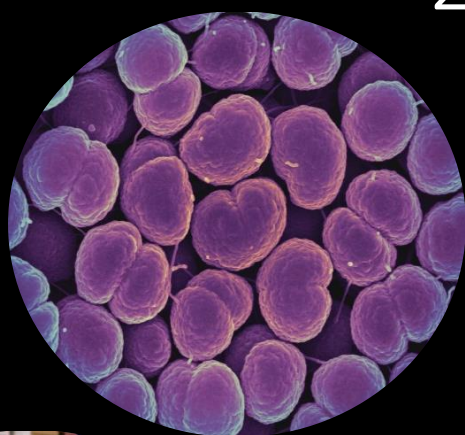
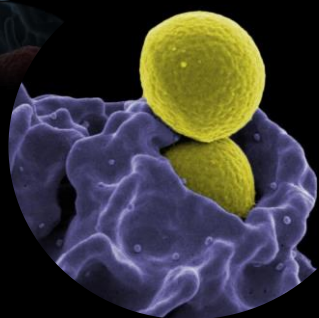
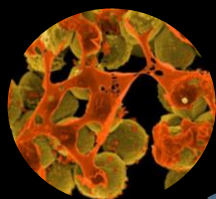


NIAID



NIAID'S Antibiotic Resistance Research Framework:

Current Status and Future Directions

2019



National Institute of Allergy and Infectious Diseases

NIAID's Antibiotic Resistance Research Framework: Current Status and Future Directions

Table of Contents

Executive Summary	1
Introduction	2
The Evolution and Accelerating Pace of Antibiotic Resistance (AR)	2
The Antibiotic Development Pipeline.....	3
NIAID: Stimulating Research on AR.....	3
Basic Research.....	3
Translational Research	4
Clinical Research.....	6
Research Resources	8
Partnerships Facilitate a Concerted Approach	9
Innovative Approaches to Addressing the AR Challenge.....	9
Conclusions	11
References	13
Appendix: 2014 Innovative Approaches and Select Accomplishments	15

NIAID's Antibiotic Resistance Research Framework: Current Status and Future Directions

Executive Summary

In 2015, the U.S. Government launched the [National Action Plan for Combating Antibiotic-Resistant Bacteria \(CARB\)](#), calling for a coordinated federal response to address the growing threat of antibiotic resistance (AR). The National Institute of Allergy and Infectious Diseases (NIAID)'s longstanding commitment to funding and conducting research related to AR is a critical component of this initiative. In 2008, NIAID made a public commitment to addressing AR through basic, translational, and clinical research¹. In 2014, NIAID documented the Institute's [significant progress in addressing AR](#) and outlined a combination of [innovative approaches](#) to be pursued as part of a comprehensive strategy. NIAID is again looking towards the future, reexamining goals, and modifying approaches to advance the field of AR research while building on previous successes.

AR is an inevitable outcome of the evolutionary principle that organisms will mutate to escape lethal selective pressure. A multifaceted approach including surveillance, infection control, improved antibiotic stewardship, new prevention measures, and new diagnostic and therapeutic strategies to combat resistant bacteria remain essential to mitigate this global threat. Increased recognition of the need for novel treatments and therapeutic approaches and the introduction of new Food and Drug Administration (FDA) regulatory approaches and incentives to facilitate antibiotic development are bringing renewed attention to this area. However, declining commercial interest in antibiotics threatens the future of the field. With some bacterial infections already untreatable by FDA-approved agents, it is imperative to continue to expand the antibiotic pipeline.

This report describes NIAID's portfolio of basic, translational, and clinical research in AR and outlines an updated array of innovative approaches based on the latest scientific advances and research opportunities to address this urgent public health priority.

Strategic Approaches to AR Research:

- **Leverage Data Science to Address AR** — Use computational approaches to integrate and analyze large, diverse datasets to accelerate the discovery and development of new therapeutics, diagnostics, and vaccines for resistant infections
- **Understand Antibiotic Failure** — Explore why antibiotics unexpectedly fail in patients with drug-sensitive infections
- **Harness the Immune System to Combat Bacterial Infections** — Enhance host immune responses through vaccines and immune-based products to prevent and treat bacterial infections
- **Realize the Promise of Rapid Diagnostics** — Develop rapid point-of-need diagnostics to facilitate appropriate treatment and antibiotic stewardship and conduct implementation studies on FDA-cleared/approved tests to demonstrate potential benefits for patient outcomes and healthcare costs
- **Reinvigorate Gram-negative Drug Discovery** — Develop tools and technologies to overcome the unique challenges of gram-negative bacteria and drive the discovery of new antibiotics for gram-negative infections
- **Non-antibiotic Products to Treat Resistant Infections** — Use non-traditional therapeutics, such as drugs that decrease bacterial virulence, live microbiome-based therapeutic products, and bacteriophages, to limit the emergence of resistance while preserving the microbiome
- **Optimize the Clinical Utility of Antibiotics** — Optimize the use of existing drugs and combination therapies to suppress the emergence of resistance and minimize toxicity

NIAID's Antibiotic Resistance Research Framework: Current Status and Future Directions

Introduction

In 2014, NIAID released a report, [NIAID's Antibacterial Research Program: Current Status and Future Directions](#), emphasizing the Institute's commitment to addressing this urgent public health threat. Since that time, NIAID has made significant progress through a robust and diverse set of activities spanning basic, translational, and clinical research. This updated research framework describes NIAID's current AR research portfolio, highlighting activities in each of these areas. In addition, the report provides updates on progress made in addressing the innovative approaches to combat AR laid out in the 2014 report (see [Appendix](#) for detailed examples), as well as updating the innovative approaches to be pursued over the next five years. While all types of microbes can exhibit resistance, this research framework is focused on bacteria (with the exception of mycobacteria). NIAID's research strategic priorities for tuberculosis are described in the [NIAID Strategic Plan for Tuberculosis Research](#).

The Evolution and Accelerating Pace of Antibiotic Resistance (AR)

Bacteria, one of the oldest life forms on the planet, have mastered the art of evading adverse conditions that threaten their existence. Selective mutations have enabled them to survive for billions of years, while also making them resistant to many of the antibiotics used to treat infections today. Increased exposure to these drugs has caused some bacterial pathogens to develop and spread genes that resist the toxicity of some drugs. This is an inevitable, natural phenomenon that cannot be eliminated². However, certain factors that contribute to the accelerating development of resistance, such as infection control precautions and antimicrobial stewardship can be controlled, and these factors should be modified to slow the progression of AR^{3,4}.

In recent decades, bacterial resistance has increased at an alarming rate. This includes resistance among gram-negative bacteria, which have acquired and spread new resistance traits especially rapidly over the past decade. In 2013, the Centers for Disease Control and Prevention (CDC) published a list of "urgent," "serious," and "concerning" domestic AR threats⁷. The CDC updated this [list in 2019](#) and "urgent" threats now include *Clostridioides difficile*, Carbapenem-resistant *Enterobacteriaceae* (CRE), drug-resistant *Neisseria gonorrhoeae*, and Carbapenem-resistant *Acinetobacter*, as well as the fungal pathogen *Candida auris*.

