PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

Fourth Public Meeting of the
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
September 19, 2016
12:30 – 5:30 p.m. ET

Department of Health and Human Services
Great Hall, Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201

Table of Contents

PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Proceedings

Welcome

Martin J. Blaser, M.D., Chair

Dr. Blaser called the meeting to order at 12:33 p.m. and welcomed the members of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), federal representatives, and other participants.

Roll Call and Rules of Engagement

Bruce G. Gellin, M.D., M.P.H., Designated Federal Official

Dr. Gellin, designated federal official for PACCARB, described the meeting process. The meeting was webcast. As a federal advisory committee, the group is subject to the guidelines of the Federal Advisory Committee Act, including disclosure of potential or apparent conflicts of interest. All PACCARB resources and information are available online at http://www.hhs.gov/ash/carb/index.html. Dr. Gellin called the roll. (Voting and non-voting members present are listed in Appendix A.)

Opening Remarks

Jewel Mullen, M.D., M.P.H., M.P.A., Principal Deputy Assistant Secretary for Health, HHS

Dr. Mullen thanked all those involved in the effort to combat antibacterial resistance, a serious issue responsible for $20 billion in direct costs and $35 billion in indirect costs in the United States alone. She said the PACCARB meeting complements the upcoming United Nations General Assembly meeting later in the week, where there is an urgent call to action to address this complex, multifactorial problem. Dr. Mullen announced that the United States had met or exceeded its first-year goals for the Combating Antibiotic-Resistant Bacteria (CARB) National Action Plan. She summarized some of those achievements, including reduction of several antibiotic-resistant diseases, phasing out the use of medically important antibiotics for growth promotion in food animals due to the Food and Drug Administration's (FDA) new judicious use policy, advancements in diagnostic testing and a federal competition to support new and innovative diagnostic tests, a public-private partnership to accelerate product development, and international collaborations around CARB.

Overview of Healthcare Infection Control Practices Advisory Committee (HICPAC)

Deborah Yokoe, M.D., M.P.H., HICPAC Co-Chair

Dr. Yokoe explained that HICPAC advises the Centers for Disease Control and Prevention (CDC) and HHS on health-care-associated infection (HAI) control and prevention, including

antimicrobial resistance. The membership represents multiple disciplines and stakeholder groups. HICPAC leads the production of guidelines on topics such as hand hygiene and preventing device- or procedure-related infections. It recently published recommendations on antibiotic stewardship aimed at professional and medical specialty societies that produce guidelines on antibiotic use.

Dr. Yokoe said HICPAC emphasizes the importance of including stewardship and infection control practices in education, training, and certification. HICPAC can provide input to PACCARB or serve as a resource for information, especially on incorporating education and principles in medical and veterinary education.

Discussion

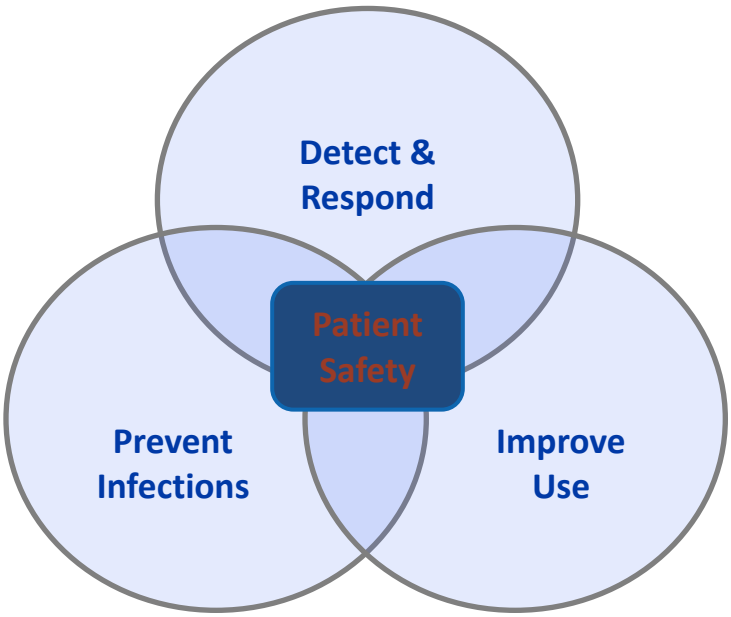
In response to Alicia R. Cole, Dr. Yokoe said Consumer's Union represents advocate groups at HICPAC, but she is open to having more public members. She said the number of liaisons is dictated by the group's charter but has increased over time. Dr. Blaser said PACCARB should take advantage of HICPAC's parallel interests in CARB.

Prevention

Prevention and Control of Antibiotic Resistance: The Public Health Approach

Beth P. Bell, M.D., M.P.H., Director, National Center for Emerging and Zoonotic Infectious Diseases, CDC

Dr. Bell said the following graphic summarizes CDC's approach to patient safety:



She outlined numerous examples of CARB efforts in each of the three overlapping areas. These efforts build on successes in decreasing HAIs. Dr. Bell emphasized that CDC funding for prevention programs is based on evidence. Regarding antibiotic-resistant infections, CDC

recognized that prevention by individual health care facilities did not adequately address the spread of disease across facilities, so it created a regional approach that accounts for the interconnectedness.

Partnerships with states such as Tennessee and New York have also helped decrease antibiotic-resistant infections. CDC is expanding its HAI and antibiotic resistance prevention programs to every state, six cities, and Puerto Rico. Funding will enhance detection and response capacity while also supporting prevention and stewardship efforts. Numerous efforts are underway to improve antibiotic use by collecting more and better data, disseminating successful efforts around stewardship and prescribing, and raising public awareness (e.g., through expansion of the Get Smart program and a national campaign on sepsis recognition).

CDC is creating a national network of regional laboratories to detect and track antibiotic resistance. To enhance tracking, CDC is supporting whole genome sequencing, which provides a precise DNA fingerprint, enabling more rapid detection of genes that lead to resistance. Such sequencing will build states' capacity to fight foodborne infections. CDC is also working with health systems to implement effective prevention strategies that emphasize antibiotic stewardship. It is collaborating with academic researchers to discover and scale up new interventions to protect patients across health systems.

