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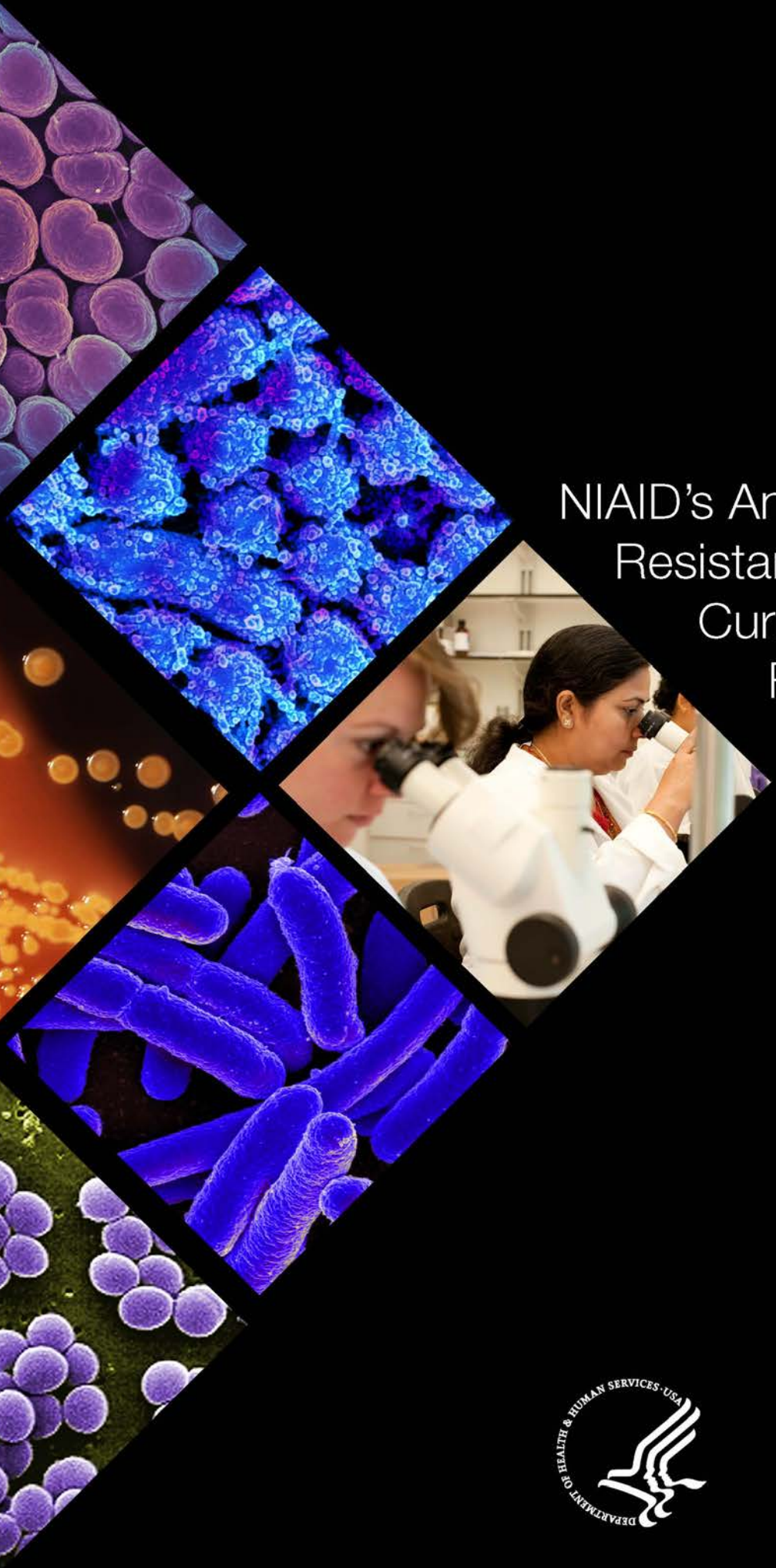

NIAID's Antibacterial Resistance Program: Current Status and Future Directions

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National Institute of Allergy and Infectious Diseases

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Table of Contents

NIAID's Antibacterial Resistance Program: Current Status and Future Directions Executive Summary

Since the 2008 publication of the *Research Agenda of the National Institute of Allergy and Infectious Diseases for Antimicrobial Resistance*, the Institute has continued to make significant advances in combatting this growing problem. Antimicrobial resistance (AR) is an inevitable outcome of the evolutionary principle that organisms will mutate to escape lethal selective pressure. As long as antibiotics are used to kill bacteria, resistance will continue to emerge. However, improved surveillance and infection control, more judicious use of antibiotics, new prevention measures, and new therapeutic strategies to combat resistant bacteria remain essential to mitigate this global threat.

