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The Antibacterial Resistance Leadership Group: Scientific Advancements and Future Directions

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In this overview, we describe important contributions from the Antibacterial Resistance Leadership Group (ARLG) to patient care, clinical trials design, and mentorship while outlining future priorities. The ARLG research agenda is focused on 3 key areas: gram-positive infections, gram-negative infections, and diagnostics. The ARLG has developed an innovative approach to clinical trials design, the desirability of outcome ranking (DOOR), which uses an ordinal measure of global outcome to assess both benefits and harms. DOOR was initially applied to observational studies to determine optimal dosing of vancomycin for methicillin-resistant *Staphylcococcus aureus* bacteremia and the efficacy of ceftazidime-avibactam versus colistin for the treatment of carbapenem-resistant Enterobacterales infection. DOOR is being successfully applied to the analysis of interventional trials and, in collaboration with the US Food and Drug Administration (FDA), for use in registrational trials. In the area of diagnostics, the ARLG developed Master Protocol for Evaluating Multiple Infection Diagnostics (MASTERMIND), an innovative design that allows simultaneous testing of multiple diagnostic platforms in a single study. This approach will be used to compare molecular assays for the identification of fluoroquinolone-resistant *Neisseria gonorrhoeae* (MASTER GC) and to compare rapid diagnostic tests for bloodstream infections. The ARLG has initiated a first-in-kind randomized, double-blind, placebo-controlled trial in participants with cystic fibrosis who are chronically colonized with *Pseudomonas aeruginosa* to assess the pharmacokinetics and antimicrobial activity of bacteriophage therapy. Finally, an engaged and highly trained workforce is critical for continued and future success against antimicrobial drug resistance. Thus, the ARLG has developed a robust mentoring program targeted to each stage of research training to attract and retain investigators in the field of antimicrobial resistance research.

Keywords. antibacterial resistance; antibacterial agents; bacterial infections; diagnostics; clinical trials.

Over the past decade, antibacterial resistance (AR) has posed an increasing threat to human health. New varieties of drug-resistant bacteria have emerged and expanded in both hospital and community settings. The coronavirus disease 2019 (COVID-19) pandemic has accelerated these trends. Despite the mounting need, prospects for both new antibiotics and the investigators needed to test them have dwindled as the pharmaceutical industry pursues a mass exodus from antibiotic development.

These developments underscore the vital, ongoing need for the Antibacterial Resistance Leadership Group (ARLG). Since its inception in 2013, the ARLG has been tasked by the National Institute of Allergy and Infectious Diseases to support a responsive, adaptable clinical research network on AR and to conduct clinical research that would not otherwise be done. A summary of ARLG priorities and key advancements is provided in Table 1, and a representation of the evolution of ARLG since inception is provided in Figure 1. The purpose of this overview is to make clinicians and investigators aware of some of the ARLG's important contributions to patient care, clinical trials design, and mentorship during its first decade and to outline programmatic priorities for the future.

Innovation and Evolution: Improving Patient Care

The ARLG has systematically conducted a series of studies in its 3 scientific priority areas of gram-positive infections, gram-negative infections, and diagnostics. Each study builds on prior results and informs studies to follow. The ARLG has focused significant efforts on the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection, the most common type of drug-resistant bacterial infection in the United States [30] and a leading cause of mortality attributable to AR globally [31]. Because vancomycin is the most widely used drug to treat serious MRSA infections, the ARLG undertook the Prospective Observational Evaluation of the Association Between Initial

Table 1. Antibacterial Resistance Leadership Group Priority Studies and Key Advancements

