REVIVE by GARDP

Post-licensing clinical trials for advancing the use of antimicrobials

Guest speakers: Steven Tong & Patrick Harris

Moderator: Holly Jackson

Host: Shirine Derakhshani

22 May 2025

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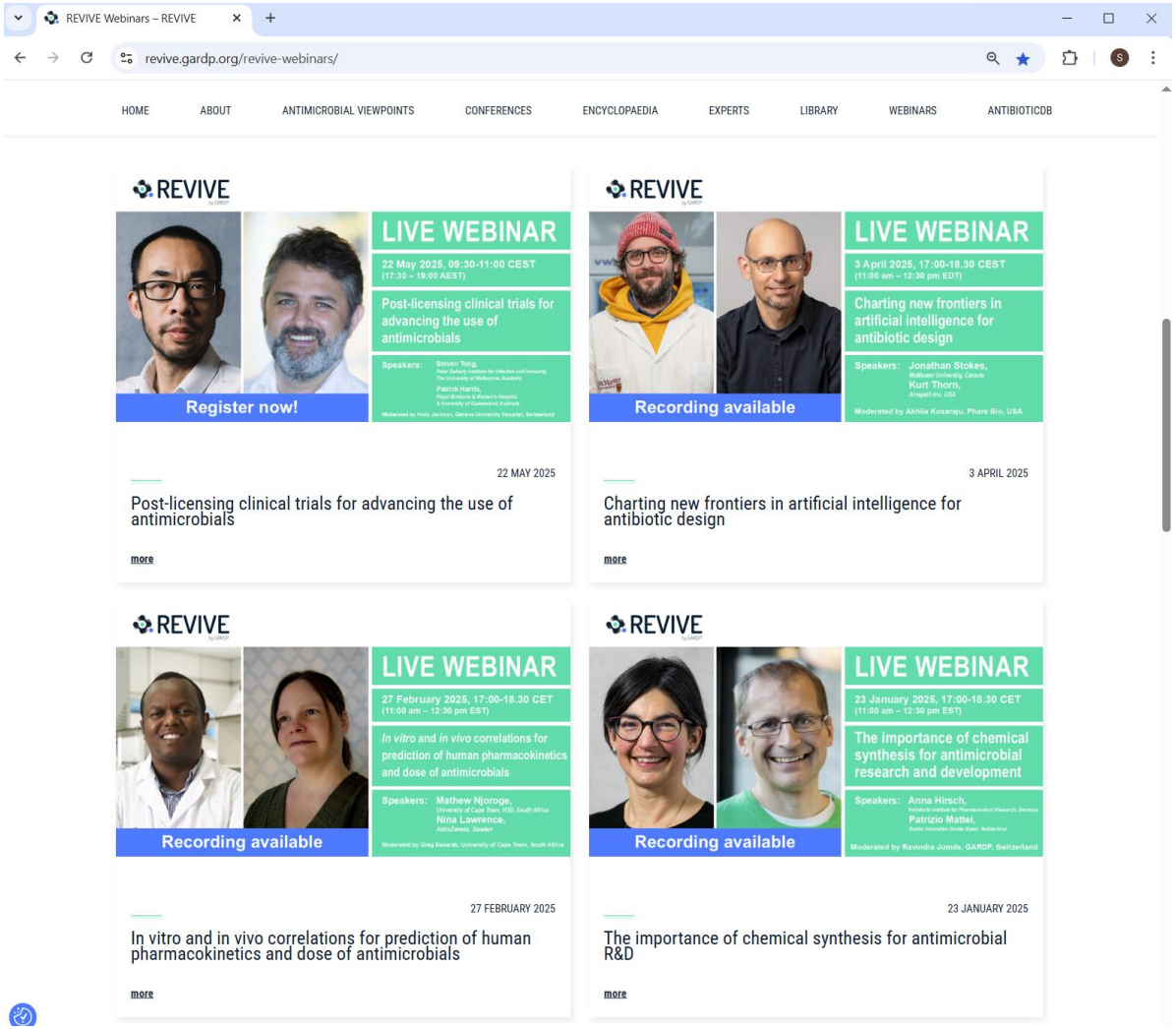

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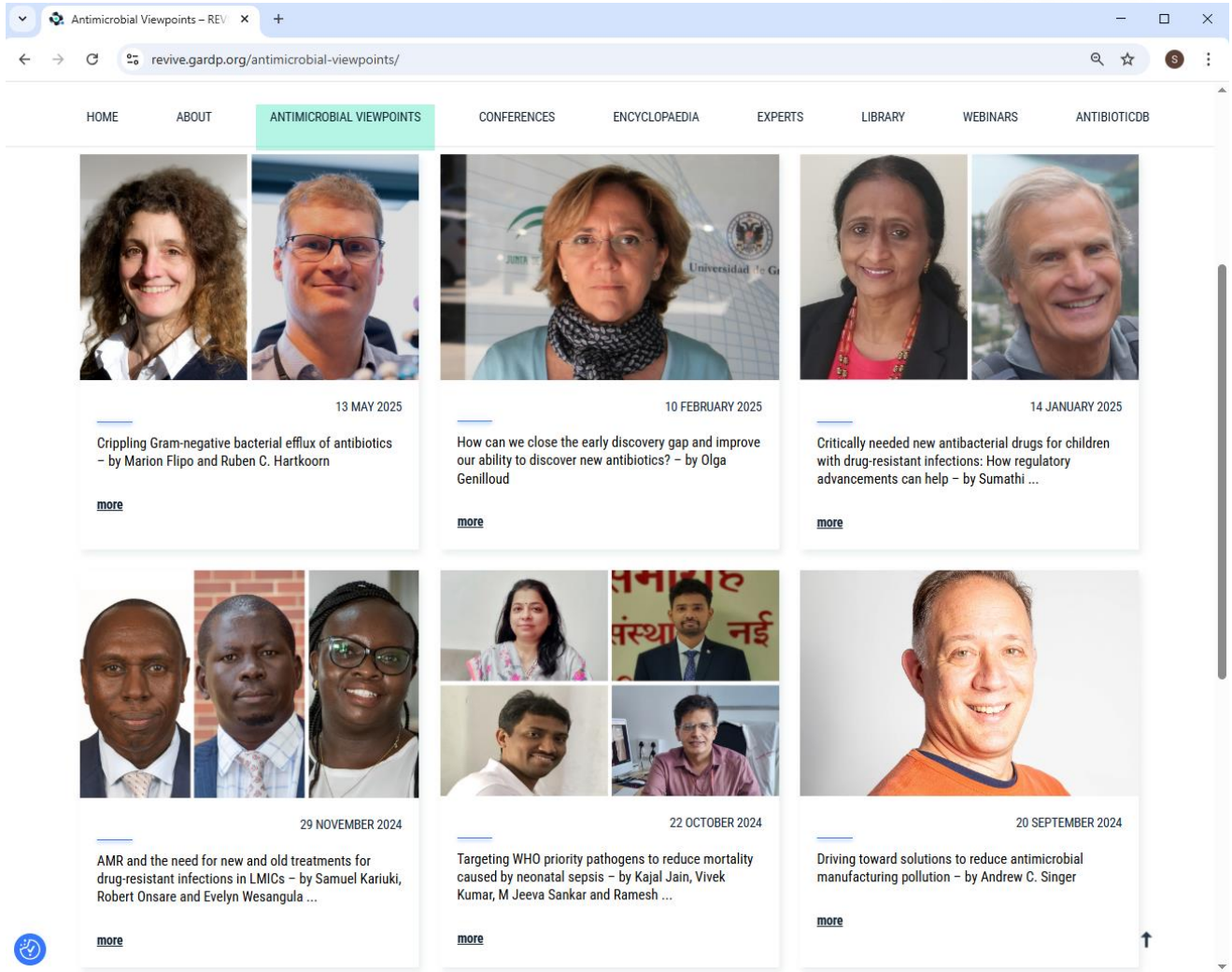

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Antimicrobial Encyclopaedia

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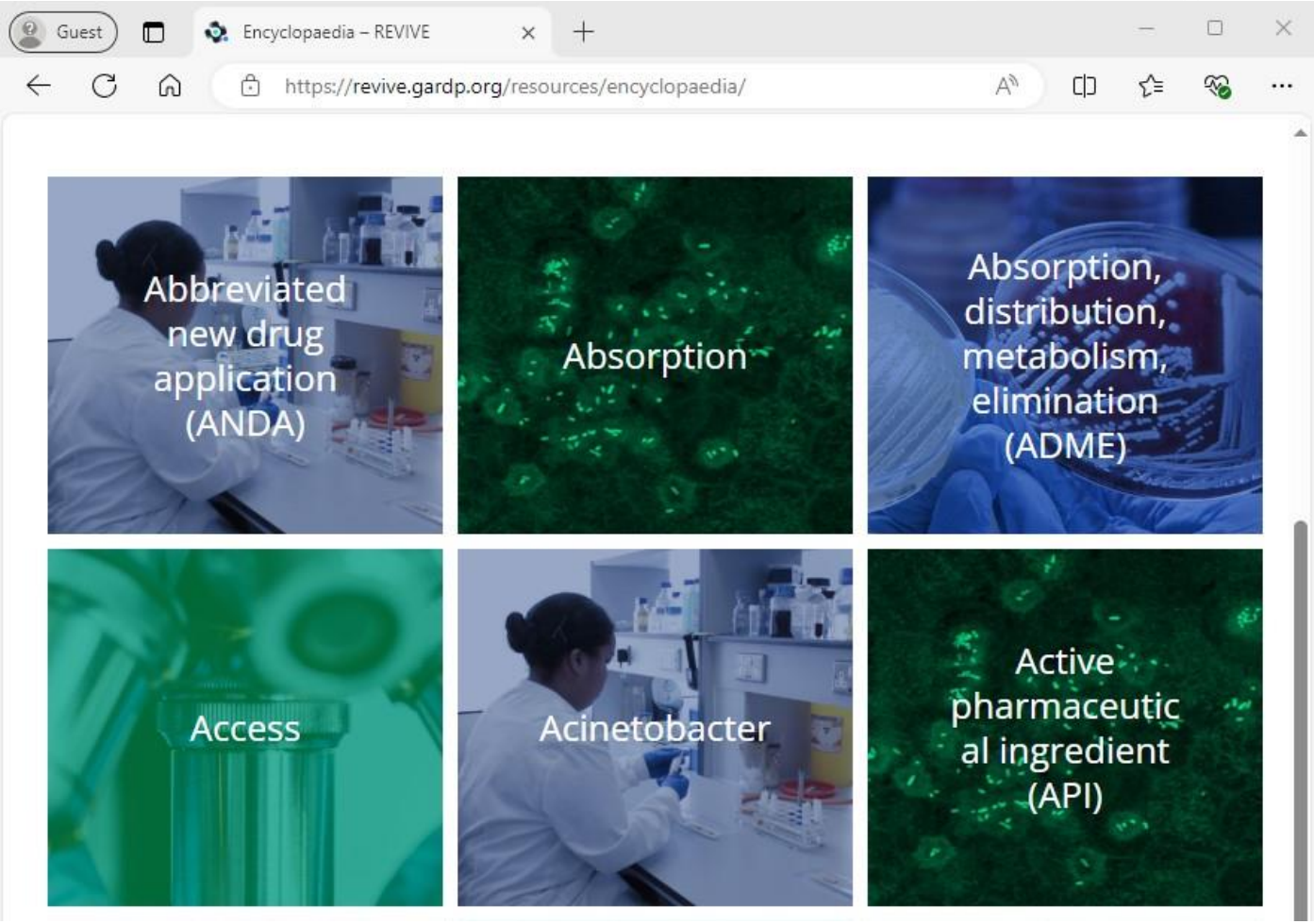