Policies and Regulations to Promote Prevention of Antibiotic Resistance and Infections

Shari Ling, M.D., Deputy Chief Medical Officer, Centers for Medicare and Medicaid Services (CMS)

Dr. Ling outlined the various programs and activities through which CMS influences payment and provider practices. The agency is updating its requirements for long-term care facilities, which will affect 15,000 facilities; the Final Rule for this effort is in final clearance. CMS is currently proposing to revise its Conditions of Participation (COPs) to include antibiotic stewardship programs that align with CDC Core Elements in hospitals and critical access hospitals. CMS has also proposed that the National Healthcare Safety Network's (NHSN's) antibiotic use module be required as part of hospital quality measure reporting. Existing CMS quality measures address HAIs and prevention through vaccination.

CMS's pay-for-performance efforts fall under the Value-Based Purchasing program. Dr. Ling emphasized that including HAIs, infectious disease (ID), and immunization in the program sends a strong signal to providers about the importance of preventing and avoiding resistant infections. CMS also provides technical assistance, working with partners such as CDC, by disseminating quality improvement tools and programs through its hospital engagement networks. Currently, CMS' quality improvement networks and organizations are recruiting nursing homes to participate in a program aimed at reducing *Clostridium difficile* infections. Other efforts involve training on using data to support prevention and antibiotic stewardship programs.

To ensure that its COPs are met, CMS is developing several pilot surveys to improve the assessment of infection prevention and control regulations, as well as antibiotic stewardship, in nursing homes and hospitals. Dr. Ling emphasized that the transition points—for example, from the hospital to the long-term care facility—are key opportunities to curtail the spread of resistant infections. She added that antibiotic stewardship is included as a quality improvement activity

under the Medicare and CHIP [Children's Health Insurance Program] Access Reauthorization Act, which aims at health care delivery system reform.

On-Farm Management Practices and Other Methods of Infection Control

Brian McCluskey, D.V.M., Ph.D., Associate Deputy Administrator, Animal and Plant Health Inspection Service, U.S. Department of Agriculture (USDA)

Dr. McCluskey said the National Animal Health Monitoring System (NAHMS) conducts periodic livestock studies every 5–10 years using questionnaires and some biological sampling. The studies are voluntary, and the confidentiality of the data is protected. Many studies collect data on antimicrobial use, but the sporadic nature of the studies does not support using these data to monitor on-farm use of antibiotics. The results are disseminated primarily to farmers and veterinarians through reports available online and through peer-reviewed publications and trade magazines. Reports are also used by cooperative extension programs and veterinary schools to better understand how to improve production and reduce infection.

Periodic NAHMS studies show some trends over time. For example, the use of footbaths by workers on farms to prevent the spread of infection in egg-laying facilities increased from about 25 percent in 1999 to nearly 80 percent in 2013. In the same time, the percent of poultry operations that restricted their employees from owning their own poultry (which raises the risk of spreading disease) increased from 75 percent to 94 percent. Similarly, studies of swine showed that the practice of continuous flow management is decreasing significantly over time. Continuous flow allows disease to be introduced as new pigs are added to the group when others are ready for market. The "all in, all out" approach decreases the risk of disease introduction.

In addition, NAHMS studies show that more dairy operations recognize the importance of calves receiving adequate, high-quality colostrum early to prevent neonatal infection. The number of operations evaluating colostrum quality and feeding calves colostrum within the first 36 hours of life (as opposed to relying on nursing) has increased substantially since 2000. As a result, respiratory and gastrointestinal infections in neonatal calves have gone down. Dr. McCluskey added that veterinary teaching hospitals and the American Animal Hospital Association certification process emphasize infection control practices.

Discussion

In response to Aileen Marty, M.D., FACP, Dr. Bell said CDC encourages state health departments and other laboratories using FDA-approved methods for detecting the spread of antibiotic-resistant infections to apply for the Antibiotic Resistance Laboratory Network in an effort to leverage existing capacity. Asked by Dr. Marty how CMS integrates the multiple components for combating antibiotic resistance into its strategic plans, Dr. Ling said that diagnostic testing is paid as a service. CMS' goal is to identify what measurement tool will show that the test was used for meaningful clinical care. Some measures address that question, and further FDA-approved evidence of test validity will help CMS gather information that can be shared broadly on how and when to use diagnostic tests.

Dr. Marty asked whether prophylactic or metaphylactic use of antibiotics in livestock contributes to antibiotic resistance. Dr. McCluskey said the evidence is conflicting, but some information may be gathered over time from the results of recent regulations eliminating the use of antibiotics for growth promotion.

Ms. Cole said CDC is funding specially trained infection preventionists, but those preventionists can only work with hospitals when invited. Meanwhile, infection rates are high and rising. Ms. Cole asked CDC to consider tying hospital funding to the use of preventionists. She also pointed out to Dr. Ling that California has 132 hospitals that are out of compliance with regulations, some for years. Dr. Bell said CDC encourages hospitals to look at their own data and address problems identified. She said CDC tries to work with hospitals to achieve good outcomes.

Responding to Angela Caliendo, M.D., Ph.D., FIDSA, Dr. McCluskey said NAHMS studies have not looked at reductions in antibiotic use on the farm. In response to Elizabeth Allen Wagstrom, D.V.M., M.S., Dr. Bell said laboratories will continue to measure phenotypic resistance in addition to whole genome sequencing, so the National Antimicrobial Resistance Monitoring System (NARMS) will still be able to track trends. One major goal is to compare sequencing data from NARMS with data from USDA and the Food and Drug Administration (FDA).

Asked by Ramanan Laxminarayan, Ph.D., M.P.H., to comment on the differences between HAI reduction efforts and antibiotic stewardship, Dr. Bell said antibiotic stewardship must be framed as a patient safety issue. For HAIs, there was a change in public perception such that HAIs were no longer considered an unavoidable but acceptable risk of hospital procedures. Dr. Bell acknowledged that antibiotic resistance is more complicated, starting with barriers to tracking antibiotic use. State-mandated reporting using the NHSN has a lot of potential for impact, she said. Similarly, CDC hopes vendors will improve the interface between NHSN and electronic medical records to make reporting easier.

