NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

First 180 Days Report

November 2015

Prepared by the Taskforce for Combating Antibiotic Resistant Bacteria

Table of Contents

Executive Summary

To address the growing public health concern about antibiotic-resistant bacteria, on September 18, 2014, President Barack Obama signed Executive Order 13676, which called for the development of a *National Action Plan* for Combating Antibiotic-Resistant Bacteria (CARB) and the formation of a Task Force to implement the *Action Plan*. The Executive Order required that:

> *Within 180 days of the release of the Action Plan and each year thereafter, the Task Force shall provide the President with an update on Federal Government actions to combat antibiotic-resistance consistent with this order, including progress made in implementing the Strategy and Action Plan, plans for addressing any barriers preventing full implementation of the Strategy and Action Plan, and recommendations for new or modified actions. Annual updates shall include specific goals, milestones, and metrics for all proposed actions and recommendations.*

This report is the 180-day report on the implementation of the Year 1 milestones in the *National Action Plan*.

The *National Action Plan* provides a five-year road map for implementing the *National Strategy for Combating Antibiotic-Resistant Bacteria's* five goals:

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.

The *National Action Plan* divides the work under each goal into objectives, sub-objectives and Year 1, Year 3, Year 5 milestones. In this report, progress in the first 180 days on the Year 1 milestones is reported for each objective. Checked boxes indicate progress is on target or that particular step to achieve the milestone is in process or complete; an unchecked box notes where progress on a milestone may be stalled due to barriers.

In the first 180 days following the release of the CARB *National Action Plan*, the United States Government (USG) has taken steps to improve antibiotic stewardship and reporting, and to increase information gathering capacities across animal and human health settings in order to advance development of rapid diagnostics and to accelerate research on new antibiotics and antibiotic alternatives. In addition, the USG is collaborating with multilateral partners to establish a common commitment to decreasing antimicrobial resistance (AMR) across the globe.

Progress on Goals

GOAL 1: Slow the emergence of resistant bacteria and prevent the spread of resistant infections. In human health, antibiotic stewardship programs continue to be introduced and evaluated in hospital settings with positive results, while antibiotic stewardship activities are starting to be advanced and promoted in nursing homes and long-term care facilities. In this first 180 days, the Centers for Disease Control and Prevention (CDC) finalized new core elements for stewardship programs in nursing home settings, and the Centers for Medicare and Medicaid Services (CMS) published a proposed rule requiring all long-term care facilities that participate in Medicare and Medicaid to have antibiotic stewardship programs in place. The USG continues to develop and optimize stewardship interventions for acute-care and outpatient settings.

In animal health, antibiotic stewardship efforts focused on the implementation of a strategy to promote judicious use of antibiotics in animal agriculture by eliminating the use of medically important antibiotics for growth promotion in food-producing animals and bringing other uses of these drugs under veterinary supervision. In early June, the Food and Drug Administration (FDA) finalized important changes to its Veterinary Feed Directive regulation to facilitate the process of bringing the use of medically important antibiotics in feed under the oversight of a veterinarian.

On June 2, 2015, both human health and animal health sides came together in support of a one-health antibiotic stewardship forum hosted by the White House.

GOAL 2: Strengthen national one-health surveillance efforts to combat resistance. The USG is planning to expand laboratory capacity to detect and track antibiotic-resistance, and to improve surveillance data integration. These laboratories will post early warning alerts and report urgent results and trends to public health authorities. Additionally, CDC and FDA launched the antibiotic-resistant isolate bank of over 160 isolates composed of collections of carbapenem-resistant Enterobacteriaceae (CRE) and other multi-drug resistant bacteria. Bacteria from this isolate bank are assembled into panels that can be used by manufacturers, academic researchers, and pharmaceutical companies to challenge and design the next generation of diagnostic tests and therapeutic agents. In addition, the USG was able to enhance the Multidrug-resistant organism Repository and Surveillance Network (MRSN) for improved AMR pathogen detection.

On the animal health side, the USG will expand retail meat testing from 6,700 to 13,400 tests per year, to better inform decisions on AMR trends. To collect more information regarding antibiotic drugs sold, FDA published a rule that includes additional proposed reporting requirements for sponsors of antibiotics that are approved for use in food-producing animals. The USG also is working to develop and implement a strategy for collecting antibiotic use and resistance on-farm data. A public meeting took place on September 30, 2015, in Washington, D.C. which sought input on plans for collecting antibiotic use and resistance data in the farm setting. Comments are being collected through November 30, 2015.

GOAL 3: Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria. The development of a rapid point-of-need test to distinguish between viral and bacterial infections will greatly aid in making antibiotic use decisions. The National Institute of Allergy and Infectious Diseases (NIAID) as part of the National Institutes of Health (NIH) awarded more than $11 million in first-year funding for nine research projects supporting enhanced diagnostics to rapidly detect AMR bacteria. The Biomedical Advanced Research and Development Authority (BARDA) is in contract negotiations to support the development of a critical AMR diagnostic platform and assay, which will provide assessments of drug-resistant infections. CMS is coordinating the development of coverage and related policies for appropriate technologies.

GOAL 4: Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines. The need to bolster the antibiotic pipeline is significant: despite the urgent need for new antibiotics, the number of products in the drug-development pipeline is small and commercial interest remains limited. Upcoming candidates can continue to diversify and improve the arsenal of antibiotic drugs; BARDA anticipates that New Drug Applications will be submitted for at least two candidates in development in FY 2016. In addition, multiple USG Departments awarded projects for the discovery and early stage development of new antibacterial products and alternatives to antibiotics in humans and animals.

GOAL 5: Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control, and antibiotic research and development. Throughout these initial 180 days, the USG worked with international partners to: pass the World Health Organization's Global Action Plan on AMR; pass the Food and Agriculture Organization resolutions for engagement and coordination in promoting work on combating AMR; continue work with European Union partners in the Transatlantic Task Force on Antimicrobial Resistance; and begin implementation of the Global Health Security Agenda with international partners.

The State Department, working with Federal partners, has successfully incorporated AMR into dialogues on the implementation of binding bilateral and multilateral Science and Technology Agreements. These agreements will provide the framework for international collaboration on critical research and development efforts.

Significant progress in the implementation of the *National Action Plan* has been made in these first 180 days. The USG has begun to lay the foundation for real change in how our country views and uses antibiotics, and the Task Force looks forward to continuing this transformative work over the next five years. The next Task Force progress report will be provided in September 2016.

Progress in First 180 Days on Year 1 Milestones by Goal

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

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

The Departments of Health and Human Services (HHS), Defense (DoD), and Veterans Affairs (VA) will review existing regulations and propose new ones to implement robust antibiotic stewardship programs that align with CDC's Core Elements. HHS, DoD, and VA will also work together to optimize standardization of stewardship programs and activities, including monitoring activities and reporting criteria.

- ☑ VA Central Office leadership published Veterans Health Administration (VHA) Directive 1031: Antimicrobial Stewardship Programs in January 2014, requiring all VA Medical Centers to establish procedures for the implementation, maintenance, and evaluation of antimicrobial stewardship programs. The VHA Stewardship Initiative has had initial success in optimizing in-patient antimicrobial use and has begun to develop example stewardship interventions for outpatient and long-term care (LTC) settings.

- ☑ CDC *Core Elements for Hospital Antibiotic Stewardship Programs* was released in early 2014; CDC continues to educate partners and provide tools for program implementation. CDC *Core Elements for Antibiotic Stewardship Programs in Nursing Homes* was released in September 2015. At the White House Forum on Antibiotic Stewardship, CDC received strong commitments from multiple LTC providers to help support implementation of these new core elements; this will extend the work into LTC settings.