Unfortunately, even as AR has accelerated, antibiotic discovery and development efforts have declined. Increased recognition of the need for novel antibiotics and the introduction of new regulatory approaches and incentives to facilitate antibacterial drug development are bringing renewed attention to this area. With some bacterial infections already untreatable by approved agents, it is imperative to continually prime the fragile pipeline of antibacterial drugs.

This report describes the National Institute of Allergy and Infectious Diseases (NIAID's) portfolio of basic, translational, and clinical research in AR and outlines a combination of innovative approaches based on the latest scientific advances to be pursued. These strategies draw on multidisciplinary partnerships, which are essential for achieving a coordinated and nimble approach to addressing AR threats as they emerge.

Strategic Approaches to Antimicrobial Resistance Research:

- **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.
- **Harnessing the Immune System to Combat Bacterial Infections**—Enhancing host immune response through immunological interventions and immunotherapeutics.
- **Disarm, But Leave Unharmed: Exploring Anti-Virulence Strategies—**Targeting bacterial virulence factors without directly killing bacteria is less likely to induce selective pressure.
- **Synthetic Microbiota: An Ecobiological Approach—**Designing microbial communities as biologic products to mitigate infectious diseases and their sequelae.
- **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.
- **Exploiting Natural Predators: the Specificity of Phage Therapy—**Using phage or phage-derived lysins to kill specific bacteria while preserving microbiota.
- **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.

As resistance increases, scientists are in a race to "outsmart" bacteria by working around the mechanisms that cause resistance. NIAID is committed to mitigating the morbidity, mortality, and costs of the growing problem of AR through a comprehensive research strategy that will evolve as new ideas and information are generated.

NIAID's Antibacterial Resistance Program: Current Status and Future Directions

Introduction

In 2008, the Research Agenda of the National Institute of Allergy and Infectious Diseases (NIAID) for Antimicrobial Resistance (AR) was published in *The Journal of Infectious Diseases*, outlining NIAID's commitment to addressing this urgent public health issue [1]. Since that time, NIAID has continued to make significant progress against this growing problem through a robust and diverse set of activities spanning basic, translational, and clinical research. This new report describes briefly NIAID's current AR research portfolio, highlighting activities in each of these areas. In addition, the report outlines a number of innovative approaches NIAID will pursue in the coming years to mitigate the emergence of AR. While all types of microbes can exhibit resistance, this research agenda is focused on bacteria (with the exception of mycobacteria). NIAID's research efforts and strategic priorities for other organisms, such as those causing malaria, influenza, and tuberculosis can be found elsewhere [2-4].

The Evolution of Antibacterial Resistance

The ability of bacteria to evolve in response to pressure from antibiotics has been recognized since the discovery of penicillin [5]. In less than a century, a complex array of factors has led to the emergence of bacteria that no longer respond to any approved antibiotics. Numerous recent calls to action [6-9] have highlighted the urgent need to respond to this growing global health threat with improved surveillance and infection control, more judicious use of antibiotics, new prevention measures, and new therapeutic strategies to combat resistant bacteria.

Bacteria can acquire resistance through mutation or through horizontal transfer of genetic information. Resistant members of a population that are exposed to the selective pressure of antibacterial drugs will be amplified, which can ultimately result in treatment failures in the clinic. Resistance genes are ancient (even pre-dating human beings) and ubiquitous [10], and some of the most worrisome resistance genes have been found in diverse environmental samples, including drinking water [11]. Furthermore, many bacterial species harboring resistance genes can colonize the human gut, skin, and other niches, where they serve as a ready source of infection when host defenses are breached. These bacteria can also serve as a source of AR genes for transfer to other bacteria, facilitating the interspecies spread of resistance.

