The Antimicrobial Resistance Crisis: The Urgent Need for Alternative Therapies

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School of Medicine,
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Eugene Applebaum College of Pharmacy & Health Sciences

- 11 accredited healthcare disciplines
  - Offers degrees or certificates to undergraduates, professional and graduate students
- Research: Cancer, Infectious Diseases, Metabolic, Neuro/Psyc

- BS: Clinical Laboratory Science, Mortuary Science, Radiologic Technology, Radiation Therapy Technology, Health Sciences
- MS: Pathologists Assistant, Physician Assistant, Pharmaceutical Sciences, Occupational Therapy
- Doctorates: Physical Therapy, Nurse Anesthesia, Pharmacy (PharmD), PhD Pharmaceutical Sciences

Background

- Born and raised in Buffalo NY - 
- Pre-Medicine Daeman University
  - Roswell Park Cancer Institute
- Associate of Science Degree
- Buffalo State University -Biology
- Northeastern University, Boston MA
  - B.S. Pharm -1979
- Hospital Pharmacist
  - South Shore Hospital – South Weymouth MA
- Wayne State University
  - PharmD -1981
- Faculty Position WSU 1981
  - DMC appointment
    - Clinical Pharmacokinetic Service
    - Pharmacokinetics Laboratory
- Microbiology/Antibiotic Resistance
  - Glenn Kaatz, MD
  - Sabbatical –Antibiotic Resistance
- Fellowship Program- 1985
- Focus
  - Antibiotic optimization and prevention of antibiotic resistance
- Associate Professor-Tenure - 1987
- Professor-Tenure -1993
- Associate Dean for Research – 2003-2011
- MPH WSU – 2005
- PhD Walden University Public Health/Epidemiology 2016

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1990, p. 792–795 Vol. 34, No. 5
0066-4804/90/050792-04$02.00/0

Vancomycin Pharmacokinetics in Burn Patients and Intravenous Drug Abusers

MICHAEL J. RYBAK,[1,2]* LISA M. ALBRECHT,[1]† JULIE R. BERMAN,[2] LAWRENCE H. WARBASSE,[3,4] AND CRAIG K. SVENSSON[1]

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1991, p. 696–700 Vol. 35, No. 4
0066-4804/91/040696-05$02.00/0

Teicoplanin Pharmacokinetics in Intravenous Drug Abusers Being Treated for Bacterial Endocarditis

MICHAEL J. RYBAK,[1,2,3,4]* STEPHEN A. LERNER,[2,4] DONALD P. LEVINE,[2,4,5] LISA M. ALBRECHT,[1,3]† PAM L. McNEIL,[4,5] GARY A. THOMPSON,[6] MICHAEL T. KENNY,[7] AND LIANNG YUH[6]

College of Pharmacy and Allied Health Professions[1] and School of Medicine,[2] Wayne State University, Departments of Pharmacy[3] and Internal Medicine,[5] Detroit Receiving Hospital and University Health Center, and Division of Infectious Diseases, Department of Medicine, Harper Hospital,[4] Detroit, Michigan 48201; Merrell Dow Research Institute, Cincinnati, Ohio 45215[6]; and Merrell Dow Research Institute, Indianapolis, Indiana 46268[7]

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American Society for Microbiology
Antimicrobial Agents and Chemotherapy
Volume 43, Issue 7, 1 July 1999, Pages 1549-1555
https://doi.org/10.1128/AAC.43.7.1549

Prospective Evaluation of the Effect of an Aminoglycoside Dosing Regimen on Rates of Observed Nephrotoxicity and Ototoxicity

Michael J. Rybak[1,2,*], Betty J. Abate[1,†], S. Lena Kang[1,†], Michael J. Ruffing[1], Stephen A. Lerner[2], and George L. Drusano[3]

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[2] Department of Internal Medicine, Division of Infectious Diseases, School of Medicine, Wayne State University, Detroit, Michigan 48201, and

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1992, p. 1109–1114 Vol. 36, No. 5
0066-4804/92/051109-06$02.00/0

Pharmacokinetics and Bactericidal Rates of Daptomycin and Vancomycin in Intravenous Drug Abusers Being Treated for Gram-Positive Endocarditis and Bacteremia

MICHAEL J. RYBAK,[1,2,3]* ELAINE M. BAILEY,[1,2,3] KENNETH C. LAMP,[1,3] AND GLENN W. KAATZ[2,4]

College of Pharmacy and Allied Health Professions[1] and Department of Medicine, Divis[illegible]n of Infectious Diseases,[2] Wayne State University, and the Anti-Infective Research Laboratory, Department of Pharmacy,[3] and Department of Medicine,[4] Detroit Receiving Hospital and University Health Center, Detroit, Michigan 4[illegible]201

Received 29 August 1991/Accepted 25 February 1992

Pharmacotherapy. 1999. 19 (11): 1252-60.

Pharmacodynamic Characterization of Nephrotoxicity Associated with Once-Daily Aminoglycoside

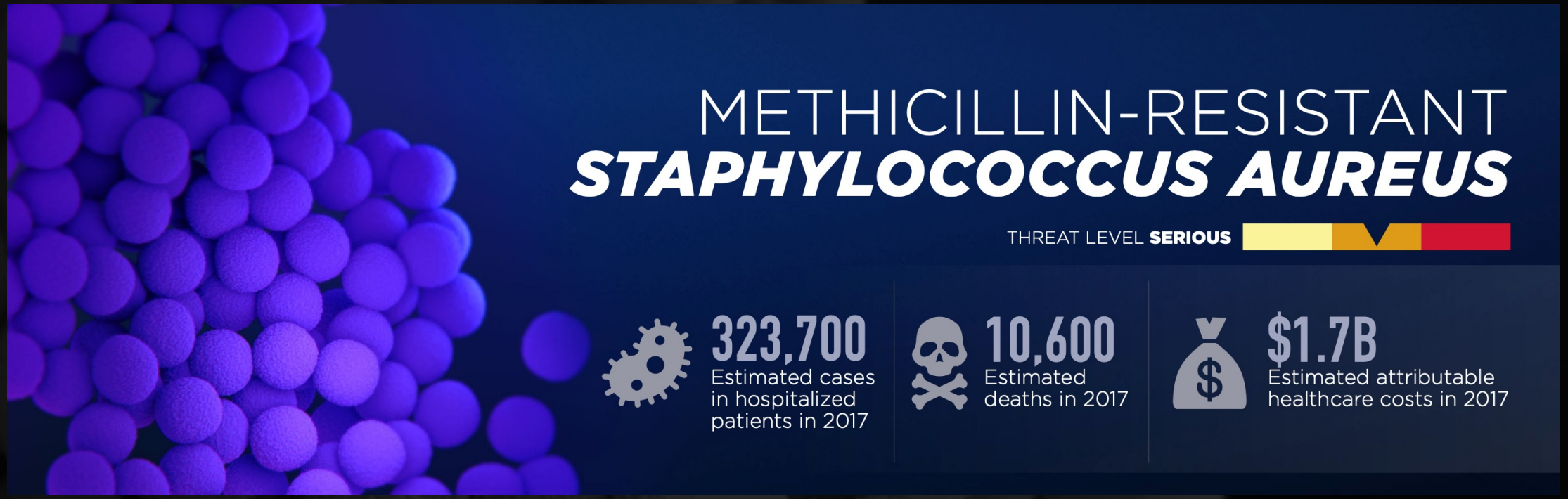
Kellie R. Murry, Pharm.D., Peggy S. McKinnon, Pharm.D., Beatriz Mitrzyk, Pharm.D., and Michael J. Rybak, Pharm.D., FCCP

Journal of Antimicrobial Chemotherapy. (1986) 17, 115-120.

Clinical use and toxicity of high-dose tobramycin in patients with pseudomonal endocarditis

Michael J. Rybak*, Steven C. Boike*, Donald P. Levine†, and Steven R. Erickson*

Department of Pharmacy and the Division of Infectious Diseases, Department of Medicine,† Detroit Receiving Hospital and University Health Center, and Wayne State University, Detroit, Michigan, U.S.A.*



Standard of care antimicrobials for serious MRSA infections

- Vancomycin
- Daptomycin
- Ceftaroline

Rybak et al. *Clin Infect Dis*. 2009. 49 (3): 325-27.
Liu et al. *Circulation*. 2015;132:1435-86.
Rybak et al. *Clin Infect Dis*. 2020. 71 (6): 1361-64.
Baddour et al. *Clin Infect Dis*. 2011. 52; (3): 285-292.

IDSA GUIDELINES

Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists

Michael J. Rybak,[1,2,3] Ben M. Lomaestro,[4] John C. Rotschafer,[5] Robert C. Moellering, Jr.,[6,7,8] Willam A. Craig,[9] Marianne Billeter,[10] Joseph R. Dalovisio,[11] and Donald P. Levine[3]

[1]Anti-Infective Research Laboratory, Department of Pharmacy Practice, College of Pharmacy & Health Sciences, and [2]Department of Medicine, School of Medicine, Wayne State University, and [3]Detroit Receiving Hospital & University Health Center, Detroit, Michigan; [4]Albany Medical Center, Albany, New York; [5]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis; [6]Shields Warren-Mallinckrodt Medical Research, [7]Harvard Medical School, and [8]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [9]University of Wisconsin School of Medicine and Public Health, Madison; and [10]Oshsner Medical Centers

Clin Infect Dis. 2009. 49 (3): 325-27. doi.org/10.1086/600877

1 Vancomycin

IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

[1]Department of Medicine, Division of Infectious Diseases, University of California-San Francisco, San Francisco, California; [2]Division of Infectious Diseases, San Francisco General Hospital, San Francisco, CA, [3]Division of Infectious Diseases, Harbor-UCLA Medical Center, Torrance, CA, [4]Divisions of Emergency Medicine and Infectious Diseases, Olive View-UCLA Medical Center, Sylmar, CA; [5]Department of Medicine, David Geffen School of Medicine at University of California Los Angeles; [6]Division of Infectious Diseases, Johns Hopkins Medical Institutions, Baltimore, Maryland; [7]Department of Pediatrics, Section of Infectious Diseases, University of Chicago, Chicago, Illinois; [8-9]Division of Healthcare Quality Promotion, Center for Emerging and Zoonotic Infectious

Clin Infect Dis. 2011. 52; (3): 285-292. doi.10.1093/cid/cir034

2 Daptomycin

Clinical Infectious Diseases

IDSA FEATURES

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Therapeutic Monitoring of Vancomycin for Serious Methicillin-resistant *Staphylococcus aureus* Infections: A Revised Consensus Guideline and Review by the American Society of Health-system Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists

Michael J. Rybak,[1,2,3] Jennifer Le,[4] Thomas P. Lodise,[5] Donald P. Levine,[2,3] John S. Bradley,[6,7] Catherine Liu,[8,9] Bruce A. Mueller,[10] Manjunath P. Pai,[10] Annie Wong-Beringer,[11] John C. Rotschafer,[12] Keith A. Rodvold,[13] Holly D. Maples,[14] and Benjamin Lomaestro[15]

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Clin Infect Dis. 2020. 71 (6): 1361-64. doi.org/10.1093/cid/ciaa303

3 Ceftaroline

4 Linezolid

AHA Scientific Statement

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

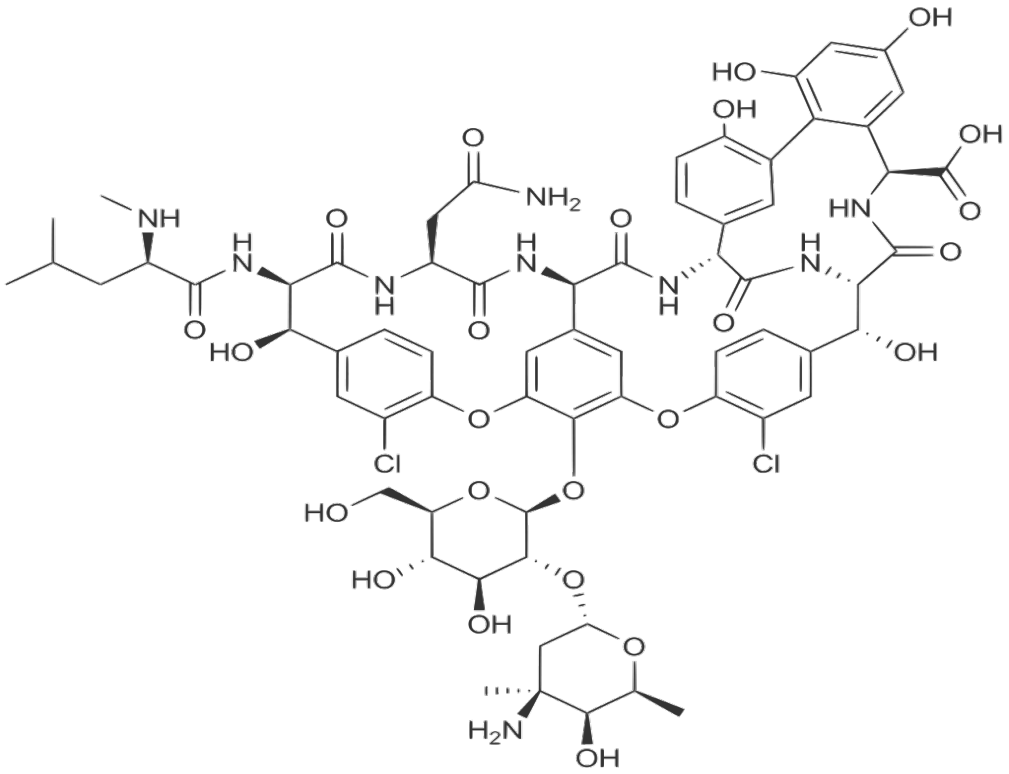
Endorsed by the Infectious Diseases Society of America

Larry M. Baddour, MD, FAHA, Chair; Walter R. Wilson, MD; Arnold S. Bayer, MD; Vance G. Fowler, Jr, MD, MHS; Imad M. Tleyjeh, MD, MSc; Michael J. Rybak, PharmD, MPH; Bruno Barsic, MD, PhD; Peter B. Lockhart, DDS; Michael H. Gewitz, MD, FAHA; Matthew E. Levison, MD; Ann F. Bolger, MD, FAHA; James M. Steckelberg, MD; Robert S. Baltimore, MD; Anne M. Fink, PhD, RN; Patrick O'Gara, MD, FAHA; Kathryn A. Taubert, PhD, FAHA; on behalf of the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council

Circulation. 2015;132:1435-86. doi: 10.1161/CIR.0000000296

Vancomcyin

- Treatment of choice for MRSA Infections
  - In clinical use since 1958
- Mechanism of action
  - Cell wall synthesis inhibitor
- Resistance:
  - Low level: hVISA, VISA
  - High level: VRSA
  - Cross-resistance (i.e., daptomycin)
- Failure rates
  - High in complicated infections (i.e., BSI, IE)
  - 30-day mortality > 20% in cBSI



Howden BP, Davies JK, Johnson PD, Stinear TP, Grayson ML,. Reduced vancomycin susceptibility in Staphylococcus aureus, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. *Clin Microbiol Rev* 2010;23:99-139. Kullar R, Davis S, Levine D, Rybak M. Impact of vancomycin exposure on outcomes in MRSA bacteremia: Support for consensus guidelines suggested targets. *Clin Infect Dis.* 2011;52(8):975-81.

