

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases Research in
Combating Antibiotic Resistance

Testimony before the
House Energy and Commerce Committee
Subcommittee on Oversight and Investigations

Dennis M. Dixon, Ph.D.
Chief, Bacteriology and Mycology Branch
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases

June 14, 2016

Mr. Chairman, Ranking Member DeGette, and members of the Committee, thank you for the opportunity to discuss antibiotic resistance, a serious and growing global health threat. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute at the National Institutes of Health (NIH) for conducting and supporting research on infectious diseases, including research on antibiotic resistance.

NIAID has a dual mandate to balance a robust research portfolio in established infectious and immunologic diseases with the capacity to respond quickly to newly emerging and re-emerging infectious diseases. Infections resistant to currently available antibiotics are among the most urgent of these emerging threats.

Antibiotic resistance is a multifaceted problem, and multiple approaches are being undertaken to work toward a comprehensive solution. These include bolstering surveillance, diagnostic capacity, hospital infection control, and the prudent use of antibiotics in both humans and animals. Biomedical research also is essential to address the problem. NIAID's longstanding research efforts in this area aim to understand the molecular basis of antibiotic resistance, to develop specific and sensitive diagnostics, to develop vaccines to prevent infections prone to resistance to antibiotics, and, importantly, to partner with the pharmaceutical industry to develop novel and improved interventions.

Antibiotic Resistance

The development and use of antibiotics to treat bacterial infections are among the greatest achievements of modern medicine. However, many of these drugs have become less effective over time as resistance to them has emerged and spread globally. The Centers for Disease Control and Prevention (CDC) estimates that each year in the United States, at least 2 million

people become infected with antibiotic-resistant bacteria and at least 23,000 people die as a result of these infections. CDC has identified the most serious antibiotic resistance threats in the United States including carbapenem-resistant Enterobacteriaceae (CRE), *Clostridium difficile*, *Neisseria gonorrhoeae*, and drug-resistant strains of *Staphylococcus aureus* such as methicillin-resistant *S. aureus* (MRSA).

The recent detection in the United States of bacteria resistant to colistin, an antibiotic of last resort, reminds us of the urgent challenge of drug resistance and the need to address its underlying causes. We were fortunate that this particular bacterial strain was treatable by other antibiotics; however, the threat remains that this type of resistance could emerge in other bacteria already resistant to most antibiotics, making them untreatable with currently available drugs.

White House Initiative on Combating Antibiotic-Resistant Bacteria

In 2014, the Administration announced a comprehensive set of new federal actions to combat the rise of antibiotic-resistant bacteria and protect public health, including the National Strategy and National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB). Key participants in the CARB effort include NIH; CDC; the Food and Drug Administration (FDA); the Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA); the United States Department of Agriculture; the Department of Defense; and others.

NIAID plays a critical role in the CARB initiative through our research mission. Additional funding provided by Congress in fiscal year (FY) 2016 has been instrumental to our efforts, particularly in the areas of microbial genome sequencing, diagnostics and drug development, and clinical research, as described below.

In addition, NIAID is participating in the Administration's National Action Plan for Combating Multidrug-Resistant Tuberculosis (MDR TB). The emergence of TB that is resistant to multiple antibiotics is a growing global concern. NIAID is leading research efforts to accelerate basic and applied research and development to combat MDR TB. This research complements other CARB efforts that target this increasingly prevalent drug-resistant infection.

NIAID Research Addressing Antibiotic Resistance

As outlined in the 2014 report entitled, "NIAID's Antibacterial Research Program: Current Status and Future Directions," NIAID supports a robust research portfolio that includes basic research on how bacteria develop resistance and cause disease; translational research to develop diagnostics, therapeutics, and vaccines; and clinical research to evaluate antibacterial products and strategies.

Basic Research and Research Resources to Facilitate Product Development

NIAID intramural scientists and extramural grantees are conducting basic research to understand microbial pathogenesis, including how bacteria colonize our bodies and evade immune defenses. NIAID-supported research also aims to discover mechanisms of antibiotic resistance. Basic research provides the foundational knowledge essential for the development of vaccines to prevent antibiotic-resistant infections and therapeutics to treat them. For example, NIAID researchers discovered that *S. aureus* produces peptide toxins critical for bacterial growth and pathogenesis in a mouse model, suggesting that the toxins themselves may be a target for development of new drugs for this important pathogen that may become resistant to methicillin or other drugs.

High-throughput genome sequencing efforts also are leading to a better understanding of bacterial pathogenesis and how antibiotic resistance develops. NIAID supports genome sequencing for a national genome sequence database of antibiotic-resistant bacteria as part of the CARB initiative. This database, being developed by NIH in collaboration with FDA and CDC, will provide a comprehensive resource for surveillance, epidemiology, and basic research into the mechanisms of antibiotic resistance. NIAID also funds a large-scale sequencing project to understand the genetics of drug resistance in TB. In addition, NIAID scientists and their colleagues have sequenced the complete genome of a drug-resistant strain of *Klebsiella pneumoniae*, which is a significant cause of hospital-acquired infections. This sequencing effort has revealed two different lineages of these bacteria with separate evolutionary histories, providing insight into the multiple pathways through which bacteria become resistant to antibiotics. Additionally, the NIAID-supported Bioinformatics Resource Centers have assembled the genome of the *Escherichia coli* containing the colistin resistance gene, *mcr-1*, isolated from the first patient in the United States (mentioned above), and has rapidly made it available to the research community for further study.