Stewardship

Antibiotic Stewardship in Acute Care Hospitals: The Intermountain Healthcare Experience

Eddie Stenehjem, M.D., M.Sc., Intermountain Health

Data demonstrate that small hospitals are much less likely than large hospitals to establish antibiotic stewardship programs or have support from ID specialists. Dr. Stenehjem described Intermountain Healthcare's effort to improve stewardship in its facilities in recognition of impending requirements. Facilities were assigned to one of three groups in a trial project:

- Program 1: Basic antibiotic stewardship education and implementation of five best antibiotic use practices that meet CDC's seven core elements of stewardship
- Program 2: Program 1 plus advanced education, some prospective auditing and feedback, and restrictions via local pharmacy control
- Program 3: Programs 1 and 2 plus full prospective auditing and feedback, restrictions via ID control, and ID review of positive blood cultures and multidrug-resistant organisms

Only the hospitals that implemented Program 3 demonstrated reductions in antibiotic use from baseline. The more interventions implemented, the greater the impact on the duration of antibiotic use. Dr. Stenehjem said the most unexpected finding was the extensive use of an ID hotline, which provided facilities unprecedented access to an ID specialist and demonstrated the

importance of providing support for all hospitals so that clinicians can review patient management and drug use. Dr. Stenehjem also noted that without the push to address stewardship from CMS, CDC, and The Joint Commission, Intermountain might not have pursued the issue.

As a result of the trial, Intermountain is instituting a telehealth program that will ensure all of its hospitals have access to an ID specialist. Eventually, hospitals outside the system will also have access. Intermountain is also tracking antibiotic use with internal benchmarking data. Dr. Stenehjem said more quality metrics are needed to help facilities better assess status and needs. He concluded that there is still no good mechanism for measuring the factors that go into evaluating appropriateness of antibiotic use.

Improving Antibiotic Use in Outpatient and Long-Term Care Settings

CAPT Lauri Hicks, D.O., CDC

CAPT Hicks cautioned against applying a one-size-fits-all mindset for improving antibiotic use to all settings. She focused on improving use as one of the three factors in the CDC triad that supports patient safety. Ideally, every patient will receive antibiotics only when needed, with the right drug selection, dose, and duration; every facility will have effective antibiotic use programs; and every provider will incorporate antibiotic stewardship principles, regardless of the size of the practice. CDC gathers data to better understand variations in antibiotic use across the United States as a first step toward the goal of reducing inappropriate use by 50 percent by 2020.

The United States uses more antibiotics than other countries, and a lot of that is unnecessary use, especially for respiratory conditions. CAPT Hicks said CDC is working to understand and address opportunities to improve antibiotic use in dental offices, retail clinics, and urgent care centers. Evidence indicates as much as 75 percent of antibiotic use in nursing homes is inappropriate. To gather more detailed information about nursing homes, CDC is conducting surveys, purchasing proprietary data, and funding a network to implement CDC's core elements in nursing homes.

CDC's Get Smart campaign was launched in 2003, building off a national campaign for appropriate antibiotic use that began in 1995. Get Smart focused initially on improving antibiotic use by physician offices for respiratory infections and later expanded to include hospitals and long-term care facilities. It has since added the goals of improving the quality of health care and preventing infections. The campaign grows every year, said CAPT Hicks, and is being implemented in other countries. CAPT Hicks described a number of efforts underway by CDC to address gaps, recognizing that increasing partnerships with CMS, private payers, the American Medical Association, and non-physician providers are all opportunities for improvement.

Improving Antibiotic Use in the Veterinary Setting

William Flynn, D.V.M, M.S. Deputy Director for Science Policy, Center for Veterinary Medicine, FDA

Dr. Flynn explained that the judicious use or stewardship of antibiotics in veterinary settings is affected by the wide variety of 1) animal species, 2) husbandry practices, and 3) stakeholders. Veterinary practices may address major food-producing animals such as cows and chickens or minor ones such as goats and honey bees. They also treat companion animals and exotic species.

Husbandry practices may involve managing disease or preventing outbreaks among very large groups of animals. The size of a farm operation can affect the density of the animal population and the rigor of disease control measures. Fostering judicious use practices on farms requires collaboration among numerous stakeholders, including the feed and pharmaceutical industries, distributors, retailers, and regulators.

To address these variations, Dr. Flynn said products for animal use should be better aligned with good stewardship practices by, for example, better labeling and more information to help assess products. Second, antimicrobial stewardship practices should be implemented or reinforced in all veterinary settings. Third, monitoring should be enhanced to assess antimicrobial use and resistance and to determine whether stewardship efforts are effective.

Toward these ends, FDA has published guidance to ensure that the labeled use conditions of medically important antimicrobials are consistent with judicious use and stewardship principles. Dr. Flynn said there is more to do, however, and FDA is seeking input on additional steps around appropriate dosages, veterinary oversight, and antimicrobial stewardship programs affecting companion animals.

While many stakeholders play a role in implementing or reinforcing stewardship in veterinary settings, the diversity of settings poses challenges. However, FDA, academia, veterinarians, and industry all have activities underway to promote improved stewardship. Further progress can be bolstered by better defining judicious use, outlining practical strategies for implementation, developing tools to promote optimal use of antimicrobials, and developing alternatives to using medically important antimicrobials.

Finally, better monitoring and appropriate indicators are needed. Success should not be defined solely as reduced use or sales of antimicrobials, but rather improved use that curbs the development of resistance. In addition to wide variations in settings and the different infrastructures of animal and human health care, the lack of funding for data systems has delayed data collection. However, USDA has planned to conduct surveys (pending funding), and FDA has already awarded two grants and plans to do more around data collection.

Discussion

John H. Rex, M.D., said there are frequent efforts to incorporate stewardship principles into new drug development, and he asked whether product labeling is an issue among providers. CAPT Hicks replied that some drugs for respiratory infections are approved for a wide range of indications while clinical guidelines suggest narrower use. She sees opportunities to work with FDA on the topic.

Ms. Cole pointed out that Intermountain Healthcare would not have moved forward on stewardship without national policies around the issue. She asked CMS to consider requiring facilities in states receiving federal funding to have ID liaison programs as a COP. She said facilities should not have the option to refuse intervention from infection preventionists on their stewardship or infection prevention programs. Dr. Ling described the federal rulemaking that CMS follows and the process for addressing violations of the COPs.

