Fiscal Years 2016 – 2025
Office of Infectious Diseases
CARB Research Overview
Department of Health and Human Services
Food and Drug Administration, Silver Spring, MD
November 2025

Public Health Impact:
As bacteria and fungi continue to develop resistance, standard treatments can become ineffective, and these infections can threaten global health. Therefore, there is an urgent need to develop new antibacterial and antifungal drugs that are active against pathogens associated with drug resistance and poor clinical outcomes to improve patient health and well-being worldwide.

FDA's roles in combatting antibacterial and antifungal drug resistance are to: (1) facilitate the development of new antibacterial and antifungal drugs to treat patients and (2) advance the science of clinical trial design.

Background:
In March 2015, the National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) was developed in response to Executive Order 13676: Combating Antibiotic-Resistant Bacteria, which was issued on September 18, 2014. The National Action Plan outlines steps for implementing the National Strategy for Combating Antibiotic-Resistant Bacteria to address urgent and serious drug-resistant threats that affect people in the U.S. and around the world. The updated National Action Plan for 2020 - 2025 continues to outline steps for implementing the National Strategy for Combating Antibiotic-Resistant Bacteria to address urgent and serious drug-resistant threats (bacteria and fungi) that affect people in the U.S. and around the world. Implementation of the National Action Plan also supports World Health Assembly resolution 67.25 (Antimicrobial Resistance), which urges countries to take urgent action at the national, regional, and local levels to combat resistance. In recent years, facilitating antifungal drug development has been added due to unmet need.
FDA convened several workshops to facilitate the development of new drugs against bacteria and fungi to help identify regulatory science research needs. Information regarding these workshops can be found on the Office of Infectious Diseases Research webpage.

FDA CARB Research Priorities
To help stimulate development programs for antibacterial and antifungal drugs where limited resources or a lack of incentives is preventing the development of new drugs, FDA has identified research areas where regulatory science can support new antibacterial and antifungal drug development. These areas include:

- Evaluate potential innovations in clinical trial design for new antibacterial and antifungal drugs such as enrollment strategies, data collection streamlining, drug development tools, clinical endpoints, and new statistical analytic approaches.
- Advance the science of non-clinical studies, pharmacokinetic studies, and/or real-world evidence studies, such as studies assessing antifungal and antibacterial resistance, and studies to address areas of unmet medical need.
- Evaluate strategies to enrich enrollment in clinical trials for new antibacterial and antifungal drugs such as the use of rapid diagnostic tests.
- Advance the science of antimicrobial drug susceptibility testing to ensure that up to date susceptibility testing interpretive criteria (breakpoints) are available for patient care and

antimicrobial stewardship. For example, provide updated data from microbiologic surveillance studies, pharmacokinetic studies, including modeling, and/or clinical outcome data to support updating susceptibility test interpretive criteria for certain antimicrobial drugs that are a high public health priority.

Consistent with the CARB goals in the area of unmet medical need, fiscal years 2016-2025 research focuses on: (1) advancing the science of antibacterial drug susceptibility testing to ensure that up-to-date breakpoints are available for patient care and antimicrobial stewardship, (2) advancing the science of in vitro models to facilitate antibacterial drug development for the treatment of uncomplicated urinary tract infections (uUTIs), (3) developing non-clinical models of serious infections caused by rare, emerging, and drug-resistant fungal pathogens associated with invasive systemic disease, (4) using big data to generate contemporaneous cohorts for study of novel antibacterials and antifungals targeting rare infections, and (5) developing an antibacterial drug harm score through automated extraction of data from the electronic health record based on defined antibacterial drug-associated adverse events (AE), (6) developing and validating novel trial endpoints to capture the clinical benefit to patients with unmet medical need, such as, those with disseminated coccidioidomycosis or nontuberculous mycobacteria pulmonary disease.

Project Descriptions for Ongoing CARB Research Studies

Creation and Validation of a Patient Reported Outcome (PRO) Instrument for the Assessment of Health-Related Quality of Life (HRQOL) in Patients with Coccidioidomycosis

- Awarded to F2G, Ltd. (FY21: 75F40121C00145)
- The objective of this study is to develop and validate a PRO measure for the management of chronic disseminated coccidioidomycosis (Valley Fever).
- Currently, there are no well-defined and validated endpoints for use in coccidioidomycosis clinical trials. The PRO instrument under development in this study aims to accurately assess the efficacy of anti-fungal treatments for coccidioidomycosis.
- This study aligns with section 2.4.1 of the Broad Agency Announcement: Evaluate potential innovations in clinical trial design for new drugs such as enrollment strategies, data collection streamlining, drug development tools, clinical endpoints, and new statistical analytic approaches.
- Study Outcomes:
    - **Poster Presentation:** Developing a Patient-Reported Outcome (PRO) Instrument for Coccidioidomycosis: The Importance of Clinician Feedback. (MSGERC 2022).
    - **Poster Presentation:** "Valley Fever is like having an airborne cancer": The lived experiences of coccidioidomycosis patients examined through online methodologies (ISOQOL 29th Annual Conference 2022).
    - **Poster Presentation:** Development of a de novo Patient-Reported Outcome Measure to Assess the Impacts of Disseminated Coccidioidomycosis (Valley Fever) on Patients living with the Condition (IDWeek 2023); Abstract available at Open Forum Infectious Diseases; doi: 10.1093/ofid/ofad500.2134.
    - **Publication:** Harvey E, Clegg J, Bresnik M, Blatt E, Hughes S, Umanzor-Figueroa C, Purdie R, Thompson GR 3rd, Symonds T. Development of a novel patient-reported outcome measure for disseminated coccidioidomycosis (valley fever). J Antimicrob Chemother. 2025 Mar 3;80(3):657-665. doi: 10.1093/jac/dkae453. PMID: 39688396; PMCID: PMC11879242.

Advancing Methods to Optimize Antimicrobial Dosing in Patients with Obesity

- Awarded to University of Michigan (FY22: 7540122C00147).
- The overall objective of this study is to develop new strategies for antimicrobial dose selection in patients with obesity. This study will: 1) establish a vancomycin pharmacomorphic model using data from a large cohort of infected patients with obesity and CT scans, and 2) compare alternate vancomycin dosing regimens based on population PK models with morphomic covariates in order to test pharmacomorphomic based vancomycin dosing to standard dosing in obese patients.
- Currently, this patient population is vulnerable to underdosing or overdosing of antimicrobials and therefore approaches to determine appropriate dosing is need. Optimization of antimicrobial dosing strategies in these patients may lead to better clinical outcomes and provide clinicians with needed information regarding dosage of antimicrobials in patients with obesity.
- This study aligns with section 2.4.2 of the Broad Agency Announcement: Advance the science of in vitro, animal model, pharmacokinetic studies, and/or real-world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children, and patients with renal or hepatic dysfunction.

Development of a Rabbit Model to Characterise Antifungal Drug Resistance

- Awarded to University of Liverpool (FY23: 75F40123C00191)
- The overarching goal is to generate data to inform the optimized dosing of the widely used antifungal, anidulafungin, to treat infections and suppress emergence of resistance. The goals of this study are: 1) develop a rabbit model of disseminated candidiasis with *C. auris* to investigate resistance emergence to anidulafungin treatment, and 2) development of a HFIM model of *C. auris* resistance using anidulafungin.
- This work will elucidate whether the PK-PD targets for anidulafungin differ for the treatment of *C. auris* and whether different mechanisms of resistance are involved. The output will be data to guide the clinical dosing regimens for anidulafungin, and PK-PD targets may also support the setting of clinical breakpoints for *C. auris*.
- This study aligns with Charge Area IIIb1b of the Broad Agency Announcement: Advance the science of in vitro, animal model, pharmacokinetic studies, and/or real-world evidence studies to facilitate drug development, including studies focused on antifungal and antibacterial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction.

Bridging the gap between urinary tract infection pharmacokinetic/pharmacodynamic in vitro models and the optimization of antibiotic selection, dosing strategies, clinical breakpoints, and novel drug development

- Awarded to Monash University (FY23: 75F40123C00185)
- The objectives of this study are: 1) assess bacterial kill and emergence of resistance in a bladder infection in vitro model, 2) establish urine-specific susceptibility breakpoints and optimize clinical dosage regimens, and 3) correlate UTI modeling with clinical and microbiological outcomes.
- This work will streamline new drug development for UTIs, guide optimized and personalized dosing schedules, and promote the preservation of antibiotic activity and clinical utility into the future.
- This study aligns with Charge Area IIIb1a of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria are available for patient care and antimicrobial stewardship.
- Study Outcomes:

- **Poster Presentation:** Assessing Amoxicillin-Clavulanate Bacterial Kill and Emergence of Resistance in an In Vitro Urinary Tract Infection Model (Monash University Bladder & Kidney Health Discovery Program Symposium, November 15th, 2024).
- **Oral Presentation:** Optimization of an In Vitro Bladder Infection Model for the Assessment of Oral Amoxicillin-Clavulanate against ESBL-producing *Escherichia coli* (Australian Society for Antimicrobials Annual Scientific Meeting, February 20th, 2025).
- **Oral Presentation:** Complexity of Treating Multidrug Resistant UTIs: Dynamic Modeling of Antimicrobial PK/PD to Inform Treatment Decision in Uncomplicated UTIs (Australian Society for Antimicrobials Annual Scientific Meeting, February 22nd, 2025).
- **Poster Presentation:** Urinary pharmacodynamic profiling of oral amoxicillin-clavulanate in a bladder infection model (ESCMID Global Conference, 2025).
- **Poster Presentation:** Nitrofurantoin efficacy and the influence of urodynamics among multidrug-resistant *Escherichia coli* in an in vitro bladder infection model (Monash University Bladder & Kidney Health Symposium, October 24th, 2025).

An Electronic Approach for Post-Market Safety Monitoring for Antibiotic-Associated Adverse Events (ABX-AEs)

- Centers of Excellence in Regulatory Science and Innovation (CERSI) cooperative agreement with Johns Hopkins University (FY23: 3U01FD005942-07S1 & (FY24: 3U01FD005942-08)
- The overall goal is to support the development of electronic health record (EHR) based algorithms for detecting adverse events associated with selected antibacterial drugs and validating the algorithms through manual chart review.
- The outcome of this project may promote early detection of safety signals to inform labeling changes and/or drug safety communications with healthcare providers.
- Study Outcomes:
  - **Publication**: Cherian JP, Jones GF, Bachina P, Helsel T, Virk Z, Lee JH, Fiawoo S, Salinas A, Dzintars K, O'Shaughnessy E, Gopinath R, Tamma PD, Cosgrove SE, Klein EY. An Electronic Algorithm to Identify Vancomycin-Associated Acute Kidney Injury. Open Forum Infect Dis. 2023 May 16;10(6):ofad264. doi: 10.1093/ofid/ofad264. Erratum in: Open Forum Infect Dis. 2023 Jul 31;10(7):ofad407. doi: 10.1093/ofid/ofad407. PMID: 37383251; PMCID: PMC10296058.

