INITIAL ASSESSMENTS OF THE NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

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PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

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Executive Summary

Both the Centers for Disease Control and Prevention and the World Health Organization have declared antibiotic resistance to be one of the most serious problems facing our national and global health systems today. While primarily a health problem – for humans and animals – it also has also been identified as a fundamental aspect of global health security. In consultation with the Secretaries of Defense and Agriculture, the U.S. Department of Health and Human Services (HHS) Secretary's establishment of the President's Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB) is one of several recent U.S. Government (USG) actions to respond to the threat. As stipulated in Executive Order 13676 and their Charter, the PACCARB advises the HHS Secretary on the programs and policies intended to support the implementation and evaluation of the National Action Plan (NAP) for Combating Antibiotic-Resistant Bacteria (CARB); all written reports created by the PACCARB will then be provided to the President by the HHS Secretary.

Following the PACCARB's inaugural public meeting on September 29, 2015, five PACCARB working groups (WGs), each aligned with one of the goals of the NAP, have made initial assessments of the USG's progress toward the goals of the NAP. This process was informed by their review of the First 180-Days Report (Progress Report), which summarizes the USG progress in achieving the milestones for the goals set by the NAP, in addition to a series of in-depth discussions with subject matter experts from federal departments and agencies about their strategies, activities, achievements, plans and challenges.

This first PACCARB report presents its findings as a result of these activities. We acknowledge that this report is an initial, non-comprehensive assessment, and that many areas still need to be explored. The PACCARB looks forward to gaining further insights and offering more comprehensive recommendations in the future.

All in all, we commend our federal partners. Since the NAP was released, the departments and agencies have been well-focused on the problem of antibiotic resistance, with much success and several notable accomplishments. The Progress Report (see Annex I) outlines all of the USG accomplishments within the first 6 months of the NAP's release. They include many examples of agencies working independently and collaboratively to reach the many milestones outlined in the NAP. Some are: the Centers for Medicare and Medicaid Services' development of a condition of participation requiring antibiotic stewardship in inpatient and long-term care settings; establishment by HHS' Biomedical Advanced Research and Development Authority and the National Institute for Allergy and Infectious Diseases of the National Institutes of Health of the CARB Biopharmaceutical Accelerator, a novel public-private partnership that will support and accelerate candidate products (drugs, vaccines, and diagnostics) into clinical development; the Department of Defense's Multidrug-Resistant Organism Repository and Surveillance Network (MRSN); and the Food and Drug Administration's final Veterinary Feed Directive rule (VFD), which is one element of their anti-antimicrobial resistance effort in the veterinary area. This strategy will bring the use of medically important antibiotics in feed and water under veterinary supervision so that they are employed only when necessary for assuring animal health. The VFD final rule outlines the process for authorizing the use of medically important antimicrobials in feed under the supervision of a licensed veterinarian, and provides veterinarians in all states with a framework for authorizing such use when needed for specific animal health purposes. Lastly, the Agency for Healthcare Research and Quality, the National Institutes of Health, and the Centers for Disease Control and Prevention have all significantly increased their investment in research

to develop better methods of combating antibiotic resistance and promoting antibiotic stewardship; this research is critically important to strengthen the knowledge base for ensuring the effectiveness of the interventions used today and for developing more effective interventions for tomorrow.

Overarching Issues and Recommendations

PACCARB identified six overarching themes that will require further attention by the USG for the NAP and the efforts of the USG to have the strongest impact in combating antibiotic-resistant bacteria:

- **Fully embracing a One Health approach:** One Health is defined as multiple disciplines and professions working locally, nationally and globally to achieve optimal health in the human, animal and environmental domains. Microbes do not respect geographical, political or species boundaries. The relationship between humans and domesticated animals in the transmission of microbes is a central principle in any rational approach to solving antimicrobial resistance (AMR). Therefore, One Health must be seen as an organizing principle to be used to better understand resistance and to generate new interventions to prevent or reduce the occurrence and transmission of antibiotic resistance. All five WGs stressed this principle, but the efforts vis-à-vis AMR in animal and human health remain largely disconnected. In addition, there needs to be further exploration of the potential contamination of the environment with antibiotics and metabolites and the impact on our health. New approaches are clearly needed. The interdisciplinary integration and dialogue between veterinary and human health institutions and subject matter experts needs to become more frequent and more in depth to ensure that our ability to combat antibiotic resistance in both human and animal populations is better coordinated and optimized.

- **A lead federal champion of the CARB initiative:** In its enormous breadth and scale, many of the USG activities take place in silos. To maximize efficiency and productivity, there needs to be improved coordination and collaboration. Leadership is critical to overcoming challenges. There is need for a champion in the USG to align all of the agencies and move the work forward efficiently and synergistically. For example, given the cross-government effort as embodied by the broad membership of the federal interagency Task Force on CARB, such a champion could be at the level of the White House, a Cabinet Secretary or Department Undersecretary with sufficient gravitas and authority to bring the relevant parties together.

- **Coordination of the federal response:** The importance of a coordinated effort across agencies and departments cannot be minimized. Although there have been many notable successes, PACCARB found that centrally coordinated mechanisms were not sufficient to ensure maximum synergy, avoidance of duplication, and coverage of all key points.

- **Resource allocation:** Combating AMR requires an adequate resource base to slow down, control, and hopefully reverse the problem. Simply stated, the USG must commit sufficient resources to solving the problem with funding continued over a long period of time. Each of the WGs found that key elements necessary to achieve the goals of the NAP are underfunded. Potential solutions could involve a combination of new monies authorized from Congress or re-budgeting within departments and agencies, or re-allocate full-time employees between agencies to reduce redundancy and cost while increasing communication and productivity for the USG.

- **Development of critical partnerships:** The USG has neither sufficient resources, omniscience about the problems, nor a sufficient pool of expertise to unilaterally solve the problem of AMR.

PACCARB underscores the utility of establishing effective partnerships with states and local agencies, tribes, private-sector organizations, commodity groups, philanthropic organizations, and international bodies. Solutions will require both local and global approaches. Although key steps have been taken, further emphasis on partnering is necessary.

- **Economic incentives for developing and deploying new diagnostic, preventive, and therapeutic tools:** Solving AMR will require new modalities, such as new antibiotics, vaccines, and diagnostics. However, despite steps to promote such development, PACCARB believes that the current economic model is inadequate not only to ensure the availability of antibiotics to treat antibiotic-resistant infections but also to prevent their emergence. These challenges will require incentives at different levels for proper stewardship to avoid unnecessary treatment (e.g., for viral infections) and an economic and commercial model that takes into account the full societal costs of AMR and that provides adequate pull to ensure the development and deployment of new therapies, preventatives, and diagnostics.

Future Work

The PACCARB presents these six themes for leadership to consider as they move toward achieving new milestones. During the next several months, the PACCARB will continue to gather relevant information about USG activities and progress, as well as the evidence-base that underpins these efforts. As part of this process, we intend to continue to engage stakeholders beyond our membership and, in the short term, seek broader feedback through the *Federal Register* to gather general and specific input from the many stakeholders who are also deeply concerned about this issue. We also look forward to requests by the HHS Secretary, in consultations with the Secretaries of Agriculture and Defense, for consideration of specific issues for which the USG is seeking our advice, in accordance with our charge. Although most of the WG activities have been focused on scientific, programmatic and policy issues, the PACCARB understands that this growing health crisis has a very human face. The morbidities and mortalities that are a result of antibiotic resistance and that impact so many lives are very real and serve as a constant reminder to us of the importance of our work.

Introduction

The great strides that we have made using antibiotics to control infectious diseases in both human and animal health are being compromised by antibiotic resistance. Although it is not a surprise that resistance is occurring, the speed, scope, and scale of the problem are unprecedented and represent a profound global concern. We have reached a point where antibiotic resistance threatens patient care, economic growth, public health, agriculture, national and global health security. Until recently, we have not had an integrated or comprehensive national strategy to address the multifaceted, rapidly expanding problem of antibiotic resistance. However, recent events have given us both a sense of urgency to act and a national plan to follow.

Recent critical actions include the following:

- The President's Council of Advisors on Science and Technology (PCAST) Report on Combating Antibiotic Resistance. (September, 2014)
- Executive Order 13676 directing federal agencies to implement the recommendations from the PCAST report, which includes creation of a federal interagency Task Force on Combating Antibiotic-Resistant Bacteria. (September 2014)
- Creation of the federal government's National Strategy (2014) and resulting National Action Plan (NAP) for Combating Antibiotic-Resistant Bacteria. (March 2015)
- Executive Order 13676 also directed the Secretary of the U.S. Department of Health and Human Services (HHS), in consultation with the Secretaries of the Departments of Defense (DoD) and Agriculture (USDA), to establish a President's Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB). (September 2015)

PACCARB Mission

As outlined in its charter, the mission of the PACCARB is to provide advice, information, and recommendations to the HHS Secretary regarding programs and policies intended to support and evaluate the implementation of the NAP, which will then be transmitted by the HHS Secretary to the President. This report is the first update by the PACCARB to assess the government's progress on its efforts to combat antibiotic-resistant bacteria within the first year of the NAP's release.

Notable Successes

All in all, we commend our federal partners. Since the NAP was published, the agencies and departments have been focused on the problem of antibiotic resistance, with much success and several notable accomplishments. The NAP's First 180-Days Report (Progress Report) and its annexes outline all of the USG accomplishments on combating antibiotic-resistant bacteria (CARB) in the first 6 months following the NAP's release (the report is available in Annex I). Still, the road ahead is long. The scope and complexity of the problem requires the whole-of-government response it is now receiving through the Executive Order, but we note that progress will be slow and require perseverance and resources matched to the task. The silver lining is the clear commitment to facing the challenge, and for that we can see a pathway toward substantial

improvement. The following examples highlight some of the substantial work accomplished by the USG:

- **Antibiotic Stewardship:**
  - The Centers for Medicare and Medicaid Services (CMS) has developed two important actions: a condition of participation (CoP) that will require antibiotic stewardship aligned with the Centers for Disease Control and Prevention (CDC) core elements in inpatient settings (this document is currently in the clearance process) and new infection control standards that will require antibiotic stewardship programs in long-term care facilities (LTCFs). These CMS actions are critical drivers for the implementation of such programs in these health care settings.
  - The Food and Drug Administration's (FDA's) overall strategy on combating antimicrobial resistance (AMR) is on track to successfully remove all growth-promotion uses of medically important antibiotics by the end of 2016. Guidance for Industry (GFIs) #209 and #213 will also bring the use of medically important antimicrobial drugs under veterinary supervision so that they are used only when necessary for assuring animal health. The final Veterinary Feed Directive (VFD) rule outlines the process for authorizing use of VFD drugs (animal drugs intended for use in or on animal feed that require the supervision of a licensed veterinarian) and provides veterinarians in all states with a framework for authorizing the use of medically important antimicrobials in feed when needed for specific animal health purposes.
- **One Health Surveillance:**
  - CDC has developed a risk-adjusted summary measure of antibiotic use in hospitals, the Antimicrobial Use Measure, which was endorsed by the National Quality Forum in January 2016. The Antimicrobial Use Measure provides a benchmark for hospitals and health systems to use in antimicrobial stewardship programs (ASPs).
  - DoD is actively involved in assisting partnering nations and institutions in standardizing data collection and analysis through its centralized laboratory, the Multidrug-resistant organism Repository and Surveillance Network (MRSN). MRSN is a highly-responsive analytical and surveillance activity that now offers whole-genome-based reports in 48-72 hours. MRSN will expand to include other USG agencies, academic researchers, health care institutions, and industry partners. MRSN has a long track record of strengthening national reference laboratories through the DoD Global Emerging Infections Surveillance and Response Section. CDC and FDA also have created a repository of resistant bacteria ahead of schedule. They have defined specific organisms to include in the repository and already have responded to specimen requests from industry and academia. The CDC Antimicrobial Resistance (AR) Isolate Bank is a curated collection of over 200 unique isolates that is pulled from CDC's repository of AR isolates, which includes over 450,000 AR isolates and over 18,000 characterized genomes.

- **Diagnostic Innovations:** The Antibiotic Resistance Leadership Group (ARLG), funded by the National Institutes of Health's (NIH's) National Institute for Allergy and Infectious Diseases (NIAID), has a packet of projects in progress that emphasize diagnostics. These include two projects ("Rapid Diagnostics in Categorizing Acute Lung Infections" and "Use of Procalcitonin Testing to Direct Antibiotic Use in Lower Respiratory Tract Infections") that assess diagnostics for common outpatient infectious disease syndromes and thus aim to fulfill a largely unmet need in this area.
- **Research and Development (R&D) on Treatment, Prevention, and Control:** HHS' Biomedical Advanced Research and Development Authority (BARDA) and NIAID jointly released a funding opportunity announcement to establish the CARB Biopharmaceutical Accelerator in February 2016. The Accelerator represents a novel public-private partnership that will support and accelerate candidate products (drugs, vaccines, and diagnostics) into clinical development.
- **International Collaboration:** International engagement coordinated between HHS, the State Department, and Department of Agriculture (USDA) with the World Health Organization (WHO), the Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), other nation states, and other relevant organizations resulted in successful adoption of WHO's Global Action Plan. This plan is consistent with the NAP's priorities, including emphasis on the One Health approach, enabling evidence-based decisions, and the need for R&D.

In addition to the many achievements described in the Progress Report, the USG has undertaken other activities to combat antibiotic resistance and made progress. Some of these are discussed in depth in the WG assessments in this report; others are listed in Annex I, which includes the Progress Report.

About This Report

Since the PACCARB's inaugural meeting on September 29, 2015, five working groups (WGs) have been seeking to better understand the many activities of the U.S. government (USG) agencies to combat antibiotic resistance. The WGs are made up of highly engaged and active members with an in-depth understanding of many facets of the issue.

Each WG is aligned with a goal of the NAP and led by a chair and vice chair from the PACCARB. The composition of each WG is outlined in Annex II. The assignment of PACCARB members to WGs was designed to provide the optimal balance of professional expertise and orientation across the five WGs. As a baseline to their fact-finding process, the WGs have reviewed the Progress Report, which summarizes the USG progress in achieving the milestones of the NAP. They also consulted with federal officials, PACCARB members with special expertise, and a number of external stakeholders, including international colleagues, and subject matter experts in several relevant fields. A summary of the frequency and nature of WG teleconferences is available in Annex III. The main body of this report represents the detailed assessments from the WGs.

The WGs acknowledge that their findings, which comprise this report, represent an initial, non-comprehensive assessment of efforts to date and many more areas must be explored. Each assessment for the respective goals of the NAP begins with a summary of the findings and broad

recommendations, including a section on the progress through the lens of the One Health concept. Notable progress and activities toward meeting the NAP milestones for the goal are then described, followed by more detailed, specific recommendations of PACCARB.

The PACCARB recognizes that the NAP's Progress Report is a baseline for assessing the direction of agency activities, and accordingly, provides this report for the HHS Secretary's consideration. We look forward to gaining further insights and making more comprehensive recommendations as our work matures and expands over the next several years.

Initial Assessment of Progress toward Goal 1: Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections

The USG has met one-year milestones in strengthening antibiotic stewardship capacity in acute care, long-term care, and outpatient settings; developing approaches to collect and assess data on antibiotic use and antibiotic resistance; developing a foundation to foster antibiotic stewardship in animals; and enhancing education and research in antibiotic stewardship and antibiotic resistance. Further solidifying this work through a One Health lens in the United States requires implementation of several interdisciplinary and collaborative activities included in the NAP that face two main barriers: inconsistent funding and insufficient interagency coordination. To truly combat antibiotic resistance and advance antibiotic stewardship activities for humans and animals, the programs in place—and those critical interdisciplinary activities to be developed—must be sustained by continuous funding and a well-coordinated interagency effort.

Broad Recommendations for Goal 1

- **Ensure sustained and enhanced funding.** Many of the activities planned as three-year milestones are extensive and require substantial institutional and behavioral changes. A "one-and-done" project funding approach is inadequate to drive significant and lasting antibiotic resistance prevention and antibiotic stewardship promotion. For example, having a robust ASP at every hospital is an aspirational goal when only approximately one third of acute care hospitals currently have ASPs. Success in establishing ASPs in both human and veterinary practice across the broad range of health care settings is directly related to funding of support personnel at the local, state, and federal levels. It is critical that state health departments are in synch with CDC's Antibiotic Resistance Solutions Initiative to establish State Healthcare-associated Infections/Antibiotic Resistance Prevention Programs (State HAI/AR Prevention Programs) and develop coordinated responses to measure and control the spread of antibiotic resistance and implement antibiotic stewardship collaborations. However, such programs will require staff with appropriate training and expertise to lead efforts over the long term. The need for continued funding also extends to clinical and applied research with a particular emphasis on implementation and behavior change for antibiotic stewardship to become the norm in both human and animal medicine.