- ☑ DoD is working with CDC, VA, and others to standardize reporting language/terms.

- ☑ In addition, CDC is partnering with the VHA to develop a protocol to pilot and scale up antibiotic stewardship interventions to improve antibiotic use for the infections that most commonly lead to inappropriate antibiotic use.

- ☑ Ahead of a Year 3 milestone, CMS proposed new LTC infection control requirements, which include having an antibiotic stewardship program.

The National Healthcare Safety Network (NHSN) will begin tracking the number of healthcare facilities with stewardship policies and programs in place.

- ☑ CDC began collecting information to track the number of healthcare facilities with stewardship policies in place through CDC's NHSN annual survey of facility users. Analysis of 2015 data is complete and will be posted on CDC's Get Smart website in November 2015. Expanding participation in the NHSN Antibiotic Use Option will also be critical to assessing the activities of hospital antibiotic stewardship programs. CDC is working with hospital systems and other partners to expand this participation.

DoD will establish a multidisciplinary group, under the purview of the Assistant Secretary of Defense for Health Affairs, to support and coordinate stewardship activities across DoD.

☑ DoD, using the 2014 CARB Executive Order and the 2015 National Defense Authorization Act as authorizing documents, is formalizing the stewardship working group and policy. The group's first meeting was September 16, 2015.

CDC and VA will apply lessons learned from the pilot projects 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 for this effort.

☑ With CDC support, VA completed lessons learned from a joint pilot project to provide clinicians with support for making prescribing decisions based on judicious use of antibiotics. A manuscript, "Variation in Outpatient Antibiotic Prescribing for Acute Respiratory Infections in the Veteran Population," was published in the Annals of Internal Medicine in July 2015. CDC is continuing to partner with the Veterans Health Administration to develop a protocol to pilot and scale up antibiotic stewardship interventions to improve antibiotic use for the infections that most commonly lead to inappropriate antibiotic use.

DoD Multidrug-Resistant Organism Repository and Surveillance Network (MRSN) will expand its detection and reporting capabilities to include C.difficile *and other high risk drug resistant pathogens.*

☑ DoD/MRSN expanded its collection parameters, including standardized means for collecting and testing *C. difficile* isolates.

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.

☑ CDC has purchased proprietary data on inpatient antibiotic use to supplement the NHSN. These data have helped CDC explore antibiotic use across hospitals in the U.S. and the potential factors that might explain that variability. NOTE: Proprietary commercial data is not a permanent solution for tracking and reporting inpatient antibiotic use data across the nation. When the NHSN module is fully utilized by hospitals, its antibiotic use and resistance data, which is collected using a standardized approach, will be a more accurate guide for local and regional efforts to reduce resistance and provide national benchmarks to compare antibiotic use.

CDC will work with healthcare and public health partners to propose new healthcare facility antibiotic use measures to the National Quality Forum (NQF).

☑ CDC worked closely with health system partners to develop a risk-adjusted summary measure of antibiotic use for endorsement by the NQF. The NQF Patient Safety Committee has approved the measure, and CDC has responded to all public comments. The measure is on track for full NQF membership vote in fall 2015.

CDC will report outpatient prescribing rates for 2011 and 2012 and use these data to target and prioritize intervention efforts.

☑ CDC published 2011 outpatient antibiotic prescribing rates in March 2015. Analyses of 2012 data and 2013 data have been completed and will be posted on CDC's Get Smart website in November 2015.

CDC will establish a benchmark (in terms of prescriptions per population) for reduction in antibiotic use.

☑ CDC is working with Pew Charitable Trusts and clinical experts to establish reduction goals for inappropriate antibiotic use in support of the 2020 benchmarks outlined in the CARB National Strategy (20 percent reduction in inpatient settings and 50 percent reduction in outpatient settings for monitored conditions and agents). The approach for establishing the outpatient goal has been finalized, and a manuscript is being drafted for publication. Final reports are expected by late 2015 or early 2016.

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.

☑ AHRQ and CDC have established a planning committee that is developing the agenda and structure for a meeting of experts and stakeholders targeted for spring 2016 to consider knowledge gaps for prevention of antibiotic-resistant healthcare-associated infections (HAI) and identify potential interventions for development, field testing, and eventual widespread implementation.

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 U.S.

☑ CDC's EIP has begun implementing an HAI prevalence survey that includes an assessment of inpatient antibiotic use and resistance in a national sample of hospitals. A similar survey was conducted in 2011. In the current survey, data collection has been expanded to include assessments of antimicrobial prescribing quality and will continue through 2016. In addition, a similar HAI prevalence survey and assessment of inpatient antibiotic use and resistance was piloted in LTC settings; data analysis is nearly complete. Based on this experience, planning and protocol development for a larger nationally representative HAI prevalence and antibiotic use survey in LTC settings is underway.

CDC EIP sites will submit applications for funding of large-scale interventions to reduce C. difficile *infections through enhanced antibiotic stewardship programs.*

☑ CDC in partnership with state partners in the Emerging Infections Program and clinical partners in the CDC Prevention Epicenters submitted an application for funding a large-scale intervention to reduce *C. difficile* infections through enhanced inpatient stewardship programs.

FDA will provide technical assistance, as appropriate, on legislative proposals being considered to streamline updating of interpretive criteria for Antimicrobial Susceptibility Test (AST) devices.

☑ FDA has provided and continues to provide technical assistance on legislative

proposals being considered to streamline updating interpretive criteria for AST devices.

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

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 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 2009-2013. This report will support the effort to monitor the antibiotic usage aspects of Guidance #213.

☑ FDA/Center for Veterinary Medicine (CVM) finalized changes to the Veterinary Feed Directive regulation to encourage manufacturers to transition the dispensing status of in-feed antibiotics covered by GFI #213 from over the counter to VFD status which requires veterinary oversight.

☑ FDA published an enhanced summary report of antibiotics sold or distributed for use in food producing animals from 2009-2013.

FDA will publish and maintain a public web listing of products affected by GFI #213.

☑ FDA/CVM has published and maintained a public web listing of products affected by GFI #213.

FDA will begin publishing periodic updates summarizing progress in adoption of the changes proposed in GFI #213.

☑ FDA/CVM has begun publishing periodic updates summarizing progress in adoption of the changes proposed in GFI #213.

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

FDA and the U.S. Department of Agriculture (USDA) will consult with livestock and veterinary organizations on the development of educational outreach materials on judicious use of antibiotics and stewardship; will meet with the American Veterinary Medical Association (AVMA) and the Association of American Veterinary Medical Colleges (AAVMC) to consider the incorporation of additional material on antibiotic-resistance and stewardship into the curricula of veterinary colleges.

☑ Educational outreach plan is under development. FDA and USDA are also participating in a task force AAVMC and Association of Public and Land-grant Universities have formed to identify education and research needs. USDA is working with species specialty veterinary organizations and producer organizations to help with the development of stewardship programs and metrics.

USDA will conduct assessments on 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.

☐ Stakeholder discussions are underway. Joint or separate meetings have been conducted with participants representing the beef, swine, and poultry sectors of agriculture production. Animal and Plant Health Inspection Service (APHIS) continues to meet with industry representatives to identify feasible surveillance streams and begin study

design and development. Assessments will be conducted based on the availability of funding.

USDA will solicit applications to the USDA Antimicrobial Resistance Initiative Program (ARIP) which aims to advance development and use of stewardship practices that assure judicious use of antibiotics.