The growing problem of AR has generated a sense of urgency at national and international levels. Over the past five years, the U.S. Government and global partners have focused increased attention on AR, including through the *U.S. National Action Plan for CARB*, the *World Health Organization (WHO) Global Action Plan*, a High-Level Meeting of the United Nations General Assembly, and meetings of the G7 and G20.

NIAID Research on Drug-resistant Fungal Infections

As bacteria are becoming increasingly resistant to antibiotics, fungal pathogens are developing resistance to antifungal drugs. Antifungal resistance is a critical public health concern, particularly in patients with invasive infections such as those caused by the fungus *Candida*. *Candida* is one of the leading causes of healthcare-associated bloodstream infections in the United States. Antifungal resistance has been identified in several *Candida* species, including the recently emerged and rapidly spreading pathogen *C. auris*, which is often multidrug-resistant. Less common fungal pathogens such as *Aspergillus* are also developing resistance to many first-line treatments. NIAID is supporting a wide range of basic and applied research to better understand the mechanisms of resistance and develop new ways to detect, treat and prevent fungal infections. This includes research to advance new treatment options and diagnostics for *Candida* and *Aspergillus*, the development of tools to determine the cause of drug resistance, and support for an experimental vaccine to protect against *Candida* infection.

The Antibiotic Development Pipeline

While AR has accelerated, the number of companies engaged in antibiotic discovery and development efforts has declined for a variety of reasons, including scientific challenges and the low return on investment of antibiotics compared with other therapeutics⁵. During the past year, numerous biopharmaceutical companies have announced plans to curtail their antibiotic research and development programs, and one company with a newly approved antibiotic declared bankruptcy⁶⁻⁸. These developments are worrisome for the future of treating patients with antibiotic-resistant infections.

There continues to be an urgent need to identify ways to preserve currently available antibiotics, develop new ones, and identify alternative treatment and prevention strategies. Several recent publications have outlined strategies to ensure a more robust antibiotic pipeline^{3,9-11}. The Pew Charitable Trusts has created an interactive tool that shows trends along the [antibiotic pipeline](#) between 2014-2018. New programs have emerged to facilitate antibiotic development^{12,13}. For example, CARB-X, a global public-private partnership to bolster innovation in antibacterial product development, was launched in 2016 to accelerate the development of products focused on the most serious drug-resistant bacteria identified by the WHO and the CDC. NIAID partners with the Biomedical Advanced Research and Development Authority (BARDA), the Wellcome Trust, the United Kingdom Government, the German Government, and the Bill & Melinda Gates Foundation to support the program and provides drug development expertise and preclinical testing services to CARB-X awardees. CARB-X and other “push” incentives have helped continually prime the antibiotic pipeline, and the call by the Infectious Diseases Society of America (IDSA) for 10 new drugs between 2010 and 2020 was successful, likely due to greater regulatory flexibility and financial incentives, such as the GAIN Act¹⁴, which provides incentives to increase the commercial value of innovative antibiotic drugs. Nevertheless, few agents in clinical development have activity against some of the most urgent AR threats, and drug candidates with novel mechanisms of action remain rare, so it is imperative to continually expand the antibiotic pipeline.

NIAID: Stimulating Research on AR

NIAID continues to make AR research a key priority. To that end, the Institute has significantly supported basic, translational, and clinical research in this area, paving the way for innovative solutions to advance the prevention, diagnosis, and treatment of drug-resistant infections. NIAID funds numerous [targeted research initiatives](#) to help drive these efforts, which has resulted in significant growth of NIAID’s AR research portfolio. In this section, select examples of NIAID’s AR activities are described, as are the comprehensive suite of research resources and preclinical services available to investigators to fill gaps in the product development pipeline.

Basic Research

NIAID’s basic research portfolio is focused on understanding the mechanisms that pathogens use to thwart host defenses; characterizing resistance mechanisms as they emerge; delineating contributors to bacterial virulence; identifying new targets for diagnostics, vaccines, and therapeutics; and discovering potential new therapeutic approaches. Examples of key findings from NIAID-supported basic research follow:

- With support from NIAID grants and the NIAID-funded Systems Biology Centers, researchers found that the sugar substitute trehalose increases the virulence of epidemic strains of *C. difficile*. They found that two epidemic types of *C. difficile* have the special ability to metabolize low levels of trehalose, and they hypothesize that the widespread use of this compound as a dietary additive may have contributed to the spread of these strains¹⁵.
- Researchers studied the genetic basis for the development of azithromycin resistance in *N. gonorrhoeae*. Azithromycin belongs to a class of antibiotics known as macrolides. This study was the first to demonstrate that *N. gonorrhoeae* can acquire macrolide resistance from other *Neisseria* species that in turn can serve as a reservoir for resistance genes. These results have public health implications and may be

used to inform the development of tools to understand the spread of antibiotic-resistant gonorrhea¹⁶.

- Researchers explored treatment options for “heteroresistant bacteria,” in which bacterial subpopulations are seemingly genetically identical but look different to different antibiotics. Infections caused by these pathogens can be treated with specific combinations of drugs that each kill one subpopulation of bacteria that is resistant to another antibiotic; thereby the combination kills the entire population. Studies on CRE clinical isolates support this theory. These findings represent a promising approach for treating certain patients with seemingly untreatable bacterial infections¹⁷.
- AR can be caused by the temporary expression of genes encoding the bacterium’s efflux pump (a structure that ejects antibiotics from bacteria), in addition to other, mutation-based mechanisms. Researchers studying an efflux pump (AcrAB-TolC) that expels multiple antibiotics found that the expression of the efflux pump’s genes was associated with higher spontaneous mutation frequencies. This study suggests that the temporary expression of these genes may trigger the evolution of permanent resistance¹⁸.
- NIAID intramural researchers led an international effort at the intersection of AR and the microbiome to reveal that the non-pathogenic [probiotic *Bacillus* can eliminate *Staphylococcus aureus*](#). When *Bacillus* species (mostly *B. subtilis*) were present in fecal samples from study participants in Thailand, *S. aureus* was never detected in their gut or nasal samples. Using a mouse model, the research team discovered that *Bacillus* secretes compounds known as fengycin lipopeptides that block *S. aureus* quorum-sensing (a mechanism which enables groups of bacteria to communicate with one another) and completely eradicates intestinal *S. aureus*. *Bacillus*-containing probiotics could be used for simple and safe *S. aureus* decolonization strategies. This probiotic approach would have numerous advantages over the present standard topical strategy involving antibiotics. The potential for a simple probiotic strategy to prevent dangerous staph infections holds immense promise in the healthcare field¹⁹.
- Immunotherapy for treating resistant bacteria is an innovative approach being advanced by NIAID intramural scientists. Use of an antibody that recognizes the ST258 capsule polysaccharide type 2 (CPS2) can boost killing of bacteria by neutrophils in human blood *in vitro*. These findings suggest the [ST258 capsule polysaccharide is a viable vaccine target antigen](#). It is now being tested in non-human primates against a carbapenem-resistant *Klebsiella pneumoniae* strain²⁰.