- **Coordinate work across agencies.** There must be continued attention to optimizing opportunities for synergies and avoiding parallel and sometimes duplicative efforts while sharing successful approaches and coordinating recommendations across federal agencies such as CDC, DoD, USDA, FDA, and the Department of Veterans Affairs (VA). It may be necessary to establish departmental and interdepartmental level leads for human (HHS) and veterinary (USDA) medicine that have the authority and responsibility for coordinating these efforts.

A One Health Approach

Sharing information and experiences across human and veterinary professions is pivotal to antibiotic stewardship goals. While the specifics of systems within human and veterinary

medicine in which antibiotic stewardship must be promoted are strikingly different, the common thread of determining optimal educational approaches and systems incentives is uniformly critical. The application of implementation science for influencing the behavior of prescribers of antibiotics for both humans and animals and the expectations of human patients and veterinary clients is of great importance. Assessment of these efforts to evaluate their impact will be important to make the case to expand resources for effective programs and redirect resources from unrewarding efforts.

To foster a One Health approach, the PACCARB recommends the following:

- **Implement efforts to share experiences in promoting adoption of antibiotic stewardship in professional curricula by faculty in colleges of human and veterinary medicine.** Direct involvement is needed, ranging from those teaching basic pharmacology and microbiology to those teaching clinical subjects and rotations. The engagement of clinical instructors across the health sciences is paramount, as attitudes and practices displayed in clinical training can counter prior suboptimal didactic messages.
- **Promote a culture of antibiotic stewardship as an integral part of continuing education and clinical practice for practicing providers and professionals.** This should include a range of practicing providers and professionals across the health sciences, including physicians, physician assistants, nurses, nurse practitioners, dentists, pharmacists, health care administrators, and others.

Goal 1 Objectives: Progress and Activities

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

Strengthening Antibiotic Stewardship

Some examples of federal agencies meeting or exceeding early milestones in developing a foundation to strengthen antibiotic stewardship capacity are as follows:

- CMS has developed a CoP (currently in agency clearance) requiring ASPs in inpatient settings and new infection control standards that require ASPs in LTCFs. Both requirements will be important drivers for implementation of ASPs. This work is complemented by The Joint Commission's (TJC's) development of an antibiotic stewardship standard requiring antibiotic stewardship across all health care settings.
- CDC has outlined the basic requirements for antibiotic stewardship activities in two Core Elements documents for nursing homes and hospitals.
- CDC released funding opportunities in March 2016 through CDC's Epidemiology and Laboratory Capacity (ELC) Cooperative Agreement to build core HAI/AR detection and response infrastructure in every state and support State HAI/AR Prevention Programs in up to 25 states.

- The Agency for Healthcare Research and Quality (AHRQ) is currently field-testing an implementation guide for antibiotic stewardship in LTCFs based on research in this area.
- CDC has initiated collection of data on national uptake of ASPs using the annual survey of the National Healthcare Safety Network (NHSN) and has set national targets for reduction in antibiotic use in partnership with the Pew Charitable Trusts.
- DoD and VA have taken initial steps to ensure that their facilities have ASPs.

This work sets the stage for the next critical phase in expanding and solidifying antibiotic stewardship capacity and capability in the United States, including the successful implementation of evidence-based antibiotic stewardship activities and continued monitoring of the impact of these programs on antibiotic resistance.

The PACCARB recommends the following to strengthen antibiotic stewardship:

- **Ensure the development of evidence-based ASPs that are positioned to drive change.** CMS should develop Interpretive Guidelines for its CoPs that specifically outline the requirements for evidence-based ASPs to drive health care organizations and individual prescribers to change current antibiotic prescribing practice. This work is of particular importance for LTCFs, many of which have no antibiotic stewardship activities. CMS and TJC should develop training and tools that allow surveyors to assess the quality of ASPs based on the Interpretive Guidelines across health care settings, rather than simply verify the existence of ASPs.
- **Enlarge and train the workforce.** Approaches are needed to maintain and expand the workforce with appropriate expertise in antibiotic use and resistance in these ASPs (e.g., physicians and pharmacists specializing in infectious disease). These will in turn facilitate the establishment and maintenance of accountable and transparent ASPs in all health care settings. Workforce development will require innovative strategies to support antibiotic stewardship work (e.g., new payment models for infectious disease physicians performing stewardship and expanded support for funding of pharmacy residency training programs in infectious disease).
- **Enhance collaboration between CMS and CDC.** Via the CDC's State HAI/AR Prevention Programs, regional antibiotic stewardship collaborations should be facilitated by state health departments, in collaboration with CMS's Quality Improvement Networks and Hospital Engagement Networks, to provide additional guidance to facilities on implementing and maintaining robust ASPs and to prescribers to promote optimal antibiotic use. This work will assist with development of interventions to optimize antibiotic use across all health care settings.
- **Ensure sustained funding.** It is imperative that programs designed to combat antibiotic resistance and improve antibiotic stewardship continue to be funded by, at a minimum, maintaining fiscal year (FY) 2016 budget funding for agencies and departments that received increased funding to support such programs. Equally important, the agencies that did *not* receive the needed increases in the current year should have funding for future fiscal years. Federal funding is also vital to local and state public health agencies; their capacity and effectiveness are reduced with reductions in federal funding.

- **Increase attention to antibiotic stewardship in outpatient settings.** The initial focus on antibiotic stewardship in inpatient health care settings is a good start, but promoting optimal antibiotic use by outpatient prescribers, particularly those not affiliated with a health system, is an especially important challenge that requires further evaluation and implementation. More understanding is needed of current factors that may serve as disincentives to antibiotic stewardship (e.g., the influence of patient satisfaction surveys when patients expect to receive antibiotics, and the high cost of diagnostics vs. the relatively low cost of antibiotics in outpatient settings). Potential mechanisms for improving antibiotic stewardship in outpatient settings are as follows:
    - Expand the Merit-Based Incentive Payment System (MIPS) to include payment incentives and penalties that promote optimal antibiotic use and expand the Physician Quality Reporting System to include quality metrics designed to reward optimal antibiotic prescribing. While these approaches are likely to be effective in influencing the prescribing practices of physicians and other providers who seek payment from CMS, they do not address prescribing in settings with self-payment, such as retail clinics.
    - Leverage the CMS' State Innovation Models Programs as a mechanism to engage with outpatient prescribers, public health agencies, other state departments (agriculture, insurance, education) and collaborate with nongovernment partners.
    - Foster collaboration with nongovernment partners, such as those identified at the June 2015 White House Forum on Antibiotic Stewardship[1].

Education Campaigns

The USG has met milestones on expanding efforts to educate on antibiotic stewardship. CDC's Get Smart campaign for human medicine included Get Smart About Antibiotics Week, which saw a 50% increase in participating partners and an increase in public awareness. Educational efforts in animal medicine such as Get Smart on the Farm seem to have minimal effect. In general, the impact of education as a primary means of changing behavior surrounding antibiotic prescribing is unclear, although widespread behavior change has been noted with long-term education campaigns, especially when coupled with reinforcing policies, such as seat belt use and smoking cessation.

The PACCARB recommends the following to ensure the success of education campaigns:

- **Investigate which messages have the most impact and are the most likely to induce behavior change among prescribers and consumers.**
- **Identify the appropriate groups and messengers to deliver the message(s).**
- **Increase funding for more robust educational campaigns with wider influence among human and veterinary sectors.** Informed by the evidence about which messages and messengers are likely to have the greatest impact, federal campaigns

[1] The White House Forum on Combating Antibiotic Resistance (2015): https://www.whitehouse.gov/blog/2015/06/02/white-house-hosts-forum-combating-antibiotic-resistance

should be done in collaboration with private stakeholders such as professional societies and academia. A follow-up to the White House Forum on antibiotic stewardship may help ensure continued engagement of nongovernment groups in prioritizing antibiotic stewardship education for members.

Surveillance

The USG has made progress on expanding efforts to develop surveillance networks to monitor for antibiotic resistance, which is the necessary first step in developing approaches to prevent the spread of antibiotic resistance. However, overall, the United States would benefit from a more robust surveillance network for antibiotic resistance that can be used to develop a coordinated response to control its spread in human and animal populations. Current surveillance activities are discussed in Goal 2. While specific activities are underway, little information exists regarding how the data have been used to lead to improvements. One successful example is a registry for patients colonized or infected with highly antibiotic-resistant bacteria developed by the CDC-funded Chicago Prevention Epicenter in collaboration with the Illinois Department of Public Health. The registry can be queried when patients are admitted to facilities, allowing them to institute precautions quickly and prevent additional spread of resistant bacteria to other patients. Approaches such as this should be replicated at a larger scale via the formation of State HAI/AR Prevention Programs.

The PACCARB recommends the following critical actions to ensure both the sustainability and the success of this work:

- **Ensure continued, stable funding of federal and state surveillance programs over many years to ensure their longevity, productivity, and the ability to monitor trends over time.**
- **Coordinate and harmonize by the CDC which data are collected, analyzed, and acted upon among the State HAI/AR Prevention Programs** to ensure that important trends in resistance are detected and tracked and that appropriate interventions can be developed across multiple different healthcare facilities in the same region.
- **Address the challenge of relying on health care institutions to voluntarily provide information and bacterial isolates (e.g CRE is not reportable in most states).** This work is complex, expensive, and not well-supported. In particular, methods to reimburse microbiology laboratories for collecting and shipping isolates to state laboratories should be investigated.

Data on Antibiotic Use in Inpatient and Outpatient Settings

Comprehensive, standardized, and risk-adjusted data on antibiotic use in inpatient and outpatient settings reported annually are critical to assess and enhance antibiotic stewardship activities in the United States. CDC has made progress towards implementing inpatient reporting via the NHSN Antimicrobial Use and Resistance (AUR) module and continues to develop methods for risk stratification of these data. CDC has reported on outpatient antibiotic use data from 2010 to 2013 and will continue purchasing proprietary data to perform this work. The Emerging Infections Program (EIP) continues to assess antibiotic use via the health-care-associated infections (HAI) prevalence surveys in both acute and long-term care settings with the addition

of the data being collected on the appropriateness of antibiotic use. Additional details about reporting of antibiotic use are discussed under Goal 2.

The PACCARB recommends the following key issues be addressed for antibiotic use reporting:

- **Increase the number of hospitals reporting antibiotic use data via the NHSN AUR module and validate the quality metric for hospital antibiotic use endorsed by the National Quality Forum.** The relationship between overall antibiotic use and appropriateness of antibiotic use is not known, and data currently reported to the AUR module are likely inadequate for complete risk adjustment. Thus, it is essential that additional work in risk stratification occurs before AUR reporting is proposed to become a pay-for-performance measure under the CMS value-based purchasing model.
- **Develop methods to assess antibiotic use at the prescriber level in outpatient settings.** Comparisons of antibiotic use among individual outpatient prescribers are likely to be an important driver in decreasing unnecessary use. Additional work is needed to obtain prescriber-level data on appropriate use and to develop mechanisms to provide direct feedback on performance to prescribers.

Research: From Basic Science to Implementation Science

The USG has expanded historically underfunded research in development and implementation of interventions to address drivers of the emergence and spread of antibiotic resistance and misuse of antibiotics. The trajectory of this work must increase over the next few years to establish a more robust evidence base for these interventions. AHRQ doubled its funding in FY 2015 and received $10 million in FY 2016 to expand its foundational research in implementation science approaches to enhance antibiotic stewardship and prevent antibiotic resistance and HAIs across all health care settings. CDC expects to dedicate about $30 million from the FY 2016 budget to continue research in reducing transmission within and between health care settings, including demonstration of the impact of a regional approach that includes collaboration between public health, hospitals, and long-term care settings to reduce transmission of antibiotic resistance. AHRQ and CDC are planning a meeting of experts and stakeholders in the spring of 2016 to identify knowledge gaps in antibiotic resistance and antibiotic stewardship and to identify potential interventions for development, testing, and eventual widespread implementation. NIH has expanded clinical research in antibiotic stewardship and antibiotic resistance largely through the NIAID's ARLG. Currently, it is not known what proportion of the $100 million allotted to NIAID in FY 2016 for antibiotic resistance will be received by the ARLG to enhance its current work.

The PACCARB recommends the following:

- **Continue progressively increasing support for agencies that are specifically directed to address interventions to reduce transmission of antibiotic resistance and optimize antibiotic use.**
- **Coordinate activities across the agencies to maximize resources available and derive synergies.**

- **Pursue research on the most effective approaches to perform antibiotic stewardship, to influence and to predict prescriber behavior, and to prevent the spread of antibiotic resistance in acute care, long-term care, and ambulatory settings.**
- **Translate the knowledge gained from research into tools for broad use.**
- **Develop a pipeline of research in this area through funding of investigators to promote a career track in antibiotic stewardship/antibiotic resistance activities.**

Regulatory Processes

FDA provides technical assistance on legislative proposals that aim to streamline regulatory processes for updating and approving or clearing antibiotic susceptibility testing (AST) devices.

The PACCARB recommends the following:

- **Legislative attention and action is needed to establish new approaches for updating antibacterial susceptibility interpretive categories that leverages the work of standards development organizations, takes advantage of electronic resources to achieve timely and efficient updating of these interpretive categories and that addresses the diversity of bacteria that cause infections in the real world.** These new approaches are needed to support appropriate therapeutic decisions and infection control practices.
- **The FDA is to consider an expedited process to for the concurrent approval of the antibiotic and its corresponding susceptibility testing.**

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.

Initial milestones have been achieved in eliminating the use of medically important antibiotics for growth promotion in food animals. The final Veterinary Feed Directive rule is in place, and by the end of 2016, it is expected that all labels of medically important antibiotics used in feed or water will reflect the requirements of GFI #209 and #213. Biannual reports on progress in label changes have been published. However, limited progress has been made in finalizing a plan for assessing the impact of the two GFIs on the extent of antibiotic use in food animals. A proposed FDA rule requiring reporting of estimates of animal-species-specific sales data is expected to be finalized this spring. To move toward more granular data about use and resistance, a combined public meeting of the USDA, FDA, and CDC in 2015 outlined potential paths forward. The FDA has worked to develop metrics, but implementation requires methods to enhance collection of on-farm antibiotic use data which requires additional funding.

The PACCARB recommends the following to address barriers to moving forward with broad stakeholder collaboration on antibiotic use in food animals:

- **Work toward consensus processes for establishing metrics for the appropriateness of antibiotic use, especially antibiotics used for preventative purposes.**

- **Work to insure such metrics are interpreted appropriately by all stakeholders when the required data become available.**
- **Reconcile concerns about confidentiality of producers and specific farms.**

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

Outreach, Education, and Stakeholder Engagement

Quality assurance programs, educational outreach strategies, expansion of antibiotic stewardship initiatives in veterinary curricula and continuing education programs, and judicious use guidelines initiated by producer and veterinary groups have been actively progressing since before the NAP, some with the assistance and input of federal agencies. These programs have been highly effective in reducing the incidence of residues from veterinary drugs and other chemicals in the food supply, but their impacts on antibiotic use and, more importantly, on antibiotic resistance have not been assessed.

In contrast to human health care, the veterinary profession is not structured in a manner that provides opportunities for incentivizing stewardship activities analogous to policy levers in human medicine, such as CMS' CoPs. An approach for food animal production could be based on the discussion and agreement on shared goals among veterinarians, producers, and their customer supply chains, leading to the expansion of system-based programs.

The PACCARB recommends the following to foster antibiotic stewardship in animals:

- **USDA and FDA should ensure financial and educational support of outreach efforts undertaken by the agricultural extension services and the nongovernmental organizations already engaged in driving antibiotic stewardship in veterinary medicine.** The USDA's National Institute for Food and Agriculture (NIFA) is making plans for research and initiative support that depend entirely on budget provisions for their grant programs. USDA has been actively engaged in determining the needs of stakeholders to direct these grant programs. Since FY 2013, NIFA's Antimicrobial Resistance (AMR) program has awarded more than $11 million to support systems-based integrated projects and conferences at the national level. Stakeholder conferences have been a key strategy for the USDA that promotes education, allows the agencies to gain important insights on priorities and policy development, and helps to establish research needs; this type of activity needs to be encouraged further and used in their planning.
- **Antibiotic use in companion animals should be considered a potential focus of stewardship activities.**

Initial Assessment of Progress toward Goal 2: Strengthen National One Health Surveillance Efforts to Combat Resistance

Strengthening One Health surveillance of antibiotic use and antibiotic-resistant bacteria is critical to inform approaches to control antibiotic-resistant infections and measure success. The One Health paradigm recognizes that antibiotic-resistant bacteria occur in and are shared between humans, animals, and the environment. The existing infrastructure, proposed activities, and available funding of various USG agencies that conduct surveillance differ substantially between the human and animal sectors. Progress in the human setting is more on track to meet the NAP goals. For surveillance in animals, some progress has been made on specific goals, but achieving parallel progress is hampered by asymmetric funding.