- ☐ USDA/National Institute of Food and Agriculture (NIFA) has yet to solicit applications. Pending the availability of FY2016 funds, ARIP objectives would be addressed through the Challenge Area and Foundational programs within NIFA's flagship Agriculture and Food Research Initiative (AFRI) program. NIFA's ARIP program anticipates funding in the amount of $33.5M in 2016. At this level, NIFA would respond, for example, by awarding a limited number of larger Coordinated Agricultural Project (CAP) grants and a greater number of standard (non-CAP) Challenge Area grants as well as basic research-only grants through the Foundational programs. However NIFA's overall anticipated budget for all AMR and AMR-related activities is estimated at $12M, distributed as $6M for new grants and $2.5M for Continuation awards in the Challenge Area, and a total of $3.75 M in the Foundational programs. The Foundational programs include AMR-related projects that will be funded through the AFRI Animal Health program, which targets research on animal health and well-being. Under this lower level of funds proposed in the House and Senate budgets ($12M), CAP awards will be replaced by an appropriate number of Standard (non-CAP) grants in the Challenge Area, and basic, research-only grants in the Foundational programs. This approach will ensure that a number of ARIP objectives would be addressed through NIFA's existing AMR program. ARIP aims to advance development and use of antibiotic stewardship practices that assure judicious use of antimicrobials in agriculture through the support of research, education, or extension/outreach projects. Overall, the projected outcomes of these programs would include the development of sustainable strategies to mitigate antimicrobial resistance, preparing the next generation of veterinary scientists and other animal care professionals, and producers and consumers, across the food chain.

  The AFRI required Request for Applications (RFA) for all FY2016 programs, including ARIP, are currently in the initial stages of preparation, pending availability of funds.

FDA and USDA will identify priority areas of research to develop and validate stewardship activities to reduce the spread of resistance.

- ☐ FDA and USDA have not completed the identification of priority areas of research, however funding from FDA has allowed the initiation of analyses of historical USDA-APHIS National Animal Health Monitoring System (NAHMS) data to evaluate some stewardship alternatives.

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.

- ☐ USDA/APHIS has met with the following veterinary groups: AVMA; American Association of Swine Veterinarians; American Association of Avian Pathologists; and American Association of Bovine Practitioners to discuss stewardship education options

and the need for information to support stewardship. In addition, APHIS has participated in discussions related to stewardship with beef producer organization personnel engaged in the industry sponsored quality assurance program.

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

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.

CDC will develop an implementation plan for the Detect Network of AMR Regional Laboratories that considers all aspects of operation, including specimen transport, testing, reporting, and data-sharing.

- ☑ CDC has begun planning to bring 5-7 existing laboratories online for AMR work. An implementation plan is under development. Additional funding needed to conduct Year 3 and Year 5 work.

- ☑ CDC, VA, and DOD are planning for a Detect Network of AMR Regional Laboratories and an international AMR communication network (CDC); and investigating the feasibility of microbiologic laboratory data sharing (VA, DOD).

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.

- ☑ DoD/MRSN announced first release of a relational database in May 2015 and is planning expanded access to authorized users.

- ☑ DoD/MRSN currently holds ~ 30,000 characterized isolates and 1,500 genomes within its repository and database.

- ☑ DoD continues support of MRSN for enterprise use and collaboration with other USG agencies.

- ☑ DoD is in the process of establishing policy to formalize the status of the MRSN as a reference laboratory for all three services.

CDC and FDA will develop a defined set of microorganisms to be included in a repository of resistant bacterial strains, including the urgent and serious threats in the National Action Plan's Table 1 (see Appendix), and a bioinformatics database to maintain detailed information on the drug susceptibilities and resistance mechanism of each repository strain.

- ☑ CDC and FDA developed a defined set of microorganisms to launch the AMR isolate bank in June 2015, with over 160 isolates composed of collections of CRE and other multi-drug resistant gram-negative rods. Within one month of launch, CDC had received and filled 18 orders from diagnostic test manufacturers, academic researchers, and pharmaceutical companies for curated panels from the bacterial bank that can be used to challenge and design the next generation of clinical tests and therapeutic agents.

By Year 3, the AMR isolate bank is expected to contain 800 isolates. Additional funding needed to complete and maintain the AMR isolate bank in future years.

DoD will post data on a representative sample of characterized isolates on a website that can be accessed by authenticated users.

☑ DoD released its relational database in May 2015, to provide access to authorized users for facility antibiotic-resistance data. At outset, access is limited to DoD though will expand once Information Assurance measures are accepted.

FDA and the National Institutes of Health (NIH) will pilot test a sequence database containing more than 550 drug resistant bacterial strains along with accompanying clinical and demographic data ("metadata"). The entries will cover a range of organisms selected by CDC to assist in diagnostic development.

☑ FDA and NIH are working together to pilot the National Database of Resistant Pathogens, initially populated with a representative dataset of about 300 strains including both genomic and associated meta/clinical data. Data were submitted to NIH/National Center for Biotechnology Information (NCBI) in early April 2015, and the pilot database is being built. Additional funding needed for Year 3 and Year 5 work.

NIH and partners will sequence additional high priority, drug resistant strains to add to the database.

☐ NIH will sequence a large number of the high priority reference strains identified by the CDC/FDA collaboration. Sequencing will be conducted by one of the NIH/NIAID funded Genome Sequencing Centers, NIH/NHGRI Sequencing Center, and CDC. These NIH Centers will each initially sequence 50 strains and a detailed sequencing strategy is now under development. It is anticipated that sequencing will begin in November 2015. High quality sequence data and strain information will be used to populate the National Database of Resistant Pathogens, with NIH-National Center for Biotechnology Information ensuring rapid public release of these genomic data.

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.

☑ DoD first release occurred in May 2015, and is contributing data to NIH/NCBI database.

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.

CDC will submit proposals for new measures for hospital reporting of data on antibiotic use to the National Quality Forum.

☑ CDC worked closely with health system partners to develop a risk-adjusted summary measure of antibiotic use for endorsement by the NQF. The NQF Patient Safety Committee has approved the measure, and CDC has responded to all public comments. The measure is on track for full NQF membership vote in fall 2015. Partners have committed to working with CDC to develop guidance for using the measure in stewardship efforts.

CDC will create a user friendly electronic portal that makes aggregated NHSN data publicly available and facilitates integrated analysis for state and regional trends and practices.

☐ CDC expects to launch the Antibiotic-resistance Patient Safety Atlas in early 2016 to provide a user-friendly electronic portal that makes aggregated national and state-specific NHSN summary data publicly available and facilitates integrated analyses of state and regional trends and practices. Updates to the Atlas would be expected yearly.

CDC will provide technical assistance to hospitals across the nation that report drug-resistance data to the National Healthcare Safety Network via the NHSN antibiotic use (AU) and AMR modules.

☑ CDC is providing technical assistance to hospitals currently reporting antibiotic use data to its NHSN. To date, 118 facilities have submitted at least one month of antibiotic use data. No facilities are currently reporting antibiotic-resistance data to NHSN. CDC is exploring options to accelerate hospital reporting of antibiotic use and resistance data to NHSN through health systems and state public health departments.

☑ A pilot project by VA, supported by the CDC, has had great success at reporting aggregated facility level data to the NHSN's Antimicrobial Use module. As of July 2015, 49 VA facilities have had in-patient antimicrobial use data imported into the NHSN module.