Translational Research

To transform basic research findings into applications that ultimately improve patient care, NIAID has expanded its translational research portfolio. NIAID is building on the [innovative approaches from the 2014 report](#) to advance the discovery and development of novel therapeutics, diagnostics, and vaccines and other preventive strategies for drug-resistant infections. NIAID has used its long-standing [Partnerships Program](#) to address important translational research and product development areas for AR. Through targeted Partnerships initiatives, NIAID is funding a broad range of projects to further expand AR research, including therapeutic discovery for antibiotic-resistant gram-negative bacteria ([RFA-AI-16-081](#)), clinically useful diagnostics for antibiotic-resistant bacteria ([RFA-AI-17-014](#)), and immunoprophylactics (drugs that harness the immune system to prevent infection) and vaccines targeting multiple antibiotic-resistant bacteria ([RFA-AI-17-017](#)). In addition, through the Centers of Excellence for Translational Research (CETR) program, NIAID is supporting research to discover and develop new therapeutic approaches against multidrug-resistant pathogens.

Therapeutics

NIAID supports a large and diverse portfolio of therapeutic candidates that focus on both validated and novel targets. Scientists are investigating novel classes of antibiotic candidates that interrupt bacterial protein synthesis or disrupt the bacterial cell wall, both proven targets for antibiotic drugs. Researchers are also exploring alternatives to small molecule antibiotics, such as therapeutic bacteriophage, microbiome-based approaches, monoclonal antibodies, small inhibitory oligonucleotides, antibacterial

peptides, anti-virulence therapies (which target bacterial virulence factors without directly killing bacteria), and compounds that modulate innate immunity. In addition, research teams are identifying novel antimicrobial compounds from natural sources, including new classes of antibiotics found in soil.

NIAID has supported multiple targeted solicitations over the past decade to advance promising therapeutic products against urgent and serious AR threats, from lead candidate to first-in-human clinical trials. Therapeutic development projects include synthetic tetracyclines that can treat different types of bacterial infections and are not subject to typical tetracycline resistance mechanisms. In August 2018, FDA approved one of these compounds (eravacycline) to treat complicated intra-abdominal infections. Antibiotic development for gram-negative infections is particularly difficult due to low permeability of the gram-negative cell wall and a variety of efflux pumps. In 2017, NIAID and The Pew Charitable Trusts co-sponsored a meeting, “[Challenges in the Discovery of Gram-negative Antibacterials: The Entry & Efflux Problem](#).” Building on momentum from the workshop, NIAID funded seven projects in 2018 to develop research tools and technologies to advance drug discovery for gram-negative infections ([RFA-AI-16-081](#)). Researchers are also evaluating combination therapies that target both essential functions and resistance factors among these tenacious pathogens⁵. NIAID is supporting the preclinical development of efflux pump inhibitors and funded Investigational New Drug (IND)-enabling studies of an oral β -lactamase inhibitor (VNRX-7145) that will be paired with ceftibuten, an existing antibiotic to treat resistant gram-negative infections. VNRX-7145 restores the effectiveness of ceftibuten against Enterobacteriaceae expressing certain classes of β -lactamases (i.e., Class A, C and/or D). Numerous other combination therapy approaches also are being explored, including immunomodulators, biofilm disruptors, and signaling inhibitors. With NIAID support, investigators are harnessing innovative technologies to transform antibiotic discovery; exploring potential antimicrobial compounds, including those from natural sources; and fostering collaborations between academia and industry partners to develop and advance promising lead candidates.

Another therapeutic approach repurposes old drugs by using new technologies to optimize dosing levels, duration, and route of administration, and to identify promising combination drug therapies based on current pharmacokinetic and pharmacodynamic (PK/PD) principles. Colistin, an antibiotic approved in the late 1950s that no longer was widely used by the 1970s due to toxicity issues, is one such drug. Researchers have developed and published dosing algorithms to inform the use of this antibiotic among critically ill patients²¹. As a potential future alternative to colistin, NIAID supports the development of next-generation polymyxins, including one candidate (SPR206) that has progressed to an industry-sponsored [Phase 1 clinical trial](#).

Diagnostics

NIAID supports both the development of rapid, multiplexed diagnostics platforms and research to identify solutions to the technical challenges of detection. Better diagnostics could provide needed clarity when distinguishing between viral and bacterial infections and deciding whether to treat with antibiotics. Diagnostics are also needed to identify the bacterial species causing the infection and determine susceptibility profiles to facilitate antibiotic stewardship and reduce the use of broad-spectrum agents. For many bacterial species, diagnosis requires culturing the organism followed by species identification and susceptibility testing. Together, this form of testing takes 48-96 hours or more, leading to delays in initiating appropriate therapy, the potential for unnecessary selective pressure, and worsened patient outcomes. Rapid diagnostics also help facilitate the clinical development of new antibiotics by reducing the size of and costs associated with performing clinical trials, which often must enroll large numbers of patients to overcome diagnostic uncertainties²².

The National Institutes of Health (NIH) and NIAID are advancing efforts to develop rapid point-of-need diagnostic tools. In 2016, NIH and BARDA announced the [Antimicrobial Resistance Diagnostic Challenge](#), a \$20 million federal prize competition. The three-step competition seeks to identify innovative and rapid point-of-need *in vitro* diagnostic tests, which help inform appropriate antibiotic

treatment and facilitate antimicrobial stewardship efforts. Up to three winners will be announced in 2020. The NIAID Division of Intramural Research initiated a new clinical laboratory program that focuses on the mechanisms of antimicrobial resistance. The program emphasizes multidrug-resistant bacteria and the development of new approaches for detecting resistance based on proteomics and sequencing. Novel approaches to rapid AR diagnostics based on mass spectrometry and nanopore sequencing are a key focus of the new laboratory. NIAID-supported researchers are also developing platforms to reduce the time needed to detect growth of bacteria that frequently cause healthcare-associated infections. Accelerating this process allows for faster identification of these bacteria and their sensitivity to antibiotics. In addition, scientists are developing rapid point-of-need diagnostic platforms to identify pathogens and determine their antibiotic susceptibility directly from patient samples, instead of culturing bacteria. Researchers are exploring this approach for gram-negative bacteria in urine and blood as well as *N. gonorrhoeae* from swab samples. Through the CETR program, investigators developed a new test to diagnose bacterial infections directly from blood samples. The test accurately detects a wide variety of bacteria and AR genes²³.

