardship.	Yes	• NIH and BARDA launched the Antimicrobial Resistance Diagnostic Challenge in September 2016. • Per NIH personnel in April 2021: The $20-million dollar AMR Diagnostic Challenge, resulted in advancing the development of novel, innovative in vitro diagnostics to improve antibiotic stewardship and decrease the continued spread of AMR pathogens. After the Challenge was announced in 2016 (Federal Prize Competition Seeks Innovative Ideas to Combat Antimicrobial Resistance), the prize was awarded in three phases, starting in 2017 and concluding in 2020. • In 2017, 10 semi-finalists were each awarded $50,000 to develop their prototypes. In 2018, five finalists were each awarded $100,000 to further develop their prototypes (Antimicrobial Resistance Diagnostic Challenge, Antimicrobial Resistance Diagnostic Challenge selects 10 semifinalists, Antimicrobial Resistance Diagnostic Challenge names five finalists). • In August 2020, Visby Medical, Inc., received $19 million as a prize for its winning diagnostic. The company's diagnostic, known as Patient-side, Disposable, Molecular PCR Diagnostic Device for *Neisseria gonorrhoeae* and Drug Resistance Markers, is a palm-size, single-use, disposable device for the detection of *N. gonorrhoeae*, the microorganism that causes GC (Antimicrobial Resistance Diagnostic Challenge; Rapid diagnostic for gonorrhea wins $19 million federal prize competition to combat antibiotic resistance).
***Objective 3.2**:* Expand the availability and use of diagnostics to improve treatment of antibiotic-resistant bacteria, enhance infection control, and facilitate outbreak detection and response in healthcare and community settings.		
Milestone	**Accomplished?**	**Comments**

Within 1 year: FDA and CMS will evaluate the potential impact of innovative regulatory pathways currently under development to foster the development of diagnostic tests by addressing issues related to Medicare reimbursement and coding.	Yes	• Per the NAP First 180 Days Report, as of November 2015, FDA continued to share information and expertise with CMS regarding any innovative regulatory pathways under development for diagnostic tests to help CMS address issues related to Medicare payment and coding of such tests. The FDA and CMS renewed their MOU in June 2015. The purpose of the MOU was to promote collaboration and enhance knowledge and efficiency by providing for the sharing of information and expertise between Federal partners. • CMS and the FDA have established the Parallel Review Program, which is a collaborative effort that is intended to reduce the time between FDA marketing approval or FDA's granting of a de novo request and Medicare coverage decisions, in order to ensure prompt and efficient patient access to safe and effective and appropriate medical devices for the Medicare population (NAP Progress Report: Year 4). • Per the GAO Report (2020): ○ FDA established a Payor Communication Task Force, which helps facilitate communication between test manufacturers and payors. Such communication is important because payors decide whether tests will be covered by insurance. According to the FDA webpage, by communicating with payors, test manufacturers could learn what data payors need to approve a test for coverage and then use this information to design clinical trials to provide that information. This process could reduce the time between when a test is cleared/approved by FDA and when it is covered. ○ A similar step FDA and CMS took to advance the use of tests was to extend the Parallel Review program indefinitely, a move they announced in 2016. This program established a mechanism for FDA and CMS to simultaneously review clinical data, with the aim of reducing the time between FDA's approval and CMS's decision on whether to pay for the test. ○ The delay between approval of an antibiotic and the availability of a test for resistance could result in suboptimal treatment and increase burdens on the healthcare system. To help address this, FDA has created a process known as coordinated development, whereby test manufacturers can submit a coordinated development plan to FDA describing the test manufacturer's intent to coordinate with the antibiotic manufacturer. Under this program, FDA shares breakpoint information from the antibiotic manufacturer with a prospective test manufacturer. FDA has said that this has reduced the delay. ○ Another FDA step to help test manufacturers speed development of tests is the establishment, in collaboration with CDC, of a centralized repository of bacterial strains

		with well-characterized antibiotic resistance profiles. These strains are available to test manufacturers and others to help them design, validate, and evaluate tests by checking that they give the correct results for bacteria whose profile of antibiotic resistance is known. ○ Finally, FDA officials also said that they offer pre-submission advice, whereby a test manufacturer can ask for initial guidance on the design of clinical studies for their tests.
Within 3 years: HHS will establish a process that allows product developers to provide data to CMS for use in developing Interpretive Guidelines that facilitate the use of tests for patient treatment, hospital infection control, and reporting of cases of disease during outbreaks.	No	• As reported in the 4th Year Progress Report, as of September 2019: "CMS has not completed the CARB Plan milestone requiring product developers to provide data to CMS for use in developing Interpretive Guidelines that facilitate the use of tests for patient treatment, infection control, and reporting of disease outbreaks." • Per HHS personnel in May 2021: CMS conducted a thorough analysis of this issue and determined that CMS does not have the authority to ask for this information in the manner described by this milestone; therefore, this milestone could not be completed.
Within 5 years: HHS will issue technical assistance and education modules and materials that assist healthcare providers and health systems in using diagnostic tests to improve patient management, enhance hospital infection control, and facilitate outbreak detection and response.	Yes	• Per HHS personnel in May 2021, this milestone has been completed. For example, CDC (within HHS) has worked with both CMS and FDA on technical assistance issues relevant to this milestone.

GOAL 4: ACCELERATE BASIC AND APPLIED RESEARCH AND DEVELOPMENT OF NEW ANTIBIOTICS, OTHER THERAPEUTICS, AND VACCINES.		
Objective 4.1*:* Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic-resistance and the spread of resistance genes that are common to animals and humans. ***Sub-Objective 4.1.1****:* Support basic research to exploit powerful new technologies, including systems biology, to advance the study of antibiotic-resistance and address the special problems posed by resistant Gram-negative pathogens such as CRE.		
Milestone	**Accomplished?**	**Comments**

Within 1 year: FDA, USDA, CDC, and NIH will host a roundtable of private and public sector experts to gather input on strategies to advance collaborative research to develop tools to combat antibiotic resistance using systems biology and other new technologies.	Yes	• Several workshops, roundtables, or webinars were held in 2016 that involved federal partners and other experts and stakeholders to discuss issues related to antibiotic resistance in animal health (NAP Progress Report: Years 1 and 2). ○ For example, in July 2016, NIH hosted a roundtable discussion with academic, private sectors, and other federal experts (including CDC, DOD, FDA, and USDA) to assess steps that can be taken to address resistance (NAP Progress Report: Years 1 and 2).
Within 3 years: A National Institute of Mathematical and Biological Synthesis (NIMBioS) working group will develop an analytic modeling framework for assessing the relationship between antibiotic use in livestock (measured at the population level) and the development of antibiotic resistance.	Yes	• In August 2016, a NIMBioS working group published online A Proposed Analytic Framework for Determining the Impact of an Antimicrobial Resistance Intervention at the National Level.
On an annual basis: HHS, NIH, FDA, USDA, CDC, DOD, and EPA will conduct a review to ensure that US Government research resources are focused on high-priority antibiotic resistance issues (including basic research on the emergence and spread of resistance genes) and facilitate use of advanced technologies in research on antibiotic resistance (e.g., whole genome sequencing (WGS), proteomics,	Yes	• This milestone has been accomplished by HHS, NIH, FDA, USDA, CDC, and DOD. This milestone is not applicable to EPA (see below for details); therefore, this milestone was classified as completed. • Per HHS personnel in May 2021: This milestone has been completed, as evidenced by the regular review implemented by agencies within HHS (e.g., NIH's portfolio reviews). • Per NIH personnel in April 2021: ○ NIH utilizes its strategic planning process and NIH/NIAID Advisory Council to ensure that NIH research is focused on high-priority AMR issues. The Council's scientists contribute technical expertise and an understanding of the needs of the research communities of academia and industry. New, targeted initiatives have been proposed and developed in each of the CARB National Action Plan active years (Recent NIAID Research Initiatives on Antimicrobial Resistance). ○ In addition, NIH supports the use of advanced and emerging technologies to provide insight into AMR pathogens, foster understanding of resistance mechanisms, and assist

metagenomics, structural biology, bioinformatics).		in the development of improved diagnostics, therapeutics, vaccines, and antimicrobial strategies. These diverse approaches include NIH/NIAID-supported programs in systems biology, WGS, structural genomics, functional genomics, and bioinformatics. • Per FDA personnel in April 2021: FDA conducts regulatory-relevant research; examples can be found via the following webpages: ○ FDA Biologics Research Projects ○ FDA Center for Drug Evaluation and Research (CDER): The Office of Infectious Disease Research Activities • The 2016-2018 USDA ARS AMR and ATA Accomplishment Summary noted the following development/accomplishments in animal health and production food and safety: ○ Colistin resistance gene (*mcr-1*) in US meat animals ○ Resistome analysis of dairy calves and lactating dairy cows ○ ColE1 plasmids contribute to the fitness of *Salmonella* Heidelberg in poultry litter ○ Impact of biotic vs. abiotic fertilizer on antibiotic resistance in soil: role of manure ○ Impact of raising beef cattle without antibiotics on occurrences of AMR • Per USDA personnel in April 2021: A number of publications show USDA ARS's work in this arena over the last 5 years: ○ Effects of in-feed chlortetracycline prophylaxis in beef cattle on AMR genes (Miller 2018) ○ Metagenomic characterization of the microbiome and resistome of retail ground beef products (Doster 2020) ○ Impact of "raised without antibiotics" beef cattle production practices on occurrences of AMR (Vikram 2017) ○ Similar levels of AMR in the US food-service ground beef products with and without a "Raised Without Antibiotics" claim (Vikram 2018) ○ AMR in US retail ground beef with and without label claims regarding antibiotic use (Schmidt 2020) • Per CDC personnel in April 2021: CDC funds annual research and works across agencies through support from the AR Solutions Initiative, which has invested $160 million in AR innovation since 2016, and by leveraging successful programs across the agency. As part of this process, CDC regularly reviews resource allocations to ensure that research remains focused on high-priority issues. These programs include: ○ Broad Agency Announcements (BAAs): contracts with educational institutions, nonprofit organizations, state and local government, and private industry for research and development to identify and evaluate strategies to combat AR.

		○ Modeling Infectious Diseases in Healthcare (MInD): virtual laboratory where researchers can investigate factors that drive spread of HAIs and simulate prevention strategies to assess their benefits. ○ Safety and Healthcare Epidemiology Prevention Research Development (SHEPheRD): requests research and other collaborative proposals from organizations to develop and conduct research and innovative prevention projects related to safety in healthcare settings. ○ Small Business Innovation Research (SBIR) provides "seed funds" for small business concerns (SBCs) to explore their technological potential and the incentive for SBCs to profit from commercialization of their innovations. • Per DOD personnel in April 2021: This milestone has been accomplished, evidenced by ongoing program review and funding decisions. • Per EPA personnel in May 2021: ○ EPA did not have a large role or sufficient budget during the 2015-2020 National Action Plan timeframe to have a research focus on antibiotic-resistance issues and, therefore, no annual review of research resources was conducted. ○ Since there was no research focus on antibiotic resistance for EPA during 2015-2020, this milestone is not applicable to EPA.
Objective 4.1: Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic-resistance and the spread of resistance genes that are common to animals and humans. ***Sub-Objective 4.1.2****:* Leverage existing partnerships, such as the NIH Antibacterial Resistance Leadership Group (ARLG), and international collaborations to reduce obstacles faced by pharmaceutical companies that are developing new antibiotics, other therapies, and vaccines. Partnerships will help identify human subjects qualified for enrollment in clinical trials of vaccines to prevent and antibiotics to treat resistant bacterial infections that occur sporadically, episodically, and/or in limited populations, generate and apply common clinical test protocols to multiple test groups of patients while sharing a common control group, and conduct other research-support activities as needed.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: NIH will work with FDA and partners in industry and academia to: • Explore features necessary for developing a more robust clinical trials infrastructure for	Yes	• Per the NAP First 180 Days Report, as of November 2015: ○ NIH and FDA had initiated a series of internal meetings to discuss how to enhance the US government's clinical trial infrastructure and utilize common clinical protocols in the future. ○ NIH, in collaboration with FDA, held three public workshops in 2014 addressing various aspects of antibacterial and diagnostics development, including a workshop focusing on common clinical protocols. • Per the GAO Report (2020):

antibacterial product development. • Assess the feasibility of applying common clinical protocols for evaluation of multiple products while sharing a common control group. This approach may facilitate clinical testing of drugs to treat Gram-negative infections such as CRE that occur sporadically or episodically in limited populations (e.g., during hospital outbreaks).		○ FDA has implemented programs and issued guidance that help address some regulatory challenges and encourage antibiotic development. In 2012, through the Generating Antibiotic Incentives Now provisions of the FDA Safety and Innovation Act, Congress created the Qualified Infectious Disease Product (QIDP) designation. Drugs that FDA designates as QIDPs, which include antibiotics and antifungals, may qualify for 5 years of additional exclusivity and fast-track or priority review designation during the FDA review process. The additional exclusivity conferred to QIDP designees is a type of "pull incentive," because it offers the potential for enhanced financial gain after a drug receives FDA approval and reaches the market. ○ As of September 2019, FDA had granted 192 QIDP designations, 24 of which it has approved for marketing. ○ In August 2017, FDA released final guidance to streamline clinical development of antibiotics for patients with unmet medical need (i.e., those with a serious bacterial disease that has few or no treatment options). ○ In November 2019, FDA met with experts from NIH NIAID, the Infectious Disease Society of America, and the Pew Charitable Trusts to better understand the current state of antibiotic clinical trials in the US, and how to enhance enrollment and research in these trials. ○ FDA officials believed it was too early to issue guidance that would be broadly applicable/useful to nontraditional product developers. For certain types of nontraditional products, the approaches and specifics of product development are varied and evolve quickly. Instead, FDA's Center for Biologics Evaluation and Research (CBER) has a program that allows developers to meet with FDA prior to beginning clinical trials to obtain advice on development-related topics. • Per FDA personnel in April 2021, FDA CDER also has a program that is designed to facilitate early communications between FDA and potential sponsors of new therapeutics (FDA Pre-IND Consultation Program). • Per NIH personnel in April 2021: ○ NIH and FDA had initiated a series of internal meetings to discuss how to enhance the US government's clinical trial infrastructure and utilize common clinical protocols in the future. ○ NIH, in collaboration with FDA, held three public workshops in 2014 addressing various aspects of antibacterial and diagnostics development, including a workshop focusing on common clinical protocols.

		○ In March 2017, NIH's ARLG published an extensive summary of its activities, describing progress, ongoing efforts, and future directions. Many of the ARLG's studies have involved innovative approaches, such as novel trial designs that optimize enrollment in therapeutic trials and increase clinical trial efficiencies (ARLG: Productivity and Innovation).
Within 1 year: NIH will expand and strengthen the ARLG network, which facilitates clinical testing and validation of new antibacterial products and conducts studies to determine how existing products can be used in optimal ways to improve the treatment of resistant infections.	Yes	• Per NIH personnel in April 2021: The ARLG added more than 100 clinical sites between March 2015 and October 2020 to perform a variety of clinical studies and trials, including: ○ COMBINE, a clinical trial to evaluate the safety, tolerability, and pharmacokinetics of a novel combination therapy (ceftazidime-avibactam and aztreonam) that shows promise for treatment of carbapenem-resistant Enterobacteriaceae infections. As of November 2020, the trial is complete (NCT03978091). ○ SCOUT-CAP, which assesses a shortened course of therapy for pediatric community-acquired pneumonia (CAP). This trial opened to enrollment in November 2016 and ended in December 2019 (NCT02891915). In October 2020, the research team announced that the study showed that short course (5 day) antibiotic treatment is superior to standard (10 day) treatment of CAP in children 6 months to 5 years of age when days of antibiotic therapy are considered. Both treatment strategies were effective in treating CAP (Childhood Pneumonia Study Shows Short-Course Antibiotics Superior to Standard of Care). ○ CRACKLE II, a prospective, multicenter, observational cohort study with the objective of providing data to aid in the design of randomized clinical trials on therapeutics and diagnostics for CRE infections (Duin 2020).
Within 1 year: FDA, USDA, CDC, and NIH will bring together experts in food production, agriculture, and public health to encourage collaborative research—from basic research to clinical testing—on antibiotic resistance.	Yes	• Several workshops, roundtables, or webinars were held in 2016 that involved federal partners and other experts and stakeholders to discuss issues related to antibiotic resistance in animal health (NAP Progress Report: Years 1 and 2). • In April 2016, USDA, FDA, and private sector partners participated in a National Academy of Sciences Food Forum workshop to discuss when, where, and how antibiotics enter the food supply, how antibiotic resistance transfers from animals to humans, and alternatives to antibiotics (NAP Progress Report: Years 1 and 2). • In July 2016, USDA hosted a stakeholder webinar with FDA, NIH, and private sector partners to discuss, prioritize, and develop strategies to help meet the most pressing animal health research education and extension needs related to antibiotic resistance (NAP Progress Report: Years 1 and 2).

		• In December 2016, USDA's ARS, in collaboration with NIH and FDA and with OIE support, organized the Second International Symposium on Alternatives to Antibiotics in Animal Production. The symposium was structured to promote public-private partnerships to enable development of alternatives to antibiotics (NAP Progress Report: Years 1 and 2).
Objective 4.2: Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.		
Milestone	**Accomplished?**	**Comments**
Within 3 years: USDA, NIH, and CDC will support research on the spread of resistance genes between zoonotic pathogens and the commensal microbiota that live in the gastrointestinal tracts of animals and humans (i.e., in animal and human microbiomes).	Yes	• Since October 2016, CDC has awarded more than $32.5 million to pilot innovative solutions and explore knowledge gaps about how antibiotic resistance spreads to and between humans, including research on how the human microbiome can be used to predict and prevent infections caused by drug-resistant microorganisms (NAP Progress Report: Year 3). • Per CDC personnel in April 2021: ○ USDA FSIS continued to partner with FDA, CDC, USDA ARS, USDA APHIS, and NLM/NCBI, under the umbrella of the "Gen-FS" consortium. The primary function of Gen-FS is to coordinate, strengthen, and lead US WGS efforts among federal and state partners and further improve public health. This interagency group is steered by agency leaders to focus on crosscutting priorities for molecular sequencing of foodborne and other zoonotic pathogens causing human illness, for data collection and analysis including AR, and to use this information to support surveillance and outbreak investigation activities. One of the focus areas under Gen-FS is genetic determinants of AR and their spread. ○ NIH, in partnership with FDA and CDC, is expanding the NIH NDARO. The web-based open-access database, developed by NLM/NCBI, contains genomic data for more than 205,000 pathogen isolates collected from publicly available information. The database includes information on high-priority bacterial threats such as *Acinetobacter*, *Klebsiella*, *Pseudomonas*, and isolates containing genes known to confer antibiotic resistance (e.g., mobile colistin resistance [mcr] and KPC) and can be searched by resistance genotypes, and, when available, antibiotic susceptibility phenotype. ○ In addition, NIH and CDC continue to sequence high-priority reference strains, as identified by CDC and FDA, to inform the development of new diagnostic tests and drugs. • The 2016-2018 USDA ARS AMR and ATA Accomplishment Summary noted the following development/accomplishments in animal health and production: ○ Defined collateral effects of the in-feed antibiotic, carbadox, on the total gut bacterial community.

		○ Evaluation of the effects of antibiotic alternatives on chicken gut microbiome using comparative metagenomic analysis. • Per NIH personnel in April 2021: ○ NIH supports a robust portfolio of basic and clinical research on the effect of antibiotics on the microbiome, how microbial communities can be used to prevent and treat resistant infections, and development of non-antibiotic therapeutics to treat infections while maintaining the integrity of the microbiome. In addition, NIH supports research to understand the spread of antibiotic resistance from animals to humans and within human microbiota. ○ NIH Funding Opportunity Announcements: ▪ NIH/NIAID is supporting research on microbiome-based therapeutics, including efforts to identify protective bacterial strains and formulate them into products to prevent and treat *C. difficile* infection. In March 2018, NIH/NIAID issued two funding opportunities (PA-18-724 and PA-18-725) to advance research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease, as well as research exploring combination antibiotic therapies to address the emergence of resistance. As of April 2021, NIAID has funded 24 projects in this area. ▪ In January 2020, NIH/NIAID issued a funding opportunity announcement to establish CARB Interdisciplinary Research Units (CARBIRUs) focused on improving our understanding of bacterial and host factors important for antibacterial resistance and infection to inform development of new approaches to prevent, diagnose, and treat antibacterial-resistant infections (RFA-AI-20-001). ○ Fecal Microbiota Transplant (FMT) Activities: ▪ In 2017, NIH/NIAID established an Interagency Agreement with FDA to address key regulatory questions regarding the manufacture of FMT products, as well as to assess the effectiveness of current donor screening recommendations by determining specificity and sensitivity of commonly used molecular diagnostic tests. In addition, NIH/NIAID and the American Gastroenterological Association have launched an FMT national registry for *C. difficile* infection (NCT03325855). The registry is designed to collect clinical data from FMT donors and recipients to assess the short- and long-term safety and effectiveness of this intervention. As of September 2020, 451 participants have enrolled in the registry. Initial results showed that 90% of patients with *C. difficile* infection recovered within 1 month

		of FMT administration (Kelly 2021). NIH/NIAID is also supporting a clinical trial to study the effectiveness of FMT for recurrent *C. difficile* infection among solid-organ transplant recipients. This Phase 2 clinical trial is examining FMT compared with vancomycin, an antibiotic often used to treat *C. difficile* diarrhea (NCT03617445). Together, this trial and the NIAID-supported FMT National Registry are adding to the growing body of safety and efficacy data that will inform the future use of FMT in treating *C. difficile* infections and more broadly how changes in the microbiota can impact long-term health outcomes. ○ Additional NIH Clinical Research Activities: Microbiome: ▪ NIH/NIAID is supporting several large-scale clinical projects to determine the stability and resilience of the human gut microbiome over time and after perturbations such as antibiotic use, e.g., the Microbial, Immune, Metabolic Perturbations by Antibiotics (MIME) study (NCT02707042), the citizen science-driven Dynamics of the Human Microbiota Study involving nearly 100 participants, and the Microbiome, Antibiotics, and Growth Infant Cohort (MAGIC) (NCT03001167). ▪ In addition, microbiome data are being collected as part of the ARLG's SCOUT-CAP trial on pediatric community-acquired pneumonia. This sub-study known as STAR (Short-course Therapy and the Antibiotic Resistome) will compare the microbiome of stool and throat swabs in children who receive the standard 10-day course of antibiotics vs. a shortened 5-day course. ○ Select Research Projects Supported and Conducted by NIH: ▪ On January 1, 2018, California's Senate Bill 27 (SB27) banned all non-therapeutic uses of antimicrobials in livestock. NIAID is supporting a project to investigate the incidence of AMR *E. coli* in livestock and humans, before and after this bill. *E. coli* is a leading cause of UTIs in humans. Researchers will analyze data from retail chicken meat and patients with UTIs, including WGS, electronic health records from more than seven million outpatients with 100,000 *E. coli* -associated UTIs per year, and proximity to industrial food animal production. ▪ NIAID-supported researchers investigated the evolution and epidemiology of a novel livestock-associated MRSA strain, which colonizes and infects urban-dwelling Danes even without a Danish animal reservoir. Genetic evidence suggests both poultry and human adaptation, with poultry meat implicated as a probable source. From a public health perspective, it is essential to continue *S.*