Inadequate funding, redundant repository and other systems, and insufficient coordination and collaboration among USG agencies and stakeholders are impediments to efficient realization of the objectives of goal 2 of the NAP. Despite these barriers, USG agencies have made important initial progress to strengthen laboratory networks for human health surveillance, enhance critical organism repositories to support research into new therapeutics and diagnostics, expand infrastructure for animal pathogen surveillance, and enhance reporting of veterinary antibiotic sales.

Broad Recommendations for Goal 2

- **Ensure sustained funding to stay on track and ultimately achieve the One Health surveillance goals in the NAP.** Failure to fund surveillance in the animal sector, in particular, leads to data asymmetries between human and animal surveillance and hampers the ability to develop informed policy or measure success in the agricultural setting. In the absence of increased funding, USG agencies will need to reestablish priorities, make budget adjustments to accommodate needed antibiotic resistance and antibiotic use surveillance and control programs, identify milestones that are unattainable due to funding constraints, and work together to reduce redundancies and overlapping activities.

- **For surveillance of antibiotic resistance, enhanced capacity and coordination in both human and animal settings may enhance surveillance capability.** Coordination of federal efforts between agencies, with state and local health agencies, with external laboratories and with external partners can provide complementary expertise and help avoid redundancy.

- **For human surveillance, address challenges in data sharing as priority items.** The low proportion of hospitals reporting antibiotic use and antibiotic resistance data to NHSN currently limits its surveillance value. Software and electronic health record (EHR) capacity to share antibiotic use and AST data should be resolved across all vendors. As outlined in the NAP, the CDC and CMS need to continue to work together to develop and implement reporting requirements through the Inpatient Quality Reporting

Program. Regulatory and financial incentives are needed for hospitals to report antibiotic use and AST data.

- **Explore partnerships with industry and other stakeholders to improve animal surveillance and gather antibiotic use data.** FDA and USDA are collaborating to advance surveillance via the existing networks and outreach to stakeholders. FDA's Center for Veterinary Medicine is expected to enhance antibiotic sales data to provide estimates of sales by species, but these species-specific data will only be estimates and do not provide details about actual usage, thus collecting on-farm antibiotic data is of critical importance.

- **Develop a strategy to address and integrate surveillance in environmental reservoirs, including soil, sewage, and surface waters to truly reflect a One Health approach.**

A One Health Approach

The One Health framework is asymmetrically addressed because of disparities in existing infrastructure and resource allocation. The absence of established surveillance networks for animal and environmental sources of antibiotic resistant bacteria embodies surveillance imbalances that should be explicitly addressed. Additionally, efforts to integrate data across public health and veterinary laboratories are not yet articulated, and practical limitations such as structural difference and differences in the key pathogens of concern may hinder implementation. The One Health approach recognizes the importance of collecting antibiotic use data in both humans and animals and surveillance of resistant organisms in the human, animal, and environmental reservoirs, including the food supply chain. Consideration of the environment, with respect to antibiotics (and their metabolites) and resistance, receives insufficient attention in the NAP.

To foster a One Health approach, the PACCARB recommends the following:

- **For surveillance to incorporate a true One Health approach, all settings where antibiotics occur should be addressed comprehensively. Therefore, areas that are currently lacking, such as surveillance of environmental reservoirs and of antibiotic use and antibiotic resistance patterns in companion animal medicine should be considered.** The importance of environmental reservoirs in One Health approaches and the tight link between humans and their pets and use of critically important antibiotics justifies surveillance in these areas.

- **Because the proposed processes to advance human and animal surveillance share common elements and approaches, laboratory networks should increase focus on how to appropriately integrate human and animal surveillance data.** Such integration can underpin policies and practical interventions to define and address emerging resistance threats.

- **To implement a One Health approach to specimen repositories, develop a structured portfolio targeting human, animal, and environmental isolates, weighted in proportion to their importance within a One Health context.** There is no preexisting

organism repository for animal pathogens, and the scope and scale of a future repository should be determined with stakeholder input. Appropriate environmental surveillance needs to be defined and linking repositories for animal, human, and environmental isolates should be considered.

Goal 2 Objectives: Progress and Activities

USG agencies have made progress on the NAP surveillance goals. More can be done to improve collaboration on infrastructure, remove technology barriers, and provide incentives to enhance data collection and reporting, particularly in the animal sector. Funding is a major constraint on meeting some of the stated milestones.

2.1 Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains and a specimen repository to facilitate development and evaluation of diagnostic tests and treatments.

USG agencies are strengthening regional public health networks and specimen repositories. Some examples include the following:

- CDC released the Epidemiology and Laboratory Capacity for Infectious Diseases (ELC) funding opportunity in March 2016 to increase state public health laboratory capacity to detect and confirm CRE, and integrate selected laboratories as the Antimicrobial Resistance Regional Laboratory Networks (AR Regional Labs).
- DoD's MRSN has advanced surveillance capacity, is effective in outbreak investigations, and provides crucial infection control support for military health care facilities. Database access for MRSN will be expanded to include other USG agencies, academic researchers, and industry partners. The MRSN repository currently holds approximately 37000 characterized isolates and 3000 genomes.
- CDC and FDA have created a repository of resistant bacteria ahead of schedule. They have defined specific organisms to include in the repository and have already responded to specimen requests from industry and academia. The CDC Antibiotic-Resistance Isolate Bank is a curated collection of over 220 unique isolates that is pulled from CDC's vast repository of AR isolates, which includes over 450,000 AR isolates and over 18,000 characterized genomes.
- CDC, FDA, and NIH are creating a pilot database by sequencing reference strains (of taxa important in the emergence of antibiotic resistance) from the CDC/FDA repository that will be the foundation on which the National Database of Resistant Pathogens can be built.

The PACCARB recommends the following to ensure these efforts have sufficient resources to accomplish the NAP milestones:

- **Ensure CDC funding to develop the AR Regional Laboratories.** The AR Regional Laboratories will require significant investment in laboratory equipment and personnel to achieve the necessary capacity. Coordination with state and local health agencies,

external laboratories, and external partners is also critical, as these entities can provide complementary expertise and support to their respective AR Regional Labs. In addition, the issue of interoperability of information systems also needs to be addressed. Such regional partnerships will facilitate effective, timely dissemination of the surveillance data to inform local stewardship and infection control efforts, especially during outbreaks.

- **Ensure DoD support to continue and enhance data collection and other CARB activities.** Enhanced coordination, especially with CDC, of the MRSN's advanced surveillance resources may substantially strengthen national surveillance capacity.

- **Facilitate improved coordination, including isolate and data sharing, of the CDC/FDA initiative with other repositories acquired under various federal initiatives to enable more efficient management of national repository resources.** Similarly, DoD should update the MRSN to facilitate sharing data with external stakeholders and allow collaboration between MRSN and the CDC/FDA initiative.

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 health care settings.

There has been progress toward developing quality measures and expanding reporting of antibiotic use. The Progress Report states that 118 facilities were reporting antibiotic use data, but none were reporting antibiotic resistance data. Some examples of progress are described here:

- To incentivize software and EHR vendors to develop products with capacity to report antibiotic use and antibiotic resistance data to the NHSN, the Office of the National Coordinator of Health Information Technology released a rule requiring that health information technology modules be capable of electronically reporting antibiotic use and antibiotic resistance data.

- CDC continues to provide technical support to hospitals that report antibiotic use data, and technical support is available for antibiotic resistance reporting.

- CDC has developed a risk-adjusted summary measure of antibiotic use in hospitals, the Antimicrobial Use Measure, which was endorsed by the National Quality Forum in January 2016. This measure provides an antibiotic use benchmark for hospitals and health systems to use in antimicrobial stewardship programs. Efforts are underway to develop guidance for hospitals and health systems on use of the measure. Additional field experience with the data from the Antimicrobial Use Measure, coupled with systematic studies, will serve to define which additional data and methods, if any, are needed to apply the measure for public reporting and other accountability purposes.

- CDC launched the HAI Antibiotic Resistance Patient Safety Atlas in early March 2016 as a user-friendly electronic portal, making aggregated state and regional NHSN data publicly available. While the Atlas data will be beneficial, it will only include limited data on resistance obtained from the NHSN Hospital-associated Infection module.

- Using the EIP platform, CDC continues to collect population-based surveillance data and isolates to track antibiotic resistance threats. EIP surveillance is expanding to include a larger and more representative population base and broader surveillance for gram-negative bacteria producing extended spectrum beta-lactamases. In addition, data collection for the Multistate Point-Prevalence Survey of HAIs, which includes antibiotic resistance data, is on track. A similar survey focused on LTCFs will launch in 2017. These data will help identify risk factors for infection and impact of interventions.

Further work is needed to ensure sustained reporting of antibiotic use and to implement reporting of antibiotic resistance in all health care settings. Information technology and EHR barriers that constrain reporting into the NHSN need to be addressed.

The PACCARB recommends the following to improve surveillance and data reporting:

- **Establish a clear regulatory requirement to report antibiotic use into NHSN or create other incentives to encourage facilities to report data.** Funding and technology challenges and competing demands prevent facilities from reporting antibiotic use and resistance data. Quality metrics may provide incentives for timely reporting over time.
- **Facilitate federal collaboration with state and local health departments and health systems.** Additional collaboration with state and local health systems could enhance antibiotic use and antibiotic resistance reporting to NHSN and expand participation but would require substantial funding.
- **Encourage broader antibiotic resistance data reporting by facilities into NHSN.** Broader reporting into the NHSN will make the CDC Atlas data more robust and meaningful.
- **Ensure funding to the VA and DoD to enable expansion of reporting from facilities to strengthen the NHSN antibiotic use module.** This includes expansion of NHSN antibiotic use reporting from DoD facilities and VA's 49 facilities to all VA acute care facilities. Funding will also be needed to initiate antibiotic resistance reporting into NHSN.
- **Ensure funding for states to continue current EIP antibiotic resistance surveillance efforts.**

2.3 Develop, expand, and maintain capacity in state and federal veterinary and food safety laboratories to conduct AST and characterize select zoonotic and animal pathogens.

Surveillance of resistance in animal isolates is currently limited to active surveillance through the National Antimicrobial Resistance Monitoring System (NARMS), while passive surveillance of *Salmonella* isolates submitted to the National Veterinary Services Laboratories is possible but funding-dependent. Substantial AST of animal isolates occurs in state laboratories, many of which are part of two USG veterinary laboratory networks: the National Animal Health Laboratory Network and the Veterinary Laboratory Investigation and Response Network. The purposes of these networks have not included AST, which is currently performed without USG funds or a mechanism to aggregate and analyze the data. USDA and FDA are collaborating to

assess current AST capabilities for animal isolates and are interfacing with stakeholders so that their work aligns with and builds on the current infrastructure.

The PACCARB recommends the following to improve collaboration, information sharing, and methods standardization through stakeholder engagement:

- **Define the specific zoonotic and animal pathogens to target and the criteria for selecting participating laboratories.** For instance, it is currently not yet clear which zoonotic and animal pathogens will be included in national antibiotic surveillance efforts or based on which criteria they will be selected, and how laboratories will be selected for participation.
- **Define the ultimate needs and scope of a national surveillance strategy for animal pathogens.** What are the goals of including animal pathogens in surveillance efforts?
- **Address procedural obstacles, such as data confidentiality, and information technology needs for efficient data aggregation.** For instance, information technology systems in individual laboratories may not be easily compatible, and confidentiality concerns may limit the sharing of data from client submissions.
- **Ensure funding to achieve longer-term milestones, including enhancing capacity with new testing platforms and establishing an organism repository.** The ability to compare and contrast between human and animal isolates and repositories should be a logical next step.

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.

CDC continues to collect resistance data on human infections caused by foodborne pathogens through the National Antimicrobial Resistance Monitoring System (NARMS). The results can now be viewed through a new web tool NARMS Now: Human Data. CDC is developing whole genome sequence–based methods for state public health departments can use for NARMS surveillance that will update the existing PulseNet data platform for detecting dispersed outbreaks due to resistant *Salmonella*. This development is on track, and should be launched in pilot sites for *Salmonella* by early FY 2017.

There has been progress to expand NARMS by USDA's Food Safety and Inspection Service and FDA and to enhance reporting of annual antibiotic sales data by FDA. Efficiency gains in sampling and testing have enabled the Food Safety and Inspection Service to expand AST and conduct some whole-genome sequencing. However, robust and sustained efforts and commensurate federal funding are needed to accomplish the stated milestones. Lack of federal funding is hindering on-farm work and constrains implementation of the NAP. Examples include the collection of farm-level surveillance data, which is on hold, and collection of resistance data, which is limited in targets and sample sizes. Timely funding is critical given an expected 12–18-month lag from receiving funding to implementation and data collection. USDA's Animal Plant Health Inspection Service and FDA are working with commodity groups towards partnerships to obtain on-farm antibiotic use data, but there is debate among stakeholders about whether and how industry efforts can complement government surveillance. Key areas of debate include

harmonization of data transparency and confidentiality concern related to industry-led data collection, as well as appropriate funding mechanisms and adequate incentives.

The PACCARB recommends the following to support monitoring efforts in food animals and retail meat:

- **Ensure FDA funding for antibiotic surveillance.** FDA received increased funds for the retail meat NARMS program. However, funding for surveillance of other sectors was denied for FY 2016.
- **Ensure USDA funding for relevant on-farm surveillance activities.** Such funding was also denied for FY 2016. Given the time required to implement proposed field activities, the lack of funding will delay or prevent timely realization of NAP milestones.

Initial Assessment of Progress toward Goal 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria

The USG has initiated several diagnostic development initiatives and funded new research to set the stage for progress in the area of diagnostics. Overall, additional funding is needed for the development of diagnostic tests for use in the outpatient setting that can rapidly distinguish bacterial from viral pathogens, specifically for upper respiratory tract infections. Effort has to be made to improve the clinical trial and regulatory expertise with transparent collaborations between companies and USG agencies responsible for these activities. Such effort is especially critical to smaller diagnostics companies that have promising innovative assays but may have limited experience or resources for performing clinical trials and conforming to the regulatory approval processes.

Broad Recommendations for Goal 3

Several overarching challenges hinder the progression of the development and use of rapid diagnostic tests.

The PACCARB recommends the following to address some of these challenges:

- **Devise economic incentives that encourage and support providers to use diagnostic tests to guide therapy, and develop a new payment model for diagnostics that encourages their use in guiding therapy rather than the empiric use of antibiotics.**
- **Cultivate robust collaboration between microbiology laboratories and ASPs to evolve towards a new way of approaching diagnostic microbiology to create user demand and acceptance of diagnostics.**
- **Identify mechanisms and approaches to reduce the cost of clinical studies of diagnostics devices and to streamline the regulatory process.** Such efforts would reduce the barriers for commercial test development in the private sector.
- **Craft a comprehensive strategy for funding outcomes studies.** Assessing the value of diagnostics depends on studies, indicating that use of newly developed diagnostics improves clinical outcomes. Data from these studies are essential for effecting changes in clinical practices.
- **Train health care providers on how to better use and interpret results of diagnostic tests.** To optimize the effectiveness of diagnostic tests, providers' use of rapid diagnostic tests, particularly for inpatients, should be coordinated with ASPs.

A One Health Approach

As the use of medically important antibiotics for growth promotion in animals is eliminated, the Food and Drug Administration (FDA) has also updated the Veterinary Feed Directive (VFD) that now gives licensed veterinarians the oversight of these drugs for use in prevention, control and

treatment. Just as in human medicine, there is an increasing need for rapid, accurate and relatively inexpensive diagnostics for growing animal populations worldwide. At the same time, such improved diagnostics could help with the surveillance function to better identify microbes and resistant bacteria in a multitude of environmental conditions.

The PACCARB recommends the following to encourage a One Health approach to meeting Goal 3 of the NAP:

- **Support the development of diagnostics that will allow veterinarians to differentiate viral and bacterial infections and more accurately prescribe antibiotics.** These areas highly overlap with the needs in human health, and it may be that diagnostics designed to detect viral pathogens in humans can also be used in animals to prevent the wide spread use of antibiotics for prevention of infections that may be viral.
- **Create incentives for the development of animal diagnostics for both the animal food industry and companion animals and assessing the utility of human diagnostics in animals.** Funding is needed because veterinary medicine lacks a viable reimbursement system and thus there is no real "market" for veterinary diagnostics.
- **Give providers in all disciplines that use antibiotics the tools and education on diagnostics to encourage appropriate use of antibiotics and to reduce waste and inappropriate use.** Such providers include human and animal health care providers, companion animal practitioners, crop agriculturists, and dentists.

Goal 3 Objectives: Progress and Activities

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 easily in a wide range of settings.