Asked by Helen W. Boucher, M.D., FIDSA, FACP, to comment on key elements of success in the Intermountain trial, Dr. Stenehjem said working closely with the hospitalists was very important. Once relationships were established, hospitalists were comfortable consulting with ID specialists for support, which led them to reduce their antibiotic prescribing.

Peter Robert Davies, B.V.Sc., Ph.D., noted that on the animal side, there is no clear understanding of what constitutes appropriate use, and on the human side, there is a need to better link treatment with patient outcomes. On the animal side, there is more enthusiasm for researching alternatives, which has not been very fruitful in other parts of the world, than for applied research to understand outcomes and risks. Dr. Davies worried about the lack of funding and trained workforce to conduct applied research on animal health. He called for more debate about investing in research on alternatives versus optimizing current use.

Innovation

Antibiotic-Resistance Research and Implementation

James Cleeman, M.D., Agency for Healthcare Research and Quality (AHRQ)

Dr. Cleeman said innovation in CARB means innovation not just in products and technology but also in stewardship and prevention. As one example of innovation in stewardship, Dr. Cleeman described a study using a personalized antibiogram that helps determine the appropriate regimen and dosage for treatment and is incorporated into the patient's electronic health record. Another is looking at evidence-based and informal influences on providers' use of antibiotics in nursing homes. The results will inform clinical decision-making tools. A third project is comparing strategies for implementing stewardship in nursing homes to determine the most effective approaches.

Innovations in implementation include the application of the Comprehensive Unit-Based Safety Program (CUSP)—developed by AHRQ and used successfully for HAI prevention—to antibiotic stewardship. Also, AHRQ is field-testing an implementation guide for nursing homes and creating a toolkit for reducing *C. difficile* infections through stewardship.

Dr. Cleeman described trials to reduce transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant *Enterobacteriaceae* (CRE) using common cleaning and prevention approaches. AHRQ is disseminating information and tools to help facilities implement prevention efforts, such as results of the CDC-AHRQ joint project, the Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA (REDUCE MRSA) trial, and a clinician-friendly CRE control and prevention toolkit that combines CDC guidelines and quality improvement approaches. Other prevention efforts include extending the REDUCE MRSA study into nursing homes to evaluate the effectiveness of a universal decolonization protocol. Another study will assess novel electronic monitoring of hand hygiene compliance in pediatric long-term care facilities. Dr. Cleeman described several efforts to adapt CUSP to further prevent specific HAIs in various settings.

AHRQ recently announced two new funding opportunities that support CARB innovation across all of these domains, including stewardship in various settings and the role of rapid diagnostics in clinical care. Additional funding is available for HAI prevention, and applicants can submit proposals for consideration under either the CARB or HAI funding opportunities.

Innovative Approaches to Preventing Infections and Improving Antibiotic Use

Clifford McDonald, M.D., CDC

Dr. McDonald said CDC focuses on current effective prevention interventions but recognizes the need for innovative approaches for the future. He described the factors associated with antibiotic-resistant HAIs and strategies to prevent them. HICPAC plays an important role in evaluating evidence, advising on the CDC research portfolio, and putting innovations into practice.

CDC provided $30 million in new antibiotic resistance research and innovation awards in 2016. Projects funded addressed, for example, new electronic outbreak detection methods, duration of antibiotic use, and use of personal protective equipment and hand hygiene. Standardizing assessment of environmental contamination is an important area of research, as there are no definitions of "clean." Another study seeks to understand the role of biofilms in infection transmission.

Whole genome sequencing is allowing investigators to see the impact of asymptomatic carriers of *C. difficile* in transmitting infections. Other efforts around *C. difficile* focus on acquired resistance and community and hospital sources of transmission. Dr. McDonald said *C. difficile* is the poster-child for a microbiome-mediated disease, and CDC is looking at categorizing microbiome disruption and promoting microbiome protection and restoration strategies. Similar strategies are part of the effort to combat CRE infections.

Microbiome susceptibility plays a huge role in antibiotic resistance, so CDC is focusing on understanding the effects of antibiotics on the microbiome. Dr. McDonald said applied research on protecting the microbiome will be key to improving antibiotic use and addressing antibiotic resistance in the future. Microbiome disruption indices could illustrate how an antibiotic affects a given patient—an example of personalized medicine. These indices would be used in conjunction with diagnostics of colonization. To assist with innovation, CDC and FDA created the Antibiotic Resistance Isolate Bank so that researchers and manufacturers have access to samples of the most recent resistant bacteria.

Alternatives to Antibiotics: Intramural Research

Cyril Gay, D.V.M., Ph.D., Agricultural Research Service (ARS), USDA

Dr. Gay pointed out that the availability of new, high-throughput genetic sequencing allows for a systems biology approach to research. Alternatives to antibiotics are broadly defined as substances that can replace therapeutic drugs, which are becoming increasingly ineffective against pathogenic bacteria, viruses, and parasites. A USDA-hosted workshop earlier this year on innovations in alternatives identified several product categories:

- Vaccines that result in reduced use of medically important antibiotics, whether that involves new or more effective vaccines
- Microbial-related products and approaches, such as fecal transplant, and organisms that better support or develop immunity

- Immune-related products and the application of new genetic information to address or prevent disease (e.g., immune-building antibodies added to animal feed to prevent disease)
- Chemicals

Dr. Gay said a lot of basic research is underway but more work is needed to translate findings into useful alternatives to antibiotics. An upcoming meeting organized by USDA and the World Organization for Animal Health (OIE) will delve into the categories further. It will include a session on regulatory pathways and will also look at product partnerships and incentives for the pharmaceutical industry to invest in these new technologies.

Alternatives to Antibiotics: Extramural Research

Mervalin Morant, Ph.D., National Institute of Food and Agriculture (NIFA), USDA

Dr. Morant explained that NIFA supports extramural research as well as education and extension. Education efforts are formal, such as curriculum development, while extension is the informal dissemination of information.

Antimicrobial resistance falls under the Agriculture and Food Research Initiative's competitive challenge grant program, which requires applicants focusing on antimicrobial resistance to address two of NIFA's three domains—research, education, and extension. A foundational funding program in 2016 supports research on understanding antimicrobial resistance and alternatives to antibiotics. (Dr. Morant pointed out that USDA had $1 million for the foundational program but does not have any guarantee of continued funding after 2016.) The challenge grant program requires grantees to create interdisciplinary teams working at an ecosystem level to better understand, characterize, and mitigate antimicrobial resistance across the food chain.