Study	Description	Status	Scientific Area
Optimize administration and repurpose existing antibacterial agents			
ACUMIN	Phase 4 open-label PK study of tetracycline antibiotic for injection following a single infusion in critically ill adults	Published [1]	GN, PK
COMBINE HFIM	Hollow fiber infection model studies to determine the optimal dosing of the combination of ceftazidime-avibactam with aztreonam against NDM-1–producing Enterobacterales	Published [2]	GN, PK
COMBINE	Phase 1 open-label study in healthy adults to evaluate the safety and PK of ceftazidime-avibactam in combination with aztreonam	Published [3, 4]	GN, PK
PROOF	Phase 1 study to evaluate PK, safety, and tolerability of 2 dosing regimens of oral fosfomycin tromethamine in healthy adults	Published [5]	GN, PK
FOCUS	Phase 4 randomized, double-blinded trial to evaluate the efficacy of oral fosfomycin versus levofloxacin in complicated urinary tract infections	Manuscript submitted	GN
PROVIDE	Prospective observational evaluation of the association between the day 2 vancomycin exposure and failure rates among adult hospitalized patients with methicillin-resistant *Staphylococcus aureus* bloodstream infections	Published [6]	GP, PK
OPTIMIZE-GNI	Phase 4 prospective, multicenter, interventional PK study to develop individualized meropenem and cefepime dosing algorithms for critically ill patients with suspected or documented antimicrobial-resistant gram-negative infections and varying degrees of renal function based on observed cystatin C serum concentrations	Study design	GN, PK
Evaluate the effectiveness of antibacterial agents alone or in combination			
DOTS	Multicenter, randomized, open-label, assessor-blinded, superiority trial to compare dalbavancin to the standard-of-care treatment for the completion of therapy in participants who have complicated *S. aureus* bacteremia or right-sided native valve infective endocarditis and who have cleared their baseline bacteremia	Enrollment complete [7]	GP
Colistin versus Ceftazidime-Avibactam	Prospective, multicenter, observational study to compare the efficacy and safety of colistin to ceftazidime-avibactam for the treatment of infections due to carbapenem-resistant Enterobacterales	Published [8]	GN
Identify and evaluate novel antiinfective agents and treatment strategies for bacterial infections			
PHAGE	Phase 1b/2, multicenter, randomized, double-blind, placebo-controlled trial of the safety and microbiological activity of a single dose of bacteriophage therapy in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*	Enrolling [9]	GN
PHAT	Isolation and characterization of lytic phages that target multidrug-resistant bacteria to generate species-specific panels of phages	Published [10, 11]	GN
SCOUT-CAP	Phase 4 double-blind, placebo-controlled, randomized trial to evaluate short-course versus standard-course outpatient therapy of community-acquired pneumonia and microbiome analysis	Published [12, 13]	GP
MeChaTeBla	Mechanistic and structural characterization of the interaction of a novel antibiotic with clinically relevant beta-lactamases	Data analysis	GN
ARGONAUT	Series of studies for the characterization of the in vitro activity of novel agents against genetically defined clinical isolates of carbapenem-resistant gram-negative bacteria	Data analysis	GN
STEP FMT	Study to determine strain temporal engraftment and persistence after FMT by identifying the specific taxa that may confer long-term multidrug-resistant colonization resistance among FMT-treated individuals in a clinical trial of renal transplant recipients undergoing FMT	Data analysis	GN, GP
TRAP-LRTI	Multicenter, randomized, placebo-controlled, noninferiority study of azithromycin treatment versus placebo in adults with suspect lower respiratory tract infection and a procalcitonin level of <0.1 ng/mL	Published [14]	GP, Dx
Global clinical and molecular epidemiology of MDROs			
CRACKLE	Multicenter, prospective cohort study to define the clinical and molecular epidemiology of carbapenem-resistant Enterobacterales in the United States	Published [15]	GN
CRACKLE-2	International prospective cohort study to define the global clinical and molecular epidemiology of carbapenem-resistant Enterobacterales	Published [16, 17]	GN
POP	International prospective cohort study to define the global clinical and molecular epidemiology of carbapenem-resistant *P. aeruginosa*	Published [18]	GN
SNAP	International prospective cohort study to define the global clinical and molecular epidemiology of carbapenem-resistant *Acinetobacter baumannii*	Manuscript submitted	GN
SHREC	Multicenter prospective cohort study that uses the MDRO network to study the clinical and molecular epidemiology of ceftriaxone-resistant *Escherichia coli* in the United States	Published [19]	GN
Identify and evaluate novel diagnostic strategies			
RADICAL	Series of studies to develop and evaluate a host-based assay to distinguish among bacterial, viral, and non-infectious etiologies of acute respiratory tract infections, which could help reduce inappropriate antimicrobial use	Published [20–22]	Dx