Many rapid diagnostic tests have been and are being developed, but they have three major shortcomings. First, they often focus on selected rare but clinically problematic infections rather than very common infections. Second, the uptake of these tests by clinicians can be very limited (based on cost, turnaround time, availability, and lack of timely information for clinicians about the value of the tests). Third, even when rapid diagnostic tests are used, they frequently do not impact treatment decisions.

A variety of diagnostic development programs and initiatives are currently being funded and progress is noted in several areas:

- NIAID is funding many research project grants specifically focused on bacterial species identification and AST. Many of these received funding as a result of 12 targeted funding opportunities since 2010 and the inclusion of this topic in the Small Business Innovation Research Program areas of interest and waiver topics. In addition, NIAID has funded and continues to fund the development of rapid diagnostics for viral respiratory tract infections, which can help clinicians make treatment decisions that curtail the overuse of antibiotics.

- While most federally-supported diagnostics research efforts were focused on biothreat pathogens, the progression toward studies focused on preventing and treating the more common multidrug-resistant organisms (MDROs) in recent years is encouraging. Many of the projects being funded by NIH and BARDA are now focused on tests intended to guide care in inpatient settings. There are tests in development to address various types of clinical presentations in the outpatient setting, including urinary tract infections and lower respiratory tract infections.

- The NIAID-funded ARLG has a variety of projects in progress with emphasis on diagnostics. These include two ("Rapid Diagnostics in Categorizing Acute Lung Infections" and "Use of Procalcitonin Testing to Direct Antibiotic Use in Lower Respiratory Tract Infections") that assess diagnostics for common outpatient infectious disease syndromes, which represents a largely unmet need. The ARLG is also funding critical studies to evaluate the real-world implementation of new diagnostic tests. For example, ARLG provided funding for a study on the clinical and economic outcomes of the FilmArray Blood Culture Identification Panel used in combination with antimicrobial stewardship. The Rapid Diagnostics for Gram-Negative Bacilli in Blood project, currently in development, will build upon these findings. The ARLG is also conducting innovative clinical trials in which tests from multiple companies are included in a single clinical study (involving a master protocol). Although the studies are complex, the ARLG has the infrastructure to conduct this work.

- BARDA and NIH are working together to create a prize for the development of a rapid diagnostic test that can improve treatment of drug-resistant infections. While generous, true development costs are substantially larger than the prize, and it is unclear whether this prize alone will be sufficient to incent companies with relevant technology platforms, especially when considering the range of tests that need to be created and the potential for the prize to be divided across multiple awardees. The clinical field will need some redundancy of diagnostics across alternative platforms.

- In addition, NIH and BARDA collaborate through a Diagnostics Integrated Program Team (IPT) within the HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). Continued collaboration between NIH and BARDA should serve as a model for other interagency efforts.

The PACCARB recommends the following to promote development of new diagnostics:

- **Fund studies of diagnostics focused on rapid genotypic and phenotypic detection of MDROs, rapid testing for distinguishing bacterial and viral pathogens, as well as detection and identification of major individual pathogens.** There are very few genotypic tests that have been cleared by the FDA for pathogens other than Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). Given the complexity of the genetics of resistance in gram negative organisms, a rapid phenotypic method may be more appropriate. There is one system under development, but none have come to market yet; those in development are working from a positive culture and not directly from a clinical specimen.

- **Consider creating two distinct award tracks under the BARDA/NIH development prize:**
    - Prize 1 would address hospitalized patients infected with MDROs. The clinical field needs simple and rapid methods to identify a broad range of resistant organisms, including new pathogens when they appear. The availability of such diagnostic tools will improve clinical care and strengthen ASPs. Tests allowing for early detection of the presence or absence of resistance genes that can be used to direct the initial dose(s) of antibiotics should be prioritized.
    - Prize 2 would focus on a rapid simple test that can be used in the outpatient setting to distinguish between bacterial and viral infections. Such a product could greatly reduce outpatient antibiotic usage for extremely common upper respiratory infections and acute otitis media. The widespread and inappropriate use of antibiotics, in part due to the lack of rapid and inexpensive diagnostic tools, is itself driving antibiotic resistance, selecting for an increased pool of resistant bacteria.
- **For the many solicitations announced, include as part of the scoring criteria the need to demonstrate that tests can be more generally applied so that promising technologies can be adapted for MDROs and important pathogens, and give such tests higher priority for funding.** Platform technologies that offer ready adaptation to new situations should make it possible to create additional tools with reduced cost. Such approaches should be prioritized.
- **Fund outcomes studies to show the utility of diagnostic tests to allow for precision of antibiotic prescribing practices.** Such studies would serve as a catalyst for health care providers and payers to adopt testing.
- **Lower the barriers to test development for commercial companies.** Practical economic incentives for companies to enter this space are lacking. Approaches that shorten the time for the development of commercially available tests by streamlining regulatory processes, supporting the costs of clinical trials, reducing the costs of the trials through planning for shared resources, and ensuring appropriate reimbursement are needed.
- **Create care pathways that provide guidelines on the use of diagnostic tests.** Experience has shown that tests are not always used, even when available. In addition, patient or provider perception of the need to act may mean that prescribing an antibiotic is seen as preferable to the deliberate choice of not prescribing. As a consequence, creation of guidance offered in the form of care pathways is needed.

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 have implemented a parallel review program and recently refreshed their memorandum of understanding. However, an area that needs to be better assessed and implemented is the development of novel strategies for payment for rapid diagnostic testing. An initiative to address this area specifically for diagnostics would incentivize providers to prioritize the use of diagnostics prior to prescribing.

The PACCARB recommends the following to increase availability and use of diagnostics.

- **Support innovative approaches to payment.** The development of an alternative economic model for diagnostics that can help reduce antibiotic resistance is critical. For example, why should a doctor or a health system order a $500 test in lieu of prescribing a $10 broad-spectrum antibiotic? The treatment price should reflect the "real" costs of the antibiotic's use—in terms of generation of resistance (and other downstream effects). The wide variations in reimbursement among the different insurance carriers should be addressed. In addition, the lack of American Medical Association Current Procedural Terminology (CPT) codes impacts reimbursement and uptake of these tests into clinical practice. The need to expand CPT codes available is tied to the innovative approaches to payment; part of the expansion includes simplifying and making the process of obtaining new CPT codes more transparent. Furthermore, there is a need to better align the FDA and CMS review processes to increase the likelihood of moving the above programs forward.

- **Develop a program to educate clinicians on the value, appropriate use, and interpretation of diagnostic tests, and promulgate professional guidelines to address the role of diagnostics.** Both training (and retraining) of clinicians from multiple disciplines are needed to effectively reduce inappropriate use of antibiotics and to improve clinical outcomes. Provider tools should be married to well-conceived and effectively implemented clinical algorithms that underline the basic cost-benefit of using the diagnostic rather than current practice of "trying" an inexpensive antibiotic first. The willingness to accept and integrate diagnostics depends on educating providers and aligning cultural and financial norms at the hospital and local levels.

- **Coordinate implementation and use of rapid tests, particularly for inpatients, with ASPs.** To optimize effectiveness and to evolve towards a new way of approaching diagnostic microbiology, a robust collaboration between microbiology laboratories and ASPs is needed. The following are recommended to create user demand for and acceptance of diagnostics:

    - Strategies for incentivizing use of diagnostic tests, rather than empiric use of antibiotics.

    - Value frameworks for new tests. The reimbursement and return on investment for diagnostic tests is uncertain in the case of human diagnostics and similarly in the case of animal diagnostics.

    - Seek international harmonization of regulatory approval and clearance pathways, and value frameworks for diagnostics, such as outcomes studies to be used by more than one country, or values related to revenue and test adoption. Standardization and harmonization would incentivize test development by providing the widest possible market.

    - Building public understanding of the role of diagnostics in antibiotic prescribing and what diagnostics can and cannot accomplish.

Initial Assessment of Progress toward Goal 4: Accelerate Basic and Applied R&D for New Antibiotics, Other Therapeutics, and Vaccines

Key areas of progress in the NAP include work on development of clinical trials networks and improved coordination between NIAID and BARDA, as seen in the recently released request for information (RFI) related to the use of a master clinical protocol for common registration trials of new antibiotics. Federal plans are in place for several innovative basic and applied research programs, in addition to launch of the biopharmaceutical incubator. Overall, the progress being made is encouraging, and we are confident that future initiatives will continue in this trajectory.

Engagement and collaboration across the USG regarding animal and human health, especially as they relate to discovery and development of new therapeutics, are essential to ensure progress toward meeting the NAP goals. It is important to remember the overarching goals of CARB are preventing the development and spread of resistant bacterial infections, as well as treating them when they occur. To this end, it will be important to incentivize development of a range of new classes of agents and to intentionally limit their use, which will dampen the rise of resistance from prevention to cure. This can provide classes of agents as “fail-safes” for patients with life-threatening infections with MDROs. Regarding the latter, it is important to have agents with different mechanisms of action so that resistance to one class, when it occurs, does not negate the utility of others. In addition, creation of narrow spectrum agents with genuinely species-specific targets might minimize the induction of resistance by other “innocent bystander” organisms. To ensure that these drugs are created, despite an anticipated limited extent of use, it will be important to create economic and commercial models that reward innovators for bringing important agents into existence even if the agents are not used.

Food safety and animal welfare are critical parts of animal health product development and regulatory review to ensure that resistance selection in both animal disease pathogens and foodborne zoonotic bacteria are appropriately addressed. In both sectors, the use of current and new antimicrobial agents and alternatives should be in accordance with appropriate ASPs to minimize the development of resistance in humans, animals, and the environment.

Barriers to the successful implementation of the NAP include lack of sufficient resources, human and financial, to support basic and applied research and investigation of the role of microbial communities (the microbiome) in human and animal health and the environment, as well as to support R&D of drug and nondrug therapies for resistant pathogens. Such resources include support for early drug development, clinical trials networks, and public-private partnerships to enable streamlined drug development. In addition, the need for enhanced coordination between agencies in this area would ensure that resources available are optimized. An additional noted barrier to success are the challenges associated with partnering between animal and human health AMR stakeholder groups that historically have not collaborated extensively.

Broad Recommendations for Goal 4

The PACCARB recommends the following to accelerate basic and applied research:

- **While appreciating the importance of prioritizing stewardship and prudent use of available therapies to treat present AMR pathogens, recognize that new antibiotics are needed as the current ones are becoming less effective and that suitable reward models must be in place to depict the value an antibiotic has both when it is used to treat an infection and when it is available in case it is needed.** Potential incentives and advances relevant to the value of both in-use and in-existence of novel antibacterial therapies include "delinkage" of the return on investment that depends on sales volumes in addition to consideration of more traditional incentives, such as tax credits, competitions, and prizes. Currently, there is a limited range of approaches to developing oral antibiotics and no viable economic model for developing antibiotics in general. Efforts are needed to evaluate the U.S. market to better understand what kinds of incentives might work best.

- **Accelerate antimicrobial R&D (including the established of regulatory guidance and addressing financial disincentives) in the pursuit of narrow-spectrum antibacterial agents.** The potential value of narrow-spectrum agents for treatment of common infections, coupled with accurate diagnostics, could further stewardship practices because they might promote less resistance due to lesser disruption of normal protective microbiota (e.g., of the type promoting *Clostridium difficile* infection) and less selection for resistance in the reservoir of commensal organisms. However, reliable clinical and regulatory pathways for developing narrow-spectrum agents do not exist, nor is there a viable financial model for development or deployment, and efforts to resolve this challenge are needed. While not a complete solution, the Limited Population Antibacterial Drug pathway currently pending in Congress would be a meaningful step towards enhancing feasibility of development programs for narrow-spectrum products. Addressing these intertwined issues is critical to addressing the most important current and likely future medical needs in AMR.

- **Allocation of funding to establish a registration trial-focused clinical network.** PACCARB lauds (a) the work done by NIAID and BARDA to create an Antimicrobial Accelerator, (b) the work done by NIAID via ARLG to implement clinical trial network(s) focused on highly resistant pathogens, and (c) the work done by BARDA to explore the creation of master protocol-based clinical trials network(s) focused on efficiently conducting registration trials in core indications. The first two of these are now launched and PACCARB strongly encourages allocation of funding to establish the registration trial-focused clinical network.

- **Capitalize on opportunities for collaboration across the USG in the area of provision of key data and materials to support the development of promising antibacterial drug candidates and vaccines that can reduce the need to treat bacterial infections.** In addition to the many services that both NIH and BARDA provide to companies interested in product development, security and data sharing concerns are key barriers to progress in this area. There is a great deal of data, knowledge, and expertise within different USG agencies that may not be freely shared owing to agency level impediments

and classifications. A standardized process for information and specimen sharing among the various participating agencies that would simplify collaboration is needed.

- **Address barriers to progress in developing and launching public-private partnerships.** Such barriers include perceived and real disincentives for sponsors and challenges in coordination between USG agencies with regard to specimen sharing, database development, and maintenance. In addition, cultural barriers to partnering among private industry, academia, and government should be addressed to enable successful partnerships.

- **Ensure harmonization of programs to allow for global development and use of therapies for AMR.**

- **Consider opportunities of leveraging the data gathered from basic research efforts that are no longer pursued for human applications.** This could also include modifying clinical candidates and pursuing development of these agents for animal indications.

A One Health Approach

USDA, with NIH, FDA, and the agriculture industry are in the process of developing an R&D strategy to promote understanding of antibiotic-resistance of animal disease pathogens and foodborne pathogens and potential for alternatives to (or improved uses of) antibiotics in food animals.

The PACCARB recommends the following actions by the agencies for an enhanced One Health approach to Goal 4:

- **Support additional research opportunities to enhance understanding of basic science questions and relevant environmental factors that facilitate the development of AMR and the spread of resistance genes that are common to animals and humans.** One such opportunity is to include more interagency emphasis on collaborations between the human and animal sectors at the basic research level. Common biology, chemistry, testing approaches, and related matters allow for diversity of input and leveraging of human capital, physical resources, and funding, as well as further assessment of potential leveraging of USDA, FDA, and other USG AMR programs.

- **Leverage opportunities for enhanced USG emphasis on the One Health approach, which connects human, animal, and environmental sectors.** Require additional coordinated efforts and initiatives among FDA, USDA, NIH, and CDC that better reflect the One Health approach by sharing information, technology, and applications across the sectors. The One Health offices within USDA, CDC, and FDA should further coordinate their plans and activities and focus collaboratively on common AMR issues. Refine collaborations and leverage technology by including the animal health sector both in public-private partnerships arrangements and incubators.

Goal 4 Objectives: Progress and Activities

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.

Many environmental factors impact AMR. However, other than in the arena of direct clinical care, these factors are not adequately understood or evaluated. An example is that the contribution of antimicrobial residues in water and soil after use in animals and humans to antibiotic resistance and the threat to humans and animals are unclear and are worthy of further investigation. At this time the contribution of these residues to resistance is unknown.

Highlights of the early work on the NAP include plans for a 2016 USDA-convened meeting of private- and public-sector experts to discuss research on AMR in food-producing animals, agriculture, and public health. This webinar will include systems biology approaches and development strategies for new technologies for basic research to clinical testing for AMR. The webinar will provide a great opportunity for engagement and collaboration across government agencies to both share resources and ideas to thwart development of AMR in animals and humans.

In the area of clinical trials networks, NIAID will continue to work with FDA and partners in industry and academia to explore developing a more robust clinical trials infrastructure and assess the feasibility of applying common clinical protocols for evaluation of multiple products. To this end, NIAID conducted a joint workshop with European funders in January 2016 that included a discussion of challenges in conducting AMR clinical trials. Furthermore, BARDA released a Request for Information on February 4th, 2016, to solicit cost and technical data to establish a clinical trials network that would utilize a common clinical trial protocol. This network would focus on conducting Phase II/III trials in traditional indications against susceptible pathogens but would utilize a common control arm, reducing time and cost to conduct these trials.

The PACCARB recommends the following to accelerate knowledge about environmental contributions to AMR:

- **Data from all USG sources about environmental contamination with antibiotic residues should be compiled and reviewed.** This might include projects initiated by USDA and the Environmental Protection Agency (EPA), among other federal agencies. This will provide an initial assessment of the extent of the problem.

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.

While no milestones are set for FY 2016, the USG is committed to increasing research focused on understanding the nature of microbial communities (microbiomes), how antibiotics and the induction of resistance affect them, and how they can be harnessed to prevent disease. We look forward to learning details of research focused on microbial communities, as this is a key area of impact of AMR in the environment and involves both animals and humans. There are already a variety of USG efforts that have focused on certain aspects of the microbiome (e.g., the Human Microbiome Project and USDA have worked to characterize a food animal microbiome). One

challenge may be that this area of inquiry has not been sufficiently well-defined in the past. USDA's Agricultural Research Service (ARS) is conducting environmental sampling to determine the prevalence of AMR bacteria in agricultural and nonagricultural settings and sampling in environments employing various agricultural management practices. In addition, ARS held an internal workshop in September 2015 in Beltsville, MD, on antibiotic resistance in agroecosystems.