Dr. Morant said the challenge grant began in 2012 with $3 million (supporting three grantees), and rose to $6 million by 2016. NIFA stretched its dollars by postponing final payouts on grants awarded earlier in the program. Currently, standard grants receive about $1 million. Some universities receive small seed grants of $150,000 per year for a couple years to help them become more competitive. NIFA received 44 applications for challenge grants in 2016. The foundational grants will support two awards of $500,000 each. Through 2015, NIFA had spent $11 million on the challenge grant program.

Current awardees are working around the country and collaborating with peers at multiple sites; grants cover a variety of species. The investigators have developed relationships that allow them to conduct on-farm research and to pass their findings and knowledge on to the farmers and animal care providers. The grantees are successfully integrating research with education and extension while also working with the private sector, FDA, and others, Dr. Morant concluded.

Discussion

In response to Kent E. Kester, M.D., FACP, FIDSA, FASTMH, Dr. Morant said USDA is in discussions with other federal agencies about possibilities for collaboration. She cautioned that collaboration across regulatory agencies is complicated by regulatory language and

requirements. Dr. Morant said NIFA's funding opportunities encourage grantees to make connections with other agencies and leverage whatever other resources they can.

Ms. Cole asked for more details about new environmental cleaning methods and how CDC is promoting adoption of its cleaning guidelines. Dr. McDonald said efforts are underway to model transmission dynamics. He thinks daily cleaning may be one approach to reducing transmission. Dr. McDonald said the first step in promulgating guidelines might focus on what is being done and what is achievable, with later efforts looking at what level of contamination equates with risk. He said facilities are cleaner now than they were 10 years ago and there is more acknowledgement that environmental services are part of infection control. The barriers to implementation are around processes, Dr. McDonald concluded, but progress is being made.

Thomas R. Shryock, Ph.D., asked whether the goal of USDA's intramural research is to support basic research that can eventually translate to product development in the private sector or to develop products or both. Dr. Gay responded that ARS aims to provide whatever research is needed, basic or applied. In the world of animal health, research needs to move beyond proof of concept. ARS supports some innovative research and has animal models to test efficacy, but it is important to identify incentives that will persuade the private sector to take an intervention to market, said Dr. Gay. ARS does a good job of collaborating with corporate, academic, and international partners, he noted.

Summary of Request for Information (RFI) Responses

Martin J. Blaser, M.D., Chair, and Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair

In April 2016, PACCARB put out an RFI on current programs and practices around antibiotic stewardship and CARB. It posed five requests:

1. Describe how organizations are influencing curricula regarding primary prevention (antibiotic stewardship, infection prevention, and control).
2. Describe how health care organizations can best:
   (a) educate and provide feedback to providers in clinics/facilities about ID diagnostic testing, optimal antibiotic prescribing, and infection prevention.
   (b) encourage and/or incentivize providers to report antibiotic use and resistance data for all patient populations.
3. Please provide examples of successful behavior change models that can be applied to preventive strategies, such as infection control and antibiotic stewardship.
4. Please provide information on the best ways to collect data on antibiotic use (and resistance) in animal agriculture through public-private collaborations.
5. Please provide information on the different resources that exist to promote the understanding of how antibiotics are being used in humans and animals in different parts of the world.

Drs. Blaser and King summarized the nature of responses to each question. Responses came from a range of stakeholders, including medical and professional societies, hospitals, academic institutions, pharmaceutical companies, food producers, patient advocates, and individual providers. Some responses provided specific, targeted suggestions, while others offered broad

recommendations. The collected input will inform PACCARB deliberations. The responses will be made available online later on this year.

Public Comments

David Joseph of Avisa Pharma Inc. described his company's novel breath test technology, a quantitative, point-of-care, whole-lung test for rapidly detecting pulmonary infections caused by certain urease pathogens. It is inexpensive and easy to administer. It provides critical clinical information in less than 10 minutes. Mr. Joseph explained how the test works, noting that it has powerful negative predictive value, which would help physicians decrease the use of antibiotics. Mr. Joseph said that despite the strong public health need for such tests, CMS has lumped this test with diagnostic laboratory tests and designated it for packaged payment under Medicare's Hospital Outpatient Prospective Payment System. The lack of adequate reimbursement makes it extremely difficult for Avisa and other companies to attract the investment needed to bring the test to market.

Mr. Joseph asked the Council to encourage CMS to exclude rapid point-of-care tests such as the Avisa breath test from packaged payment. More broadly, he asked the Council to consider reimbursement incentives that can encourage manufacturers to bring to market other new technologies that will end the fight against antibiotic resistance.

John Boyce of J.M. Boyce Consulting, LLC, hoped the Council would give greater importance to strategies that have been shown to directly reduce transmission of resistant pathogens, such as hand hygiene. The important role of hand hygiene is supported by a number of mathematical models, including some that demonstrate it is more effective at reducing the spread of antibiotic-resistant bacteria than is limiting the duration of antibiotic use. Mr. Boyce encouraged the Council to add improving hand hygiene as one of its strategies to achieve National Action Plan Goal 1 of reducing the spread of resistant bacteria. He also encouraged the Council to seek funding to expand national efforts to improve hand hygiene in health care facilities.

Sheila Heitzig of the American Academy of Allergy, Asthma, and Immunology presented her organization's recently finalized position statement on encouraging penicillin allergy testing as a means of addressing antibiotic stewardship. She said that 10 percent or more of U.S. adults have a penicillin allergy noted in their electronic medical record, yet more than 95 percent of those are able to take penicillin without any allergic reaction. The Academy believes this discrepancy represents an important opportunity to relieve some pressure on other antibiotic products. Such testing can result in reduced use of health care resources and improved patient outcomes. Ms. Heitzig said her organization welcomes an opportunity for further discussion about this testing process.

Kevin Kavanagh representing Health Watch USA said the FDA should expand its ban on antimicrobial agents in household soaps to encompass other over-the-counter disinfectants and products, especially last-line-of-defense antibiotics found in topical ointments, such as polymyxin B found in Polysporin, Neosporin, and triple antibiotic ointment.