AR is a complex and multifaceted problem that is driven by many factors, including:

- Bacterial population density in health care facilities, which allows transfer of bacteria within a community and enables resistance to emerge;
- Inadequate adherence to proven hospital hygiene measures;
- An increasing number of high risk populations, including chemotherapy, dialysis, and transplant patients as well as those in long-term care facilities;
- Overuse of antibiotics in agriculture;
- Global travel and trade, which can lead to transfer of resistant infections and resistance genes;
- Poor sanitation in certain areas, which can contaminate water systems and spread resistant bacteria in sewage;
- Inappropriate use of antibiotics in human medicine (e.g., for viral infections);
- Overprescribing of broad-spectrum drugs, which can exert selective pressure on commensal bacteria and predispose to secondary infection; and
- Lack of rapid diagnostics to help guide appropriate use of antibiotics.

Fundamentally, however, AR is an inevitable outcome of the evolutionary principle that organisms will mutate to escape lethal selective pressure. As long as we use antibiotic agents designed to kill bacteria, antibiotic resistance will continue to emerge.

The Accelerating Pace of Resistance

Over the past several years, bacterial resistance has increased at an alarming rate. This includes resistance among Gram-negative bacteria, which have acquired new resistance traits especially rapidly over the past decade. The Centers for Disease Control and Prevention (CDC) has developed a list of "urgent," "serious," and "concerning" domestic AR threats [7]. The "urgent" threats include CRE, *Clostridium difficile*, and Drug-resistant *Neisseria gonorrhoeae*.

Gram-negative bacteria include Carbapenem-Resistant Enterobacteriaceae (CRE), which are resistant to all, or almost all, classes of antibiotics and have been detected in 44 states and around the world [7]. One subset of CRE carries the *Klebsiella Pneumoniae* Carbapenemase (KPC) gene; this subset is now endemic in the Northeastern and Mid-Atlantic states [7]. Another threat emerged in 2008 with the identification of an enzyme called New Delhi Metallo-Beta-Lactamase (NDM). Like KPC, NDM has been found in a wide variety of Gram-negative bacteria and confers resistance to nearly all classes of antibiotics. Bacteria bearing the gene for NDM are now endemic in the Indian subcontinent and the UK, and more than 90 cases have been detected in the United States [12]. While CRE infections are still largely confined to healthcare settings, the emergence of *Escherichia coli* expressing Extended-Spectrum Beta-Lactamases (ESBLs) in community settings may portend the emergence of CRE in the community.

C. difficile is the most common cause of antibiotic-associated diarrhea worldwide and has surpassed Methicillin-Resistant *Staphylococcus aureus* (MRSA) as the most common hospital-acquired infection in some U.S. hospitals [13]. *C. difficile* infections (CDI) have become particularly difficult to treat; emergent strains that are causing the current epidemic harbor an intrinsic ability to cause more severe disease compared with other toxigenic isolates [14]. Furthermore, the rate of recurrence after standard antibiotic treatment is approximately 20-25 percent and the risk of recurrence increases with each event [15]. Approximately 500,000 cases of CDI occur each year resulting in 14,000 deaths in the United States [7]. The increased burden of disease has resulted in excess medical costs, which by most estimates have reached over one billion dollars annually. A number of factors have contributed to the increased rate and severity of CDI, including increased use of broad-spectrum antibiotics, emergence and spread of resistant and highly toxigenic strains of *C. difficile*, and an aging population in the United States.

There are an estimated 820,000 cases of gonorrhea, caused by *N. gonorrhoeae*, in the U.S. each year. Gonorrhea was successfully treated with penicillin G for about four decades after the drug's introduction in 1943. In the early 1980s *N. gonorrhoeae* began accumulating resistance to most major classes of antibiotics and many strains are now Multidrug-resistant. Worldwide, current treatment options are limited to the extended-spectrum cephalosporins, cefixime, and ceftriaxone, and the CDC no longer recommends cefixime due to the increasing prevalence of isolates with decreased susceptibility to this drug [16].