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.

In the realm of R&D of new therapeutics, several USG initiatives were implemented, including the following:

- NIAID has funded new grants and contracts received in response to targeted funding opportunities to advance the development of therapeutics for bacterial infections. In addition, NIAID provides preclinical service support to foster drug development, including in vitro and in vivo testing of new candidate therapeutics for multidrug resistant bacteria, which lowers the risk and fills the gaps for new entries into AMR discovery and development efforts.
- The DoD Chemical and Biological Defense Program/Defense Threat Reduction Agency plans to submit an Investigational New Drug (IND) application to FDA to initiate clinical investigation of a new DoD-funded antibiotic.
- The DoD's Joint Science and Technology Office (JSTO) is also funding efforts to complete preclinical development of a novel topoisomerase inhibitor, with IND application submission planned in 2017.
- The NIAID-funded ARLG is advancing five interventional clinical trial protocols with a goal of initiating enrollment in two by the end of this year. ARLG leadership and investigators are also studying several novel trial designs. Antimicrobial discovery research is being conducted at the Walter Reed Army Institute of Research (WRAIR) by the U.S. Military Infectious Disease Research program as a part of military wound infection research.
- DoD's MRSN, also based at WRAIR, is a unique federal asset that contains the largest well-characterized repository of resistant bacterial isolates—a significant federal resource that can support the development of novel therapeutic agents.

The PACCARB recommends the following to intensify R&D of new therapeutics:

- **Strategies for discovery of new agents should be managed independently to ensure diversity of approaches.** Later stages of clinical development may be usefully coordinated, recognizing that a variety of strategies may be required to reinvigorate the pipeline. An example of this approach is the recently proposed BARDA initiative to consider creation of several clinical trial networks for testing of new antibacterial agents. Similarly, the existing NIAID Vaccine and Treatment Evaluation Units are a good example of coordinated development.

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

In the realm of nontraditional therapeutics, government agencies, with a variety of external partners, are pursuing R&D of new nontraditional antibacterial products (e.g., monoclonal antibodies, vaccines, or microbiota-based therapeutics) and adjunctive therapies to restore the activity of existing drugs:

- NIAID made multiple recent awards and issued several AMR-related initiatives focused on development of novel AMR strategies, including development of nontraditional and host-targeted therapeutics, as well as research on antivirulence and immune-based therapies, adjunctive therapies, and biofilm inhibitors.
- DoD plans to implement laboratory use of new microfluidic technologies to detect antibodies that inhibit antibiotic-resistant bacteria and has ongoing testing of nontraditional therapeutics such as bacteriophage. DoD's JSTO has planned initiation of mechanistically novel therapies for 2016. DoD's Office of the Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs (OASD NCB) and JSTO continue to evaluate a previously developed drug product as part of a new combination therapy targeted at difficult-to-treat pathogens. OASD NCB will award two new contracts that: (i) focus on development of nontraditional therapeutics that are less likely to lead to the development of resistance; (ii) focus on evaluating drug combinations that may decrease the emergence of drug resistance; and (iii) explore revitalization 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.
- USDA, with NIH, FDA, and the agriculture industry, will develop an R&D strategy to promote understanding of antibiotic-resistance of animal disease pathogens and foodborne pathogens and potential for alternatives to (or improved uses of) antibiotics in food animals. While still at a preliminary stage, USDA and HHS are evaluating options to address jointly developing an R&D strategy. ARS is organizing a workshop for FY 2016 with other USG agencies and stakeholders on alternatives to antibiotics in animal production. The aim of the workshop is to conduct a gap analysis and assess the outcome of the first international symposium in 2012 on alternatives to antibiotics in animal production.
- The HHS National Vaccine Advisory Committee developed a report with recommendations in June 2015, *Call for Greater Consideration for the Role of Vaccines in National Strategies to Combat Antibiotic-Resistant Bacteria*. The report emphasized that by preventing infectious diseases, vaccines can limit the use of antibiotics. It encouraged an examination of the vaccine market to assess whether given the different market incentives than those proposed to stimulate antibiotic development are needed to accelerate vaccine development and other novel prevention strategies to combat antibiotic resistance.

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.

The USG has made strides in expanding ongoing efforts in data sharing to support the development of novel drugs and vaccines:

- Agencies including NIH/NIAID are working toward making available to the public genomic sequence data, proteomic data, and other related AMR data sets generated with USG funding. They are also working to ensure that necessary data protections are provided.
- DoD will develop and maintain three specimen panels as a critical resource for evaluating the efficacy of novel antibiotic therapies against multidrug-resistant Select Agents. The panels will be available through the Select Agent Core Antibiotic Screening Program.
- DoD has initiated efforts to generate panels of molecularly characterized multidrug-resistant, nonbacterial select surrogates of bio-warfare agents. Work will continue in 2016 and be applied more broadly to multidrug-resistant clinical panels in house. Completing clinical trials of new products to treat infections with resistant Select Agents within five years will be subject to the availability of funds. While these DoD programs focus on biodefense, lessons learned here could be broadly valuable to the larger area of AMR.
- DoD's MRSN, in addition to its disease surveillance role, has the largest repository within the USG of well-characterized antibiotic-resistant organisms. The unexpected deletion of funding for this and other non-biodefense DoD CARB efforts in the 2016 National Defense Authorization Act imperils the significant role that DoD plays in the overall federal response to combating AMR.
- To address barriers to feasible and efficient development of new therapeutics for resistant bacteria, BARDA recently released an RFI seeking information from a variety of potential development organizations and stakeholders with expertise in developing antibacterial therapies on methods to approach a pragmatic clinical trials network to efficiently conduct registration trials using a master protocol for core indications that can be used to enable product registration (e.g., complicated urinary tract infections, complicated intra-abdominal infections, and hospital-acquired/ventilator-associated bacterial pneumonia). These networks would be designed to rigorously study these common infections in U.S. patients. Ultimately, therapies for other important infections could be studied in parallel protocols in an efficient and ongoing manner.

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

The PHEMCE ensures coordination with the U.S. 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 IPT on Antimicrobials was reconstituted as the AMR IPT to address AMR more broadly, to include non-biothreat pathogens of serious or urgent concern as designated by CDC. BARDA announced on September 16, 2015, that it entered into a new portfolio partnership with AstraZeneca to develop new antibiotics.

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.

BARDA and NIAID collaborated to successfully release a funding opportunity announcement to establish the CARB Biopharmaceutical Accelerator in February 2016. The Accelerator represents a novel public-private partnership that will support research and development to accelerate candidate products (drugs, vaccines, and diagnostics) into clinical development. The continuance of this initiative and the provision of funding for this and potentially future innovative incubators are imperative. This initiative promises to spur innovative product development at all stages, including higher risk early programs and more costly full development programs. These efforts will be further enabled by creations of the clinical trials network now being explored by BARDA. Engagement of a wide range of experts, including experienced discovery scientists, developers, regulators and business leaders, will be critical to success of the partnership. We are excited and fully supportive of this endeavor.

Initial Assessment of Progress toward Goal 5: Improve International Collaboration and Capacities for Antibiotic-resistance Prevention, Surveillance, Control, and Antibiotic R&D

AMR presents itself as one of the major challenges of the 21st century, and it is clear that national-level action in every country is needed if it is to be met globally. The United States has two major reasons for its international engagement on AMR. First, AMR is a global health security issue: global events may have serious consequences for the future of public health and health care for all. Security is linked with a humanitarian interest in limiting resistance to safeguard the health of U.S. citizens and populations in other countries, particularly those that face a high burden of infectious diseases and are particularly vulnerable to the threat of antibiotic resistance. Second, there are important lessons to learn from other nations that have longer-standing programs and from nongovernmental organization on how to track, study, and contain AMR bacteria.

Overall, the USG agencies involved in international activities have performed remarkably well on pursuing the milestones in the NAP while constrained by tight budgets. Additional international work by the agencies beyond what is included in the Progress Report is ongoing but is not mentioned in this review. The USG partners with multinational UN agencies (WHO, OIE, and FAO) and bilateral partners. U.S. financial and technical support to these international groups for AMR is an extension of its broader engagement and involvement with these partners. Nevertheless, given U.S. interests in AMR, the NAP has reinforced the importance of these relationships and realigned some priorities.

Broad Recommendations for Goal 5

By their nature, the Goal 5 milestones encourage a checkbox approach to progress and should be complemented by a stronger set of outcome measures that contribute to a qualitative narrative of success that may or may not be captured by milestones alone. The milestones are too sharply focused on technical assistance and place much less emphasis on health as an element of foreign policy and other tools that are equally essential to the successful achievement of the core objectives. More than for any other objective, success in the international domain depends heavily on how the USG partners work with sovereign nations and independent organizations, and progress on these dimensions should be captured to assess whether engagement is in the right direction.

Resources (both financial and human) are limited, so it is important to ensure that efforts are focused on priority areas with a high likelihood of success and improvement in health outcomes in key countries. Beyond this, coordinating globally is difficult, as is defining the most appropriate role for the United States in these efforts. The NAP focus is currently directed at very specific goals that miss important aspects. Some examples are provided in this report, e.g., the narrow definition of surveillance and the lack of specificity about infection prevention while antibiotic stewardship is singled out. Although animal-related efforts are important, it appears that there are capacity barriers for doing more than is presently ongoing.

The PACCARB recommends the following to improve international collaboration and capacity:

- **Measure the effectiveness of the international strategy in reaching NAP goals in the next phase by choosing a few indicators that clearly measure outcomes of interest (in addition to the current process and output indicators).** Currently, the NAP offers a set of objectives but not an overall narrative of expected impact. Priority-setting is needed to ensure that global health security and other NAP goals are reached.
- **Ensure that resources commensurate with NAP international collaboration goals are provided to the relevant USG agencies.** The adequacy of funding, personnel, and other resources to meet NAP goals is unclear. Value for money of resources deployed should be assessed using outcome measures developed to measure the effectiveness of the international strategy in reaching NAP goals.
- **Expand involvement to include additional countries beyond those already engaged.** Engagement is especially important with countries where antibiotic use is increasing steeply, such as developing countries with rapidly growing livestock and poultry populations and expanding healthcare utilization. These countries can reap great benefits from collaboration with the United States, and the United States gains by helping control antibiotic resistance in the countries from which it is most likely to spread.
- **Leverage the expertise and resources of a range of nongovernmental assets.** Professional societies, academia, and both the for-profit and nonprofit sectors can have an expanded role to play in global antibiotic resistance control efforts.
- **Broaden the currently narrow actions related to animal health to a more comprehensive One Health perspective.** This recommendation requires agencies to include broader animal health and environmental sector participation in all aspects of basic research, currently focused more on human health.
- **Expand engagement with other governments, pharmaceutical and diagnostic industries, and academia across the world in R&D.** Although international collaborations are under way, NAP goals will need more extensive engagement with a wider range of partners in both the public and private sectors.

A One Health Approach

Goal 5 of the NAP is oriented mainly toward human health and includes only very specific aspects of animal health or environmental aspects of antibiotic resistance at the international level. Available resources appear to be weighted heavily to the human pathogen goals and priorities. The opportunity to improve the infrastructure for animal health in key countries, similar to efforts to improve public health capabilities, would benefit the United States by ensuring food safety, public health, and animal health. Conflicts between controlling AMR and issues of food security in developing countries may be an especial concern. International collaboration at USDA is limited to some domestic activities with international relevance. To some extent, the lack of a One Health strategy in U.S. global engagement reflects divisions in how domestic programs are organized and financed.

The PACCARB recommends the following to support a One Health approach to Goal 5:

- **Environmental aspects of antibiotics and antibiotic-resistant bacteria should be considered.** The potential for including relevant agencies, such as the U.S. EPA in the NAP would contribute to a One Health approach. The WHO Global Action Plan, Objective 4, II. Secretariat, action (vi) states: "Develop standards and guidance (within the tripartite collaboration with FAO and OIE), based on best available evidence of harms, for the presence of antimicrobial agents and their residues in the environment, especially in water, wastewater and food (including aquatic and terrestrial animal feed)."[2]
- **A common understanding of One Health on a global basis is needed.** The operational definition of One Health by USG recognizes that the health of humans is connected to the health of animals and the environment.

Goal 5 Objectives: Progress and Activities

5.1 Promote laboratory capability to identify at least three of the seven WHO priority AMR pathogens using standardized, reliable detection assays.

National, regional, and local AMR data are critical to guide prevention efforts including infection prevention and control and antibiotic stewardship programs. CDC has been actively involved in the planning and development of WHO's Global Antimicrobial Resistance Surveillance System (GLASS). GLASS aims to be the premier global repository of data generated by recognized laboratory partners, which can include private laboratories that have the confidence of the national government. DoD is actively involved in assisting partnering nations in standardizing data collection and analysis through its centralized MRSN and the Global Emerging Infections Surveillance and Response Section. CDC has also been providing technical assistance to establish laboratory-based national surveillance systems in Global Health Security (GHS) and non-GHS bilateral partner countries (e.g., India, Kenya, Vietnam, and Thailand). DoD has a long track record of strengthening national reference laboratories. These efforts support the GHS Agenda (GHSA) in key countries and ultimately the GLASS program. These agencies are limited, however, by funding; similarly, their ability to share information is limited by international and bilateral agreements.

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.

A major activity of FDA and USDA is working with WHO, OIE, and the Pan American Health Organization in capacity building for surveillance. FDA and USDA are also contributing to OIE's efforts to develop a procedure and standards for data quality and for annual data collection from OIE member countries on the use of antimicrobial agents in food-producing animals with the aim of creating an OIE global database to be managed in parallel with the World Animal Health Information System. The identification of partner laboratories to conduct AST of animal-origin foodborne pathogens is underway. Objective 5.4.1 is related to the determination of

[2] Available at: http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1

"resistant" bacteria and has application for this objective. Although there is no specific mention of activity on surveillance to detect antibiotic resistance in animal disease pathogens for year one, it is a year-three milestone that could be addressed during discussions with partner laboratories.

The PACCARB recommends the following to improve surveillance and data sharing efforts globally:

- **Expand surveillance to include molecular typing and transmission tracing.** Antibiotic susceptibility surveillance is important for guiding local treatment decisions (human and animal) and informing antibiotic use policies, among other objectives, but broader global functions require such expansion.
- **Expand surveillance to support systems outside of the United States and Europe, in countries that are the likely incubators for new antibiotic-resistant bacteria that can spread worldwide.** This should build on existing efforts by US and other countries in support of the GHSA's Antimicrobial Resistance Action Package.
- **Look to the already successful U.S.-E.U. experience as a learning opportunity for guiding partnerships with other regions.** The private sector also has a role to play. For example, private laboratories in many countries, especially those that are part of large commercial networks, while not necessarily representing national populations, are more likely to work to international quality standards, and these data should be seen more broadly as valuable resources.[3]

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

The main current engagement is a U.S.-European Union (EU) system through the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) for analyzing and sharing information on a series of recommendations. CDC, with the European Centre for Disease Prevention and Control (ECDC) via TATFAR, has contributed to harmonizing interpretive categories for antibiotic-resistant human pathogens, which can be of benefit to information sharing through GLASS. The U.S.-E.U. analysis and communication of resistance trends and data via a common system is progressing and is planned to be used globally under the direction of WHO. Agencies, working through TATFAR, are establishing an international working group to generate data to address the identified knowledge gaps about antibiotic-resistant bacteria in animals and antibiotic use in agriculture.

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

International collaborations with partner countries by the leading agencies have been successful in advancing the GHSA and WHO's Global Action Plan. Efforts to improve national capabilities and data sharing are progressing. There is overlap with Objective 5.1 in some instances with regard to providing technical assistance. Some overlap with TATFAR recommendation #18 is

[3] See, e.g., ResistanceMap, http://resistancemap.cddep.org/, and the Asian Network for Surveillance of Resistant Pathogens (ANSORP) http://www.apfid.org/06_ansorp/ansorp_01.htm.

noted, too, with regard to data sharing. TATFAR work, led by CDC and ECDC, has contributed to harmonizing interpretive categories for AMR surveillance of human isolates, which could be useful to programs in other countries. There does not appear to be a similar effort for animal disease pathogens.

The PACCARB recommends the following:

- **Harmonize interpretive categories (e.g., definition of resistance).** Harmonization efforts could include representation from the animal sector for animal disease pathogens to complement the work of CDC. Overall, a reasonable start has been made on this large and critical element of the NAP, but much greater coordination among the federal agencies will be required going forward, and further attention should be given to operationalizing One Health.
- **Support research on country-specific and regional drivers of antibiotic resistance.** This also includes cost-effective interventions, operational research to adapt strategies to diverse settings, and continued evaluation of interventions.