Table 1. Continued

Study	Description	Status	Scientific Area
RADICAL-3	Prospective, randomized, interventional, pilot study to estimate the clinical utility of the host response-bacterial/viral test run on a novel platform in emergency department patients with acute, febrile respiratory infection	Study design	Dx
MASTER RADICAL	MASTER protocol to advance the validation of platforms measuring the RADICAL test, including an evaluation of the impact of specimen type and specimen storage conditions	Data analysis	Dx
RADICAL 510(k)	Prospective, multicenter study to assess the performance of host gene expression signature in blood specimens to discriminate between bacterial and viral infections	Study design	Dx
MASTERMIND-GC	Cross-sectional study to evaluate the diagnostic accuracy of multiple commercially available NAATs for detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* from oropharyngeal and rectal sites	Published [23]	Dx
MASTERMIND-BSI	MASTER protocol for evaluating multiple rapid diagnostics for identification of bacteria directly from blood samples	Start-up	Dx
MASTERMIND-RING	MASTER protocol for evaluating multiple diagnostics for direct-from-specimen NAATs for detection of ciprofloxacin resistance in *N. gonorrhoeae*	Protocol development	Dx
BCID	Prospective, randomized, controlled trial to evaluate the clinical and economic impact of rapid identification and susceptibility testing of pathogens growing in blood culture bottles	Published [24]	Dx
RAPIDS-GN	Multicenter, prospective, randomized, controlled trial to evaluate standard culture and AST versus rapid identification and AST for patients with confirmed gram-negative bacteremia	Published [25]	Dx, GN
FAST	International, prospective, randomized trial to evaluate clinical outcomes among patients with gram-negative bacteremia who have blood culture evaluation using standard methods versus rapid antibiotic susceptibility testing	Start-up	Dx, GN
DIFFR	Study to optimize a novel molecular diagnostic to detect *Clostridioides difficile* toxin mRNA expression in stool, determine its analytical performance characteristics, and evaluate the clinical sensitivity and specificity relative to gold-standard methods	Data analysis	Dx, GP
PNEUMONIA DIRECT PILOT	Prospective, observational, diagnostic feasibility study to determine the accuracy of pathogen- and host-directed testing for the diagnosis of ventilator-associated pneumonia	Protocol development	Dx, GN, GP
GENO-STELLAR	Web-based genomic-epidemiological tool for antimicrobial resistance prediction	Platform launched [26]	Dx, GN
REPORT-ABC	Study evaluating laboratory reporting practices of rapid testing performed on positive blood cultures	Published [27]	Dx
PST	Comparative evaluation of 2 assays for PST to assess reproducibility of PST methods needed to support clinical trials of phage therapy	Manuscript submitted	Dx, GN
Create innovations in clinical trial design [28]			
DOOR	Desirability of outcome ranking: patient-centric benefit-risk evaluation paradigm for the design, analysis, and interpretation of clinical trials of bacterial infection syndromes	…	…
QOL	Quality of life: incorporate the patient perspective as an outcome in clinical trials of bacterial infection syndromes	…	…
DOOR MAT	Desirability of outcome ranking for the management of antimicrobial therapy: framework for assessing antibiotic selection strategies in the presence of drug resistance	…	…
SMART-COMPASS	Sequential, multiple-assignment, randomized trials for comparing personalized antibiotic strategies: a trial design to compare strategies	…	…
MASTERMIND	MASTER protocol for simultaneously evaluating multiple infection diagnostics with a single patient's sample(s), providing efficiencies of specimen collection and characterization	…	…
BED-FRAME/AWA	Benefit-risk evaluation of diagnostics: a FRAMEwork and average weighted accuracy: systematic and pragmatic approach to evaluate and compare diagnostic alternatives to aid in clinical decision-making	…	…
Clinically adjudicated reference standards	Approach to use clinically adjudicated reference standards for evaluation of diagnostic test accuracy when a predefined gold standard is lacking or the test's accuracy potentially exceeds that of its predecessors [29]	…	…

Abbreviations: AST, antimicrobial susceptibility testing; Dx, diagnostics; BSI, bloodstream infection; FMT, fecal microbiota transplantation; GN, gram-negatives; GP, gram-positives; MDRO, multidrug-resistant organism; NAAT, nucleic acid amplification test; NDM, New Delhi metallo-β-lactamase; PK, pharmacokinetic(s); PST, phage susceptibility testing.