CDC has also named a number of "serious" resistance threats, including Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, ESBLs, Vancomycin-resistant *Enterococcus*, Multidrug-resistant *P. aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella typhi*, Drug-resistant *Shigella*, MRSA, and Drug-resistant *Streptococcus pneumonia* [7]. While these bacteria are not listed in the CDC's highest threat category, resistance is unpredictable and therefore it is essential to support research to understand and combat these organisms.

The Antibiotic Development Pipeline

Even as AR has accelerated, antibiotic discovery and development efforts have declined, with many major pharmaceutical companies discontinuing their antibiotic development programs over the past decade [17]. This decline is due to a number of factors, including the low return on investment of antibacterials compared with other therapeutics, difficulty in identifying new compounds via traditional discovery methods, and regulatory requirements necessitating large and complex clinical trials for approval [18]. Increased recognition of the need for new antibiotics and the introduction of new regulatory approaches and incentives to facilitate antibacterial drug development [19,20] have brought renewed attention to this area. A recent review of antibacterial candidates in clinical development demonstrated a marked increase in investigational agents compared with 2011 [21]. Nevertheless, with some bacterial infections already untreatable by approved agents, it is imperative to continually prime the fragile pipeline of antibacterial drugs.

NIAID: Stimulating Research on Antibacterial Resistance

NIAID continues to make antimicrobial (including antibacterial) research a key priority. To that end, the Institute has made significant investments in this area through the support of basic, translational, and clinical research, paving the way for innovative solutions to advance prevention, diagnosis, and treatment of resistant infections. These efforts have helped advance the development of numerous products, with a recent program assessment revealing that NIAID has helped support at least 25 percent of the antibiotics currently in clinical development.

Basic research leads to better understanding of resistance factors, pathogenesis, and host-pathogen interactions. Translational research advances novel findings into products for AR. Finally, well-designed and properly implemented clinical trials are needed to bring products through regulatory approval and to guide clinical practice. NIAID has been supporting each stage of research and development to meet the challenge of AR. Over the past seven years alone, NIAID has supported numerous targeted research initiatives to help drive the growth of NIAID's AR research portfolio. In this section, NIAID's ongoing activities are described, as are the comprehensive suite of research resources and services available to investigators to fill gaps in the product development pipeline.

Basic Research

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

a) Understanding host-pathogen interactions is critical to designing effective interventions to combat disease. *S. aureus* produces a toxin that targets a host protein, ADAM10. Scientists discovered that the toxin not only damages endothelial cells directly, but also binds to ADAM10 to increase its enzymatic activity leading to loss of specific cellular functions and increased pathology. Inhibiting ADAM10 provides a novel approach for treating sepsis caused by *S. aureus* that is less likely to increase AR [22].

b) Characterizing resistance mechanisms holds great promise for the design of combination therapeutics. KPC and NDM are among the thousands of β-lactamases that enable bacteria to resist antibiotics [23]. By characterizing the sequence and structure of this ever-growing family of enzymes, scientists are moving towards design of new β-lactamase inhibitors [24]. Another area of interest is the ability of certain bacteria to create dormant subpopulations of "persister" cells,

which are unresponsive to current antibiotics that target active metabolic processes. A compound has been discovered that can bring these persisters out of their dormant state and kill them [25]. Finally, research is ongoing to understand biofilm formation, efflux pump structure and assembly, porin regulation, and other resistance mechanisms—research that has the potential to unlock clues that would restore the utility of old drugs.

c) Researchers have discovered numerous new antibacterial targets and have found new ways to exploit old targets. For example, scientists have used the exquisite binding specificity of bacteriophage lysins to identify the enzyme 2-epimerase, which is required for bacterial growth. These findings led to the design of epimerox, a small-molecule inhibitor that prevents growth and lethality of several Gram-positive pathogens, including *S. aureus* and *Bacillus anthracis*. Importantly, resistance to epimerox was not detected in *B. anthracis* or *S. aureus* [26]. In addition, recent detailed understanding of the bacterial ribosome has uncovered new binding sites that are bringing new insight to this known antibiotic target.