Clearly, antibiotic stewardship is important, but there appears to be a disconnect between concerns regarding low levels of environmental contamination from agriculture and animal

husbandry versus those associated with household products. Low levels of contamination are optimal for promoting resistance. In addition, said Mr. Kavanagh, much work needs to be done to prevent patient-to-patient transmission. Standards are too lax, and those that exist lack the specificity needed for controlling highly infectious dangerous pathogens, such as MRSA. In the United States, MRSA bloodstream infections were trending downward, but recent reports and Hospital Compare show the trend rising.

The Council should guard against the appearance of deflection with their concentration on efforts with agriculture and funding of the pharmaceutical industry, Mr. Kavanagh continued. This Council needs to ensure that health care institutions make the needed investments in prevention and patient safety, along with setting well-defined standards for screening, isolation, environmental cleaning, appropriate staffing, and worker safety. Finally, in response to Dr. Cleeman's presentation, Mr. Kavanagh said that, in his opinion, there are some significant research integrity problems with the REDUCE-MRSA study, and he recommended caution in using it to direct national policy.

Amanda Jezek of the Infectious Diseases Society of America (IDSA) said that prioritizing resources will be very challenging because antibiotic resistance is complex, and multiple solutions are necessary. A One Health approach involving human, animal, and environmental health is essential. Robust data collection and surveillance on antibiotic use and resistance patterns are needed to better understand the problems and evaluate interventions. Stewardship is also needed, and IDSA is encouraged by recent progress. IDSA strongly encourages CMS to finalize this year its proposals for stewardship requirements in all hospitals and long-term care facilities.

IDSA is an eager partner in these efforts. It is developing a new training curriculum and offering robust continuing medical education to ensure that ID physicians are ready to lead stewardship programs. IDSA also recognizes that preventing infections is the best way to protect patients and limit the need to use antibiotics. Incentives for antibiotic and diagnostics are also necessary. We cannot prevent every infection, and, even with stewardship, bacteria continue to evolve. A robust and renewable antibiotic pipeline is needed for current patients with hard-to-treat infections and future patients who will face tomorrow's threats. Bold economic incentives and innovative regulatory pathways are needed to achieve this goal.

Lastly, a strong ID physician workforce is needed to carry out much of this work. Unfortunately fewer and fewer young physicians are pursuing such training, and without new investment, we may not have the next generation of ID physicians that we need, said Ms. Jezek. However, this week's United Nations meeting on antimicrobial resistance signifies an unprecedented international focus on this issue and presents a tremendous opportunity to catalyze meaningful change for patients in public health. Now is the time for the United States to lead the world in bold and robust approaches to combat resistance.

Carole Moss said she is an experienced patient safety advocate based in California. She asked that the Council's meeting allow time for survivors and families of survivors to share their personal stories. When PACCARB was put together about a year ago, said Ms. Moss, advocates were hopeful and thankful that finally a team of experts would be focused on solutions to reduce

the harm that happens daily in hospitals, health care facilities, and communities. Given the level of expertise and credentials of the members, there was hope that PACCARB would create a basic plan of action that the public could rally around and that would reduce the numbers of deaths and suffering from antibiotic-resistant bacterial infections, just like other countries have done.

But after a full year of participating in these meetings, the level of hope and enthusiasm has dramatically changed. Until today, said Ms. Moss, the public has seen no actionable effort on PACCARB's part to end this preventable epidemic of hospital-acquired infections as a priority. This issue does not need new clinical trials or new antibiotics. Rather, affordable, point-of-care, rapid diagnostic solutions for viruses or bacteria should be expedited, and hospitals should be required to use them. Proven best practices for preventing the spread of antibiotic-resistant bacterial infections should be enforced in health care facilities among inpatient and outpatients. Bedless hospitals are here, and they are a game-changer. We need to get back to basics: cleaning, screening, and isolating patients. Ms. Moss said PACCARB needs to give back to the many victims and their families a sense of hope, otherwise this is just another committee that has no spirit.

Lisa McGiffert of Consumer's Union called on PACCARB to use the power of CMS to shape proper antibiotic use through payment incentives and policies. For example, CMS should require that the diagnosis and indication for a prescription be included on every prescription. Information from pharmacies certified to serve Medicare patients should be available to CMS as well as to other government agencies like CDC without having to pay a lot of money for proprietary information. This is a public health crisis, and we need to use the power that we have to get that information out so we can target where the problems are and who needs to do the most work, said Ms. McGiffert.

Consumer's Union recommends using payment incentives to increase use of rapid testing. Also, there should be accountability for stewardship programs, because if it is not mandated, it does not get done. Accountability should occur through tracking of antibiotic use and antibiotic resistance locally. Ms. McGiffert said CMS can facilitate a solution to this problem by requiring the enforcement side of the system to collaborate with the helping side. There is a firewall between infection control experts and the people in the health departments who inspect and respond to complaints. They do not talk to each other, and they do not share information. The health departments have enforcement power, and the experts do not. When an inspector finds a problem with infection control, that inspector should be armed with information about the history of that hospital's infection record and should be able to mandate that experts in the infection control division go in and help that hospital. Right now those experts have to wait to be invited. This has to change in order to create accountability for the lowest performing hospitals.

Christian John Lillis of the Peggy Lillis Foundation said he is troubled by the continued absence of patients and caregivers as presenters and witnesses before this panel. Ms. Cole is truly amazing but cannot alone represent the breadth and variety of patient advocacy in the community. This is not a minor issue. Patient safety advocates often say, "Nothing about me without me." Yet there is little input from patients to PACCARB outside of the public comment period. Mr. Lillis read aloud the names of 17 people who died as a result of antibiotic-resistant infections so that they would be recognized and counted (please refer to the PACCARB webcast

to hear the full comment and list of names: http://www.hhs.gov/ash/advisory-committees/paccarb/meetings/upcoming-meetings/september-19-2016-public-meeting/index.html). He implored PACCARB and all those in charge of the health and safety of our citizens to do better at ensuring patients and caregivers are represented in forums like this one.