Rationale for Combination Therapy

Improved Patient Response

- Reduction in time to resolution of symptoms

Improved Drug Performance

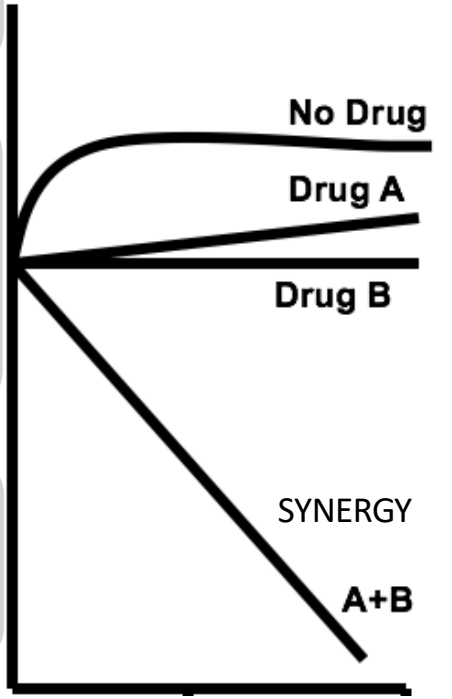
- Potential for synergy
- Lower PK/PD target threshold
- Increased killing
- Decreased time to bacterial eradication

Lower Antibiotic Exposures

- Dose sparing
- Dose de-escalation
- Reduction of adverse effects

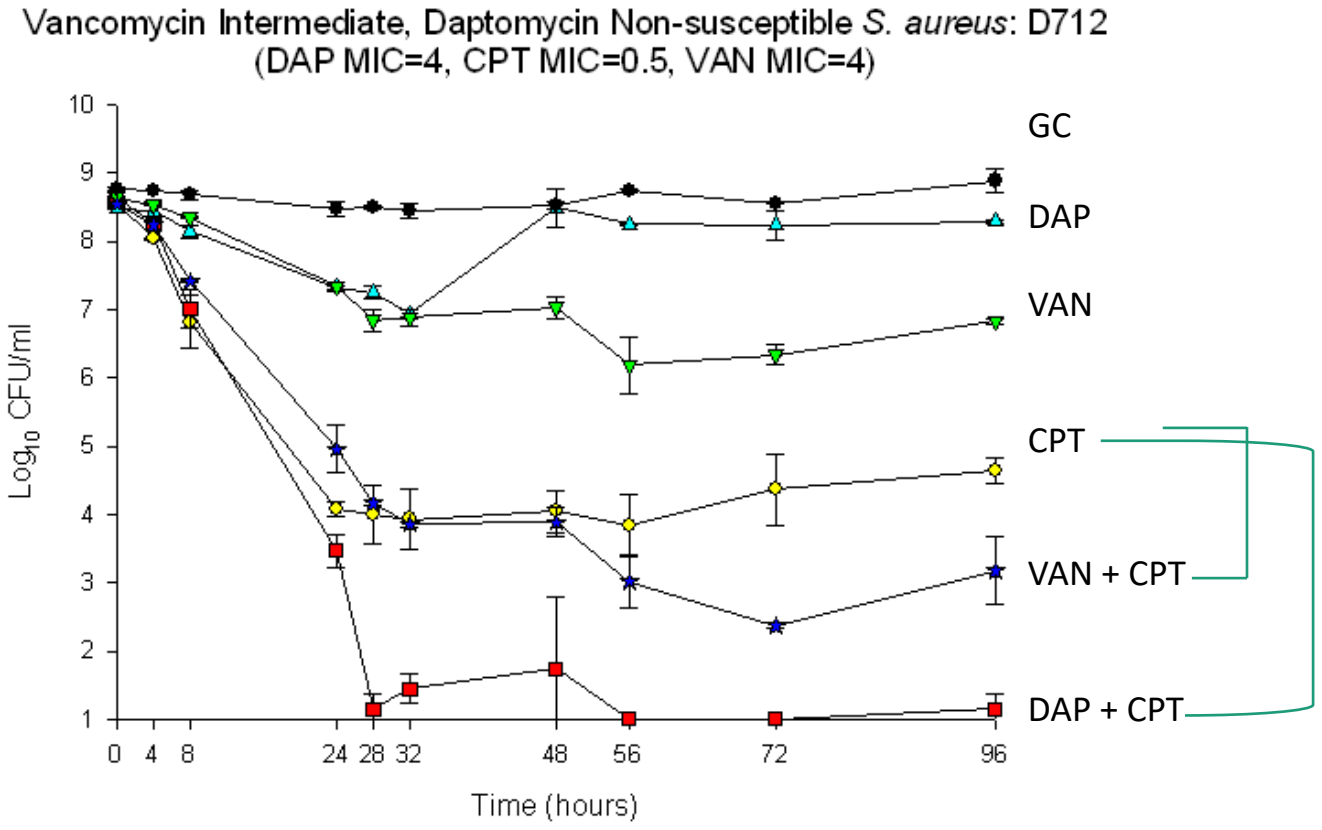
Reduction of the potential for Resistance

- Due to lower exposures
- Elimination/reduction of relapse and recurrence



Rodríguez-Gascón et al., 2021,Pharmaceutics 13:833

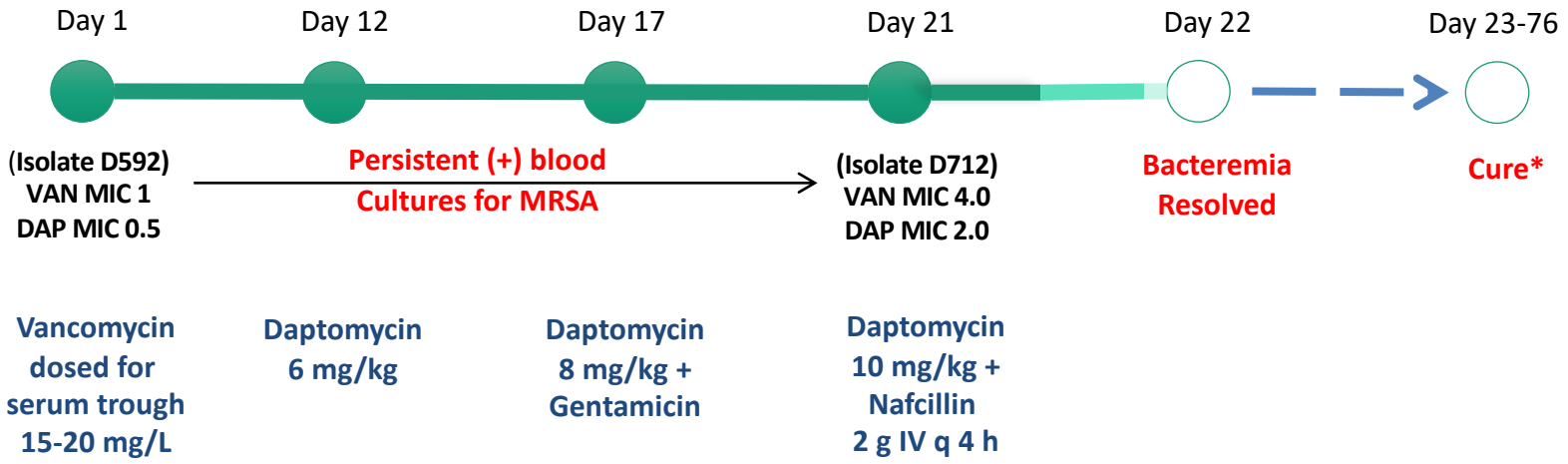
Combination Daptomycin or Vancomycin with Ceftaroline for Daptomycin and Vancomycin Non-susceptible *S. aureus*



Daptomycin 10 mg/kg/day
Vancomycin 2g q 12 h
Ceftaroline 600 mg q 8 h

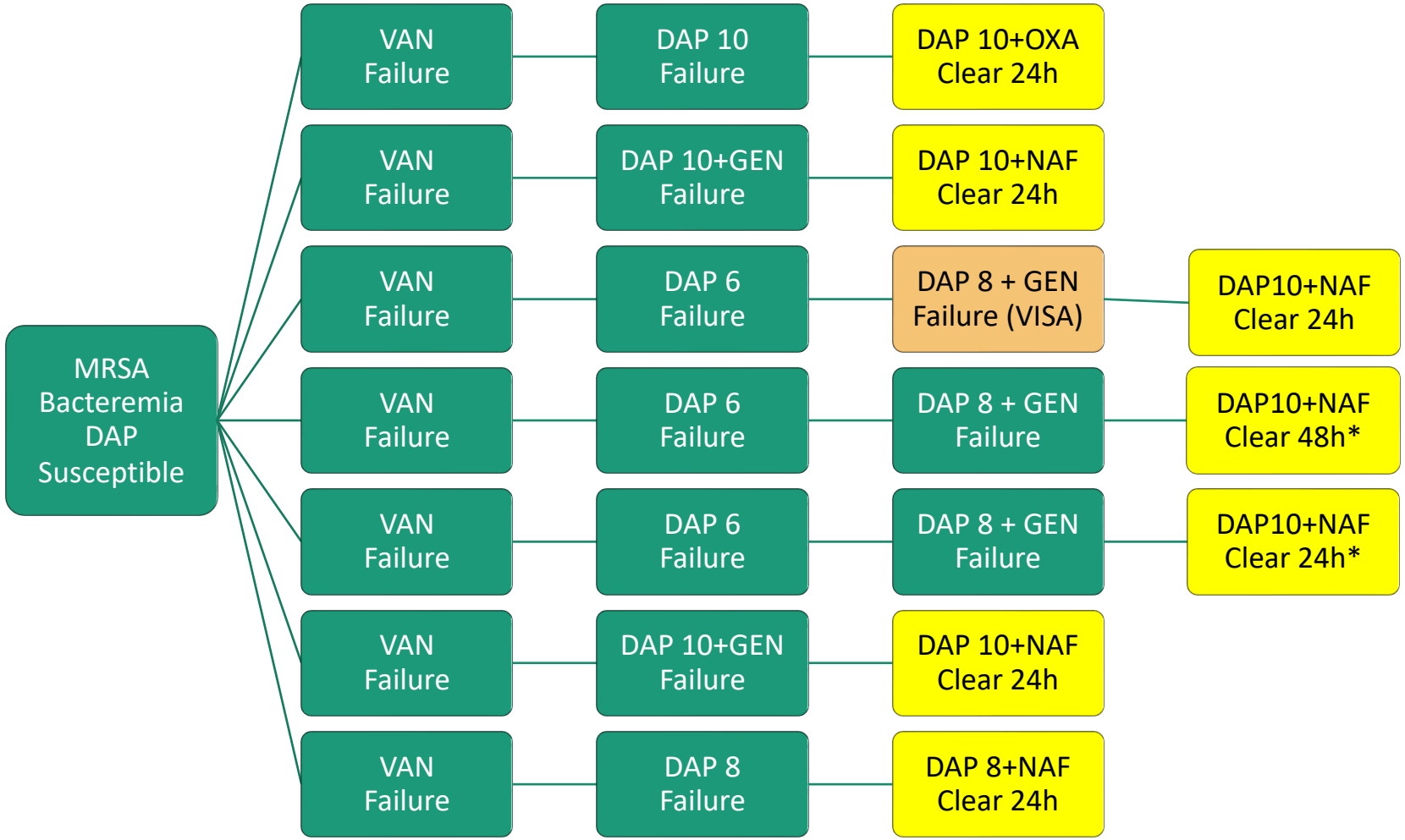
Werth, B. et al. *Antimicrob Agents Chemother*. 2013;57:66-73.

CASE IN POINT: Patient with persistent MRSA/VISA Bacteremia, Recalcitrant to Vancomycin or Daptomycin Therapy, Resolved Upon Addition of ***Nafcillin***



Adapted from: Sakoulas, G. et al. *J Mol Med*. 2014. 92:139-149.

Rapid MRSA Bacteremia Clearance with High-Dose Daptomycin plus a β-lactam

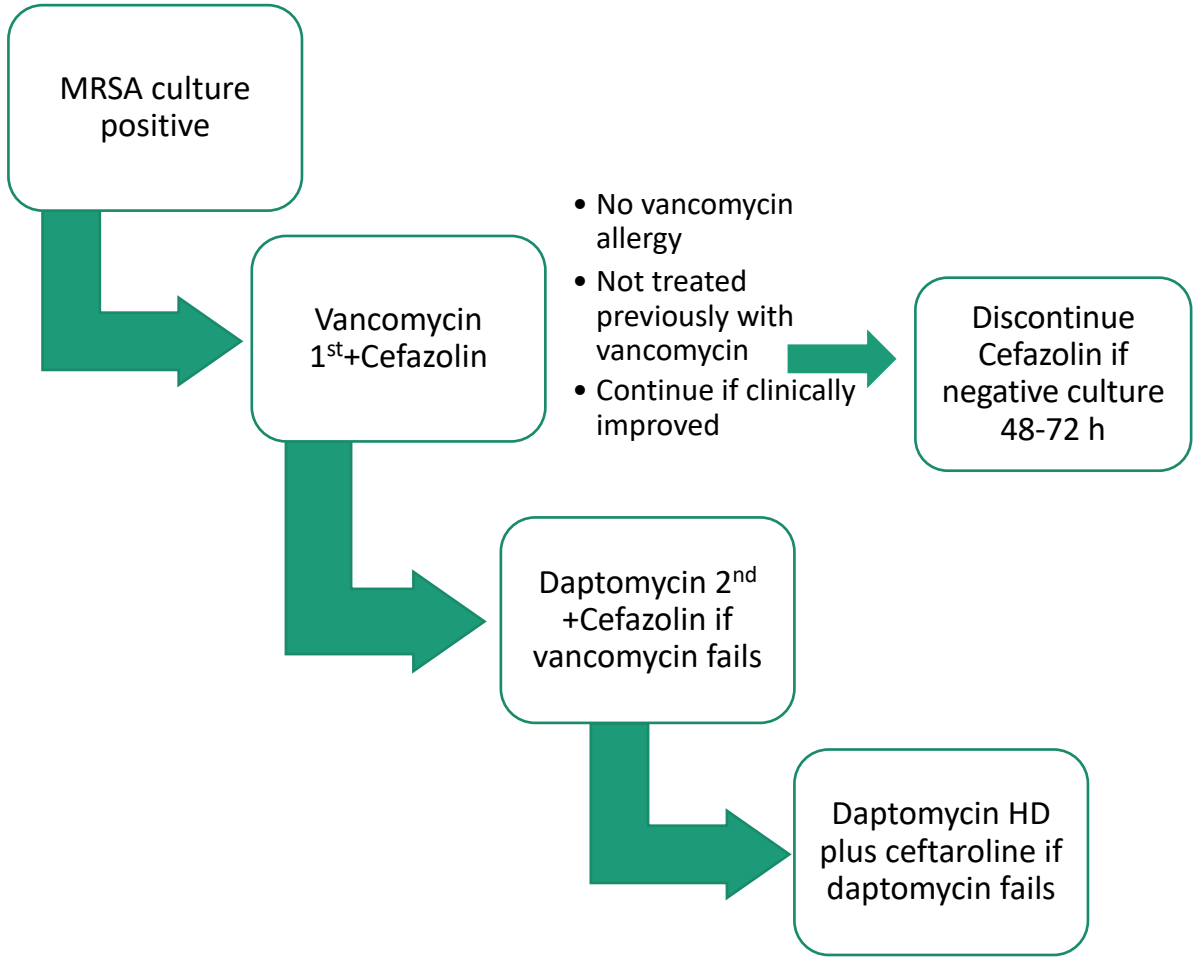


*Relapsed – 12 wks & 8 wks post-therapy – 1 cleared w/another course,;1 died w/VISA PV IE VAN MIC 3; DAP MIC 1.5 Red VISA; DAP MIC 2-4 - Additional studies performed on the isolates from this case

Adapted from: Dhand A, Bayer AS, Pogliano J et al. Use of antistaphylococcal β-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant *Staphylococcus aureus*: role of enhanced daptomycin binding. CID 2011:53:158-63.