Vaccines and Other Preventive Strategies

Several licensed vaccines target bacterial infections, including *Streptococcus pneumoniae* and *Haemophilus influenzae type b* and have markedly reduced infections caused by these organisms and the need for antibiotics to treat them. According to the CDC's 2019 report on [Antibiotic Resistance Threats in the United States](#), the pneumococcal conjugate vaccine PCV13 alone prevented 30,000 invasive pneumococcal infections from 2010-2013. Additional preventive tools to combat AR are needed, but progress towards effective countermeasures remains a challenge. In 2018, the Wellcome Trust and the Boston Consulting Group issued a report entitled [Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities](#). The report assesses vaccine development potential for antibiotic-resistant pathogens and provides recommended actions to advance the field. Currently, no approved vaccines exist for healthcare-associated infections. However, such interventions could significantly reduce the burden of disease in a cost-effective manner if applied to selected populations such as older adults, patients at hospital discharge, and people at risk for recurrent infection²⁴. Immunoprophylactics also hold promise as an effective strategy against AR. While most of these products are still in development, the FDA approved in 2016 an anti-toxin monoclonal antibody therapy shown to reduce the rate of recurrent *C. difficile* infection, a potentially life-threatening diarrheal illness. With this as proof of concept, NIAID-supported researchers are continuing to develop novel immunoprophylactic and vaccine candidates targeting a variety of healthcare-associated pathogens, including drug-resistant gram-negative bacteria as well as *C. difficile*. For pathogens such as *C. difficile*, *Pseudomonas aeruginosa*, and *S. aureus*, some vaccine candidates mitigate the acute symptoms and disease progression, while others are being designed to prevent infection by blocking or reducing colonization.

While the licensed meningococcal B vaccine, Bexsero, has recently shown promise against gonorrhea, previous vaccine candidates specifically targeting *N. gonorrhoeae* were disappointing, likely due to the high degree of variation of surface proteins elaborated by the organism^{25,26}. Despite these early setbacks, NIAID has continued to support research on *N. gonorrhoeae* vaccine antigens, disease pathogenesis, and the human immune response. In 2019, NIAID funded six Sexually Transmitted Infections Cooperative Research Centers to develop vaccines to prevent gonorrhea, chlamydia, and syphilis. The program aims to foster the development of early-stage vaccine candidates with the potential for further preclinical development and testing in clinical trials.

Clinical Research

Leadership Group on AR

Well-designed and implemented clinical trials, an essential part of NIAID's AR program, are supported through investigator-led efforts and multiple NIAID clinical trial networks. In 2013, NIAID launched a major clinical effort to address AR, the [Antibacterial Resistance Leadership Group \(ARLG\)](#). Studies conducted by the ARLG include clinical testing of new drugs to treat multidrug-resistant gram-negative

bacteria, evaluating diagnostic devices in clinical settings, and optimizing treatment regimens to reduce the emergence of resistance. The ARLG draws on the creativity of the global research community by inviting concept submissions to identify and address AR priorities. The ARLG is also committed to mentoring the next generation of clinical scientists in the field of AR and accepts applications for [fellowships and early-stage investigator seed grants](#). NIAID renewed funding for the program in fiscal year 2020.

Through the ARLG, NIAID is supporting observational studies to help better understand the scope of the problem of AR. With international partners, the ARLG is conducting studies, known as SNAP, CRACKLE, and POP, to examine the risk factors and outcomes of infections caused by *Acinetobacter*, CRE, and *Pseudomonas*, respectively. The studies will characterize the global molecular epidemiology of these pathogens, provide insight into potential barriers to enrolling patients with these organisms in clinical trials, and build a network of sites that can participate in future trials evaluating new interventions.

Therapeutics

NIAID-supported clinical trials are evaluating shortened courses of treatment, optimized treatment regimens, and the effectiveness of older, off-patent antibiotics. Optimizing dosing levels, duration, route of administration, and use of combination drug therapy, according to current PK/PD principles, can suppress the emergence of resistance and minimize toxicity. While most clinical trials comparing a short to standard course of antibiotics have found no difference, scientists reported in 2016 that a [five-day treatment regimen](#) for middle ear infections in young children was less effective than the standard 10-day regimen²⁷. NIAID currently is supporting both the [SCOUT trial](#) and [SCOUT-CAP trial](#) to determine the most effective duration of treatment for pediatric urinary tract infections and community-acquired pneumonia. These trials aim to determine if a shorter course of antibiotics—five days instead of 10—is effective against these infections in children. Other NIAID-funded studies on optimized treatment regimens determined that [two common antibiotic treatments](#), clindamycin and trimethoprim–sulfamethoxazole, work well against bacterial skin infections caused by community-associated methicillin-resistant *S. aureus* (MRSA)²⁸⁻³².

Clinical trials are being conducted to evaluate the utility of existing drugs, alone and in novel combination regimens. NIAID is funding the [OVERCOME trial](#) to assess the use of colistin for the treatment of multi-drug resistant gram-negative bacterial infections when used alone or in combination with a carbapenem, and to examine whether either treatment strategy is more likely to reduce the emergence of resistance to colistin. The ARLG is conducting the [COMBINE clinical trial](#) to evaluate the safety, tolerability, and pharmacokinetics of a novel combination therapy, ceftazidime-avibactam and aztreonam, that shows promise for certain CRE infections. NIAID is also funding a [Phase 1 clinical trial](#) of an intravenous formulation of fosfomycin to explore the product as a treatment option for bacterial lung infections. Intravenous fosfomycin is approved in Europe but not in the United States.

NIAID has advanced the development of multiple new therapeutic options to treat and prevent resistant infections. In 2018, a [Phase 2 clinical trial](#) found that a novel antibiotic, zoliflodacin, was well-tolerated and successfully cured most cases of uncomplicated gonorrhea³³. The candidate antibiotic was awarded Fast Track status by the FDA and has progressed to [Phase 3 clinical testing](#), sponsored by the Global Antibiotics Research and Development Partnership, in the Netherlands, South Africa, Thailand, and the United States. Additional studies on new therapeutics include trials to evaluate novel antibiotics with broad gram-negative antibacterial activity, such as the tetracycline [TP-271](#) and β -lactamase inhibitor [VNRX-5133](#) in combination with cefepime (a previously approved antibiotic) to treat resistant infections. VNRX-5133 has advanced to a [Phase 3 clinical trial](#) supported by BARDA. Another novel approach to combat AR is the use of non-antibiotic treatment options, including fecal microbiota transplant (FMT). A [NIAID-supported clinical trial](#) is assessing the safety and efficacy of microbial restoration using full-spectrum fecal microbiota preparations, pre-screened for infectious agents and antibiotic-resistant organisms, in individuals with one or more recurrences of *C. difficile* infection.