		aureus surveillance at the human-animal interface to quickly detect evolutionary and epidemiologic changes and to intervene to protect human health (Larsen 2016). In a related paper, researchers from this team reported that livestock-associated MRSA clonal complex 398 (LA-MRSA CC398) was an increasing cause of bacteremia in Denmark from 2010-2015. Most patients lived in rural areas, but had no contact with livestock. WGS data supported that Danish pigs are the most likely source of LA-MRSA CC398 infections in humans (Larsen 2017). ▪ NIH/NIAID is supporting a study to quantify the exchange of MDR strains of *E. coli* and mobile genetic elements (e.g., plasmids) between food-animals and children living in peri-urban communities east of Quito, Ecuador, where small-scale food-animal production is widely practiced. ▪ NIH/NIAID supported research on the systems biology of microbiome-mediated resilience to antibiotic-resistant pathogens. Scientists investigated the intestinal flora of hospitalized patients and used mathematical modeling to identify bacterial species and their metabolic products that reduce the risk of infection by three prevalent antibiotic-resistant bacteria. These studies may lead to the development of new approaches to treat and prevent antibiotic-resistant infections. ▪ To better understand and prevent healthcare-associated infections caused by MDR bacteria, NIH/NHGRI intramural scientists are using whole genome and whole plasmid sequencing and analysis. These researchers are investigating mechanisms of AMR and developing methods for prompt detection and recognition of common, emerging, and novel strains of resistant bacteria. Under this initiative, the NIH team has sequenced 45 clinical and 69 environmental CRE isolates collected at the NIH Clinical Center. In February 2018, NIH scientists from NHGRI and the NIH Clinical Center reported that genomic analysis of hospital plumbing revealed a diverse reservoir of bacterial plasmids conferring carbapenem resistance (Weingarten 2018). ▪ In a fundamental study published *in the New England Journal of Medicine* in December 2018, NIH scientists from NIH/NHGRI and the NIH Clinical Center published a genomic and epidemiologic investigation of a cluster of MDR *Sphingomonas koreensis* infections at the NIH Clinical Center. Genetically similar strains of *S. koreensis*, a rarely reported Gram-negative waterborne pathogen, were traced to 12 patients from 2006 through 2016. This study suggests the

		hospital plumbing system as a possible reservoir for this opportunistic pathogen (Johnson 2018). This study was a collaboration with scientists at the Division of High-Consequence Pathogens and Pathology, Centers for Disease Control and Prevention. The NIH team continues their collaborative work to investigate the origins, distribution, and remediation of MDR waterborne organisms that colonize some of the domestic water fixtures in the NIH Clinical Center. ▪ To directly test the effect of antibiotics on the human-associated microbial communities, scientists from NIH/NHGRI and NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases performed a prospective, randomized pilot study at the NIH Clinical Center of four clinically-relevant antibiotic regimens using doxycycline, cephalexin or trimethoprim/sulfamethoxazole (TMP/SMX), and investigated microbial alterations following introduction of systemic antibiotics to healthy human volunteers. Samples from skin, oral sites and stool were collected before, during, and up to 1 year after antibiotic use, and shotgun metagenomic sequencing was performed. Taxonomic analysis showed that subjects receiving doxycycline and TMP/SMX exhibited significantly greater changes of skin microbial communities than subjects receiving cephalexin. Bacterial culturing revealed emergence and persistence of antibiotic-resistant Staphylococci, harboring classic antibiotic resistance genes, from subjects after receiving doxycycline and TMP/SMX. ▪ NIH/NIAID intramural researchers led an international effort at the intersection of AMR and the microbiome to reveal that the probiotic Bacillus can eliminate *S. aureus*. When Bacillus was present in fecal samples from study participants in Thailand, *S. aureus* was never detected in their gut or nasal samples. Using a mouse model, the research team discovered that Bacillus secretes compounds known as fengycin lipopeptides that block *S. aureus* quorum-sensing (a mechanism which enables groups of bacteria to communicate with one another) and completely eradicates intestinal *S. aureus*. Bacillus-containing probiotics could be used for simple and safe *S. aureus* decolonization strategies. Such a probiotic approach would have numerous advantages over the present standard topical strategy involving antibiotics. The potential for a simple probiotic strategy to prevent potentially dangerous staph infections holds immense promise in the healthcare field (Piewngam 2018, NIH Study Finds Probiotic Bacillus Eliminates Staphylococcus Bacteria).

Within 3 years: USDA, in consultation with NIH and CDC, will support research to map the gut microbiome of at least one food animal, using metagenomic techniques and "big data" analysis tools. This research will advance understand antibiotic treatments disrupt the normal gut microbiome and how animal growth may be promoted without antibiotics It may also suggest ways to treat bacterial animal diseases without using antibiotics.	Yes	• The 2016-2018 USDA ARS AMR and ATA Accomplishment Summary noted the following development/accomplishments in animal health and production: ○ Evaluation of the effects of antibiotic alternatives on chicken gut microbiome using comparative metagenomic analysis. • Per USDA personnel in April 2021: The following publication is also pertinent to this milestone: The in-feed antibiotic carbadox induces phage gene transcription in the swine gut microbiome (Johnson 2017).
***Objective 4.3**:* Intensify research and development of new therapeutics and new and improved vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: • The Chemical and Biological Defense Program (CBDP) and the Defense Threat Reduction Agency (DTRA) will submit an Investigational New Drug (IND) application to FDA to initiate the clinical investigation of an antibiotic developed with DOD funding. • CBDP/DTRA will award two new contracts to industry partners to accelerate advancement of novel small-molecule antibiotic therapies that circumvent known resistance mechanisms or	Partially	CBDP/DTRA will submit an Investigational New Drug (IND) application to FDA to initiate the clinical investigation of an antibiotic developed with DOD funding. • As of November 2015, DOD/Joint Science and Technology Office (JSTO) was funding efforts to complete preclinical development of a novel drug (topoisomerase inhibitor) with IND submission planned for 2017 (NAP First 180 Days Report). • As of 2017, WRAIR had established an industry-based approach to efficiently screen and evaluate new antibiotic candidate compounds, and to help government, academic, and industry partners further develop candidates and progress faster toward IND submissions to the FDA (NAP Progress Report: Years 1 and 2). • Per DTRA personnel in May 2021, the IND was expected for Emergent BioSolutions compound GC-072. An IND was not filed for GC-072 because it failed toxicology studies in 2019. Therefore, this portion of the milestone was not met. CBDP/DTRA will award two new contracts to industry partners to accelerate advancement of novel small-molecule antibiotic therapies that circumvent known resistance mechanisms or potentiate the therapeutic efficacy of existing antibiotics (e.g., combination therapies). This activity will leverage

potentiate the therapeutic efficacy of existing antibiotics (e.g., combination therapies). This activity will leverage ongoing efforts to develop treatments for infections caused by Select Agents (pathogens that might be used as biological weapons).		ongoing efforts to develop treatments for infections caused by Select Agents (pathogens that might be used as biological weapons). • Per DTRA personnel in May 2021: ○ Since 2014, DTRA has awarded several new contracts for novel therapeutics, as well as established joint programs with BARDA, to establish biodefense utility for advanced antibacterial candidates. ○ Investments include discovery in novel non-beta lactam penicillin-binding protein (PBP) inhibitors (Venatorx), development of next generation fluoroquinolone, finafloxacin (MerLion), ARV-1801 (sodium fusidate, Arrevus), as well as oral tebipenem (Spero) and taniborbactam/cefepime (Venatorx) in partnership with BARDA. ○ DTRA also has multiple investments in innate defense regulators that may be used as adjunctive therapies with antibiotics. ○ This portion of the milestone has been met.
Within 3 years: NIH will arrange for clinical trials networks such as the Antibacterial Resistance Leadership Group (ARLG), (see Objective 4.1.2) to test a Gram-negative therapeutic agent with the goal of addressing use in a limited-population setting such as a hospital.	Yes	• Per NIH personnel in April 2021: ○ NIH/NIAID-supported scientists completed enrollment of a Phase 1 trial evaluating zoliflodacin, a novel antibiotic for the treatment of GC infection (NCT03404167). Zoliflodacin progressed to a global Phase 3 clinical trial sponsored by the Global Antibiotic Research and Development Partnership (NCT03959527). ○ NIH/NIAID's clinical research portfolio includes clinical trials assessing novel formulations and combinations of existing antibiotics. NIH/NIAID is supporting research on the intravenous formulation of the broad-spectrum antibiotic fosfomycin (also known as Contepo), which is not currently available in the US. NIH/NIAID's investment in preclinical and early clinical testing of this drug enabled a small company to complete a successful Phase 2/3 clinical trial (Wenzler 2017). This study found that Contepo is an effective treatment for hospitalized patients with complicated UTIs or acute pyelonephritis. An ongoing Phase I trial is investigating lung levels of this antibiotic. ○ The NIH/NIAID supported ARLG was created in June 2013 to develop, prioritize, and implement a clinical research agenda on antibacterial resistance (ARLG). Funding was renewed in 2019 for an additional 7 years, through November 2026. As of October 2020, the ARLG has received more than 150 study proposals, initiated more than 50 studies, included data from greater than 21,000 subjects, and published more than 150 manuscripts. The ARLG is exploring novel treatment regimens comprised of licensed antibiotics:

		▪ In January 2017, the ARLG reported that ceftazidime-avibactam may be superior to colistin for treating KPC-producing CRE infections (van Duin 2018). ▪ The clinical trial, known as ACUMIN, examined the pharmacokinetics (PK) and pharmacodynamics of intravenous minocycline in critically-ill patients with Gram-negative infections in the intensive care unit (ICU) (NCT03369951, Lodise 2021). This trial will help inform how to use this new formulation of an older drug. ▪ A Phase 1 trial, known as the PROOF study, generated safety and PK data to inform future research on the expanded use of Monurol (oral fosfomycin) for outpatient treatment of complicated UTI (cUTI) (NCT02570074, Wenzler 2018). ○ NIH/NIAID is supporting the OVERCOME study – a randomized controlled Phase 3 trial to determine how best to use an older antibiotic, colistin, in patients with multi-drug resistant infections (NCT01597973). The trial has the potential to provide valuable information about the utility of colistin for Gram-negative bacterial infections (i.e., CRE and MDR *Acinetobacter)* when used alone, or in combination with a carbapenem. NIAID has aligned with European Union (EU) clinical trial infrastructure (under the Innovative Medicines Initiative's CLIN-NET and LAB-NET networks established by the COMBACTE project) to add European and Israeli sites and enable more timely enrollment in this important trial. This trial includes study sites in the US, Israel, Italy, Greece, Bulgaria, Thailand, and Taiwan.
Within 3 years: NIH will launch a research program that uses systems biology to identify new drug targets that can be used to develop antibiotic drugs with new modes of action that make the development of resistance less likely.	Yes	• Per NIH personnel in April 2021: ○ NIH/NIAID expanded support for systems biology projects, genomic sequencing, and structural genomics for AMR. In 2016, NIAID awarded six projects under RFA-AI-14-064, Systems Biology and Antibacterial Resistance, that use a multi-disciplinary systems biology approach to identify, quantify, model and predict the dynamics of the molecular interactions of antibiotic-resistant pathogens and their hosts during disease initiation, progression or in response to treatment (RFA-AI-14-064). These projects are modeling the host-pathogen molecular networks for bacteria such as *S.s aureus*, *C. difficile* and carbapenem-resistant Enterobacteriaceae using experimental and computational techniques, and the resulting network models will provide a comprehensive framework to identify more effective therapeutic targets and strategies for these pathogens. Since their inception in 2016, these six centers have published over 200 peer-reviewed papers in high-impact journals and deposited thousands of AMR datasets into the public domain. Leveraging experimental and clinical datasets, a highlight of these Centers is

		that they have developed models that can predict both patient disease severity and signatures associated with AMR emergence. Specific examples include: ▪ The Center has demonstrated how global transcriptomic bacterial responses are a predictive model for antibiotic sensitivity and resistance across seven different species (Zhu 2020). ▪ A large, comprehensive study underscores how the gut microbiome composition post—stem-cell transplantation in cancer patients predicts patient survival (Peled 2020). ▪ The Center has published work demonstrating that serum biomarkers are capable of predicting 30-day all-cause mortality and adverse outcomes of patients at time of *C. difficile* diagnosis (Dieterle 2020). ▪ Discovered and validated an association between patient genetic factors and the duration of MRSA blood infection. The work correlates a shorter time to resolution of MRSA blood infection in patients with a specific genotype. Additional work to integrate genomics, host response, and metabolomics into a MRSA predictive model near completion (Medie 2019). ▪ The sugar substitute, trehalose, increases the virulence of epidemic strains of *C. difficile*. The authors found that two epidemic types of *C. difficile* have the special ability to metabolize low levels of trehalose, and they hypothesize that the widespread use of this compound as a dietary additive may have contributed to the spread of these strains (Collins 2018). ○ The NIH/NIAID-supported Structural Genomics Centers have generated more than 600 structures of proteins from pathogens associated with AMR, including *C. difficile*, *A. baumannii*, *P. aeruginosa, Klebsiella, Enterobacter, Streptococcus pneumoniae, S. aureus, and N. gonorrhoeae* (Structural Genomics Centers for Infectious Diseases). By determining the structures of unique proteins related to antibiotic resistance mechanisms and vaccine candidates, researchers are providing new insights about the mechanisms and evolution of resistance. The structures are deposited and available in the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (RCSB PDB).
Within 3 years: NIH will assist research partners who are developing novel classes of antibacterial drugs in	Yes	• Per NIH personnel in April 2021: ○ NIH support helps investigators advance potential new drugs from the conceptual stage through early clinical testing. For example, NIH/NIAID has supported preclinical development, investigational new drug submissions, and four Phase 1 clinical trials for

submitting IND applications to FDA.		the novel tetracycline TP-271 (NCT03450187 or NCT03234738 or NCT03024034 or NCT02724085) and two Phase 1 clinical trials for the beta-lactamase inhibitor VNRX-5133 (NCT02955459 or NCT03332732). Both of these products have broad-spectrum activity against multiple bacteria, including difficult-to-treat Gram-negative strains. NIH/NIAID also supported IND-enabling studies and in January 2020, launched a Phase 1 clinical trial to test the safety and PK of an orally bioavailable, broad-spectrum small molecule beta-lactamase inhibitor (VNRX-7145) in human subjects (NCT04243863). ○ Through SBIR awards to VenatoRx Pharmaceuticals Inc., NIH/NIAID is supporting preclinical development of a therapeutic candidate (VNRX-4099) from a new class of ultra-broad spectrum carbapenems with activity against MRSA, Enterobacteriaceae and *P. aeruginosa,* with the goal of advancing it to IND filing status. The compound will be evaluated in combination with VNRX-5133, as a potential new single-treatment option against MDR pathogens in the ICU and other hospital settings.
Within 5 years: NIH will support initial testing and validation of two new products (antibacterial drugs, novel therapeutics, or vaccines) to treat or prevent multidrug resistant Gram-negative pathogens. Once validated, these products will be transitioned to ASPR/BARDA or pharmaceutical companies for advanced development, including clinical efficacy trials (see also Objective 4.4).	Yes	• Per NIH personnel in April 2021: ○ NIH/NIAID provides critical early support to enable promising antibacterial candidates to progress to advanced development. Examples include: ▪ With NIH/NIAID funding, researchers developed a new state-of-the-art chemistry platform to synthesize novel tetracyclines (including TP-271 reported under sub-objective 4.6). In August 2018, FDA approved one of these compounds (known as XERAVA or eravacycline) to treat complicated intra-abdominal infections. ▪ NIH/NIAID's investment in preclinical and early clinical testing of the intravenous formulation of the broad-spectrum antibiotic fosfomycin (Contepo, Wenzler 2017) enabled industry to complete a successful Phase 2/3 clinical trial (NCT02753946) and, in 2018, submit a new drug application to FDA. The clinical trial showed that intravenous fosfomycin is an effective treatment for hospitalized patients with complicated UTIs or kidney infection. In 2019, NIH/NIAID began conducting a Phase 1 clinical trial designed to assess the lung levels of fosfomycin to support its future development as a treatment for US patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (Revisiting Fosfomycin, a "Forgotten" Antibiotic, NCT03910673). ▪ NIH/NIAID-supported investigators have completed Phase 1 and Phase 2 clinical trials for the novel oral antibiotic zoliflodacin, which has shown promise as a treatment for uncomplicated GC (NCT03613649, NCT03404167, NCT02257918,

		Novel Antibiotic Shows Promise in Treatment of Uncomplicated Gonorrhea, Taylor 2018). In 2019, this product advanced to a global Phase 3 clinical trial to be conducted by the Global Antibiotic Research and Development Partnership (GARDP) (GARDP, NCT03959527). ○ Several companies have built on previous NIAID support to further develop and commercialize their products for Gram-negative infections: ▪ Following NIAID-supported preclinical development and early clinical testing, the novel beta-lactamase inhibitor VNRX-5133 (VenatoRx Pharmaceuticals, Inc.) combined with cefepime has progressed to advanced development. In 2019, BARDA and DTRA partnered with VenatoRx to advance the development of Cefepime/VNRX-5133 (now known as taniborbactam). In 2020, the GARDP announced a collaboration with VenatoRx to complete development of Cefepime/VNRX-5133. With support from BARDA and GARDP, VenatoRx is conducting a global Phase 3 trial for treatment of complicated UTIs with Cefepime/VNRX-5133 (NCT03840148). In addition, the company announced a license agreement in Asia in 2018. ○ NIAID supported preclinical development of the next generation polymyxin SPR206 (Spero Therapeutics, Inc.). Building on this support, the company conducted a Phase 1 clinical trial which found the drug to be well tolerated. DOD has also provided funding for nonclinical and clinical research to advance SPR206. SPR206 has been granted QIDP designation by the FDA for the treatment of cUTIs and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. The company announced a license agreement in Asia in 2019.
Within 5 years: CBDP/DTRA will complete pre-clinical testing of an additional antibiotic drug and will support clinical trials of two new products to treat infections with Select Agents.	Yes	• Per DTRA personnel in May 2021: ○ DTRA transitioned the drug omadacycline (NUZYRA) from nonclinical biodefense testing to Project BioShield, wherein the sponsor (Paratek) is seeking FDA approval for an anthrax indication with BARDA funding. ○ DTRA has established joint programs with BARDA to establish biodefense utility for advanced antibacterial candidates currently in clinical trials (oral tebipenem (Spero) and taniborbactam/cefepime (Venatorx). ○ DTRA will also be supporting an exploratory clinical trial for melioidosis in FY2022.
***Objective 4.4**:* Develop non-traditional therapeutics, vaccines, and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.		
Milestone	**Accomplished?**	**Comments**

Milestones: Therapeutics and strategies for use in humans	--	--
Within 1 year: NIH will fund new projects to support the discovery and development of new types of antibacterial products (e.g., monoclonal antibodies, vaccines, or microbiota-based therapeutics), as well as adjunctive therapies to restore the activity of existing antibiotic drugs.	Yes	• Per NIH personnel in April 2021: ○ NIAID had made multiple awards and issued several AMR-related initiatives focused on development of novel strategies to address AMR, including non-traditional and host-targeted therapeutics development, as well as research on systems biology, anti-virulence, immune-based therapies, adjunctive therapies and biofilm inhibitors. ○ NIAID provides preclinical service support to foster drug development, including in vitro and in vivo testing of new candidate therapeutics for MDR bacteria.
Within 1 year: DOD will implement laboratory use of new microfluidic technologies to detect antibodies that inhibit antibiotic-resistant bacteria.	Yes	• Per the NAP First 180 Days Report, as of November 2015: ○ DOD/JSTO had planned initiation of mechanistically novel therapies (source sensitive) for 2016. ○ DOD/Office of the Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs and JSTO continued evaluation of a previously developed drug product as part of a new combination therapy. • Per DOD personnel in April 2021, this work is being done, although remains in research use only (i.e., not in clinical use).
Within 1 year: DOD will award: • Two new contracts focused on development of non-traditional therapeutics that are less likely to lead to the development of resistance (e.g., immunomodulators, therapeutic antibodies, or host-directed therapies). • Two new contracts focused on evaluating drug combinations that may decrease the emergence of drug resistance.	Yes	• The GAO Report (2020) detailed DOD funding for research on treatments for antibiotic-resistant infections. Highlights included: ○ Since 2012, DTRA has awarded 21 projects to study treatments for antibiotic-resistant infections, totaling ~$178 million. ○ Since 2012, US Army Medical Research and Material Command has funded 50 projects to study treatments for AR infections, totaling $66.2 million. Projects study a range of product types, such as traditional antibiotics, bacteriophages, peptides, and others. ○ Since 2016, WRAIR has supported 16 projects (five intramural and 11 extramural) totaling ~$10 million. All of the projects are studying traditional drug candidates, and all but one target gram-negative bacteria. Two of the projects are conducted jointly, through an interagency agreement with NIH institutes. The institute also conducts a bacteriophage project in partnership with a private company, which, as of January 2019, had completed phase 1 clinical trials.

• Two new contracts to explore revitalization and/or reformulation of antibacterial drug candidates that have failed to enter preclinical or clinical development due to undesirable characteristics related to solubility, pharmacokinetics, or toxicity.		○ During FY2014 through FY201, DARPA, through its Pathogen Predators program, studied living bacteria that prey upon pathogenic Gram-negative bacteria through $17.1 million to four grantees. • Per DTRA personnel in May 2021: DTRA has funded three programs in innate immune regulators, all three of which are leveraging programs that are in various stages of advanced maturity. <u>Two new contracts focused on development of non-traditional therapeutics.</u> • As of November 2015, DOD/WRAIR continued antibacterial screening efforts to identify novel compounds with activity against resistant *Klebsiella* spp. or *Acinetobacter* spp. using both DOD/WRAIR assets for animal models and clinical isolates and non-DOD collaborations as source of potential compounds (NAP First 180 Days Report). • As reported in 2017, DOD's Defense Health Program MIDRP was funding novel therapeutics and delivery technology efforts, specifically those looking at inhibiting and dispersing biofilms of biofilms of infected wounds. Phage cocktails also were under development, with a recent successful clinical use by US Navy researchers in a resistant Gram-negative infection (NAP Progress Report: Years 1 and 2). • As of 2020, Navy Medical Research Center researchers were investigating several types of nontraditional products, such as bacteriophages and probiotics, in collaboration with DOD partners, academic researchers, and industry partners. The bacteriophage research was being conducted jointly with the WRAIR and a private company (GAO Report). • Per DTRA personnel in May 2021: DTRA has funded four nontraditional therapeutic antibacterial programs, discovering monoclonal antibodies, antimicrobial peptides, and capsule degrading enzymes. <u>Two new contracts focused on evaluating drug combinations.</u> • DOD/JSTO, in collaboration with US Army Medical Research Institute for Infectious Diseases (USAMRIID), expected to complete a systematic combinatorial evaluation for identifying pairing of FDA-approved drugs in new combinations in FY2016 (NAP First 180 Days Report). • Per DTRA personnel in May 2021: ○ DTRA/JSTO, in collaboration with USAMRIID, continues the program to identify novel combinations of FDA-approved drugs (and devices) that may be used to treat bacterial infections. To date, no promising synergistic combinations have advanced past murine proof-of-concept efficacy screening. USAMRIID did identify that the combination of dexamethasone along with beta-lactam antibiotics decreased the liability of these

		antibiotics in the treatment of plague; however, in light of the availability of newer generation antibiotics, this line of inquiry was paused. ○ DTRA/JSTO has identified a synergistic combination of ARV-1801 (sodium fusidate, not FDA-approved, Arrevus) and ceftazidime in inhibiting *B. pseudomallei* growth in vitro. This combination is being advanced into clinical trials for melioidosis in Thailand in FY2022. <u>Two new contracts to explore revitalization and/or reformulation of antibacterial drug candidates.</u> • As of November 2015, DOD had not yet identified second revitalization candidates, though "this is balanced by efforts to develop technologies for targeted delivery methods" (NAP First 180 Days Report). • DTRA has funded two programs to discover and advance novel formulation technologies to enhance standard of care or revitalize suboptimal antibiotics for treatment of biothreat pathogen infections.
Within 3 years: NIH, with guidance from FDA, will support development and evaluation of novel approaches for treatment of drug-resistant infections.	Yes	• Per NIH personnel in April 2021: ○ Non-traditional Approaches: ▪ NIH/NIAID also supports research on innovative alternatives to antibiotics. In 2016, NIAID awarded approximately $5 million in funding for 24 research projects seeking to develop non-traditional therapeutics for bacterial infections (RFA-AI-14-066). These awards include projects on microbiome-based approaches, and bacteriophages (viruses that can attack and destroy harmful bacteria), among other strategies. Starting in 2015, NIH entered an Interagency Agreement with FDA to address key regulatory considerations related to using bacteriophages for decolonization of vancomycin-resistant enterococci (VRE) and MRSA. To support development of bacteriophage therapies, FDA and NIH/NIAID co-hosted a workshop in July 2017, Bacteriophage Therapy: Scientific and Regulatory Issues Public Workshop. ○ New Therapeutic Candidates and Treatment Regimens: ▪ NIH/NIAID-supported scientists conducted Phase 1 clinical testing for an oral first-in-class antibiotic, CRS3123 (Crestone Inc.), intended to treat *C. difficile* (NCT02106338 or NCT01551004, Nayak 2017). Under a BAA contract award, NIH/NIAID plans to advance the novel therapeutic to a Phase 2 clinical trial. Crestone has been granted Fast Track and QIDP designations for CRS3123.