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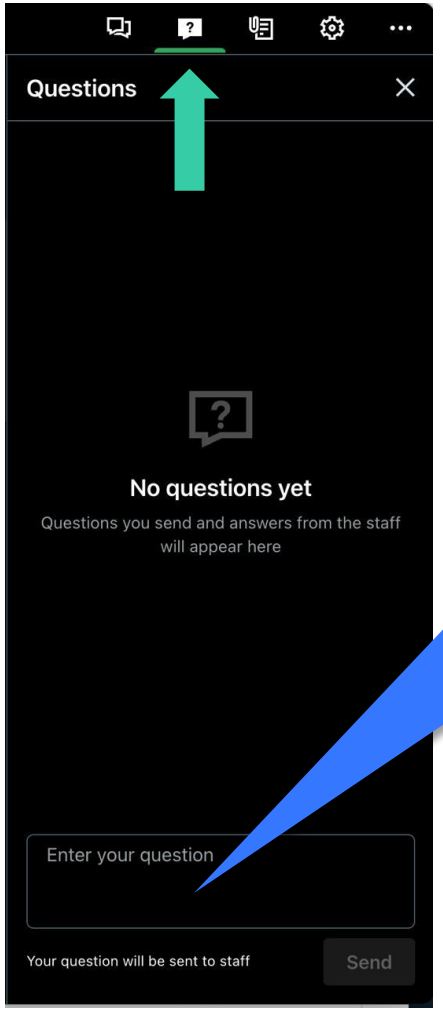
How to submit your questions

REVIVE by GARDP

If your question is addressed to a specific speaker, please include their name when submitting the question.



Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

Today’s speakers

REVIVE by GARDP

Post-licensing clinical trials for advancing the use of antimicrobials

Moderator:
Holly Jackson
Infection Control Program, Geneva University Hospitals & Faculty of Medicine, Switzerland

Steven Tong
Peter Doherty Institute for Infection and Immunity, The University of Melbourne, Australia

Patrick Harris
Royal Brisbane & Women's Hospital & University of Queensland, Australia

Steven Tong

Steven Tong is an actively practising infectious diseases physician at the Royal Melbourne Hospital. He is a Professor of Infectious Diseases at the Department of Infectious Diseases, Melbourne Medical School, University of Melbourne. His research includes leading large adaptive platform trials for infections due to Staphylococcus aureus and acute respiratory tract infection.

Post-licensing clinical trials for advancing the use of antimicrobials: Trials for gram-positive bacteria

Professor Steven Tong
Doherty Institute
Royal Melbourne Hospital
University of Melbourne

@steventong.bsky.social @syctong @snap_trial

REVIVE GRADP webinar

May 22 2025

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Conflicts of interest

AstraZeneca advisory board for clinical trial of prevention of *S. aureus* bloodstream infection

Royalties from UpToDate

Outline

Epidemiology and burden of disease – *Staphylococcus aureus* and *Enterococcus* bloodstream infections

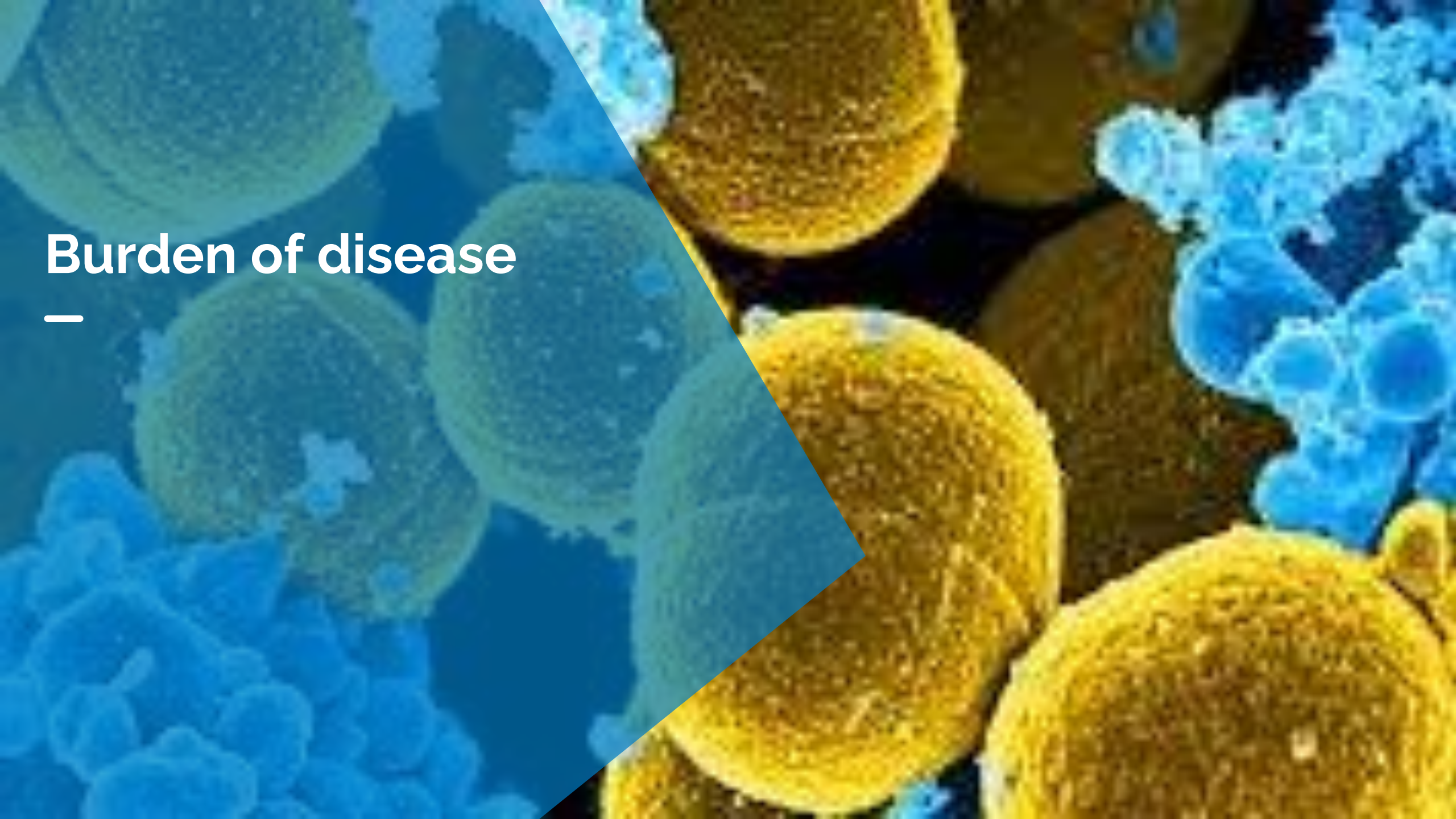
Licensed antibiotics for *S. aureus* and *Enterococcus*