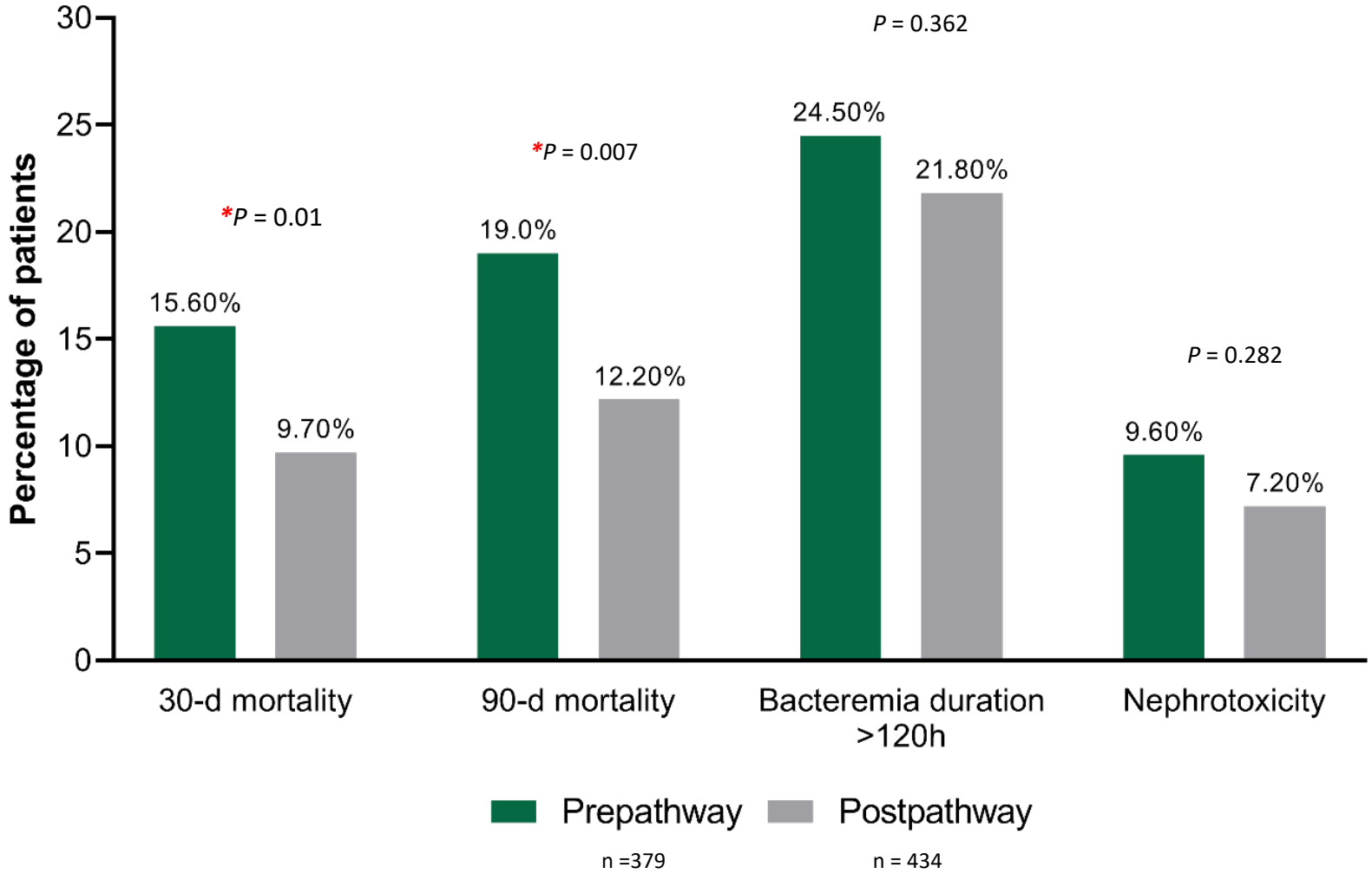
β-lactam adjuvant Therapy for MRSA Bacteremia: *Translating bench to bedside*

- Review of MRSA Bacteremia at the DMC
  - Up to 30% mortality
- MRSA Pathway- 2016
  - Based on laboratory experience with combination therapy
  - Published clinical studies



Alosaimy S. et al. *Open Forum Infect Dis.* 2021. May 23;8(7):ofab261.

Combination Beta-Lactam Pathway for MRSA Bacteremia: STAPH Study



Alosaimy S. et al. *Open Forum Infect Dis.* 2021. May 23;8(7):ofab261. doi: 10.1093/ofab261.

Phage Therapy: An adjunct to Antibiotic Treatment?

Michael J. Rybak, PharmD, MPH, PhD, FCCP, FIDSA, FIDP

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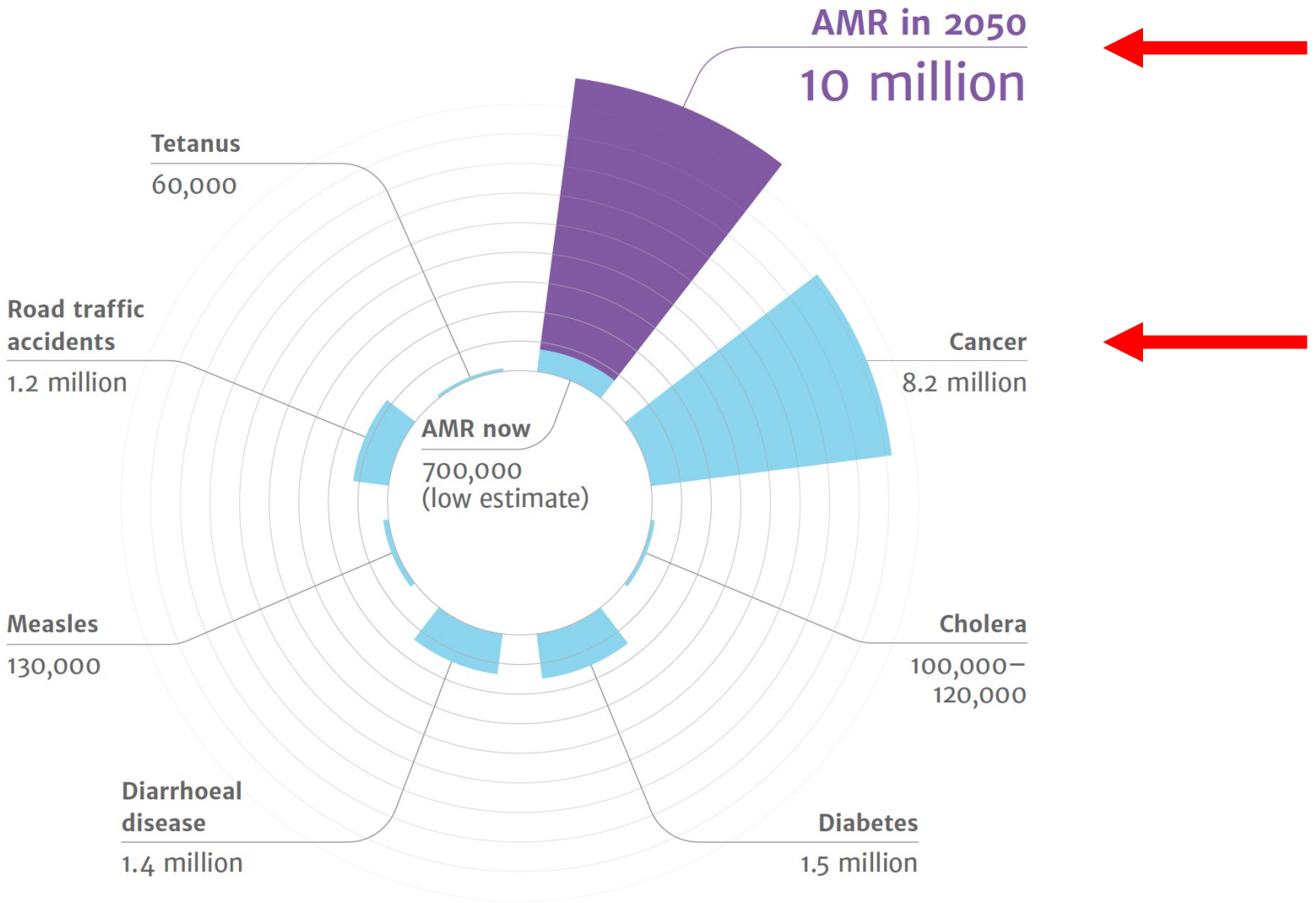
Disclosures

- Received grant support, advisor or have spoken on behalf of:
  - Abbive, Amplify (now Armata), Contrafect, Entasis, La Jolla, Merck, Paratek, Shionogi, T2 Biosystems

  - NIH R21 AI163726 (PI)
  - NIH R01 AI1300056-04 (Co-Inv, A. Bayer, PI)
  - NIH R01 AI148342-03 (Co-Inv, C. Arias, PI)
  - Michigan Department of Health and Human Resources (PI)

Deaths Attributable to AMR Every Year



Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance. 2016 https://amr-review.org

Marilieke E. et al. Plos Medicine 2016. https://doi.org/10.137/journal.pmed.1002184

Two major goals of the National Action Plan (2020-2025) for combating AMR

Accelerate basic and applied research for development of novel therapeutics.

Slow the emergence of AMR bacteria and prevent their spread.

https://www.cdc.gov/drugresistance/us-activities/national-action-plan.html

CDC

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *Clostridioides difficile*
- Carbapenem-resistant Enterobacteriacea
- Drug-resistant *Neisseria gonorrhoeae*

WHO

Panel: WHO priority list for research and development of new antibiotics for antibiotic-resistant bacteria

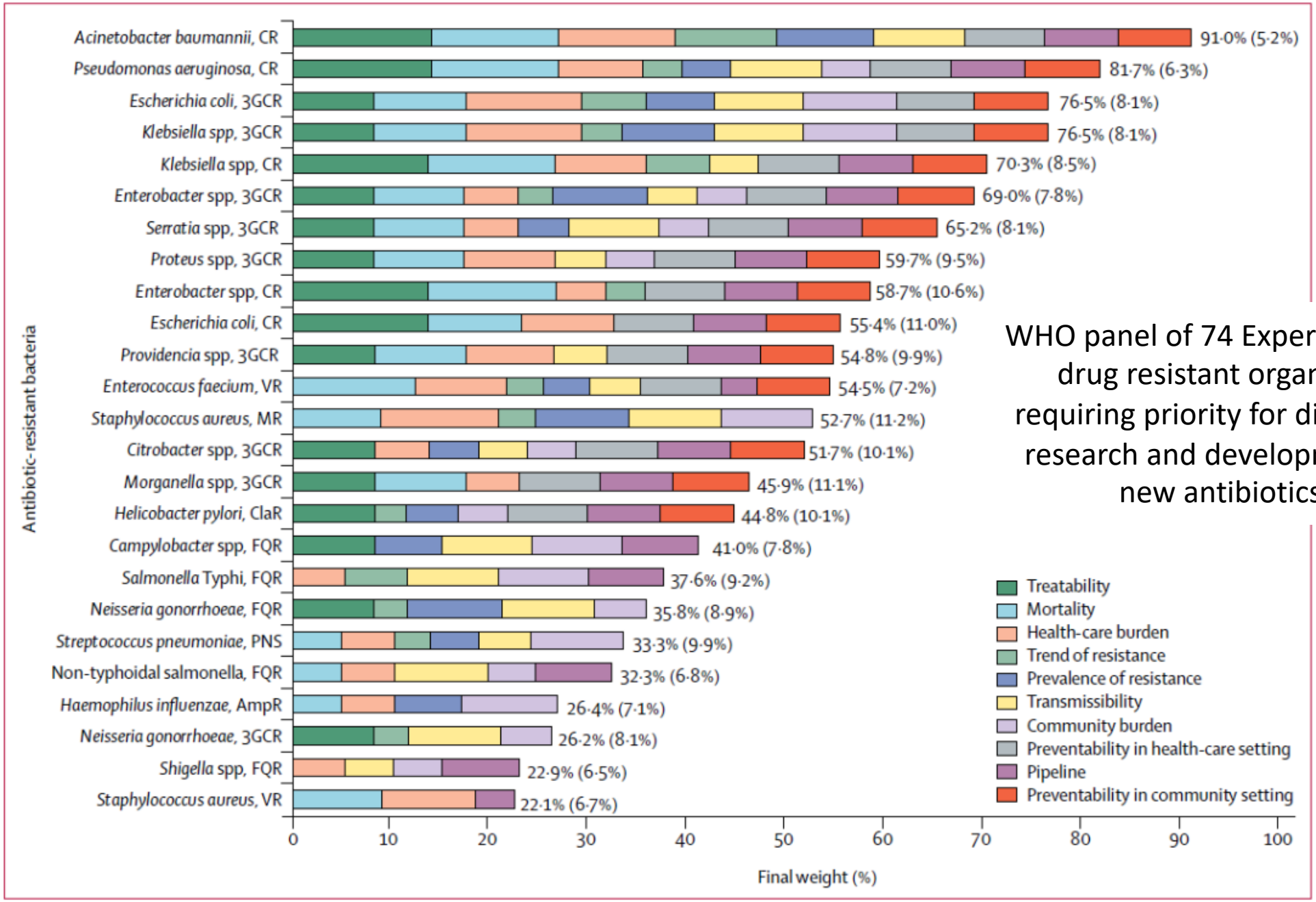
- Multidrug-resistant and extensively-resistant Mycobacterium tuberculosis

Other priority bacteria:

Priority 1: Critical

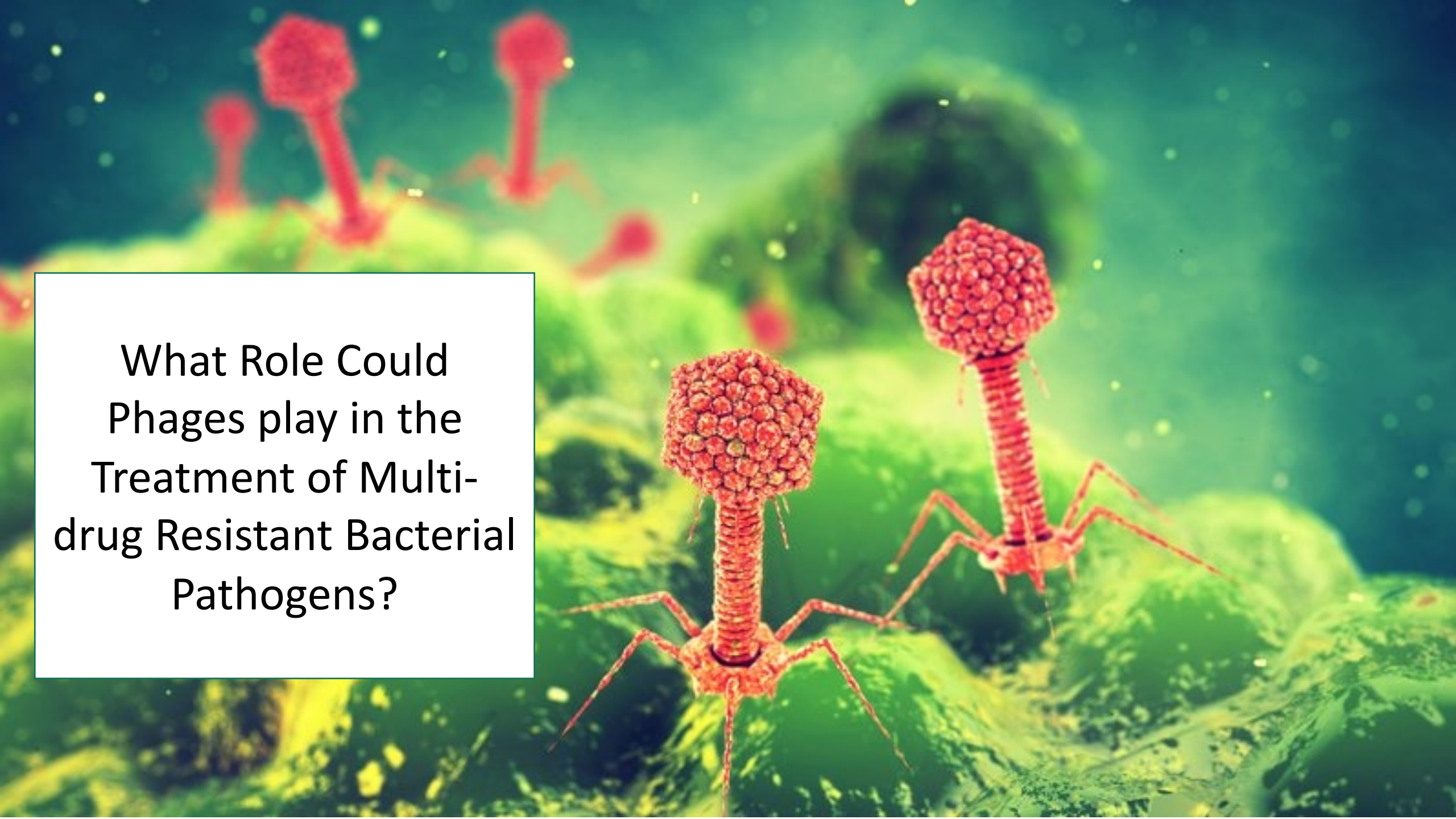
- *Acinetobacter baumannii*-carbapenem resistant
- *Pseudomonas aeruginosa*, carbapenem resistant
- Enterobacteriaceae, carbapenem resistant, third generation cephalosporin resistant

US Centers for Disease Control and Prevention 2019
Tacconelli et al. *Lancet Infect Dis*. 2018;18(3):318-27.



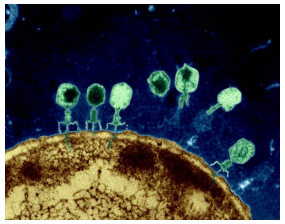
WHO panel of 74 Experts: multi-drug resistant organisms requiring priority for discovery, research and development of new antibiotics

Tacconelli et al. *Lancet Infect Dis.* 2018;18(3):318-327



What Role Could Phages play in the Treatment of Multi-drug Resistant Bacterial Pathogens?

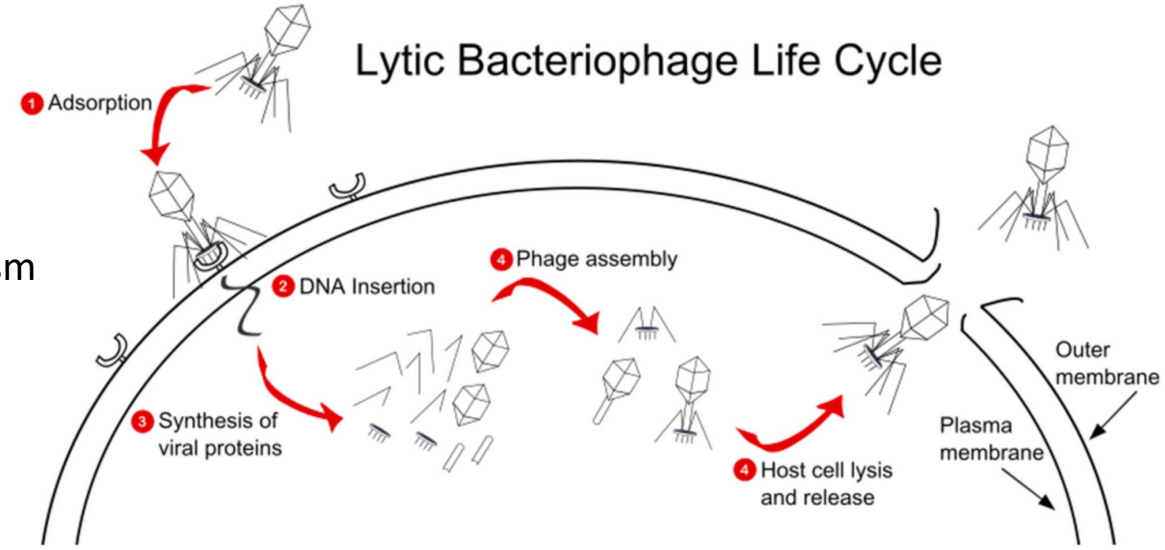
What are Phages?



Viruses that infect bacteria

Nature’s “ check on bacteria

Most abundant organism 10^{31}



Highly specific

Harnessed as treatment For the last 100 years but not FDA approved

Good safety profile generally considered safe

Holger D, Kebriaei R, Morrisette T, et al. *Antibiotics*. 2021; 10(5):556. doi: 10.3390/antibiotics10050556

Antibiotics vs. Bacteriophages

- Static molecules
- Broad host ranges
- Easier to commercialize
- Antimicrobial resistance challenging

- Dynamic, living organisms
- Extremely narrow host range
- Highly individualized
- High therapeutic Index
- Commercialization challenging
- Bacterial resistance to phage can be an issue
- Appears to be effective against biofilms

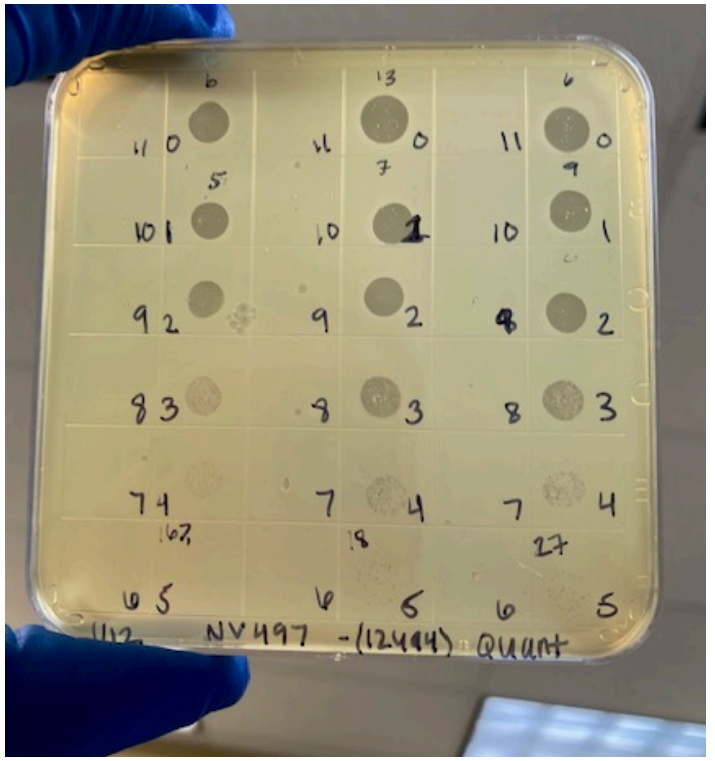
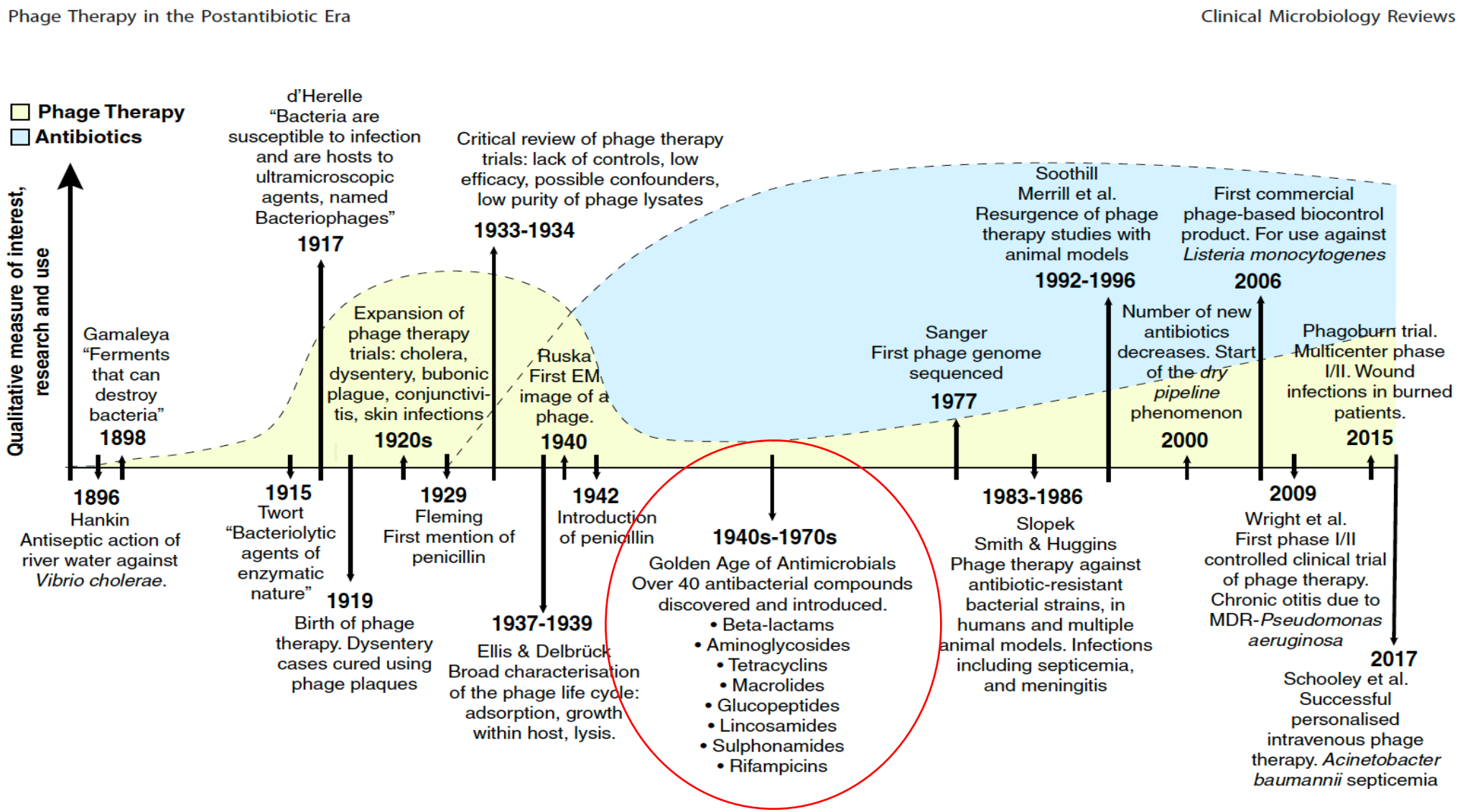


Photo courtesy Anti-Infective Research Lab

History of Phage Therapy



Fernando L., Atlamirano G, Barr J, *Clin Microbiol Rev*. 2019. 32;(2):e00055-18.

Phage Therapy: Commercial Cocktails for Empiric and Customized Treatment

- **Staphylococcal Bacteriophage**: *S. aureus*
- **PYO Bacteriophage**: *S. aureus, E. coli, Streptococcus, Pseudomonas, Proteus*
- **ENKO Bacteriophage**: *Shigella, Salmonella, E.coli, Staphylococcus*
- **INTESTI Bacteriophage**: *Shigella, Salmonella, Staphylococcus spp. Proteus, E. coli, Pseudomonas aeruginosa, E. faecalis*
- **SES Bacteriophage**: *Staphylococus, E. coli, Streptococcus*
- **FERSISI Bacteriophage**: *Staphylococcus, Streptococcus*
- **Auto Bacteriophage**: customized “individual phage”

ELIAVA
Phage Therapy Center

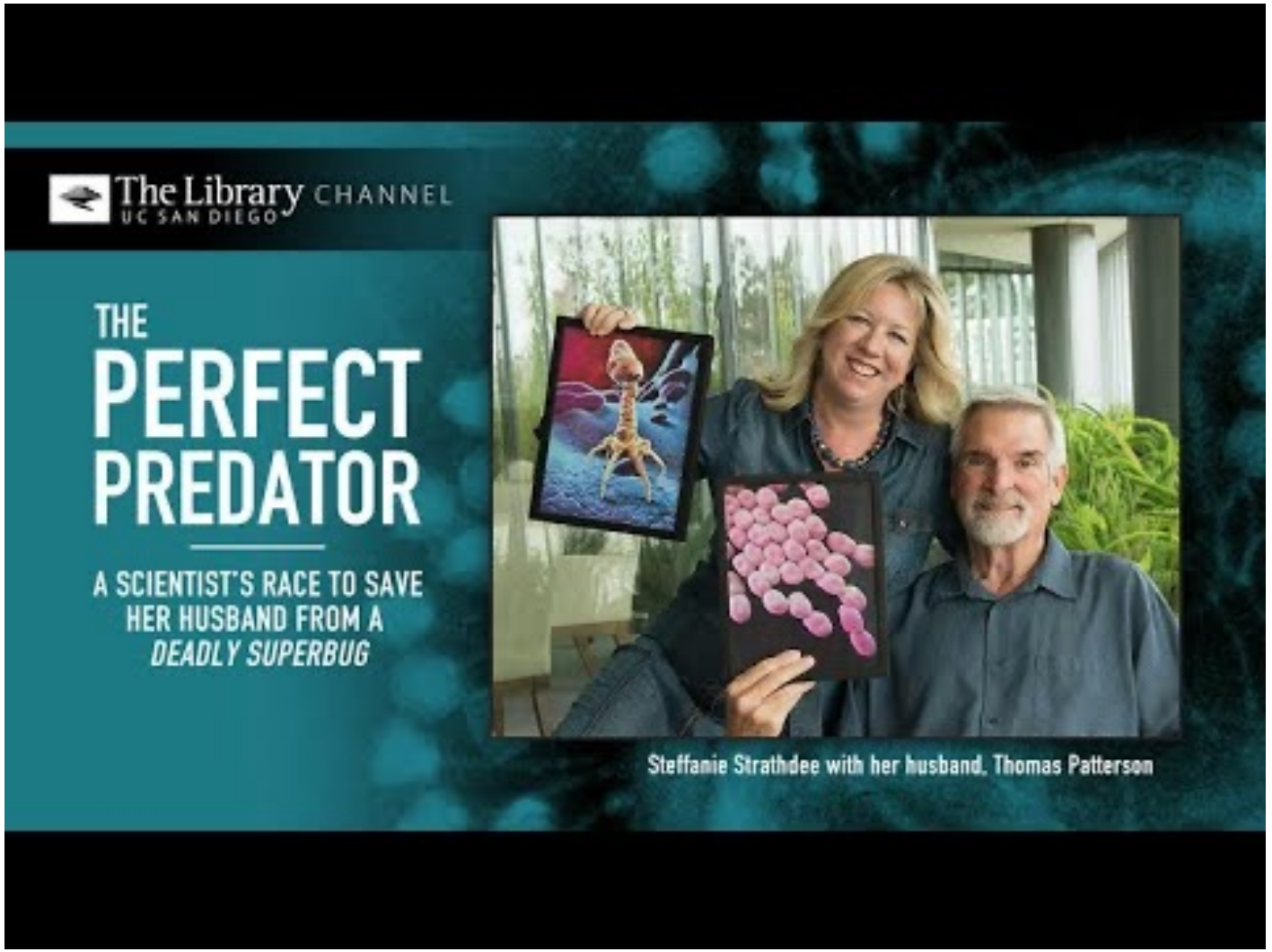
Tbilisi, Georgia

Eliava Phage Therapy for Bacterial Persistance: Case Examples

	Patient 1	Patient 2	Patient 3
Age (yrs)	43	64	72
Gender	male	female	female
Diagnosis	Cystic fibrosis	Primary ciliary dyskinesia, bronchiectasis	Chronic cystitis, bacterial vaginitis
Main Causative Pathogen	*P. aeruginosa*	*P. aeruginosa*	*K. pneumoniae*
Route of administration	Oral, inhalation via nebulizer	Oral	Oral, vaginal suppositories
Other phages included	Custom PA, PYO, Intesti	Custom PA, Staph phage	Custom KP, Intesti, SES
Antibiotics included	None*	None	Vaginal suppositories: metronidazole, miconazole, polymyxin B/neomycin
Phage duration of therapy	Jan 2017-Feb 2021	Sept 2018-present	June 2018-June-2019

Zaldastanishvili E et al. *Viruses* 2021. 13, 1901. https://doi.org10.3390/v13101901

Personalized Phage Therapy for Disseminated MDR- *Acinetobacter baumanni* infection



- 2016 Egypt vacation
- MDR *A. baumannii* pancreatitis
- Univ California-San Diego
- Critical Condition-Comatose
- Phage cocktails-Texas A&M Univ, Dept of US Navy, Ampliphi
- Rapid response starting 48h post phage therapy
- 2019 Publication of “The Perfect Predator”

Schooley RT et al. *Antimicrob Agents Chemother*. 2017. 61(10) e00954-17.