d) The myriad virulence factors that bacteria use to cause disease are the subject of intense basic research efforts, many of which have potential to yield novel therapeutics. For example, the Pseudomonas type III secretion system, the numerous toxins excreted by *S. aureus* and C. *difficile,* and quorum sensing, which enables groups of bacteria to communicate with one another and change behavior to cause disease, are all being pursued as potential therapeutic targets [27].

e) Using molecular approaches to block the expression of genes encoding virulence factors is another promising strategy. This can be done by co-opting a naturally occurring mechanism (known as CRISPR [clustered regularly interspaced short palindromic repeats]) to create enzymes that recognize and destroy particular transcripts. Alternatively, synthetic DNA/RNA analogs can be used to silence gene expression and thereby mitigate infection.

f) Building on the success of fecal microbiota transplants in treating *C. difficile*-associated diarrhea [28], researchers are identifying correlations between disease outcomes and diversity of gut microbiota, with the goal of preventing and treating *C. difficile* infection with targeted manipulation of gut pathogens. These studies are also elucidating innate and adaptive immune responses in patients with CDI.

Translational Research

In order to transform basic research findings into applications that ultimately improve patient care, NIAID has expanded its translational research portfolio. Novel therapeutics can focus on enhancing host immunity or target bacteria in unique ways that are less likely to induce resistance. Rapid diagnostics will allow clinicians to swiftly determine appropriate treatments for infected individuals and facilitate antibacterial stewardship by reducing the use of broad-spectrum drugs. Vaccines could significantly reduce the burden and spread of disease by preventing infections.

Therapeutics

NIAID supports a large and varied portfolio of therapeutic candidates that focus on both validated and novel targets. For example, scientists are investigating 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 monoclonal antibodies, small inhibitory oligonucleotides, and antibacterial peptides.

NIAID has supported multiple, targeted solicitations over the past decade to advance promising therapeutic products against a number of high priority pathogens, from lead candidate to first-in-human clinical trials. Therapeutic development projects currently supported by NIAID include the creation of

synthetic tetracyclines that can treat different types of bacterial infections and are not subject to typical tetracycline resistance mechanisms, and therapeutics containing gallium citrate, a metal with well-documented antibacterial properties. In addition, combination therapies that target both essential functions and resistance factors hold promise for treating tenacious Gram-negative infections [21]. For instance, NIAID is supporting the preclinical development of β-lactamase inhibitors and efflux pump inhibitors that can be paired with previously approved antibiotics to treat resistant infections. Numerous other combination therapy approaches are also being explored, including immunomodulators, biofilm disruptors, and signaling inhibitors. Another therapeutic approach repurposes old drugs by using new technologies to optimize dosing levels, duration, 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 fell out of widespread use in the 1970s due to toxicity issues is one such drug. NIAID-supported researchers discovered that delivering a higher initial or "loading" dose of colistin both enhances its effectiveness and reduces toxic side effects [29].

Diagnostics

NIAID supports both the development of multiplexed diagnostics platforms and research to identify solutions to technical challenges of detection. Diagnostics are essential for identifying bacterial species; susceptibility profiles enable appropriate treatment and facilitate antibacterial stewardship by reducing the use of broad-spectrum agents. For many bacterial species, diagnosis requires culturing the organism followed by susceptibility testing. Together, this form of testing takes 48-96 hours or more, leading to delays in the initiation of appropriate therapy, the potential for unnecessary selective pressure and worsened patient outcomes. Another important role for rapid diagnostics is in facilitating the clinical development of new antibacterial drugs by reducing the size of and costs associated with performing clinical trials, which often must enroll large numbers of patients to overcome diagnostic uncertainties [30].

One priority area for clinicians and public health officials is the rapid and accurate diagnosis of respiratory infections. Rapid diagnostics enable more targeted and effective treatments, which may help limit the emergence of resistance. NIAID has supported development of the FilmArray system which uses multi-stage PCR to quickly and simultaneously detect 17 respiratory viruses and 3 bacteria. NIAID has also supported translational research to help guide the treatment of individual patients with sepsis. Investigators have elucidated the molecular fingerprints that differ between sepsis patients who survive and those who die. Metabolomes and proteomes of patients were measured at hospital admittance; profiles of survivors differed markedly from those of patients who died. An algorithm derived from clinical features together with measurements of five metabolites predicted patient survival [31]. If integrated into patient care, this test could guide antibiotic selection.