☑ In spring 2015, ONC and CMS each proposed rules that would provide hospitals the option to qualify for electronic health record incentive payments by electronically reporting antibiotic use and resistance data to CDC's NHSN. The agencies are reviewing public comments on the proposed rules.

CDC will host a meeting of EIP Investigators to consider ways to improve EIP surveillance for drug-resistance threats. Outcomes of the meeting will include refined protocols and standard operating procedures to enable EIP surveillance of additional threats.

☑ 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.

CDC EIP sites will pilot methodology to incorporate at least one additional urgent or serious threat into surveillance activities.

☑ CDC has 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.

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

USDA and FDA will assess current capacities and protocols within National Animal Health Laboratory Network (NAHLN) and Veterinary Laboratory Investigation and

Response Network (Vet-LIRN) member laboratories and identify capacity development needs to support nationwide AMR surveillance for zoonotic pathogens and pathogens of importance to animal health.

☑ USDA-APHIS has begun assessing current capacities and protocols within NAHLN and Vet-LIRN member laboratories.

☐ With funding requested for FY 2016, FDA's Vet-LIRN will begin to develop the funding opportunity for laboratories to obtain the needed equipment, staffing and infrastructure to participate in the testing.

USDA and FDA will develop standardized protocols for assessing proficiency in susceptibility testing.

☐ FDA/CVM and USDA are discussing coordinating efforts to meet this milestone. As resources become available, a project plan will be developed and implemented.

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.

☑ FDA's Vet-LIRN has begun discussions with the USDA's NAHLN. APHIS is collaborating with the American Association of Veterinary Laboratory Diagnosticians (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.

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.

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.

☐ The USDA-APHIS plan for longitudinal collection of biologic samples and antibiotic use data on-farm is on hold pending funding. Further development and implementation is contingent on receiving requested financial and human resources for FY2016 and beyond.

☑ USDA-Food Safety and Inspection Service (FSIS) has expanded its Pathogen Reduction/Hazard Analysis and Critical Control Point (PR/HACCP) sampling program to include additional product classes (pork) and commodities (chicken parts, pork cuts), and the pathogens (*Salmonella* and *Campylobacter*) isolated from these programs will be analyzed for antimicrobial resistance and characterized using whole genome sequencing on a routine basis in FY2016.

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.

☑ FDA has begun publishing enhanced annual summary reports on the sale and distribution of antibiotics approved for use in food producing animals. These annual reports include additional data tables to provide more detailed information and to improve transparency. The enhanced annual summary report for the 2012 reporting year was published on October 2, 2014; the enhanced report for 2013 was published on April 10, 2015. Subsequent annual reports will be issued using this new, expanded format.

FDA will publish a proposed regulation that includes additional proposed reporting requirements for sponsors of antibiotics approved for use in food-producing animals.

☑ FDA has published a proposed regulation that includes additional proposed reporting requirements for sponsors of antibiotics approved for use in food-producing animals; proposed regulation was published on May 19, 2015.

USDA and FDA will seek public input on a plan for collecting drug use and resistance data on farms.

☑ FDA, with USDA and CDC, coordinated the planning of a public meeting to seek input on plans for collecting antibiotic use and resistance data on the farm. The meeting was conducted on September 30, 2015, and comments are being accepted via the public docket through November 30, 2015.

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.

☑ As part of the National Antimicrobial Resistance Monitoring System (NARMS) program, FSIS will expand AMR susceptibility and whole genome sequencing analysis on isolates derived from its PR/HACCP program to include pork and chicken parts on a routine basis in FY2016.

☑ As part of the NARMS program, FDA will expand retail meat testing in 2015-2016 by increasing the number of retail meat tests performed from 6,700 per year to 13,400 per year. The NARMS program has begun contributing bacterial isolates for whole genome sequencing and cataloguing. Whole genome sequencing data from all historical salmonella isolates from retail meats (2002-2012) will be submitted to NCBI in 2015. This represents progress towards Year 3 milestones.

☐ Collection of biologic samples is anticipated as part of the design and implementation of further NAHMS on-farm studies, pending availability of funding.

☐ National Veterinary Services Laboratories (NVSL) Diagnostic Bacteriology Laboratory (DBL) continues to contribute *Salmonella* isolates and sequencing data recovered from veterinary diagnostic surveillance streams to the expanded NARMS program. In conjunction with this, NVSL-DBL is also evaluating options for conducting AMR surveillance on additional bacterial isolates submitted to NVSL. Expansion is subject to the availability of funds.

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

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.

NOTE: No Year 1 milestones for this objective. Ahead-of-schedule progress is reported below for Year 3 milestones.

NIH will fund at least five new projects aimed at the development of rapid diagnostics

☑ In April, 2015, NIAID awarded more than $11 million in first-year funding for nine research projects supporting enhanced diagnostics to rapidly detect antimicrobial-resistant bacteria. The awardee institutions will develop tools to identify certain pathogens that frequently cause infections in health care settings and, specifically, those that are resistant to most antimicrobials.

☑ Since the release of the *National Action Plan*, NIAID has funded several new investigator-initiated grants working to develop novel diagnostic platforms to detect bacterial threats of high importance to public health.

ASPR/BARDA will fund at least three new diagnostic development projects that involve next-generation sequencing, multiplex molecular assay or other new technologies that shorten the time needed for reliable and accurate detection of drug resistance.

☑ BARDA has drafted language for a Broad Agency Announcement to solicit white papers and proposals for funding to develop diagnostics to identify and inform treatment of antimicrobial-resistant bacterial infections, including next-generation sequencing, multiplexed molecular assays, and other new technologies. This solicitation was released in October 2015.

☑ BARDA is presently in contract negotiations to support development of their first AMR diagnostic platform and assay. The first assay will be for identification of Anthrax infection and determination if the infection is due to a multi-drug resistant strain, but with additional assay development AMR diagnostic assays for high priority public health drug-resistant infections may be performed on the same platform. Award of this advanced research and development contract is expected in 2015.

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.

☐ Ahead of a 3 Year milestone, BARDA and NIH are working together to initiate a prize for development of a rapid diagnostic test that can improve treatment of drug-resistant infections and facilitate antibiotic stewardship. An interagency working group has been established, a public consultation has been held and public comment has been received from key stakeholders. A draft challenge announcement is being developed and will be

issued in early 2016.

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

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 payment and coding.

- ☑ FDA continues to share information and expertise with CMS regarding any innovative regulatory pathways currently under development for diagnostic tests to help CMS address issues related to Medicare payment and coding of such tests. CMS will continue to work on coverage and related policies for appropriate technologies, including potential diagnostics for the Medicare population. The FDA and CMS renewed their Memorandum of Understanding (MOU) on June 25, 2015. The purpose of the MOU is to promote collaboration and enhance knowledge and efficiency by providing for the sharing of information and expertise between the Federal partners.

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

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.

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.

☑ USDA has begun planning for a webinar that will include private and public experts to discuss collaborative research on antibiotic-resistance in food producing animals, agriculture, and public health. This webinar, which is scheduled for FY2016, will include systems biology approaches and development strategies for new technologies for basic research to clinical testing for AMR.

NIH will work with FDA and partners in industry and academia to: (a) explore features for developing a more robust clinical trials infrastructure for antibacterial product development; (b) assess the feasibility of applying common clinical protocols for evaluation of multiple products while sharing a common control group.

☑ On June 1, 2015, NIH and FDA initiated a series of internal meetings to discuss how to enhance the USG's clinical trials 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.

☑ NIH is planning a joint workshop with European funders for early 2016 that will include a discussion of challenges in the conduct of clinical trials to address antibacterial resistance.