Open Forum Infectious Diseases

MAJOR ARTICLE

Lessons Learned From the First 10 Consecutive Cases of Intravenous Bacteriophage Therapy to Treat Multidrug-Resistant Bacterial Infections at a Single Center in the United States

Saima Aslam,[1,2] Elizabeth Lampley,[2] Darcy Wooten,[1] Maile Karris,[1] Constance Benson,[1,2] Steffanie Strathdee,[1,2] and Robert T. Schooley[1,2]

[1]Division of Infectious Diseases and Global Public Health, University of California, San Diego, La Jolla, California, USA, and [2]Center for Innovative Phage Applications and Therapeutics, University of California, San Diego, La Jolla, California, USA

Background. Due to increasing multidrug-resistant (MDR) infections, there is an interest in assessing the use of bacteriophage therapy (BT) as an antibiotic alternative. After the first successful case of intravenous BT to treat a systemic MDR infection at our institution in 2017, the Center for Innovative Phage Applications and Therapeutics (IPATH) was created at the University of California, San Diego, in June 2018.

Aslam S et al. *Open Forum Infect Dis.* 2020. 7(9): doi: 10.1093/ofid/ofaa389

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

MINIREVIEW

Considerations for the Use of Phage Therapy in Clinical Practice

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- **Review:**
- 2000-August 2021
- English-language only
- Reviewed:
  - 14,841 abstracts
  - 968 manuscripts
- **65 cases total**
- Age: 2-88 years
- Female: 17; 26%, Male: 44; 68%
- Unknown 4; 6%

Targeted Organisms:

P. aeruginosa- 22
S. aureus- 22
Acinetobacter- 7
Polymicrobial- 7
K. pneumoniae- 6
S. epidermidis- 3
Achromobacter- 2
E. coli- 2
M. abscessus- 2
Burkholderia dolosa- 1
E. faecalis- 1
E. faecium- 1
GBS- 1

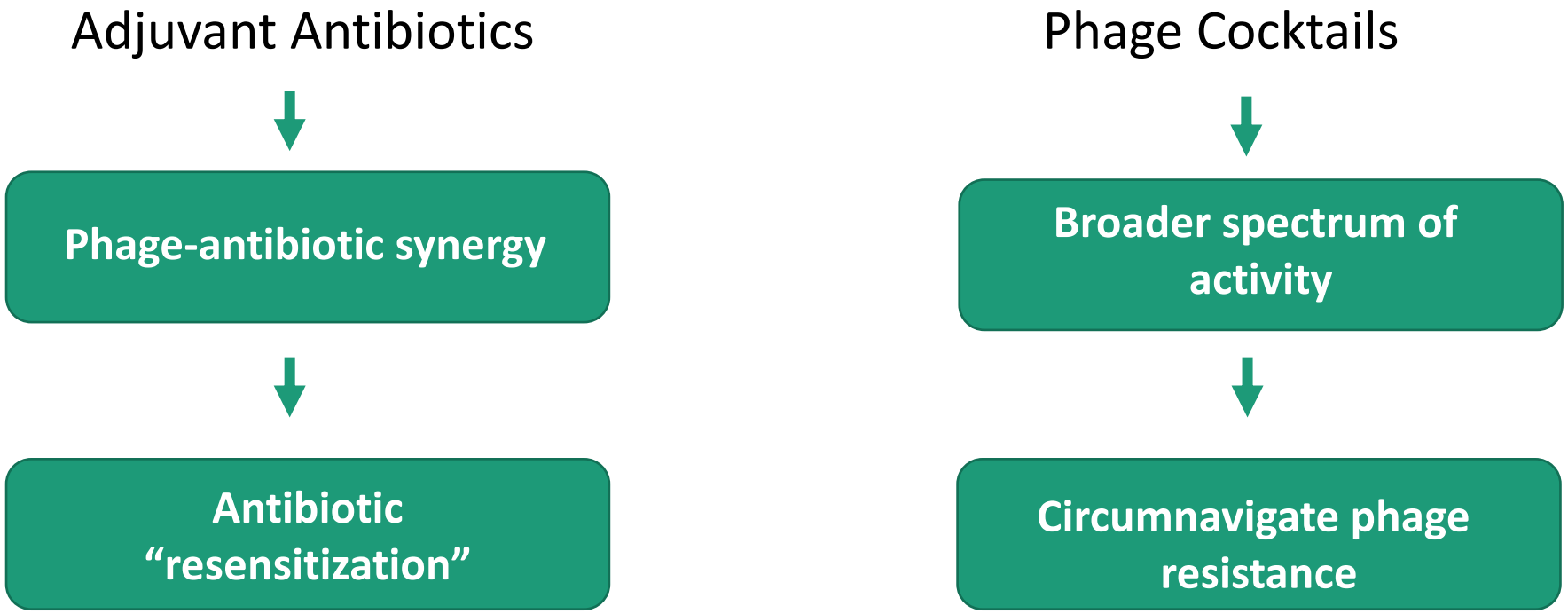
Suh et al. *Antimicrob Agents Chemother*. 2022. 66(3): e02071-21

Phage Therapy Knowledge Gaps

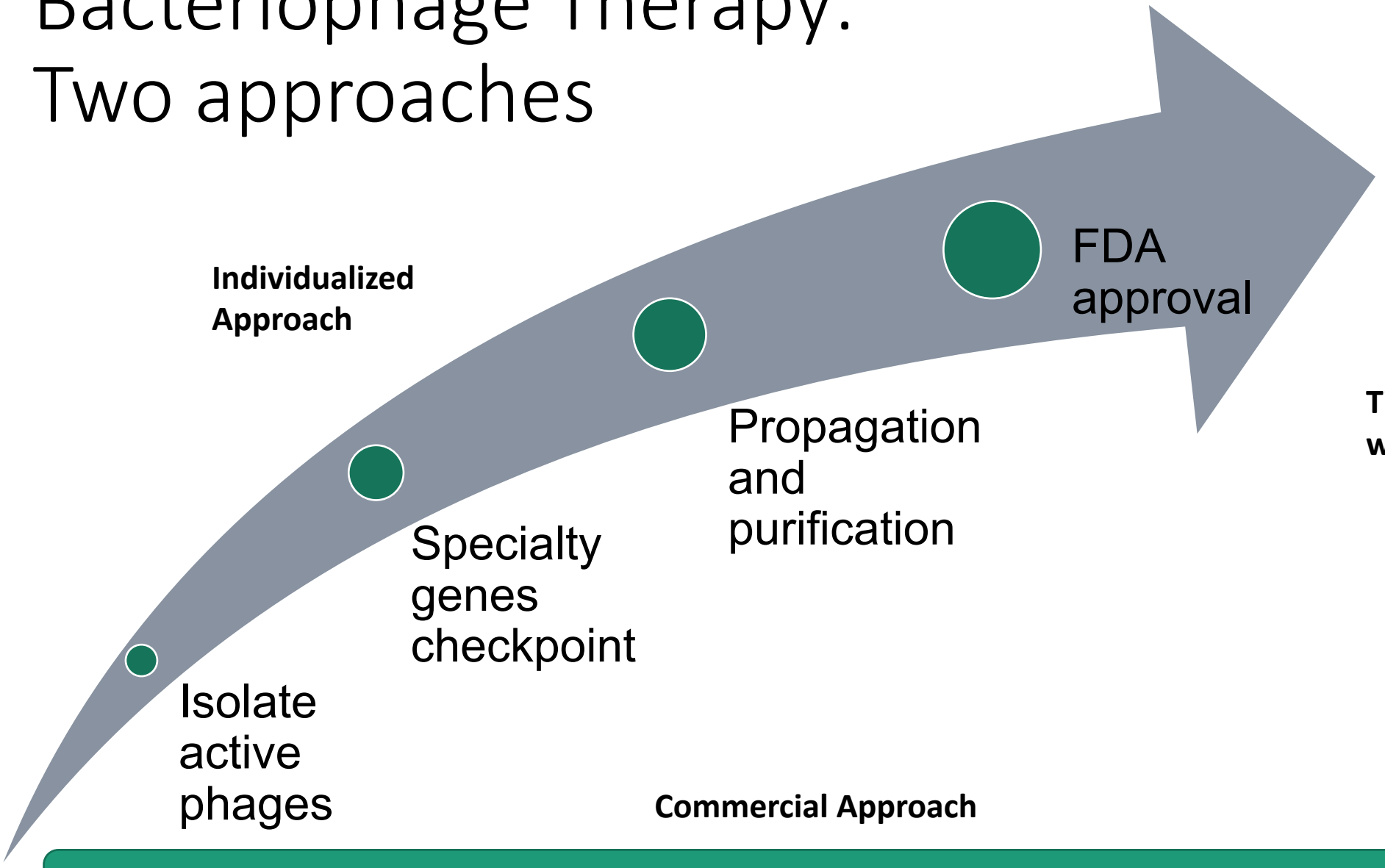
- Infection types
- Efficacy: alone, + antibiotics
- Safety
- Antibiotics combination
  - Synergy, additive, antagonism
- PK/PD optimization
- Dosing/frequency/route/duration
  - Concurrent with antibiotic/sequential?
- Immune system impact

Suh et al. *Antimicrob Agents Chemother*. 2022. 66(3): e02071-21

Phage-Antibiotic Combinations Preserving Antibiotics Through “Smart Design”

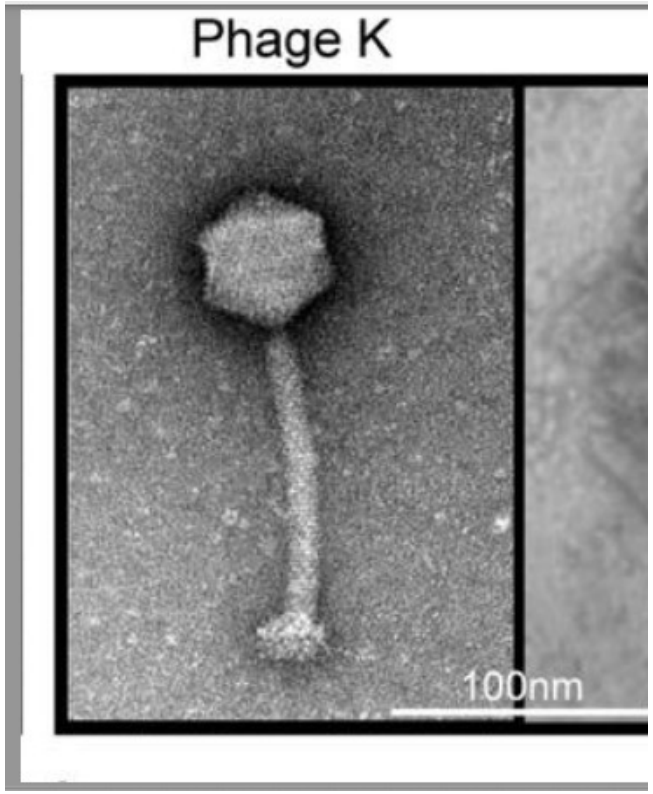


Bacteriophage Therapy: Two approaches



Bacteriophage AB-SA01 Cocktail in Combination with Antibiotics against MRSA-VISA in an Ex-vivo SEV PK/PD model

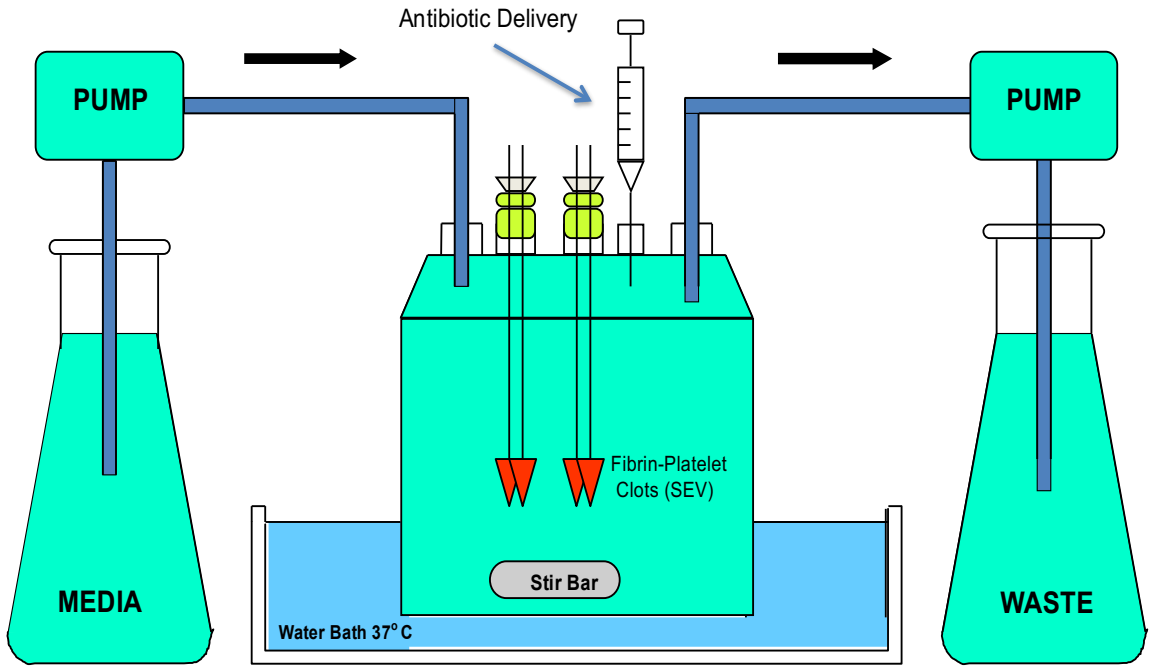
- Evaluated AB-SA-01
  - Consist of 3 myoviruses related to Staphylococcus phage K
    - Sa83, Sa87 and J-Sa36
    - 1.5 x 10^8 PFU/ml
  - MRSA
    - D712 (DNS-VISA, agr2, USA100, ST-5)
      - MICs: DAP=4, VAN=4, CFZ>64, CPT=0.5 mg/L
  - Time-kill analysis
    - ½ MIC of antibiotics or peak conc. if resistant (CFZ)
    - Phage = 7.5 x 10^6 PFU/ml
    - Bactericidal > 3 and synergy > 2 $\log_{10}$ CFU/ml reduction



Kebriaei R et al. *Antimicrob Agents Chemother*. 2021. 65 (1):e01863-20.