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.

The traditional USG role in product development has been to support basic and some applied research, domestically, mainly at universities, to underpin product development. The NAP tasks the agencies to incentivize development of product candidates and contribute to early phase research. While not specific to the NAP, NIH has, for some years, offered a range of product development services and tools for all types of drugs, including antibiotics that are available internationally to incentivize product development among public- and private-sector partners. These gap-filling resources lower the risk for new entries into AMR discovery and product development. Agency members of TATFAR continue to improve communication and outreach to raise awareness of research priorities and actions on innovation efforts, such as the Innovative Medicines Initiative and other workshop meetings on antibacterial development topics. Clinical trial issues remain a focus of international consultations with agency participation.

Through TATFAR, NIH coordinates with other USG agencies and European funders to align international research activities within existing resources. NIH and TATFAR partners conduct joint presentations at international scientific meetings to help raise awareness about available funding resources and opportunities. NIH is coordinating with several international initiatives that predate the NAP, including the Joint Programming Initiative on Antimicrobial Resistance, and the European Innovative Medicines Initiative's *New Drugs 4 Bad Bugs program.*. Progress is reported through targeted symposia, regular meetings, and other formal and informal contacts among researchers and programmatic officials. NIH also pursues bilateral work with countries that are among the most important in terms of antibiotic resistance. The advancement of international collaborations on animal health candidate products remains for the future; however, the One Health perspective suggests that collaborative opportunities for participation in basic research endeavors exist and could be arranged between human and animal sector researchers. BARDA has participated in international meetings on innovation as well.

The PACCARB recommends the following to refine the international R&D activities described in the Progress Report:

- **Strengthen the emphasis on animal health product research efforts with USDA or other agencies at a basic research level.**
- **Enhance engagement with private-sector partners (e.g. companies, research institutes), whether domestic or international, for leveraging approaches to incentivize new drug development and diagnostics to benefit stewardship efforts in key countries.**

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

The United States has tremendous expertise and experience in improving public health through policies and practices that prevent and control the spread of infection. This is an urgent need for such policies and practices, particularly in countries where the infectious disease burden is high and health infrastructure poor. As with much of the rest of the NAP, the focus here is on human health.

Efforts to raise awareness of the WHO Global Action Plan at the Group of Seven (G7) level are ongoing, as are multiagency efforts for supporting the GHSA in member countries. The United States Agency for International Development (USAID) is the main USG actor in this area, with significant contributions from CDC. USAID has been engaged in assistance to individual countries toward developing national plans (e.g., South Africa and Ethiopia) and to broader organizations (e.g., the Ecumenical Pharmaceutical Network) that have some AMR focus. It extends support for health care infrastructure, which includes specific AMR-related aspects, such as supporting hospital drug and therapeutic committees, tools for essential drug programs, educational resources, operations research, and a range of other activities. USAID supports participation of professionals and policy decision-makers in national, regional, and global forums. Likewise, CDC has been providing technical assistance in the development of national plans and infection control policies (e.g., as in India, Vietnam, and Kenya). CDC and the State Department are working with ministries of health and key institutions to reduce AMR through infection prevention and control programs. In addition, the TATFAR and WHO have promoted and provided materials for annual antibiotic awareness weeks which are being widely adopted by countries.

The PACCARB recommends the following:

- **Ensure continued engagement with national governments that includes development of implementable policies.** Such policies are key to strengthening health care systems sustainably. In addition, the experience gained from the USG's domestic implementation of the NAP can be applied internationally to overcome unanticipated barriers or meet unforeseen needs by other countries.

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

No year-one milestones were set for this goal, but USAID has supported a number of relevant

activities on drug quality and safety, supply chains, essential medicines lists, and other related topics.

5.8 Coordinate regulatory approaches by collaborating with international organizations such as FAO and OIE to harmonize international data submission requirements and risk assessment.

FDA is represented on the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance. USDA and FDA have direct participation in groups such as the Veterinary International Conference on Harmonization, the International Medical Device Regulators Forum, the International Cooperation in Animal Biologics, and the Codex Alimentarius regarding food safety to promote multinational regulatory approaches, which may provide a path forward to greater One Health awareness and action. Regulatory convergence is anticipated to foster R&D efforts on a global basis. The FDA shares resources, personnel, and data with the European Medicines Agency to coordinate development of new drugs, ongoing safety, and manufacturing monitoring.

The PACCARB recommends the following:

- **Harmonize NAP objectives with those of international organizations and prioritize the goals of greatest importance for near-term work.**
- **Seek to align global organization programs to allow for harmonization of regulatory pathways and studies for animal health products.**

Conclusion

The progress made by the USG on efforts to combat antibiotic resistance during the period detailed in the Progress Report is substantial. Recognizing the challenges facing agencies and departments, we applaud their ability to implement so much in such little time. However, as noted frequently, much has yet to be accomplished and we hope that the 6 overarching themes identified in the executive summary, in addition to the specific recommendations outlined in the body of the report, provide a framework for a successful path forward. We look forward to further engagement with our federal partners, and especially the public, as we continue to fulfill our mission by providing advice, information, and recommendations to the Secretary of HHS regarding programs and policies intended to support and evaluate the implementation of the NAP.

ANNEX I – The National Action Plan for Combating Antibiotic-Resistant Bacteria: First 180-Days Progress Report

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

First 180 Days Report

November 2015

Prepared by the Taskforce for Combating Antibiotic Resistant Bacteria

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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 sp*p. 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

ANNEX II– Working Group Membership Rosters

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ANNEX III – Summary of Working Group Calls

Working Group (WG) and Leads*	Date and Time	Topic of Discussion	Presenters	Summary of Meeting
WG - 1 Antibiotic Stewardship **Led by Dr. Sara Cosgrove (Chair) and Dr. Michael Apley (Vice Chair)**	Nov 4, 2015	Working Group (WG) Introductory Call	Sara Cosgrove (Chair) and Michael Apley (Vice Chair)	The Chairs of the WG held an introductory call to discuss the path forward for the Working Group's activities. They provided an overview of the goals and objectives and discussed the types of presentations they would like to have to help inform their work.
	Nov 18, 2015	The Role of State Health Departments	Jewel Mullen - Association of State and Territorial Health Officials (ASTHO) Marion Kainer - Council of State and Territorial Epidemiologists (CSTE)	On behalf of the Connecticut Health Department, Dr. Mullen gave a presentation on the State's role in public health, their coordinated efforts with the USG, surveillance and stewardship activities on AMR, and the challenges facing State health departments. In continuing these activities. Dr. Kainer also provided an overview of State health departments' activities on combating AMR, including stewardship activities, policies, and obstacles in sustaining these programs.
	Dec 2, 2015	Antibiotic Stewardship and Surveillance	Margaret VanAmringe - The Joint Commission (TJC) William T. Flynn - Food and Drug Administration (FDA)	Ms. VanAmringe talked about TJC's Standards related to antibiotic stewardship, including its collaboration with government and professional groups. Dr. Flynn provided an overview of Guidance for Industry (GFI) #209 and its progress, and discussed federal efforts to enable the monitoring of antibiotic use in food animals.
	Dec 16, 2015	Centers for Medicare and Medicaid Services (CMS) Programs and Activities	Shari Ling - Centers for Medicare and Medicaid Services (CMS) Thomas Hamilton (CMS) Dan Schwartz (CMS)	CMS provided the WG with an overview of their authorized programs and activities and answered questions from the WG members.

WG - 1	Jan 6, 2016	CDC Perspective – In and Out-Patient Stewardship/Surveillance	Arjun Srinivasan (CDC) Lauri Hicks (CDC)	Dr. Srinivasan discussed CDC's role in in-patient stewardship and surveillance for both acute and long-term care. Dr. Hicks provided an overview of the CDC's outpatient stewardship activities, including CDC's Get Smart program.
	Jan 20, 2016	American Hospital Association Stewardship Activities	John R. Combes - American Hospital Association (AHA)	The call was dedicated to Dr. Combes' presentation on AHA's stewardship activities and their work on promoting antibiotic stewardship programs in acute care hospitals across in the U.S. In addition to discussing the barriers facing hospital implementation of stewardship programs, he talked about the development of tool kits to facilitate hospital implementation of such activities.
	Feb 3, 2016	Animal Health Perspectives on Stewardship	Jeff Bender - American Veterinary Medical Foundation (AVMA) Harry Snelson - American Association of Swine Veterinarians (AASV) Gatz Riddell - American Association of Bovine Veterinarians (AABV) Randall S. Singer - American Association of Avian Pathologists (AAAP)	Dr. Bender presented on the Task Force for Antimicrobial Stewardship in Companion Animal Practice. Dr. Snelson provided an overview of the AASV's activities on AMR, including their Judicious Use guidelines, educational outreach programs, and stewardship plans. Dr. Riddell's presentation focused on AMR stewardship in veterinary medicine, in particular cattle. He discussed the veterinarian client patient relationship and extra-label drug use. Dr. Singer's presentation focused on the drivers for antibiotic stewardship in poultry, along with the principle of responsible use for poultry.

WG – 2 **One Health Surveillance** **Led by Elizabeth Jungman (Chair) and Dr. Peter Davies (Vice Chair)**	Nov 5, 2015	WG Introduction and Data Systems	Elizabeth Jungman (Chair) and Peter Davies (Vice Chair)	The Chairs provided the WG with an overview of the goals and objectives, expectations, and frequency of calls to be held. A separate discussion on the data collection systems and lab networks also took place.
	Nov 17, 2015	Surveillance and Data Systems	CDC, FDA, DoD, USDA, NIH	The call was dedicated to discussion of the current federal surveillance systems and lab networks for both human and animal data.
	Dec 8, 2015	Antibiotic Resistance Surveillance	Susan E. Sharp - American Society of Microbiology (ASM) Kelly Wroblewski - Association of State and Public Health Laboratories (APHL) Mark G. Papich - Clinical and Laboratory Standards Institute (CLSI) Rodger Main - Veterinary Diagnostic Lab (VDL)	Dr. Sharp presented the ASM's perspective on how to help optimize interactions among the multiple public health laboratories to better address AMR. He also suggested best practices to help combine resistant bacteria data derived from various U.S. human and animal health disease surveillance systems. Ms. Wroblewski presented on antimicrobial susceptibility testing in public health laboratories. She discussed the challenges and solutions for responding to the threat of antimicrobial resistance for State public health laboratories, and the solutions. Dr. Papich briefly outlined the role of CLSI-VAST in relation to the State VLDs and AAVLD. He also discussed the opportunities and obstacles to the use of aggregated VDL AST data for general surveillance of antibiotic resistance in animal isolates at a national level. Dr. Main provided an overview of the impediments to accessing and sharing information from regional public health laboratory networks, animal laboratory networks, and specimen repositories. He also discussed the relationship between the state VDLs and the federal networks (NAHLN, VET-LIRN).

WG – 2	Dec 15, 2015	Antibiotic Use Surveillance	Vikas Gupta - CareFusion Nancy L. Losben - Omnicare John Martin - Premier Inc. Rich Carnevale – (Liaison Council Member) John R Glisson - U.S. Poultry & Egg Association	Dr. Gupta provided an overview of the MedMined data system, presented information on CareFusion's data sources for in/out-patient use, and discussed their current limitations on data availability and sources. Ms. Losben discussed the use of long-term care pharmacy dispensing data to facilitate annual reporting of antibiotic use in both inpatient and outpatient settings. Mr. Martin provided an overview of the 3 primary types of electronic data collection tools: THERADOC, Quality Advisor, and CECity. Dr. Carnevale presented on animal antibiotic use data collection in food-producing animals. Dr. Glisson provided an overview of the largest poultry trade association in the world, including their collaborating organizations and surveillance activities in gathering poultry antibiotic use data.
	Jan 19, 2016	Federal Funding and Feedback on Questions	Trinka Coster - Pharmacovigilance Center (PVC), Department of Defense (DOD) Gary Roselle - Department of Veterans Affairs (VA) Megan Hayden - Centers for Medicare and Medicaid Services (CMS)	COL Coster provided an overview of DoD's Pharmacovigilance Center (PVC), including their monitoring and future development plans. Part of the discussion was also dedicated to the FY2016 budget. Dr. Roselle provided insight on the extent to which FY2016 appropriations are going to the VA's CARB activities and the expected dedicated funding in the FY2017. Dr. Roselle also discussed plans for the VA pilot project. Ms. Haydan provided an overview of CMS' role in increasing antibiotic-use reporting in hospitals, in addition to the SAAR measure.

WG - 2			Michael Craig - Centers for Disease Control and Prevention (CDC) Jean Richard and Mike Beach - National Antimicrobial Resistance Monitoring System (NARMS)	Mr. Craig discussed CDC's CARB activities planned for FY2016 and how CDC is currently working with CMS on public reporting of data. He also discussed the status of CDC's plans to expand lab capacity. Mr. Richard and Mr. Beach discussed the capacity of NARMS to allow links to be made between human and animal surveillance systems. They also discussed the system design that would facilitate drawing links to enhance understanding of how use in one setting affects resistance in that and other settings.
	Feb 2, 2016	Federal Feedback	U.S. Department of Agriculture (USDA) Food and Drug Administration (FDA)	The USDA and FDA provided additional feedback on their activities relative to objectives 2.3 and 2.4, include the veterinary lab capacity and infrastructure network and NARMs. They also answered questions asked by the WG members.
WG - 3 Diagnostic Innovations **Angela Caliendo (Chair) and John Rex (Vice Chair)**	Nov 9, 2015	Framework and Needs Assessment	Angela Caliendo (Chair) and John Rex (Co-Chair)	The first call was used for planning purposes. Based on sub-objectives 3.1 and 3.2, it was decided to divide the focus in two topics – diagnostic tests under development and challenges in making those tests available. WG members suggested they gather information from various perspectives including manufacturer/industry, clinical laboratory, patient care, clinician, hospitalist, regulatory, and payer.
	Nov 23, 2015	Diagnostics Under Development	Robin Patel - Antibacterial Resistance Leadership Group (ARLG) John Rex (Council Member)	Dr. Patel provided an overview of the diagnostics pipeline, discussed several studies, and said that ARLG provides consultation but no formal gap analysis. Dr. Rex summarized findings from two recent diagnostic workshops held in the United Kingdom.
	Dec 7, 2015	Industry Perspective	Christine Ginocchio - Biomerieux John Rex (Council Member)	Dr. Ginocchio discussed diagnostic test development, including key characteristics of rapid tests, molecular detection, antibiotic susceptibility testing, role and types of biomarkers, cost for a diagnostic, and reimbursement.

WG - 3	Dec 21, 2015	Clinical Laboratory and Patient Care Perspectives	Steve Young - University of New Mexico Gregory Storch - Washington University	Dr. Young provided insight into the diagnostic pipeline and described the needs for testing from a clinical laboratory perspective. From a patient care perspective, Dr. Storch discussed pathogen detection and host response tests, characteristics of the perfect diagnostic test, and clinical barriers.
	Jan 4, 2016	Various Perspectives of Diagnostics	Tobi Karchmer - Biomedical Diagnostics (BD) Jeffrey Gerber - University of Pennsylvania Sajeev Handa - Rhode Island University Scott Flanders - University of Michigan	Dr. Karchmer discussed diagnostics on the outpatient and inpatient sides and the challenges in development. Dr. Gerber described his study about the variability of antibiotic prescribing in children and an intervention study that sought to improve variability. The hospitalists, Drs. Handa and Flanders, discussed obstacles and potential solutions to use of rapid diagnostic testing.
	Jan 11, 2016	Animal Diagnostics	Beth Byrum - Ohio Department of Agriculture Beth Harris and Matt Erdman - National Veterinary Services Laboratories (NVSL)	From the states perspective, Dr. Byrum discussed the role of veterinary diagnostic labs in the detection and monitoring of antimicrobial-resistant bacteria. She described trends in animal diagnostics and the use of sequencing tools. Drs. Harris and Erdman provided an overview of the National Veterinary Service Laboratories (NVSL), to include the Diagnostic Bacteriology Laboratory and the National Animal Health Laboratory Network (NAHLN).

WG - 3	Feb 1, 2016	Regulatory and Payer Perspectives The Diagnostics Prize	Rochelle Fink - Food and Drug Administration/ Centers for Medicare & Medicaid Services (FDA/CMS) Tamara Syrek-Jensen and Shari Ling - Centers for Medicare & Medicaid Services (CMS) Robert Eisinger - National Institutes of Health (NIH) Rodney Wallace - Biomedical Advanced Research and Development Authority (BARDA)	Drs. Fink and Syrek-Jensen described the Parallel Review Program. They discussed the purpose of the program, which is to reduce the time between the Food and Drug Administration (FDA) marketing approval and a CMS national coverage determination (NCD). They also answered questions from the WG members regarding the CMS and FDA regulatory review and coverage coordination activities. Drs. Eisinger and Wallace provided an overview of the antimicrobial resistance rapid, point-of-care diagnostic challenge and sought feedback from the members of the WG.
	Feb 22, 2016	Economic Models	Ramanan Laxminarayan (Council member)	Dr. Laxminarayan discussed the economics of diagnostics & information. He explained how we have the choice to increase the value of information by focusing on information needs, improving usability and usefulness of information, lowering decision maker constraints, and prioritizing information investments in areas that have ability to produce greatest economic value.