Pharmacodynamics of Daptomycin against *Enterococcus faecium* and *Enterococcus faecalis* in the Murine Thigh Infection Model

- Awarded to Hartford Hospital (75F40125C00085)
- The aims of this project are: 1) to refine the methodology for establishing a neutropenic murine thigh infection model using *Enterococcus spp*.; 2) assess the efficacy of daptomycin exposures equivalent to human doses of 6, 8, 10, and 12 mg/kg/day in the refined murine neutropenic thigh infection model; and 3) determine daptomycin efficacy targets for stasis and 1-$\log_{10}$ CFU reduction, probability of target attainment, and cumulative fraction of response.
- The overall goal of this project seeks to improve the in vivo growth of Enterococci in the murine neutropenic thigh infection model by using enhanced growth conditions and humanized antibiotic exposure to help in defining optimal treatment regimens and dosage for challenging enterococcal infections.
- This study aligns with Charge Area IIIb1a of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria.

Developing studies needed to define clinical and/or surrogate endpoints that can be used for the regulatory approval of decolonizing agents, microbiome therapies, or similar products

- Awarded to University of Maryland Baltimore (75F10125C00049)
- The objectives of this project are: 1) to perform a systematic review of existing data describing the relationship between the use of decolonizing agents, the subsequent effect on colonization, and the risk of subsequent adverse clinical outcomes, 2) to develop and propose specific studies needed to establish evidence and support FDA approval of decolonizing agents.
- Development of decolonizing agents is challenging, in part, due to the size of the clinical trials that would be required to evaluate the effect of an investigational product on a clinical outcome. The identification of decolonizing surrogate endpoints through this project may support future development efforts for decolonizing agents.
- This study aligns with Charge Area IIIb1c of the Broad Agency Announcement: Evaluate potential innovations in clinical trial design for new drugs

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Previously Funded Studies:

Development of an Automated and Sustainable Electronic Approach for Data Mining to Evaluate Clinical Outcomes of Patients with Bacterial Infections

- Awarded to Johns Hopkins University School of Medicine (FY16: HHSF223201610070C)
- The objective of this project was to develop the coding needed for the electronic transfer of selected clinical data for patients with gram-negative bacteremia (bloodstream infection) in a commonly used electronic health records (EHR) system. The transferred data populated a database for the evaluation of clinical outcomes considering patient characteristics and antibacterial drug breakpoints (the standards used by laboratories to report susceptibility of bacteria isolated from a patient to different antibacterial drugs).
- This study addressed an important regulatory science priority. The paucity of clinical outcomes data results in increasing reliance upon pharmacokinetic modeling for breakpoint updating with a trend toward lowering breakpoints primarily based on this modeling. The lowering of breakpoints may have stewardship implications as the use of second- and third-line agents may increase. The availability of this clinical outcome information is expected to be useful in discussions concerning revising breakpoints.
- Study Outcomes:
    - **Publication:** Fabre V, Amoah J, Cosgrove SE, Tamma PD. Antibiotic Therapy for Pseudomonas aeruginosa Bloodstream Infections: How Long Is Long Enough? Clin Infect Dis. 2019 Nov 13;69(11):2011-2014. doi: 10.1093/cid/ciz223. PMID: 30882137; PMCID: PMC7320076.
    - **Publication:** Fox MT, Amoah J, Hsu AJ, Herzke CA, Gerber JS, Tamma PD. Comparative Effectiveness of Antibiotic Treatment Duration in Children With Pyelonephritis. JAMA Netw Open. 2020 May 1;3(5):e203951. doi: 10.1001/jamanetworkopen.2020.3951. PMID: 32364593; PMCID: PMC7199115.
    - **CDER Impact Story**: Exploiting Real-World Data to Optimize the Use of Antibiotics; November 2021.

Evaluation of the Measurement Properties of Patient-Reported Outcome (PRO) Instruments in Patients with Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

- Awarded to ICON Clinical Research LLC (FY16: HHSF223201610100C)
- The objectives of this contract were to carry out psychometric evaluations of new Patient Reported Outcome (PRO) instruments for Community-Acquired Bacterial Pneumonia (CABP), Hospital-Acquired Bacterial Pneumonia (HABP), and Acute Bacterial Skin and Skin Structure Infection (ABSSSI). These CABP-specific, HABP-specific, and ABSSSI-specific PRO instruments may be submitted for qualification in accordance with both the FDA PRO guidance and the FDA drug development tool (DDT) qualification draft guidance.
- These objectives addressed the improvement of clinical endpoints for antibacterial drug trials listed in the Broad Agency Announcement (FDABAA-17-00123; section 2.4). The overall goals of this project were to develop qualified instruments for each disease that can be used by drug developers for the qualified context of use in IND and NDA/BLA submissions.

Bridging Novel Laboratory Animal and Hollow Fiber Infection Models to Evaluate Central Nervous System Penetration of Drugs in Infants

- Awarded to Duke University (FY16: HHSF223201610082C)
- The overall goal of this project was to develop and evaluate a new paradigm for evaluating CNS penetration of antibacterial drugs in human neonates. The objectives of this project were: (1) develop and validate a rabbit model of CNS infection and define the pharmacodynamics of the antibacterial drugs meropenem and tobramycin for the treatment of meningitis, (2) develop and validate a hollow fiber infection model (HFIM) of neonatal meningitis to characterize the pharmacodynamics of meropenem and tobramycin by evaluating bacterial killing and emergence of antimicrobial resistance, (3) bridge the preclinical results to infants using population PK-PD modeling to guide dosing regimens of meropenem and tobramycin for treatment of meningitis in infants.
- The study may help identify new approaches to study antibacterial drugs in infants, with the goal of obtaining the information needed to label an antibacterial drug for pediatric use more efficiently.
- Study Outcomes:
    - **Poster Presentation**: Development of an Experimental Model of Bacterial Meningoencephalitis to Facilitate Antimicrobial Drug Development for Neonates. (ESCMID/ASM Conference 2019)
    - **Publication:** Farrington N, McEntee L, Johnson A, Unsworth J, Darlow C, Jimenez-Valverde A, Hornik C, Greenberg R, Schwartz J, Das S, Hope W. Pharmacodynamics of Meropenem and Tobramycin for Neonatal Meningoencephalitis: Novel Approaches to Facilitate the Development of New Agents to Address the Challenge of Antimicrobial Resistance. Antimicrob Agents Chemother. 2022 Apr 19;66(4):e0218121. doi: 10.1128/aac.02181-21. Epub 2022 Mar 22. PMID: 35315689; PMCID: PMC9017387.
    - **Oral Abstract:** Pharmacodynamics of meropenem and tobramycin for neonatal meningoencephalitis: novel approaches to facilitate the development of new agents to address the challenge of antimicrobial resistance (ECCMID 2022).

Rabbit Models of *Pseudomonas aeruginosa* Acute Pneumonia, Severe Sepsis, and Ventilator-Associated Pneumonia for Novel Antibacterial Development

- Awarded to University of California, San Francisco (FY17: HHSF223201710112C)
- The objectives of this contract were to advance the development of rabbit infection models as a translational approach for testing new drug candidates for the treatment of serious infections caused by *Pseudomonas aeruginosa* in humans.
- This study aligned with section 2.4.2 of the Broad Agency Announcement (FDABAA-17-00123) to advance the science of animal model development to facilitate antibacterial drug development.
- Study Outcomes:
    - **Publication:** Nguyen NTQ, Gras E, Tran ND, Nguyen NNY, Lam HTH, Weiss WJ, Doan TNM, Diep BA. Pseudomonas aeruginosa Ventilator-Associated Pneumonia Rabbit Model for Preclinical Drug Development. Antimicrob Agents Chemother. 2021 Jun 17;65(7):e0272420. doi: 10.1128/AAC.02724-20. Epub 2021 Jun 17. PMID: 33972247; PMCID: PMC8218622.
    - **Publication:** Aguiar-Alves F, Le HN, Tran VG, Gras E, Vu TTT, Dong OX, Quetz JS, Cheng LI, Yu L, Sellman BR, Stover CK, DiGiandomenico A, Diep BA. Antivirulence Bispecific Monoclonal Antibody-Mediated Protection against Pseudomonas aeruginosa Ventilator-Associated Pneumonia in a Rabbit Model. Antimicrob Agents Chemother. 2022 Feb 15;66(2):e0202221. doi: 10.1128/AAC.02022-21. Epub 2021 Dec 13. PMID: 34902264; PMCID: PMC8846318.

Development of a Porcine Model of Ventilator-Associated Pneumonia Caused by *Acinetobacter baumannii*

- Awarded to Lovelace Biomedical & Environmental Research Institute (FY17: HHSF223201710130C)
- The objective of this contract was to advance the development of porcine infection models as a translational approach for testing new drug candidates for the treatment of serious infections caused by *Acinetobacter baumannii* in humans.
- This study aligned with section 2.4.2 of the Broad Agency Announcement (FDABAA-17-00123) to advance the science of animal model development to facilitate antibacterial drug development.