Guidelines for *S. aureus* and *Enterococcus*

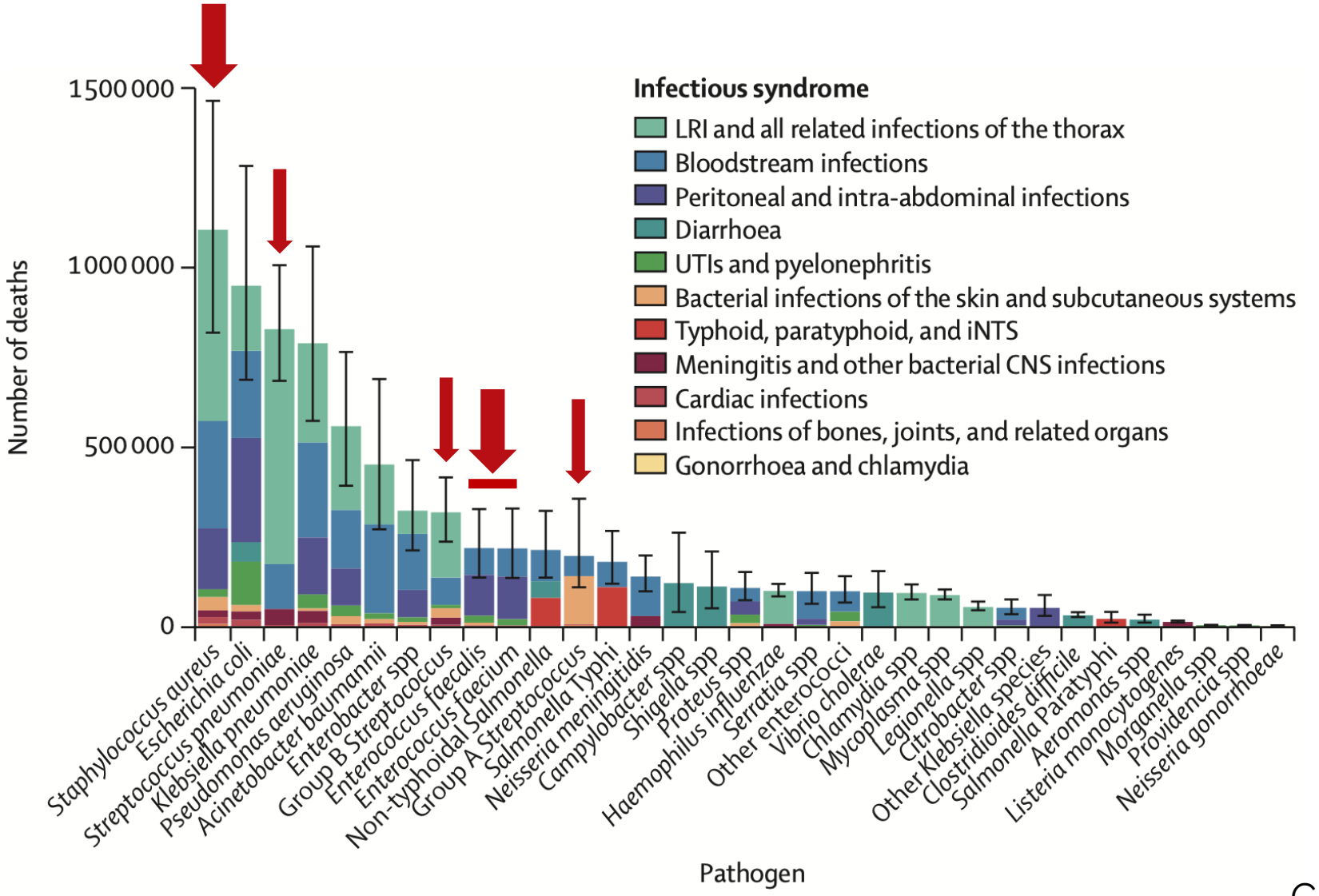
Obvious gaps in knowledge

A way forward – investigator initiated clinical trials

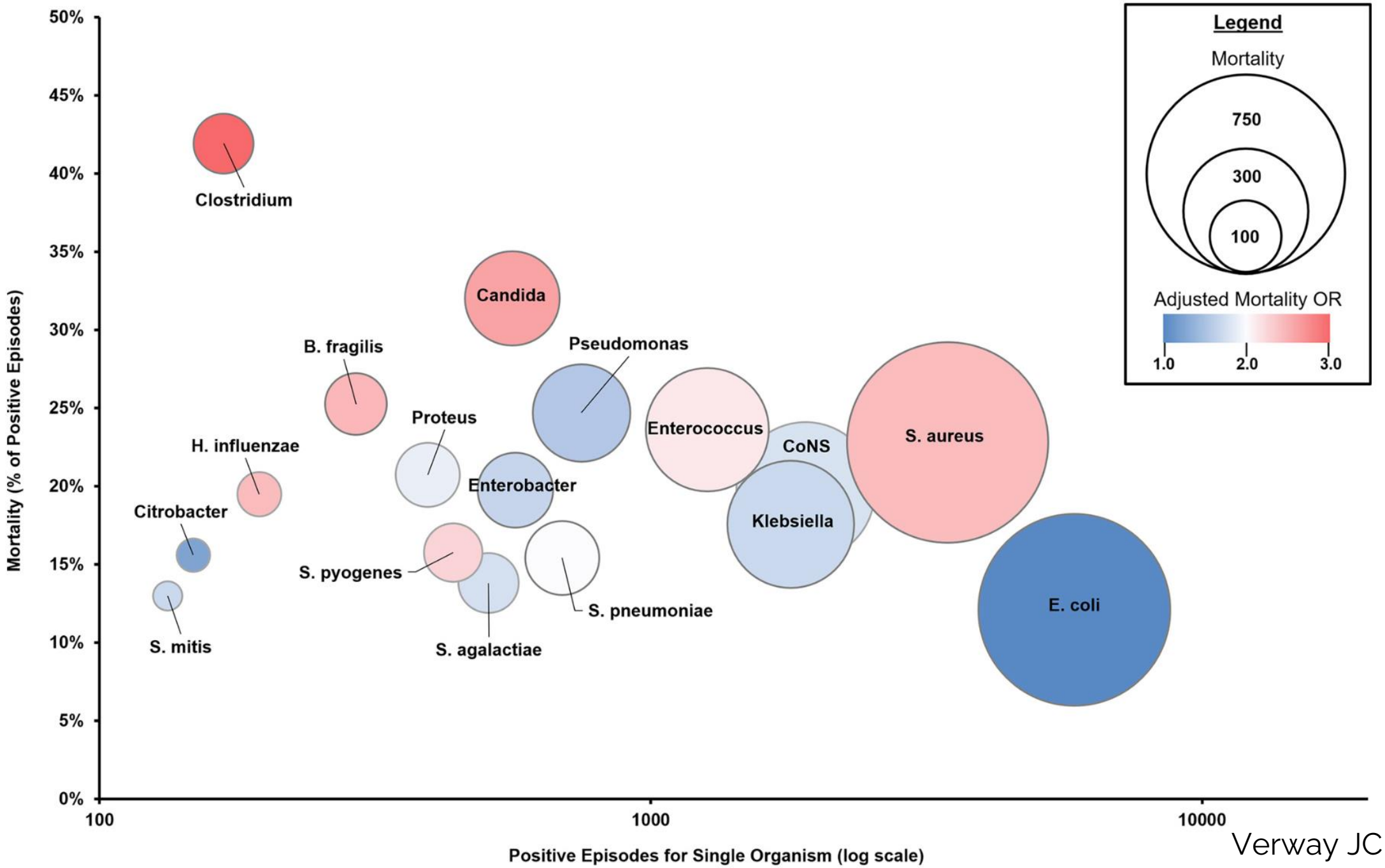
Burden of disease



S. aureus causes >1M deaths / year

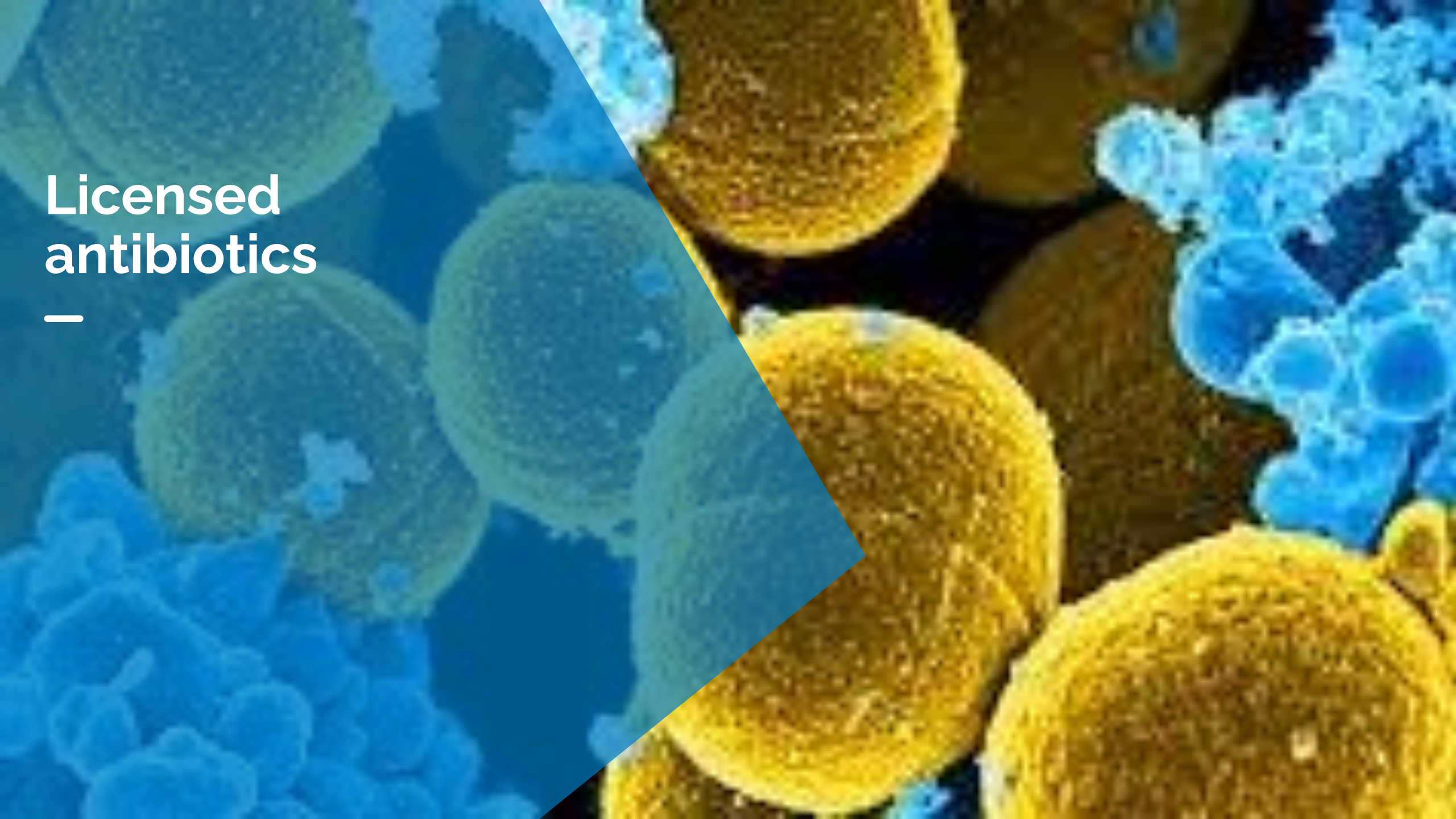


GBD AMR collaborators Lancet 2022



Verway JCM 2022

Licensed antibiotics



FDA licensed antibiotics for *S. aureus* and *Enterococcus*

S. aureus bacteremia		
Daptomycin	Bacteremia and R sided IE	2006
Ceftobiprole	Bacteremia and R sided IE	2024

VRE		
Linezolid	Bacteremia	2000
Quinupristin-dalfopristin	VRE faecium infections	1999

Registrational trials – daptomycin

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

Authors: Vance G. Fowler, Jr., M.D., M.H.S., Helen W. Boucher, M.D., G. Ralph Corey, M.D., Elias Abrutyn, M.D., Adolf W. Karchmer, M.D., Mark E. Rupp, M.D., Donald P. Levine, M.D., +19 , for the S. aureus Endocarditis and Bacteremia Study Group Author Info & Affiliations

Published August 17, 2006 | N Engl J Med 2006;355:653-665 | DOI: 10.1056/NEJMoa053783 | VOL. 355 NO. 7