Vaccines

Currently there are no approved vaccines or other immunoprophylactics for hospital-acquired infections, but such interventions could significantly reduce the burden of disease in healthcare settings in a cost-effective manner if applied to selected populations [32]. Large efficacy trials of *S. aureus* vaccines conducted to date have failed, in part due to inadequate understanding of correlates of protection for *S. aureus* [33]. Recent data from NIAID-supported investigators suggest that T-cell responses are crucial for protection from *S. aureus* [34]. Multiple groups of NIAID-supported researchers are exploring different approaches for *S. aureus* vaccine development, and several of these researchers have formed partnerships with industry to advance their vaccine candidates into the clinic.

Early vaccine candidates for *N. gonorrhoeae* were also disappointing, likely due to the high degree of variation of surface proteins elaborated by the organism. Despite these early setbacks, NIAID has continued to support research on *N. gonorrhoeae* vaccine antigens, pathogenesis, and immune responses. Investigators have identified several potential vaccine antigens that are conserved among strains and have conducted initial preclinical development of vaccine candidates targeting some of them. The recent

finding that *N. gonorrhoeae* forms biofilms in humans [35] has led to the discovery of targets for an anti-biofilm vaccine [36]. Finally, recent studies suggest that T-cell responses may be important for protection from *N. gonorrhoeae* infection [37], which yields new directions for vaccine research.

Clinical Research

Well-designed and implemented clinical trials are an essential part of NIAID's AR program and are supported through multiple NIAID clinical trial networks and investigator-led efforts. These efforts are already having an impact. For example, prescriptions for acute rhinosinusitis represent a large proportion of outpatient antibiotic use, yet evidence to support antibiotic treatment for the condition is limited. A NIAID-supported randomized controlled trial demonstrated that a 10-day course of amoxicillin compared with placebo showed no difference in symptoms at day three of treatment, supporting current recommendations to avoid routine antibiotic treatment for uncomplicated rhinosinusitis[38]. In addition, NIAID collaborated with the CDC to conduct a trial comparing two new antibiotic regimens using existing drugs—injectable gentamicin in combination with oral azithromycin and oral gemifloxacin in combination with oral azithromycin—for the treatment of gonorrhea. Both regimens successfully treated gonorrhea infections, providing more treatment options for healthcare providers in anticipation of the emergence of resistance to current therapeutic regimens [39].

NIAID also supports multiple clinical trials aimed at identifying ways to optimize the use of currently licensed antibacterials (Table 1). Strategies to reduce selective pressure include shorter treatment courses, combination therapies, and the use of alternative, non-antibiotic treatment strategies. These trials are addressing skin and soft tissue infections caused by community-acquired (CA) MRSA, otitis media, urinary tract infections, and bacteremia. To generate options for more effectively treating pneumonia, NIAID is supporting a clinical trial to test the safety of an inhaled formulation of colistin, which could increase lung concentrations of the drug.

Table 1. Clinical Trials to Optimize the Use of Currently-Licensed Antibacterials

Target infection	Treatment	Objectives
Uncomplicated skin and soft-tissue infections (SSTI) caused by CA-MRSA	• Clindamycin, trimethoprim-sulfamethoxazole, placebo (incision and drainage without antibiotics) • Clindamycin, trimethoprim-sulfamethoxazole, cephalexin, placebo (incision and drainage without antibiotics)	Avoid unnecessary use of antibiotics
Staphylococcus bacteremia	Protocol-based algorithm vs. standard-of-care using vancomycin	Shortened course of treatment
Urinary tract infection in children	5 days vs. 10 days of protocol-approved, physician-selected antibiotic	Shortened course of treatment
Acute otitis media in children	5 days vs. 10 days of protocol-approved, physician-selected antibiotic	Shortened course of treatment
Bacteremia and HAP/VAP[1] caused by extremely Drug-resistant *Acinetobacter baumannii*, *Pseudomonas* and CRE[2]	Colistin vs. colistin plus meropenem	Optimized regimen
Bacteremia and VAP caused by resistant GNB	Meropenem IV vs. meropenem plus aminoglycoside, IV and inhaled	Optimized regimen
Neisseria gonorrhoeae	1 dose vs. 2 doses vs. 3 doses Cefixime vs. Cefixime plus Azithromycin	Optimized regimen