Vancomycin Exposure and Failure Rates Among Adult Hospitalized Patients With Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections (PROVIDE) study [6] to examine the relationship between vancomycin dosing and patient outcomes. PROVIDE relied on the desirability of outcome ranking (DOOR), a landmark statistical methodology developed by the ARLG to assess patient outcomes. DOOR uses an ordinal ranking that combines both safety and efficacy to
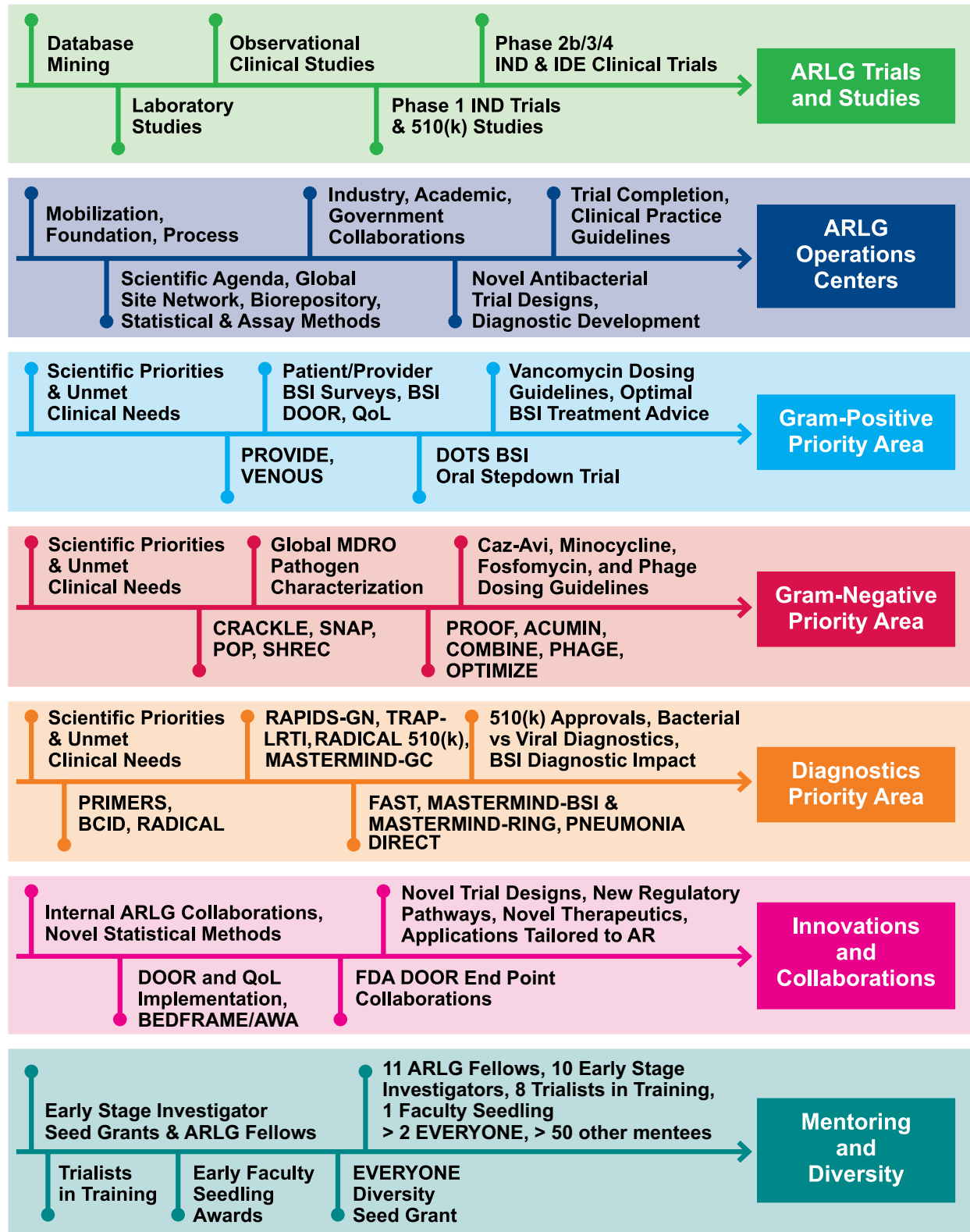
Figure 1. Evolution of the ARLG since inception. See Table 1 and text for names and brief descriptions of trials. Abbreviations: AR, antibacterial resistance; ARLG, Antibacterial Resistance Leadership Group; caz-avi, ceftazidime-avibactam; FDA, US Food and Drug Administration; GC, Gonorrhea-Chlamydia; IND, investigational new drug application; IDE, investigational device exemption; MDRO, multidrug-resistant organism; PRIMERS, platforms for rapid identification of MDR-gram-negative bacteria and evaluation of resistance studies; VENOUS, vancomycin-resistant enterococcal BSI outcomes study.