Copyright © 2006

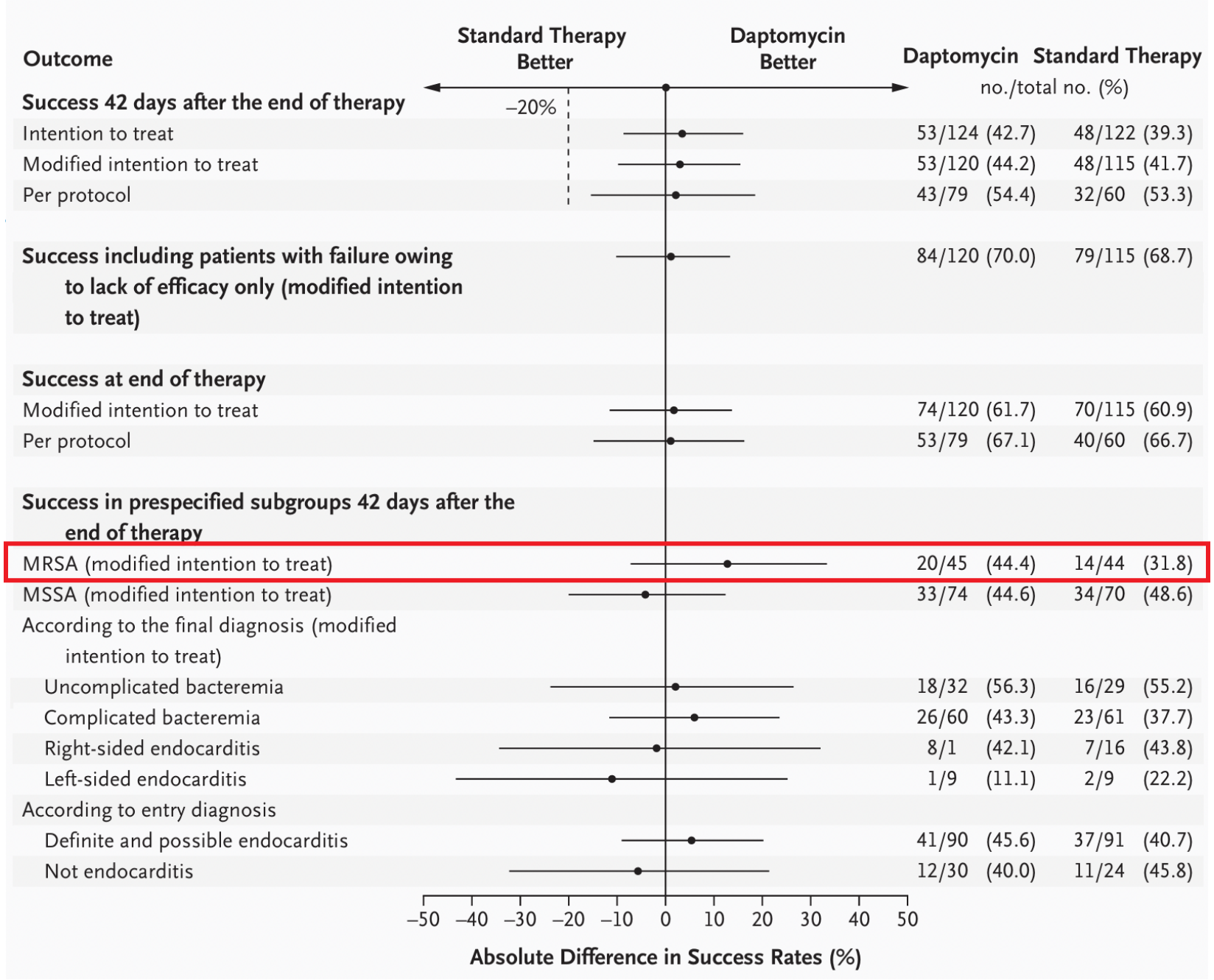
246 participants

Daptomycin vs standard therapy

Primary outcome: treatment success at 42 days after end of therapy

Non-inferiority with absolute margin of 20% (assuming 65% treatment success)

Fowler NEJM 2006



Non-inferiority met

No difference in mortality (10.8% daptomycin, 11.3% SOC)

Only 89 patients with MRSA

Mortality rate:

Daptomycin: 12/45 (27%)

Vanc/gent: 8/43 (19%)

Fowler NEJM 2006
Reym JAC 2008

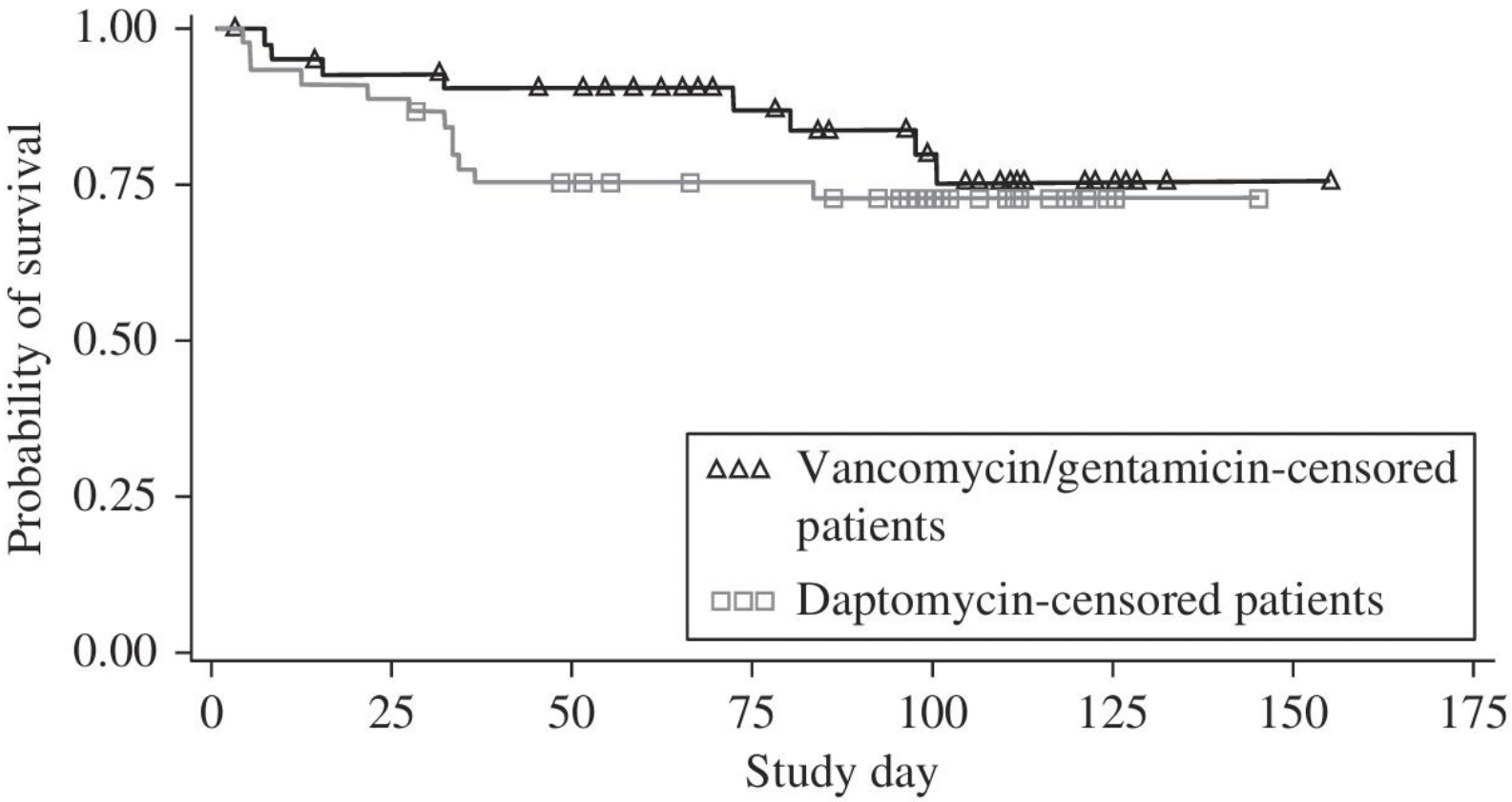


Figure 1. The Kaplan–Meier plot of overall survival. Wilcoxon $P = 0.25$, log-rank $P = 0.42$.

Reym JAC 2008

My point!

Where we most want to use daptomycin (MRSA)

- Only 89 patients
- Wide confidence intervals for treatment success difference
- Mortality no different (potentially worse)

No clinical trials to address this question since

Registrational trials – ceftobiprole

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner, H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski, M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr, M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert, and V.G. Fowler, Jr., for the ERADICATE Study Group*

390 participants

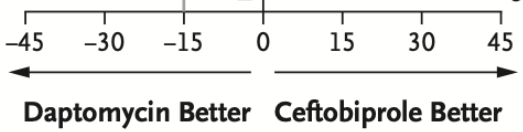
Ceftobiprole vs daptomycin

Primary outcome: Overall treatment success 70 days after randomization

Non-inferiority with absolute margin of 15% (assuming 40% treatment success)

Holland NEJM 2024

Subgroup	Ceftobiprole	Daptomycin	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
All patients	132/189 (69.8)	136/198 (68.7)	2.0 (–7.1 to 11.1)
Age at written informed consent			
18 to <65 yr	98/131 (74.8)	101/135 (74.8)	0.6 (–9.8 to 10.9)
≥65 yr	34/58 (59)	35/63 (56)	6.9 (–10.5 to 24.3)
Sex			
Male	93/128 (72.7)	92/140 (65.7)	8.0 (–2.8 to 18.8)
Female	39/61 (64)	44/58 (76)	–11.3 (–27.7 to 5.1)
Baseline category of complicated *S. aureus* bacteremia			
Soft-tissue infection	81/116 (69.8)	80/121 (66.1)	4.5 (–7.3 to 16.3)
S. aureus bacteremia excluding soft-tissue infection	51/73 (70)	56/77 (73)	–1.7 (–15.9 to 12.6)
Osteoarticular infection	23/32 (72)	24/35 (69)	2.9 (–19.7 to 25.6)
Abdominal abscess	18/26 (69)	22/29 (76)	–9.7 (–33.3 to 13.9)
Hemodialysis	13/24 (54)	15/25 (60)	–4.6 (–32.5 to 23.3)
Persistent *S. aureus* bacteremia	8/16 (50)	8/16 (50)	–0.0 (–35.9 to 35.9)
Infective endocarditis on right side of heart	10/15 (67)	7/10 (70)	–6.6 (–40.1 to 27.0)
Baseline *S. aureus* infection			
Methicillin-susceptible	100/141 (70.9)	97/146 (66.4)	4.8 (–5.9 to 15.5)
Methicillin-resistant	31/45 (69)	38/49 (78)	–8.3 (–25.3 to 8.6)
Previous antibiotic use			
Yes	92/139 (66.2)	85/134 (63.4)	2.9 (–8.4 to 14.2)
No	40/50 (80)	51/64 (80)	–0.2 (–15.0 to 14.6)
Trial cohort			
Cohort 1	68/97 (70)	62/96 (65)	7.6 (–5.6 to 20.8)
Cohort 2	64/92 (70)	74/102 (72.5)	–3.4 (–16.1 to 9.3)



Non-inferiority met

Only 13 deaths in total

Only 94 patients with MRSA

Wide CI with primary outcome

Holland NEJM 2024

My point!

—

Where we most want to use ceftobiprole (MRSA)