A Preclinical Mouse Model of *Acinetobacter baumannii* Infection for Antibacterial Development

- BAA contract awarded to University of Southern California (FY17: HHSF223201710199C)
- The project was aimed at refinement of an established mouse model of *Acinetobacter baumannii* pneumonia and bacteremia infection.
- This study aligned with section 2.4.2 of the Broad Agency Announcement to advance the science of animal model development to facilitate antibacterial drug development.
- Study Outcomes:
    - **Publication**: Nielsen TB, Yan J, Luna B, Spellberg B. Murine Oropharyngeal Aspiration Model of Ventilator-associated and Hospital-acquired Bacterial Pneumonia. J Vis Exp. 2018 Jun 28;(136):57672. doi: 10.3791/57672. PMID: 30010650; PMCID: PMC6102004.
    - **Publication**: Luna BM, Yan J, Reyna Z, Moon E, Nielsen TB, Reza H, Lu P, Bonomo R, Louie A, Drusano G, Bulitta J, She R, Spellberg B. Natural history of Acinetobacter baumannii infection in mice. PLoS One. 2019 Jul 18;14(7):e0219824. doi: 10.1371/journal.pone.0219824. PMID: 31318907; PMCID: PMC6638954.
    - **Publication**: Luna B, Trebosc V, Lee B, Bakowski M, Ulhaq A, Yan J, Lu P, Cheng J, Nielsen T, Lim J, Ketphan W, Eoh H, McNamara C, Skandalis N, She R, Kemmer C, Lociuro S, Dale GE, Spellberg B. A nutrient-limited screen unmasks rifabutin hyperactivity for extensively drug-resistant Acinetobacter baumannii. Nat Microbiol. 2020 Sep;5(9):1134-1143. doi: 10.1038/s41564-020-0737-6. Epub 2020 Jun 8. PMID: 32514072; PMCID: PMC7483275.
    - **Publication**: Jiao Y, Yan J, Vicchiarelli M, Sutaria DS, Lu P, Reyna Z, Spellberg B, Bonomo RA, Drusano GL, Louie A, Luna BM, Bulitta JB. Individual Components of Polymyxin B Modeled via Population Pharmacokinetics to Design Humanized Dosage Regimens for a Bloodstream and Lung Infection Model in Immune-Competent Mice. Antimicrob Agents Chemother. 2023 May 17;67(5):e0019723. doi: 10.1128/aac.00197-23. Epub 2023 Apr 6. PMID: 37022153; PMCID: PMC10190254.
    - **Publication**: Jiao Y, Yan J, Sutaria DS, Lu P, Vicchiarelli M, Reyna Z, Ruiz-Delgado J, Burk E, Moon E, Shah NR, Spellberg B, Bonomo RA, Drusano GL, Louie A, Luna BM, Bulitta JB. Population pharmacokinetics and humanized dosage regimens matching the peak, area, trough, and range of amikacin plasma concentrations in immune-competent murine bloodstream and lung infection models. Antimicrob Agents Chemother. 2024 Mar 6;68(3):e0139423. doi: 10.1128/aac.01394-23. Epub 2024 Jan 30. PMID: 38289076; PMCID: PMC10916399.

Development of a Mouse Model for Preclinical Screening of Investigational Drugs Against *Pseudomonas aeruginosa*

- BAA contract awarded to University of Louisville School of Medicine (FY18: HHSF22320180171C)
- The project aims were: (1) to validate this model against multiple *P. aeruginosa* isolates with different drug resistance profiles by establishing the LD_{50} and natural history for each isolate and (2) to establish dosing parameters for two control antibiotics using PK/PD analysis/models so that these antibiotics can be used as controls/comparators to better gauge the efficacy of novel investigational drugs against *P. aeruginosa*.
- This study aligned with section 2.4.2 of the Broad Agency Announcement (to advance the science of animal model development to facilitate antibacterial drug development.
- Study Outcomes:
    - **Publication:** Warawa JM, Duan X, Anderson CD, Sotsky JB, Cramer DE, Pfeffer TL, Guo H, Adcock S, Lepak AJ, Andes DR, Slone SA, Stromberg AJ, Gabbard JD, Severson WE, Lawrenz MB. Validated Preclinical Mouse Model for Therapeutic Testing against Multidrug-Resistant Pseudomonas aeruginosa Strains. Microbiol Spectr. 2022 Oct 26;10(5):e0269322. doi: 10.1128/spectrum.02693-22. Epub 2022 Sep 12. PMID: 36094219; PMCID: PMC9603883.

Understanding Markets for Antibacterial Drug Development

- Interagency Agreement between FDA and HHS Office of the Assistant Secretary for Planning and Evaluation (FY18: 224183013S; FY19: 75F40119S30008)
- The goals of the project were to understand the: (1) market for antibacterial drugs, (2) incentives for developing new antibacterial drugs, and (3) social value of developing new bacterial drugs.
- The project aimed to: (1) undertake a comparison of the development and production costs, clinical value, and market performance of a cohort of recent antibacterial approvals with an appropriate control group, (2) analyze potential market failures in the antibacterial drug market, and (3) predict future market failure and how to address them.
- Study Outcomes:
    - **Poster Presentation:** Integrating Existing Metrics to Assess Comparative Real-World Clinical Effectiveness of Recently Approved Antimicrobial Drugs (Academy Health Annual Research Meeting, June 2021)
    - **Issue Brief:** Sullivan C, Kolbe A. Understanding Markets for Antimicrobial Drugs: Issue Brief [Internet]. Washington (DC): Office of the Assistant Secretary of Planning and Evaluation (ASPE); 2023 Aug. PMID: 38691037.
    - **Report:** Sertkaya A, Franz C. Antimicrobial Drugs Market Returns Analysis: Final Report [Internet]. Washington (DC): Office of the Assistant Secretary for Planning and Evaluation (ASPE); 2022 Dec 16. Report No.: 0360.00.006. PMID: 38691038.
    - **Report:** Sertkaya A, McGeeney JD, Franz C, Berger C, Stokes-Cawley O, Rodman N. Antimicrobial Drugs - Burden of Antimicrobial Resistance: Final Report [Internet]. Washington (DC): Office of the Assistant Secretary for Planning and Evaluation (ASPE); 2022 Dec 26. Report No.: 0360.00.006. PMID: 38691036.
    - **Report:** Sertkaya A, Berlind A, McGeeney JD, Berger C, Stokes-Cawley O. Analysis of Market Challenges for Antimicrobial Drug Development in the United States: Final Report [Internet]. Washington (DC): Office of the Assistant Secretary for Planning and Evaluation (ASPE); 2022 Dec 23. Report No.: 0360.00.006. PMID: 38691034.
    - **Publication:** Sertkaya A, McGeeney JD, Sullivan C, Kolbe A, Beleche T, Murphy S, Berlind A, Jessup A. Assessing the state of antibacterial drug discovery through patent analysis. Int J Antimicrob Agents. 2024 Feb;63(2):107051. doi: 10.1016/j.ijantimicag.2023.107051. Epub 2023 Dec 8. PMID: 38072169.

Estimating the National Market Size for Novel Gram-negative Active Agents

- Interagency Agreement between FDA and National Institutes of Health (FY18: 224183008S)
- Project aims were: (1) quantify the opportunities for empiric and targeted antibacterial therapy for patients within the *Cerner Healthfacts* dataset with infections secondary to Gram-negative (GN) isolates displaying resistance to: (a) all first-line treatment options including carbapenems where novel agents with superior efficacy and toxicity profiles would be optimal and (b) extended-spectrum cephalosporins for which new carbapenem-sparing agents could be utilized and (2) work collaboratively with HHS economists to generate national market projections for novel agents that either spare carbapenems or retain activity when existing first-line gram-negative active agents remain inactive.
- This study aimed to provide an understanding of the real-world market size for new agents with activity against resistant GN pathogens with limited treatment options could inform appropriate use, mitigate over-reliance on carbapenems, and ensure balance in aligning both incentives and investments.
- Study Outcomes:
    - **Poster Presentation:** Strich JR, Warner S, Lai Y, Demirkale CY, Powers JH, Danner RL, et al. 2251. Estimating the Need for Novel Gram-Negative Active Antibiotics in US Hospitals. doi: 10.1093/ofid/ofz360.1929. (IDWeek 2019)
    - **Oral Presentation:** Difficult-to-Treat Resistance (DTR) as a Metric to Quantify the Need for Novel Gram-Negative Antibiotics in US Hospitals (OND Extramural Research Science Day, September 2, 2020).
    - **Publication:** Strich JR, Warner S, Lai YL, Demirkale CY, Powers JH 3rd, Danner RL, Kadri SS. Needs assessment for novel Gram-negative antibiotics in US hospitals: a retrospective cohort study. Lancet Infect Dis. 2020 Oct;20(10):1172-1181. doi: 10.1016/S1473-3099(20)30153-5. Epub 2020 Jun 4. PMID: 32505231; PMCID: PMC7272178.

MIC Breakpoints

- Interagency Agreement between FDA and National Institutes of Health (FY19: 75F40119S30002; FY20: 75F40120S30046)
- The project aimed: (1) develop an approach using *Cerner Healthfacts* dataset to determine whether there is a correlation between patients stratified by existing *in vitro* MIC breakpoints and those stratified by clustering of risk-adjusted clinical outcome, (2) identify the strengths and limitations of this approach, and (3) compare findings from this approach with any relevant published literature concerning MIC breakpoints for the same drug-bug combination analyzed.
- The FY20 study focused the MIC breakpoints and clinical outcomes analysis on *Stenotrophomonas maltophilia* and various relevant antimicrobial agents.
- The expected outcome from this study was an adjusted odds ratio of in-hospital mortality stratified by existing MIC breakpoints. Data from this study will help to further define the relationship between MIC breakpoints and risk-adjusted clinical outcomes.
- Study Outcomes:
    - **Publication:** Strich JR, Lawandi A, Warner S, Demirkale CY, Sarzynski S, Babiker A, Dekker JP, Kadri SS. Association between piperacillin/tazobactam MIC and survival among hospitalized patients with Enterobacterales infections: retrospective cohort analysis of electronic health records from 161 US hospitals. JAC Antimicrob Resist. 2023 Apr 6;5(2):dlad041. doi: 10.1093/jacamr/dlad041. PMID: 37034120; PMCID: PMC10077023.
    - **Publication:** Sarzynski SH, Lawandi A, Warner S, Demirkale CY, Strich JR, Dekker JP, Babiker A, Li W, Kadri SS. Association between minimum inhibitory concentration values and mortality risk in patients with *Stenotrophomonas maltophilia* infections: a retrospective

cohort study of electronic health records from 148 US hospitals. JAC Antimicrob Resist. 2023 Apr 28;5(2):dlad049. doi: 10.1093/jacamr/dlad049. PMID: 37124072; PMCID: PMC10141776.