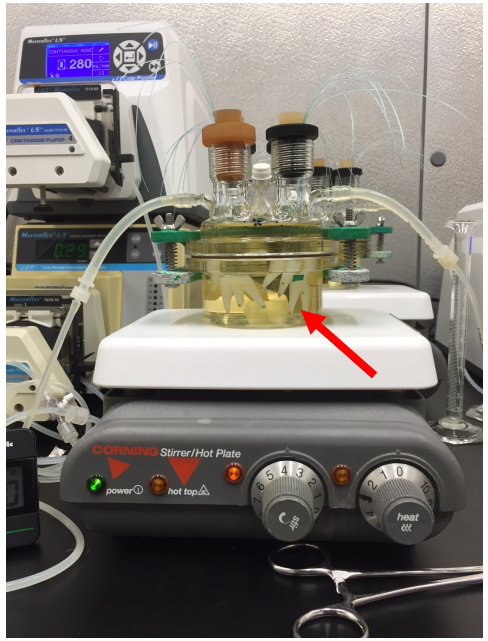
Ex Vivo Pharmacokinetic/Pharmacodynamic SEV Model

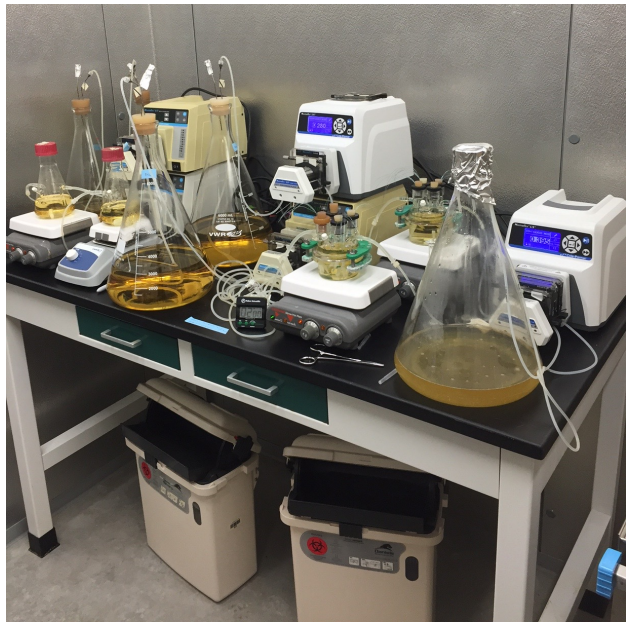
Developed an *Ex-Vivo* simulated endocardial vegetation (SEV) model	• Proctor & Gamble Animal Alternative Research Grant
SEVs	• Consists of human fibrin, platelets, high bacterial burden and thrombin
Glass Model Apparatus	• Filled with media to support bacterial growth, sample ports to retrieve SEVs over time for bacterial quantification
Computerized peristaltic pumps	• Allows for simulation of humanized antibiotic pharmacokinetics
Validated vs. 4 rabbit infective endocarditis models	• Hershberger E, Coyle, EA, Kaatz GE, Zervos MJ, Rybak, MJ. *Antimicrob Agents Chemother*. 2000. Jul;44(7):1921-4.



Ex-vivo SEV PK/PD Model

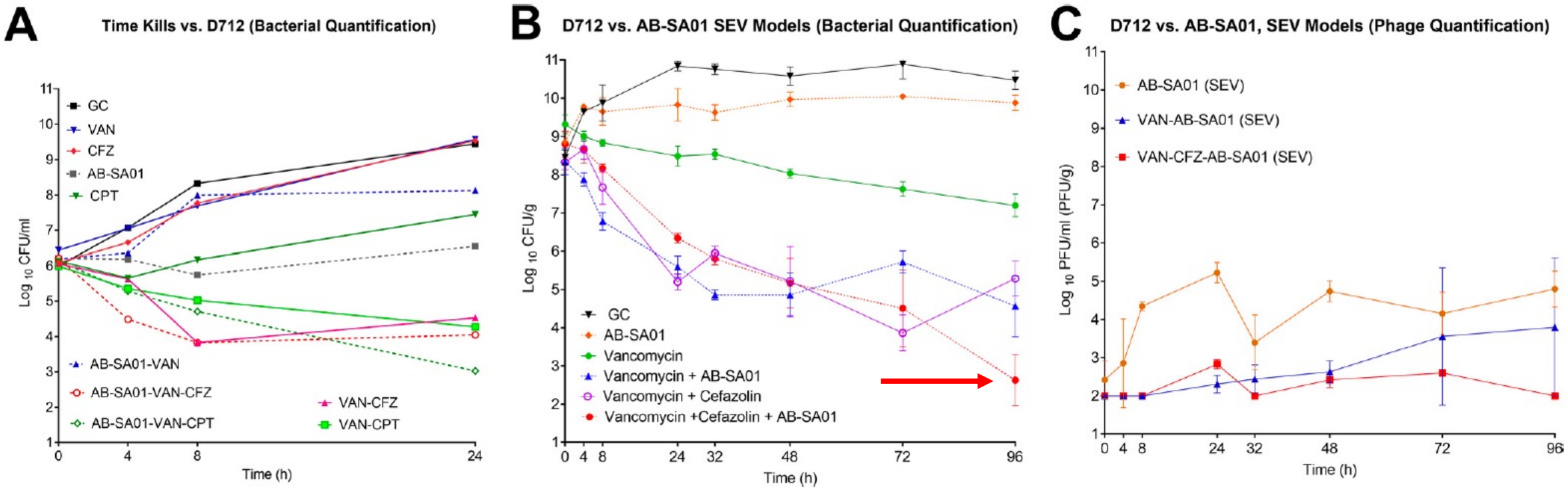
- Ex-vivo PK/PD model
  - Simulated endocardial vegetations
  - D712: 10^9 $\log_{10}$ CFU/0.5g SEV
  - Phage 1.5 x 10^8 PFU/ml q 12 h x 96 h
- Antibiotics
  - VAN 2 g q 12 h x 96h
  - CFZ 2 g q 8 h x 96h





Kebriaei R et al. *Antimicrob Agents Chemother*. 2021. 65 (1):e01863-20.

Ex-Vivo PK/PD SEV Model: Results



Kebriaei R et al. *Antimicrob Agents Chemother*. 2021. 65 (1):e01863-20.

Bacteriophages: *S. aureus, Enterococcus faecium, Pseudomonas aeruginosa*

Collaborators

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  - Chief of Bacteriophage Science Division
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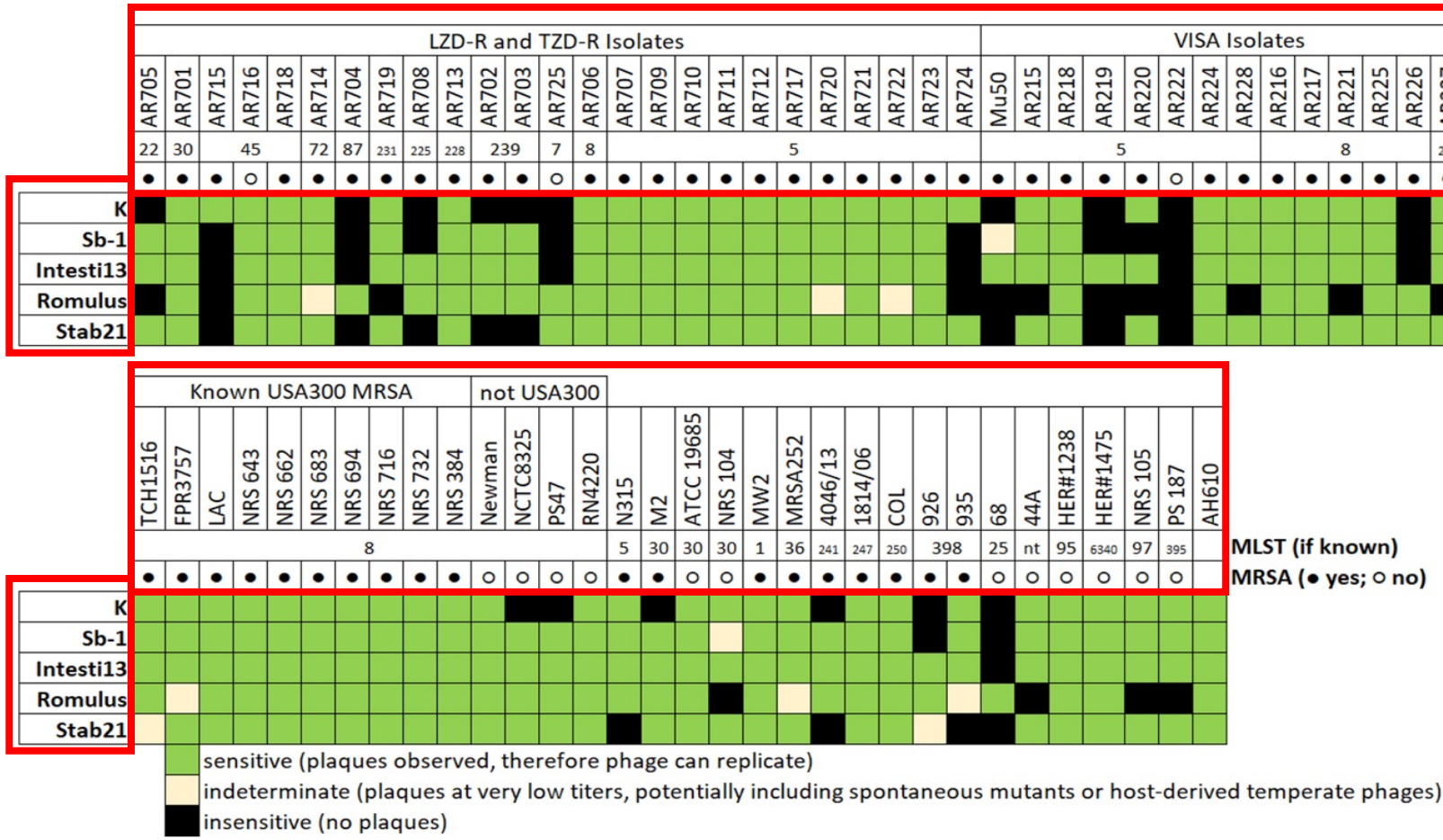
- Robert Bonomo, MD
  - Cleveland VA Medical Center, Case Western Reserve University, Cleveland , OH

Phage-antibiotic Co-therapy Composition Optimization against *S. aureus*



Phages

- *Herelleviridae* and *Twortvirinae* family
- K phage obtained from ATCC
- Sb-1 from Eliava Institute, Tbilisi, Georgia
- Stab21 isolated from Albania
- Romulus isolated in Belgium

Fig 1. Plaque-based host range for 5 short-listed phages in our collection that gave the best coverage of the screened 72 strain library. Collectively, 69/72 (96%) of strains were sensitive to at least one of Sb-1, Intesti13, or Romulus. *LZD-R=linezolid-resistant, ST=multilocus sequence type, TZD-R=tedizolid-resistant, VISA=vancomycin-intermediate *S. aureus*.

Supported by NIAID R21 AI163726
Research in Progress

Phage Screening Genome Similarity

	Romulus (NC_020877)	Stab21 (LR215719*)	Sb-1 (NC_023009)	Intesti13	K (NC_005880*)
Romulus (NC_020877)	100	42.5	44.8	43.3	43.1
Stab21 (LR215719*)		100	87.4	91.1	92.4
Sb-1 (NC_023009)			100	95.4	92.2
Intesti13				100	96.8
K (NC_005880*)					100

Percent genome similarity of five phages (constructed in VIRIDIC using single genome copies)

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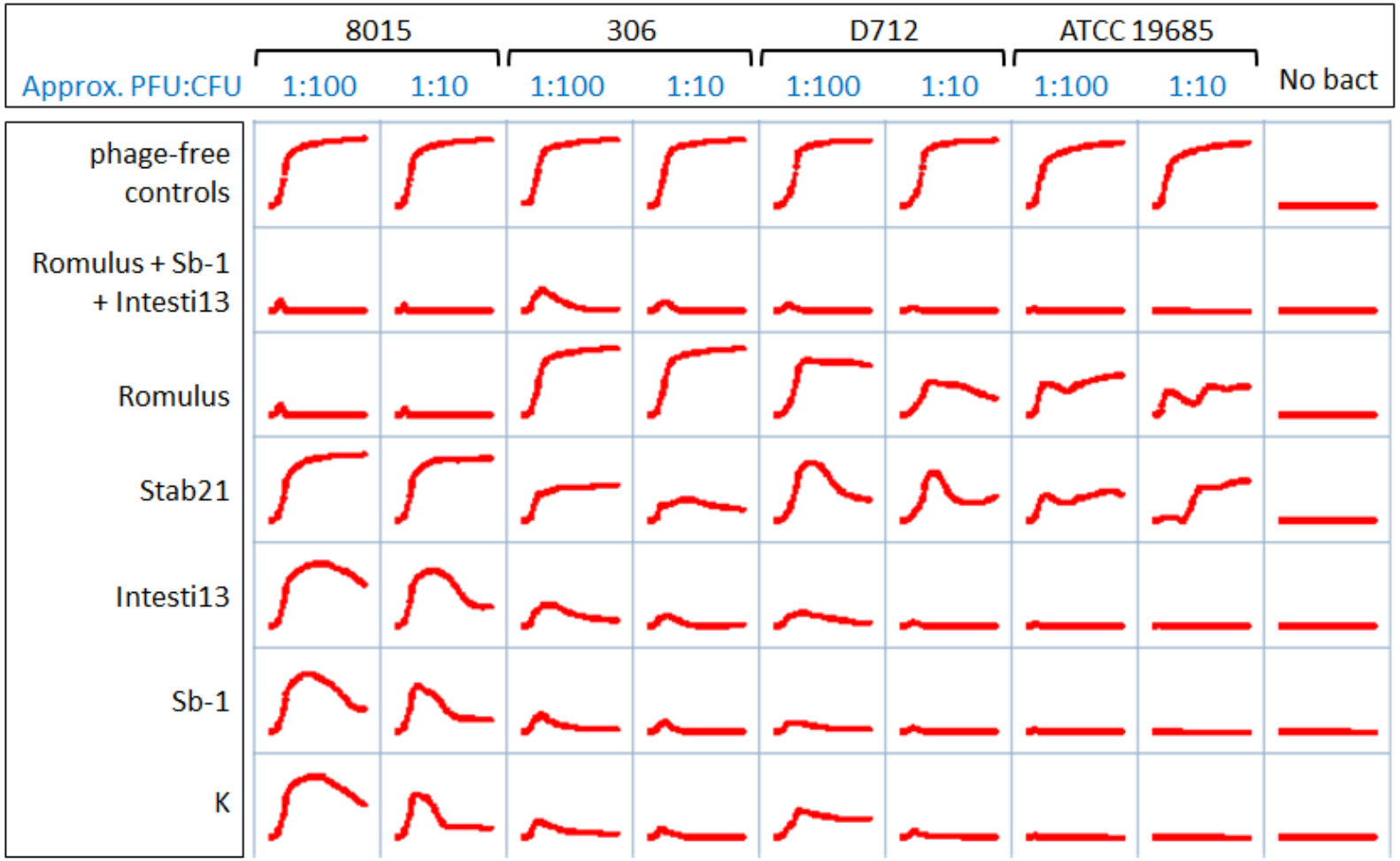
Research in Progress