measure the totality of the patient experience for one treatment versus another. DOOR is particularly well suited for determining optimal drug exposure (ie, the exposure that maximizes efficacy and safety). PROVIDE showed that higher vancomycin exposure, measured as area under the drug concentration-time curve (AUC), did not improve efficacy and was associated with a higher rate of acute kidney injury. In contrast, an optimal drug exposure of 24-hour AUC ≤515 mg/L × hour was associated with lower rates of both treatment failure and acute kidney injury. These results directly led to current treatment guidelines for vancomycin dosing for MRSA [32]. The ARLG undertook the Dalbavancin as an Option for Treatment of *S. aureus* bacteremia (DOTS) trial, a phase 2b superiority randomized, controlled trial (RCT) comparing 2 doses of dalbavancin a week apart with standard intravenous therapy for the treatment of complicated *S. aureus* bacteremia [7]. DOTS demonstrates the application of DOOR in an interventional study [7]. If successful, DOTS will change treatment for MRSA and methicillin-susceptible *S. aureus* bacteremia and illustrate the advantages of DOOR in clinical trial design. Enrollment was completed in July 2023.

The ARLG has also focused on critical unmet needs posed by multidrug-resistant (MDR) gram-negative bacteria by establishing the Multidrug Resistant Organism (MDRO) Network. Through the MDRO Network, the ARLG characterized the clinical and molecular epidemiology of the following critical priority pathogens identified by the World Health Organization (WHO): carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii* complex.

The ARLG established the Consortium on Resistance Against Carbapenems in Klebsiella and Other Enterobacteriaceae (CRACKLE) to characterize the clinical and molecular epidemiology of CRE in the United States and globally (CRACKLE-). In these studies, outcome data were collected for patients treated with colistin, considered at the time to be the first-line agent, or ceftazidime-avibactam, of promising but unproven efficacy for CRE. DOOR was used to perform efficacy, safety, and risk–benefit analyses for colistin compared with ceftazidime-avibactam. The differences were striking, with a more than 3-fold reduction in 30-day mortality (32% for colistin, 9% for ceftazidime-avibactam) and a 64% probability of a better overall outcome with ceftazidime-avibactam [8]. Since its publication in 2018, this article has been cited more than 500 times and has served as the basis for treatment guidelines to use ceftazidime-avibactam instead of colistin for CRE [33].