Development of a Novel PRO Tool for Use in Clinical Trials to Measure Symptoms in Patients with Non-Cystic Fibrosis Bronchiectasis (NCFB) with and without Non-Tuberculous Mycobacterial (NTM) Lung Infection

- Awarded to INSMED, INC (FY19: 1U01FD006687-01)
- The specific aims of this project were: (1) conduct concept elicitation research to identify the unique symptoms and experience of people diagnosed with NCFB with and without NTM, (2) conduct a non-interventional study in order to validate a novel draft Patient Reported Outcome (PRO) instrument for NCFB, and (3) evaluate the PRO developed in aim 1 to be fit-for-purpose in assessing symptoms among patients with NCFB and NTM and by contrasting the performance of the core PRO between patients diagnosed with NCFB with and without NTM.
- Currently, there are no validated endpoints to advance new therapies for populations with NCFB with or without NTM lung infection. The overall goal of this project was to develop a novel PRO instrument that is advanced to the stage of readiness to be included in a clinical trial to allow qualification for drug development and regulatory decision making in the NCFB field. The qualified PRO could then help design and conduct better clinical trials as well as lead to better interpretation of anti-infective drug trials for NCFB.
- Study Outcomes:
    - **Presentation:** Progress on the Development of Symptom Assessment for Bronchiectasis. Presented by Dr. Kevin Mange at the NTM Research Consortium Meeting; Portland, OR; November 3, 2023.
    - **Presentation:** Progress on the Development of Symptom Assessment for Bronchiectasis. Presented by Dr. Kevin Mange at the NTM Research Consortium Meeting; Portland, OR; November 8, 2024.
    - **Poster Presentation:** Development and Validation of the Symptom Assessment for Bronchiectasis (SABRE) for the FDA Qualification Program: A Novel Patient-Reported Outcome Instrument to Measure Symptoms of Non-Cystic Fibrosis Bronchiectasis (ISPOR Conference 2025).

Natural Language Processing (NLP) of Electronic Health Records (EHRs) to Advance Understanding of Antimicrobial Resistance (AMR)

- Awarded a Task Order to the MITRE Corporation (FY19: 75F40119F80474).
- This proof of concept study aimed to: (1) demonstrate a tightly focused application of Natural Language Processing (NLP) on a set of Electronic Health Records (EHRs) using a database to understand the utility of NLP analysis of EHRs for antimicrobial resistance (AMR) relevant information, (2) conduct NLP that analyzes unstructured notes in EHRs, such as anonymized hospital admission and discharge notes, and assess whether we can train the machine to recognize in notes that certain events took place, such as a patient had an abscess drained or had infected hardware removed from their body.
- The purpose of this study was to conduct a NLP proof of concept study on a single topic (i.e., source control) and a single use case to assess the benefits and limitations of NLP in automating analysis of information relevant to AMR in EHRs. This information will be the basis to build a full NLP annotation study in the future.

A Human Microbiome Disruption Model

- Interagency Agreement between FDA and Centers for Disease Control and Prevention
- In FY19 (75F40119S30012), CDC continued to support studies to understand the microbiome disruption potential for antibiotics. Specifically, CDC will fund a study, using both FDA-CDER IAA and CDC AR funds to identify and validate biomarkers of microbiome disruption in a microbiome model to measure antimicrobial disruption of gastrointestinal (GI) microbiome. This project aimed to advance the science of measuring antibiotic-specific human microbiome disruption.
- Data from these studies will be important to develop a standard test that predicts adverse events from antimicrobial use. This knowledge will help identify where preventative or restorative interventions, as well as new narrower-spectrum antibiotic development, can help to mitigate risks for patients taking antibiotics.

Development of Rabbit Animal Models of Ventilator-Associated Bacterial Pneumonia (VABP) Produced by Carbapenem-Resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

- Awarded to Weill Medical College of Cornell University (FY20: 75F40120C00140)
- The objectives of this study were: 1) develop a rabbit model of carbapenem-resistant *P. aeruginosa* VAP, 2) develop a rabbit model of carbapenem-resistant *A. baumannii* VAP, 3) characterize the pulmonary pathophysiology, microbiology, and pharmacology of the rabbit VAP models, 4) investigate one or more new antibacterial agents in the VAP models.
- The study is expected to result in the development of two rabbit models of VAP. Currently, there are no well characterized VAP animal models which use carbapenem-resistant bacterial strains. These rabbit models would provide the nonclinical foundation for future development of antimicrobials against resistant infections.
- This study aligned with section 2.4.2 of the Broad Agency Announcement to advance the science of animal model development to facilitate antibacterial drug development.
- Study Outcomes:
    - **Poster Presentation:** Petraitis V, Petraitiene R, Naing E. 2557. Development of Rabbit Models of Ventilator-Associated Carbapenem-Resistant Acinetobacter baumannii Pneumonia (IDWeek 2023). Open Forum Infect Dis. 2023 Nov 27;10(Suppl 2):ofad500.2174. doi: 10.1093/ofid/ofad500.2174. PMCID: PMC10678937.
    - **Publication:** Petraitis V, Petraitiene R, Kavaliauskas P, Naing E, Garcia A, Zigmantaite V, Grigaleviciute R, Kucinskas A, Pockevicius A, Stakauskas R, Walsh TJ. Development of rabbit models of ventilator-associated bacterial pneumonia produced by carbapenem-resistant *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2024 Jun 5;68(6):e0020524. doi: 10.1128/aac.00205-24. Epub 2024 Apr 30. PMID: 38687014; PMCID: PMC11620515.

Development of Modernized *Acinetobacter baumannii* Susceptibility Guidance for Recommended Antimicrobial Agents using Pharmacometric Approaches.

- Awarded to the University of Wisconsin System (FY20: 75F40120C00111)
- The overall objective for this study was to characterize the contemporary *A. baumannii* minimum inhibitory concentration (MIC) for various antibiotics (e.g., minocycline, ciprofloxacin, etc.). The study will characterize PK-PD of each antibiotic using validated mouse-thigh and mouse-lung infection models and to identify candidate STIC for each antibiotic by integrating animal model-derived PK-PD relationships and PK model-derived human exposures through Monte Carlo simulation in the context of contemporary MIC distribution data.
- The results of this study may improve clinical guidance for the care of patients suffering with multi-drug resistant *A. baumannii* infections.

- This study aligned with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.
- Study Outcomes:
    - **Publication**: Lepak AJ, Trang M, Hammel JP, Sader HS, Bhavnani SM, VanScoy BD, Pogue JM, Ambrose PG, Andes DR; United States Committee on Antimicrobial Susceptibility Testing. Development of Modernized Acinetobacter baumannii Susceptibility Test Interpretive Criteria for Recommended Antimicrobial Agents Using Pharmacometric Approaches. Antimicrob Agents Chemother. 2023 Apr 18;67(4):e0145222. doi: 10.1128/aac.01452-22. Epub 2023 Mar 22. PMID: 36946729; PMCID: PMC10112158.

Pharmacodynamics of Minocycline, Levofloxacin, and Trimethoprim/Sulfamethoxazole Against *Stenotrophomonas maltophilia*: Implications for Susceptibility Breakpoint Revisions.

- Awarded to the Hartford Hospital (FY20: 75F40120C00171)
- The overall objective for this study was to determine the *in vivo* pharmacodynamics of minocycline and levofloxacin and *in vitro* pharmacodynamics of trimethoprim/sulfamethoxazole against clinically representative *S. maltophilia*.
- The results of this study may assist in revising or updating the current susceptibility breakpoints for certain antibiotics against *S. maltophilia*.
- This study aligned with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.
- Study Outcomes:
    - **Poster Presentation**: Fratoni AJ, Nicolau DP, Kuti JL. Levofloxacin pharmacodynamics against *Stenotrophomonas maltophilia* in a neutropenic murine thigh infection model: implications for susceptibility breakpoint revision (World Microbe Forum 2021).
    - **Oral Abstract**: Fratoni AJ, Nicolau, DP, Kuti JL. *In Vivo* Efficacy of Human Simulated Minocycline against *Stenotrophomonas maltophilia* (IDWeek 2021); Abstract available via Open Forum Infectious Diseases; doi: 10.1093/ofid/ofab466.065.
    - **Poster Presentation**: Fratoni AJ, Nicolau, DP, Kuti JL. Minocycline Pharmacodynamics against *Stenotrophomonas maltophilia* in a Neutropenic Murine Thigh Infection Model (IDWeek 2021); Abstract available at Open Forum Infectious Diseases; doi:10.1093/ofid/ofab466.1297
    - **Publication:** Fratoni AJ, Nicolau DP, Kuti JL. Levofloxacin pharmacodynamics against Stenotrophomonas maltophilia in a neutropenic murine thigh infection model: implications for susceptibility breakpoint revision. J Antimicrob Chemother. 2021 Dec 24;77(1):164-168. doi: 10.1093/jac/dkab344. PMID: 34542637.
    - **Publication:** Fratoni AJ, Nicolau DP, Kuti JL. Minocycline pharmacodynamics against Stenotrophomonas maltophilia in the neutropenic murine infection model: implications for susceptibility breakpoints. J Antimicrob Chemother. 2022 Mar 31;77(4):1052-1060. doi: 10.1093/jac/dkac018. PMID: 35134195.
    - **Publication:** Lasko MJ, Gethers ML, Tabor-Rennie JL, Nicolau DP, Kuti JL. *In Vitro* Time-Kill Studies of Trimethoprim/Sulfamethoxazole against Stenotrophomonas maltophilia versus Escherichia coli Using Cation-Adjusted Mueller-Hinton Broth and ISO-Sensitest Broth. Antimicrob Agents Chemother. 2022 Mar 15;66(3):e0216721. doi: 10.1128/aac.02167-21. Epub 2022 Jan 10. PMID: 35007135; PMCID: PMC8923228.
    - **Publication:** Lasko MJ, Tabor-Rennie JL, Nicolau DP, Kuti JL. Trimethoprim/sulfamethoxazole pharmacodynamics against Stenotrophomonas maltophilia in the in vitro chemostat model.

J Antimicrob Chemother. 2022 Sep 14:dkac304. doi: 10.1093/jac/dkac304. Epub ahead of print. PMID: 36101486.

Expanding Current and Future Susceptibility Testing Criteria with Genotypic Data: Comparative Efficacy of Human-Simulated Exposures of Ceftazidime/Avibactam, Imipenem/Relebactam, and Meropenem/Vaborbactam against Oxa-48-β-lactamase-Producing Enterobacterales in the Neutropenic Murine Thigh Infection Model.

- Awarded to the Hartford Hospital (FY20: 75F40120C00152)
- The study aimed to advance the field of susceptibility breakpoint determination by assessing the contribution of bacterial genotype to antibiotic efficacy. Current breakpoint decisions are made based primarily on the MIC phenotype. This study will utilize genotypic profiles, phenotypic MIC testing, and a neutropenic murine (mouse) thigh infection model to determine whether genotypic information should be considered as part of the antibiotic breakpoint determination package.
- The results of this study may help guide utilization practices for relevant antibiotics such as meropenem-vaborbactam, ceftazidime-avibactam, or imipenem-relebactam when treating resistant infections.
- This study aligned with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.
- Study Outcomes:
    - **Poster Presentation:** Phenotypic assessment of carbapenem and carbapenem/β-lactamase inhibitor activity against OXA-48-producing Enterobacterales: The challenge of variable hydrolysis and definitive breakpoints (World Microbe Forum 2021).
    - **Publication:** Asempa TE, Kois AK, Gill CM, Nicolau DP. Phenotypes, genotypes and breakpoints: an assessment of β-lactam/β-lactamase inhibitor combinations against OXA-48. J Antimicrob Chemother. 2023 Mar 2;78(3):636-645. doi: 10.1093/jac/dkac425. PMID: 36626311.