		▪ Investigators in NIH/NIAID's Centers of Excellence for Translational Research (CETR) program are helping to discover novel antimicrobial compounds, including a new class of antibiotics (known as malacidins) found in soil (Hover 2018). ▪ NIH/NIAID supported investigators have identified a promising combination therapy of Ceftazidime-Avibactam and Fosfomycin for the treatment of MDR *P. aeruginosa*. In both in vitro and mouse model studies, this antibiotic combination showed a significant decrease in the bacterial burden of MDR *P. aeruginosa* (Papp-Wallace 2019). ▪ The ARLG and other NIH-supported investigators are conducting clinical trials to determine optimal use of licensed antibiotics (e.g., duration, dosage, whether antibiotic treatment is required at all) for bacterial infections, including pediatric CAP, UTIs, and Gram-negative infections. NIH-supported scientists found that, in young children, shortened treatment for middle ear infection is less effective than the standard course (Hoberman 2016), and that in adults and children, two off-patent antibiotic treatments (clindamycin and trimethoprim–sulfamethoxazole) work very well against bacterial skin infections caused by community-associated MRSA (Miller 2015, Talan 2016, Talan 2016). In October 2020, another NIH/NIAID-supported research team announced that that short course (5-day) antibiotic treatment is superior to standard (10-day) treatment of CAP in children 6 months to 5 years of age. Both treatment strategies were effective in treating CAP (Childhood Pneumonia Study Shows Short-Course Antibiotics Superior to Standard of Care). ▪ In February 2018, NIAID funded seven projects under RFA-AI-16-081, Partnerships for the Development of Tools to Advance Therapeutic Discovery for Select Antimicrobial-Resistant Gram-Negative Bacteria (R01), which aimed to support the development of novel predictive assays, models and/or research tools based on penetration and efflux of small molecules to facilitate therapeutic discovery for CRE, MDR *Acinetobacter* and/or MDR *P. aeruginosa*. Additional details are available at: RFA-AI-16-081. Related to this topic, in February 2017, NIH and The Pew Charitable Trusts Antibiotics Innovation Program cosponsored a meeting, "Challenges in the Discovery of Gram-negative Antibacterials: The Entry & Efflux Problem."

		▪ Under the Omnibus BAA contract for FY2020, NIH/NIAID has funded five projects developing novel anti-microbial therapeutics, four of which are specifically targeted at Gram-negative bacteria (2019 NIAID Omnibus Broad Agency Announcement). ○ Preventive and Decolonization Strategies: ▪ Preventive strategies, such as vaccines, are important tools to complement therapeutic approaches and keep pace with the increasing threat of AMR: • NIH/NIAID is supporting early development of several vaccine candidates for *C. difficile* and *N. gonorrhoeae*. In addition, under the Omnibus BAA contract for the 2020 fiscal year, NIH/NIAID has funded two projects developing vaccines against pathogens associated with AMR (2019 NIAID Omnibus Broad Agency Announcement). • In 2019, NIH/NIAID established six Sexually Transmitted Infections (STIs) Cooperative Research Centers focused on developing vaccines to prevent syphilis, GC, and chlamydia. At the end of the program, each center is expected to identify at least one candidate vaccine ready for testing in clinical trials (NIH Awards Will Advance Development of Vaccines for Sexually Transmitted Infections). • In 2018, NIH/NIAID funded three projects for vaccine and immunoprophylactics (products that harness the immune system to prevent disease) targeting AMR Gram-negative bacteria in healthcare settings (RFA-AI-17-017). For example, one project takes a novel approach to vaccination against *P. aeruginosa* infection by targeting filamentous bacteriophages (Pf phages), which are expressed from the bacterial genome, and that enhance *P. aeruginosa* pathogenicity and contribute to antibiotic resistance. The investigators found that immunizing mice against Pf phages resulted in decreased incidence of infection with Pf phage-carrying *P. aeruginosa*. Additionally, they found that topical application of Pf phage-targeting antibodies on infected mouse wounds led to reduced *P. aeruginosa* infection. Preliminary results from this project suggest the development of a promising candidate vaccine against an AMR priority pathogen (Sweere 2019). • NIH/NIAID is also supporting research exploring monoclonal antibodies for prevention and treatment of bacterial infections. For example,

		NIH/NIAID scientists identified use of an antibody that recognizes ST258 capsule polysaccharide type 2 as a way to boost killing of *K. pneumoniae* bacteria by neutrophils in human blood *in vitro*. In addition, findings suggest the ST258 capsule polysaccharide is a viable vaccine target antigen (Kobayashi 2018, NIH Scientists Describe Potential Antibody Approach for Treating Multidrug-Resistant Klebsiella pneumoniae). The EVADE trial, partially conducted through the ARLG, is evaluating the safety of the experimental monoclonal antibody MEDI3902 and its ability to prevent pneumonia caused by *P. aeruginosa* in mechanically-ventilated patients. This trial was completed in 2019 (NCT02696902). • Immunotherapy for treating resistant bacteria and preventing disease is an innovative approach being advanced by NIH/NIAID scientists. A carbapenem-resistant *K. pneumoniae* strain classified as multi-locus sequence type 258 (ST258) is widespread in the US and is usually multidrug resistant. Thus, treatment of ST258 infections is often difficult. Use of an antibody that recognizes ST258 can boost killing of bacteria by neutrophils in human blood in vitro. NIH/NIAID investigators developed an ST258 pneumonia non-human primate model and successfully used an ST258 vaccine to moderate disease severity in these animals (Malachowa 2019). • NIH/NIAID investigators studying a process of bacterial communication, known as quorum-sensing, demonstrated that bacteria that are incapable of participating in deficient in a form of bacterial communication called quorum-sensing dysfunctional bacteria have a significant survival advantage in biofilm infections. This advantage arises from the ability of quorum-sensing deficient bacteria because they form dense and enlarged biofilms that provide resistance to phagocyte attacks. Their results link the benefit of quorum-sensing dysfunctional mutants in vivo to biofilm-mediated immune evasion and explain why quorum-sensing mutants are frequently isolated from biofilm-associated infections and provide guidance for the therapeutic application of quorum-sensing blockers (He 2019). ▪ In 2019, NIH/NIAID-supported researchers announced results from a large, randomized clinical trial that compared two infection control techniques for

		healthcare settings. These strategies were rapidly incorporated into practice within the network of US community hospitals where the trial took place. The trial evaluated whether daily bathing with chlorhexidine gluconate (CHG)—and in those patients with MRSA, adding the nasal antibiotic mupirocin—more effectively reduced hospital-acquired bacterial infections than bathing with ordinary soap and water. While no statistically significant difference between the two intervention groups was seen within the population overall, the researchers did find that one subset of patients—those with medical devices—experienced a substantial benefit if they received the CHG/mupirocin intervention. The ABATE (Active Bathing to Eliminate) Infection involved about 330,000 adult patients in non-intensive care units in the HCA Healthcare system. In 2020, NIH/NIAID funded the team to conduct a cluster-randomized trial looking at ways to reduce the use of unnecessary broad-spectrum antibiotics for abdominal or skin and soft tissue infections (Results of Trial to Stem Hospital-Acquired Bacterial Infections Published, NCT02063867, Huang 2019). AHRQ is developing a toolkit to help the field implement the findings of the ABATE Infection Trial. ▪ In collaboration with an extramural investigator, NIH/NHGRI intramural scientists are assessing the effects of the antiseptic CHG on human skin microbiomes. CHG bathing in the US is widely used for pre-operative purposes and daily ICU cleansing in response to studies and clinical trials demonstrating large reductions in infections and multidrug-resistant organisms. This broad and sustained use of CHG has raised concerns about unintended consequences to the skin microbiome. The team performed a pilot clinical study on residents in skilled nursing facilities with/without CHG to test the effect on the skin microbiome. 360 samples total from three body sites (axilla, inguinal crease, nares) at three time points of 40 subjects (20 using routine soap, 20 using CHG) were received, processed for DNA and sequenced. CHG decolonization arm samples have higher abundances of Enterobacteriaceae, in particular Proteus and Providencia, genera have been shown to be resistant to CHG.
Within 3 years: DOD will investigate genes encoding antibodies that target drug-resistant bacteria and might	Yes	• Per DOD personnel in April 2021: Work related to this milestone is being done on a regular basis; of note, WRAIR is involved with this work.

be used in immunoprophylactic treatments.		• Per DTRA personnel in May 2021: DTRA has four programs in discovery of monoclonal antibodies that may be used as prophylaxis, post-exposure prophylaxis, and/or treatment of infection with biothreat bacterial infections.
Within 5 years: NIH will support the identification of alternative dosing strategies (e.g., combination therapies and shortened durations) that improve treatment for two bacterial pathogens of public health concern.	Yes	• Per NIH personnel in April 2021: ○ NIH/NIAID supports research to identify new treatment strategies to optimize and preserve the use of currently available antibiotics for bacterial infections. Optimizing dosing levels, duration, route of administration, and use of combination drug therapy, according to current pharmacokinetic and pharmacodynamic principles, can suppress the emergence of resistance and minimize toxicity. ▪ In 2016, NIH/NIAID-supported scientists reported that, in young children, shortened treatment for middle ear infection is less effective than the standard course (Hoberman 2016). ○ NIH/NIAID-supported investigators are conducting clinical trials to: ▪ Compare a short course of therapy (5 days) to standard of care (10 days) in children with CAP (NIH/NIAID-funded ARLG SCOUT-CAP trial; NIAID-Sponsored Study to Assess Shorter-Duration Antibiotics in Children, NCT02891915) and UTIs (SCOUT; NCT01595529). In October 2020, researchers announced that the SCOUT-CAP study showed that short course (5-day) antibiotic treatment is superior to standard (10-day) treatment of CAP in children 6 months to 5 years of age. Both treatment strategies were effective in treating CAP (Childhood Pneumonia Study Shows Short-Course Antibiotics Superior to Standard of Care). ▪ Determine the utility of colistin for multi-drug resistant Gram-negative bacterial infections when used alone, or in combination with a carbapenem (OVERCOME trial, NCT01597973). ▪ Evaluate the safety, tolerability, and pharmacokinetics of a novel combination therapy (ceftazidime-avibactam and aztreonam) for carbapenem-resistant Enterobacteriaceae (ARLG COMBINE trial, NCT03978091). ▪ Examine the PK and pharmacodynamics of intravenous minocycline in critically ill patients with Gram-negative infections in the ICU. This trial will help inform how to use this new formulation of an older drug (ARLG ACUMIN trial, NCT03369951). ○ In an NIH/NIAID-funded study, researchers evaluated an algorithm to identify patients with Staphylococcal bacteremia who can be treated safely with shorter courses of therapy. The study found that use of the algorithm was associated with significant reductions in duration

		of antibiotic therapy and a noninferior rate of clinical success in patients with simple or uncomplicated bacteremia (Holland 2018).
Within 5 years: NIH will launch clinical trials for two new products to treat or prevent high-priority bacterial pathogens and transition them to ASPR/BARDA or pharmaceutical companies for advanced development.	Yes	• Per NIH personnel in April 2021: ○ NIH/NIAID is advancing vaccine candidates and other novel preventive strategies to prevent bacterial and antibiotic-resistant infections. For example: ▪ NIH/NIAID-supported investigators have completed a Phase 1 clinical trial evaluating the safety and immunogenicity of two vaccine candidates for *Shigella sonnei* (NCT01336699, Frenck 2018) and in collaboration with WRAIR, is conducting a Phase 2 trial to further investigate one of these candidates in a human infection challenge model (NCT04242264). ▪ NIAID is planning to conduct a Phase 2 clinical trial to examine whether Bexsero, a vaccine licensed to prevent meningitis caused by *N. meningitidis* Type B, can also protect against infection with *N. gonorrhoeae*. The study is expected to begin enrolling approximately 2,000 healthy adults at risk for GC in late 2020. ▪ For more than 20 years, NIH/NIAID and NIH/National Institute of Diabetes and Digestive and Kidney Diseases have supported fundamental research underpinning the development of a novel UTI vaccine candidate. Scientists have built upon this work to develop an investigational vaccine known as the FimCH vaccine. The biotechnology company Sequoia Vaccines funded a Phase 1A/B trial which found that the vaccine reduced recurrent UTIs. Subsequently, the FDA granted compassionate use authorization for the FimCH vaccine among patients suffering from recurrent UTIs not responding to the standard of care. ▪ The EVADE trial, partially conducted through the ARLG, is evaluating the safety of the experimental monoclonal antibody MEDI3902 and its ability to prevent pneumonia caused by *P. aeruginosa* in mechanically-ventilated patients. This trial was completed in 2019 (NCT02696902). ○ NIH/NIAID is advancing research on non-traditional therapeutic approaches to combat AMR, including bacteriophage, live microbiome-based products and novel therapeutic candidates that may provide an alternative to antibiotics. ▪ NIH/NIAID is funding a clinical trial to evaluate a bacteriophage-based approach for managing *Shigella* infections and the ARLG is planning the Phase 2 PHAGE study to test the safety and microbiological activity of bacteriophage treatment in cystic fibrosis patients with *P. aeruginosa* infections.

		▪ As of September 2020, there are two microbiome-based projects in CARB-X, including one graduate. NIH/NIAID contributed to both projects by providing subject matter expertise. ○ Since 2014, NIAID has supported development of novel small molecule candidates (known as mannosides) to treat and prevent UTIs. Instead of killing bacteria, mannosides prevent them from being able to stick to the walls of the bladder, thus allowing the body to naturally eliminate the infection. In 2016, the company (Fimbrion Therapeutics, Inc.) signed a collaboration agreement with GlaxoSmithKline to further develop the mannoside technology; the companies have identified an orally available candidate for potential clinical testing. In September 2020, the product advanced to become part of the CARB-X portfolio.
Within 5 years: Scientists at the Walter Reed Army Institute of Research will transition one antibiotic drug candidate to advanced development.	Yes	• Since 2016, WRAIR has supported 16 projects (five intramural and 11 extramural) totaling ~$10 million. All of the projects are studying traditional drug candidates, and all but one target Gram-negative bacteria. Two of the projects are conducted jointly, through an interagency agreement with NIH institutes. The institute also conducts a bacteriophage project in partnership with a private company, which, as of January 2019, had completed phase 1 clinical trials (GAO Report). • Per DOD personnel in April 2021: This is an aspirational goal, and the candidate, although not yet in advanced development, is moving through the development process. • Per DTRA personnel in May 2021, DTRA/JSTO transitioned the following additional antibiotic candidates into advanced development between 2014-20: ○ Gepotidacin (GSK) ○ Omadacycline (Paratek) ○ Oral tebipenem (Spero) ○ Taniborbactam/cefepime (Venatorx)
Milestones: Therapeutics and strategies for use in animals	--	--
Within 1 year: USDA, in collaboration with NIH, FDA, and the agricultural industry, will develop a research and development strategy to promote understanding of antibiotic-resistance and the creation of	Yes	• Per the NAP First 180 Days Report, as of November 2015: ○ USDA and HHS were evaluating options to address developing a research and development (R&D) strategy. For example, USDA and FDA CVM had discussed collaborating on evaluating ways to incentivize development of alternative therapeutics to address disease. ○ In September 2015, USDA ARS held an internal workshop on "Antibiotic-resistance in Agroecosystems." The objectives of the workshop included: identifying and prioritizing

alternatives to (or improved uses of) antibiotics in food animals.		research concerns and gaps; and developing research plans, milestones, and projected publications. ○ USDA ARS was organizing a workshop for FY2016 on alternatives to antibiotics in animal production. • As of 2017, USDA ARS was implementing alternatives-to-antibiotics R&D projects, including products that could reduce the use of medically important antibiotics through vaccines, bacterial-derived products, immune-related products, phytochemicals, and other chemicals and enzymes (NAP Progress Report: Years 1 and 2). • Per USDA personnel in April 2021: USDA develops action plans which are essentially strategy documents. See the Animal Health, Animal Production, and Food Safety action plans. • Per NIH personnel in April 2021: US government agencies worked collaboratively to address Goal 4 of the CARB National Action Plan regarding public and private sector engagement on strategies to advance collaborative research. In July 2016, the NIH hosted a roundtable discussion with experts from academics, private sectors, and other federal agency partners (CDC, DOD, FDA, and USDA) to assess steps that can be taken to address AMR. In July 2016, USDA hosted a stakeholder webinar with FDA, NIH, and private-sector partners to discuss, prioritize, and develop strategies to help meet the most pressing animal health research education and extension needs related to AMR. NIH/NIAID and FDA CBER organized a joint workshop, Bacteriophage Therapy: Scientific and Regulatory Issues, that was held in July 2017.
Within 1 year: USDA will solicit proposals that comprehensively develop research and outreach programs targeting development of novel alternatives to antibiotics for use in animals.	Yes	• As of 2017, USDA ARS had initiated two Cooperative Research and Development Agreements (CRADAs) to enable the development, registration, and commercialization of alternatives to antibiotics: ○ USDA ARS collaborated with university and public health partners on the Comprehensive Antibiotic Resistance Database (CARD) and on the development of a One Health antimicrobial stewardship program in Washington State (NAP Progress Report: Years 1 and 2). • In FY2015, USDA awarded $3.4 million through its Agricultural and Food Research Initiative competitive grants program (NAP Progress Report: Years 1 and 2). • In May 2016, USDA awarded $5.7 million for projects to develop novel systems approaches to investigate the ecology of antibiotic resistance; for alternative practices that mitigate emergence, spread, or persistence of resistant pathogens within the agricultural ecosystems; to identify critical control points for mitigating AMR pre- and post-harvest; to design innovative training, education, and outreach resources for users across the food chain; and to design studies to evaluate impacts (NAP Progress Report: Years 1 and 2).

		• In FY2016, USDA NIFA funded six projects that addressed alternatives to antibiotics, including infection prevention and immune modulation in animals (NAP Progress Report: Years 1 and 2). • In 2016 and 2017, USDA ARS funded 11 alternative to antibiotic intramural research proposals (NAP Progress Report: Years 1 and 2).
Within 3 years: USDA-funded research teams will develop three candidate alternatives to antibiotics used for promoting growth in animals (e.g., drugs or probiotic treatments) that do not disrupt the normal flora of the gut of food animals and enhance animal immune systems and resistance to disease.	Yes	• The USDA ARS Animal Biosciences & Biotechnology Laboratory initiated several research projects: ○ "Alternatives to antibiotics: development novel strategies to improve animal welfare and production efficiency in swine and dairy" began in July 2017. One objective is to develop alternative strategies to replace/reduce the use of conventional antibiotics for improved growth, animal health, and product safety. This includes developing alternative antimicrobials to treat/prevent disease in swine and dairy (USDA ARS #433349). ○ "Novel integrated nutrition and health strategies to improve production efficiencies in poultry" began in September 2017. The focus is to minimize challenges to gut health that compromise growth with an objective specific to alternatives of antimicrobials to maintain efficient growth in chickens (USDA ARS #433683). ○ "Effects of the antioxidant environment of the gut lumen on growth, metabolite and microbial composition in broiler chickens" began in July 2019. The overarching goal is to develop and optimize management strategies that replace traditional antimicrobial growth promoters to control low level inflammation in the intestinal tract of domestic farm animals to preserve efficient nutrient absorption for growth and well-being (USDA ARS #434530). • The USDA ARS Bacterial Epidemiology & Antimicrobial Resistance Research team initiated the research project "Monitoring and molecular characterization of antimicrobial resistance in foodborne bacteria" in March 2016. The project is focused on high-priority bacteria (e.g., *Salmonella, Campylobacter*) and includes applying the intervention strategy approach and comparing the microbial quality of the treated poultry against control product (USDA ARS #430182). • The 2016-2018 USDA ARS AMR and ATA Accomplishment Summary noted the following developments/accomplishments in animal health and production: ○ Antibiotic growth promoters alter the chicken intestinal metabolome; results provide the framework for future studies to identify natural antibiotic alternatives to improve poultry growth performance. ○ Discovered an antibiotic alternative for newly weaned and transported piglets. ○ Identified a new natural antibiotic alternative for swine.

		○ Novel prebiotics and probiotics reduce stress/pathogen-induced mortality and production losses in chickens. • Per USDA ARS personnel in April 2021: The process for developing alternatives to antibiotics is multi-stage, including discovery, development, and technology transfer; this process takes time and much of this work is ongoing.
Within 5 years: USDA-funded research teams will develop non-traditional alternatives to antibiotics that can be used (alone or in combination with existing antibiotics) to treat at least three priority bacterial pathogens of livestock and poultry.	Yes	• The USDA ARS Animal Biosciences & Biotechnology Laboratory initiated the following research projects: ○ "Developing alternatives to drug strategies to reduce economic losses due to enteric diseases in poultry" began in March 2017. One objective is to investigate effects of different antibiotic alternatives on coccidian parasites. The approach includes evaluating new antibiotic alternatives for chicken cell line growth promotion and innate immunity-enhancing potential using ARS disease models for enteric pathogens of poultry (USDA ARS #432520). ○ "Improving bovine production efficiency through reproductive biotechnologies" began in June 2020. One objective is to investigate plant-derived antimicrobials as an alternative to antibiotics in cell culture for contamination eradication and prevention/treatment of mycoplasma-induced bovine diseases (USDA ARS #437961). • The 2016-2018 USDA ARS AMR and ATA Accomplishment Summary noted the following developments/accomplishments in animal health and production and food safety: ○ A subunit vaccine against *Streptococcus suis* in swine ○ Use of *Lactobacillus acidophilus* fermentation products as an alternative to subtherapeutic antibiotic use in nursery pig diets ○ Discovered an antibiotic alternative for newly weaned and transported piglets ○ Identified a new natural antibiotic alternative for swine (*Nigella sativa*) ○ Evaluation of the effects of antibiotic alternatives on chicken gut microbiome using comparative metagenomic analyses ○ Novel immunomodulatory host-derived antimicrobial peptides as antibiotic alternatives to mitigate enteric pathogen-mediated gut damage in commercial broiler chickens ○ Nanoparticles improve vaccines against coccidiosis ○ Use of the biotherapeutic G-CSF as a prophylactic and alternative to antibiotics to prevent postweaning *S. suis* in swine ○ Reduction of *Salmonella* and *E. coli* in beef cattle using sodium chlorate as an alternative to antibiotics

		• Per the Progress Report: Year 4, in FY2018, seven patent applications were filed and patents were awarded for technologies to combat AMR. • Per the Progress Report: Year 4, in 2019 there were 25 intramural research projects that perform AMR and antibiotic alternatives research and 13 one-year mini-proposals that were funded through an internal funding call to address emergent questions within AMR and alternatives to antibiotics (ATA) research.