- Only 94 patients
- Wide confidence intervals for treatment success difference

No clinical trials to address this question since

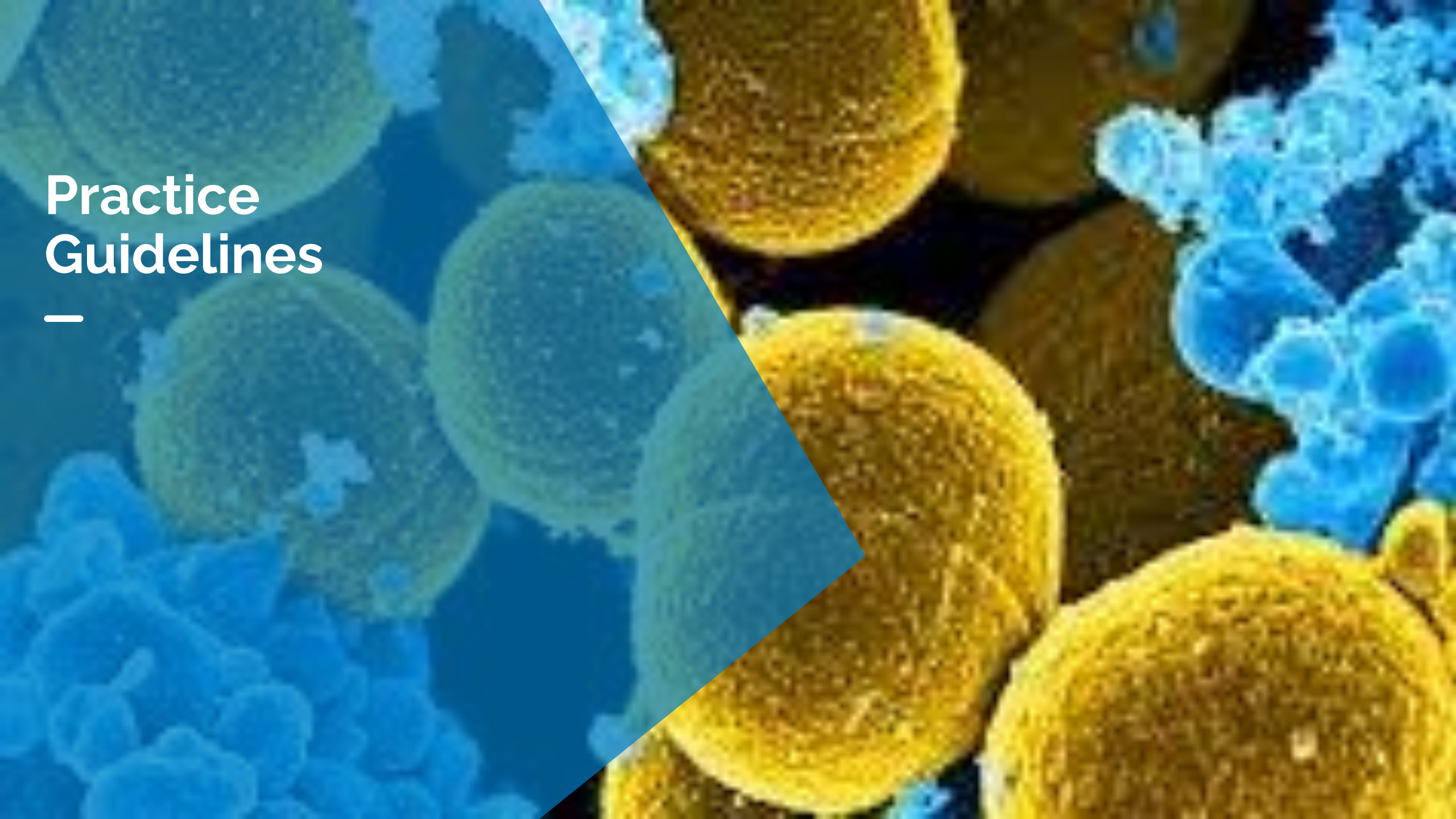
Registrational trials – linezolid for VRE

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Adults ± Children		
Antony SJ et al	Clinical experience with linezolid in the treatment of resistant Gram-positive infections	*Journal of the National Medical Association* (2001); 93:386-91.
Birmingham MC et al	Linezolid for the treatment of multi-drug resistant, Gram-positive infections: experience from a compassionate-use study	*Clinical Infectious Diseases* (2003); 36:15-68.
Chien JW et al	Use of linezolid, an oxazolidinone, in the treatment of multidrug-resistant Gram-positive bacterial infections	*Clinical Infectious Diseases* (2000); 30:146-51.
Moise PA et al	The efficacy and safety of linezolid as treatment for *Staphylococcus aureus* infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin	*Journal of Antimicrobial Chemotherapy* (2002); 50:1017-26.
Rayner CR et al	Linezolid in the treatment of osteomyelitis: results of compassionate use experience	*Infection* (2004); 32:8-14.
Study 025	Linezolid (PNU-100766) given intravenously or orally for compassionate use in patients with significant, resistant bacterial infections	Interim report of the trial M/1260/0025, September 1999.
Study 054A	Linezolid for the treatment of vancomycin-resistant enterococcal infections: a double-blind trial comparing 600mg	Final report of the trial M/1260/0054A, September 1999.

Two trials
Tigecycline vs linezolid:
15 patients
Daptomycin vs linezolid:
50 patients

Australian Pharmaceuticals Benefits Advisory Committee; meeting July 2013
Florescu JAC 2008
Carpenter CID 2004
McKinnel CID 2015

Practice Guidelines



Guidelines: *S. aureus* bacteremia and infective endocarditis

	AHA[1]	ESC[2]	WikiGuidelines[3]
MSSA	1. Nafcillin or oxacillin 2. Cefazolin (if allergy)	1. (Flu)cloxacillin 2. Cefazolin (if allergy)	1. Cefazolin 2. Flucloxacillin, nafcillin, oxacillin
MRSA	1. Vancomycin 2. Daptomycin	1. Vancomycin 2. Daptomycin combined with cloxacillin, ceftaroline, or fosfomycin	1. Vancomycin 2. Daptomycin
Prosthetic valve	Add rifampin and gentamicin	Add rifampin and gentamicin	Add rifampin

1. Baddour Circulation 2015
2. Delgado EHJ 2023
3. McDonald JAMA NO 2023

Guidelines: *Enterococcus* bacteremia and infective endocarditis

	AHA[1]	ESC[2]	WikiGuidelines[3]
Enterococcus faecalis	Ampicillin / penicillin plus 1. Gentamicin 1. Ceftriaxone	Ampicillin plus 1. Ceftriaxone 2. Gentamicin	Ampicillin plus 1. Ceftriaxone
VRE	1. Linezolid 1. Daptomycin	Daptomycin combined with ampicllin, ertapenem, ceftaroline, or fosfomycin	1. Linezolid 1. Daptomycin

1. Baddour Circulation 2015
2. Delgado EHJ 2023
3. McDonald JAMA NO 2023

Methicillin-susceptible *S. aureus*

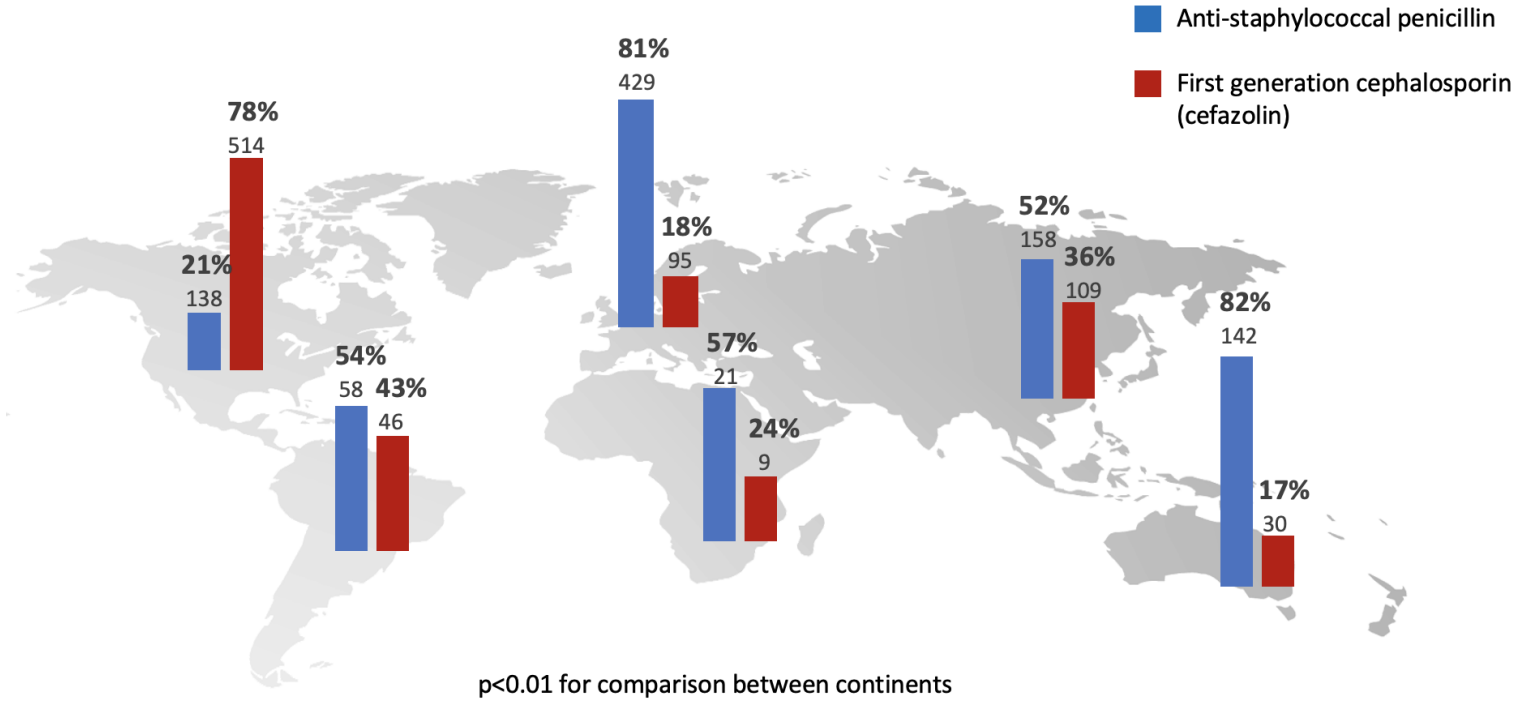
Cefazolin or antistaphylococcal penicillins

Clinical Infectious Diseases
MAJOR ARTICLE

Global Differences in the Management of *Staphylococcus aureus* Bacteremia: No International Standard of Care

Annette C. Westgeest,[1,2] David T. P. Buis,[3] Kim C. E. Sigaloff,[3] Felicia Ruffin,[1] Leo G. Visser,[2] Yunsong Yu,[4] Emile F. Schippers,[2,5] Merel M. C. Lambregts,[2] Steven Y. C. Tong,[6,7] Mark G. J. de Boer,[2,8] and Vance G. Fowler Jr [1,9]