WG - 4 Treatment, Prevention, Control R&D **Helen Boucher (Chair) and Kent Kester (Vice Chair)**	Nov 18, 2015	Framework Overview	Helen Boucher (Chair) and Kent Kester (Vice Chair)	After discussing the proposed framework and key questions to ask stakeholders about how they support research and development of novel therapeutics, the Chairs gathered input from each member of the WG about their preferred focus area, proposed approach, and stakeholder identification.
	Dec 2, 2015	Incentives	Joe Larsen - Biomedical Advanced Research and Development Authority (BARDA) Edward Cox - Food and Drug Administration (FDA) John Rex (Council Member)	Dr. Larsen explained how the BARDA Model works to address market failures by engaging companies and establishing public-private partnerships to incentivize antibiotic research and development. Dr. Cox described FDA's expedited programs, including vaccine incentives and the Qualified Infectious Disease Product (QIDP) designation.
	Dec 16, 2015	Clinical Trial Networks	Vance Fowler and Chip Chambers - Antibacterial Resistance Leadership Group (ARLG) Dennis Dixon - National Institute of Allergy and Infectious Diseases (NIAID)	Drs. Fowler and Chambers described the mission of ARLG, its networks, study sites, collaborations, and several challenges it faces. Dr. Dixon discussed NIAID's clinical trial capabilities to address antibiotic resistance, including basic research, product development/translational research, and clinical research.
	Dec 23, 2015	Clinical Trial Networks	John Holcomb - Texas Trauma Institute (UT) John Rex (Council Member)	As an example of a successful trial network, Dr. Holcomb described the trauma network and emphasized the importance of funding and site selection and the need for high quality data. Dr. Rex described, in detail, the proposed design and cost of an ongoing, sustainable trial network to support testing of new drugs.

WG – 4	Jan 27, 2016	Role of Animal Health	Rich Carnevale (Liaison Council Member) Lonnie King (Vice Chair) Thomas Shryock (Council Member) Randy Singer (Council Member)	Drs. Carnevale, King, Shryock and Singer covered the key issues and challenges in animal health studies and development and the role of animal health studies/regulatory framework, as it pertains to development of new therapeutics for resistant pathogens.
	Feb 10, 2016	Streamlined Development and Narrow Spectrum Indications	John Rex (Council Member) Edward Cox - Food and Drug Administration (FDA)	Dr. Rex discussed the importance of nomenclature, superiority vs. inferiority clinical trials, streamlined pathways to development, and the issues with pathogen-focused pathways Dr. Cox discussed the development of antimicrobial agents to treat narrow spectrum infections.
	Feb 17, 2016	Development of Narrow Spectrum Drugs for Oral and Respiratory Infections Legal Framework to Address AMR	John Rex (Council Member) Kevin Outterson - Boston University (BU) Law & BU School of Public Health	Dr. Rex discussed challenges with oral antibacterial agents from a developer's perspective. Mr. Outterson provided an overview of oral antibiotic drug development, which focused on oral v. intravenous, the pipeline, and economics.

WG - 5 International Collaboration on CARB **Led by: Ramanan Laxminarayan (Chair), Thomas Shryock (Vice Chair)**	Nov 16, 2015	Introductory Call	Ramanan Laxminarayan (Chair) and Thomas Shryock (Vice Chair)	The Chairs of the WG held an introductory call to discuss the path forward for the Working Group's activities. They provided an overview of the goals and objectives, and each member was asked to choose which sub-objective (1-4) he/she would like to focus on.
	Dec 3, 2015	Federal Role in the overall International CARB Effort	CDC, DoD, OGA, State, USAID, USDA	The purpose of the discussion was to assess the status of current USG activities with respect to international collaborations and surveillance, and to identify areas in which current activities could be further improved.
	Dec 17, 2015	Coordination of International AMR Activities	Marc Sprenger - World Health Organization (WHO) Brian Evans - World Organisation for Animal Health (OIE) Olga B. Jonas - The World Bank	Dr. Sprenger discussed the concept of delinkage and the sales of AMR products, vaccines and their correlation with decreased antibiotic use, and how One-health affects all other work streams. Dr. Evans discussed how curbing the emergence of antimicrobial resistance requires global, multi-sector harmonisation of the strategies and measures designed to improve the coordination of environmental policies, human health, animal health and environmental policies. Dr. Evans also discussed the OIE collaborations with numerous international organisations, such as WHO, FAO, the Codex Alimentarius Commission (CAC), which are key partners for sharing information and formulating recommendations to ensure that antimicrobial agents maintain their efficacy, promote prudent and responsible use of these agents, and facilitate access to quality drugs. Ms. Jonas discussed the economics of AMR and understanding how different measures will actually be implemented in various countries; implementation will have to be justified with regards to cost/benefit. She also discussed the estimated cost of AMR surveillance expansion and improvement.

WG - 5	Jan 14, 2016	European AMR Efforts	Koen Van-Dyck and John Ryan- European Commission DG - SANTE Dominique Monnet - European Centre for Disease Prevention and Control (ECDC) Marco Cavaleri and Jordi Torren - European Medicines Agency (EMA)	Drs. Van Dyck and Ryan discussed the collective EU efforts to monitor AMR on both the human and animal sides. Mr. Monnet discussed the ECDC's activities on AMR and collaborative efforts to date. Dr. Cavaleri provided an overview of EMA activities, highlighting the evolution of EU regulatory standards for the development of new antibiotics. EMA has been involved in many activities aimed at improving the harmonization of regulatory requirements. He discussed alternative therapeutic approaches to tackle AMR, such as bacteriophages, and the modernization of Summary of product characteristics (SmPCs) of "old antibiotics." Mr. Torren discussed EMA activities addressing AMR. The presentation covered The Committee for Medicinal Products for Veterinary Use (CVMP) strategy on antimicrobials and TATFAR.
	Jan 28, 2016	International Collaborations on AMR	Wondossen A. Gebreyes - International Congress on Pathogens at the Human Animal Interface (ICOPHAI) Kamini Walia - Indian Council of Medical Research (ICMR) Marc Mendalson - University of Cape Town, South Africa	Dr. Gebreyes discussed the International Congress on Pathogens at the Human Animal Interface (ICOPHAI) efforts to curb Antimicrobial Resistance. He talked about the Molecular Epidemiology of MDR, and the Global Innovation Initiative (GII). Dr. Walia provided an overview on the Indian Council of Medical Research (ICMR). The presentation covered topics such as capacity-building and the strengthening of hospital infection control to detect and prevent AMR in India. He said that there is collaboration between ICMR and NIAID on AMR. Professor Mendalson gave an overview of South African efforts to CARB. He discussed animal health surveillance and antibiotic stewardship interventions. He believes that South Africa is a source of AMR support in the region.

WG - 5			Pilar Ramón-Pardo - Pan American Health Organization/World Health Organization (PAHO)	Dr. Ramón-Pardo discussed international collaborations on AMR, including those efforts to collect routine laboratory, healthcare-associated infections, and neonatal outbreak data in the Americas. The WHO is creating a template to guide other countries in developing their own National Action Plans.
	Feb 11, 2016	Draft Report	Ramanan Laxminarayan (Chair) and Thomas Shryock (Vice Chair)	This call was devoted to the draft report. The discussion was based on member comments on the initial draft, to include an evaluation of the 180-day report, the One-Health approach, and overcoming barriers to success.

*All working group activities were held in closed session, as stipulated per the Federal Advisory Council Act. All non-federal and non-member presenters were asked to sign non-disclosure agreements as well. This table is a non-inclusive summary of the working group's activities that have led to the development of their report for presentation to the voting members of the PACCARB. This table exemplifies the frequency and diversity of some of the meetings that were held. Additional written responses were sent to the working groups by stakeholders that are not reflected in this summary table.

ANNEX IV – PACCARB Membership Roster

PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

DESIGNATED FEDERAL OFFICIAL

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Deputy Assistant Secretary for Health
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
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Professor of Microbiology
Director, Human Microbiome Program
NYU School of Medicine
New York City, NY

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Dean, College of Veterinary Medicine
Executive Dean, Health Science Colleges
Ohio State University
Columbus, OH

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Professor, Department of Clinical Sciences
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Associate Professor of Medicine
Tufts University School of Medicine
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Director of the Division of General Internal Medicine
Alpert Medical School
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Alicia R. Cole
Founder
Alliance for Safety Awareness for Patients
Sherman Oaks, CA

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Associate Professor of Medicine
Division of Infectious Diseases
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Translational Science and Biomarkers
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Director, Health Travel Medicine Program and Vaccine Clinic
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Chief Academic Officer and The C. Anderson Hedberg, MD Professor of Internal Medicine
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Designated Representative:
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Association of State and Territorial Health Officials
Designated Representative:
Jay C. Butler, MD
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National Association of Directors of Nursing Administration in Long Term Care
Designated Representative:
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National Pork Producers Council
Designated Representative:
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The Pew Charitable Trusts
Designated Representative:
Elizabeth Jungman, JD, MPH
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ANNEX V – PACCARB Charter and Authorizing Legislation

Accessible version of the charter

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

CHARTER

PRESIDENTIAL ADVISORY COUNCIL ON COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Authority

Executive Order 13676, dated September 18, 2014, requires establishment of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (Advisory Council). Activities of the Advisory Council are governed by the provisions of Public Law 92-463, as amended (5 U.S.C. App.), which sets forth standards for the formation and use of federal advisory committees.

Objectives and Scope of Activities

Executive Order 13676 directs the Secretary of Health and Human Services (Secretary) to establish the Advisory Council in consultation with the Secretaries of Defense and Agriculture. The Advisory Council will provide advice, information, and recommendations to the Secretary regarding programs and policies intended to support and evaluate the implementation of Executive Order 13676, including the National Strategy for Combating Antibiotic-Resistant Bacteria (Strategy) and the National Action Plan for Combating Antibiotic-Resistant Bacteria (Action Plan). The Advisory Council shall function solely for advisory purposes.

Description of Duties

In carrying out its mission, the Advisory Council will provide advice, information, and recommendations to the Secretary regarding programs and policies intended to:

1. „ Preserve the effectiveness of antibiotics by optimizing their use;

2. „ Advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship;

3. „ Strengthen surveillance of antibiotic-resistant bacterial infections;

4. „ Prevent the transmission of antibiotic-resistant bacterial infections;

5. „ Advance the development of rapid point-of-care and agricultural diagnostics;

6. Further research on new treatments for bacterial infections;

7. Develop alternatives to antibiotics for agricultural purposes;

8. Maximize the dissemination of up-to-date information on the appropriate and proper use of antibiotics to the general public and human and animal healthcare providers; and

9. Improve international coordination of efforts to combat antibiotic resistance.

Agency or Official to Whom the Committee Reports

As stipulated in Executive Order 13676, the Advisory Council provides advice, information, and recommendations to the Secretary. The Secretary will provide the President with all written reports created by the Advisory Council.

Support

To the extent permitted by law and subject to the availability of appropriations, the Department of Health and Human Services (HHS) shall provide the Advisory Council with such funds and support as may be necessary for the performance of its functions. Management and support services provided to the Advisory Council will be the responsibility of the Office of the Assistant Secretary for Health (OASH), which is a coordinating and program office within the Office of the Secretary.

To the extent permitted by law, the agencies that comprise the Task Force for Combating Antibiotic-Resistant Bacteria shall provide the Advisory Council with such information as it may require for purposes of carrying out its functions.

Estimated Annual Operating Costs and Staff Years

The estimated annual cost for operating the Advisory Council, including compensation and travel expenses for members, but excluding staff support is $472,000. The estimate for annual person years of staff support required is 5.0, at an estimated annual cost of $654,017.

Designated Federal Officer

The Assistant Secretary for Health (ASH), in consultation with the Secretary, will select the Designated Federal Officer (DFO) from among full-time or permanent part-time staff within OASH or another organizational component within the HHS, who have knowledge of the subject matter and skills and experience necessary to manage the Advisory Council. The ASH may appoint an Alternate DFO, who will carry out the assigned duties in the event that the DFO cannot fulfill the assigned responsibilities for the Advisory Council. In the absence of a DFO

or Alternate DFO, the ASH will temporarily appoint one or more permanent full-time or part-time program staff to carry out the assigned duties.

The DFO will schedule and approve all meetings of the Advisory Council and of its respective subcommittees. The DFO will prepare and approve all meeting agendas. The DFO may collaborate with the Advisory Council Chair in this activity, and when deemed appropriate, with chairs of any existing subcommittees that have been established by the Advisory Council. The DFO, Alternate DFO, or designee will attend all meetings of the Advisory Council and all meetings of any subcommittees/working groups that have been assembled to assist the Advisory Council. The DFO has authority to adjourn meetings, when it is determined to be in the public interest, and the DFO can be directed by the Secretary or designee to chair meetings of the Advisory Council.

Estimated Number and Frequency of Meetings

The Advisory Council will meet, at a minimum, two times per fiscal year depending on the availability of funds. Meetings will be open to the public, except as determined otherwise by the Secretary, or other official to whom authority has been delegated, in accordance with guidelines under Government in the Sunshine Act, 5 U.S.C. 552b(c). Notice of all meetings will be provided to the public in accordance with the Federal Advisory Committee Act (FACA), Public Law 92-463, as amended (5 U.S.C. App.). Meetings will be conducted and records of the proceedings will be kept, as required by applicable laws and Departmental policies. A quorum is required for the Advisory Council to meet to conduct business. A quorum will consist of a majority of the Advisory Council's voting members.

When the Secretary or designee determines that a meeting will be closed or partially closed to the public, in accordance with stipulations of Government in the Sunshine Act, 5 U.S.C. 552b(c), then a report will be prepared by the DFO that includes, at a minimum, a list of the members and their business addresses, the Advisory Council's functions, date and place of the meeting, and a summary of the Advisory Council's activities and recommendations made during the fiscal year. A copy of the report will be provided to the Department Committee Management Officer.

Duration

Continuing. The Advisory Council was established by an Executive Order; no specific end date was established for the Advisory Council to operate.

Termination

Unless renewed by appropriate action prior to its expiration, the charter for the Advisory Council will expire two years from the date it is filed.

Membership and Designation

The Advisory Council will consist of not more than 30 members, including the voting and non-voting members and the Chair and Vice Chair. The Secretary will designate the Chair and Vice Chair from among the voting public members of the Advisory Council who have demonstrated ability both to lead the work of similar bodies and to work effectively in partnership with federal agencies and partner organizations.

Voting Members. There will public voting members selected from individuals who are engaged in research on, or implementation of, interventions regarding efforts to preserve the effectiveness of antibiotics by optimizing their use; advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship; strengthen surveillance of antibiotic-resistant bacterial infections; prevent the transmission of antibiotic-resistant bacterial infections; advance the development of rapid point-of-care and agricultural diagnostics; further research on new treatments for bacterial infections; develop alternatives to antibiotics for agricultural purposes; maximize the dissemination of up-to-date information on the appropriate and proper use of antibiotics to the general public and human and animal healthcare providers; and improve international coordination of efforts to combat antibiotic resistance.

The public voting members will represent balanced points of view from human biomedical, public health, and agricultural fields to include surveillance of antibiotic-resistant infections, prevention and/or interruption of the spread of antibiotic-resistant threats, or development of rapid diagnostics and novel treatments. The public voting members may be physicians, veterinarians, epidemiologists, microbiologists, or other health care professionals (e.g., nurses, pharmacists, others); individuals who have expertise and experience as consumer or patient advocates concerned with antibiotic resistance, or in the fields of agriculture and pharmaceuticals; and they also may be from State or local health agencies or public health organizations. The voting public members will be appointed by the Secretary, in consultation with the Secretaries of Defense and Agriculture. All public voting members will be classified as special Government employees (SGEs).

Ex-officio Members (non-voting). The Advisory Council will include members selected to represent various federal agencies, including HHS, DoD, and USDA, that are involved in the development, testing, licensing, production, procurement, distribution, and/or use of antibiotics and/or antibiotic research. The federal *ex- officio* members shall possess the knowledge, skills, experience, and expertise necessary to generate informed and intelligent recommendations with respect to the issues mandated by Executive Order 13676. Federal agencies will be invited to participate as non-voting *ex-officio* members of the Advisory Council, as it is deemed necessary by the Secretary, in consultation with the Secretaries of Defense and Agriculture, to accomplish the mission the Advisory Council.