Diagnostics

The development of rapid, accurate diagnostics is critical to ensuring optimal stewardship of antibiotics. NIAID funds multiple studies on new diagnostic products that can quickly and simply identify infectious agents and help guide treatment. Researchers are seeking to determine if a [molecular bacterial DNA test](#) can reliably identify gonorrhea infections that may be successfully treated with a single dose of ciprofloxacin. This test potentially could allow healthcare providers to reintroduce ciprofloxacin as an oral treatment for gonorrhea, instead of the current practice of using antibiotics delivered by injection. Through the ARLG, scientists are developing ways to help healthcare workers determine if antibiotic treatment is needed. In the TRAP-LRTI study, ARLG investigators are evaluating whether low blood levels of the protein [procalcitonin](#) can reliably indicate whether a person's lower respiratory tract infection is caused by a viral or bacterial pathogen. Through the RADICAL study, ARLG scientists are harnessing gene expression patterns to develop a simple blood test to determine if a patient's respiratory symptoms stem from a bacterial infection, viral infection, or no infection at all. These studies could aid in collective efforts to reduce the inappropriate use of antibiotics.

NIAID is also supporting studies on improving the utility of current diagnostics. Recently, an ARLG study known as [MASTER GC](#) found that two licensed diagnostics accurately detected gonorrhea and chlamydia in extragenital samples. The two tests were previously approved for testing samples from the reproductive system and urinary tract. Chlamydia and gonorrhea can be found in the pharynx and rectum among undiagnosed individuals – many of whom have no symptoms – who can continue to spread the infections. Based on data from the MASTER GC study, both diagnostics were approved for testing in extragenital sites, filling a significant gap in the prevention and control of gonorrhea and chlamydia.

Preventive Strategies

NIAID is supporting multiple clinical trials evaluating ways to prevent bacterial infections. A [large clinical trial known as ABATE](#), initiated through the NIH Common Fund and managed by NIAID, compared two infection control techniques in non-intensive care units. The study found that daily bathing with the antiseptic soap chlorhexidine—and in those patients with MRSA, adding the nasal antibiotic mupirocin – substantially benefitted patients with medical devices, such as central venous catheters or lumbar drains³⁴. The decolonization strategy has since been implemented in hospitals involved in the trial as a best practice for patients needing these devices.

NIAID is funding trials on novel monoclonal antibody therapies aimed at preventing resistant infections. One trial, [called EVADE](#), is being partially conducted through the ARLG to evaluate the safety of the investigational medicine MEDI3902 and its ability to prevent pneumonia caused by *P. aeruginosa* in mechanically-ventilated patients.

NIAID also is supporting research to evaluate whether certain approved vaccines are cross-protective. For example, NIAID is planning to conduct a Phase 2 clinical trial to examine whether Bexsero, a vaccine licensed to prevent meningitis caused by *N. meningitidis* Type B, can also protect against infection with *N. gonorrhoeae*. The study is expected to enroll approximately 2,000 healthy adults at risk for gonorrhea.

Research Resources

NIAID has built a comprehensive set of product development services and research tools and technologies to facilitate the development of the next generation of vaccines, diagnostics, and therapeutics. These services make critical data, expertise, standardized research materials, and state-of-the-art technologies available to eligible investigators worldwide at no charge. The purpose of these resources is not to develop a product from start to finish but rather to lower the financial risk to product developers by providing critical information and resources to fill specific gaps in the product development pipeline.

NIAID provides cutting-edge technologies, such as genome sequencing, structural genomics, and bioinformatics, which are essential to understanding the genetic basis of resistant organisms, to the scientific

community. The Institute supports several Bioinformatics Resource Centers that host data on infectious disease pathogens and vectors and provide critical tools to help scientists use high-performance computing, machine learning, and other approaches to advance infectious disease research. NIH has also developed the open-access [National Database of Antibiotic Resistant Organisms](#), which contains genomic data for pathogen isolates collected from publicly available information. Scientists from all over the world can access and leverage these databases to foster understanding of resistance mechanisms and inform development of improved diagnostics, vaccines, therapeutics, and antibiotic strategies.

Preclinical programs to advance drug development include *in vitro* and animal model screening tools and a comprehensive suite of capabilities to enable Investigational New Drug applications. In addition to being made available to the scientific community, these preclinical services are being used to support the product development efforts of a diverse portfolio of projects, including CARB-X awardees. NIAID also provides well-characterized reagents such as bacterial isolates for researchers through NIAID-funded repositories. These repositories include the [BEI Resources Repository](#), which provides microorganisms and reagents to the scientific community, and a [virtual biorepository](#) established by the ARLG to provide well-characterized gram-positive and gram-negative clinical isolates for the development of diagnostic tests, novel antimicrobial compounds, and for studies evaluating mechanisms of resistance.

Finally, NIAID supports a number of clinical trials networks to evaluate new products and approaches to address AR. These include the [Phase 1 Clinical Trial Units for Therapeutics](#) and the [Vaccine and Treatment Evaluation Units](#). Information regarding NIAID resources may be found at: <https://www.niaid.nih.gov/research/resources>.

Partnerships Facilitate a Concerted Approach

Because AR is a complex problem with many drivers, combating it requires a multifaceted approach. Besides research other components of an effective response to the challenge include the following: improved surveillance, better infection control, improved stewardship of antibiotics in human and veterinary medicine and agriculture, expanded campaigns to raise public awareness, incentives for the development of new products, and new regulatory paradigms. Therefore, collaboration among partners from multiple disciplines is essential for achieving a coordinated and flexible approach to addressing AR threats as they emerge. NIAID works closely with many partners responsible for these other essential areas, most notably through CARB-X, the federal interagency CARB Task Force, and the Trans-Atlantic Taskforce on Antimicrobial Resistance (TATFAR).

Innovative Approaches to Addressing the AR Challenge

In the 2014 report, NIAID identified several approaches as the most promising components of a comprehensive strategy to address the AR challenge. NIAID has made a concerted effort to investigate and advance these approaches through scientific workshops, targeted funding opportunities, and other research activities (see [Appendix](#)). These strategies were meant to be dynamic and evolve over time. To that end, in preparing this 2019 update, NIAID released a [Request for Information](#) to solicit feedback from the research community about ways to refine and expand upon this list. In addition to stakeholder input, NIAID AR experts reviewed the latest scientific advances to identify the following promising areas that have the potential to transform our understanding of and ability to prevent, diagnose, and treat antibiotic-resistant infections.

- **Leveraging Data Science to Address AR**

Computational approaches are expected to accelerate the discovery and development of new therapeutics, diagnostics, and vaccines for antibiotic-resistant infections and inform more personalized treatment plans in clinical settings. Researchers are generating large and diverse datasets through high-throughput experimental technologies (e.g., genomics, proteomics, and metabolomics) that provide insights into the interactions between bacteria, hosts, the microbiome, and antibiotics. Researchers

often conduct sophisticated computational analyses to combine publicly available and shared data across studies to answer new questions and inform future experiments. Computational approaches that mine electronic health records, data from digital health devices, and social media are also used to generate evidence to enhance findings from AR-related clinical trials. Optimally, enabling these data-driven approaches requires efforts by the scientific community to develop shared computational tools, such as research software, algorithms, and data analysis platforms. Additionally, adoption of FAIR (Findable, Accessible, Interoperable, and Re-usable) principles across the scientific community is expected to expand and enrich biomedical knowledge to better inform the diagnosis, treatment, and prevention of antibiotic-resistant infections³⁵.