Metallo-β-Lactamase (MBL) Resistance in Enterobacterales: Is It Time to Rethink our In Vitro Assessment Tools?

- Awarded to the Hartford Hospital (FY20: 75F40120C00164)
- The study aimed to assess whether carbapenem therapy can be utilized to effectively manage serious infections due to MBL-producing *Enterobacterales*. This will be achieved by evaluating the effect that zinc concentrations may have on the MIC interpretation of the activity of carbapenems. It has been observed that conventional susceptibility testing, using conventional culture media, may impair the interpretation of the activity of carbapenems against MBL-producing *Enterobacterales*. This has been attributed to the higher zinc concentration in conventional culture media as compared to the zinc levels present *in vivo*.
- This study may result in the modification or refinement of the current methods for *in vitro* antimicrobial susceptibility testing and the protocols for the selection of effective treatment for patients with MBL-producing *Enterobacterales* infections.
- This study aligned with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.
- Study Outcomes:
    - **Oral Presentation:** Efficacy of B-lactam Therapy against Infections Caused by Metallo-B-lactamase (MBL)-Producing Enterobacterales: Bridging the Susceptibility Testing Gap (IDWeek 2022).

- **Publication:** Kamilia Abdelraouf, Christian M Gill, Matthew Gethers, Giusy Tiseo, Simona Barnini, Marco Falcone, Francesco Menichetti, David P Nicolau, Deciphering the Efficacy of the β-Lactams in the Face of Metallo-β-lactamase Derived Resistance in Enterobacterales: Supraphysiologic Zinc in the Broth is the Culprit, *Open Forum Infectious Diseases*, 2024;, ofae228, https://doi.org/10.1093/ofid/ofae228

Leveraging the Microbiome to Improve Patient Management and Control of Antibiotic Resistance in Cystic Fibrosis Patients.

- Interagency Agreement between FDA and Centers for Disease Control and Prevention (FY20: 75F40120S10020).
- The aims of this study were: 1) Determine the treatment drivers (e.g., drug selection, dosage, and treatment duration) of microbiome disruption and competitive release of resistant *P. aeruginosa* in defined polymicrobial contexts; 2) Determine the drivers of microbiome disruption and competitive release of resistant *P. aeruginosa* in *ex vivo* microbial communities of Cystic Fibrosis (CF) patient sputa; 3) Determine the drivers of competitive release of resistant pathogens in CF patients under antibiotic treatment
- Results from this study may guide understanding on how various antibiotic treatments impact the lung microbiome. Long term, this study may contribute to the development of microbiome indices for antibiotics and a standard approach that prevents adverse events resulting from antimicrobial use, such as the emergence of antibiotic-resistant organisms.
- Study Outcomes:
  - **Publication:** Varga JJ, Zhao CY, Davis JD, Hao Y, Farrell JM, Gurney JR, Voit E, Brown SP. Antibiotics Drive Expansion of Rare Pathogens in a Chronic Infection Microbiome Model. mSphere. 2022 Aug 16:e0031822. doi: 10.1128/msphere.00318-22. Epub ahead of print. PMID: 35972133.
  - **Publication**: Wollein Waldetoft K, Sundius S, Kuske R, Brown SP. Defining the Benefits of Antibiotic Resistance in Commensals and the Scope for Resistance Optimization. mBio. 2023 Feb 28;14(1):e0134922. doi: 10.1128/mbio.01349-22. Epub 2022 Dec 7. PMID: 36475750; PMCID: PMC9972992.
  - **Publication**: Wollein Waldetoft K, Brown SP. Evolving antibiotic spectrum. Proc Natl Acad Sci U S A. 2022 Oct 11;119(41):e2214267119. doi: 10.1073/pnas.2214267119. Epub 2022 Oct 3. PMID: 36191212; PMCID: PMC9565054.
  - **Publication**: Aspenberg M, Maad Sasane S, Nilsson F, Brown SP, Wollein Waldetoft K. Hygiene may attenuate selection for antibiotic resistance by changing microbial community structure. Evol Med Public Health. 2023 Jan 18;11(1):1-7. doi: 10.1093/emph/eoac038. PMID: 36687161; PMCID: PMC9847546.
  - **Publication:** Olivença DV, Davis JD, Kumbale CM, Zhao CY, Brown SP, McCarty NA, Voit EO. Mathematical models of cystic fibrosis as a systemic disease. WIREs Mech Dis. 2023 Aug 6:e1625. doi: 10.1002/wsbm.1625. Epub ahead of print. PMID: 37544654.
  - **Publication:** Rattray JB, Lowhorn RJ, Walden R, Márquez-Zacarías P, Molotkova E, Perron G, Solis-Lemus C, Pimentel Alarcon D, Brown SP. Machine learning identification of Pseudomonas aeruginosa strains from colony image data. PLoS Comput Biol. 2023 Dec 13;19(12):e1011699. doi: 10.1371/journal.pcbi.1011699. PMID: 38091365; PMCID: PMC10752536.
  - **Publication**: Alseth EO, Custodio R, Sundius SA, Kuske RA, Brown SP, Westra ER. The impact of phage and phage resistance on microbial community dynamics. PLoS Biol. 2024 Apr 22;22(4):e3002346. doi: 10.1371/journal.pbio.3002346. PMID: 38648198; PMCID: PMC11034675.

Understanding the Development and Use of Clinical Practice Guidelines for Infectious Diseases.

- Interagency Agreement between FDA and HHS Office of the Assistant Secretary for Planning and Evaluation (FY 20, FY 21: 75F40120S30020).
- In FY 20 the study aims included: 1) explore how to support evidence-based clinical practice in the treatment of antibiotic-resistant infectious disease, 2) address knowledge gaps around the effective development and updating of clinical practice guidelines.
- In FY 21 ASPE planned to finish analyses and disseminate results from the study at a public stakeholder meeting and also through peer-reviewed publication.
- This study explored considerations that make the treatment of resistant infections different than other areas of clinical practice. Furthermore, the study may lead to more effective development of antibacterial treatment guidelines by exploring best practices used during treatment guideline development. More effective treatment guidelines for infectious diseases would positively affect patient outcomes.
- Study Outcomes:
    - **Public Webinar:** Developing Sound, Timely, and Useful Infectious Disease Guidelines: Experts Share What They've Learned (June 23, 2022).
    - **Publication:** Powell RE, Felt-Lisk S, Chen A, Sullivan C. Optimizing clinical guidelines to address antimicrobial-resistant infections: A conceptual framework reflecting stakeholder perspectives. Antimicrob Steward Healthc Epidemiol. 2023 Feb 16;3(1):e30. doi: 10.1017/ash.2022.319. PMID: 36865700; PMCID: PMC9972534.

Assessment of Residual Needs for Novel Gram-negative Active Agents: A Real-world Post-Approval Pharmacoepidemiologic Analysis, U.S. Hospital, 2019-2020

- Interagency Agreement between FDA and National Institutes of Health (FY 21: 75F40121S30021).
- This study aimed to confirm and validate previous work conducted (FY18, NIH) by using the Premier Inc. database. Study Aims included: 1) quantify the opportunities for empiric and targeted treatment with antibacterial therapy for inpatients between 2019-2020 with suspected or confirmed infections secondary to Gram-negative isolates displaying high level resistance, 2) assess the impact of the FDA approved gram-negative active antibiotics since 2015 with activity against carbapenem-resistant gram-negative infections on current market estimates.
- This study provided information to help better understand the current landscape for novel gram-negative antibiotics during 2019-2020 and assess the impact of recently approved antibiotics on potential future market size.
- Study Outcomes:
    - **Publication:** Strich JR, Mishuk A, Diao G, Lawandi A, Li W, Demirkale CY, Babiker A, Mancera A, Swihart BJ, Walker M, Yek C, Neupane M, De Jonge N, Warner S, Kadri SS; National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative. Assessing Clinician Utilization of Next-Generation Antibiotics Against Resistant Gram-Negative Infections in U.S. Hospitals : A Retrospective Cohort Study. Ann Intern Med. 2024 Apr 19. doi: 10.7326/M23-2309. Epub ahead of print. PMID: 38639548.
    - **Related Editorial:** Howard-Anderson J, Boucher HW. New Antibiotics for Resistant Infections: What Happens After Approval? Ann Intern Med. 2024 Apr 19. doi: 10.7326/M24-0192. Epub ahead of print. PMID: 38639541.

Expanded Metabolomic Interrogation of an Intestinal Microbiome Disruption Model.

- Interagency Agreement between FDA and Centers for Disease Control and Prevention (FY 21: 75F40121S30022).
- The overarching goal of this study was to create an experimental culture system that identifies agents that disrupt or protect the human intestinal microbiome. This study expanded upon initial successes (FY19, CDC) to identify additional markers of microbiome disruption by monitoring different metabolite types and by using a broader array of disrupting antimicrobial agents. This work will improve system reliability and interpretability, and will distinguish qualitatively different modes of disruption.
- Data from these studies may be important to develop a standard test that predicts adverse events from antimicrobial use. This knowledge may help identify where preventative or restorative interventions, as well as new narrower-spectrum antibiotic development, can help to mitigate risks for patients taking antibiotics

Development of Pulmonary Nontuberculous Mycobacterial Disease Symptom Scale (NTM-SS), Pulmonary NTM Infection

- Awarded to Oregon Health and Science University (FY21: 75F40121C00120)
- The objective of this study was to develop, test, and validate a disease-specific patient-reported outcome (PRO) measure in well-characterized population of patient with NTM
- Clinical trials for NTM treatment have been limited by the lack of validated measures (e.g., PROs) to assess clinical benefit. This study aimed to develop a NTM-specific PRO in order to improve clinical trial design and identify more effective treatments for patients with NTM pulmonary disease.
- This study aligned with section 2.4.1 of the Broad Agency Announcement: Evaluate potential innovations in clinical trial design for new drugs such as enrollment strategies, data collection streamlining, drug development tools, clinical endpoints, and new statistical analytic approaches.