NIH will expand and strengthen the Antibacterial Resistance Leadership Group (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.

☑ NIH-ARLG has four interventional clinical trials currently in protocol development for which additional clinical sites will be required. At least one of these trials is expected to begin enrollment within the *National Action Plan's* one-year timeframe. In addition, new non-interventional trials and studies have begun or will begin within the one-year timeframe.

☑ In June 2015, the ARLG published a paper in Clinical Infectious Diseases outlining an innovative trial design that can be used to assess the risks and benefits of new strategies to optimize antibiotic use.

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.

☑ USDA has begun planning for a webinar that will include private and public experts to discuss collaborative research on antibiotic-resistance in food producing animals, agriculture and public health. This webinar, scheduled for FY2016, will include systems biology approaches and development strategies for new technologies for basic research to clinical testing for AMR.

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.

NOTE: No Year 1 milestones for this 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.

The Chemical and Biological Defense Program/DTRA will submit an Investigational New Drug (IND) application to FDA to initiate the clinical investigation of a new antibiotic developed with DoD funding.

☑ DoD/Joint Science and Technology Office (JSTO) is funding efforts to complete preclinical development of a novel drug (topoisomerase inhibitor) with IND submission planned in 2017.

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

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 drugs.

☑ NIAID has recently 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. In addition, NIAID provides preclinical service support to foster drug development, including *in vitro* and *in vivo* testing of new candidate therapeutics for multi-drug resistant (MDR) bacteria, which lowers the risk as well as fills the gaps for new entries into AMR discovery and development efforts. For additional information on NIAID activities in this area, please see the Appendix.

DoD will implement laboratory use of new microfluidic technologies to detect antibodies that inhibit antibiotic-resistant bacteria.

☑ DoD/JSTO has planned initiation of mechanistically novel therapies (source sensitive) for 2016.

☑ DoD/Office of the Assistant Secretary of Defense/Nuclear, Chemical, Biological/Chemical and Biological Defense and JSTO continues evaluation of a previously developed drug product as part of a new combination therapy.

DoD will award: (a) two new contracts focused on development of non-traditional therapeutics that are less likely to lead to the development of resistance; (b) two new contracts focused on evaluating drug combinations that may decrease the emergence of drug resistance; (c) 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.

- ☑ DoD/JSTO, in collaboration with United States Army Medical Research Institute for Infectious Diseases, will complete a systematic combinatorial evaluation for identifying pairing of FDA-approved drugs in new combinations in FY 2016.

- ☑ DoD/Walter Reed Army Institute of Research (WRAIR) continues 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.

- ☑ Second revitalization candidate has not yet been identified, although this is balanced by efforts to develop technologies for targeted delivery methods.

USDA, with NIH, FDA, and the agriculture industry, will develop a research and development strategy to promote understanding of antibiotic-resistance and the creation of alternatives to (or improved uses of) antibiotics in food animals.

- ☑ USDA and HHS are evaluating options to address developing a research and development strategy. For example, USDA and FDA/CVM have discussed collaborating on evaluating ways to incentivize development of alternative therapeutics to address disease.

- ☑ USDA/Agricultural Research Service (ARS) held an internal workshop September 9-10, 2015 in Beltsville, MD on "Antibiotic-resistance in Agroecosystems." The objectives of the workshop included: identifying and prioritizing research concerns and gaps; and developing research plans, milestones, and projected publications. A final workshop report was completed.

- ☑ USDA/ARS is organizing a workshop for FY2016 on alternatives to antibiotics in animal production, which will include other USG agencies and stakeholders. The purpose of this workshop will be to conduct a gap analysis and assess the outcome of the first International Symposium on Alternatives to Antibiotics in Animal Production and potential impact and opportunities for U.S animal agriculture.

USDA will solicit proposals that comprehensively develop research and outreach programs targeting development of novel alternatives to antibiotics for use in animals.

- ☑ ARIP will be implemented as a Food Safety Challenge Area program within NIFA's flagship AFRI program contingent on the availability of funds.

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.

Agencies with existing capabilities will ensure that genomic sequence data, proteomic data, and other related AMR data sets generated with USG funding will be made publically available in a manner consistent with protecting personally identifiable information.

☐ NIH/NIAID anticipates that data generated will be made freely available via deposition into publicly accessible and searchable international databases such as GenBank and National Center for Biotechnology Information and to the NIH/NIAID-funded databases such as Division of Microbiology and Infectious Diseases Bioinformatics Resource Center or other databases designated and approved by NIAID. 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.

DoD will develop three specimen panels as a critical resource for evaluating the efficacy of novel antibiotic therapies against multi-drug resistant (MDR) Select Agents. The panels will include: (a) resistant bacterial isolates suitable for work in lower-level (BSL-2) biocontainment laboratories, (b) multidrug resistant strains of Select Agents, and (c) 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.

☑ DoD initiated efforts to produce panels of MDR non-bacterial select agent surrogates of biowarfare agents including comprehensive molecular characterization. Work will 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 will be subject to the availability of funds.

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

HHS Public Health Emergency Medical Countermeasures Enterprise (*PHEMCE) will ensure coordination with the US Task Force for CARB in promoting public-private partnerships to develop new and next-generation countermeasures to target AMR bacteria that present a serious or urgent threat to public health.*

☑ The PHEMCE Integrated Product Team (IPT) on Antimicrobials was reconstituted as the Antimicrobial Resistance IPT to address the problem of antimicrobial resistance more broadly, to include non-biothreat pathogens of serious or urgent concern as designated by CDC.

ASPR/BARDA will create at least one additional portfolio partnership with a pharmaceutical or biotechnology company to accelerate development of antibacterial drugs.

☑ ASPR/BARDA announced on September 16, 2015, that it entered into a new portfolio partnership with AstraZeneca to develop new antibiotics. New portfolio partnerships are subject to the availability of increased resources.

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.

ASPR/BARDA and NIH will work with a consortium of industry partners to develop a strategy for establishing the Antibiotic-resistance Biopharmaceutical Incubator.

- ☐ ASPR/BARDA and NIAID are currently engaged in market research for the Incubator – no funding can be allocated for implementation of the Incubator before FY 2017 (Year 3 and Year 5 milestones require implementation of the Incubator).

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

5.1 Promote laboratory capability to identify at least three of the seven World Health Organization (WHO) priority antimicrobial resistant (AMR) pathogens using standardized, reliable detection assays.

CDC and USAID will work with ministries of health in at least 12-15 countries to complete laboratory proficiency assessments, and will assess expansion of bilateral relationships to additional countries

☐ CDC will conduct laboratory proficiency assessments through the Global Health Security Agenda (GHSA) by the end of FY2016.

DoD will work with international partner labs to identify and enhance local proficiency and capabilities and will conduct assessments on an annual basis.

☑ DoD/MRSN is 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.

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

USDA, FDA, and CDC will develop a plan, in partnership with WHO, the Pan American Health Organization (PAHO), and other international organizations to identify key partner laboratories that conduct AMR testing of animal foodborne pathogens.

☑ USDA/FSIS has contacted regional partners to identify a common vehicle to survey regional capability and capacity for AMR monitoring, and for potential participation in international training seminar for Latin America.

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

CDC will work with the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) partners to develop a common U.S.-European Union (E.U.) system for sharing and analyzing bacterial resistance patterns for pathogens identified as urgent and serious threats in the National Action Plan's Table 1. (See Appendix B)

☐ CDC and European Centre for Disease Prevention Control (ECDC) are both pursuing plans to launch (CDC) and enhance (ECDC) web-based interactive tools for analysis of antibiotic-resistant threat surveillance data. CDC will proceed with the aim of harmonizing surveillance data and analysis to the extent possible so that comparisons can be made.