- **Understanding Antibiotic Failure**

Antibiotic treatment failure is easily explained when caused by an antibiotic-resistant organism. However, for a small fraction of patients, antibiotic treatment fails even when the pathogen is not resistant but susceptible to the antibiotic. Several explanations could account for this discrepancy, including the ability of bacteria to resist antibiotics through non-inherited mechanisms like heteroresistance, tolerance, or persistence; cloaking of bacteria within biofilms where antibiotics cannot penetrate; or host factors that reduce the patient's ability to fight infection. Improved understanding of the various causes of resistance that are not clearly explained by bacterial genetics and their contribution to clinical failure in different types of infections has the potential to increase successful outcomes in the clinic.

- **Harnessing the Immune System to Combat Bacterial Infections**

Vaccines have proven effective in reducing the incidence of certain bacterial pathogens that may become resistant (e.g., *S. pneumoniae*). Vaccine development against many other pathogens causing urgent and serious health threats has proven much more challenging. However, the recent finding that the meningococcal Type B vaccine may protect against *N. gonorrhoeae* suggests that vaccination against certain bacterial resistance threats may be effective^{25,26}. In addition, several monoclonal antibody candidates are being clinically tested to potentially prevent and/or treat certain healthcare-associated infections in at-risk or infected populations, and strategies to modulate the innate immune system are also being explored. It is important to continue to better understand correlates of immunity and vaccine protection, employ state-of-the-art vaccinology and platform approaches, such as the use of adjuvants and alternative vaccination routes, and develop target product profiles to successfully develop these products.

- **Realizing the Promise of Rapid Diagnostics**

Diagnostics have the promise to help patients receive optimal treatment faster, markedly improve antibiotic stewardship, prevent outbreaks, and co-facilitate antibiotic development. Technologies for rapid identification of pathogens and drug susceptibility have advanced over the past five years. However, many research and development gaps remain, including better tests to detect pathogens directly from normally sterile primary specimens, such as blood and cerebrospinal fluid; tests that can distinguish colonization from infection; tests to rapidly distinguish between bacterial and respiratory infections caused by viruses or fungi; rapid, phenotypic antimicrobial susceptibility tests; and tests that can be performed at point-of-need decision/provision or that can themselves be provided over-the-counter. In certain settings, tests to rapidly identify non-bacterial agents causing acute febrile illness or respiratory symptoms would also reduce the unnecessary use of antibiotics for these conditions. In addition, in order to optimally implement FDA-approved tests, clinical laboratories, clinicians, and payors need to have access to data from implementation studies. Data from these studies help demonstrate that use of a new diagnostic test improves patient outcomes, facilitates improved antibiotic stewardship, and/or reduces overall patient care costs. These studies are often not performed for FDA licensure but are critical for optimal deployment.

- **Reinvigorating Gram-negative Drug Discovery**

The development of new antibiotics is a major focus of NIAID's translational work to address AR. However, discovery of new antibiotics, especially for gram-negative bacteria, remains a major barrier to a robust drug pipeline. The double membrane of the gram-negative cell wall presents a significant obstacle for potential drugs to cross (penetration), and harbors special proteins that actively pump potential drugs out of the cell (efflux). In order to facilitate therapeutic discovery for gram-negative bacteria, there is a need for predictive assays, new models, and improved research tools to better understand cell wall penetration and efflux of small molecules. In addition, libraries of chemical compounds optimized for antibiotic discovery are needed to conduct more fruitful screening campaigns and to generate a more comprehensive understanding of chemical modifications that may increase the activity of potential drugs for gram-negative pathogens. Further exploring natural products, the source of many existing antibiotics, could also enhance libraries of new chemical starting points for antibiotic compounds. Finally, if barriers to the development and use of narrow spectrum drugs can be overcome, additional narrow spectrum compounds may be available for development.

- **Non-antibiotic Products to Treat Resistant Infections**

Since the publication of NIAID's AR report in 2014, interest and investment in a diverse array of non-traditional therapeutics has grown substantially. Non-traditional therapeutics, such as drugs that disarm bacterial virulence, live microbiome-based therapeutic products, and bacteriophages, represent innovative ways to combat AR. These novel approaches, which may be less likely to promote resistance or to negatively impact the microbiome than traditional antibiotics, should be further explored and developed. NIAID will continue to stimulate these approaches by directly funding basic, translational, and clinical research to develop specific products, further defining the critical path to licensure, and convening public scientific meetings to discuss challenges in developing these products.

- **Optimizing the Clinical Utility of Antibiotics**

There have been a number of new antibiotics approved over the past five years that may represent better treatment options for patients with resistant or recalcitrant infections. However, data on specific indications of interest to clinicians or in high-risk patient populations are often not generated as part of regulatory approval packages. Comparative effectiveness studies evaluating different drugs or drug combinations, innovations in clinical trial designs (novel endpoints, pragmatic and adaptive designs, platform trials), and pharmacokinetic studies of how antibiotics or drug combinations are processed by the body (*in vitro*, animal, and human) are critical to inform optimal treatment strategies. Furthermore, many data gaps remain regarding the optimal dose, duration, route of administration, and use of combination drug therapy in older, off-patent antibiotics to suppress the emergence of resistance. Finally, strategies to inhibit bacterial adaptation or reduce the spread of AR genes through plasmids or other mobile elements may limit the development of resistance and prolong the use of existing antibiotics.

Conclusions

The biomedical research and product development supported by NIAID are critical for developing novel ways to diagnose, prevent, and treat bacterial infections. The CDC's updated *Antibiotic Resistance Threats Report* is a stark reminder of the challenges that face the world now and in the immediate future.

While AR is an inescapable fact of biology that will always present formidable challenges, NIAID is committed to mitigating the morbidity, mortality, and costs of the growing problem by:

- Supporting basic research to better understand resistant bacteria and identify new ways to combat them;
- Facilitating the translation of basic research findings into new products and approaches;

- Conducting clinical research to test new interventions and better understand how to use the existing arsenal of antibiotic drugs;
- Offering tools and resources to the scientific community to facilitate the highest-quality research and provide a flexible infrastructure to respond to emerging needs;
- Encouraging the development of vaccines and other preventive measures, rapid diagnostics, and new therapeutics with limited resistance potential; and
- Working collaboratively to ensure a multifaceted approach to combat bacterial resistance.

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Appendix: 2014 Innovative Approaches and Select Accomplishments

The 2014 edition of *NIAID's Antibacterial Resistance Program: Current Status and Future Directions* report outlined seven innovative approaches to address AR. These approaches were the most promising components identified for a comprehensive research strategy. Since the publication of the 2014 report, NIAID has made significant investments and advances for each approach. Select achievements are outlined in this Appendix. The Appendix is not intended to be comprehensive.