A Critical Look at Cefepime Breakpoints *In Vivo*: An Assessment of Cefepime Activity against Carbapenemase-producing *Enterobacterales* with Unexpected Cefepime-Susceptibility and Cefepime Susceptible-Dose Dependent Phenotypic Profiles

- Awarded to Hartford Hospital (FY21: 75F40121C00128)
- The overall objective of this study was to advance the science of susceptibility testing and reporting as well as breakpoint determination as it pertains to cefepime activity against bacteria that produce prevalent carbapenemases such as *Klebsiella pneumoniae* carbapenemase (KPC).
- Results from this study will determine the therapeutic implications of administering cefepime when the infecting isolate demonstrates discordance between its genotype and phenotype, as well as provide insights on the appropriate phenotypic test that can resolve this discrepancy when encountered in the clinic.
- This study aligned with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.
- Study Outcomes:
    - **Poster Presentation:** Comparison of Broth Microdilution and BD Phoenix for Cefepime Susceptibility Testing among Carbapenem-Resistant Enterobacterales (CRE) (ASM Microbe 2023).
    - **Presentation:** An Assessment of Cefepime Pharmacokinetic/Pharmacodynamic Profile against Carbapenem-resistant Enterobacterales that test as Cefepime-Susceptible or -Susceptible-Dose Dependent (ASM Microbe 2023)

- **Publication:** Fouad A, Gill CM, Simner PJ, Nicolau DP, Asempa TE. Cefepime in vivo activity against carbapenem-resistant Enterobacterales that test as cefepime susceptible or susceptible-dose dependent in vitro: implications for clinical microbiology laboratory and clinicians. J Antimicrob Chemother. 2023 Sep 5;78(9):2242-2253. doi: 10.1093/jac/dkad229. PMID: 37522258.
- **Publication:** Fouad A, Simner PJ, Nicolau DP, Asempa TE. Comparison of BD Phoenix and disk diffusion to broth microdilution for determining cefepime susceptibility among carbapenem-resistant Enterobacterales. J Clin Microbiol. 2024 Jun 12;62(6):e0152023. doi: 10.1128/jcm.01520-23. Epub 2024 May 7. PMID: 38712928; PMCID: PMC11237536.

Ampicillin-Sulbactam against *Acinetobacter baumannii* infections: Pharmacokinetic/Pharmacodynamic Appraisal of Current Susceptibility Breakpoints and Dosing Recommendations

- Awarded to Hartford Hospital (FY21: 75F40121C00184)
- The objective of this study was to assess the pharmacokinetics and pharmacodynamics of ampicillin-sulbactam against *A. baumannii* infections in the murine pneumonia model. The outcomes from the infection model will be correlated to the ampicillin-sulbactam *in vitro* susceptibility interpretive criteria (breakpoints) to assess the capability of these breakpoints to predict *in vivo* outcomes.
- This study represents the first comprehensive assessment of the PK/PD of ampicillin-sulbactam against *A. baumannii* infection which aims to provide insights to assess the suitability of the current established breakpoints.
- The study aligned with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.
- Study Outcomes:
  - **Oral Presentation**: Abouelhassan Y, Kuti JL, Nicolau DP, Abdelraouf K. Sulbactam against *Acinetobacter baumannii* Pneumonia: Pharmacokinetic/Pharmacodynamic Appraisal of Current Dosing Recommendation. (IDWeek 2022). Abstract available at Open Forum Infectious Diseases; doi: 10.1093/ofid/ofac492.118
  - **Poster Presentation**: Sulbactam for Acinetobacter baumannii Pneumonia: Stratification of Sulbactam Pharmacokinetics/Pharmacodynamics (PK/PD) Targets According to Sulbactam and Carbapenem Susceptibilities (ASM Microbe 2023).
  - **Poster Presentation**: blaOXA-23 is a Predictor of Lack of Sulbactam Efficacy against Acinetobacter baumannii Pneumonia (ASM Microbe 2023)
  - **Oral Presentation**: blaOXA-23 is a Predictor of Lack of Sulbactam Efficacy against Acinetobacter baumannii Pneumonia (ASM Microbe 2023)
  - **Publication**: Abouelhassan Y, Nicolau DP, Abdelraouf K. Defining optimal sulbactam regimens for treatment of Acinetobacter baumannii pneumonia and impact of blaOXA-23 on efficacy. J Antimicrob Chemother. 2024 Jul 13:dkae229. doi: 10.1093/jac/dkae229. Epub ahead of print. PMID: 38997215.
  - **Publication**: Abouelhassan Y, Kuti JL, Nicolau DP, Abdelraouf K. Ampicillin-sulbactam against Acinetobacter baumannii infections: pharmacokinetic/pharmacodynamic appraisal of current susceptibility breakpoints and dosing recommendations. J Antimicrob Chemother. 2024 Jul 20:dkae218. doi: 10.1093/jac/dkae218. Epub ahead of print. PMID: 39031073.
  - **Publication**: Abouelhassan Y, Kuti JL, Nicolau DP, Abdelraouf K. Pharmacokinetic/pharmacodynamic analysis of sulbactam against *Acinetobacter baumannii* pneumonia: establishing *in vivo* efficacy targets in the epithelial lining fluid. JAC

Antimicrob Resist. 2024 Dec 20;6(6):dlae203. doi: 10.1093/jacamr/dlae203. PMID: 39712636; PMCID: PMC11660682.

β-lactam Continuous Versus Intermittent Infusion and Associated Bacterial Resistance and Therapy Outcomes in Critically ill Patients with Severe Pneumonia

- Awarded to University of Florida (FY21: 75F40121C00157)
- The goal of this study was to conduct a randomized, controlled clinical trial that aims to identify the benefits and risk of β-lactam continuous versus intermittent infusion in critically ill patient with severe pneumonia caused by gram-negative pathogens who have been admitted to the ICU. The study will compare the clinical, microbiological, and safety outcomes between the two groups of patients.
- This study attempted to fill a knowledge gap concerning the development of antimicrobial resistance between different infusion strategies of β-lactam antimicrobials. Results may guide future dosing recommendations of antimicrobials and help identify patients who could benefit from prolonged infusion to achieve better drug exposure and therapy outcome.
- This study aligned with section 2.4.2 of the Broad Agency Announcement: Advance the science of in-vitro, animal model, pharmacokinetic studies, and/or real-world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction
- Study Outcomes:
    - **Publication:** Maranchick NF, Trillo-Alvarez C, Kariyawasam V, Venugopalan V, Kwara A, Rand K, Peloquin CA, Alshaer MH. A Randomized Clinical Trial of Bayesian-Guided Beta-Lactam Infusion Strategy and Associated Bacterial Resistance and Clinical Outcomes in Patients With Severe Pneumonia. Ther Drug Monit. 2024 Feb 1;46(1):95-101. doi: 10.1097/FTD.0000000000001144. Epub 2023 Nov 15. PMID: 38018847; PMCID: PMC10769161.

Continuous versus Intermittent Infusions of β-lactam Antibacterial Drugs: Impact on Resistance and Outcomes in Sepsis

- Awarded to The University of Queensland (FY21: 75F40121C00126)
- The aim of this study was to explore the relationship between β-lactam antibacterial exposure (accounting for antibacterial concentration, bacterial susceptibility, and method of administration) and clinical outcomes (e.g., all-cause 90-day mortality, clinical cure at day 14 post-randomization) of sepsis patients observed in the BLING III clinical trial (NCT03213990). This study was a sub-study of the BLING III clinical trial and was a prospective observational study only.
- The goal of this study was to provide data to better understand the optimal dosing method and method of exposure of β-lactam antimicrobials that lead to better clinical outcomes in patients with sepsis.
- This study aligned with section 2.4.2 of the Broad Agency Announcement: Advance the science of in-vitro, animal model, pharmacokinetic studies, and/or real- world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction
- Study Outcomes:
    - **Publication**: Dulhunty JM, Brett SJ, De Waele JJ, et al. Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis: The BLING III Randomized Clinical

Trial. *JAMA*. Published online June 12, 2024. doi:10.1001/jama.2024.9779. PMID: 38864155; PMCID: PMC11170452.

Evaluating the Impact of Extended-Infusion B-lactam Administration Strategies on Improving Clinical Outcomes and Reducing the Subsequent Emergence of Antimicrobial Resistance

- Awarded to Johns Hopkins University School of Medicine (FY21: 75F40121C00127)
- The overarching objective of this study was to determine whether prolonging the infusion time of B-lactam therapy for the treatment of Gram-negative bloodstream infections improves patient outcomes while reducing the emergence of subsequent resistance to the B-lactam agent initially administered.
- This study provided needed information regarding the association between extending antibiotic administration and reducing the emergence of resistance. Results from this study may help inform clinicians of treatment strategies to better optimize patient outcomes.
- This study aligned with section 2.4.2 of the Broad Agency Announcement: Advance the science of in-vitro, animal model, pharmacokinetic studies, and/or real-world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction
- Study Outcomes:
    - **Poster Presentation**: Karaba SM, Hyoung Lee J, Fiawoo S, Cosgrove SE, Tamma P. 203. Evaluating the Impact of Extended-Infusion Beta-Lactam Therapy on Clinical Outcomes and the Subsequent Emergence of Resistance in Adults with Gram-Negative Bloodstream Infections. Open Forum Infect Dis. 2023 Nov 27;10(Suppl 2):ofad500.276. doi: 10.1093/ofid/ofad500.276. PMCID: PMC10678729. (IDWeek 2023)
    - **Publication:** Karaba SM, Cosgrove SE, Lee JH, Fiawoo S, Heil EL, Quartuccio KS, Shihadeh KC, Tamma PD. Extended-Infusion β-Lactam Therapy, Mortality, and Subsequent Antibiotic Resistance Among Hospitalized Adults With Gram-Negative Bloodstream Infections. JAMA Netw Open. 2024 Jul 1;7(7):e2418234. doi: 10.1001/jamanetworkopen.2024.18234. PMID: 38954416; PMCID: PMC11220563.