Phage Growth Suppression of MRSA (DNS-VISA)



Phage activity assessed by bacterial population suppression in broth. PFU:CFU ratios are as plate inoculation

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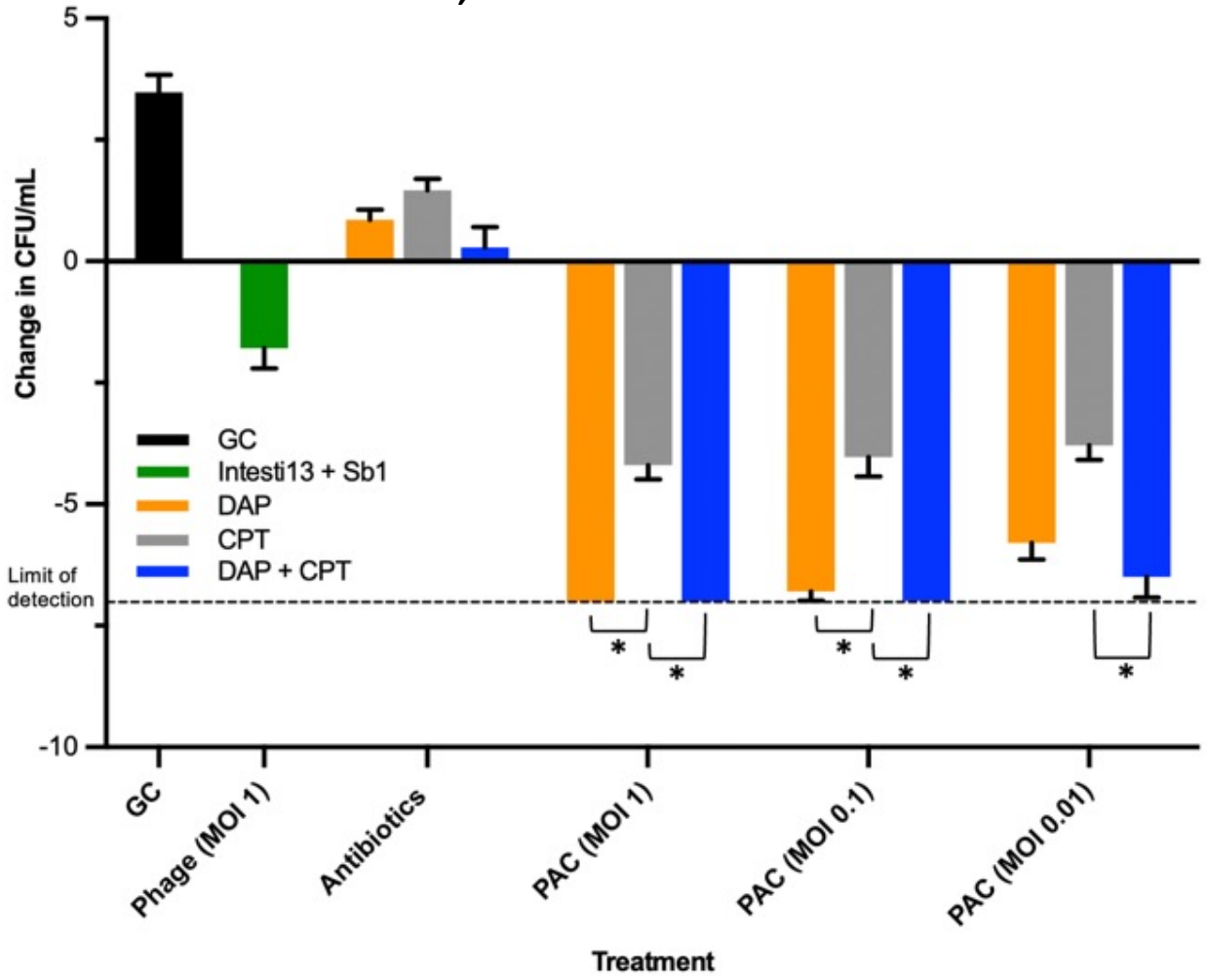
Research in Progress

Preliminary Time Kill Analysis

MRSA C4: DAP MIC=4, VAN MIC =2, CPT = 0.5 mg/L

Phage: Sb-1, Intesti13

Bacterial quantification in 24 TKA of DAP and CPT (each 0.5 x MIC) combined with phages Intesti13 And Sb-1 at varying MOI against DNS MRSA strain C4
***P* values determined with one-way ANOVA and Tukey's Post hoc test. *, *P*<0.05**



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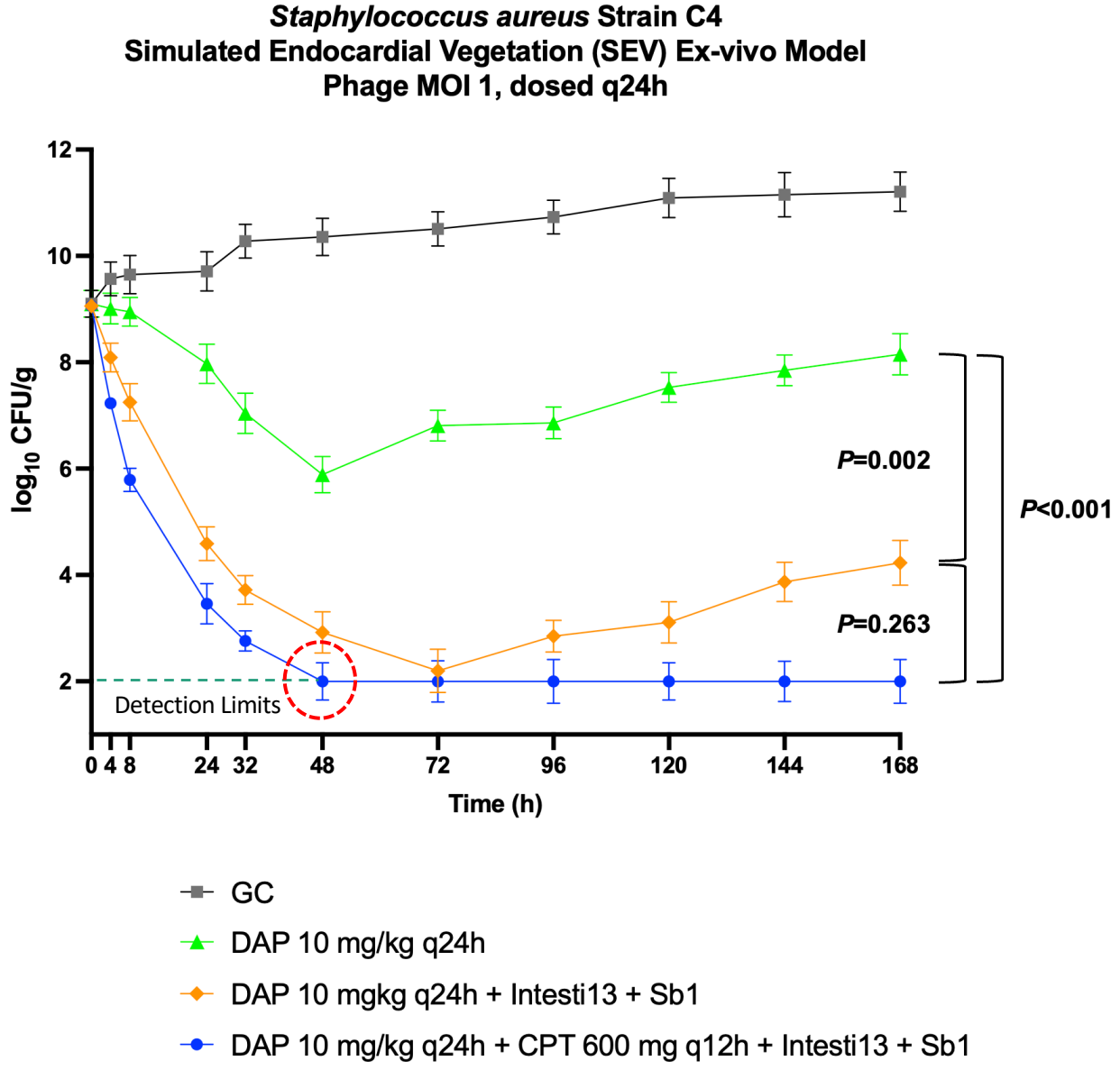
Phage Cocktail Evaluation: SEV PK/PD Model



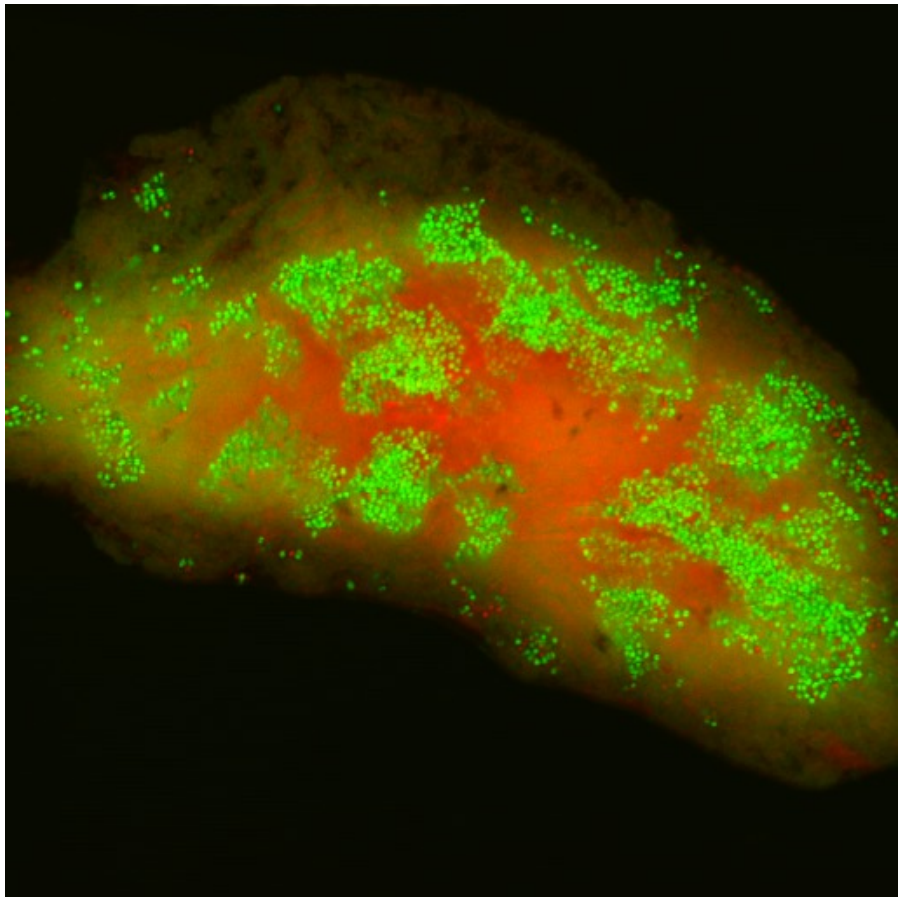
MRSA C4: DAP MIC=4, VAN MIC =2, CPT =0.5 mg/L

Phage: Sb-1, Intesti13

Research in Progress 2023

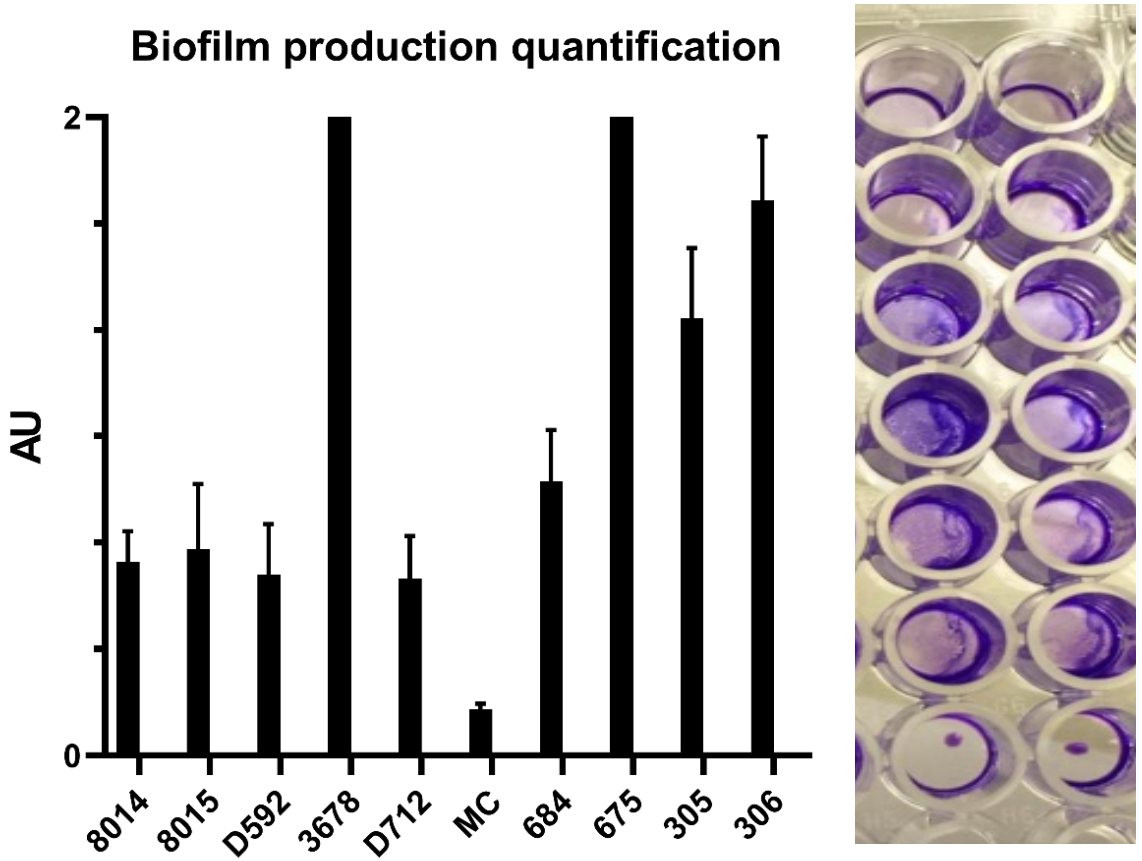
Medical Device Infections (MDI) and Impact of Bacterial Embedded Biofilm

- MDIs associated with substantial morbidity and significant healthcare expenditures
- *S. aureus* and coagulase-negative staphylococci are most common pathogens
- Bacterial embedded biofilms significantly reduce antibiotic activity