A. MSSA bacteremia – first choice antibiotics



p<0.01 for comparison between continents

Westgeest CID 2023

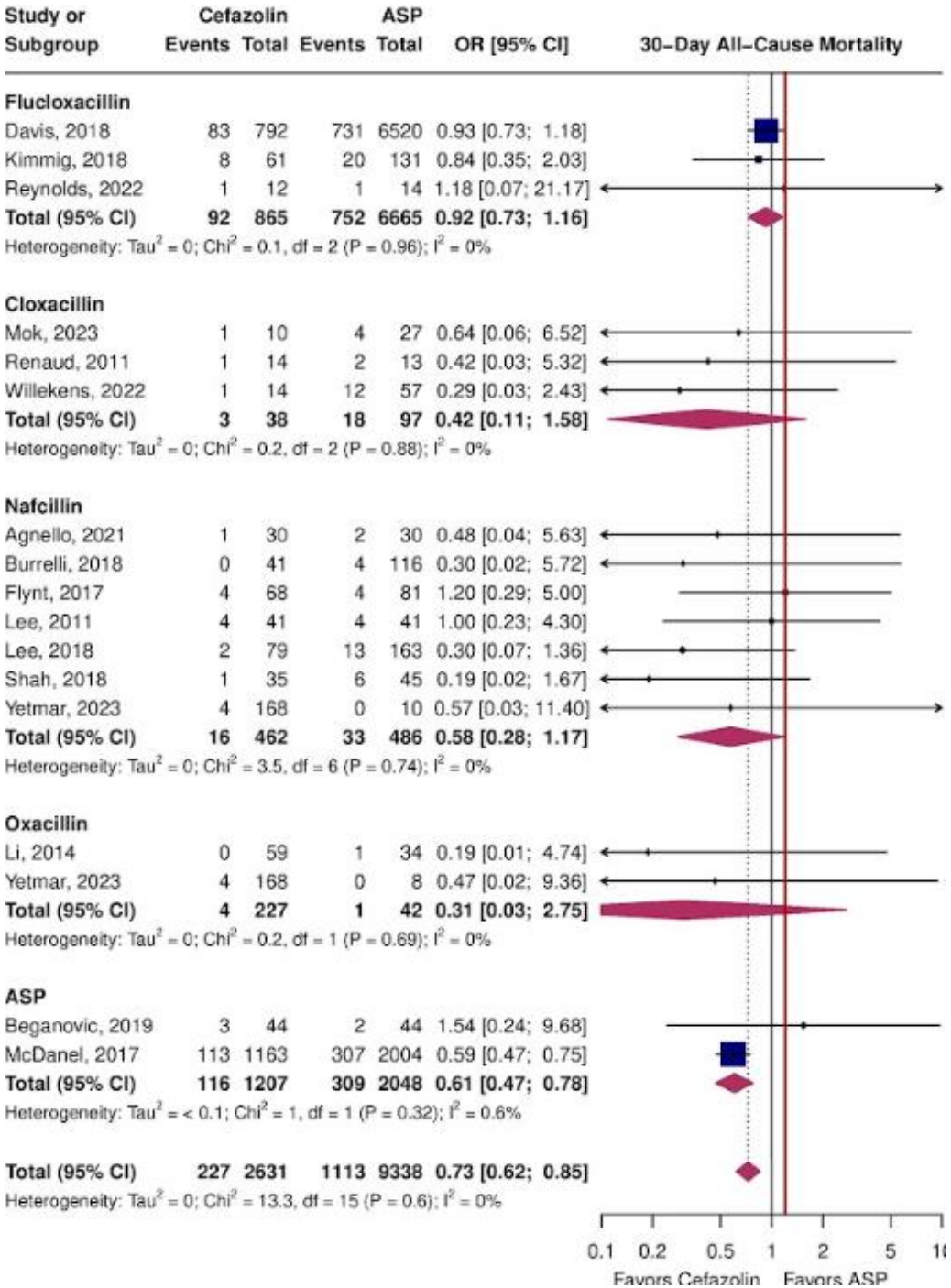
Cefazolin vs ASPs

Systematic review meta-analysis of all observational studies of cefazolin vs anti-staphylococcal penicillins

Cefazolin <u>associated</u> with lower all-cause mortality

Cefazolin <u>associated</u> with fewer adverse effects

Prosty CMI 2025



Prosthetic valve *S. aureus* endocarditis

Study, First Author	Design	Study Years	Sample Size
Karchmer et al, 1983 [27]	Retrospective cohort	1975–1980	23
Karchmer et al, 1983 [24]	Retrospective cohort	1975–1980	46
Ramos-Martínez et al, 2018 [26]	Prospective registry	2008–2016	94
Le Bot et al, 2021 [25]	Retrospective cohort	2000–2018	180

Open Forum Infectious Diseases
MAJOR ARTICLE

Deconstructing the Dogma: Systematic Literature Review and Meta-analysis of Adjunctive Gentamicin and Rifampin in Staphylococcal Prosthetic Valve Endocarditis

Jonathan H. Ryder,[1,0] Steven Y. C. Tong,[2,3] Jason C. Gallagher,[4] Emily G. McDonald,[5] Irani Thevarajan,[2,3] Todd C. Lee,[5,a] and Nicolás W. Cortés-Penfield[1,a]

'Therefore, it appears the initial 1989 AHA guideline recommendations for and subsequent practice of combination therapy in staphylococcal PVE might be based on retrospective comparisons involving only 6 patients who received appropriate monotherapy without an adjunctive agent.'

Ryder OFID 2022

E. faecalis infective endocarditis

Guidelines:

Ampicillin / penicillin plus

1. Gentamicin; OR

1. Ceftriaxone

Clinical Infectious Diseases
MAJOR ARTICLE

Revisiting the Evidence Base That Informs the Use of Adjunctive Therapy for *Enterococcus faecalis* Endocarditis: A Systematic Review and Meta-Analysis

Connor Prosty,[1,0] Mark Sorin,[1] Khaled Katergi,[2] Roy Khalaf,[1] Clare Fogarty,[1] Malick Turenne,[1] Todd C. Lee,[3,4,5,a] and Emily G. McDonald[4,5,6,a]

The clinical evidence that supports this practice [of combination therapy] is limited to 30 patients treated with monotherapy, predominantly originating from a flawed 1954 study.

Prosty CID 2025

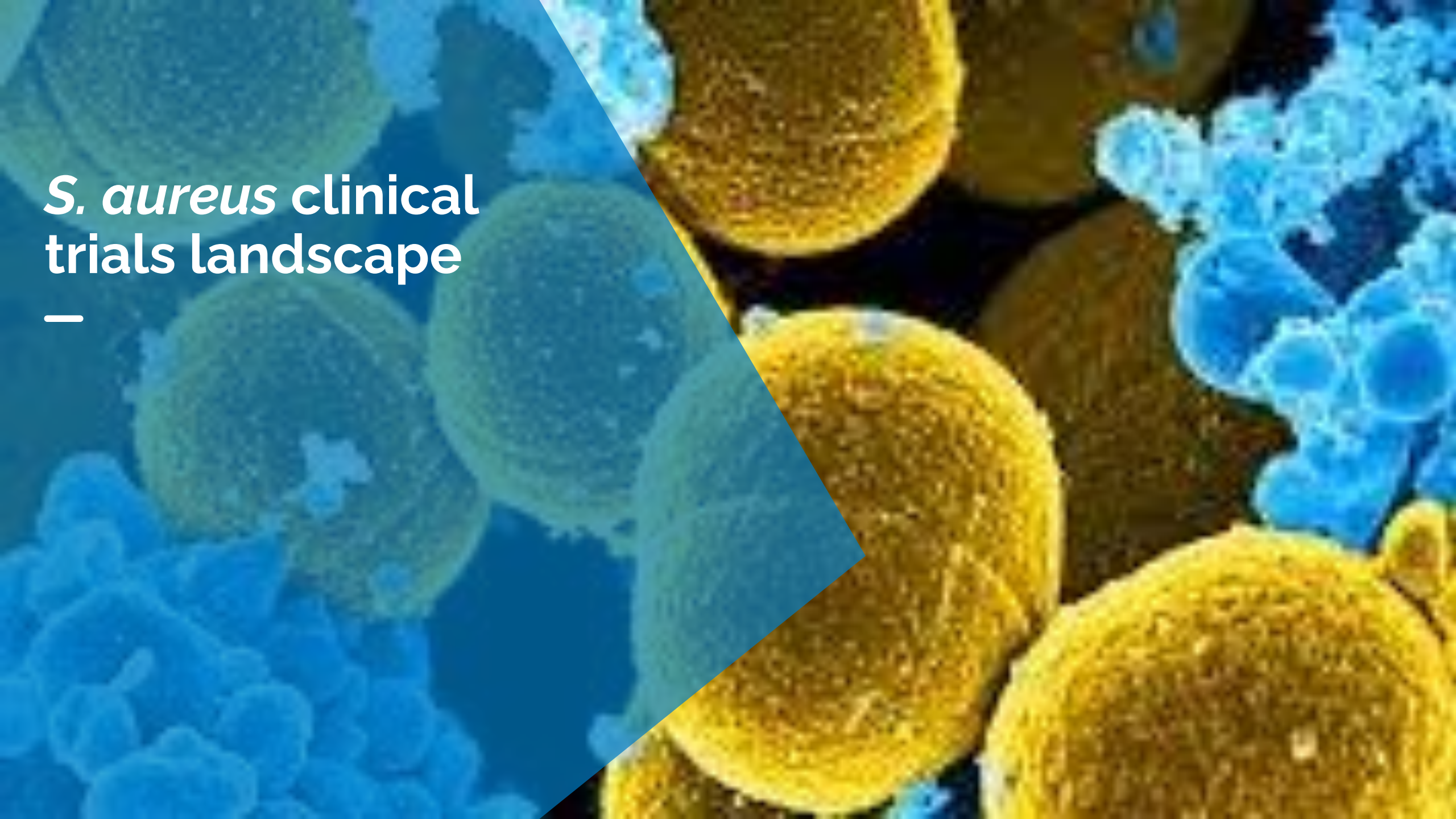
The problem

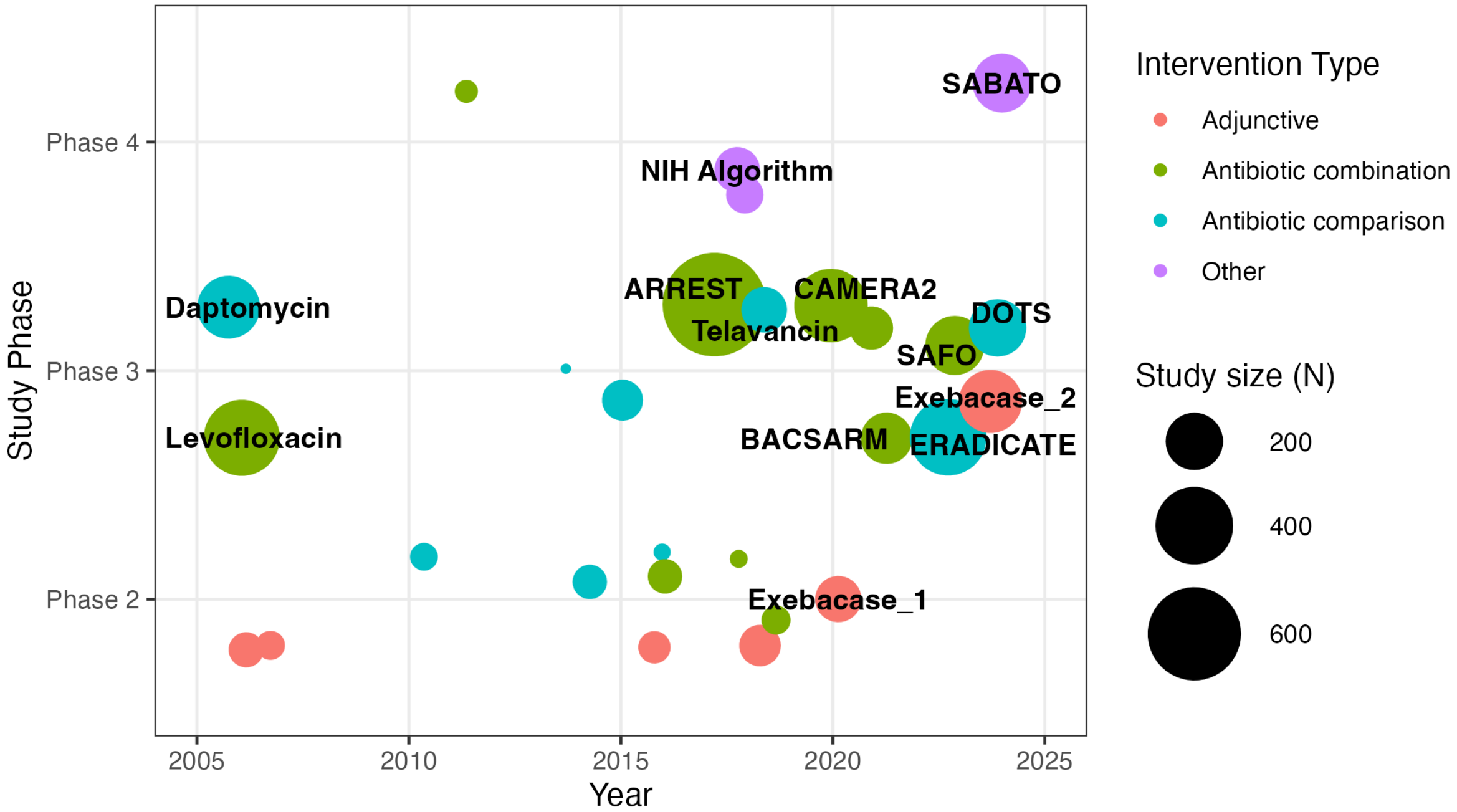
Registrational trials may not (often do not) address clinically relevant questions