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.

☑ As a member of TATFAR, the USG is co-leading a working group with the European Union to implement Recommendation #18. The working group has been formed and met in-person at the TATFAR meeting October 22-23, 2015, in Luxembourg**.** During this meeting, the working group completed an inventory of identified knowledge gaps, including existing work in the areas of research, surveillance and risk analysis. Based on this inventory, the working group identified a sub-set of knowledge gaps which represent a high priority for collaboration.

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

US agencies, led by CDC and USAID, will engage stakeholders in establishing harmonized definitions of drug resistance for surveillance programs.

☑ CDC has engaged U.S. and E.U. breakpoint setting agencies and European-CDC surveillance experts through TATFAR to discuss harmonization of definitions of resistance. During the October 22-23, 2015, Luxembourg meeting of TATFAR, both sides agreed to begin with definitions of resistance that would facilitate implementation of the WHO Global Antimicrobial Resistance Surveillance System.

DoD will continue to engage and support existing and newly identified international partners through sharing of technological packages for surveillance and reporting purposes.

☑ DoD has 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 *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* (3/7 WHO priority pathogens), as well as other carbapenemase-resistant pathogens.

U.S. agencies, led by State and HHS, will develop a strategy for working with partner countries to elevate the issue of AMR as an international priority for global health security.

☑ State, HHS and USDA have enhanced bilateral and multilateral engagement to mobilize international financial, political, and operational support to combat antimicrobial resistance. Successes include 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 antibiotic-resistance 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; and enhancing foreign policy engagement by U.S. embassy personnel.

U.S. agencies, led by HHS/OGA, will support the development of the WHO Global Action Plan on AMR. As part of this effort, U.S. 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.

☑ HHS, State, and USDA coordinated international engagement with the WHO, the Food and Agriculture Organization (FAO), OIE, Member States, and other relevant organizations resulting in successful adoption of the WHO's Global Action Plan,

consistent with U.S. CARB priorities including an emphasis on One Health, enabling evidence-based decisions, and research and development.

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.

U.S. agencies, led by HHS, will work with WHO, FAO, OIE, and other international partners to accelerate investment in research to develop point-of-care (POC) diagnostics, vaccines, and drugs to combat resistant bacteria, as well as to investigate the microbiomes of food animals.

- ☑ Under the auspices of TATFAR, NIAID holds 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 recently signed a joint Letter of Intent to collaborate with the Indian Council of Medical Research on a joint project to address antibacterial resistance. Possible topics under discussion include diagnostics development and testing, molecular epidemiology and systems biology. NIAID program officials and NIAID-funded researchers plan to travel to India in FY2016 to discuss collaborations in more detail.

- ☑ A NIAID representative participated in WHO consultations on action plans for sexually transmitted infection vaccines and diagnostics, including multidrug resistant *N. gonorrhoeae.*

- ☑ NIAID and the European Medicines Initiative's New Drugs for Bad Bugs program are co-sponsoring a one day meeting (planned for early 2016) to explore barriers to efficient clinical trials of antibacterial drugs. BARDA and FDA will also play key roles at this meeting.

- ☑ TATFAR members met in Luxembourg in October, 2015 to chart the next 5-year TATFAR implementation period, with input from E.U. member states.

- ☑ NIAID and the Swedish Research Council are co-sponsoring a workshop (planned for early 2016) to promote international collaboration among antibacterial resistance researchers.

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

U.S. agencies, led by HHS/OGA, will collaborate with the global community to ensure that the WHO Global Action Plan (GAP) on Antimicrobial Resistance incorporates approaches and interventions that benefit all healthcare programs and calls for the development of national plans to combat antibiotic-resistance).

- ☑ The WHO GAP on AMR, adopted in May 2015, calls for the development of WHO Member State national action plans within two years.

☑ Through GHSA, and other venues including the G7, the U.S. and partner countries are developing a repository of national action plans in collaboration with the WHO Secretariat and are promoting partnerships between countries.

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

NOTE: No Year 1 milestones for this objective.

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

FDA and USDA will contribute to and participate in global or regional cooperation with international organizations, including Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal 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.

☑ The VICH expert working group on electronic submission of adverse event reporting had a teleconference September 2015 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 acknowledgment for the respective industry submissions.

USDA will maintain the U.S. commitment to VICH and IICAB, expanding the Global Outreach Forum to: (a) promote the use of VICH guidance for safety, quality, potency, and effective use of vaccines outside of the three cooperating major regions (the U.S., Japan, and the European Union); (b) facilitate input from a broadened base of participating countries and economies.

☑ USDA-APHIS is maintaining the U.S. commitment to VICH and IICAB, expanding the Global Outreach Forum by continuing to participate in the annual Veterinary Biologics Training Program held in Ames, 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.

USDA will plan and participate in at least three VICH Global Outreach Forums over the first two years.

☑ USDA/Foreign Agriculture Service (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.

USDA will hold at least one international meeting in collaboration with IICAB to discuss US regulatory policy in a workshop setting.

☑ USDA/APHIS in collaboration with IICAB held a Potency Specifications—U.S. Regulatory Policy Workshop on April 21-22, 2015, in Ames, Iowa.

Appendix A

Below are additional activities that were carried out in the first 180 days which supported the overall National Action Plan goals, but were not tied to specific Year One objectives or milestones.

MEETINGS, WORKGROUPS and ADVISORY COUNCILS

- A WHO-sponsored meeting – *Overcoming gaps in R&D on AMR* – was held in Brasilia, Brazil, March 26-27, 2015. Participants included representatives from leading research and research funding agencies from a number of countries including the U.S. and Brazil, and partner organizations like the WHO and OIE. Discussions included:
  - Developing a global agenda on research and development on AMR.
  - The critical need to encourage and support R&D through new collaborative and financial models, to develop practical and feasible approaches to extend the lifespan of antimicrobial medications, and the development of novel diagnostics and antimicrobial medications.
  - The need for wide engagement on innovation and R&D on AMR and improved collaboration between countries by working with WHO, the Food and Agriculture Organization (FAO), OIE and others to promote a coherent and global approach through the WHO Global Action Plan. (Goal 5)

- CDC, USDA and FDA collaborated in the planning and outreach to key stakeholders in support of a One-Health Antibiotic Stewardship Forum held by the White House on June 2, 2015. As part of the event, more than 150 key human and animal health stakeholders (e.g., healthcare systems, diagnostic and pharmaceutical companies, food companies, retailers, patient advocates) highlighted commitments to implement changes over the next five years to slow the emergence of resistant infections. (Goal 1)

- In June 2015, the National Vaccine Advisory Committee submitted an analysis to the Assistant Secretary for Health regarding the role vaccines play in strategies to combat antibiotic-resistance including the promotion of antibiotic stewardship. The Committee:
  - Emphasized that increased uptake of recommended vaccines among children, adolescents, and adults plays a critical role through the prevention of infections and by reducing transmission of antibiotic-resistant strains.
  - Put forth a number of recommendations to better incorporate vaccines into these efforts including the need for a community of stakeholders committed to combating antibiotic-resistance to regularly engage the vaccine stakeholder community and vice versa to optimize antibiotic stewardship efforts. (Goal 1)