Within 5 years:
USDA-supported researchers will study genes that confer resistance to high-priority agricultural animal diseases (e.g., Bovine Respiratory Disease Complex) to facilitate genetic selection for animals with less susceptibility to infections whose treatments typically require significant use of antibiotics.
	Yes	• The USDA ARS Animal Biosciences & Biotechnology Laboratory initiated the research project "Alternatives to antibiotics: development novel strategies to improve animal welfare and production efficiency in swine and dairy" in July 2017. One study objective is to develop and/or utilize molecular tools to understand the role of genes relevant to health, growth, or intestinal function in swine and dairy with the goal of identifying targets for alternatives to antibiotic growth promotants. This includes targeting specific bovine genes for editing that are relevant to health and milk production/quality (USDA ARS #433349).
		• Per the Progress Report: Year 4, in 2019 there were 25 intramural research projects that perform AMR and ATA research and 13 one-year mini-proposals that were funded through an internal funding call to address emergent questions within AMR and ATA research.
		• The 2016-2018 USDA ARS AMR and ATA Accomplishment Summary noted the following developments/accomplishments in animal health and production and food safety:
		  ○ Genetic selection for resistance to foodborne pathogens in poultry
		  ○ Host genetic background influence on early molecular signatures of vaccine responsiveness

Objective 4.5: Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates and promising vaccines that can reduce the need to treat bacterial infections.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: NIH and ASPR/BARDA will implement a strategy for assisting research partners who are developing novel classes of antibacterial drugs in fulfilling the requirements of FDA IND applications.	Yes	• In 2016-17, the Powered by CARB-X portfolio had awarded funds to 18 innovative projects in six countries targeting the most drug-resistant forms of Gram-negative bacteria (2016 CARB-X Annual Report). • Per NIH personnel in April 2021: CARB-X is a non-profit partnership launched by BARDA, the Wellcome Trust, and NIH/NIAID. CARB-X is headquartered at the Boston University School of Law and funders currently include BARDA, Wellcome Trust, the UK Government's Global Antimicrobial Resistance Innovation Fund (GAMRIF), the German Government, and BMGF, with in-kind support from NIAID. Other partners include RTI International, California Life Sciences Institute, DTRA, Massachusetts Biotechnology Council (MassBio) and the Broad Institute of MIT and Harvard.

		• In March 2017, CARB-X announced awards to 11 biotech companies and research teams for drug discovery and development (CARB-X Overview, CARB-X News 2017). • Per NIH personnel in April 2021: Additional awards were made in subsequent years and as of September 2020, a total of 69 companies/candidates are supported by CARB-X.
Within 1 year: NIH and ASPR/BARDA will meet on a semi-annual basis with investigators who participate in the Antibiotic Resistance Biopharmaceutical Incubator (see Objective 4.7) to evaluate progress in providing technical resources for *in vitro* and *in vivo* screening of resistant pathogens of public health concern.	Yes	• CARB-X is governed by the Joint Oversight Committee (JOC), which acts as the board of directors with full oversight for CARB-X operational and financial activities, ensuring the highest scientific and ethical standards. The JOC meets quarterly to assess overall performance (CARB-X Joint Oversight Committee). • CARB-X infrastructure includes company support teams (CSTs) that meet with investigators quarterly to assess progress and provide technical assistance (The CARB-X Process). • Per NIH personnel in April 2021: Once CARB-X was established ahead of schedule, this metric was achieved.

Within 1 year:
Agencies with existing capabilities will ensure that genomic sequence data, proteomic data, and other related AR data sets generated with US Government funding will be made publically available in a manner consistent with protecting personally identifiable information.
	Yes	• The NDARO, which was developed in 2015 and is maintained by NCBI, is a collaborative, cross-agency, centralized hub for researchers to access AMR genomic data to facilitate real-time surveillance of pathogenic organisms.
		• Per NIH personnel in April 2021: Over the past few years, NIH has led an effort to enhance rigor and reproducibility in biomedical research. This effort included updates to peer review criteria to enhance reproducibility of research findings through increased scientific rigor and transparency. In addition, NIH convened journal editors to release a consensus statement on a set of principles to ensure published studies are reproducible, robust, and transparent (NIH Rigor and Reproducibility).
		• Per CDC personnel in April 2021: Federal agencies released several new open antibiotic resistance data tools, including interactive and customizable maps and tables showing antibiotic resistance patterns, to make it easier and faster for the public to find out how antibiotic resistance has changed over time.
		  ○ CDC's Antibiotic Resistance Patient Safety Atlas provides interactive data on antibiotic use and healthcare-associated infections caused by AR bacteria.
		  ○ CDC's NARMS Now: Human Data provides interactive AR data on bacteria transmitted commonly through food, and will soon include multi-drug resistant combinations.
		  ○ FDA, USDA, and CDC's NARMS Now: Integrated Data provides enteric bacterial isolate-level data from humans, retail meats, and food animals.

		○ CDC and FDA launched the CDC & FDA Antibiotic Resistance Isolate Bank, a centralized, curated repository of nearly 500 unique isolates pulled from CDC's repository of AR isolates; this repository includes more than 450,000 AR isolates and more than 18,000 characterized genomes.
Within 1 year: DOD will develop three specimen panels as a critical resource for evaluating the efficacy of novel antibiotic therapies against multidrug-resistant Select Agent. The panels will include: (1) resistant bacterial isolates suitable for work in lower-level (BSL-2) biocontainment laboratories, (2) multidrug resistant strains of Select Agents, and (3) attenuated strains of multidrug resistant Select Agents. The panels will be maintained within DOD and will be available through the Select Agent Core Antibiotic Screening Program.	Yes	• Per the NAP First 180 Days Report, as of November 2015, DOD had initiated efforts to produce panels of MDR non-bacterial select agent surrogates of bio-warfare agents, including comprehensive molecular characterization. Work was to continue in 2016 and be applied to MDR clinical panels in-house. Completing clinical trials of two new products to treat infections with resistant Select Agents within five years was noted as subject to the availability of funds. • Per DTRA personnel in May 2021: DTRA/JSTO has generated at USAMRIID surrogate panels of: (1) resistant bacterial isolates suitable for work in lower-level (biosafety level 2 [BSL-2]) biocontainment laboratories, and (2) attenuated strains of multidrug-resistant Select Agents. In vitro screening against these strains is available to partners through the Core Antibiotic Screening Program. MDR strains of Select Agents remains precious, with one strain available at a DOD partner laboratory of a cipro-resistant anthrax and several strains of standard-of-care resistant *B. pseudomallei*. • Per DOD personnel in April 2021, this milestone has been accomplished.
Within 3 years: NIH and ASPR/BARDA will identify at least twelve candidate products for preclinical development support and support three candidate products from preclinical development through IND submission (see also Objective 4.4).	Yes	• As of October 2018 (NAP Progress Report: Year 3), CARB-X was supporting research and development of 45 promising antibacterial products, eight of which had advanced to phase 3 clinical development. • In August 2017, Vabomere (a BARDA-supported antibiotic from the Medicines Company) was approved by the FDA for treatment of complicated UTIs (NAP Progress Report: Year 3). • In June 2018, the FDA approved ZEMDRI (Plazomicin), also supported by BARDA, for treatment of UTIs caused by drug-resistant bacteria (NAP Progress Report: Year 3). • In August 2018, the FDA approved XERAVA (Eravacycline), also supported by BARDA, for treatment of complicated intra-abdominal infections caused by resistant bacteria (NAP Progress Report: Year 4). • Per NIH personnel in April 2021:

		○ NIAID provides preclinical service support to fill gaps in the product development pathway, including in vitro and in vivo testing of new candidate therapeutics for MDR bacteria (Resources for Researchers). Since the launch of the CARB National Action Plan in 2015, NIAID has provided preclinical services for numerous products, including novel antibiotic candidates; vaccine candidates for AMR infections; non-traditional antibiotic products, such as bacteriophage; and compounds to be used in conjunction with existing antibiotics to restore their effectiveness. NIAID also tests new candidate therapeutics in standard mouse models of bacterial thigh and lung infections, which can provide initial in vivo indications of efficacy, as well as in more detailed models of bacterial infection, which can provide additional data on a candidate's performance. These projects complement numerous relevant projects that were begun in previous fiscal years. ○ In 2016, NIAID made five awards for the preclinical development of new antibacterial products under RFA-AI-15-024, Partnerships for the Development of Host-Targeted Therapeutics to Limit Antimicrobial Resistance. The projects are focused on development of candidate therapeutics targeting human functions that facilitate infection, replication, virulence, proliferation and/or pathogenesis of select bacterial pathogens for which drug resistance poses a significant public health concern. In June 2017, NIH/NIAID awarded six projects for preclinical development of therapeutics and vaccines addressing AMR threats (RFA-AI-16-034). These projects include immune-based therapeutics (for *C. difficile* and MDR *N. gonorrhoeae*), novel antibiotics (for MDR *N. gonorrhoeae,* Gram-negative bacteria, and broad-spectrum antibacterials), and a vaccine candidate (for *Shigella*/enterotoxigenic *E. coli*). Results from this award include the development of a vaccine candidate for *N. gonorrhoeae* (Gulati 2019).
Within 5 years: All agencies will ensure that genomic sequence data, proteomic data, and other related AR data sets generated with US Government funding will be made publicly available in a manner consistent with protecting personally identifiable information.	Yes	• The NDARO, which was developed in 2015 and is maintained by NCBI, is a collaborative, cross-agency, centralized hub for researchers to access AMR genomic data to facilitate real-time surveillance of pathogenic organisms. • Per NIH personnel in April 2021: NIH/NIAID rapidly releases AR data sets into publicly accessible and searchable databases developed by NIH/NCBI (e.g., GenBank and the National Database of Antibiotic Resistant Organisms) and the NIH/NIAID-funded Bioinformatics Resource Center. Clinical metadata, genomic, or other data sets, or a subset of the clinical and other metadata that may potentially identify human subjects of samples shall not be released in openly accessible public databases. • Per CDC personnel in April 2021:

		○ CDC is supporting capacity in 44 states to implement WGS of *Salmonella* and other enteric pathogens, and all states had this testing capacity by summer 2018. States are increasingly submitting representative isolates from foodborne outbreaks to CDC-NARMS, now supporting investigations of more than 150 foodborne disease clusters per year. ○ When PulseNet identifies a multistate outbreak, these sequences allow CDC to quickly analyze isolates and report on susceptibility. These foundational tools will ensure progress towards decreasing the time to detect and characterize resistant pathogens. CDC has sequenced over 40,000 isolates, including resistant pathogens causing healthcare-associated infections and resistant enteric pathogens *Salmonella, Shigella, Campylobacter*, and *E. coli* O157, and deposited those whole genome sequences in NLM/NCBI for public access. ○ CDC has also made significant progress updating the US domestic TB surveillance system with molecular drug susceptibility testing reporting and developing electronic reporting between state surveillance systems and CDC labs. Clinical service is being transitioned from conventional to next generation sequencing methods. More than 1,200 isolates of *M. tuberculosis* have undergone WGS to evaluate resistance mechanisms and microevolution during TB treatment. CDC has identified new mutations that confer resistance to isoniazid that will improve the accuracy of rapid molecular tests for the identification of resistance. These activities support strategies and goals under both the CARB National Action Plan and the National Action Plan for Combating MDR-TB. ○ Sequencing data from these various programs are publicly available through the NCBI database.
***Objective 4.6**:* Enhance opportunities for public-private partnerships to accelerate research on new antibiotics and other tools to combat resistant bacteria.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: The HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) will ensure coordination with the US Task Force for Combating Antibiotic-Resistant Bacteria in promoting public-private partnerships to develop new and next-generation	Yes	• Per the NAP First 180 Days Report (November 2015), the PHEMCE Integrated Product Team (IPT) on Antimicrobials was reconstituted as the Antimicrobial Resistance IPT to address the problem of AMR more broadly, to include non-bio threat pathogens of serious or urgent concern as designated by CDC. • Per the PHEMCE's Multiyear Budget for Fiscal Years 2017-2021, investments in broad spectrum antimicrobials to address gaps in antimicrobial needs for threats caused by gram negative bacteria were consistent with the objectives National Action Plan.

countermeasures to target antibiotic-resistant bacteria that present a serious or urgent threat to public health.		
Within 1 year: ASPR/BARDA will create at least one additional portfolio partnership with a pharmaceutical or biotechnology company to accelerate development of antibacterial drugs.	Yes	• As outlined in the NAP Progress Report: Years 1 and 2, BARDA awarded portfolio partnerships to Roche, the Medicines Company, and Pfizer for the clinical stage development of candidate antibiotics and diagnostics.
Within 3 years: At least two antibiotic drugs developed by portfolio partners for treatment of an urgent or serious pathogen will enter Phase III clinical evaluation.	Yes	• As of October 2018 (NAP Progress Report: Year 3), CARB-X was supporting research and development of 45 promising antibacterial products, eight of which had advanced to phase 3 clinical development.
Within 5 years: IND applications for at least two additional antibiotic drugs developed by portfolio partners will be submitted for FDA approval.	Yes	• In August 2017, VABOMERE (a BARDA-supported antibiotic from the Medicines Company) was approved by the FDA for treatment of complicated UTIs (NAP Progress Report: Year 3). • In June 2018, the FDA approved ZEMDRI (plazomicin), also supported by BARDA, for treatment of UTIs caused by drug-resistant bacteria (NAP Progress Report: Year 3). • In August 2018, the FDA approved XERAVA (eravacycline), also supported by BARDA, for treatment of complicated intra-abdominal infections caused by resistant bacteria (NAP Progress Report: Year 4). • Per NIH personnel in April 2021: NIH/NIAID supports studies that generate data required for IND submissions and has facilitated IND applications for multiple novel antibiotic candidates, including intravenous and oral formulations of the novel broad-spectrum tetracycline TP-271, broad-spectrum beta-lactamase inhibitors VNRX-5133 (administered intravenously) and VNRX-7145 (orally bioavailable), novel next generation polymyxin SPR206 (with broad Gram-negative antibacterial activity), and novel oral first-in-class antibiotic, GLS362E, to treat *C. difficile* infection.
Objective 4.7*:* Create a biopharmaceutical incubator – a consortium of academic, biotechnology and pharmaceutical industry partners – to promote innovation and increase the number of antibiotics in the drug-development pipeline.		
Milestone	**Accomplished?**	**Comments**

Within 1 year: ASPR/BARDA and NIH will work with a consortium of industry partners to develop a strategy for establishing the Antibiotic Resistance Biopharmaceutical Incubator (ARBI).	Yes	• Per NIH personnel in April 2021: ASPR/BARDA and NIAID completed market research in FY2015 to inform development of a strategy for establishing the ARBI. • In July 2016, BARDA launched CARB-X, which is a 5-year $450 million partnership between BARDA, NIH, the Wellcome Trust, the UK Government and the BMGF. ” (CARB-X Overview). As of this report, the German Government is also a funding partner.
Within 3 years: The ARBI will be operational, with technical services in place to facilitate toxicology studies, animal challenge studies, and other activities needed to accelerate drug development.	Yes	• During the first two years of operations, the CARB-X portfolio had expanded to include 33 antibacterial products, including antibacterial drugs, vaccines, diagnostics and non-traditional products, including 10 new antibiotics classes. For every $1 CARB-X has invested in early development and Phase 1 clinical trials, follow-on private capital has invested $7, for a total of $548M. Since the inception of the program, NIH/NIAID has provided technical support and preclinical drug development services to more than half of CARB-X awardees to further advance the development of new products (NAP Progress Report: Year 3). • Per NIH personnel in April 2021: Support continues for CARB-X, established by NIH/NIAID and BARDA in 2016 through a cooperative agreement with Boston University. CARB-X expanded in 2018, when the UK Government and BMGF joined the effort with a combined $50 million commitment. CARB-X is now a $500 million five-year public private partnership funded by BARDA, NIH/NIAID, Wellcome Trust, the UK Government, the German Government, and BMGF. CARB-X aims to accelerate global antibacterial innovation and transition antibacterial products into clinical development. (as of September 2020, Resources for Researchers). NIH/NIAID’s historical support has helped small companies strengthen their product development skills, including growing and advancing their portfolios of antibacterial products. The full CARB-X portfolio is available [online].
On an annual basis (after the ARBI is operational [which is to happen within 3 years]): ASPR/BARDA and NIH will assess progress in meeting ARBI’s five-year goals: identifying at least five targets for novel therapeutics, generating *in vivo* data to validate at least three of these targets, generating at least three	Yes	• The CARB-X JOC includes representatives from BARDA and NIH (CARB-X Joint Oversight Committee). • CARB-X has produced annual progress reports since 2016, which can be accessed on the CARB-X website (CARB-X Annual Reports). • Per NIH personnel in April 2021: Since the inception of the CARB-X program, NIH/NIAID has provided technical support and preclinical drug development services (Resources for Researchers) to approximately 50% of CARB-X awardees to further advance the development of new antibacterial products (as of September 2020), including five products that graduated or advanced to Phase 1 clinical trials. These services fill critical gaps for researchers working toward product development. For example, NIH/NIAID makes available: laboratory tests of candidate

antibacterial drug candidates, and transitioning at least two of these candidates from preclinical testing to submission of an FDA IND application to begin clinical trials.		products for antimicrobial activity, animal models of infection, and manufacturing of candidate products to enable early-stage clinical testing.

GOAL 5: IMPROVICE INTERNATIONAL COLLABORATION AND CAPACITIES FOR ANTIBIOTIC-RESISTANCE PREVENTION, SURVEILLANCE, CONTROL, AND ANTIBIOTIC RESEARCH AND DEVELOPMENT.		
Objective 5.1: Promote laboratory capability to identify at least three of the seven WHO priority antimicrobial resistant (AMR) pathogens using standardized, reliable detection assays.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: CDC and the US Agency for International Development (USAID) will work with ministries of health in at least twelve to fifteen countries to complete laboratory proficiency assessments, and will assess expansion of bilateral relationships to additional countries.	Yes	• The Global Health Security Agenda (GHSA) was developed in 2014. In the first 5 years, 11 of the participating countries demonstrated successful detection and reporting of antimicrobial resistant pathogens in the last 12 months (i.e., as of 2019) (Key Achievements in 5 years of GHSA). • Through the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), CDC and DOD have worked with the EU, Canada, and Norway to harmonize surveillance practices. The US and EU have made significant progress toward harmonizing lab definitions for detecting AMR, including colistin definitions for resistant Gram-negative bacteria like *E. coli*. These efforts will help the US and EU determine when bacteria are resistant to antibiotics, thus providing opportunities to enhance infection prevention and control to prevent the spread of resistant infections. • Both CDC and USAID are involved in the GHSA. Through the GHSA AMR Action Package, self-assessments of laboratory networks and AMR surveillance have been completed in all 17 GHSA Phase One countries, and country-specific work plans have been generated to assist the implementation of surveillance. Through multi-lateral collaboration, including global health security work, CDC assisted ministry of health partners with the development, initiation, or implementation of national action plans and surveillance networks in India, Vietnam, Thailand, Senegal, Georgia, Tanzania, Ethiopia, and Kenya. Based on laboratory assessments completed during FY2016, additional support for laboratory strengthening in these countries and additional GHSA countries will provide health ministries with improved AMR data to inform policy (NAP Progress Report: Years 1 and 2). • Per USAID personnel in April 2021: Through the US engagement in the GHSA, USAID provided support to 15 countries to strengthen veterinary laboratory AMR surveillance.

Within 1 year:
DOD will work with international partner laboratories to identify and enhance local proficiency and capabilities and will conduct assessments on an annual basis.
	Yes	• As of November 2015, DOD/MRSN was collaborating with Israel for advanced pathogen characterization and bioinformatics sequencing pipeline development, as well as assessing and assisting with outbreak response in Kenya, Uganda, Peru, Honduras, and Thailand (NAP First 180 Days Report).
		• As of 2017, the MRSN at the WRAIR remained as the central focus for international DOD surveillance efforts, in collaboration with the Armed Forces Health Surveillance Branch-Global Emerging Infections Surveillance (AFHSB-GEIS) (NAP Progress Report: Years 1 and 2).
		  ○ Per the NAP Progress Report: Years 1 and 2, additional collaborations as of 2017 included:
		  ▪ The GEIS network included Peru, Egypt, Kenya, Uganda, Ghana, Liberia, Philippines, Cambodia, Nepal, and Europe.
		  ▪ The Israeli Defense Force, Kenya, Thailand, and Honduras.
		  ▪ JMI laboratories/SENTRY Program, which receives isolates from more than 50 countries.
		  ▪ The Army Pharmacovigilance Center and Navy/Marine Corps Epi-data Center, as members of the charted ASWG (the coordinating body for implementation of the DOD antimicrobial stewardship program).
		• As of 2018, ACESO had promoted microbiology infrastructure and capacity in Ghana by supporting the maintenance and purchase of equipment. Additional on-site specimen laboratory testing protocols, including rapid diagnostic assays, had been trained-on and deployed in Ghana. (NAP Progress Report: Year 3).
		• As of 2018, ACESO supported a collaboration between the American Society for Microbiology (ASM) and West African partners to validate chromogenic media approaches for bacterial identification that eliminated the need for sheep's blood, streamlined the identification process, and reduced overall cost (NAP Progress Report: Year 3).