Live-dead staining of *S. aureus* embedded biofilm

Phage Activity Against *S. aureus* Biofilm



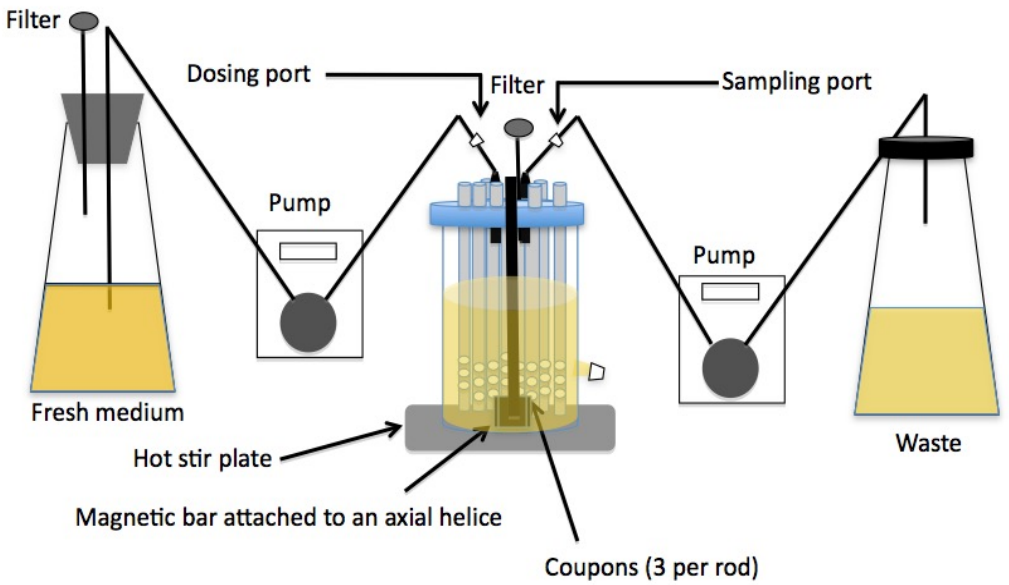
MRSA strains with varying DAP, VAN and CPT Susceptibility

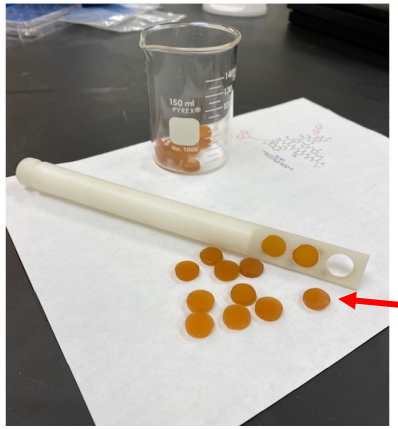
Strain	**D712**		**8014**	
Antibiotic	MIC (mg/L)	MBMIC (mg/L)	MIC (mg/L)	MBIC (mg/L)
DAP	4	8	0.5	8
VAN	4	8	2	8
CPT	0.5	4	1	1

Biofilm formation by three strain pairs, relative to S. aureus 3678 (reference biofilm strain ATCC35556) positive control and media only (MC) negative control

Supported by NIAID R21 AI163726
Research in Progress

CDC Biofilm Reactor Model

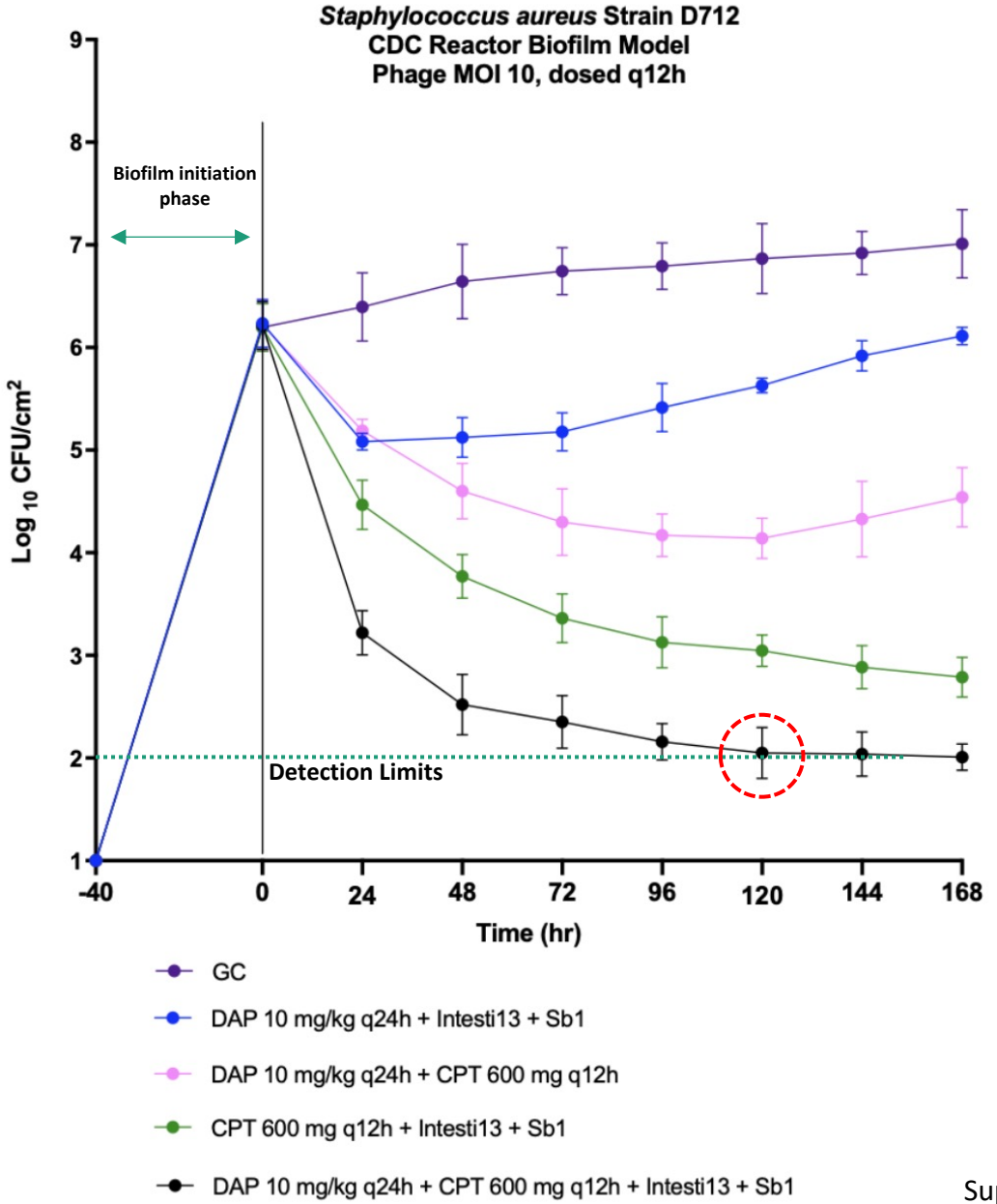




Jahanbakhsh S. et al. *Antimicrob Agents Chemother*. 2018. 62(8); e000567-18

Phage Cocktail Activity Against D712 Biofilm

VAN BMIC = 8, DAP BMIC = 8, CPT BMIC = 4 mg/L



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Research in Progress

Cationic antimicrobial host defense peptides

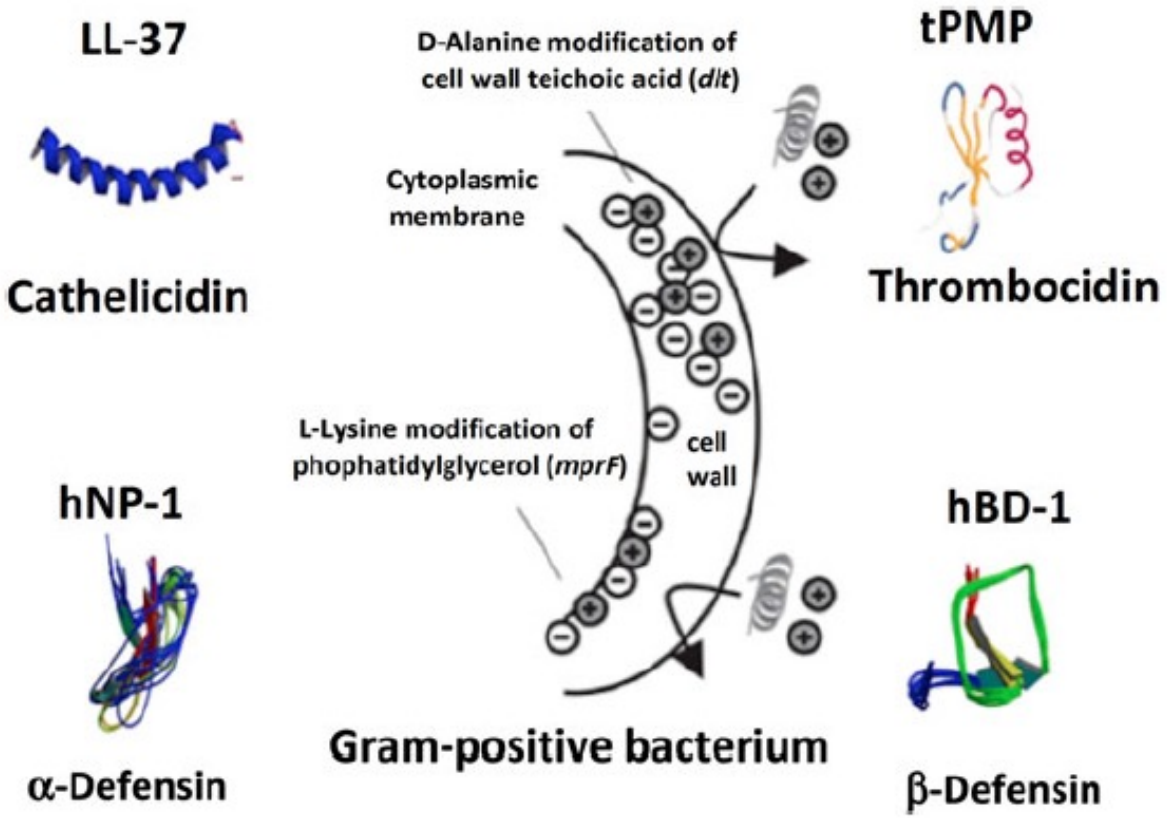

Figure 1. Examples of cationic antimicrobial host defense peptides. Abbreviations: hBD-1, human beta-defensin-1; hNP-1, human neutrophil peptide-1; mprF, multiple peptide resistance factor; tPMP, thrombin-induced platelet microbicidal protein.

Clin Infect Dis. 2014:59 (15): 1455-61

JCM
Journals.ASM.org

Human Cathelicidin LL-37 Resistance and Increased Daptomycin MIC in Methicillin-Resistant *Staphylococcus aureus* Strain USA600 (ST45) Are Associated with Increased Mortality in a Hospital Setting

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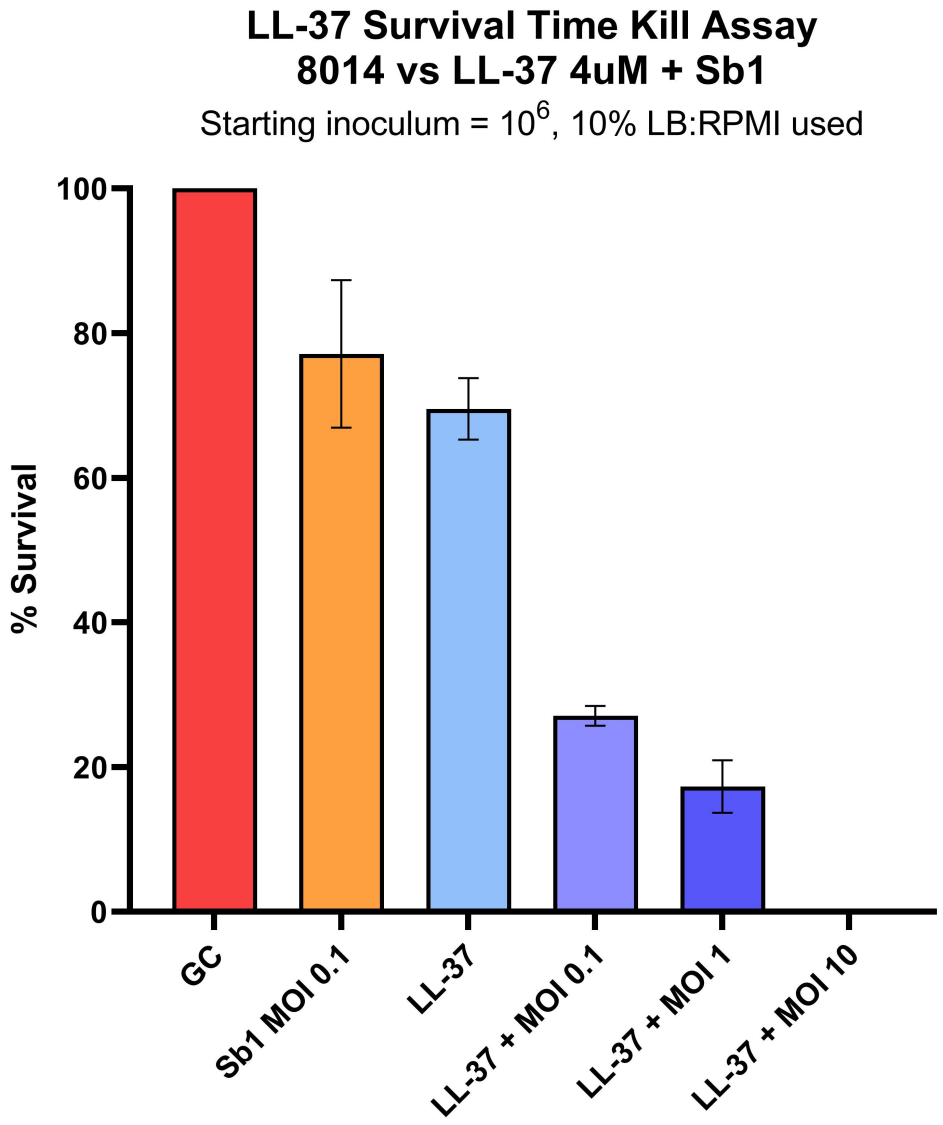
University of California San Diego School of Medicine, La Jolla, California, USA[a]; Henry Ford Hospital, Wayne State University School of Medicine, Detroit, Michigan, USA[b]

Bacteremia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) USA600 has been associated with increased patient mortality. We found that USA600 MRSA exhibited significantly increased resistance to human cathelicidin LL-37 killing and daptomycin MIC creep compared to non-USA600 MRSA. Virulent health care-associated MRSA strains may coevolve innate host defense peptide and antibiotic resistances.

J Clin Microbiol. 2014;52 (6): 2172-74.

Impact of of Phage on Innate Immune Factors



VAN MIC = 1, DAP = 2 mg/L, OX MIC = > 64 mg/L

Research in Progress 2023

In Summary

- Phage therapy continues to evolve
- Many therapeutic questions remain
- Majority of experience is compassionate use
- Empiric versus individualized therapy
- Role of phage-antibiotic combinations
- Standardization is needed for clinical trials

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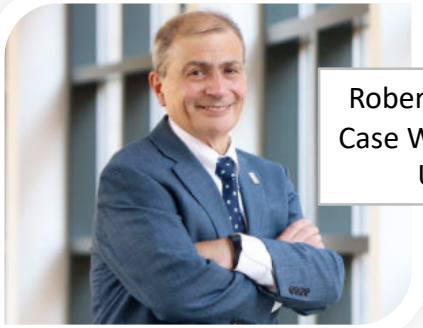

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