Liaison Representatives (non-voting). The Advisory Council structure also may include non-voting liaison representatives from organizations and/or interest groups that have involvement in the development, testing, licensing, production, procurement, distribution, and/or use of antibiotics and/or antibiotic research. Individuals from among the following sectors may be invited to serve as non-voting liaison representatives:

- Professional organizations representing: infectious disease; epidemiology; infection control; physicians; nurses; pharmacists; microbiologists; veterinarians
- Public health organizations representing laboratories, health officials, or epidemiologists (state/territorial, county, or local)
- Organizations advocating for patients and consumers
- Organizations representing state departments of agriculture
- Hospitals
- Foundations with an interest in antibiotic resistance and promoting antibiotic stewardship
- National Preparedness and Response Science Board
- Pharmaceutical industry – human health
- Pharmaceutical industry – animal health
- Vaccines
- Food producer (livestock)
- Food producer (poultry)
- Food producer (seafood)
- *In vitro* diagnostics
- Food retailer
- Food processor
- Animal feed producers
- Farm bio-security

Invitations may be extended to other organizations and/or interest groups to participate as non-voting liaison representatives, as it is deemed necessary by the Secretary or designee to accomplish the established mission of the Advisory Council.

Terms and Compensation. The public voting and non-voting liaison representative members will be appointed to serve for overlapping terms of up to four years. Any member who is appointed to fill the vacancy of an unexpired term will be appointed to serve for the remainder of that term. The Chair and Vice Chair will be appointed to serve for three years, unless otherwise specified. Terms of more than two years are contingent upon renewal of the Advisory Council charter by appropriate action prior to its expiration. A member may serve after the expiration of their term until their successor has taken office, but no longer than 180 days.

Pursuant to an advance written agreement, the public voting members shall receive no stipend from the federal government for the services they perform during their tenure on the Advisory

Council. However, the public voting members are entitled to receive per diem and reimbursement for travel expenses incurred for attending meetings of the Advisory Council, as authorized by 5 U.S.C. Sec. 5703, as amended, for persons who are employed intermittently in the Government service. The non-voting liaison representatives may be allowed to receive per diem and any applicable expenses for travel that is performed to attend meetings of the Advisory Council in accordance with federal travel regulations.

Subcommittees/Working Groups

With approval or recommendation of the Secretary or designee, the Advisory Council may establish standing and *ad hoc* subcommittees and/or working groups to provide assistance for carrying out its function. These subgroups may consist of members of the Advisory Council, as well as other individuals (federal and non-federal) who are concerned and knowledgeable about antibiotic-resistant bacteria and other topics pertaining to the Advisory Council mission.

The Department Committee Management Officer will be notified upon establishment of each subcommittee or working group, and will be provided information on its name, membership, function, and estimated frequency of meetings. All reports and recommendations of a subcommittee or workgroup must be reported back to the full Advisory Council for action. No activity of a subcommittee or working group can be given directly to the Secretary without being provided for discussion by the full Advisory Council.

Recordkeeping

Records of the Advisory Council and the respective subcommittees or working groups will be handled in accordance with General Schedule 26, Item 2 or other approved agency records disposition schedule. These records will be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

Filing Date: MAR 24 2015

Approved:

MAR 24 2015

Date

Sylvia M. Burwell

Sylvia M. Burwell

Presidential Documents

Executive Order 13676 of September 18, 2014

Combating Antibiotic-Resistant Bacteria

By the authority vested in me as President by the Constitution and the laws of the United States of America, I hereby order as follows:

Section 1. *Policy.* The discovery of antibiotics in the early 20th century fundamentally transformed human and veterinary medicine. Antibiotics save millions of lives each year in the United States and around the world. The rise of antibiotic-resistant bacteria, however, represents a serious threat to public health and the economy. The Centers for Disease Control and Prevention (CDC) in the Department of Health and Human Services (HHS) estimates that annually at least two million illnesses and 23,000 deaths are caused by antibiotic-resistant bacteria in the United States alone.

Detecting, preventing, and controlling antibiotic resistance requires a strategic, coordinated, and sustained effort. It also depends on the engagement of governments, academia, industry, healthcare providers, the general public, and the agricultural community, as well as international partners. Success in this effort will require significant efforts to: minimize the emergence of antibiotic-resistant bacteria; preserve the efficacy of new and existing antibacterial drugs; advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship; strengthen surveillance efforts in public health and agriculture; develop and promote the use of new, rapid diagnostic technologies; accelerate scientific research and facilitate the development of new antibacterial drugs, vaccines, diagnostics, and other novel therapeutics; maximize the dissemination of the most up-to-date information on the appropriate and proper use of antibiotics to the general public and healthcare providers; work with the pharmaceutical industry to include information on the proper use of over-the-counter and prescription antibiotic medications for humans and animals; and improve international collaboration and capabilities for prevention, surveillance, stewardship, basic research, and drug and diagnostics development.

The Federal Government will work domestically and internationally to detect, prevent, and control illness and death related to antibiotic-resistant infections by implementing measures that reduce the emergence and spread of antibiotic-resistant bacteria and help ensure the continued availability of effective therapeutics for the treatment of bacterial infections.

Sec. 2. *Oversight and Coordination.* Combating antibiotic-resistant bacteria is a national security priority. The National Security Council staff, in collaboration with the Office of Science and Technology Policy, the Domestic Policy Council, and the Office of Management and Budget, shall coordinate the development and implementation of Federal Government policies to combat antibiotic-resistant bacteria, including the activities, reports, and recommendations of the Task Force for Combating Antibiotic-Resistant Bacteria established in section 3 of this order.

Sec. 3. *Task Force for Combating Antibiotic-Resistant Bacteria.* There is hereby established the Task Force for Combating Antibiotic-Resistant Bacteria (Task Force), to be co-chaired by the Secretaries of Defense, Agriculture, and HHS.

(a) Membership. In addition to the Co-Chairs, the Task Force shall consist of representatives from:

(i) the Department of State;

(ii) the Department of Justice;

(iii) the Department of Veterans Affairs;

(iv) the Department of Homeland Security;

(v) the Environmental Protection Agency;

(vi) the United States Agency for International Development;

(vii) the Office of Management and Budget;

(viii) the Domestic Policy Council;

(ix) the National Security Council staff;

(x) the Office of Science and Technology Policy;

(xi) the National Science Foundation; and

(xii) such executive departments, agencies, or offices as the Co-Chairs may designate.

Each executive department, agency, or office represented on the Task Force (Task Force agency) shall designate an employee of the Federal Government to perform the functions of the Task Force. In performing its functions, the Task Force may make use of existing interagency task forces on antibiotic resistance.

(b) *Mission.* The Task Force shall identify actions that will provide for the facilitation and monitoring of implementation of this order and the National Strategy for Combating Antibiotic-Resistant Bacteria (Strategy).

(c) *Functions.*

(i) By February 15, 2015, the Task Force shall submit a 5-year National Action Plan (Action Plan) to the President that outlines specific actions to be taken to implement the Strategy. The Action Plan shall include goals, milestones, and metrics for measuring progress, as well as associated timelines for implementation. The Action Plan shall address recommendations made by the President's Council of Advisors on Science and Technology regarding combating antibiotic resistance.

(ii) 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. The Task Force shall take Federal Government resources into consideration when developing these proposed actions and recommendations.

(iii) In performing its functions, the Task Force shall review relevant statutes, regulations, policies, and programs, and shall consult with relevant domestic and international organizations and experts, as necessary.

(iv) The Task Force shall conduct an assessment of progress made towards achieving the milestones and goals outlined in the Strategy in conjunction with the Advisory Council established pursuant to section 4 of this order.

Sec. 4. *Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria.* (a) The Secretary of HHS (Secretary), in consultation with the Secretaries of Defense and Agriculture, shall establish the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (Advisory Council). The Advisory Council shall be composed of not more than 30 members to be appointed or designated by the Secretary.

(b) The Secretary shall designate a chairperson from among the members of the Advisory Council.

(c) The Advisory Council shall provide advice, information, and recommendations to the Secretary regarding programs and policies intended to: preserve the effectiveness of antibiotics by optimizing their use; advance

research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship; strengthen surveillance of antibiotic-resistant bacterial infections; prevent the transmission of antibiotic-resistant bacterial infections; advance the development of rapid point-of-care and agricultural diagnostics; further research on new treatments for bacterial infections; develop alternatives to antibiotics for agricultural purposes; maximize the dissemination of up-to-date information on the appropriate and proper use of antibiotics to the general public and human and animal healthcare providers; and improve international coordination of efforts to combat antibiotic resistance. The Secretary shall provide the President with all written reports created by the Advisory Council.

(d) Task Force agencies shall, to the extent permitted by law, provide the Advisory Council with such information as it may require for purposes of carrying out its functions.

(e) To the extent permitted by law, and subject to the availability of appropriations, HHS shall provide the Advisory Council with such funds and support as may be necessary for the performance of its functions.

Sec. 5. *Improved Antibiotic Stewardship.* (a) By the end of calendar year 2016, HHS shall review existing regulations and propose new regulations or other actions, as appropriate, that require hospitals and other inpatient healthcare delivery facilities to implement robust antibiotic stewardship programs that adhere to best practices, such as those identified by the CDC. HHS shall also take steps to encourage other healthcare facilities, such as ambulatory surgery centers and dialysis facilities, to adopt antibiotic stewardship programs.

(b) Task Force agencies shall, as appropriate, define, promulgate, and implement stewardship programs in other healthcare settings, including office-based practices, outpatient settings, emergency departments, and institutional and long-term care facilities such as nursing homes, pharmacies, and correctional facilities.

(c) By the end of calendar year 2016, the Department of Defense (DoD) and the Department of Veterans Affairs (VA) shall review their existing regulations and, as appropriate, propose new regulations and other actions that require their hospitals and long-term care facilities to implement robust antibiotic stewardship programs that adhere to best practices, such as those defined by the CDC. DoD and the VA shall also take steps to encourage their other healthcare facilities, such as ambulatory surgery centers and outpatient clinics, to adopt antibiotic stewardship programs.

(d) Task Force agencies shall, as appropriate, monitor improvements in antibiotic use through the National Healthcare Safety Network and other systems.

(e) The Food and Drug Administration (FDA) in HHS, in coordination with the Department of Agriculture (USDA), shall continue taking steps to eliminate the use of medically important classes of antibiotics for growth promotion purposes in food-producing animals.

(f) USDA, the Environmental Protection Agency (EPA), and FDA shall strengthen coordination in common program areas, such as surveillance of antibiotic use and resistance patterns in food-producing animals, interspecies disease transmissibility, and research findings.

(g) DoD, HHS, and the VA shall review existing regulations and propose new regulations and other actions, as appropriate, to standardize the collection and sharing of antibiotic resistance data across all their healthcare settings.

Sec. 6. *Strengthening National Surveillance Efforts for Resistant Bacteria.* (a) The Task Force shall ensure that the Action Plan includes procedures for creating and integrating surveillance systems and laboratory networks to provide timely, high-quality data across healthcare and agricultural settings, including detailed genomic and other information, adequate to track resistant bacteria across diverse settings. The network-integrated surveillance

systems and laboratory networks shall include common information requirements, repositories for bacteria isolates and other samples, a curated genomic database, rules for access to samples and scientific data, standards for electronic health record-based reporting, data transparency, budget coordination, and international coordination.

(b) Task Force agencies shall, as appropriate, link data from Federal Government sample isolate repositories for bacteria strains to an integrated surveillance system, and, where feasible, the repositories shall enhance their sample collections and further interoperable data systems with national surveillance efforts.

(c) USDA, EPA, and FDA shall work together with stakeholders to monitor and report on changes in antibiotic use in agriculture and their impact on the environment.

(d) Task Force agencies shall, as appropriate, monitor antibiotic resistance in healthcare settings through the National Healthcare Safety Network and related systems.

Sec. 7. *Preventing and Responding to Infections and Outbreaks with Antibiotic-Resistant Organisms.* (a) Task Force agencies shall, as appropriate, utilize the enhanced surveillance activities described in section 6 of this order to prevent antibiotic-resistant infections by: actively identifying and responding to antibiotic-resistant outbreaks; preventing outbreaks and transmission of antibiotic-resistant infections in healthcare, community, and agricultural settings through early detection and tracking of resistant organisms; and identifying and evaluating additional strategies in the healthcare and community settings for the effective prevention and control of antibiotic-resistant infections.

(b) Task Force agencies shall take steps to implement the measures and achieve the milestones outlined in the Strategy and Action Plan.

(c) DoD, HHS, and the VA shall review and, as appropriate, update their hospital and long-term care infectious disease protocols for identifying, isolating, and treating antibiotic-resistant bacterial infection cases.

Sec. 8. *Promoting New and Next Generation Antibiotics and Diagnostics.* (a) As part of the Action Plan, the Task Force shall describe steps that agencies can take to encourage the development of new and next-generation antibacterial drugs, diagnostics, vaccines, and novel therapeutics for both the public and agricultural sectors, including steps to develop infrastructure for clinical trials and options for attracting greater private investment in the development of new antibiotics and rapid point-of-care diagnostics. Task Force agency efforts shall focus on addressing areas of unmet medical need for individuals, including those antibiotic-resistant bacteria CDC has identified as public and agricultural health threats.

(b) Together with the countermeasures it develops for biodefense threats, the Biomedical Advanced Research Development Authority in HHS shall develop new and next-generation countermeasures that target antibiotic-resistant bacteria that present a serious or urgent threat to public health.

(c) The Public Health Emergency Medical Countermeasures Enterprise in HHS shall, as appropriate, coordinate with Task Force agencies' efforts to promote new and next-generation countermeasures to target antibiotic-resistant bacteria that present a serious or urgent threat to public health.

Sec. 9. *International Cooperation.* Within 30 days of the date of this order, the Secretaries of State, USDA, and HHS shall designate representatives to engage in international action to combat antibiotic-resistant bacteria, including the development of the World Health Organization (WHO) Global Action Plan for Antimicrobial Resistance with the WHO, Member States, and other relevant organizations. The Secretaries of State, USDA, and HHS shall conduct a review of international collaboration activities and partnerships, and identify and pursue opportunities for enhanced prevention, surveillance, research and development, and policy engagement. All Task Force

agencies with research and development activities related to antibiotic resistance shall, as appropriate, expand existing bilateral and multilateral scientific cooperation and research pursuant to the Action Plan.

Sec. 10. *General Provisions.* (a) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.

(b) Nothing in this order shall be construed to impair or otherwise affect:

(i) the authority granted by law to an executive department or agency, or the head thereof; or

(ii) the functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(c) This order is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.

(d) Insofar as the Federal Advisory Committee Act, as amended (5 U.S.C. App.) (the ''Act''), may apply to the Advisory Council, any functions of the President under the Act, except for that of reporting to the Congress, shall be performed by the Secretary in accordance with the guidelines issued by the Administrator of General Services.

THE WHITE HOUSE,
September 18, 2014.

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ANNEX VI – Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
AMR	antimicrobial resistance
ARLG	Antibacterial Resistance Leadership Group
ARS	Agricultural Research Service
ASP	antibiotic stewardship program
AST	antimicrobial susceptibility test
Atlas	HAI Antibiotic Resistance Patient Safety Atlas
AUR	Antimicrobial Use and Resistance
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
CoP	condition of participation
CPT	Current Procedural Terminology
CRE	carbapenem-resistant Enterobacteriaceae
DoD	Department of Defense
ECDC	European Centre for Disease Prevention Control
EHR	electronic health record
EIP	Emerging Infections Program
EU	European Union
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FY	Fiscal Year
G7	group of seven
GFI	Guidance for Industry
GHSA	Global Health Security Agenda
GLASS	Global Antimicrobial Resistance Surveillance System
HAI	health-care-acquired infections (also health-care-associated infections)
HHS	U.S. Department of Health and Human Services
IND	Investigational New Drug
IPT	Integrated Product Team
JSTO	Joint Science and Technology Office
LTCF	long-term care facility
MDRO	Multidrug resistant organism
MRSN	Multidrug-resistant Organism Repository and Surveillance Network
NAP	National Action Plan
NARMS	National Antimicrobial Resistance Monitoring System
NHSN	National Healthcare Safety Network
NIAID	National Institute for Allergy and Infectious Diseases
NIFA	National Institute for Food and Agriculture
NIH	National Institutes of Health
OASD NCB	Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs
OIE	World Organization for Animal Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PCAST	President's Council of Advisors on Science and Technology

PHEMCE	HHS Public Health Emergency Medical Countermeasures Enterprise
R&D	Research and Development
RFI	Request for Information
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
TJC	The Joint Commission
USAID	United States Agency for International Development
USDA	United Stated Department of Agriculture
USG	United States Government
VA	Department of Veterans Affairs
VFD	Veterinary Feed Directive
WG	Working Group
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research