Within 3 years: CDC and USAID will provide technical assistance to foreign ministries of health on developing national plans for strengthening laboratory-based surveillance for antimicrobial resistance, and will complete assessments of	Yes	• Through the GHSA AMR Action Package, self-assessments of laboratory networks and AMR surveillance have been completed in all 17 GHSA Phase One countries, and country-specific work plans have been generated to assist the implementation of surveillance (NAP Progress Report: Years 1 and 2). • Through multi-lateral collaboration, including global health security work, CDC assisted ministry of health partners with the development, initiation, or implementation of national action plans and surveillance networks in India, Vietnam, Thailand, Senegal, Georgia, Tanzania, Ethiopia, and Kenya. Based on laboratory assessments completed during FY 2016, additional support for

laboratory capacity in additional counties.		laboratory strengthening in these countries and additional GHSA countries will provide health ministries with improved AMR data to inform policy (NAP Progress Report: Years 1 and 2). • CDC, both through engagement with the GHSA and through the Antibiotic Resistance Solutions Initiative (ARSI) aligned with the WHO *Global Action Plan*, supports the 17 Phase I countries and Thailand, Georgia, and the Caribbean Community (CARICOM) by providing technical assistance to ministries of health on national plans and policies for antibiotic resistance surveillance and infection prevention and control in healthcare facilities (NAP Progress Report: Year 3). CDC has worked with public health, laboratory, and global partners such as the WHO to: ○ Develop and deploy a laboratory assessment tool for AMR surveillance; ○ Pilot tele-mentoring and training between US and international clinical labs; ○ Develop training resources for resource-limited settings; ○ Provide tools to contain CRE in resource-limited settings, including a field guide for implementation of WHO core components for infection prevention and control, both released in 2017; and ○ Support response to outbreaks of antibiotic resistant organisms. • Since 2015, WHO has been implementing the Global Antimicrobial Resistance Surveillance System (GLASS), with support from the CDC. GLASS has a country-level laboratory assessment tool as part of the program. The purpose of the laboratory assessment tool is to assess the capacity of National Reference Laboratories (NRL) to meet requirements for AMR testing and to identify needs for capacity building using a standardized approach and methodology. • CDC has also developed the Laboratory Assessment of Antibiotic Resistance Testing Capacity (LAARC) was designed for use in resource-limited settings to: ○ Evaluate the technical skill and expertise of clinical bacteriology laboratories. ○ Evaluate the quality management practices related to bacterial identification and AST. ○ Generate numerical indicators of quality and capacity in 15 domains of laboratory practice. ○ Aid development of work plans for improvement. ○ Monitor the status of laboratory improvements over time. • Per USAID personnel in April 2021: USAID strengthens countries' AMR surveillance through US engagement in the GHSA. USAID supports improvements in laboratory capacity, including promoting the incorporation of necessary microbiology reagents and supplies into the national supply chain. Additionally, USAID supports knowledge management, integration, and reporting of AMR data, including utilization of the WHONET system. Examples include:

		○ In Mali, USAID supported the completion of a web-based platform to increase data sharing and storage for surveillance documents and bulletins. The website is tailored to meet the national government's needs, and trainings for site administrators were developed and implemented. The website will improve the government's ability to archive and publish surveillance data. ○ USAID worked with the Government of Guinea to finalize the national AMR surveillance guide and AMR capacity strengthening plan. USAID provided technical assistance and training of trainers on the microbiology training modules—developed through USAID support—to strengthen AMR detection and surveillance and the conduct of cultures and testing for priority pathogens in human health laboratories. ○ USAID worked with the Government of Tanzania to finalize the development, review, and approval of national standard operating procedures for AMR surveillance. USAID also worked with 26 key laboratories and administration staff in four USAID-supported sentinel sites to increase capacity for AMR surveillance. USAID developed/submitted a costed medium-term procurement plan for AMR commodities and provided necessary microbiology commodities to four AMR surveillance sites to ensure laboratories could adequately test for AMR. USAID supported enhancement and implementation of the national diagnostics supply chain logistics system. USAID also supported the identification of interoperability requirements for aligning LabNet and the national electronic Integrated Disease Surveillance and Response System. ○ In Ethiopia, USAID conducted an assessment to identify potential opportunities for integrating human and animal health disease reporting systems, including AMR surveillance under One Health; supported the diagnostics supply chain management system to ensure AMR detection; and improved the efficiency of AMR surveillance data management, including by supporting WHONET installation training and data entry at five phase II surveillance sites and supporting the preparation of the annual AMR surveillance report that incorporated results from both human and animal health sectors.
Within 5 years: Public health laboratories in at least fifteen partner countries will be able to identify at least three of the seven WHO priority AMR pathogens and will report their	Yes	• Per CDC personnel in April 2021: CDC has been promoting laboratory capacity in 17 countries. As of December 2019, 15 countries have reported gains above baseline. For example, in Vietnam, CDC and partners have improved laboratory and surveillance capacity in 16 clinical laboratories around the country including a central reporting system.

results to WHO, to international surveillance networks, and—in the case of a public health emergency of international concern—to International Health Regulations (IHR) focal points.		
***Objective 5.2**:* Collaborate with WHO, OIE, and other international efforts focused on the development of integrated, laboratory-based surveillance to detect and monitor antibiotic resistance in relevant animal and human foodborne pathogens.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: USDA, FDA, and CDC will develop a plan, in partnership with WHO, the Pan American Health Organization, and other international organizations to identify key partner laboratories that conduct AMR testing of animal foodborne pathogens.	Yes	• Per the NAP First 180 Days Report, as of November 2015, USDA FSIS had contacted regional partners to identify a common vehicle to survey regional capability and capacity for AMR monitoring, and for potential participation in an international training seminar for Latin America. • As reported in 2017, USDA FSIS and CDC representatives participate in international organizations whose goals are to optimize antibiotic use in animals, reduce AMR, build consensus, and harmonize methods (NAP Progress Report: Years 1 and 2). • USDA FSIS collaborates with Pan American Health Organization (PAHO) and the International Network of Food Analysis Laboratories to document regional capability for AMR work (NAP Progress Report: Years 1 and 2). • FDA, USDA, and CDC continue to work with public health and international partners (APHL, TATFAR, WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance [AGISAR], The Food and Agriculture Organization of the United Nations [FAO], The World Organisation for Animal Health [OIE], International Health Regulations-Joint External Evaluation [IHR-JEE], and the World Bank) to optimize antibiotic use in animals, reduce antibiotic resistance, build consensus, harmonize methods, and improve surveillance (NAP Progress Report: Year 3). • Per CDC personnel in April 2021: CDC is working with the WHO to develop a Global Emerging AMR reporting portal. This portal will facilitate global communication of new or emerging resistance threats through engaging a group of global partner laboratories. In 2017, CDC and WHO developed a draft document, "Emerging AMR reporting framework and risk assessment" which defines the framework, rules, and protocols for early reporting of new antimicrobial resistance. WHO has solicited feedback from member countries, and in the next year, will pilot test the framework and develop the IT portal. • Per USDA personnel in April 2021: USDA has been involved with Codex Alimentarius activities, such as the development of guidelines for integrated surveillance and updating an old code of

		practice on antibiotic stewardship. USDA and FDA co-chair the US delegation on the Codex task force on antimicrobials.

Within 3 years:
USDA and FDA, in conjunction with CDC and international partners, will:
• Develop a process for assessing national and regional capabilities for surveillance of antibiotic resistance in animal and human foodborne pathogens.
• Identify challenges to harmonizing AMR data requirements and collection methods on an international scale.
• Assess the current status of national capabilities for molecular diagnostics and epidemiology and address the need for access to these capacities.
• Identify additional partners who can assess laboratory testing proficiencies and provide training for technology transfer.
• Work with regional partners to monitor the emergence and spread of resistance genes in animal and foodborne pathogens on an ongoing
	Yes	Develop a process for assessing national and regional capabilities for surveillance of antibiotic resistance in animal and human foodborne pathogens.
		• Per CDC personnel in April 2021:
		  ○ By 2019, CDC continues to support capacity building for AR surveillance in priority regions, through leadership with the WHO as an Enterics and Fungal Collaborating Center.
		  ○ In addition, CDC NARMS, through WHO AGISAR, provided mentorship for a project in Argentina to implement integrated surveillance of AR in humans and poultry.
		  ○ CDC continues to fund grantees for projects to collect data from international travelers on healthcare acquired and enteric disease infections, including risk factors and resistance characteristics.
		
		Identify challenges to harmonizing AMR data requirements and collection methods on an international scale.
		• Per FDA personnel in April 2021: FDA has been active in this area (e.g., collecting data on AMR, antimicrobial sales data for agriculture, etc.). There is interest in capturing and comparing AMR data internationally, and work is ongoing (e.g., related to mechanisms for capturing data).
		
		Assess the current status of national capabilities for molecular diagnostics and epidemiology and address the need for access to these capacities.
		• Per CDC personnel in April 2021: CDC worked with WHO, TATFAR, and PulseNet International (PNI) to address the need for international AR capacity; these activities are continuing.
		
		Identify additional partners who can assess laboratory testing proficiencies and provide training for technology transfer.
		• Per CDC personnel in April 2021: CDC worked with WHO, TATFAR, and PNI to identify potential additional partners that can help build capacity; these activities are continuing.
		
		Work with regional partners to monitor the emergence and spread of resistance genes in animal and foodborne pathogens on an ongoing basis, using molecular techniques.
		• Per CDC personnel in April 2021:

basis, using molecular techniques. • Expand activities conducted through other USG-funded activities (e.g., the Asia-Pacific Economic Cooperation) to inventory existing worldwide laboratory resources and assess the need for national and regional improvements to support surveillance for drug-resistant animal and human foodborne pathogens. These efforts will include expansion of training opportunities in pathogen characterization and diagnostics.		○ Between 2016 and 2020, CDC has trained at least 74 people from at least 17 countries in WGS laboratory and analysis methods. Trainings were closely coordinated with PAHO in Central/South America, the WHO Eastern Mediterranean Regional Office (EMRO) and CDC-country offices. ○ CDC has also provided technical assistance on building IT infrastructure and WGS capacity to the Regional WGS Groups in PulseNet Latin America and Caribbean, PulseNet Middle East, CDC-Kenya, CDC-Thailand, and CDC-Georgia. ○ Additionally, CDC participated in the 2018 International Food Safety Authorities Network (INFOSAN) meeting, contributing to discussions on strengthening foodborne disease surveillance networks through implementing WGS. ○ Finally, CDC contributed WGS and AMR expertise as well as editorial comments on the recently published WHO report "Whole genome sequencing for surveillance of antimicrobial resistance." Expand activities conducted through other USG-funded activities (e.g., the Asia-Pacific Economic Cooperation) to inventory existing worldwide laboratory resources and assess the need for national and regional improvements to support surveillance for drug-resistant animal and human foodborne pathogens. These efforts will include expansion of training opportunities in pathogen characterization and diagnostics. • As reported in 2018: ○ FDA CVM supports regional capacity building of AR surveillance by supporting the WHO *Global Action Plan* and is mentoring a project in Argentina to help implement an integrated surveillance program on AMR along the food chain (NAP Progress Report: Year 3). ○ FDA is contributing to the WHO *Global Action Plan* through development and implementation of global integrated surveillance for extended spectrum beta-lactamase (ESBL)-producing *E. coli* using a One Health approach (NAP Progress Report: Year 3). ○ Further, FDA CVM also supports the WHO *Global Action Plan* by contributing to WHO's Critically Important List of Antimicrobials for Human Medicine, a guideline used globally to encourage the prudent use of antimicrobials in both human and veterinary medicine (NAP Progress Report: Year 3). • As reported in 2019, USDA FSIS strengthened collaborations in AMR activities: ○ To enhance understanding of AMR activities and partnerships in Latin America, USDA FSIS in collaboration with the FDA engaged with the Red Interamericana de Laboratorios

		de Análisis de Alimentos (RILAA) (aka Interamerican Network of Food Analysis Laboratories [INFAL]), PAHO, PulseNet Latin America, and the Inter-American Institute for Cooperation on Agriculture (IICA) (NAP Progress Report: Year 4). ○ FSIS conducted training on food safety, antimicrobial susceptibility testing, and surveillance for international partners including representatives from Latin America (NAP rogress Report: Year 4). ○ Additional international collaborations included work with regional partners to identify a common vehicle to survey regional capability and capacity for AMR monitoring, establish international proficiency programs, and standardize antimicrobial susceptibility methods, with collaborators including the Asia-Pacific Economic Cooperation and RILAA (INFAL) (NAP Progress Report: Year 4). • Per USDA personnel in April 2021: As a continuation of USDA FSIS's international engagements, in September 2018, FSIS hosted a 5-day training for international partners at FSIS's Eastern Laboratory in Athens, Georgia, US. The training was titled "USDA FSIS Laboratory Seminar for International Government Officials" and was attended by 20 participants from 16 countries, including four countries in Latin America. Among the topics covered were CARB-related topics such as AST, NARMS, and WGS - Procedures, Data Analyses, and Data Usage.
Within 3 years: DOD will develop a scalable, evidence-based database of global information on antimicrobial resistance and issue annual reports of findings.	Yes	• DOD's GEIS Network includes an AMR section. AMR surveillance projects primarily focus on identifying multidrug-resistant organisms in populations of interest around the world. In FY2018, the AMR Focus Area supported projects at 12 DOD partner laboratories, and expanded its portfolio to include prospective surveillance efforts for HAIs and/or STIs in Nepal, Ghana, Djibouti, and the Dominican Republic, while continuing surveillance with partner nations Cambodia, Egypt, Honduras, Jordan, Kenya, Peru, the Philippines, Republic of Georgia, Thailand, and Uganda (AFHSB 2018 Annual Report). • Armed Forces Health Surveillance Division shares annual reports online.
Within 5 years: USDA, FDA, and CDC will initiate regional collaborations to monitor the emergence and spread of resistance genes in food, animal, and human foodborne pathogens, using genome sequencing techniques.	Yes	• The emergence of *mcr-1*, a genet that confers resistance to the antibiotic colistin, was first identified in China in 2015 on a plasmid. The US government began conducting surveillance for *mcr-1* in the US after its identification. When no *mcr-1* gene was detected at first, researchers from USDA's ARS developed new methods to enhance detection of colistin-resistant bacteria from the contents of food animals. ARS scientists screened >2,000 samples using PCR and isolated two *E. coli* strains that contained the *mcr-1* gene on a plasmid (NAP Progress Report: Years 1 and 2). • The 2016-2018 USDA ARS AMR and ATA Accomplishment Summary noted a number of developments/accomplishments in food safety, such as: the development of immunoassays to

		monitor colistin-resistant bacteria in food-producing animals, production environments, meat, and poultry; identifying the antibiotic resistance profiles of bacteria from all-natural, antibiotic-free broilers; and genomic sequencing of antimicrobial resistant *E. coli* from Nigeria.
		• The Agricultural Antibiotic Resistance (AgAR) Network, a group of USDA ARS scientists working on issues related to environmental dimensions of antibiotic resistance, has coordinated and recently started cross-location, multi-year studies to characterize and quantify antibiotic resistant bacteria and antibiotic resistance genes in applied food-animal production environments, and has been working over the past year to develop a database that will allow intra- and inter-agency and public sharing of ARS antibiotic resistance data sets (NAP Progress Report: Years 1 and 2).
		• Per CDC personnel in April 2021:
		  ○ CDC hosted three scientists responsible for food testing from the Dubai Central Laboratory (DCL) from July 3-7, 2017, to learn about implementing WGS for foodborne disease surveillance, including resistance genes. DCL is a champion in the region for adopting WGS and advocates for surveillance.
		  ○ CDC also jointly organized a "Workshop on the Coordination and Capacity Building of the PulseNet Middle East Laboratory Network" in Oman in 2018 to 1) review current status of foodborne disease surveillance; 2) review implementation of recommendations from past PulseNet Middle East meeting; 3) discuss achievements/challenges in the region; and 4) update participants on testing technologies including WGS.

Within 5 years: USDA and FDA will work with CDC and international partners to provide training in laboratory methodologies (in-country or within the US) and initiate collaborations to promote training as opportunities arise.	Yes	• USDA APHIS's NVSL provides diagnostic training and outreach programs for domestic and international visitors. An annual training catalogue is available on the USDA APHIS website, and laboratories also provide customized learning events, twinning projects, and long-term collaboration initiatives (USDA APHIS Diagnostic Training and Visitor Coordination at the NVSL). • FDA and the University of Texas Medical Branch, Galveston National Laboratory, collaborate to provide an annual training course on how to meet good laboratory practice (GLP) requirements in BSL-4 facilities (FDA Training Course: Achieving Data Quality and Integrity in Maximum Containment Laboratories). • As reported in 2019, USDA FSIS conducted training on food safety, antimicrobial susceptibility testing, and surveillance for international partners including representatives from Latin America (NAP Progress Report: Year 4). • Per USDA personnel in April 2021: As a continuation of USDA FSIS's international engagements, in September 2018, FSIS hosted a 5-day training for international partners at FSIS' Eastern Laboratory in Athens, Georgia, US. The training was titled "USDA FSIS Laboratory Seminar for

		International Government Officials" and was attended by 20 participants from 16 countries, including four countries in Latin America. Among the topics covered were CARB-related topics such as AST, NARMS, and WGS - Procedures, Data Analyses, and Data Usage.
Within 5 years: USDA, FDA, and CDC will work through existing laboratory and public health networks—such as PulseNet International and the Red Interamericana de Laboratorios de Análisis de Alimentos (RILAA)—to transfer technology and train local partners.	Yes	• As reported in 2019, USDA FSIS strengthened collaborations in AMR activities: ○ To enhance understanding of AMR activities and partnerships in Latin America, USDA FSIS in collaboration with the FDA engaged with RILAA (aka INFAL), PAHO, PulseNet Latin America, and the IICA (NAP Progress Report: Year 4). ○ USDA FSIS conducted training on food safety, antimicrobial susceptibility testing, and surveillance for international partners including representatives from Latin America (NAP Progress Report: Year 4). ○ Additional international collaborations included work with regional partners to identify a common vehicle to survey regional capability and capacity for AMR monitoring, establish international proficiency programs, and standardize antimicrobial susceptibility methods, with collaborators including the Asia-Pacific Economic Cooperation and RILAA (INFAL) (NAP Progress Report: Year 4). • Per USDA personnel in April 2021: As a continuation of USDA FSIS's international engagements, in September 2018, FSIS hosted a 5-day training for international partners at FSIS' Eastern Laboratory in Athens, Georgia, US. The training was titled "USDA FSIS Laboratory Seminar for International Government Officials" and was attended by 20 participants from 16 countries, including four countries in Latin America. Among the topics covered were CARB-related topics such as AST, NARMS, and WGS - Procedures, Data Analyses, and Data Usage. • Per CDC personnel in April 2021: ○ Since 2016, CDC has trained at least 74 people from at least 17 countries in WGS laboratory and analysis methods. Trainings were closely coordinated with the PAHO in Central/South America, the WHO EMRO in the Middle East, and CDC-country offices. ○ CDC has also provided technical assistance on building IT infrastructure and WGS capacity to the Regional WGS Groups in PulseNet Latin America and Caribbean, PulseNet Middle East, CDC-Kenya, CDC-Thailand, and CDC-Georgia. ○ Additionally, CDC participated in the 2018 INFOSAN meeting, contributing to discussions on strengthening foodborne disease surveillance networks through implementing WGS. ○ Finally, CDC contributed WGS and AMR expertise as well as editorial comments on the recently published WHO report, GLASS Whole Genome Sequencing for Surveillance of Antimicrobial Resistance.

Objective 5.3: Develop a mechanism for international communication of critical events that may signify new resistance trends with global public and animal health implications.		
Milestone	**Accomplished?**	**Comments**

Within 1 year:
CDC will work with TATFAR partners to develop a common US-EU system for sharing and analyzing bacterial resistance patterns for pathogens identified as urgent and serious threats in Table 1.
	Yes	• Per CDC personnel in April 2021:
		  ○ Through TATFAR, CDC and DOD have worked with the EU, Canada, and Norway to harmonize surveillance practices.
		  ○ The US and EU have made significant progress toward harmonizing lab definitions for detecting AMR, including colistin definitions for resistant Gram-negative bacteria like *E. coli*. These efforts will help the US and EU determine when bacteria are resistant to antibiotics, thus providing opportunities to enhance infection prevention and control to prevent the spread of resistant infections.

Within 1 year: HHS/Office of Global Affairs (OGA), USDA, FDA and CDC will work with TATFAR partners to address TATFAR Recommendation #18, which calls for the formation of an international working group to identify key knowledge gaps about transmission of drug-resistant bacteria in animals and the use of antibiotics in animal agriculture.	Yes	• USDA and FDA participated in the October 2015 TATFAR meeting, during which high-priority knowledge gaps related to AMR were identified. During the meeting, specific actions were identified by which added benefit would be gained from transatlantic cooperation (TATFAR Report on Recommendation 18). The inventory of identified knowledge gaps included existing work in the areas of research, surveillance, and risk analysis (NAP First 180 Days Report). • USDA became a member of TATFAR in 2017 (NAP Progress Report: Year 3). As a part of TATFAR, USDA shared information related to regulatory, research and technical issues for addressing AMR in animal agriculture. Specifically, USDA APHIS VS Center for Veterinary Biologics explained US processes for veterinary vaccine approvals, USDA ARS held a panel session on alternatives to antibiotics at the 2018 TATFAR physical meeting, and USDA Office of the Chief Scientist initiated sharing information on antibiotic stewardship initiatives amongst TATFAR members (NAP Progress Report: Year 3). • FDA, USDA, and CDC continue to work with public health and international partners (APHL, TATFAR, WHO AGISAR, FAO, OIE, IHR-JEE, and the World Bank) to optimize antibiotic use in animals, reduce antibiotic resistance, build consensus, harmonize methods, and improve surveillance (NAP Progress Report: Year 3).
Within 3 years: CDC will work with WHO and other partners to develop a secure website for real-time sharing of international surveillance data on antimicrobial resistance in order to facilitate early warning and	Yes	• Per CDC personnel in April 2021: FDA, USDA, and CDC continue to work with public health and international partners (APHL, TATFAR, WHO AGISAR, FAO, OIE, IHR-JEE, and the World Bank) to optimize antibiotic use in animals, reduce antibiotic resistance, build consensus, harmonize methods, and improve surveillance. CDC NARMS, through WHO AGISAR, also supports work in Argentina to implement integrated antibiotic resistance surveillance in humans and poultry. WHO Emerging Antimicrobial Resistance Reporting (EAR) is established and is shared between organizations.

notification of significant events to WHO, regional and international disease surveillance networks (e.g., European Centre for Disease Prevention and Control), and IHR. These efforts will make use of data-sharing practices developed by the US and TATFAR (see above). Steps include developing terms of reference, assessing IT requirements, and identifying mechanisms for validating and sharing information.		• In 2015, the WHO launched GLASS, with support from the CDC. The aim of GLASS is to support global surveillance and research in order to strengthen the evidence base on AMR and help informing decision-making and drive national, regional, and global actions.
Within 3 years: CDC will deploy the website in partnership with the international community and will help test, monitor, evaluate, and improve its utility.	Yes	• The development phase for GLASS was from 2015 through 2019. The website is complete and country-level focal points gained access in 2018. Promotional materials for implementation have been developed and disseminated to promote uptake.
Within 3 years: USDA will identify next steps in addressing knowledge gaps about development and spread of antibiotic resistance in animals, based on the conclusions of the work group formed in fulfillment of TATFAR Recommendation #18 (see above).	Yes	• As reported in 2018, USDA shared information related to regulatory, research, and technical issues for addressing AMR in animal agriculture. Specifically, USDA APHIS VS Center for Veterinary Biologics explained US processes for veterinary vaccine approvals, USDA ARS held a panel session on alternatives to antibiotics at the 2018 TATFAR physical meeting, and USDA Office of the Chief Scientist initiated sharing information on antibiotic stewardship initiatives amongst TATFAR members (NAP Progress Report: Year 3). • As reported in 2018, FDA, USDA, and CDC continue to work with public health and international partners (APHL, TATFAR, AGISAR, FAO, OIE, IHR-JEE, and the World Bank) to optimize antibiotic use in animals, reduce antibiotic resistance, build consensus, harmonize methods, and improve surveillance (NAP Progress Report: Year 3). • Per USDA personnel in April 2021: The USDA ARS's Meat Safety and Quality Research Unit, US Meat Animal Research Center has been investigating knowledge gaps about transmission of drug-resistant bacteria in animals and the use of antibiotics in animal agriculture. Links to publications include: ○ Specific Antibiotic Resistance Goals (2020)

		○ Antimicrobial Resistance in US Cull Cow Processing (2020) ○ No Change in Risk from Antibiotic Resistant Salmonellosis from US Beef (2020) ○ Effect of Tylosin in Cattle Feed on Antimicrobial Resistance (2020) ○ Cropland Amendment with Beef Cattle Manure Minimally Affects Antimicrobial Resistance (2020) ○ Antimicrobial Resistance in US Pork Chops (2019) ○ Antimicrobial Resistance Levels in US Ground Beef (2018) ○ In-Feed CTC Effect on Antimicrobial Resistance Genes (2018) ○ Functional *bla*KPC-2 in US Cattle Feces (2018) ○ Impact of RWA Beef Cattle Production on AMR (2017) ○ In-Feed CTC Effect on Animal Health and AMR (2016) ○ Antimicrobial Resistance in Beef Cows (2016) ○ Antimicrobial Resistance in the Beef Continuum (2015) ○ Antimicrobial Resistance in Livestock and Municipal Environments (2015) ○ Cephalosporin-Resistant E. coli from Feedlot Cattle (2013)
Within 5 years: CDC and other US agencies will help ensure access to—and full participation by—public health authorities in all WHO member countries.	Yes	• Per CDC personnel in April 2021: CDC, as a WHO Collaborating Center, assembles, analyzes, and contributes data to the WHO GLASS on an annual basis for the following priority pathogens: *N. gonorrhoeae, Shigella spp.* and *Salmonella spp*.; reviews and provides input to newly drafted WHO guidance documents; and supported the development of the WHO EAR portal with associated risk assessment components. Presently EAR module development is complete and the module is a functional component within the WHO GLASS IT platform for sharing of preliminary or early warning information regarding potential EAR events by Member States, WHO Collaborating Centers, WHO IHR focal points, AMR surveillance networks, and research institutions.
Within 5 years: USDA will engage TATFAR and other regional partners in sharing information about drug-resistance trends with implications for animal health.	Yes	• Per USDA personnel in April 2021: ○ USDA joined TATFAR as a member in 2017. ○ USDA led Action item 1.6 regarding antibiotic stewardship to engage with TATFAR partners (i.e., EU, Norway, Canada) quarterly on antibiotic stewardship in animals. While AMR affecting animal health is not a major problem, there are some disease conditions such as respiratory disease in cattle where AMR can be problematic. The AVMA Committee on Antimicrobials, on which USDA and others in the federal government participate, drafted a review of AMR in animals in the US, published in 2020, and that document could serve as information for the international community in the future (AVMA Antimicrobial-resistant pathogens affecting animal health).