Information on awards made under each funding opportunity announcement included below can be found by querying NIH's Research Portfolio Online Reporting Tools (RePORT) at: <https://report.nih.gov/index.aspx>. For answers to frequently asked questions about NIH RePORT data and conducting searches please visit: <https://report.nih.gov/faq.aspx?sid=2>.

I. Systems Biology and Antibacterial Resistance: New Directions for Drug Discovery—Using a holistic approach to examine molecular networks of host-pathogen interactions and global changes in response to drug exposure.
<ul style="list-style-type: none">• In FY 2016, NIAID awarded 6 projects to model the host-pathogen molecular networks for bacteria such as <i>S. aureus</i>, <i>C. difficile</i> and CRE using experimental and computational techniques (RFA-AI-14-064, Systems Biology and Antibacterial Resistance). The resulting network models will provide a framework to identify more effective therapeutic targets and strategies for addressing these pathogens.• Researchers reported that the sugar substitute trehalose increases the virulence of epidemic strains of <i>C. difficile</i>. They found that two epidemic types of <i>C. difficile</i> have the special ability to metabolize low levels of trehalose, and they hypothesize that the widespread use of this compound as a dietary additive may have contributed to the spread of these strains (https://www.ncbi.nlm.nih.gov/pubmed/29310122).• Researchers found that autologous fecal microbiota transplantation (auto-FMT) is a safe, effective way to help replenish beneficial gut bacteria in cancer patients who require intense antibiotics during allogenic hematopoietic stem cell transplantation (https://www.ncbi.nlm.nih.gov/pubmed/30257956).• Researchers are using big data and machine learning algorithms to predict risk of <i>C. difficile</i> in hospitalized patients five days prior to infection (https://www.ncbi.nlm.nih.gov/pubmed/29576042).
II. Harnessing the Immune System to Combat Bacterial Infections—Enhancing host immune response through vaccine, immunoprophylactics, and other immunological interventions.
<ul style="list-style-type: none">• In FY 2019, NIAID established six Sexually Transmitted Infections Cooperative Research Centers focused on developing vaccines to prevent syphilis, gonorrhea and chlamydia. The grants will support collaborative, multidisciplinary research on the bacteria that cause the sexually transmitted infections (RFA-AI-18-005, Sexually Transmitted Infections Cooperative Research Centers: Vaccine Development).• In FY 2016, NIAID awarded five projects focusing on the development of host-targeted therapeutics for infections caused by several pathogens, including MRSA and CRE (RFA-AI-15-024, Partnerships for the Development of Host-Targeted Therapeutics to Limit Antibacterial Resistance).• In FY 2018, NIAID funded three projects for vaccine and immunoprophylactics targeting AR gram-negative bacteria in healthcare settings (RFA-AI-17-017, Partnerships for the Development of Vaccines and Immunoprophylactics Targeting Multiple Antimicrobial-Resistant Bacteria).• NIAID is supporting early development of several vaccine candidates for <i>C. difficile</i> and <i>N. gonorrhoeae</i>.

<ul style="list-style-type: none"> • NIAID is supporting research exploring monoclonal antibodies for prevention and treatment of bacterial infections, including: Phase 2 Proof-of-concept Study to Evaluate the Efficacy and Safety of MEDI3902 in Mechanically Ventilated Patients for the Prevention of Nosocomial Pneumonia Caused by <i>Pseudomonas Aeruginosa</i> (EVADE, https://www.clinicaltrials.gov/ct2/show/NCT02696902). • NIAID has hosted and co-hosted several workshops focused on vaccine development for drug-resistant pathogens, including: <i>Staphylococcus</i> (2010 and 2013), multidrug-resistant gonococci (2015), and <i>C. difficile</i> (2018).
<p>III. Disarm, But Leave Unharmful: Exploring Anti-Virulence Strategies—Targeting bacterial virulence factors without directly killing bacteria is less likely to induce selective pressure.</p>
<ul style="list-style-type: none"> • In FY 2016, NIAID awarded 24 research projects for the development of non-traditional therapeutics (RFA-AI-14-066, Non-Traditional Therapeutics that Limit Antibacterial Resistance). Funded projects support development of secretion system inhibitors, adhesion inhibitors, quorum sensing and biofilm inhibitors, anti-toxin approaches, and other anti-virulence drugs. • In FY 2015, NIAID made 14 awards for the discovery and early stage development of new antibacterial products (RFA-AI-14-026, Development of Novel Therapeutics for Select 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.
<p>IV. Synthetic Microbiota: An Ecobiological Approach—Designing microbial communities as biologic products to mitigate infectious diseases and their sequelae.</p>
<ul style="list-style-type: none"> • NIAID is supporting research on microbiome-based therapeutics, including efforts to identify protective bacterial strains and formulate them into products to prevent and treat <i>C. difficile</i> infection. • In FY 2019 under targeted program announcements, NIAID funded seven projects to advance research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease, as well as research exploring combination antibiotic therapies to address the emergence of resistance (PA-18-724 and PA-18-725, Generating New Insights and Mechanistic Understanding of Antibiotic Resistance Development). • In FY 2016, NIAID awarded 24 research projects for the development of non-traditional therapeutics, including microbiome-based therapeutics (RFA-AI-14-066, Non-Traditional Therapeutics that Limit Antibacterial Resistance). • NIAID is supporting a Phase 1/2 clinical trial: Microbial Restoration for Individuals With One or More Recurrences of Clostridium Difficile Associated Disease (https://www.clinicaltrials.gov/ct2/show/NCT03548051) • NIAID, in collaboration with the American Gastroenterological Association, is supporting the establishment of a Fecal Microbiota Transplant National Registry (https://clinicaltrials.gov/ct2/show/study/NCT03325855) • NIAID has co-hosted several workshops on the microbiota and microbiome-based products, including the “Science and Regulation of Live Microbiome-Based Products Used to Prevent, Treat, or Cure Diseases in Humans” workshop with FDA (2018).
<p>V. Less is Better: Diagnostics to Guide Use of Narrow-Spectrum Therapeutics—Decreasing selective pressure by enabling the use of therapeutics targeted to a pathogen or group of pathogens.</p>
<ul style="list-style-type: none"> • NIH and BARDA continue progress on the Antimicrobial Resistance Diagnostic Challenge, which launched in September 2016. The competition seeks to identify innovative and rapid point-of-need diagnostic <i>in vitro</i> tests, which help inform appropriate antibiotic treatment and facilitate antimicrobial stewardship efforts. This 3-Step competition was developed with technical and regulatory expertise from the CDC and FDA, as well as public input. The total prize for the Challenge is \$20M with prizes to be awarded in three phases, starting in 2017 and concluding in 2020. NIH and BARDA each contributed \$10 million to the challenge.