- In August 2015, USD/APHIS engaged the AAVLD to stand up a joint working group to provide input on designing an implementation plan to leverage AMR data generated in U.S. veterinary diagnostic laboratories. The working group will:
  - Develop and administer a survey to veterinary diagnostic laboratories in FY 2015.
  - Develop recommendations for standardized antimicrobial testing and data collection, and identify concerns/gaps that may impede the implementation of this plan. (Goal 2)

- In August 2015, FDA/CVM and U.S. Fish and Wildlife Service experts delivered two workshops in China on the efficacy (therapeutic) and safety of drugs in aquaculture. In September 2015, FDA/CVM and USDA-FSIS experts delivered two workshops in China on food quality of aquaculture products, including safety assessments of drugs used in fisheries, minimum regulatory limits and monitoring drug residues in aquaculture products, and judicious uses of drugs in fisheries. (Goal 5)

- The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (Advisory Council) had its inaugural meeting on September 29, 2015. The Advisory Council will provide advice, information, and recommendations to the HHS Secretary on the implementation of the CARB National Strategy. (Goal 1)

- CDC has begun planning its annual *Get Smart about Antibiotics Week* for November 2015. CDC anticipates that the 2015 event will be larger than years past with increased and more diverse partnerships (including global partners) based on commitments received at the White House Forum on Antibiotic Stewardship, and the fact that the WHO will launch its *World Antibiotic Awareness Week* to coincide with CDC's event. (Goal 1)

- Planning is underway for the *International Scientists Training Seminar* scheduled for June 2016. Topics will include antimicrobial susceptibility testing, and discussions of laboratory networks to enhance capacity. (Goal 5)

- FDA/CVM has made progress on Year 3 work with the establishment of a National Institute of Mathematical and Biological Synthesis Working Group. The Working Group has begun developing an analytic modeling framework for assessing the relationship between antibiotic use in livestock (measured at the population level) and the development of antibiotic-resistance. (Goal 4)

RESEARCH

- CDC is supporting a research project led by the University of Maryland and Johns Hopkins Hospital on implementing antibiotic "time outs." CDC is also engaging state health departments, particularly where antibiotic use is highest, to establish new local partnerships to improve antibiotic use. (Goal 1)

- Ahead of the Year 3 milestone, the CDC Prevention Epicenters Program has already begun to evaluate some novel AMR prevention tools in diverse healthcare settings. For example, the use of a novel intervention bundle designed to stop the spread of carbapenem-resistant *Enterobacteriaceae*, in long-term acute care hospitals (LTACH) led to a 56 percent reduction in CRE bloodstream infections. LTACHs play a strategically important role as part of coordinated regional AMR interventions to prevent transmission of AMR threats within a community In 2015, the CDC Prevention Epicenter Program will complete a cluster randomized controlled trial of enhanced disinfection of hospital environment to prevent transmission of AMR pathogens. In addition, the Prevention Epicenters are evaluating novel tools related to the microbiome, biomarkers, and information exchange platforms to facilitate AMR prevention efforts. (Goal 1)

- Ahead of a Year 3 Milestone, AHRQ has more than doubled its support in FY2015, as

compared to FY2014, for research to develop improved methods and approaches for combating antibiotic-resistance and conducting antibiotic stewardship activities in multiple healthcare settings. In FY2015, AHRQ has funded five continuing and eight new grants for a total of thirteen grants that address antibiotic-resistance and antibiotic stewardship in long-term care, ambulatory, and hospital settings. AHRQ plans to translate the research findings into antibiotic-resistance prevention tools that can be implemented by healthcare providers in a variety of care settings. (Goal 1)

- The NIH/NIAID-funded PathoSystems Resource Integration Center (PATRIC) (the all-bacterial Bioinformatics Resource Center http://www.patricbrc.org) has been serving the broad scientific community for more than eight years. PATRIC provides the scientific community with free access to comprehensive bacterial genome sequence data, bioinformatics tools, workspaces, and other data sets relevant to genomic analysis and systems biology. PATRIC is working with NCBI on the establishment of a National Database for AMR which would share knowledge, genomic and clinical metadata, bioinformatics tools and pipelines, and training modules. (Goal 2)

- NIH is expanding computational tool and method development for resistant bacteria:
  - NIH/NCBI is developing suites of tools for genomic data analysis and identification of resistance genes.
  - The NIH/NIAID-funded Genome Sequencing Centers are continuing to develop bioinformatics pipelines and tools for AMR data management and comparative genome analysis. (Goal 2)

- DoD is collaborating with other USG agencies to share laboratory data, standardize the data dictionary, and upload both laboratory- and antimicrobial-use data representing the entire Military Health System enterprise into the NHSN. (Goal 2)

- USDA-APHIS is evaluating options for development of a proficiency panel on AMR testing for U.S. veterinary diagnostic laboratories, and evaluating alternative methods such as whole genome sequencing for screening isolates for antimicrobial resistance. (Goal 2)

- As part of its annual research review on high priority issues, in FY2016, the Environmental Protection Agency (EPA) is planning to evaluate the impact of resource recovery efforts on antibiotic-resistant bacteria in wastewater. (Goal 4)

- USDA-NIFA is currently funding long-term research projects to study the ecology of resistance and identify intervention strategies to diminish use, and several international collaborative events to advance and enhance common understanding of the science of AMR. Active projects that promote the understanding of antibiotic-resistance include:
  - *Prevention:* minimizing AMR in poultry and cattle production, reducing bovine and poultry respiratory diseases, critical control points in the spread of antibiotic-resistance from manure to raw produce, vaccine for bovine mastitis, development of a probiotic delivery platform of enzybiotics as an alternative to antibiotics;
  - *Surveillance:* early disease identification systems in cattle, AMR surveillance training and education program for next generation of specialists, surveillance for AMR bacteria in South Carolina poultry; and
  - *Treatment:* renewable AMR treatment for modular conveyor belts. (Goal 4)

- Ahead of a Year 3 milestone, the ARLG is in discussions with companies with Gram-negative therapeutic candidates that may be ready for clinical evaluation within the timeframe of possible CARB funding. (Goal 4)

- Ahead of a Year 3 milestone, the IND for TP-271, a novel tetracycline that is active against many drug-resistant bacteria, went into effect in August 2015. In addition, the sponsor of TP-271 announced that the drug was granted Fast Track and Qualified Infectious Disease Product designations by the FDA, and that phase 1 clinical testing is expected to begin soon. (Goal 4)

- At least three antibiotic drugs developed by portfolio partners are already in Phase 3 clinical investigation. (Goal 4)

- In 2015, USDA/ARS supported the development of bacteriophages, cytokines, vaccines, plant-derived products, and enzymes that can help reduce the use of antibiotics. (Goal 4)

- HHS (NIH, CDC), USDA, DOD and EPA are planning their annual review to ensure USG research resources are focused on high-priority antibiotic-resistance issues. (Goal 4)

- NIAID recently made 14 awards for the discovery and early stage development of new antibacterial products under RFA-14-026, Development of Novel Therapeutics for Select Pathogens, which focused in part on new therapeutics for Gram-negative pathogens. Many of these projects are focused on novel strategies to combat antibacterial resistance, such as anti-virulence, immune-based therapies, adjunctive therapies, and biofilm inhibitors. (Goal 4)

- NIAID recently funded 4 contracts under BAA-NIAID-DMID-NIH-AI-2014007, Targeting Therapeutics Development to Relieve Bottlenecks. Among the candidates small molecule therapeutics being supported is a quorum sensing inhibitor, which is able to restore susceptibility to existing drugs in multiple MDR Gram-negative pathogens. (Goal 4)