Development and Validation of CRRT-Specific Beta-Lactam Population Pharmacokinetic Models to Guide Treatment for Patients with Hospital-acquired Pneumonia

- Awarded to Midwestern University (FY22: 75F40122C00134)
- The primary objective of this study is to develop precision dosing models in critically ill patients with HAP requiring CRRT. This will facilitate the development and evaluation of optimal HAP-specific dosing regimens for cefepime in this population.
- Currently in patients with HAP who are critically ill we observe variability in PK. This results in decreased effectiveness of treatments whose effectiveness depends on achieving adequate PK/PD exposures. Results from this study will lead to the development of validated PK models and accurate dosing guidance to optimize concentrations of cefepime in these patients which may improve clinical outcomes.
- This study aligns with section 2.4.2 of the Broad Agency Announcement: Advance the science of in vitro, animal model, pharmacokinetic studies, and/or real-world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children, and patients with renal or hepatic dysfunction.
- Study Outcomes:

- **Poster Presentation:** Pulmonary Target PK/PD Attainment Rates Among Cefepime Treated Patients Admitted to the ICU with Hospital-Acquired Pneumonia Requiring Renal Replacement (IDWeek 2025)

Development of Modernized Susceptibility Guidance for Oral Cephalosporin Antimicrobial Agents Using Pharmacometric Approaches

- Awarded to University of Wisconsin (FY22: 75F40122C00128)
- The overall objective of this study was to apply modern pharmacometric approaches in evaluating breakpoints for oral cephalosporins that guide treatment in patients with uncomplicated bacterial infections. The aims of this study include: 1) characterization of contemporary E. coli and S. aureus MIC distribution for the commonly prescribed cephalosporins, 2) PK/PD characterization of each drug using a validated mouse-thigh model, and 3) identification of candidate breakpoints for each antimicrobial.
- Results of this study will ensure that up to date breakpoints are available, by using modern methods, for clinicians and thereby improve clinician treatment decisions.
- This study aligned with section 2.4.4 of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria are available for patient care and antimicrobial stewardship.
- Study Outcomes:
  - **Poster Presentation**: Identification of In Vitro Susceptibility Test Interpretive Criteria for Oral Cephalosporin Antimicrobial Agents against *Escherichia coli* and *Staphylococcus aureus* (Poster P2273, ECCMID 2024).

Development of Modernized Susceptibility Guidance for Azithromycin and Ceftriaxone Against Neisseria Gonorrhoeae Using Pharmacometric Approaches

- Awarded to Institute for Clinical Pharmacodynamics (FY22: 75F40122C0128)
- The overall objective of this study was to apply a modern pharmacometric-based method to reevaluate current azithromycin and ceftriaxone breakpoints for *N. gonorrhoeae*. Aims of the study include: 1) characterization of azithromycin and ceftriaxone MIC distributions for *N. gonorrhoeae*, 2) PK-PD characterization of azithromycin and ceftriaxone against *N. gonorrhoeae* using a hollow-fiber in vitro infection model, and 3) identify candidate azithromycin and ceftriaxone *N. gonorrhoeae* STIC.
- Results of this study will ensure that up to date breakpoints are available for clinicians when treating patients with uncomplicated gonorrhea thereby improving clinician treatment decisions.
- This study aligned with section 2.4.4 of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria are available for patient care and antimicrobial stewardship.
- Study Outcomes:
  - **Poster Presentation**: Identification of Azithromycin and Ceftriaxone *In Vitro* Susceptibility Test Interpretive Criteria for *Neisseria gonorrhoeae* (Poster E0556, ECCMID 2024).

Development of Modernized Susceptibility Guidance for Oral Sulfamethoxazole-Trimethoprim Using Pharmacometric Approaches

- Awarded to Institute for Clinical Pharmacodynamics (FY22: 75F40122C00174)
- The goal of this study was to apply a modern pharmacometric approach to evaluate sulfamethoxazole-trimethoprim breakpoints for *K. pneumoniae* and *E. coli* arising from uncomplicated urinary tract (uUTI) infections.
- Results of this study will ensure that up to date breakpoints are available for clinicians when treating patients with uUTI.
- This study aligned with section 2.4.4 of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria are available for patient care and antimicrobial stewardship.
- Study Outcomes:
    - **Poster Presentation**: Identification of *In Vitro* Susceptibility Test Interpretive Criteria for Sulfamethoxazole-trimethoprim Against *Escherichia coli* and *Klebsiella pneumoniae* (Poster P1159, ECCMID 2024).

Ex Vivo Modeling, Simulation, and In Vivo Pharmacokinetic Validation to Guide Antimicrobial Dosing Recommendations for Patients on Continuous Renal Replacement Therapy

- Awarded to Hartford Hospital (FY22: 75F40122C00130)
- This study aimed to improve dosing recommendation for antimicrobials used in patients on continuous renal replacement therapy (CRRT). The objectives of this study are to conduct ex vivo CRRT assessments of cefepime, meropenem, levofloxacin, and micafungin, followed by simulation of dosing regimens for varied clinical CRRT scenarios, and finally validation of exposures in critically ill patients receiving these agents as standard of care while supported by CRRT.
- Currently, labeling for novel antimicrobials rarely include specific dosing recommendations for patients on CRRT. As such, clinicians are left without much guidance on dose selection for treatment. Results from this study may be used to demonstrate a path forward for determining optimized dosage recommendations for new antimicrobials in patients on CRRT.
- This study aligned with section 2.4.2 of the Broad Agency Announcement: Advance the science of in vitro, animal model, pharmacokinetic studies, and/or real-world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children, and patients with renal or hepatic dysfunction.
- Study Outcomes:
    - **Poster Presentation**: Ex Vivo Assessment of Levofloxacin Clearance During Continuous Renal Replacement Theory (ASM Microbe 2024)
    - **Poster Presentation**: Meropenem Transmembrane Clearance in an Ex Vivo Continuous Renal Replacement Model (ASM Microbe 2024)
    - **Oral Presentation:** Ex vivo Assessment of Cefepime (FEP) Clearance during Continuous Renal Replacement Therapy (CRRT) and Clinical Validation of Optimized Dosing Regimens (IDWeek 2024); PMCID: PMC11777932.
    - **Publication:** Koenig C, McGrath CP, Roenfanz HF, Shen Y, Monogue ML, Nicolau DP, Kuti JL. Clinical validation of antimicrobial dosing regimens for continuous renal replacement therapy based on an ex vivo dosing algorithm. J Antimicrob Chemother. 2025 Aug 1;80(8):2269-2279. doi: 10.1093/jac/dkaf199. PMID: 40576018.
    - **Publication:** McGrath C, Koenig C, Roenfanz HF, Shen Y, Nicolau DP, Kuti JL. An ex vivo model to determine transmembrane clearance of antimicrobials during continuous renal

replacement therapy. J Antimicrob Chemother. 2025 Aug 1;80(8):2109-2116. doi: 10.1093/jac/dkaf177. PMID: 40444723.

Assessment of the Impact of the IDSA Guidance for the Treatment of Gram-Negative Infection on Use of New Antibiotics in U.S. Healthcare Facilities

- Interagency Agreement between FDA and the National Institutes of Health (FY22: 75F40122S30009).
- The objective of this study was to measure the quantitative impacts of the recent IDSA guidance for the treatment of AMR Gram-negative infections on prescribing patterns of new antibiotics in the U.S. The aims of this study were: 1) to assess recent (2019-2022) utilization patterns of new gram-negative active antibiotics at the hospital and patient level, and 2) to describe the trends in utilization of FDA approved gram-negative active antibiotics relative to the publication of the IDSA management guidance at the hospital and patient level using an interrupted time series analysis, controlling for pandemic effect.
- Understanding these trends may inform projections of new antibiotic prescriptions, evaluate the utility of, and need for more nimble guidances for antimicrobial prescribing and the need for higher quality trials, and provide a benchmark response in prescribing behavior that will inform future studies.
- Study Outcomes:
    - **Publication**: Walker MK, Diao G, Warner S, Babiker A, Neupane M, Strich JR, Yek C, Kadri SS; National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH–ARORI). Carbapenem use in extended-spectrum cephalosporin-resistant Enterobacterales infections in US hospitals and influence of IDSA guidance: a retrospective cohort study. Lancet Infect Dis. 2024 Apr 25:S1473-3099(24)00149-X. doi: 10.1016/S1473-3099(24)00149-X. Epub ahead of print. PMID: 38679036.

Understanding Methodological and Data Challenges to Estimating the Health and Economic Burden of Antimicrobial Resistance

- Interagency Agreement between FDA and HHS Office of the Assistant Secretary for Planning and Evaluation (FY22: 75F40122S30010).
- The objective of this study was to better understand current challenges when estimating the burden of AMR to better guide action to improve future AMR burden estimates. This study built upon ASPE's FY18 and FY19 studies. The current FY22 study aimed to provide a comprehensive summary of the current methods for estimating the future health and economic burden of AMR. The review considered existing data and methodological limitations for generating estimates of AMR burden and identify potential avenues for addressing these limitations.
- Results of this study may lead to more accurate AMR burden calculations in the future. This may guide the U.S. Government's effort to combat AMR and effectively plan for and improve patient care in the future.

Identify Metabolomic Features Shared by *in vitro* and *in vivo* Human Intestinal Microbiome Disruption

- Interagency Agreement between FDA and the Centers for Disease Control and Prevention (FY22: 75F40122S30012; FY23: 75F40212S30010).
- The overarching goal of this study was to create an experimental culture system that characterizes the intestinal microbiome disruption potential of antibiotic, probiotic, pharmacologic, and dietary agents. The current prototype system tracks multiple metabolite biomarkers of disruption in a static vial reactor system (SVRS) culture. The objective of this this project is to validate these

biomarkers by monitoring them in human subjects with and without antibiotic-mediated disruption.
- This work may yield an SVRS protocol that confirms characteristics of in vivo microbiome disruption in humans exposed to antimicrobials. With this confirmation, future studies can solely focus on and investigate markers of disruption that are relevant to humans.

A modified susceptibility testing protocol for predicting polymyxin in vivo efficacy

- Awarded to University of Southern California (FY22: 75F40122C00138)
- The main objective of this study was to determine whether MIC testing using the standard culture media (MHII) or RPMI broth better predicts in vivo antibacterial efficacy. Specific aims of this study include: 1) determine the MICs for colistin and polymyxin b using the standard culture medium (MHII) or RPMI, and 2) validate the in vivo predictive efficacy of MICs determined in either MHII or RPMI media using a human equivalent dosing regimen in an *A. baumannii* mouse model of infection.
- Results of this study will ensure that accurate susceptibility testing methods are available to correctly predict polymyxin b treatment outcomes.
- This study aligns with section 2.4.4 of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria are available for patient care and antimicrobial stewardship.
- Study Outcomes
    - **Publication:** Rubio J, Yan J, Miller S, Cheng J, Li R, Builta Z, Aoyagi K, Fisher M, She R, Spellberg B, Luna B. Polymyxins retain in vitro activity and in vivo efficacy against "resistant" Acinetobacter baumannii strains when tested in physiological conditions. Antimicrob Agents Chemother. 2024 Oct 8;68(10):e0072524. doi: 10.1128/aac.00725-24. Epub 2024 Sep 6. PMID: 39240097; PMCID: PMC11459914.