Unfortunately, ceftazidime-avibactam is not an option for New Delhi metallo-β-lactamase (NDM)-producing Enterobacterales, high rates of which were identified in the CRACKLE studies. This reinforced the need for effective therapies for infections caused by these pathogens. Building on initial reports from ARLG investigators suggesting that coadministration of aztreonam and ceftazidime-avibactam could represent a treatment option for NDM-producing Enterobacterales infections [34], the ARLG initially undertook hollow fiber infection model (HFIM) studies to identify optimal doses of these drug combinations [2]. Building on these results, the ARLG conducted a phase 1 trial of healthy volunteers to confirm dosing schedules predicted in the HFIM work [3, 4], providing clinicians with guidance for dosing and safety considerations. Future studies are planned to test the clinical effectiveness of aztreonam + ceftazidime-avibactam as well as other novel antibiotics in patients with serious infections caused by NDM-producing pathogens.

The ARLG's Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and associated carbapenemases (POP) cohort study sought to define the clinical characteristics and frequency of CRPA infections globally [18]. Identification of dramatic regional differences in the mechanisms and clinical impact of carbapenem resistance in *P. aeruginosa* globally confirmed the need to pursue multiple treatment options, including nontraditional ones, for this pathogen. This discovery motivated the ARLG to evaluate bacteriophages as a possible treatment for *P. aeruginosa*.

A central concept guiding the ARLG approach to phages is that if they are intended to be used as a drug, they must be tested and developed as such to advance the field beyond anecdotal reports. To that end, the ARLG published guidance outlining clinical, laboratory, and pharmacokinetic considerations of phage therapy [35]. Additionally, with industry and government collaborators, the ARLG helped to advance methods for susceptibility testing. This document, which has been downloaded more than 11 500 times in the 2 years since its publication, provides the basis for the ARLG's phase 1b/2, multicentered, randomized, double-blind, placebo-controlled trial of the Safety and Microbiological Activity of a Single Dose of Bacteriophage Therapy in Cystic Fibrosis Subjects Colonized with *Pseudomonas aeruginosa* (PHAGE) trial (ClinicalTrials.gov identifier: NCT05453578) [9]. Currently enrolling, PHAGE will allow a comprehensive evaluation of phage safety, antibacterial activity, pharmacokinetics, susceptibility testing, and emergence of resistance to therapy.

Innovation and Evolution: Diagnostics

As 1 of its 3 scientific priority areas, the ARLG is addressing the need for better diagnostics in the AR sphere. The ARLG pioneered the use of MASTERMIND, an innovative trial design that allows simultaneous testing of multiple diagnostic platforms in a single study [36]. In brief, MASTERMIND studies involve a study protocol that provides equitable sample access for each diagnostic platform involved in the study. Care is taken to ensure that optimal assay conditions are met for each tested platform. At the completion of a MASTERMIND study, each company receives the necessary performance data for its

diagnostic platform to support possible regulatory filing. Using this approach, MASTERMIND-GC supported FDA approval for 2 molecular assays for the detection of extragenital *N. gonorrhoeae* or *Chlamydia trachomatis* [23] in a single clinical trial. Additional MASTERMIND studies are being designed for other indications. MASTERMIND-RING will evaluate molecular tests to predict ciprofloxacin resistance or susceptibility in *N. gonorrhoeae*, and MASTERMIND-BSI will evaluate rapid diagnostics for bloodstream infections.

Viral upper respiratory infections are one of the leading reasons for unnecessary antibiotic prescriptions. To address this, the ARLG has focused on methods to differentiate bacterial from viral etiologies of respiratory infection. The ARLG has partnered with Biomeme and is pursuing 510k approval from the FDA for the Rapid Diagnostics in Categorizing Acute Lung Infections (RADICAL) platform, which assays host gene expression patterns to differentiate bacterial and viral infection. Ultimately, the ARLG plans to test the clinical utility of the RADICAL assay by randomizing patients who present to the emergency department with acute respiratory infection to either standard care or RADICAL-guided treatment. The Targeted Reduction of Antibiotics using Procalcitonin in Lower Respiratory Tract Infection (TRAP-LRTI) study, a double-blind, noninferiority RCT, compared azithromycin with placebo in outpatients with clinically suspected nonpneumonia LRTIs and procalcitonin levels ≤0.25 ng/mL [14]. The primary analysis, which used the standard frequentist approach, found placebo not to be noninferior to azithromycin for clinical improvement at day 5. Interestingly, the secondary DOOR analysis of a global patient outcome based on clinical benefits and harms showed no significant difference between treatment groups, but azithromycin was associated with more solicited adverse events [14].