[1]HAP—Hospital acquired pneumonia; VAP—Ventilator-associated pneumonia
[2]CRE—Carbapenem-resistant Enterobacteriaceae

In addition, methods to reduce pathogen load in healthcare facilities by decolonizing patients who carry potentially pathogenic bacteria are being explored through NIAID-supported clinical trials. One group of investigators is studying the effectiveness and impact of different methods of decolonizing patients in non-ICU hospital settings. NIAID is also supporting a Phase I safety trial of a novel agent for nasal decolonization of *S. aureus* that—in contrast to commonly used agents—does not appear to induce resistance. In another study, investigators are determining whether nasal decolonization of neonates can reduce rates of staphylococcal infection.

In 2013, NIAID launched the Antibacterial Resistance Leadership Group (ARLG), a major new clinical effort to address AR. The ARLG has developed a research agenda identifying the most pressing clinical questions in AR. Studies conducted by the ARLG may include clinical testing of new drugs to treat Multidrug-resistant Gram-negative bacteria, evaluating diagnostic devices in clinical settings, evaluating the effectiveness of new antibacterial stewardship programs, and optimizing treatment regimens to reduce the emergence of resistance. The ARLG is drawing 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 is accepting applications for fellowships and early stage investigator seed grants.

Research Resources

NIAID has built a comprehensive set of product development services and research tools and technologies to facilitate development of the next generation of vaccines, diagnostics, and therapeutics (Figure 1). 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 assist researchers in developing a particular product from start to finish, but rather to lower the financial risk to product developers by providing limited, but critical, information to fill specific gaps in the product development pipeline.

Cutting edge technologies, such as genome sequencing, proteomics, and bioinformatics, which are essential to understanding the genetic basis of resistant organisms, are available to researchers. NIAID recently initiated new studies of important antibiotic-resistant bacterial pathogens including sequencing the genomes of more than 500 CRE isolates. Support for preclinical activities to foster drug development, include *in vitro* and animal model screening tools and a comprehensive suite of Investigational New Drug-enabling capabilities. For example, NIAID supported essential toxicity testing for a candidate monoclonal antibody with potential as a therapeutic for *S. aureus* infections. Well-characterized reagents such as bacterial isolates are also available for researchers. Finally, NIAID supports a number of clinical trials networks to evaluate new products and approaches to address AR. Information regarding these resources may be found at www.niaid.nih.gov/research/resources/dmid.

Figure 1. NIAID offers research resources to support the development of diagnostics, vaccines, and therapeutics through all stages of the product development pipeline.

Partnerships Facilitate a Concerted Approach

Because AR is a complex problem with many drivers, combatting it requires a multifaceted approach. In addition to the basic, translational, and clinical research supported by NIAID, improved surveillance, better infection control, wise 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 are all needed for an effective response to the challenge. Therefore, collaboration among partners from multiple disciplines is essential for achieving a coordinated and nimble approach to addressing AR threats as they emerge. NIAID works closely with many partners who are responsible for these other essential areas, most notably through the Interagency Taskforce on Antimicrobial Resistance, the Trans-Atlantic Taskforce on Antimicrobial Resistance and the World Health Organization "Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*."

Innovative Approaches to Addressing the AR Challenge

No single approach will suffice to address the rapidly growing threat of AR. Rather, a combination of innovative tactics based on the latest scientific advances is required. In addition to the projects described above, NIAID has identified the following approaches as the most promising components of a comprehensive strategy to address the AR challenge. Any approach to AR must by definition be evolutionary. Thus, these strategies are meant to be dynamic and to incorporate new ideas and information as science advances.