Development of In vivo Pharmacometric Approaches to Guide Antifungal Dosing and Susceptibility Breakpoint Determination for Drug Resistant Aspergillus

- Awarded to University of Wisconsin-Madison (FY23: 75F40123C00143)
- The overarching goal of this proposal was to apply pharmacometric approaches to identify a preclinical aspergillosis infection model endpoint that correlates with outcomes in patients. The goals of this study are: 1) utilize clinical *A. fumigatus* isolates that are defined as susceptible and resistant based upon clinical outcome, MIC, and resistance genotype, and 2) utilize an animal model of invasive lung infection in which we closely mimic triazole drug exposure observed in patients using humanized treatment regimens.
- These approaches will define the quantitative outcome in the model expected to correlate with success or failure in patients.
- The study aligns with Charge Area IIIb1b of the Broad Agency Announcement: Advance the science of in vitro, animal model, pharmacokinetic studies, and/or real- world evidence studies to facilitate drug development, including studies focused on antifungal and antibacterial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction.

Characterizing beta-lactam efficacy against metallo-beta lactamase producing bacteria in zinc-limited culture media

- Awarded to University of Southern California (FY23: 75F40123C00137)
- The aims of this study were to characterize the antibiotic susceptibility testing method that best predicts in vivo efficacy against a panel of *S. maltophilia* clinical isolates. The specific aims of this study were to: 1) Determine susceptibility of beta-lactam antibiotics using MHII, ID-MHII (chelated MHII), ID-MHII + 10 µM ZnCl2/MnCl2, RPMI-1640, RPMI-1640 + 10 µM ZnCl2/MnCl2, or MHII agar, and 2) Compare in vitro results in Aims 1 to in vivo efficacy in mice of ceftazidime (CAZ) treatment.
- These finding have the potential to make available to patients an already approved, safe, highly effective therapeutic that is being missed due to potential inaccuracy of the CLSI-approved method to predict efficacy against MBL-expressing bacteria.
- This study aligns with Charge Area IIIb1a of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria are available for patient care and antimicrobial stewardship.

Characterizing azithromycin efficacy against carbapenem-resistant Gram-negative bacteria in bicarbonate containing culture media

- Awarded to University of Southern California (FY23: 75C40123C00128)
- The aims of this study were: 1) Define macrolide sensitivity against carbapenem-resistant A. baumannii., and 2) Validate the in vivo predictive efficacy of azithromycin (AZM) therapy based on MICs determined with MHII, MHII + bicarbonate, or RPMI-1640.
- AZM is an FDA approved antibiotic and is one of the most abundantly used antibiotics annually in the United States. Therefore, the outcomes of this project may support the rapid clinical translation of AZM as a promising therapeutic option for the treatment of carbapenem-resistant *A. baumannii* infections.
- This study aligns with Charge Area IIIb1a of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria are available for patient care and antimicrobial stewardship.

Development of Modernized Susceptibility Guidance for Ampicillin and Vancomycin for Enterococcus Species Using Pharmacometric Approaches

- Awarded to Institute for Clinical Pharmacodynamics (FY23: 75F40123C00140)
- The overarching goal of this proposal was to apply modern pharmacometric approaches to evaluate the ampicillin and vancomycin susceptibility testing interpretive criteria (STIC) for enterococci. The goals of this project included: 1) Characterization of the contemporary ampicillin and vancomycin MIC distribution for *E. faecalis* and *E. faecium*, 2) PK-PD characterization of ampicillin and vancomycin against *E. faecalis* and E. *faecium* in a neutropenic murine invasive enterococcal infection model, and 3) Identify candidate ampicillin and vancomycin STIC for Enterococcus.
- In support of FDA goals, the objectives outlined in this proposal will deliver a modern pharmacometric-based candidate ampicillin and vancomycin STIC for enterococci.
- This study aligns with Charge Area IIIb1a of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria are available for patient care and antimicrobial stewardship.
- Study Outcomes
    - Poster Presentation: Characterization of Ampicillin and Vancomycin Pharmacokinetics-Pharmacodynamics in a Neutropenic Murine Invasive Enterococcal Infection Model (IDWeek 2025)

- Oral Presentation: Identification of Ampicillin and Vancomycin In Vitro Susceptibility Test Interpretive Criteria for *Enterococcus faecalis* and *Enterococcus faecium* (IDWeek 2025)

Using big data to generate contemporaneous cohorts for study of novel antimicrobials targeting rare infections

- Interagency Agreement between FDA and the National Institutes of Health (FY23: 75F40123S30006)
- The aims of this study were: 1) to develop a well-characterized catalogue of Difficult to Treat Resistance (DTR) gram-negative infection (GNI) organism-site combinations that reports aggregate estimates of population characteristics and real-world antibacterial and supportive care patterns as well as mortality and safety outcomes with confidence intervals based on center-level differences in outcomes, and 2) estimate sample sizes of future interventional trials evaluating novel antimicrobial drugs based on event rates in each DTR GNI organism-site combination.
- This study aimed to identify patterns of extreme resistance within our DTR GNI isolates (e.g., pan-resistance to all tested/ available antimicrobial classes) and quantify their incidence, to inform future descriptive studies of these subgroups.

Using Big Data to Generate a Contemporaneous Cohort of Invasive Fungal Disease (IFD)

- Interagency Agreement between FDA and the National Institutes of Health (FY24: 75F40124S30028)
- The aims of this study were: 1) curate algorithms to identify high-reliability subsets of i) invasive mold infection and ii) multi-drug resistant Candidiasis based on international consensus definitions within large real-world clinical and administrative datasets, and 2) describe the incidence, patient characteristics, treatment regimens, and outcomes of patients admitted to U.S. hospitals in recent years with rare IFD in a large all payer real world database and compare estimates to published estimates.

Development of Modernized Susceptibility Guidance for Nitrofurantoin Dosing Using a Dynamic Urinary Tract In Vitro Infection Model and Pharmacometric Approaches

- Awarded to Institute for Clinical Pharmacodynamics (FY24: 75F40124C00080)
- This aims of this study were to: 1) complete contemporary characterization of nitrofurantoin MIC distributions against *E. coli* and *K. pneumoniae*, 2) conduct PK-PD characterization of nitrofurantoin against *E. coli* and *K. pneumoniae* using the “humanized” two-compartment in vitro infection model, and 3) identify candidate nitrofurantoin susceptibility test interpretative criteria (STIC).
- The overarching goal of this research was to utilize a “humanized” two-compartment in vitro uUTI model that mimics human bladder voiding patterns and antibiotic urine concentration-time profiles to characterize the PK-PD of nitrofurantoin against a panel of bacteria known to cause urinary tract infections.
- This study aligns with Charge Area IIIb1a of the Broad Agency Announcement: Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria.

Relevant Publications by FDA Staff and Fellows Supported by CARB Funding:

- Dheman N, Mahoney N, Cox EM, Farley JJ, Amini T, Lanthier ML. An Analysis of Antibacterial Drug Development Trends in the US, 1980 - 2019. Clin Infect Dis. 2020 Jun 25:ciaa859. doi: 10.1093/cid/ciaa859. Epub ahead of print. PMID: 32584952.

- Bart SM, Farley JJ, Bala S, Amini T, Cox E. Geographic shifts in antibacterial drug clinical trial enrollment: implications for generalizability. Clin Infect Dis. 2020 Mar 12:ciaa246. doi: 10.1093/cid/ciaa246. Epub ahead of print. PMID: 32161946.

- Waack U, Weinstein EA, Farley JJ. Assessing Animal Models of Bacterial Pneumonia Used in Investigational New Drug Applications for the Treatment of Bacterial Pneumonia. Antimicrob Agents Chemother. 2020 Apr 21;64(5):e02242-19. doi: 10.1128/AAC.02242-19. PMID: 32122895; PMCID: PMC7179594.

- Bart SM, Nambiar S, Gopinath R, Rubin D, Farley JJ. Concordance of early and late endpoints for community-acquired bacterial pneumonia trials. Clin Infect Dis. 2020 Jun 25:ciaa860. doi: 10.1093/cid/ciaa860. Epub ahead of print. PMID: 32584969.

- Bart SM, Rubin D, Kim P, Farley JJ, Nambiar S. Trends in hospital-acquired and ventilator-associated bacterial pneumonia trials. Clin Infect Dis. 2020 Nov 11:ciaa1712. doi: 10.1093/cid/ciaa1712. Epub ahead of print. PMID: 33173946.

- Byrne JM, Waack U, Weinstein EA, Joshi A, Shurland SM, Iarikov D, Bulitta JB, Diep BA, Guina T, Hope WW, Lawrenz MB, Lepak AJ, Luna BM, Miesel L, Phipps AJ, Walsh TJ, Weiss W, Amini T, Farley JJ. FDA Public Workshop Summary: Advancing Animal Models for Antibacterial Drug Development. Antimicrob Agents Chemother. 2020 Oct 26:AAC.01983-20. doi: 10.1128/AAC.01983-20. Epub ahead of print. PMID: 33106262.

- Waack U, Joshi A, Jang SH, Reynolds KS. Variations in pharmacokinetic-pharmacodynamic target values across MICs and their potential impact on determination of susceptibility test interpretive criteria. J Antimicrob Chemother. 2021 Aug 4:dkab282. doi: 10.1093/jac/dkab282. Epub ahead of print. PMID: 34347077.

- Kadry N, Natarajan M, Bein E, Kim P, Farley J. Discordant Clinical and Microbiological Outcomes Are Associated With Late Clinical Relapse in Clinical Trials for Complicated Urinary Tract Infections. Clin Infect Dis. 2023 May 24;76(10):1768-1775. doi: 10.1093/cid/ciad010. PMID: 36625164.

- Kinamon T, Gopinath R, Waack U, Needles M, Rubin D, Collyar D, Doernberg SB, Evans S, Hamasaki T, Holland TL, Howard-Anderson J, Chambers H, Fowler VG, Nambiar S, Kim P, Boucher HW. Exploration of a Potential Desirability of Outcome Ranking Endpoint for Complicated Intra-Abdominal Infections Using 9 Registrational Trials for Antibacterial Drugs. Clin Infect Dis. 2023 Aug 22;77(4):649-656. doi: 10.1093/cid/ciad239. PMID: 37073571; PMCID: PMC10443999.

More information on the research activities and future research opportunities can be found on FDA's Office of Infectious Diseases Research webpage: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-infectious-diseases-research-activities