Delays in the clinical availability of antimicrobial susceptibility results for patients with bloodstream infections (BSI) potentially contribute to antibiotic overuse. Additionally, patients may not receive antibiotics active against the bacterium with which they are infected. The ARLG conducted 2 RCTs to evaluate the clinical impact of rapid diagnostics for positive blood culture bottles. In the Blood Culture Identification (BCID) study, use of a rapid multiplex polymerase chain reaction panel reported with templated comments reduced treatment of contaminants and use of broad-spectrum antibiotics when compared with standard blood culture bottle processing [24]. Benefits were most evident in patients with gram-positive bacteremia, which was hypothesized to be due to the dearth of clinically actionable information on the susceptibility of gram-negative bacteria. Accordingly, the Rapid Identification and Susceptibility Testing for Gram-negative Bacteremia (RAPIDS-GN) trial evaluated organism identification and phenotypic antimicrobial susceptibility testing using the Accelerate PhenoTest BC Kit (Accelerate

Diagnostics, Tucson, AZ; RAPID) directly on positive blood culture bottles. In patients with gram-negative bacteremia, the median time to antibiotic escalation (for resistant bacteria) and deescalation (for nonresistant bacteria) was significantly shorter in the RAPID diagnostic arm [25]. Based on the results from the BCID and RAPIDS-GN studies, the ARLG recently published best practice guidelines supporting use of rapid tests on positive blood culture bottles with guidance on rapid reporting [27]. However, neither the BCID nor RAPIDS-GN platform was shown to improve the outcomes of patients with bloodstream infections. This finding is potentially due to the low rates of MDR gram-negative bacteria, for which a shorter time to effective antibiotic therapy would presumably afford the greatest potential benefit in either of the 2 US-based studies. As a result, the Fast Antibiotic Susceptibility Testing for Gram-negative Bacteremia (FAST) trial is designed to test whether rapid phenotypic susceptibility testing of positive blood culture bottles leads to improved outcomes in patients with gram-negative bacterial bloodstream infections in clinical settings with high rates of AR. FAST is leveraging a metabolomic-based rapid phenotypic susceptibility platform.

Innovation and Evolution: Clinical Trials Design

Advances in AR research and study design have the potential to improve not just one study but a generation of studies. In addition to improving patient care and clinical practice, the ARLG has focused on enhancing the ways clinical trials are conducted and analyzed. For example, the ARLG began work with the novel clinical trials end point DOOR [28] through analyses of observational studies but now has applied this methodology to RCTs. The longer-term goal is to bring these innovations into the mainstream. To this end, the ARLG has established the Innovations Working Group, a unique National Institutes of Health (NIH)–FDA collaboration tasked with generating publicly available deliverables that could be used to support FDA approval and package insert language for novel antibacterials. Projects fall into 2 workstreams: DOOR-type end points and health-related quality-of-life measures for the 4 most common licensing indications for antibacterial agents: acute bacterial skin and skin structure infections, complicated urinary tract infection (cUTI), complicated intraabdominal infection (cIAI), and hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP). This collaboration has been further strengthened by the creation of an FDA Antibacterial Drug Resistance (DOOR) Fellowship made possible by the FDA through the Oak Ridge Institute for Science and Education (ORISE). To date, DOOR end points have been published for cUTI [37] and cIAI [38]. A manuscript describing DOOR for HABP/VABP is being finalized. The ARLG has also designed a DOOR app, freely available online to the scientific community

for use in performing DOOR-type analyses (https://methods.bsc.gwu.edu/) [39].

The ARLG has also developed several innovative advances to execute and analyze studies that involve diagnostic platforms. In addition to the MASTERMIND approach, the Benefit-Risk Evaluation of Diagnostics: A Framework (BED-FRAME) provides a means of communicating the expected impact of diagnostic application and trade-offs of diagnostic alternatives to guide decision-making [40]. The ARLG has pioneered application of RCTs to diagnostics to inform when and how they should be used, and this guidance is being adopted by the scientific community [25]. Additionally, the ARLG has assembled a web-searchable biorepository of well-characterized MDR bacteria that are available without cost to the scientific community (https://arlg.org/laboratory-center-strain-access/) [41].