Follow-up trials are not happening

Guidelines are not informed by randomised clinical trials

S. aureus clinical trials landscape



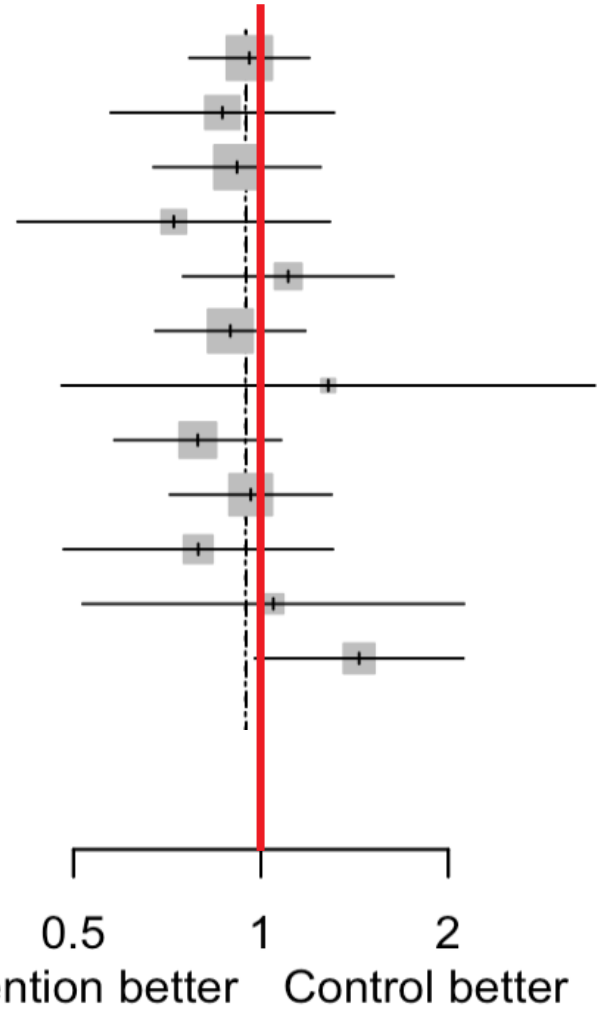

Study Phase
Phase 4
Phase 3
Phase 2
Year
2005
2010
2015
2020
2025
SABATO
NIH Algorithm
ARREST
CAMERA2
Telavancin
DOTS
SAFO
Daptomycin
Exebacase_2
Levofloxacin
BACSARM
ERADICATE
Exebacase_1
Intervention Type
Adjunctive
Antibiotic combination
Antibiotic comparison
Other
Study size (N)
200
400
600

Treatment effects

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%-CI
Daptomycin	67	120	67	115	0.96	[0.77; 1.20]
Levofloxacin					0.87	[0.57; 1.31]
ARREST					0.92	[0.67; 1.25]
NIH Algorithm					0.72	[0.41; 1.29]
Telavancin	25	47	25	52	1.11	[0.75; 1.63]
CAMERA2	59	170	68	175	0.89	[0.68; 1.18]
DASH	8	53	6	51	1.28	[0.48; 3.44]
BACSARM					0.79	[0.58; 1.08]
ERADICATE					0.96	[0.71; 1.30]
SAFO					0.79	[0.48; 1.31]
SABATO	14	108	13	105	1.05	[0.52; 2.12]
Exebacase_2	67	165	24	85	1.44	[0.98; 2.12]

Nothing shown to be superior to SOC

Trials not large enough to show superiority



Clinical Infectious Diseases

MAJOR ARTICLE

Global Differences in the Management of *Staphylococcus aureus* Bacteremia: No International Standard of Care

Annette C. Westgeest,[1,2] David T. P. Buis,[3] Kim C. E. Sigaloff,[3] Felicia Ruffin,[1] Leo G. Visser,[2] Yunsong Yu,[4] Emile F. Schippers,[2,5] Merel M. C. Lambregts,[2] Steven Y. C. Tong,[6,7] Mark G. J. de Boer,[2,8] and Vance G. Fowler Jr [1,9]

Online survey

Social media

Over 20 days – 2031 responses from 71 countries

North America: 701 (35%)
Europe: 573 (28%)
Asia: 409 (20%)

Oceania: 182 (9%)
South America: 124 (6%)
Africa: 42 (2%)

Westgeest CID 2023

Less than 4,500 patients randomised in *S. aureus* bloodstream infection trials

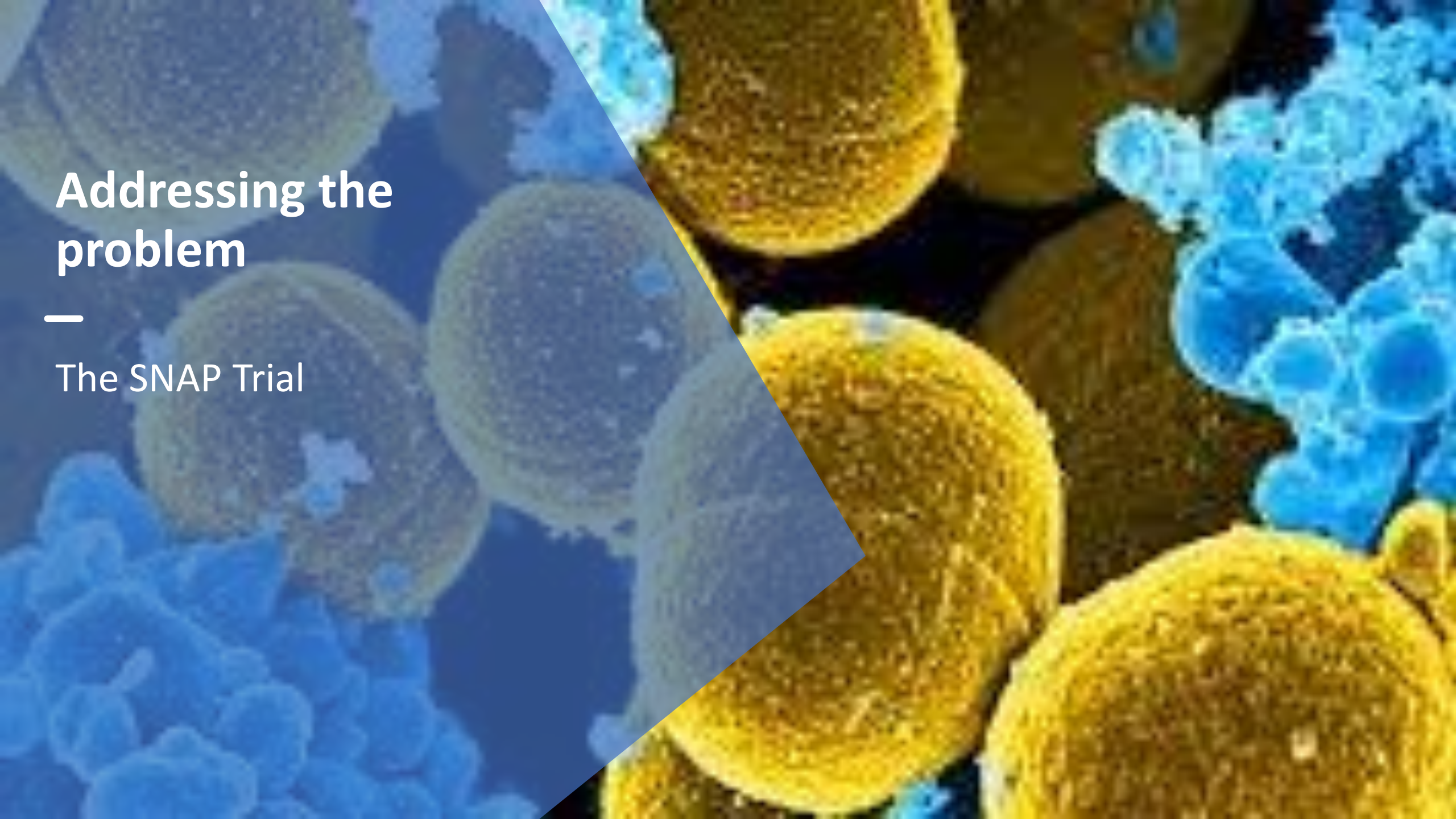
even higher in clinical practice.[10] Now, more than ever, a clinical trials network of experienced sites is needed to prioritise the most pressing clinical questions and conduct pragmatic trials in *S aureus* bacteraemia and other bacterial syndromes. Ultimately, the responsibility for such a network falls to the clinical community, as we define fundamental questions on how to best treat patients with *S aureus* bacteraemia.