Objective 5.4: Promote the generation and dissemination of information needed to effectively address antibiotic-resistance. ***Sub-Objective 5.4.1:*** Support consistent international standards for determining whether bacteria are resistant to antibiotics.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: US agencies, led by CDC and USAID, will engage stakeholders in establishing harmonized definitions of drug resistance for surveillance purposes (e.g., by standardizing interpretive criteria for analyzing the results of antibiotic susceptibility tests).	Yes	• Through TATFAR, CDC and DOD have worked with the EU, Canada, and Norway to harmonize surveillance practices. The US and EU have made significant progress toward harmonizing lab definitions for detecting AMR, including colistin definitions for resistant Gram-negative bacteria such as *E. coli*. These efforts will help the US and EU determine when bacteria are resistant to antibiotics, thus providing opportunities to enhance infection prevention and control to prevent the spread of resistant infections. • The GLASS system included harmonized definitions and methods for surveillance of drug resistance.
Within 1 year: As part of these efforts, DOD will continue to engage and support existing and newly-identified international partners through sharing of technological packages for surveillance and reporting purposes.	Yes	• As reported in 2015, DOD had ongoing efforts to promote a standardized approach for data collection, sharing, and detection assay development, aided by partnerships within the GHSA and Medical Countermeasures Consortium, namely targeting *E. coli, K. pneumoniae*, and *S. aureus*, as well as other carbapenemase-resistant pathogens (NAP First 180 Days Report). • As noted in 2017, through TATFAR, CDC and DOD had worked with the EU, Canada, and Norway to harmonize surveillance practices (NAP Progress Report: Years 1 and 2).
Within 3 years: US agencies, led by CDC, will work with the six WHO regional surveillance networks to implement harmonized definitions of resistance for surveillance programs integrating data on WHO and CDC priority pathogens.	Yes	• Per CDC personnel in April 2021: ○ Through TATFAR, CDC, FDA, and DOD have worked with the EU, Canada, and Norway to develop guidance for assessing appropriateness of human antibiotic use and a review of antibiotic reduction goals in TATFAR countries, provide consultation and collaborate on point-prevalence surveys, and harmonize surveillance practices. The USDA became a TATFAR Member in 2017. ○ The US and EU have harmonized breakpoint definitions for colistin and Gram-negative bacteria (Enterobacteriaceae*, Acinetobacter* spp. and *P. aeruginosa*) and identified priority areas for harmonization moving forward. ○ In 2018, the CLSI will review data for *N. gonorrhoeae* breakpoints, finalize the Enterobacteriaceae fluoroquinolone breakpoint decision, consider harmonization of test methods for *S. pneumoniae*, and establish a process for prospective harmonization of disk diffusion test methods of antimicrobial susceptibility testing.

		○ CDC, in collaboration with TATFAR partners, WHO, and non-TATFAR countries, also coordinates the US Antibiotic Awareness Week, that coincides with other international observances.
Objective 5.4: Promote the generation and dissemination of information needed to effectively address antibiotic-resistance. ***Sub-Objective 5.4.2***: Develop international collaborations to gather country-specific and regional information on drivers of antibiotic resistance, identify evidence-based interventions, adapt these strategies to new settings, and evaluate their effectiveness.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: US agencies, led by the Department of State and HHS, will develop a strategy for working with partner countries to elevate the issue of antibiotic resistance as an international priority for global health security.	Yes	• As of November 2015, the Department of State, HHS, and USDA had enhanced bilateral and multilateral engagement to mobilize international financial, political, and operational support to combat AMR. Successes included: ○ The 2015 G7 commitment to develop or review and effectively implement national action plans and support other countries as they develop their own national action plans. ○ Incorporation of AMR into dialogues on implementation of binding bilateral Science and Technology Agreements that provide the framework for international collaboration on critical research and development efforts. ○ Bilateral and multilateral public and animal health dialogues. ○ Enhancing foreign policy engagement by US embassy personnel (NAP First 180 Days Report). • Per HHS personnel in April 2021: ○ HHS considers this milestone completed, although there is not an open source/publically-published strategy. ○ As part of the Executive Order that established a task force, HHS was directed to put together an international working group. The working group is led by the HHS OGA, the Department of State, and USDA. The group developed a formal policy process to determine the best approaches for addressing issues related to AMR (e.g., relating with the G7 and Group of 20 (G20) countries, increasing participation in the GHSA, working with the tripartite with international organizations, etc.). This group was chaired at the Assistant Secretary level when set up and continues at the working level. ○ The public-facing work, such as WHO's *Global Action Plan on Antimicrobial Resistance*, shows the result of the internal work within the US government.
Within 1 year: US agencies, led by HHS/OGA, will support development of the *WHO Global Action Plan on*	Yes	• As of November 2015, HHS, Department of State, and USDA coordinated international engagement with the WHO, FAO, OIE, Member States, and other relevant organizations. This coordination resulted in the successful adoption of WHO's *Global Action Plan*, consistent with US

Antimicrobial Resistance. As part of this effort, US agencies will support the inclusion of provisions that require open access to research data on factors that drive the emergence of resistance and strategies to prevent its spread.		CARB priorities including emphasis on One Health, enabling evidence-based decisions, and research and development (NAP First 180 Days Report). • The WHO *Global Action Plan on Antimicrobial Resistance* was published in 2015; however, it doesn't mention open access to research data. Per HHS personnel in April 2021: Although open access to research data may not be currently available, HHS has supported the inclusion of provisions to require open access to research data.
Within 3 years: The Department of State, HHS, and other agency partners will convene a group of international stakeholders to discuss best practices for research collaborations on antimicrobial resistance, including methodologies, data-sharing policies, management plans and interoperability.	Yes	• As reported in 2018, to fulfill the commitment to establish an International Stakeholders group, US government members participated in multiple fora and conferences with international partners, including: the GHSA AMR Action Package, TATFAR, the UK, and Wellcome Trust-sponsored Call to Action meeting, Prince Mahidol Award Conference, Center for Strategic and International Studies sponsored meetings on "Winning the Fight Against Drug Resistance" and Protecting Health Security, World Health Summit, and United Nations (UN) General Assembly side events on Spurious and Falsified Medicines and Stewardship. In addition, OGA facilitated bilateral meetings where AMR was a priority topic of discussion between HHS and the Ministries of Health from the EU, Netherlands, Japan, Canada, and Argentina (NAP Progress Report: Year 3). • In July 2017, OGA hosted WHO leaders for a discussion on policy and efforts with the CARB Task Force. A second visit with WHO principals was hosted in March 2018 to introduce new WHO leadership on AMR to HHS and USDA principals (NAP Progress Report: Year 3). • Per HHS personnel in April 2021: The Department of State is involved with work on this milestone. As part of the Executive Order that established a task force, HHS was directed to put together an international working group. The working group is led by OGA, the Department of State, and USDA.
Within 3 years: US agencies will work with WHO, FAO, and OIE to support implementation of the *WHO Global Action Plan on Antimicrobial Resistance* by: • Assessing country-specific and regional factors that drive the development of antimicrobial resistance, building on existing risk management frameworks	In progress	Assessing country-specific and regional factors that drive the development of AMR, building on existing risk management frameworks such as the Codex Alimentarius. • This activity has been accomplished per the bullets below. • In June 2017, the Codex Alimentarius Commission approved work for the Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance within three to four years to develop international guidance on AMR by: 1) updating the 2005 Code of Practice to Minimize and Contain AR; 2) drafting guidelines for integrated surveillance (NAP Progress Report: Year 3). • As reported in 2018, NIH/NIAID was supporting several AMR sequencing and bioinformatics projects in Thailand and India to better understand molecular mechanisms of AMR and patterns of resistance. NIH/NIAID and the Indian Council of Medical Research were collaborating as of 2018 on a pilot project using genomics, bioinformatics, and systems biology to compare

such as the Codex Alimentarius. • Establishing a global database to collect harmonized quantitative data on the use of antibacterial agents in animals. • Forging partnerships aimed at reducing the use of medically-important antibiotics for growth promotion in food animals.		multidrug-resistant *Acinetobacter* strains from neonatal intensive care units in India and the US (NAP Progress Report: Year 3).Per USAID personnel in April 2021: ○ USAID funded CDC to evaluate third-party water, sanitation, and hygiene (WASH) in healthcare facilities interventions in 10 countries (Tanzania, Mali, Burkina Faso, Kenya, Ghana, Niger, Haiti, Ethiopia, Uganda, Rwanda). ○ USAID worked with country counterparts to conduct infection prevention and control (IPC) national assessments using the WHO's national ICP assessment tool 2 (IPCAT2) in Ethiopia, Mali, Senegal, Uganda, Côte d'Ivoire. USAID worked with country counterparts to conduct IPC facility assessments using the Infection Prevention and Control Assessment Framework (IPCAF) in Bangladesh, Cameroon, Côte d'Ivoire, Ethiopia, Tanzania, and Uganda; Kenya used a national assessment tool. As of September 2020, 111 facilities have undergone IPCAF assessment with USAID's support. ○ USAID supported re-assessments to evaluate progress and adoption/value of interventions: examples include: ▪ In Ethiopia, USAID supported the re-assessment of IPC practices in four hospitals using IPCAF baseline results to measure progress after Medicines, Technologies, and Pharmaceutical Services (MTaPS) interventions. All four hospitals showed improvement in their IPCAF scores. ▪ In Kenya, USAID supported follow-up visits to 16 target facilities to assess if IPC standards were being met and activities performed according to action plans. As a result of IPC interventions, IPC committees had been established in all 16 facilities. ▪ In Tanzania, after IPCAF baseline assessments at six hospitals between October 2019 and January 2020, follow-up assessments in May 2020 demonstrated that all hospitals scored higher indicating the success of USAID-supported interventions. ▪ USAID supported AMR stewardship and IPC work in the agriculture sector in Côte d'Ivoire and Mali by engaging AMR technical working groups and conducting rapid assessments using tools adapted from IPCAT2 and IPCAF. In total, 67 veterinary clinics, slaughterhouses and poultry farms have undergone an IPC and hygiene assessment. <u>Establishing a global database to collect harmonized quantitative data on the use of antibacterial agents in animals.</u>

		• This activity is in progress per the bullets below.
		• Per HHS personnel in April 2021:
		  ○ This milestone has not been fully completed due to lack of dedicated resources; however, work is ongoing and HHS remains interested in moving this database forward.
		  ○ All countries that are member states of OIE, FAO, and WHO submit surveillance data to those organizations. Over the last five years, efforts have been made to determine how best to integrate and harmonize the data. Unfortunately, there are technical differences regarding how the US and EU report data that challenge data integration/harmonization (e.g., differences in how the US reports a cow's weight vs. how the EU reports that weight). There are also differences in standards and guidelines used in the US and EU. There is currently an effort by WHO for GLASS to be adapted to be more integrated.
		
		Forging partnerships aimed at reducing the use of medically-important antibiotics for growth promotion in food animals.
		• This activity has been accomplished (and work is ongoing) per the bullets below.
		• Per HHS personnel in April 2021:
		  ○ From the 71st United Nations General Assembly (UNGA) High-Level Meeting on AMR in 2016, language in the High Level Declaration commits all countries to take steps towards reducing the use of medically-important antibiotics for growth promotion in food animals. Although specific deadlines for this work were not specified, the global community agreed to reduce the use of antibiotics for growth promotion.
		  ○ Efforts towards implementing this work are staggered and depend on countries' resources.
		  ○ Although the EU, US, and many Asian Pacific countries have worked towards this goal, HHS noted that all have done it differently. For example, the US considers certain drugs to be antimicrobials that the EU does not, and vice versa.
		  ○ A common theme HHS has heard from Health Ministry colleagues is that there is also the regulatory dimension and regulatory reach to consider. For example, not all countries have the same level of capacity to regulate on-farm activities.
		• USAID, through a One Health approach with FAO and WHO in Asia and Africa, to develop a more comprehensive understanding of current patterns of antibiotic use and regulatory practices within the livestock and aquaculture industries (NAP Progress Report: Year 3).
		• USAID is promoting best practices and prudent use of antibiotics across the animal-health value chains (NAP Progress Report: Year 3).

		• As of 2018, USAID was working in 10 countries in Asia and 14 countries in Africa to strengthen One Health national AMR plans (NAP Progress Report: Year 3). • USAID is involved with the GHSA (USAID GHSA Fact Sheet, GHSA website).
Within 5 years: The Department of State, HHS, and other agency partners will continue to promote antibiotic resistance as an international health priority by raising the issue of antibiotic resistance during bilateral consultations and multilateral forums and by advancing implementation of the GHSA Antimicrobial Resistance Action Package.	Yes	• In 2016, world leaders at the 71st UN General Assembly High-Level Meeting on AMR affirmed AMR as a grave threat to human health and adopted a UN Resolution calling for specific global multi-sectoral actions to combat AMR, including the US priority position of universal high-level commitment by all nations across sectors. The US Delegation, led by the Secretary of HHS, announced the US commitment and actions to combat AMR, and called for global cooperation on the issue (Progress Report: Years 1 and 2). • In December 2017, the Department of State worked with HHS, USDA, US Department of the Interior, and other agencies to secure language regarding antibiotic pollution in the environment at the Third UN Environment Assembly in Nairobi. The language calls on the UN Environment Program Secretariat to work with other UN system agencies to support the strengthening of the evidence base regarding antibiotics in the environment, while also calling on member states to consider evidence-based policy measures (Progress Report: Year 3). • In September 2018, CDC and the OGA launched the Antimicrobial Resistance Challenge at the UN General Assembly to catalyze global action against antibiotic resistance. A year later, CDC announced this challenge had resulted in nearly 350 commitments from government health officials, pharmaceutical and health insurance companies, and others from 33 countries to make formal commitments that further the progress against AMR, such as by improving appropriate antibiotic use (GAO Report, CDC AMR Challenge). • As reported in 2020, the HHS OGA has collaborated with other countries, including those participating in the TATFAR program, to promote the appropriate use of antibiotics internationally (GAO Report). • Per HHS personnel in April 2021: HHS currently chairs the GHSA Antimicrobial Resistance Action Package. HHS noted that participation in the GHSA Action Package, including among nongovernmental organizations, has increased during the course of HHS's chairmanship.
Objective 5.4: Promote the generation and dissemination of information needed to effectively address antibiotic-resistance. ***Sub-Objective 5.4.3:*** Provide technical assistance as needed to underdeveloped and developing nations to improve their capacity to detect and respond effectively to antibiotic resistance.		
Milestone	**Accomplished?**	**Comments**
Within 3 years: CDC will develop bilateral agreements with twelve to fifteen	Yes	• Per CDC personnel in April 2021: CDC, both through engagement with the GHSA and through the ARSI aligned with the WHO *Global Action Plan*, supports the 17 Phase I countries and Thailand, Georgia, and CARICOM by providing technical assistance to ministries of health on national plans

countries to develop country-specific surveillance strategies, and will assess expansion of these activities to additional countries (see also Objective 5.1).		and policies for AR surveillance and infection prevention and control in healthcare facilities. CDC has worked with public health, laboratory, and global partners such as WHO to: ○ Develop and deploy a laboratory assessment tool for AMR surveillance. ○ Pilot tele-mentoring and training between US and international clinical labs. Develop training resources for resource-limited settings. ○ Provide tools to contain CRE in resource-limited settings, including a field guide for implementation of WHO core components for infection prevention and control, both released in 2017. ○ Support response to outbreaks of antibiotic resistant organisms.
Within 3 years: CDC and other US agencies will assist partner countries with development and implementation of national strategies for infection prevention and control in healthcare facilities.	Yes	• Per CDC personnel in April 2021: CDC, both through engagement with the GHSA and through the ARSI aligned with the WHO *Global Action Plan*, supports the 17 Phase I countries and Thailand, Georgia, and CARICOM by providing technical assistance to ministries of health on national plans and policies for AR surveillance and infection prevention and control in healthcare facilities. CDC has worked with public health, laboratory, and global partners such as WHO to: ○ Develop and deploy a laboratory assessment tool for AMR surveillance. ○ Pilot tele-mentoring and training between US and international clinical labs. Develop training resources for resource-limited settings. ○ Provide tools to contain CRE in resource-limited settings, including a field guide for implementation of WHO core components for infection prevention and control, both released in 2017. ○ Support response to outbreaks of AR organisms.
Within 5 years: CDC and other US agencies will assist at least fifteen countries with collection of resistance surveillance data and data-sharing with stakeholders.	Yes	• Per CDC personnel in April 2021: CDC, both through engagement with the GHSA and through the ARSI aligned with the WHO *Global Action Plan*, supports the 17 Phase I countries and Thailand, Georgia, and CARICOM by providing technical assistance to ministries of health on national plans and policies for AR surveillance and infection prevention and control in healthcare facilities. CDC has worked with public health, laboratory, and global partners such as WHO to: ○ Develop and deploy a laboratory assessment tool for AMR surveillance. ○ Pilot tele-mentoring and training between US and international clinical labs. Develop training resources for resource-limited settings. ○ Provide tools to contain CRE in resource-limited settings, including a field guide for implementation of WHO core components for infection prevention and control, both released in 2017. ○ Support response to outbreaks of antibiotic resistant organisms.

***Objective 5.5**:* Establish and promote international collaboration and public-private partnerships to incentivize development of new therapeutics to counter antibiotic resistance, including new, next-generation, and other alternatives to antibiotics, vaccines, and affordable, rapidly deployable, point-of-need diagnostics.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: US agencies, led by HHS, will work with WHO, FAO, OIE, and other international partners to accelerate investment in research to develop point-of-care diagnostics, vaccines, and drugs to combat resistant bacteria, as well as to investigate the microbiomes of food animals. For example, US agencies and partners in industry and academia will work with TATFAR partners to advance collaborations with EU nations to facilitate translational and clinical research on tools to slow the emergence and spread of antimicrobial resistance. US agencies will also explore collaborations with the New Drugs 4 Bad Bugs (ND4BB) programs of the Innovative Medicines Initiative.	Yes	• Per the NAP First 180 Days Report, the following activities were noted accomplished or ongoing as of November 2015: ○ Under the auspices of TATFAR, NIAID holds annual biannual and ad hoc phone calls with the European Commission's Directorate General for Research and Development in order to exchange and align research priorities. ○ NIH had signed a joint Letter of Intent to collaborate with the Indian Council of Medical Research on a joint project to address antibacterial resistance. ○ An NIAID representative participated in WHO consultations on action plans for sexually transmitted infection vaccines and diagnostics, including for multidrug resistant *N. gonorrhoeae*. ○ NIAID and the European Medicines Initiative's New Drugs for Bad Bugs program were planning to co-sponsor a meeting in early 2016 to explore barriers to efficient clinical trials of antibacterial drugs. ○ TATFAR members met in Luxembourg in October 2015 to chart the next 5-year TATFAR implementation period, with input from EU member states. ○ NIAID and the Swedish Research Council were planning to co-sponsor a workshop in early 2016 to promote international collaboration among antibacterial resistance researchers. • The US is a founding member of the Global AMR R&D Hub, which was called for in the 2017 G20 Leader's statement to coordinate and collaborate with fellow donor countries and foundations on AMR R&D. As reported in 2018, the HHS OGA holds a seat on the board and continues to advocate for the US government approach to R&D and economic incentives (Progress Report: Years 1 and 2). • NIH's engagement with TATFAR has facilitated the alignment of US and EU AMR research activities and greater access to important patient populations. As of 2018, NIH/NIAID was supporting a phase 3 clinical trial evaluating the optimal use of an older antibiotic (colistin), alone or in combination with a carbapenem, in patients with MDR Gram-negative infections. In 2017 and 2018, European clinical trials networks joined this trial (Progress Report: Year 3). • As reported in 2018, the ARLG was adding US sites to ongoing international efforts supported by industry and the Brussels-based Innovative Medicines Initiative Joint Undertaking and the