Collaborations

Collaborations with industry partners, governmental agencies, and academic study sites around the world have been vital to ARLG's mission over the past decade. The ARLG has provided companies with epidemiologic data on MDR pathogens, well-characterized bacterial isolates from the ARLG Biorepository, consultative advice for a sponsor's clinical trial, clinical sample matrices for diagnostic development, and clinical trial infrastructure to execute MASTERMIND-based collaborative studies. In other projects, the ARLG has received study drug or diagnostic tests for interventional trials, industry expertise on antibiotics or diagnostic platforms involved in ARLG studies, and access to industry-owned datasets from phase 2 and 3 clinical trials to advance DOOR development. The ARLG has also fostered intergovernmental agency collaborations. One example is the FDA-NIH collaboration to develop DOOR end points. The FDA has also interacted with the ARLG Laboratory Center (eg, MASTERMIND-RING, Phage Task Force) and with the ARLG Innovations Working Group through regular meetings with patient representatives and (with appropriate firewall protection given FDA involvement) industry members. This collaboration has led to the publication of 2 DOOR end points for antibacterial indications [37, 38] and the creation of an ORISE fellowship by the FDA to support a trainee to work at the FDA on DOOR end point development. Importantly, this partnership is fully consistent with the CARB National Action Plan for a concerted response to AR [42].

Central to ARLG's mission has been collaboration with thought leaders, both domestic and international, to successfully define the clinical and molecular epidemiology of WHO critical pathogens. As a result, the ARLG currently involves more than 120 investigators from 6 countries. Having actively worked with Combatting Bacterial Resistance in Europe (COMBACTE), the ARLG is currently reestablishing a memorandum of understanding for COMBACTE's replacement organization, the European Clinical Research Alliance on Infectious Diseases. In summary, the ARLG believes that the global threat of AR will continue to require an ongoing collaborative approach with international investigators, companies, and government entities.

Mentoring

Not to be overlooked is the need to address the declining workforce of investigators pursuing careers in AR and antiinfective drug development. To this end, the ARLG has established a strong mentoring program. This investment is beginning to deliver returns as 6 of 12 (50%) trainees from the first cycle of ARLG have secured K23s or other career development awards. Even more encouraging, several current ARLG studies, including MASTERMIND-BSI, DOTS, and FAST, are currently being led by trainees from the initial grant cycle.

ARLG: The Future

Progress in the design and conduct of clinical trials and diagnostics, recently accentuated by the necessities of the COVID-19 pandemic, offers new approaches for evaluating antibacterial compounds, treatments, and tests. As more antibacterials active against MDR gram-negative bacteria become available, platform trials comparing multiple interventions, including unconventional approaches such as phage therapy, become possible. Such trials would leverage local resources and international collaborations developed within the MDRO Network. Optimal management of *S. aureus* bloodstream infections, particularly those caused by MRSA, remains elusive. New diagnostic technologies, such as the detection of microbial cell-free DNA in plasma, have the potential to reduce antibiotic use by individualizing antibiotic therapy duration for patients with bloodstream infections [43]. Advances in artificial intelligence and access to ever-larger clinical databases make real-world data ever more powerful, particularly when results of RCTs are unavailable.

Diagnostics for detecting bacterial infections and identifying antibacterial resistance remain a top priority for the ARLG. The ARLG's MASTERMIND studies are well suited for evaluating diagnostic platforms in terms of performance, informed by advanced reference standards [29]; RCTs are valuable clinical utility studies particularly as diagnostics provide progressively faster genotypic and phenotypic data for bacterial infections. Marrying the host response with pathogen detection has the potential to improve the diagnosis and, ultimately, outcomes of ventilator-associated pneumonia and other infections.

The ARLG will continue to adapt and evolve to respond to the threat of AR by building on its greatest assets: its team of investigators, its collaborative relationships, and those in the greater scientific community [44].

Notes

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