- In January 2015, NIAID released RFA-AI-11-066, Non-Traditional Therapeutics that Limit Antibacterial Resistance (R21/R33). The purpose of this Funding Opportunity Announcement is to solicit applications for early-stage translational research projects focused on discovery and development of novel non-traditional therapeutics that provide alternative treatment modalities for infected patients and address the growing health care threat of increasing antibiotic-resistance. (Goal 4)

- In June 2015, NIAID released RFA-AI-15-024, Partnerships for the Development of Host-Targeted Therapeutics to Limit Antibacterial Resistance (R01). The purpose of this Funding Opportunity Announcement is to solicit research applications for milestone-driven projects focused on preclinical development of candidate therapeutics that target host-encoded functions required for infection, replication, virulence, proliferation, and/or pathogenesis of select bacterial pathogens for which drug resistance poses a significant public health concern. (Goal 4)

- Ahead of Year 3 milestones, in June 2015, NIAID released a funding opportunity entitled *Systems Biology and Antibacterial Resistance* (RFA-AI-14-064) soliciting applications that

use a multi-disciplinary systems biology approach to study the molecular interaction networks of the pathogen and the host in association with antibacterial resistance or in response to treatment of antibacterial resistant infections. (Goal 4)

- Since the issuance of the *National Action Plan*, NIAID has established contracts for *in vitro* and *in vivo* testing of new candidate therapeutics for multiple drug-resistant bacteria. Examples include: MIC and MIC90 testing against panels of drug susceptible and resistant strains of *Staphylococcus aureus, Enterococcus* spp, *Streptococcus pneumoniae, Acinetobacter baumanii, Klebsiella, pneumoniae, E. coli, Enterobacter* spp and *Psudomonas aeruginosa*; Lung and thigh infection models; Urinary tract infection model; *C. difficle* infection model, and *S. aureus* and Vancomycin-Resistant *Enterococcus* decolonization models for testing bacteriophage products. These efficacy screening services complement services that were already underway. (Goal 4)

- Since the issuance of the *National Action Plan* in March 2015, NIAID has provided preclinical services for the following products: *Shigella* vaccine candidate, *S. aureus* vaccine candidate, defined product for Fecal Microbiota Transplant clinical trials, and a novel *S. aureus* therapeutic. These projects complement numerous relevant projects that were already underway prior to the issuance of the *National Action Plan*. (Goal 4)

- Each year, NIH funds hundreds of grants and contracts focused on bolstering basic understanding of antibacterial resistant pathogens and developing products to diagnose, prevent, and treat these pathogens. More information can be found in the NIH RePORTER, an online search tool that allows the public to mine funded research based on a number of different search criteria http://projectreporter.nih.gov/reporter.cfm.

REPORTS

- In August 2015, CDC released "CDC Vital Signs: Stop the Spread of Antibiotic-resistance " to increase awareness around AMR and provide a call to action. This issue of Vital Signs was based on new CDC scientific information to make immediate, nationwide improvements in infection control and antibiotic prescribing to stop spread of AMR infections and *C. difficile* by implementing public health-led coordinated prevention approaches, which have the potential to more completely address the emergence and spread of AMR threats than independent facility-based efforts. (Goal 1)

- In August 2015, FDA, USDA, and CDC released the NARMS 2012-2013 Integrated Report. CDC also released NARMS Now: Human Data, an interactive tool that contains AMR data from bacteria isolated from humans as part of NARMS, which makes it easier and quicker to find out how AMR has changed over the past 20 years for four bacteria transmitted commonly through food—*Campylobacter, E. coli O157, Salmonella,* and *Shigella*.

OTHER ACTIVITIES

- Ahead of the Year 3 milestones, CDC provided limited FY2015 funding to 12 states to begin leveraging existing staff and partnerships to initiate State HAI/antibiotic-resistance

Prevention (Protect) Programs. These pilot programs will establish the infrastructure to improve antibiotic use and reduce transmission of resistant pathogens. Expansion of these pilots, incorporate experience into technical packets, and to additional states is subject to the availability of funds. (Goal 1)

- USDA's Agricultural Marketing Service (AMS) initiated audits in 2015 related to AMR in poultry facilities. AMS serves as a third-party verifier for the School Food Focus Certified Responsible Antibiotic Use-standard for which producers are allowed to use medically important antibiotics only when prescribed by a veterinarian to treat illness and prevent disease in chickens. Producers are not allowed to use antibiotics for growth promotion. (Goal 1)

- Ahead of Year 5 milestones, USDA/Foreign Agriculture Service supported ongoing joint USDA-FDA/CVM outreach and training to Chinese Ministry of Agriculture stakeholders involved in:
    - drug residue monitoring and efforts to promote judicious uses of medically important antimicrobial agents in food animals; and
    - risk assessment and approval of veterinary drugs. (Goal 5)

Appendix B

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

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

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

Appendix C

AAVLD	American Association of Veterinary Laboratory Diagnosticians
AAVMC	Association of American Veterinary Medical Colleges
AFRI	Agriculture and Food Research Initiative
AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AHRQ	Agency for Healthcare Research and Quality
AMR	antimicrobial resistance
AMS	Agricultural Marketing Service
APHIS	Animal and Plant Health Inspection Service
ARBI	Antibiotic Resistance Biopharmaceutical Incubator
ARIP	Antimicrobial Resistance Initiative Program
ARLG	Antibacterial Resistance Leadership Group
ARS	Agricultural Research Service
AST	Antimicrobial Susceptibility Test
AU	antibiotic use
AVMA	American Veterinary Medical Association
BARDA	Biomedical Advanced Research and Development Authority
CARB	Combating Antibiotic-Resistant Bacteria
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CRE	carbapenem-resistant Enterobacteriaceae
CVM	Center for Veterinary Medicine
DBL	Diagnostic Bacteriology Laboratory
DoD	Department of Defense
ECDC	European Centre for Disease Prevention Control
EIP	Emerging Infections Program
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization
FAS	Foreign Agriculture Service
FDA	Food and Drug Administration
FSIS	Food Safety and Inspection Service
GFI	Guidance For Industry
GHSA	Global Health Security Agenda
HAI	healthcare-associated infections
HHS	Department of Health and Human Services
IICAB	Institute for International Cooperation in Animal Biologics
IMDRF	International Medical Device Regulators Forum
IND	Investigational New Drug
IPT	Integrated Product Team
JSTO	Joint Science and Technology Office
LTACH	long-term acute care hospitals
LTC	long-term care
MDR	multi-drug resistant
MOU	Memorandum of Understanding
MRSN	Multidrug-resistant organism Repository and Surveillance Network
NAHLN	National Animal Health Laboratory Network

NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
NCBI	National Center for Biotechnology Information
NHGRI	National Human Genome Research Institute
NHSN	National Healthcare Safety Network
NIAID	National Institute for Allergy and Infectious Diseases
NIFA	National Institute of Food and Agriculture
NIH	National Institutes of Health
NQF	National Quality Forum
NVSL	National Veterinary Services Laboratories
OGA	Office of Global Affairs
OIE	World Organization for Animal Health
OSTP	Office of Science and Technology Policy
PAHO	Pan American Health Organization
PATRIC	PathoSystems Resource Integration Center
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
POC	point-of-care
PR/HACCP	Pathogen Reduction/Hazard Analysis and Critical Control Point
RFA	Request for Applications
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
USDA	United Stated Department of Agriculture
USG	United States Government
VA	Department of Veterans Affairs
Vet-LIRN	Veterinary Laboratory Investigation and Response Network
VFD	Veterinary Feed Directive
VHA	Veterans Health Administration
VICH	International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal Products
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research