- **Systems Biology and Antibacterial Resistance: New Directions for Drug Discovery**
  Traditional molecular approaches have focused on identifying specific pathogen and host genes as potential drug targets. Unprecedented opportunities are now available to examine biological systems (i.e., metabolic, immunologic, signaling, and regulatory pathways) beyond their individual components. These holistic approaches offer new research strategies to understand the functional molecular networks generated by the interactions of the host with the pathogen in response to therapeutic treatment. Systems biology can shed light on antibacterial mechanisms of action; identify host and pathogen gene targets for rational combination chemotherapy to suppress resistance; drive drug repurposing; and provide a framework for the discovery and development of novel antibacterial interventions and therapeutics.

- **Harnessing the Immune System to Combat Bacterial Infections**
  Bacterial pathogens can rapidly overwhelm innate defense mechanisms and AR can severely limit therapeutic options for acute treatment. Host immune response can be enhanced through immunological intervention strategies (novel vaccine platforms, modulation of innate immunity) and immunotherapeutics (pathogen-specific human antibodies). These may include creating pathogen-specific vaccines for protection of at-risk populations or developing therapeutic antibodies (monoclonal or polyclonal) for clinical management of AR infections.

- **Disarm, But Leave Unharmed: Exploring Anti-Virulence Strategies**
  New therapeutic approaches that target bacterial virulence factors to prevent disease without requiring direct killing of bacteria may provide solutions that are less likely to induce selective pressure. There is a broad knowledge base on virulence factors, such as toxins, iron acquisition systems, secretion systems, quorum sensing pathways, biofilms, and adhesins, which can be tapped for this novel therapeutic approach. In addition to translational work, new preclinical testing paradigms will need to be developed to bring these novel approaches to the clinic.

- **Synthetic Microbiota: An Ecobiological Approach**
  Rational design of microbial communities as biologic products can treat, prevent, cure, or mitigate infectious diseases or their sequelae. Current approaches harness existing functional constituents of the microbiota and their products to restore health to the host. Physicians and

clinician scientists use fecal microbiota transplants to treat infectious diseases such as *C. difficile*-associated diarrhea, and NIAID has supported research to develop the use of microbial biotherapeutics as adjunct therapy to antibiotic treatment for bacterial vaginosis. Future potential resides in the refinement of translational tools, such as *ex vivo* models that recapitulate microbial ecosystems, and in expansion of these approaches to treat infectious diseases at other anatomical sites, such as the skin or respiratory tract.

- **Less is Better: Diagnostics to Guide Use of Narrow-Spectrum Therapeutics**
  One key strategy to decrease selective pressure is to utilize targeted therapeutics specific for a pathogen or group of pathogens. Such narrow-spectrum antibiotics are currently not appropriate for many infections due to insufficient diagnostic capabilities. A combination of novel technologies (e.g., 'omics) and innovative solutions to practical challenges (e.g., low pathogen load in bloodstream infection) must be brought to bear to bring novel, rapid diagnostics into clinical practice.

- **Exploiting Natural Predators: The Specificity of Phage Therapy**
  Lytic bacteriophage are viruses that infect and kill specific bacteria with the help of enzymes called lysins. Therapeutic and prophylactic products consisting of phage and phage-derived lysins hold promise for targeted killing of specific bacteria while preserving the microbiota. While phages have been used clinically in some countries for decades, their use in the U.S. has been limited. Process improvements in the production, quality assurance, and validation of these products are required, and carefully controlled clinical studies will be needed to establish efficacy in treating drug-resistant pathogens. Applications such as de-colonization procedures may prove to be effective ways to decrease pathogen load while preserving microbiota.

- **Teaching Old Drugs New Tricks: Extending the Clinical Utility of Antibacterial Drugs**
  While NIAID supports several clinical trials to optimize the use of currently licensed antibacterials, significant knowledge gaps remain. 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. In addition, off-patent antibacterials should be explored for their potential to treat serious resistant infections.

Conclusions

As resistance increases, scientists are in a race to "outsmart" bacteria by working around the mechanisms that cause resistance. The biomedical research and product development supported by NIAID form an important basis for the development of novel ways to diagnose, prevent, and treat bacterial infections. While antibacterial resistance 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 of AR 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 antibacterial 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;
- Working collaboratively to ensure a multifaceted approach to combat bacterial resistance.

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