Mae Wu with the Natural Resources Defense Council said it is clear that there is a huge gap between what is being done on the human side and the animal side. On the human side, regulations and requirements to receive funding have been essential to getting needed changes implemented. Programs rely on data on how and why antibiotics are used to manage resistance. Volumes are important. The most basic metric of a program is whether or not it results in lowered antibiotic use. We know what pathogens are the problems, and what types of uses need to be eliminated.

On the animal side, there is no clear description of the problem and a lack of data on how and why antibiotics are used on the farm level. The FDA has not set targets for reduction in use. To target prevention of the resistance, we need to know what are the major reasons for the use of antibiotics, said Ms. Wu. The USDA should be able to list the conditions that result in the most use and focus prevention measures on those uses.

Stewardship is difficult enough in hospitals. Today's meeting illustrated how some hospitals could not get approval for needed changes to better manage resistance until a new regulation required it. In humans, it may be inappropriate to give someone an antibiotic for a respiratory infection, but in animals, antibiotics are regularly used without signs of illness for disease.

The ultimate objective of the European Commission's animal programs is to prevent disease in order to avoid antibiotics. They do not have programs that use antibiotics in the name of preventing disease, as the FDA does in this country. As Dr. Flynn mentioned, this use could be continuous for months on end. We have to find ways to use fewer antibiotics, said Ms. Wu. Just today, the Department for Environment, Food, and Rural Affairs in the United Kingdom committed to reduce its antibiotics in agriculture by 18 percent by 2018. The Natural Resources Defense Council recommends new policies in animal agriculture that promote reducing antibiotic use by preventing disease, rather than promoting the use of antibiotics in the name of preventing disease.

The PACCARB members reviewed additional comments submitted in writing.

Council Reflections

Dr. Blaser invited Council members to reflect on the proceedings of the day. Robert A. Weinstein, M.D., said more antibiotic use data are needed; some human data may come from CMS initiatives, but there does not appear to be any mechanisms to gather animal data. He also called for more public reporting of long-term infection control activities. Publicizing such information drives hospital improvements. Dr. Weinstein said he believed some of the simple infection control practices used in humans should be considered for animals, because the example from Dr. McCluskey about moving from continuous flow to the all-in, all-out approach in swine was a practice adopted in hospital nurseries 70 years ago. Finally, Dr. Weinstein

advocated for collaboration with HICPAC to ensure that prevention activities and proven guidelines are promulgated.

Dr. Caliendo said multiple people have brought up throughout the day the notion of a diagnostic that can distinguish infection from no infection or virus from bacteria, but the reality is that no such test exists, which speaks to the need for continued investment and development. Dr. Caliendo noted that some tests may be helpful but are not being used, and she pointed to a comment in response to the RFI suggesting that clinical microbiology laboratories should be directed to upgrade their technology. She acknowledged that cost is a barrier. Finally, providers should not only use rapid tests that are available but also trust the results, which requires changing behavior.

Dr. Kester was impressed by the example from Intermountain Healthcare as one case study of a best practice to try to optimize antibiotic stewardship within an integrated health system. Yet the Council is also hearing that ID as a specialty is becoming less and less attractive for medical school graduates. Most antibiotic prescriptions are not written by ID clinicians. Dr. Kester said the workforce issue should be considered as important as research and development, and PACCARB should consider how it can influence practice, policy, and opinion. Finally, Dr. Kester felt that USDA and FDA should consider joint funding of projects and initiatives around topics of mutual interest.

Helen W. Boucher, M.D., FIDSA, FACP, suggested PACCARB discuss synergizing human and animal epidemiology and intervention studies. She said IDSA research indicates the top reason that medical students do not pursue ID as a specialty is the compensation. From a policy perspective, there should be increased focus on “intellectual” medicine, as compared with “procedural” medicine. Dr. Boucher hoped federal agencies would consider the distinctions in their reimbursement decisions.

Ms. Cole said a common theme of the presentations was the need for funding and policies. Where there is funding, however, it should be tied to policy, so that all of the innovations, incentives, programs, and studies do not rely on voluntary implementation. Where there are evidence-based best practices, policies should ensure that end-users can incorporate them. Ms. Cole pointed out that PACCARB and the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (or CARB-X) are both concentrating on National Action Plan Goals 3, 4, and 5. PACCARB should also look more closely at goals 1 and 2—preventing the spread of infections and strengthening surveillance.

Dr. Cosgrove said now that more stewardship and infection control policies are in place, efforts should be made to ensure that hospital surveyors and accreditors truly understand what constitutes effective implementation. She called for close attention to implementation and evaluation of the implementation.

Dr. Wagstrom said that as farm operations have gotten bigger, they are more likely to take advantage of efficiencies of scale. Just as the largest hospitals are most likely to establish antibiotic stewardship programs, large farms may be able to establish stewardship programs,

provide standard operating procedures for antibiotic use and veterinary oversight, and perhaps provide electronic records to track antibiotic use.

Ramanan Laxminarayan, Ph.D., M.P.H., said CDC's successful efforts to reduce HAIs are encouraging, particularly as recent literature shows no change in antibiotic use per capita in hospitals from 2006 to 2012. CMS involvement is critical, as it can drive appropriate practice through reimbursement policies.

Dr. Laxminarayan hoped PACCARB would be more ambitious on stewardship. He said the amount of money you should be willing to pay to delay an investment of a billion dollars on a new antibiotic is really the interest rate you will get on the billion dollars. If the entire stock of antibiotics in use now is worth $100 billion, at an interest rate of 5 percent, we should be willing to pay $5 billion a year just to delay the investment for another year, but we do not spend anything close to that. Dr. Laxminarayan said more investment is needed. However, it is often easier to organize activities to encourage new technology and products than promote traditional prevention mechanisms such as hand hygiene.

Dr. Laxminarayan also said the One Health philosophy is not coming through strongly in activities so far. He hoped that PACCARB would encourage funding and activities to address One Health priorities, but he said creative thinking is needed to do so. Currently, representatives of human and animal health are giving parallel presentations to PACCARB, but PACCARB needs to consider how to bring One Health to life.