- In FY 2015, NIAID awarded nine projects to support enhanced diagnostics to rapidly detect antimicrobial-resistant bacteria, including pathogens that frequently cause healthcare-associated infections ([RFA-AI-14-019](#), Partnerships for Diagnostics to Address Antimicrobial Resistance of Select Bacterial Pathogens).
- In FY 2018, NIAID awarded five projects to support development of diagnostic platforms that detect bacterial pathogens listed in CDC's 2013 report *Antibiotic Resistance Threats in the United States*, and determine associated antimicrobial sensitivity and/or resistance. ([RFA-AI-17-014](#), Partnerships for Development of Clinically Useful Diagnostics for Antimicrobial-Resistant Bacteria).
- The ARLG is developing and testing diagnostic tools to help inform treatment options. Specific project examples include:
 - A Randomized Double-Blinded, Placebo-Controlled Trial of Antibiotic Therapy in Patients With Lower Respiratory Tract Infection (LRTI) and a Procalcitonin Level (TRAP-LRTI, <https://www.clinicaltrials.gov/ct2/show/NCT03341273>)
 - Performance of Nucleic Acid Amplification Tests for the *Detection of N. gonorrhoeae and Chlamydia trachomatis* in Extragenital Sites (MASTER GC, <https://clinicaltrials.gov/ct2/show/NCT02870101>).
 - A simple blood test that analyzes patterns of [gene expression](#) to determine if a patient's respiratory symptoms stem from a bacterial infection, viral infection, or no infection at all (RADICAL)
 - Two rapid diagnostic candidates that can accurately predict whether *Pseudomonas*, *Acinetobacter*, *E. coli* and *Klebsiella* isolates were susceptible or resistant to carbapenems (PRIMERS IV <https://www.ncbi.nlm.nih.gov/pubmed/30239599>, PRIMERS III <https://www.ncbi.nlm.nih.gov/pubmed/27795336>, PRIMERS I and II <https://www.ncbi.nlm.nih.gov/pubmed/26409063>).
- NIAID has supported development of five new FDA-cleared diagnostic products, including tests for urinary tract infections, pneumonia, and sexually transmitted infections (i.e., gonorrhea and chlamydia). The ARLG helped advance several of these products.
- NIAID supported a study on the Clinical Validation of a Molecular Test for Ciprofloxacin-Susceptibility in *N. Gonorrhoeae* (<https://www.clinicaltrials.gov/ct2/show/NCT02961751>)

VI. Exploiting Natural Predators: The Specificity of Phage Therapy—Using phage or phage-derived lysins to kill bacterial pathogens while preserving microbiota.

- In FY 2020, NIAID issued a funding opportunity to support basic and translational research to address knowledge gaps that hinder the development and regulation of bacteriophage used to prevent and treat drug-resistant bacterial infections ([RFA-AI-19-065](#), Understanding Phage Biology to Support the Development of Bacteriophage Therapy).
- In FY 2016, NIAID funded 24 research projects to develop non-traditional therapeutics, including several focused on bacteriophage ([RFA-AI-14-066](#), Non-Traditional Therapeutics that Limit Antibacterial Resistance).
- In 2015, NIH established an Interagency Agreement with FDA's Center for Biologics Evaluation and Research to address key regulatory considerations relevant to using bacteriophages for decolonization of the drug-resistant nosocomial pathogens, vancomycin-resistant Enterococci and MRSA.
- In 2015, NIAID organized a workshop on "Bacteriophage Therapy: An Alternative Strategy to Combat Drug Resistance." FDA and NIAID co-sponsored a follow-up workshop "[Bacteriophage Therapy: Scientific and Regulatory Issues](#)" in 2017.
- NIAID is conducting preclinical testing of several phage-based products including efficacy testing in animal models, toxicology studies, and product development planning services.

VII. Teaching Old Drugs New Tricks: Extending the Clinical Utility of Antibacterial Drugs—Optimizing use of existing drugs and combination therapies to suppress emergence of resistance and minimize toxicity.

- NIAID is supporting research to guide the optimal use of existing antibiotics for gram-negative infections. International teams of NIAID-funded researchers are making progress in diverse areas involving PK and rational combinations for existing polymyxin antibiotics as well as drug discovery and development for next-generation polymyxins. NIAID-supported researchers collected PK data for critically ill patients receiving intravenous colistin. Based on their findings, they developed and published dosing algorithms to inform use of this antibiotic (<https://www.ncbi.nlm.nih.gov/pubmed/28011614>).
- NIAID has supported or is continuing to support a number of clinical trials aimed at optimizing the use of existing drugs and combination therapies. Select examples include:
 - Uncomplicated Skin and Soft Tissue Infections Caused by Community-Associated Methicillin-Resistant Staphylococcus Aureus (<https://www.clinicaltrials.gov/ct2/show/NCT00730028>; <https://www.ncbi.nlm.nih.gov/pubmed/25785967>, <https://www.ncbi.nlm.nih.gov/pubmed/28657870>)
 - Strategies Using Off-Patent Antibiotics for Methicillin Resistant S. Aureus "STOP MRSA" (<https://www.clinicaltrials.gov/ct2/show/NCT00729937>, <https://www.ncbi.nlm.nih.gov/pubmed/28535235>, <https://www.ncbi.nlm.nih.gov/pubmed/27025829>, <https://www.ncbi.nlm.nih.gov/pubmed/26962903>)
 - Treatment Algorithm to Reduce the Use of Vancomycin in Adults With Blood Stream Infection (Bacteremia) (<https://clinicaltrials.gov/ct2/show/NCT01191840>, <https://www.ncbi.nlm.nih.gov/pubmed/30264119>)
 - The SCOUT Study: "Short Course Therapy for Urinary Tract Infections in Children" (<https://clinicaltrials.gov/ct2/show/NCT01595529>)
 - Efficacy of Short-Course Antimicrobial Treatment for Children With Acute Otitis Media and Impact on Resistance (<https://clinicaltrials.gov/ct2/show/NCT01511107>, <https://www.ncbi.nlm.nih.gov/pubmed/28002709>)
 - Trial for the Treatment of Extensively Drug-Resistant Gram-negative Bacilli (OVERCOME, <https://clinicaltrials.gov/ct2/show/NCT01597973>)
 - The Pharmacokinetics of Extended Duration High-Dose Cefixime Co-administered With Azithromycin for the Decreased Susceptibility of Neisseria Gonorrhoeae: A Phase I Pilot Study (<https://www.clinicaltrials.gov/ct2/show/NCT02708992>)
 - A Phase IV Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate Short Course vs. Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP, <https://www.clinicaltrials.gov/ct2/show/NCT02891915>)
 - A Trial to Evaluate the Pharmacokinetics and Safety of AVYCAZ in Combination With Aztreonam (COMBINE, <https://www.clinicaltrials.gov/ct2/show/NCT03978091>). This trial is based on findings from earlier NIAID-supported studies (<https://www.ncbi.nlm.nih.gov/pubmed/29020404>, <https://www.ncbi.nlm.nih.gov/pubmed/28167541>).
 - Minocycline Pharmacokinetics (ACUMIN, <https://www.clinicaltrials.gov/ct2/show/NCT03369951>)