		Combating Antimicrobial Resistance in Europe (COMBACTE) consortium. This included a phase 2 trial evaluating an investigational monoclonal antibody to prevent pneumonia caused by *P. aeruginosa* (Progress Report: Year 3). • As noted in 2018, NIH continues to engage new international partners and increase global research collaborations. For example, the ARLG was conducting an observational clinical study on CRE at sites in the US, Australia, South America, China, and Singapore (Progress Report: Year 3).
Within 3 years: US agencies and partners in industry and academia will establish or expand additional international partnerships to advance research to reduce AR through the development of point-of-care diagnostics, vaccines, and drugs.	Yes	• In September 2018, CDC and the OGA launched the Antimicrobial Resistance Challenge at the UN General Assembly to catalyze global action against antibiotic resistance. A year later, CDC announced this challenge had resulted in nearly 350 commitments from government health officials, pharmaceutical and health insurance companies, and others from 33 countries to make formal commitments that further the progress against AMR, such as by improving appropriate antibiotic use (GAO Report, CDC AMR Challenge). The five commitment areas of the AMR Challenge were (1) tracking and data, (2) infection prevention and control, (3) antibiotic use, (4) environment and sanitation, and (5) vaccines, therapeutics, and diagnostics. • Per HHS personnel in April 2021: Work relevant to this milestone was a priority for the 2015-20 National Action Plan. HHS's success in this area has driven interest on this topic from other countries (e.g., research on point-of-care diagnostics, vaccines, and drugs; identifying economic incentives). After CARB-X was implemented and became successful, HHS helped BARDA and Wellcome Trust identify international partners to join CARB-X. • Per NIH personnel in April 2021: ○ NIH's engagement with TATFAR has facilitated alignment of US and EU AMR research activities and greater access to critically important patient populations. NIH/NIAID is supporting a Phase 3 clinical trial evaluating the optimal use of an older antibiotic (colistin), alone or in combination with a carbapenem, in patients with MDR Gram-negative infections (NCT01597973). In 2017 and 2018, European clinical trials networks joined this trial. In addition, the ARLG added US sites to ongoing international efforts supported by the Brussels-based Innovative Medicines Initiative's COMBACTE consortium. This includes a Phase 2 trial (EVADE), evaluating an investigational monoclonal antibody to prevent pneumonia caused by *P. aeruginosa* (NCT02696902). NIH continues to engage new international partners and increase global research collaborations. For example, the ARLG has completed an observational clinical study on MDR organisms at sites in the US, Australia, New Zealand, South America, Central America, China, Singapore, and the Middle East, and has entered into a strategic alliance

		with COMBACTE. In November 2018, the ARLG and University Medical Center Utrecht signed an MOU to ensure coordination among US and European clinical research efforts. The MOU enables more efficient collaboration between US and EU clinical research networks (Collaborations Strengthen Global Fight against Antibacterial Resistance). ○ NIH/NIAID supported several AMR sequencing and bioinformatics projects in Thailand and India to better understand molecular mechanisms of AMR and patterns of resistance. NIH/NIAID and the Indian Council of Medical Research collaborated on a pilot project using genomics, bioinformatics and systems biology to compare MDR *Acinetobacter* strains from neonatal ICUs in India and the US. ○ Per USAID personnel in April 2021: USAID supports the Coalition for Epidemic Preparedness Innovations' (CEPI's) mission is to stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks (CEPI 2020).
Within 3 years: USDA will establish or expand five collaborative international partnerships to facilitate research regarding development of alternatives to antibiotics, as well as vaccines and new antimicrobial drugs that are less likely to develop resistance.	Yes	• Reports for the following symposiums are available online (Alternatives to Antibiotics Animal Health Care): ○ In 2016, the 2nd International Symposium, Alternatives to Antibiotics, Challenges and Solutions in Animal Production took place in Paris, France. ○ In 2019, the 3rd International Symposium, Alternatives to Antibiotics, Challenges and Solutions in Animal Health and Production took place in Bangkok, Thailand (Callaway 2021). • Per USDA ARS personnel in April 2021: ARS, in collaboration with FDA, NIH, and the support of international partners, including the support of OIE and the European Medicines Agency (EMA), successfully recruited leading internationally-recognized experts to help organize a symposium in December 2019.
Objective 5.6: Support countries to develop and implement national plans to combat antibiotic resistance and strategies to enhance microbial stewardship.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: US agencies, led by HHS/OGA, will collaborate with the global community to ensure that the *WHO Global Action Plan on Antimicrobial Resistance* incorporates approaches and interventions that benefit all	Yes	• The WHO *Global Action Plan on Antimicrobial Resistance*, adopted in May 2015, calls for the development of WHO Member State national action plans within 2 years (NAP First 180 Days Report). • As of November 2015, through the GHSA, and other venues including the G7, the US and partner countries were developing a repository of national action plans in collaboration with the WHO Secretariat and are promoting partnerships between countries (NAP First 180 Days Report). • Per HHS personnel in April 2021:

healthcare programs and calls for the development of national plans to combat antibiotic resistance (see also Sub-Objective 5.4.2).		○ WHO has been keeping track of which countries have national action plans to combat antibiotic resistance (WHO Antimicrobial Resistance Library of National Action Plans). ○ With few exceptions (mostly in conflict areas), countries have national action plans in place. Not all countries have funded and implemented the national action plans, however, and the next, critical step is to help countries develop strategies to implement the plans (e.g., building infrastructure). OGA recently deployed an OGA personnel member to the WHO AMR Directorate to work on the implementation of in-country national action plans.
Within 3 years: CDC and USAID will provide technical assistance to foreign ministries of health and agriculture to advance the use of tools and interventions that have proven successful at slowing the spread of resistance in healthcare and agricultural settings (e.g., infection prevention and control and antibiotic stewardship programs in hospitals).	Yes	• Per CDC personnel in April 2021: CDC, both through engagement with the GHSA and through the ARSI aligned with the WHO *Global Action Plan*, supports the 17 Phase I countries and Thailand, Georgia, and CARICOM by providing technical assistance to ministries of health on national plans and policies for AR surveillance and infection prevention and control in healthcare facilities. CDC has worked with public health, laboratory, and global partners such as WHO to: ○ Develop and deploy a laboratory assessment tool for AMR surveillance. ○ Pilot tele-mentoring and training between US and international clinical labs. Develop training resources for resource-limited settings. ○ Provide tools to contain CRE in resource-limited settings, including a field guide for implementation of WHO core components for infection prevention and control, both released in 2017. ○ Support response to outbreaks of antibiotic resistant organisms. • Under the GHSA, USAID has assisted 10 countries in training health providers on how to reduce HAIs. For example, in 200 health facilities in Sierra Leone, USAID funded improvements in water and sanitation, and trained staff on infection prevention and control (NAP Progress Report for Years 1 and 2).
Within 3 years: US agencies, led by USAID and CDC, will support at least four low- and middle-income countries (LMICs) in developing and/or operationalizing national antimicrobial resistance containment plans, national healthcare-facility infection prevention and control plans,	Yes	• Per CDC personnel in April 2021: CDC has assisted in the development of national plans and operational strategies for India, Vietnam, Senegal, Georgia, and Kenya. CDC has assisted with the initiation of AMR containment programs through improved infection prevention and control in Vietnam, Thailand, Vietnam, and Kenya. CDC has assisted partners with outbreaks of AMR organisms in India, Vietnam, Kenya, Panama, and Fiji. • USAID assisted Swaziland (Eswatini) in developing a national containment strategic plan for 2017-2021 (NAP Progress Report: Years 1 and 2). • USAID assisted the National AMR Advisory Committee in Ethiopia with a plan of action to guide interventions (NAP Progress Report: Years 1 and 2).

antimicrobial stewardship strategies, or comparable packages of interventions.		• USAID implements a pilot AMR stewardship program targeting the animal health sector in Senegal to promote rational use of antibiotics in the livestock sector (NAP Progress Report: Year 3). • As of 2018, USAID was working in 10 countries in Asia and 14 countries in Africa to strengthen One Health national AMR plans (NAP Progress Report: Year 3).

Within 5 years:
US agencies, led by USAID and CDC, will:
• Support at least three additional LMICs in developing and/or operationalizing national antimicrobial resistance containment plans, national healthcare facility infection prevention and control plans, antimicrobial stewardship strategies, or comparable packages of interventions.
• Support the implementation of national infection prevention and control programs in at least twenty priority healthcare facilities in eight LMICs.
• Support operational research that leads to remedial actions and improved antibiotic use in at least eight healthcare facilities in four LMICs.
• Develop and disseminate at least four global technical leadership documents/reports for use by LMICs and the
	Yes	• As of 2018, USAID was working in 10 countries in Asia and 14 countries in Africa to strengthen One Health national AMR plans (NAP Progress Report: Year 3).
		• Per CDC personnel in April 2021:
		  ○ CDC has assisted in the development of national plans and operational strategies for India, Vietnam, Senegal, Georgia, and Kenya.
		  ○ CDC has assisted with the initiation of AMR containment programs through improved infection prevention and control in Vietnam, Thailand, Vietnam, and Kenya.
		  ○ CDC has assisted partners with outbreaks of AMR organisms in India, Vietnam, Kenya, Panama, and Fiji.
		  ○ CDC has assisted with the implementation of infection prevention and control programs in over 40 facilities in Kenya, Uganda, Sierra Leone, Liberia, South Africa, Thailand, India, Vietnam, and Colombia.
		  ○ CDC has or is conducting operational research that will yield important data to guide policy on antibiotic use and infection control in 15 facilities in India, Vietnam, South Africa, Kenya, Senegal, Chile, Bangladesh, and Botswana.
		  ○ CDC has developed and disseminated (or is in the process of finalizing) a global tool for antibiotic stewardship in resource-limited settings; a tool to assess readiness of laboratories to conduct AR surveillance; protocols for HAI surveillance in resource-limited settings; infection control guidelines for resource-limited settings; and infection control training materials for resource-limited settings.
		  ○ CDC is working with WHO to draft guidance for Antimicrobial Resistance National Reference Laboratories. This guidance will include what testing capacities are needed at the national level and what methods for testing are recommended.
		• Per USAID personnel in April 2021:
		  ○ Through its partnership with FAO, USAID has supported the development and implementation of national action plans to address AMR in 10 countries (Bangladesh, Cambodia, Democratic Republic of the Congo [DRC], Kenya, Laos, Indonesia, Senegal, Sierra Leone, Tanzania, Vietnam).

global community, that review approaches, results, lessons learned, and recommendations related to key antibiotic containment strategies.		○ In 11 GHSA countries, USAID helped establish and/or facilitate meetings on AMR with representation from organizations involved in the countries' One Health activities to enhance multi-sectoral implementation of national action plans on AMR. ○ In Côte d'Ivoire, USAID supported the AMR technical working group to develop and finalize an advocacy document to accompany the NAP-AMR, a NAP-AMR governance handbook, and the national AMR policy document. ○ In Bangladesh and Kenya, USAID supported the drafting of complementary monitoring and evaluation frameworks for the NAP-AMR to support their implementation. ○ USAID supported the government of Ethiopia in drafting and implementing the second edition of the Strategy for the Prevention and Containment of Antimicrobial Resistance (2015-2020) including supported the National AMR Advisory Committee in developing a plan of action. ○ In Uganda, USAID is supporting efforts to develop/operationalize an online information exchange platform for stakeholders in human, animal, and environmental sectors to support implementation of NAP-AMR activities. ○ In South Africa, USAID supported the finalization and publication of the AMR implementation plan and the development and operationalization of provincial AMR plans. ○ In Sierra Leone, USAID supported the development of a draft National Strategic Plan on Antimicrobial Resistance 2017-2021, and expanded its support for ongoing pharmaceutical sector strengthening interventions in the country to include Drug and Therapeutics Committees. ○ In Swaziland (Eswatini), USAID assisted the Ministry of Health in developing and finalizing a draft of the National Antimicrobial Resistance Containment Strategic Plan 2017-2021 of the Kingdom of Swaziland (Eswatini). ○ USAID helped Burkina Faso, Cameroon, Côte d'Ivoire, and Mali assess their national AMS policies, guidelines, and regulations in both the human and animal sectors. ○ In Namibia, USAID supported technical assistance to the Ministry of Health and Social Services AMR technical working group (TWG) to review and finalize the situational analysis regarding strategies to combat AMR and the multisector action plan for containing AMR in Namibia. ○ Through USAID's support (almost $2.8 billion since 2001) of GAVI, the Vaccine Alliance, more than 60 countries have introduced pneumococcal conjugate vaccine (USAID Immunization).

		○ In 25 priority countries, USAID has supported partners to strengthen coverage and quality of maternal, newborn, and child health platforms to diagnose, treat, and apply rational antimicrobial use for infections (USAID Child Health). ○ USAID assisted countries in planning and implementing a range of innovative training activities from curriculum design/reform and e-learning course development to in-service training-of-trainer workshops. Examples include: ▪ USAID partners strengthened capacities of local e-learning trainers in Burkina Faso, Kenya, Mali, Senegal, and Tanzania, and introduced them to distance learning platforms, equipping counterparts with competencies required to prevent healthcare associated infections and support institutionalization of IPC/AMS practices. ▪ USAID collaborated with Knowledge for Health to develop a two-part e-Course on AMR, which is available on the Global Health eLearning Center. Between September 16, 2016 (date of publication of the revised version) and May 20, 2020, a total of 7,015 individuals from 129 countries had taken the Part 1 course and earned certificates after completing and passing all the required tests. Similarly, between November 11, 2015 (date of publication of the revised version) and May 20, 2020, a total of 4,819 individuals from 117 countries had taken the course and earned certificates after completing and passing the tests. ▪ In Kenya, USAID collaborated with the National Nurses Association of Kenya, the Ministry of Health, and a task force comprising key medical professional associations to develop a continuing professional development- and re-licensure-linked in-service IPC training curriculum and implementation strategy for delivery through professional associations. ▪ Through One Health Workforce and One Health Workforce Next Gen USAID has supported a number of activities that focus on training the current and future health workforce about the importance of mitigating AMR. ○ In more than 25 countries, USAID supports local governments and stakeholders to strengthen WASH systems at household, community, and institutional levels. With USAID support, partners have pioneered the Clean Clinic Approach, a quality improvement strategy to strengthen WASH in health facilities (USAID Water and Sanitation). ○ USAID provides direct support to designated health facilities to strengthen IPC in nine countries. This includes establishing or strengthening IPC committees and/or helping those committees develop action plans. Of the 77 health facilities, 62 have functioning

		IPC committees, 24 are using standardized tools to monitor IPC and improve practices, and 47 are using continuous quality improvement (CQI) as a way to identify and address IPC deficiencies. ○ Using an infection control self-assessment tool (ICAT) developed with support from USAID, USAID partners helped country stakeholders develop, implement, and monitor infection prevention and control practices in hospitals. In Namibia and South Africa, ICAT was adapted as an official tool to improve IPC practices. ○ In Ethiopia, USAID helped develop, print, and distribute 4,000 sets of standard operating procedures to regional health bureaus and 400 hospitals as part of the Ministry of Health's plan for building capacity to produce alcohol-based hand rub locally. ○ In eight countries, USAID provides direct support to 75 health facilities to strengthen AMS practices. ○ USAID supports GHSA partner countries in updating their Essential Medicines Lists and/or standard treatment guidelines to reflect WHO AWaRe (Access, Watch, Reserve) classification of antimicrobials. ○ USAID supported mHealth interventions (i.e., use of mobile and wireless technologies to support the achievement of health objectives) through the development of mobile application for dissemination of standard treatment guidelines and the essential medicines list in South Africa, and through piloting SMS-based adherence reminder system for patients receiving antiretroviral treatment in Namibia. ○ USAID supported the implementation and completion of the research project "Using Electronic Pharmacy Dispensing Data for Surveillance of Outpatient Antibiotic Consumption and Monitoring of Antibiotic Prescribing Practices at District and Provincial Hospitals in the South African Public Sector: A Feasibility Study in North West Province." ○ USAID provided mini-grants to three Ecumenical Pharmaceutical Network (EPN) member organizations and supported EPN headquarters in providing technical assistance and oversight to them to design, implement, and report on antimicrobial stewardship- and containment-related interventions. This included participation from the Zimbabwe Association of Church-Related Hospitals, Gertrude's Children's Hospital in Kenya, and the Christian Health Association of Malawi. ○ USAID supported the creation of six how-to guides to provide a standard and step-wise approach to the GHSA activity implementation process, a list of steps, and available resources, all of which countries can adapt for their own implementation plans: ▪ A technical guide to implementing WHO's AWaRe antibiotic classification

		▪ A technical guide to implementing a continuous quality improvement approach to strengthen IPC programs at health facilities ▪ A technical guide to strengthening the multisectoral coordination body to address AMR ▪ A technical guide to IPC facility program assessment and development of IPC improvement plans ▪ A technical guide to implementing facility-level antimicrobial stewardship programs ▪ A technical guide to learning and capacity development to address AMR ○ The USAID-funded Systems for Improved Access to Pharmaceuticals and Services Program published the following seminal documents: ▪ *Enhancing Health Outcomes for Chronic Diseases in Resource-Limited Settings by Improving the Use of Medicines: The Role of Pharmaceutical Care* provides a framework, scope, and standards for implementing pharmaceutical care in LMICs. ▪ *Systems-based Approaches to Improving Medication Adherence* describes strategies and tools that help to address adherence using a systems strengthening approach. ▪ *Developing, Implementing, and Monitoring the Use of Standard Treatment Guidelines* is a how-to-manual that provides practical guidance on the various aspects of standard treatment guidelines development and management and includes multiple tools, templates, examples, and country/local-level case studies. ▪ *Revising Preservice Curriculum to Incorporate Rational Medicine Use Topics* details how to incorporate rational medicine use and AMR components in health professional training programs and includes several tools and templates to facilitate the process. ▪ *Building Coalitions for Containing Antimicrobial Resistance* describes experiences and lessons learned from Systems for Improved Access to Pharmaceuticals and Services (SIAPS) in building coalitions against AMR at the country and regional levels and includes user-friendly implementation tools and templates. ○ Through USAID support to FAO, the following were developed: ▪ Antimicrobial resistance policy review and development framework

		▪ Regional Antimicrobial Resistance (AMR) Monitoring and Surveillance Guidelines Series: Volume 1: Monitoring and surveillance of AMR in bacteria from healthy animals intended for consumption
Within 5 years: US agencies, led by HHS/OGA, the Department of State and USAID, will support international advocacy and coordination to contain the common threat of antimicrobial resistance, through collaboration with WHO and other partners and participation in multilateral forums, such as the 4th International Conference on Improving Use of Medicines (ICIUM).	Yes	• In December 2017, the Department of State worked with HHS, USDA, US Department of the Interior, and other agencies to secure language regarding antibiotic pollution in the environment at the Third UN Environment Assembly in Nairobi. The language calls on the UN Environment Program Secretariat to work with other UN system agencies to support the strengthening of the evidence base regarding antibiotics in the environment, while also calling on member states to consider evidence-based policy measures (NAP Progress Report: Year 3). • From September 2017 to April 2018, the Department of State leveraged its "Diplomacy Lab" program to engage US-based academic teams investigating (1) technologies for better sampling of antibiotic pollution in the environment and (2) awareness-raising materials produced by WHO and others, to study their efficacy in conveying clear and accurate AMR information to non-scientific audiences (NAP Progress Report: Year 3). • In Year 4 of the CARB National Action Plan, the Department of State focused on activities to empower on-the-ground action, such as: ○ The Department of State deployed Dr. Michael Osterholm as a Science Envoy for Global Health Security for a one-year appointment, beginning in July 2018. During this time, Dr. Osterholm engaged foreign governments, spoke at major conferences, and used public diplomacy activities to encourage governmental transparency and citizen involvement in global health security issues. Dr. Osterholm visited Australia, Ghana, Indonesia, Malaysia, New Zealand, and Vietnam (NAP Progress Report: Year 4). • In December 2018, the Department of State, along with CDC, the US Geological Survey, the World Bank, the Massachusetts Institute of Technology, and the Governments of Singapore and Australia, convened a workshop on implementing AMR national action plans in Southeast Asia under the US-Singapore Third Country Training Program (NAP Progress Report: Year 4). • USAID, through a One Health approach with FAO and WHO in Asia and Africa, worked to develop a more comprehensive understanding of current patterns of antibiotic use and regulatory practices within the livestock and aquaculture industries (NAP Progress Report: Year 3). • USAID is promoting best practices and prudent use of antibiotics across the animal-health value chains (NAP Progress Report: Year 3). • As of 2018, USAID was working in 10 countries in Asia and 14 countries in Africa to strengthen One Health national AMR plans (NAP Progress Report: Year 3). • USAID is involved with the GHSA (USAID GHSA Fact Sheet, GHSA website).

Within 5 years:
USDA will use Veterinary Accreditation training modules—including the Judicious Use Module —to assist countries in at least three WHO regions in developing sustainable veterinary service capacity to monitor and slow antibiotic resistance and to report outbreaks of drug resistant disease to WHO, international surveillance networks, collaborative reporting structures, or (when appropriate) to International Health Regulations (IHR) focal points.
	Partially	• Per USDA personnel in April 2021:
		  ○ USDA APHIS worked on translating modules, though there were some challenges. For example, many of the modules are designed for a US audience (e.g., focused on FDA's VFD) and the general ones (e.g., general module on antibiotic stewardship) brought questions of who would be responsible for web hosting and updating the modules that required funding for translating services.
		  ○ The modules were translated into Spanish.
		  ○ USDA APHIS shared the translated modules with their Foreign Agriculture Service (FAS).
		• In May 2016, in response to a request from Vietnam's Ministry of Agriculture and Rural Development (MARD), USDA previewed MARD's draft, One Health Strategic Plan for Zoonotic Diseases, 2016-2020, which included MARD's planned actions for combatting antibiotic resistant bacteria, and provided technical feedback to MARD. In May 2017, USDA also provided MARD feedback on Vietnam's proposed National Action Plan for the Reduction of Antimicrobial Use and Antimicrobial Resistance in Livestock Production and Aquaculture.

Within 5 years: USDA will translate the Judicious Use Module into three other languages.	Partially	• Per USDA personnel in April 2021, the modules were translated into Spanish. This milestone was not fully met (i.e., translation into one language instead of three languages) because of resource limitations.
***Objective 5.7**:* Partner with other nations to promote quality, safety, and efficacy of antibiotics and strengthen their pharmaceutical supply chains.		
Milestone	**Accomplished?**	**Comments**
Within 3 years: US agencies, led by USAID, will support country systems to enhance access to and appropriate use of quality-assured, safe, effective essential antibiotics through improved medicines, regulatory capacity and quality assurance systems, modern procurement practices, reliable and secure supply chains,	Yes	• USAID supported Ministries of Health in six countries (Angola, Guinea, Mozambique, Namibia, South Africa, and Ukraine) to develop/revise national essential medicine lists (NAP Progress Report: Years 1 and 2). • USAID support resulted in WHO Prequalification of manufacturers for seven products, including amoxicillin, cycloserine, streptomycin, and capreomycin (NAP Progress Report: Year 3). • In FY2016, USAID facilitated the training of >1,100 individuals from 19 countries on topics concerning the quality assurance of medicines, to include inspection, Good Manufacturing Practices, post-marketing surveillance, quality control, and registration (NAP Progress Report: Years 1 and 2). • In three countries (Bangladesh, the Philippines, Senegal), USAID supported the development of national strategic plans for the health sector that strengthen regulatory capacity, establish

and equitable pharmaceutical services in at least four LMICs.		efficient medicine registration systems, and reduce backlogs and wait times for registration (NAP Progress Report: Years 1 and 2).
		• USAID supported strengthening of regulatory capacity and improving processes for registering medicines in six countries (Angola, Bangladesh, DRC, Ethiopia, Mozambique, Namibia (NAP Progress Report: Years 1 and 2).
		  ○ In Ethiopia, USAID supported the regulatory authority to expedite the review of dossiers, eliminate the backlog of new medicine applications, and reduce the registration lead time for fast-track medicines from an average of 24 months to 4.5 months (NAP Progress Report: Year 3).
		• USAID supported three countries (Bangladesh, Mozambique, Namibia) in implementing a web-based regulatory information system (Pharmadex) (NAP Progress Report: Years 1 and 2).
		• With the Promoting the Quality of Medicines (PQM) program:
		  ○ USAID developed/updated 745 new quality assurance policies, procedures, or guidelines in four countries (Nigeria, Indonesia, Mozambique, Ethiopia) (NAP Progress Report: Year 3).
		  ○ USAID worked with 62 manufacturers to improve the supply of quality-assured essential medicines (NAP Progress Report: Year 3).
		• USAID supported a new Master's of Regulatory Affairs program at Addis Ababa University in Ethiopia (NAP Progress Report: Year 3).
		• Working with SIAPS (which was active from 2011 to 2018), USAID developed a two-part online course on AMR that has trained people from 73 countries (NAP Progress Report: Years 1 and 2, SIAPS website).

Within 5 years: US agencies, led by USAID, will: • Support country systems that enhance access to quality-assured, safe, effective essential antibiotics in at least eight LMICs. • Develop and disseminate at least four global technical leadership documents/reports, for use by LMICs and the global	Yes	Support country systems that enhance access to quality-assured, safe, effective essential antibiotics in at least eight LMICs. • In FY2016, USAID facilitated the training of >1,100 individuals from 19 countries on topics concerning the quality assurance of medicines, to include inspection, Good Manufacturing Practices, post-marketing surveillance, quality control, and registration (NAP Progress Report: Years 1 and 2). • In three countries (Bangladesh, the Philippines, Senegal), USAID supported the development of national strategic plans for the health sector that strengthen regulatory capacity, establish efficient medicine registration systems, and reduce backlogs and wait times for registration (NAP Progress Report: Years 1 and 2).

community, that review approaches, results, lessons learned, and recommendations on access to quality-assured, safe, effective antibiotics and issues related to regulation, quality assurance, and patient safety in the use of antibiotics.		• USAID supported strengthening of regulatory capacity and improving processes for registering medicines in six countries (Angola, Bangladesh, DRC, Ethiopia, Mozambique, Namibia (NAP Progress Report: Years 1 and 2).
		• USAID supported three countries (Bangladesh, Mozambique, Namibia) in implementing a web-based regulatory information system (Pharmadex) (NAP Progress Report: Years 1 and 2).
		• With the PQM program:
		  ○ USAID developed/updated 745 new quality assurance policies, procedures, or guidelines in four countries (Nigeria, Indonesia, Mozambique, Ethiopia) (NAP Progress Report: Year 3).
		  ○ USAID worked with 62 manufacturers to improve the supply of quality-assured essential medicines (NAP Progress Report: Year 3).
		• Per USAID personnel in April 2021:
		  ○ Since 2015, USAID has provided technical assistance to medicines regulatory authorities (MRAs) in 10 countries (Bangladesh, Ethiopia, Guinea, Indonesia, Liberia, Mali, Mozambique, Nigeria, Pakistan, and Senegal) to develop or revise national policies and regulations, as well as legislation to ensure quality assurance topics were adequately covered and that the overarching regulatory framework was appropriate to their context and met internationally accepted standards.
		  ○ USAID provided technical assistance to the national medicines regulatory authorities in Bangladesh, Mozambique, Nepal, Philippines and Rwanda to assist them to raise the maturity level according to the WHO Global Benchmarking Tool classification with the aim of attaining maturity level 3, which is a functional regulatory authority.
		  ○ USAID supported the development and updating of the legal and regulatory framework in Mozambique, Nepal and Rwanda, and documented and implemented quality management systems in in these countries.
		  ○ USAID improved key regulatory processes for product registration by conducting assessments of registration systems in 10 countries (Bangladesh, DRC, Mali, Mozambique, Nepal, Philippines, Rwanda, Senegal, Tanzania, and Uganda) to identify barriers that impede access to maternal, newborn, and child health (MNCH) medicines and medicines in general.
		  ○ From 2015-2020, USAID-supported national drug quality control laboratories in the following countries achieved international recognition (ISO/IEC 17025 accreditation or WHO Prequalification) for laboratory competency, affirming their ability to produce reliable and accurate data: Ghana, Indonesia, Kenya, Myanmar, Nigeria, and Pakistan.