Aileen M. Marty, M.D., FACP, said the proceedings underline the key problem, which is a disjointed health care system that complicates efforts to combat antibiotic resistance. Left to their own devices, every industry will pursue solutions that have worked in the past. Organizations are reluctant to cede control of decision-making power and resources to allow for policies that streamline the cost of health care and lead to the best practice for the population, not just for one individual group. PACCARB needs to integrate animal and human efforts for all relevant areas, from hand washing to research to surveillance to stewardship to basic human kindness. The Council's work should help toward achieving a solution to antibiotic resistance that is multifactorial and includes economic and social science. The members' commitment can achieve something that at times seems somewhat impossible, said Dr. Marty.

Dr. King praised the Intermountain model, which highlighted the importance of having support available to help clinicians do the right thing and change behavior when needed. He noted that USDA's funding for research is a fraction of that provided by the National Institutes of Health (NIH) for human research, and until that disparity is addressed, the One Health approach will never come to fruition. Dr. King appreciated the reminder from all of CDC's presenters that patient safety is at the center of all efforts. He acknowledged that some interventions are changing behavior, and more research is needed to understand why those interventions worked. Dr. King pointed out that leadership is vital for successful stewardship.

Finally, Dr. King appreciated Ms. Cole's efforts to remind the Council about what patients affected by antibiotic-resistant bacteria go through. He said that while not all of the Council members have undergone such experiences, all are patient advocates.

Dr. Blaser also appreciated how CDC linked patient safety and stewardship. He said PACCARB will launch an initiative on stewardship in the coming months. Dr. Blaser was encouraged by CMS' presentations and noted that CMS has the muscle to make things happen. He was also encouraged by the events of this week focusing on antimicrobial resistance at the United Nations, the World Bank, and the Food and Agricultural Organization and by the pharmaceutical industry. He was hopeful that there is momentum to overcome inertia.

Finally, Dr. Blaser thanked the public commenters for holding the Council's feet to the fire, because the issues at stake are important

Closing Remarks and Adjournment

Dr. Blaser said that in response to Secretary Burwell's request in March, PACCARB established working groups on incentives for development of therapeutics, diagnostics, and vaccines. Other efforts on prevention and stewardship will follow. On behalf of himself and Vice Chair Dr. King, Dr. Blaser thanked all of those involved in the meeting. He adjourned the meeting at 5:31 p.m.

I hereby certify that to the best of my knowledge, the foregoing minutes of the proceedings are accurate and complete.

Martin J. Blaser, M.D., Chair
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Appendix A: Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) Members

PACCARB Voting Members Present September 19, 2016

Martin J. Blaser, M.D., Chair
Michael D. Apley, D.V.M., Ph.D., DACVCP
Helen W. Boucher, M.D., FIDSA, FACP
Angela Caliendo, M.D., Ph.D., FIDSA
Alicia R. Cole
Sara E. Cosgrove, M.D., M.S.
Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair
Peter Robert Davies, B.V.Sc., Ph.D.
Kent E. Kester, M.D., FACP, FIDSA, FASTMH
Ramanan Laxminarayan, Ph.D., M.P.H.
Aileen M. Marty, M.D., FACP
John H. Rex, M.D.
Thomas R. Shryock, Ph.D.
Randall Singer, D.V.M., M.P.V.M., Ph.D. (by phone)
Robert A. Weinstein, M.D.

Organizational Liaisons Present

Animal Health Institute
Richard Carnevale, V.M.D.

Association of State and Territorial Health Officials
Jay C. Butler, M.D. (by phone)

National Pork Producers Council
Elizabeth Allen Wagstrom, D.V.M., M.S.

The Pew Charitable Trusts
Elizabeth Jungman, J.D., M.P.H.

Ex Officios Present

U.S. Department of Health and Human Services

Beth P. Bell, M.D., M.P.H. (alternate Michael Craig also present), Director, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention
Dennis M. Dixon, Ph.D. (alternate Jane Knisely also present), Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health
William Flynn D.V.M, M.S. (for Peter Lurie, M.D.), Deputy Director for Science Policy, Center for Veterinary Medicine, Food and Drug Administration
Shari Ling, M.D., Deputy Chief Medical Officer, Centers for Medicare and Medicaid Services

U. S. Department of Defense

David Smith, M.D., Deputy Assistant Secretary of Defense for Health Readiness Policy and Oversight

Paige Waterman, M.D., FACP, FIDSA, Antimicrobial Resistance Lead, Armed Forces Health Surveillance Center-Global Emerging Infectious Disease Surveillance

U. S. Department of Agriculture

Neena Anandaraman D.V.M, M.P.H. (for Steve Kappes, Ph.D.), Veterinary Science Policy Advisor, Agricultural Research Service

David Goldman, M.D., Chief Medical Officer and Assistant Administrator, Office of Public Health Science, Food Safety and Inspection Service

Brian McCluskey, D.V.M., Ph.D., Associate Deputy Administrator, Animal and Plant Health Inspection Service

Designated Federal Official

Bruce G. Gellin, M.D., M.P.H., Deputy Assistant Secretary for Health, Office of the Assistant Secretary for Health, Department of Health and Human Services

Advisory Council Staff

Tiffany Allen Archuleta, M.P.H., M.Ed., Senior Research Coordinator, PACCARB, New York University Langone Medical Center

Laura Gottschalk, Ph.D., ORISE Fellow

Jomana F. Musmar, M.S., Ph.Dc., Advisory Council Manager, Office of the Assistant Secretary for Health, Department of Health and Human Services

MacKenzie Robertson, Committee Management Officer, Office of the Assistant Secretary for Health, Department of Health and Human Services

Ayah O. Wali, M.P.H., Committee Management Officer, Office of the Assistant Secretary for Health, Department of Health and Human Services

Glossary of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
ARS	Agricultural Research Service
CARB	combating antibiotic-resistant bacteria
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
COPs	Conditions of Participation
CRE	carbapenem-resistant *Enterobacteriaceae*
CUSP	Comprehensive Unit-Based Safety Program
FDA	Food and Drug Administration
HAI	health-care-associated infection
HHS	Department of Health and Human Services
HICPAC	Healthcare Infection Control Practices Advisory Committee
ID	infectious disease
IDSA	Infectious Diseases Society of America
MRSA	methicillin-resistant *Staphylococcus aureus*
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
NHSN	National Healthcare Safety Network
NIFA	National Institute of Food and Agriculture
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
REDUCE MRSA	Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate methicillin-resistant *Staphylococcus aureus*
RFI	request for information
USDA	U.S. Department of Agriculture