NIAID also provides a comprehensive set of research resources and services designed to reduce the risk to product developers and to help move concepts and candidate products along the research pipeline. These include genome sequencing, quality-controlled research reagents and clinical specimens, drug screening, and animal models to accelerate antibacterial product discovery.

In addition, NIAID is expanding its Antibiotic Resistance Leadership Group (ARLG) and other clinical trial networks, such as the Vaccine and Treatment Evaluation Units, for clinical research on antibiotic resistance. This expansion, facilitated by the CARB initiative and

associated funding, will increase the capacity to evaluate new antibacterial products and strategies and move needed countermeasures along the research and development pipeline.

Diagnostics

Rapid, point-of-care diagnostic tests can be important in determining precisely which drugs will be effective against a given infection, thereby reducing the inappropriate use of broad-spectrum antibiotics. Currently, broad-spectrum antibiotics that target a wide range of bacteria are often prescribed when a diagnosis is not available prior to starting treatment. The CARB initiative is incentivizing the development of rapid, point-of-care diagnostics to identify antibiotic-resistant bacteria and inform treatment of these infections. NIH and BARDA are collaborating to fund a \$20 million diagnostic prize, and NIH held a public consultation and web-based forum to solicit comments on the technical criteria and performance characteristics of diagnostics to be considered for the prize. In addition, NIAID recently awarded more than \$11 million in first-year funding for research projects supporting enhanced diagnostics to detect antibiotic-resistant bacteria. The grantees in this program will work to develop rapid, sensitive, and specific diagnostic tools that do not rely on the time-consuming process of growing the bacteria, which is how bacterial infections are often diagnosed currently.

NIAID also supports clinical studies through its ARLG to improve diagnosis of drug-resistant infections. The ARLG is developing a study to test procalcitonin, a biomarker that could help clinicians distinguish between bacterial and viral lower respiratory tract infections. Such a biomarker could help to reduce inappropriate use of antibiotics for viral infections, an important driver of the development of antibiotic resistance. Other ongoing ARLG studies are comparing the performance of existing diagnostics and validating new tools including platform diagnostics to rapidly identify antibiotic-resistant bacteria.

NIAID also has supported the development and validation of a test that can rapidly identify TB and simultaneously detect resistance to rifampicin, an antibiotic commonly used to treat TB. This test, and next-generation versions of the test, currently are being implemented in developing countries to diagnose TB, including drug-resistant TB.

Therapeutics

NIAID is screening new compounds and repurposing existing drugs to provide better options to treat antibiotic-resistant infections. In addition, many novel approaches are being explored, including monoclonal antibodies, bacteriophages, and strategies targeting the microbiome or the host immune system. NIAID recently awarded approximately \$5 million in funding for 24 research projects seeking to develop non-traditional therapeutics for bacterial infections. These awards are investigating novel therapies such as bacteriophages, probiotics, and nanoparticles to treat or prevent infections. NIAID intramural researchers also are exploring a novel treatment for TB called host-directed immunotherapy. Rather than targeting the bacteria directly, this approach involves manipulating the body's response to TB, using a regimen that includes zileuton, a clinically approved drug for asthma, to target components of the immune response. In addition, NIAID-supported scientists recently identified the drug teixobactin using an innovative iChip platform that allows researchers to screen natural products from bacteria that live in soil. This drug has a novel mechanism of action and has shown promise against several antibiotic-resistant microbes. Although teixobactin is still under development, potentially it could be a new tool to treat drug-resistant bacteria.

Optimizing the use of existing drugs also can help limit the development of antibiotic resistance. To this end, NIAID funds clinical studies testing new formulations, dosing regimens, or combination therapies of currently approved drugs such as colistin. NIAID-supported

researchers recently found evidence that two off-patent antibiotics, clindamycin and trimethoprim/sulfamethoxazole, work equally well against bacterial skin infections caused by MRSA, indicating that these infections can be treated successfully and inexpensively with either therapy. In addition, an ongoing NIAID-supported Phase IV clinical trial is comparing different combinations of existing antibiotics for treatment of gonorrhea, a disease for which drug resistance is a growing concern.

Vaccines

Developing vaccines to prevent infectious diseases can help prevent the inappropriate use of antibiotics and the development of antibiotic resistance. NIAID is developing vaccines to prevent infections for which treatment options are jeopardized by the emergence of drug resistance, notably staphylococcal infections and gonorrhea. Vaccines for viral infections such as influenza also may help reduce the use of antibiotics, which are often used inappropriately to treat viral infections, or appropriately used to treat bacterial infections that sometimes develop following viral infections. NIAID is working to develop vaccines for influenza, including several promising universal influenza vaccine candidates. A universal influenza vaccine could reduce or eliminate the need for annual seasonal influenza vaccines and provide long-lasting protection against multiple strains of influenza, including seasonal and pandemic influenza. Such a vaccine could lessen the burden of influenza and associated secondary bacterial infections, thereby reducing the need for antibiotics.

Conclusion

NIAID is committed to a robust and comprehensive research effort to address antibiotic resistance and is fostering collaborations with partners in academia, industry, and the federal

government. NIAID will continue to support promising research to develop and test new antibiotics as well as methods to help prevent the further spread of antibiotic resistance.