		○ Since 2015, USAID provided technical assistance to more than 30 manufacturers in USAID-supported countries for locally-produced to improve good manufacturing practices and the quality of product produced. Between 2015 and 2020, 16 quality-assured anti-TB medical products (API [active pharmaceutical ingredient] and FPP [finished pharmaceutical product]) and five quality-assured API sources for neglected tropical diseases were recognized by international organizations as meeting quality standards. ○ USAID programs strengthened regulatory capacity and improved processes for medicines registration in Angola, Bangladesh, DRC, Ethiopia, Mozambique, and Namibia. Three of these countries (Bangladesh, Mozambique, and Namibia) adopted and/or implemented the internationally endorsed Common Technical Document format and specifications to standardize the medicines registration application process. With USAID support, Bangladesh, Ethiopia, Mozambique, and Namibia implemented the registration module of a web-based regulatory information system (Pharmadex) that makes their processes more efficient and transparent. USAID also supported DRC to install similar software to computerize and reduce biases throughout the medicines registration process. ○ In Ethiopia, USAID supported the integration of a Good Manufacturing Practices roadmap into the National Plan of Action for Pharmaceutical Manufacturing Development in Ethiopia (2015-2025). In 2016, in collaboration with Jimma University, USAID supported the Ethiopian regulatory authority (Food, Medicine and Health Care Administration and Control Authority) to evaluate 467 dossiers, which eliminated the backlog of new medicine applications in the country. ○ In Cameroon, Mali, Swaziland (Eswatini), Burundi, Namibia, Uganda, Kenya, and Ethiopia, USAID helped establish forecasting and supply planning coordination committees, with specific terms of reference, across health programs to create more streamlined, horizontal, and reliable quantification systems. Also, quantification interventions implemented by USAID Partners contributed to the increase in availability in commodities at the central warehouse and health facility levels in many USAID-supported countries. For example, in Mali, Ethiopia, and DRC, the decrease in stock-outs from baseline was equal to 22%, 22%, and 62%, respectively. ○ The SUGEMI pharmaceutical management system in the Dominican Republic that USAID helped develop encourages health facilities to report their stock status and receive feedback, thereby ensuring that medicine availability remains high. During the final

		quarter of 2016, health facilities reported that adult antiretroviral availability was 93%, while essential medicines availability was 92%. Develop and disseminate at least four global technical leadership documents/reports, for use by LMICs and the global community, that review approaches, results, lessons learned, and recommendations on access to quality-assured, safe, effective antibiotics and issues related to regulation, quality assurance, and patient safety in the use of antibiotics. • Per USAID personnel in April 2021: ○ Since 2015, USAID has supported the development of seven product information reports for key medical products, including antibiotics, to provide critical information and guidance to manufacturers and stakeholders. ○ USAID developed the Medicines Quality Database (MQDB), a free, web-based internationally referenced database. The MQDB has results for over 17,000 medicines quality tests conducted by USAID and country counterparts in 16 countries in Africa, Central and South America, and Southeast Asia. ○ USAID supported the development of Training on Pharmaceutical and Medical Commodities Supply Chain Management in Humanitarian Response Settings, which helps with building capacity of humanitarian aid partner staff on humanitarian supply chain management for the effective delivery of pharmaceuticals and medical commodities. ○ USAID supported the development of Developing a Central Medical Store Strategic Plan: 10 Steps for Global Health Professionals, a resource for developing a CMS strategic plan to align pharmaceutical supply chain objectives with overall public-sector health supply chain strategies.
***Objective 5.8**:* Coordinate regulatory approaches by collaborating with international organizations such as FAO and OIE to harmonize international data submission requirements and risk assessment guidelines related to the licensure and/or approval of veterinary medicinal products, including antibacterial agents, vaccines, and diagnostics, to the extent possible.		
Milestone	**Accomplished?**	**Comments**
Within 1 year: FDA and USDA will contribute to and participate in global or regional cooperation with international organizations, including AGISAR, the International Cooperation on	Yes	• In September 2015, the VICH expert working group on electronic submission of adverse event reporting met via teleconference to discuss implementation of global harmonized pharmacovigilance guidelines. Discussion included routine maintenance of finalized pharmacovigilance guidelines, the finalization of the validation procedures for electronic submission of adverse event reports from industry to their respective regulatory authority, and the creation and use of harmonized xml electronic messages to be sent by regulatory authorities as acknowledgement for the respective industry submissions (NAP First 180 Days Report).

Harmonization of Technical Requirements for Registration of Veterinary Products (VICH), the Institute for International Cooperation in Animal Biologics (IICAB), and the International Medical Device Regulators Forum (IMDRF), regarding development of vaccines, antibacterial drugs, and diagnostic tests for use in agriculture, and regarding risk assessments of the use of medically-important antibiotics in agriculture.		• In December 2016, USDA and OIE co-hosted a symposium on alternatives to antibiotics in animal production. The objectives were to highlight promising research results and novel technologies, assess challenges associated with their commercialization and use, and provide actionable strategies to support their development. Participants also discussed issues pertaining to regulatory pathways (e.g., in Europe, the US, and Taiwan) for licensing novel technologies and alternative approaches (CIDRAP ASP Policy Update 2017). • As reported in 2017, the FDA and USDA were collaborating with international organizations on the development of vaccines, antimicrobial drugs, and diagnostic tests for use in agriculture (NAP Progress Report: Years 1 and 2).
Within 1 year: USDA will maintain the US commitment to VICH and IICAB, expanding the Outreach Forum to: • Promote the use of VICH guidance for safety, quality, potency and effective use of vaccines outside of the three cooperating major regions (the US, Japan, and the European Union). • Facilitate input from a broadened base of participating countries and economies.	Yes	• Per the NAP First 180 Days Report, as of November 2015, USDA APHIS was maintaining US commitment to VICH and IICAB, expanding the Global Outreach Forum by continuing to participate in the annual Veterinary Biologics Training Program held in Iowa and sponsored by USDA APHIS, Center for Veterinary Biologics, and Iowa State University. The training course gives participants an overview of the scientific principles of vaccines and vaccination, and of the USDA regulatory process for assuring the purity, safety, potency, and efficacy of veterinary biologics. • The International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH) is a trilateral (EU-Japan-USA) program aimed at harmonizing technical requirements for veterinary product registration. • The Institute for International Cooperation in Animal Biologics (IICAB) is noted on the USDA website, specifically for the IICAB's annual Veterinary Biologics Training Program (USDA APHIS CVB website).
Within 1 year: USDA will plan and participate in at least three VICH Global	Yes	• USDA representatives participated in the following VICH Outreach Forums in 2015-2016 (VICH Library VICH Outreach Forum Minutes): ○ 5th meeting on February 24-25, 2015 in Washington, DC, USA ○ 6th meeting on October 26-27, 2015 in Tokyo, Japan

Outreach Forums over the first two years.		○ 9th meeting on November 14-16, 2017 in Tokyo, Japan • Per USDA personnel in April 2021: The USDA FAS contributed to and provided support at a VICH workshop on June 24, 2015, in Dar Es Salaam, Tanzania. USDA APHIS is currently working with steering and working groups that continue to harmonize regulatory policies for veterinary biologics and diagnostic test kits.
Within 1 year: USDA will hold at least one international meeting in collaboration with IICAB to discuss US regulatory policy in a workshop setting.	Yes	• USDA APHIS, in collaboration with IICAB, held a Potency Specifications - US Regulatory Policy Workshop on April 21-22, 2015, in Ames, Iowa (NAP First 180 Days Report).
Within 3 years: FDA and USDA will consult with regional health authorities about their processes for achieving regulatory approval of new antibacterial drugs, diagnostics, and vaccines for use in medicine and agriculture and for conducting risk assessments on the use of medically-important antibiotics in agriculture.	Yes	• As reported in 2017, FDA had met with regulatory counterparts from the EMA and Japan's Pharmaceuticals and Medical Devices Agency to discuss approaches for evaluating antibacterial drugs in clinical trials (NAP Progress Report: Years 1 and 2). • In December 2016, USDA ARS, in collaboration with NIH NIAID and FDA and with the support of OIE, organized the Second International Symposium on Alternatives to Antibiotics (ATA) Challenges and Solutions in Animal Production. As of 2018, the meeting has led to one publication with authors from FDA and EMA, which highlights the regulatory pathways needed to enable licensing of alternatives to antibiotics (NAP Progress Report: Year 3, Ioannou 2018).
Within 5 years: FDA and USDA will engage China and additional interested partner countries to exchange technical information and harmonize approaches for risk assessment and regulation of veterinary medicinal products.	Yes	• USDA FAS supported ongoing USDA-FDA CVM outreach and training to Chinese Ministry of Agriculture stakeholders involved in: (1) drug residue monitoring and efforts to promote judicious use of medically important antimicrobial agents in food animals; and (2) risk assessment and approval of veterinary drugs (NAP First 180 Days Report). • Per USDA personnel in April 2021: ○ Through the Scientific Cooperation Exchange Program and in collaboration with China's Ministry of Agriculture (MOA), a US multi-disciplinary team, led by Michigan State University, visited Nanjing University, the China Agricultural University, and two institutes and a research center of the Chinese Academy of Sciences in June 2017, for cooperation on estimating and managing risks of antibiotic resistant bacteria in agriculture. The program focused on methods for molecular genetic surveillance of antimicrobial resistant bacteria in livestock, crops, and farmland.

		○ Through the OIE's World Fund for Animal Health, USDA collaborated with OIE to deliver the OIE Regional Workshop on the Database on Antimicrobial Agents Intended for Use in Animals in Americas workshop on September 27-28, 2019, in Jamaica, back-to-back with the American Committee of Veterinary Medicines annual seminar. Participants included OIE National Focal Points for Veterinary products from 23 OIE Members, along with representatives from FAO and regional animal health organizations, and private sector observers from the Americas region. The workshop focused on antimicrobial use (AMU) data collection and collation, AMU-related OIE standards and guidelines (e.g., animal biomass denominator), and transitions of the current data management system into a new database, and opportunities (e.g., stakeholder engagement) to improve the quality of AMU data collection and increase the efficiency of AMU data management with the new system. The workshop also promoted OIE Members' participation and response (94% overall) to the OIE's Fourth Annual Report on Antimicrobial Agents Intended for Use in Animals that was published in February 2020.
Within 5 years: FDA and USDA will work with OIE and other international partners on development of standardized methods of reporting antimicrobial drug use in animals.	Yes	• As reported in 2018, FDA CVM has collaborated with the Public Health Agency of Canada, USDA APHIS, and US and Canadian representatives on the OIE Global Harmonized Database ad hoc group, regarding biomass correction, normalization denominators, antimicrobial sales and sue data collection and reporting, and the OIE Global Harmonized Database reporting methods and formats. An interoffice working group conducted a case study of a US-specific approach to applying a biomass correction to antimicrobial sales data to help identify challenges to harmonizing global AMR requirements. While this method will not produces values directly comparable to the EMA ESVAC method, it will be a biomass correction representing new animal drug approvals and animal population and weights in the US. FDA published the proposed biomass denominator method in a Federal Register Notice in August 2017 and - as of October 2018 - was in the process of evaluating public comments received (NAP Progress Report: Year 3). • Per USDA personnel in April 2021: ○ USDA and FDA report together annually to OIE on antibiotic use data. ○ In September 2019, USDA APHIS personnel attended a Region of the Americas meeting in Jamaica that included a workshop on reporting antimicrobial use data. USDA APHIS personnel participated in a follow-up webinar in September 2020 and presented on NAHMS studies and how data collection on antimicrobial use is addressed in the US.

ACRONYMS

AAVLD: American Association of Veterinary Laboratory Diagnosticians; AAVMC: American Association of Veterinary Medical Colleges; ABATE: Active Bathing to Eliminate; ACESO: Austere Environments Consortium for Enhanced Sepsis Outcomes; AE: Armed Forces Europe; AFHSB: Armed Forces Health Surveillance Branch; AFRI: Agriculture and Food Research Initiative; AGISAR: Advisory Group on Integrated Surveillance of Antimicrobial Resistance; AHRQ: Agency for Healthcare Research and Quality; AMR: Antimicrobial resistance; AMU: Antimicrobial use; AP: Armed Forces Pacific; APHIS: Animal and Plant Health Inspection Service; APHL: Association of Public Health Laboratories; API: Active pharmaceutical ingredient; APM: Alternative payment model; AR: Antibiotic resistance; ARBI: Antibiotic Resistance Biopharmaceutical Incubator; ARG: Antimicrobial resistance gene; ARGC: antibiotic-resistant gonorrhea; ARI: Acute respiratory infection; ARLG: Antibacterial Resistance Leadership Group; ARMoR: Antibiotic Resistance Monitoring and Research; ARS: Agricultural Research Service; ARSI: Antibiotic Resistance Solutions Initiative; ASM: American Society for Microbiology; ASPR: Assistant Secretary for Preparedness and Response; AST: Antibiotic/antimicrobial susceptibility testing; ASTF: Antimicrobial Stewardship Taskforce; ASWG: Antimicrobial Stewardship Working Group; ATA: Alternatives to antibiotics; AU: Antimicrobial use/Antibiotic use; AUR: Antibiotic use and resistance; AVMA: American Veterinary Medical Association; AWaRE: Access, Watch, Reserve; BAA: Broad Agency Announcement; BARDA: Biomedical Advanced Research and Development Authority; BMGF: Bill & Melinda Gates Foundation; BRD: Bovine respiratory disease; BSL: Biosafety level; CAP: Community-acquired pneumonia; CARB: Combating Antibiotic-Resistant Bacteria; CARB-X: Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator; CARBIRUs: Combating Antibiotic-Resistant Bacteria Interdisciplinary Research Units; CARD: Comprehensive Antibiotic Resistance Database; CARICOM: Caribbean community; CAUTI: Catheter-associated urinary tract infections; CBDP: Chemical and Biological Defense Program; CBER: Center for Biologics Evaluation and Research; CDC: Centers for Disease Control and Prevention; CDER: Center for Drug Evaluation and Research; CDI: *Clostridioides difficile* infection; CDRH: Center for Devices and Radiological Health; CEAH: Center for Epidemiology & Animal Health; CEPI: Coalition for Epidemic Preparedness Innovations; CETR: Centers of Excellence for Translational Research; CfC: Condition for Coverage; CFR: Code of Federal Regulations; CHG: Chlorhexidine gluconate; CLSI: Clinical and Laboratory Standards Institute; CMS: Centers for Medicare & Medicaid Services; COP: Conditions of participation; COMBACTE: Combating Antimicrobial Resistance in Europe; CQI: Continuous quality improvement; CRADA: Cooperative Research and Development Agreement; CRE: Carbapenem-resistant Enterobacterales; CST: Company support team; CSTE: Council of State and Territorial Epidemiologists; CUSP: Comprehensive Unit-based Safety Program; cUTI: Complicated urinary tract infection; CVM: Center for Veterinary Medicine; DARPA: Defense Advanced Research Projects Agency; DC: District of Columbia; DCL: Dubai Central Laboratory; DHA: Defense Health Agency; DOD: Department of Defense; DOT: Directly observed therapy; DRC: Democratic Republic of the Congo; DTRA: Defense Threat Reduction Agency; EAR: Emerging Antimicrobial Resistance Reporting; eDOT: Electronic directly observed therapy; eGISP: Enhanced Gonococcal Isolate Surveillance Project; EIP: Emerging Infections Program; ELC: Epidemiology and Laboratory Capacity; ELR: Electronic laboratory reporting; EMA: European Medicines Agency; EMRO: Eastern Mediterranean Regional Office; EPA: Environmental Protection Agency; EPN: Ecumenical Pharmaceutical Network; ESBL: Extended spectrum beta-lactamase; EU: European Union; FAO: Food and Agriculture Organization of the United Nations; FAS: Foreign Agriculture Service; FDA: Food and Drug Administration; FMT: Fecal microbiota transplant; FPP: Finished pharmaceutical product; FSIS: Food Safety Inspection Service; FY: Fiscal year; G7: Group of Seven; G20: Group of Twenty; GAMRIF: Global Antimicrobial Resistance Innovation Fund; GAO: Government Accountability Office; GARDP: Global Antibiotic Research and Development Partnership; GC: Gonorrhea; GEIS: Global Emerging Infections Surveillance; GFI: Guidance for Industry; GHSA: Global Health Security Agenda; GISP: Gonococcal Isolate Surveillance Project; GLASS: Global Antimicrobial Resistance Surveillance System; GLP: Good laboratory practice; HAC: Hospital-acquired condition; HAI: Healthcare-associated infection; HAIC: Healthcare-Associated Infections Community Interface; HCA: Hospital Corporation of America; HEDIS®: Healthcare Effectiveness Data and Information Set; HHS: Department of Health and Human Services; HIIN: Hospital Improvement Innovation Networks; HRSA: Health Resources and Services Administration; ICAT: Infection control self-assessment tool; ICIUM: International Conference on Improving Use of Medicines; ICU: Intensive care unit; IG: Interpretive Guideline; IHR: International Health Regulations; IHS: Indian Health Service; IICA: Inter-American Institute for Cooperation on Agriculture; IICAB: Institute for International Cooperation in Animal Biologics; IMDRF: International Medical Device Regulators Forum; IND: Investigational new drug; INFAL: Interamerican Network of Food Analysis Laboratories (aka RILAA); INFOSAN: International Food Safety Authorities Network; IPC: Infection prevention and control; IPCAF: Infection Prevention and Control Assessment Framework; IPCAT2: Infection Prevention and Control Assessment Tool 2; IPT: Integrated Product Team; IQR: Inpatient Quality Reporting; IT: Information technology; JEE: Joint External Evaluation; JOC: Joint Oversight Committee; JSTO: Joint Science and Technology Office; KPC: *Klebsiella pneumoniae* carbapenemase; KPC-KP: *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*; LAARC: Laboratory Assessment of Antibiotic Resistance Testing Capacity; LMICs: Low- and middle-income countries; LTACH: Long-term acute-care hospital; LTC: Long-term care; MACRA: Medicare Access and CHIP Reauthorization Act; MARD: Ministry of Agriculture and Rural Development; MassBio: Massachusetts Biotechnology Council; MDR: Multidrug-resistant; MDRO: Multidrug-resistant organism; MDR-TB: Multidrug-resistant tuberculosis; MDSTR: Molecular drug susceptibility testing reporting; MHS: Military Healthcare System; MIC: Minimum inhibitory concentration; MIDRP: Military Infectious Disease Research Program; MIME: Microbial, Immune, Metabolic Perturbations by Antibiotics; MAGIC: Microbiome, Antibiotics, and Growth Infant Cohort; MInD: Modeling Infectious Diseases in Healthcare; MIPS: Merit-Based Incentive Payment System; MNCH: Maternal, newborn, and child health; MOA: Ministry of Agriculture; MOU: Memorandum of Understanding; MQDB: Medicines Quality Database; MRA: Medicines regulatory authority; MRSA: Methicillin-resistant *Staphylococcus aureus*; MRSN: Multidrug-Resistant Organism Repository and Surveillance Network; MTaPS: Medicines, Technologies, and Pharmaceutical Services; MuGSI: Multi-site Gram-negative Surveillance Initiative; NAHLN: National Animal Health Laboratory Network; NAHMS: National Animal Health Monitoring System; NAP: National Action Plan; NARMS: National Antimicrobial Resistance Monitoring

System; NCBI: National Center for Biotechnology Information; NCQA: National Committee for Quality Assurance; NDARO: National Database of Antibiotic Resistant Organisms; NHGRI: National Human Genome Research Institute; NHSN: National Healthcare Safety Network; NIAID: National Institute of Allergy and Infectious Diseases; NIFA: National Institute of Food and Agriculture; NIH: National Institutes of Health; NIMBioS: National Institute of Mathematical and Biological Synthesis; NLM: National Library of Medicine; NQF: National Quality Forum; NRL: National Reference Laboratories; NTSSCR: National TB Surveillance System Case Reporting; NVAP: National Veterinary Accreditation Program; NVSL: National Veterinary Services Laboratories; OCONUS: Outside of the continental United States; OIE: World Organisation for Animal Health; OGA: Office of Global Affairs; ONC: Office of the National Coordinator for Health Information Technology; ORA: Office of Regulatory Affairs; OTC: Over-the-counter; PAHO: Pan American Health Organization; PBP: Penicillin-binding protein; PCR: Polymerase chain reaction; Pf phages: Filamentous bacteriophages; PHEMCE: Public Health Emergency Medical Countermeasures Enterprise; PIP: Promoting Interoperability Program; PK: Pharmacokinetics; PNI: PulseNet International; PQM: Promoting the Quality of Medicines; PQRS: Physician Quality Reporting System; PT: Proficiency test; QIDP: Qualified Infectious Disease Product; QIN: Quality Improvement Network; QIN-QIO: Quality Innovation Network-Quality Improvement Organization; QPP: Quality Payment Program; R&D: Research & Development; RCSB: Research Collaboratory for Structural Bioinformatics; RILAA: Red Interamericana de Laboratorios de Análisis de Alimentos (aka INFAL); RNA: Ribonucleic acid; SAAR: Standardized Antimicrobial Administration Ratio; SBC: Small business concern; SBIR: Small Business Innovation Research; SDO: Standards developing organizations; SHEPheRD: Safety and Healthcare Epidemiology Prevention Research Development; SHERLOCK: Specific High Sensitivity Enzymatic Reporter UnLOCKing; SIAPS: Systems for Improved Access to Pharmaceuticals and Services; SMX: Sulfamethoxazole; SRA: Sequence Read Archive; SSuN: STD Surveillance Network; STAR: Short-course Therapy and the Antibiotic Resistome; STD: Sexually transmitted disease; STI: Sexually transmitted infection; SURRG: Strengthening the United States Response to Resistant Gonorrhea; TATFAR: Transatlantic Taskforce on Antimicrobial Resistance; TB: Tuberculosis; TMP: Trimethoprim; TWG: Technical working group; UK: United Kingdom; UN: United Nations; US: United States; USAID: United States Agency for International Development; USAMRIID: United States Army Medical Research Institute for Infectious Diseases; USDA: United States Department of Agriculture; USG: United States government; UTI: Urinary tract infection; VA: Department of Veterans Affairs; Vet-LIRN: Veterinary Laboratory Investigation and Response Network; VFD: Veterinary Feed Directive; VHA: Veteran's Health Administration; VICH: International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products; VRE: Vancomycin-resistant enterococci; VS: Veterinary Services; WASH: Water, sanitation, and hygiene; WGS: Whole genome sequencing; WHO: World Health Organization; WRAIR: Walter Reed Army Institute of Research; WRNMMC: Walter Reed National Military Medical Center