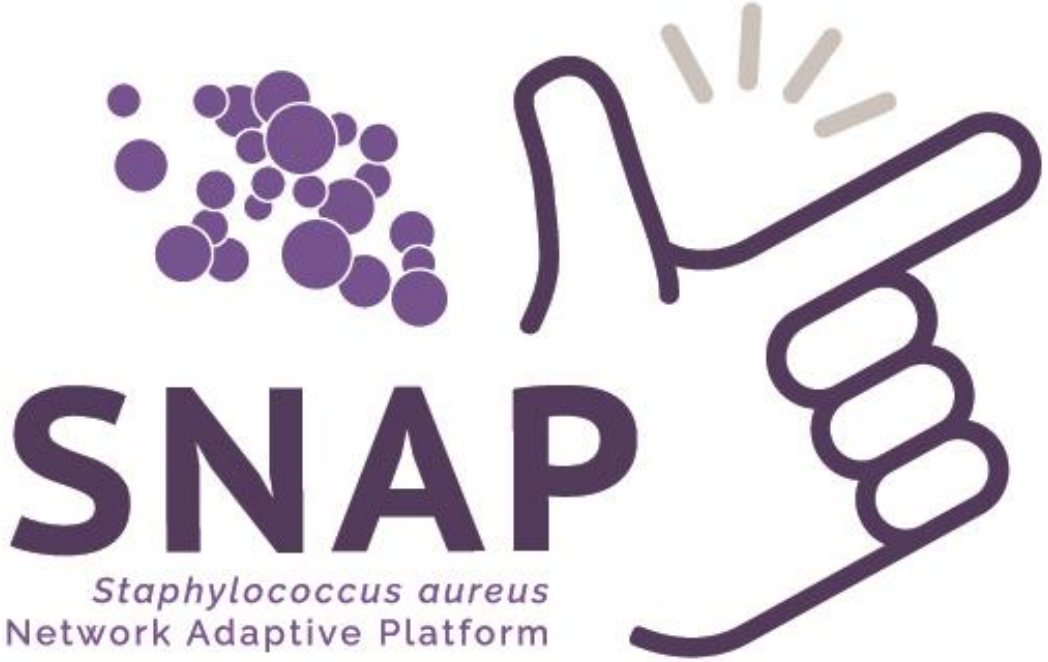
Holland and Fowler
Lancet 2017

Randomised care rather than random care

Addressing the problem

The SNAP Trial





https://www.snaptrial.com.au/

The platform

Silo	Antibiotic Backbone Domain	Adjunctive Treatment Domain	Early Oral Switch Domain	Diagnostic Domain
PSSA	(Flu)cloxacillin* vs Penicillin	Clindamycin vs No clindamycin*	Continued IV* versus early oral switch At 7 days At 14 days	PET/CT vs No PET/CT
MSSA	(Flu)cloxacillin* vs Cefazolin			
MRSA	(Vancomycin vs Dapto) vs (Vancomycin vs Dapto) plus cefazolin			
	Paediatrics			

The platform – new domains

Silo	Antibiotic Backbone Domain	Adjunctive Treatment Domain	Early Oral Switch Domain	Diagnostic Domain	Infective endocarditis	Adjunctive II
PSSA	(Flu)cloxacillin* vs Penicillin	Clindamycin vs No clindamycin*	Continued IV* versus early oral switch At 7 days At 14 days	PET/CT vs No PET/CT	Rifampin vs No Rifampin	Fosfomycin vs No fosfomycin
MSSA	(Flu)cloxacillin* vs Cefazolin					
MRSA	(Vancomycin vs Dapto) vs (Vancomycin vs Dapto) plus cefazolin					
	Paediatrics					

Core primary and secondary outcomes

Primary

All cause mortality at 90 days

Key Secondary

All-cause mortality at 14, 28 and 42 days after platform entry

Microbiological treatment failure

- Positive sterile site culture for *S. aureus* [of the same silo as the index isolate] between 14 and 90 days after platform entry

Domain specific outcomes

Acute kidney injury

Hepatotoxicity

Statistical aspects

Bayesian hierarchical logistic regression model (adjusted for age, other domain eligibilities and interventions, country, epoch)

Scheduled analyses every 500 participants

Decision thresholds for primary outcome:

- Non-inferiority: Prob(OR <1.2) > 0.99
- Futility of non-inferiority: Prob(OR <1.2) < 0.01
- Superiority: Prob(OR <1.0) > 0.99
- Futility of superiority: Prob(OR <1/1.2) < 0.01

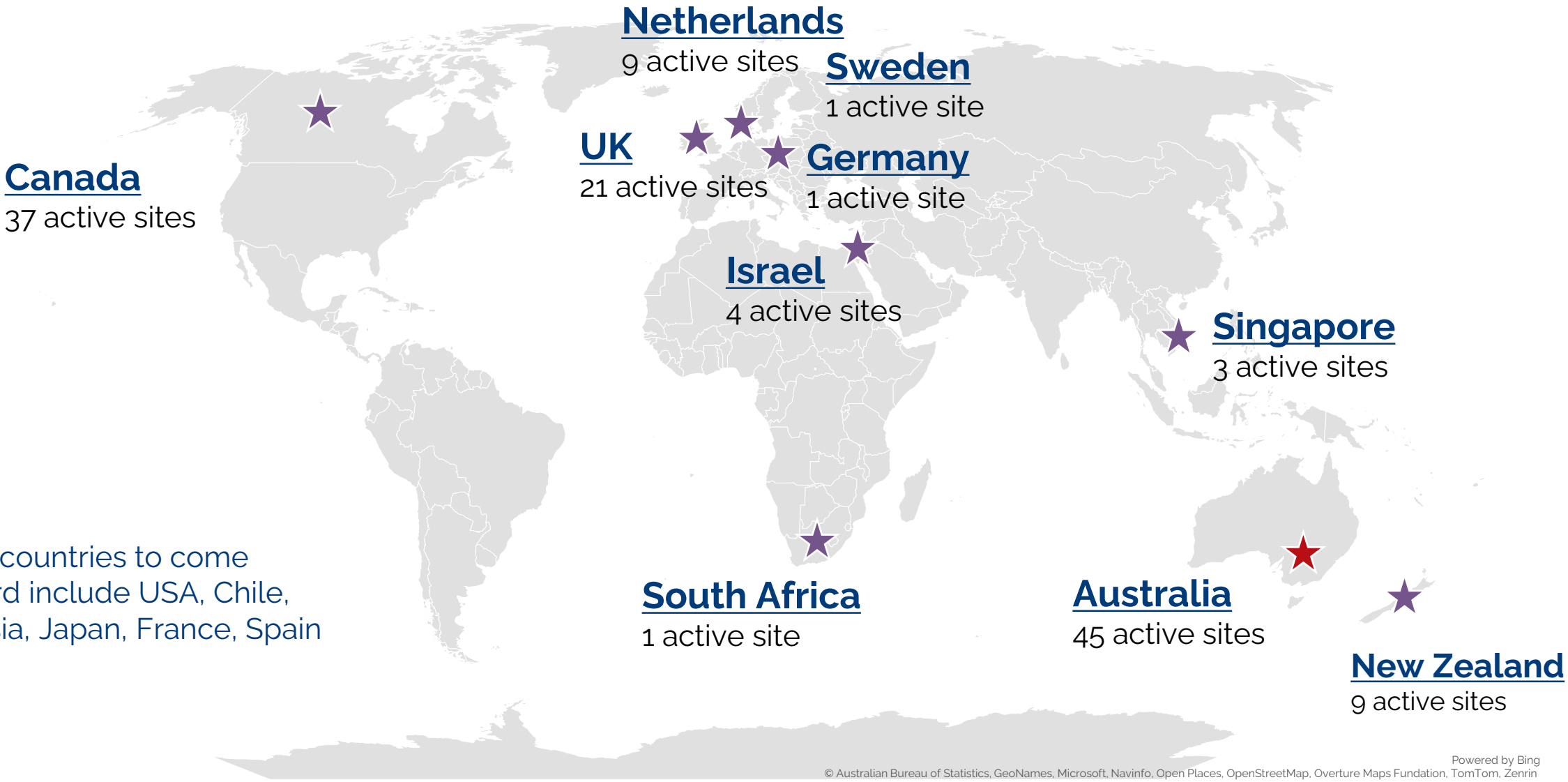
Simulations

Demonstrated domain-specific control of type 1 error and adequate power to met decision criteria by max N.

Hypothesis testing

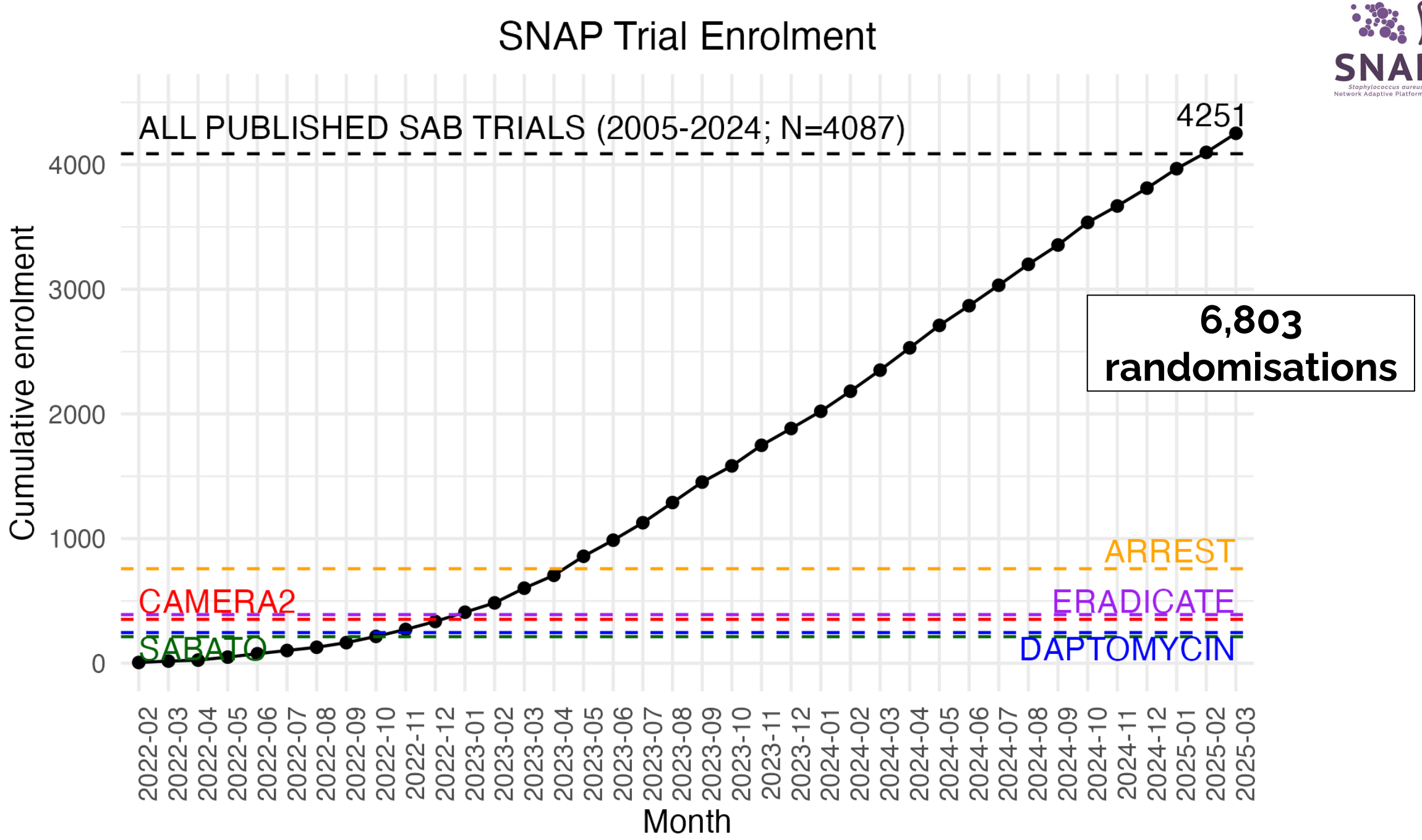
Silo	Backbone	Adjunctive	Early oral switch
PSSA	Non-inferiority; *then if met*: Superiority	Superiority	Non-inferiority
MSSA	Non-inferiority; *then if met*: Superiority		
MRSA	Superiority		

Global Trial: 130+ sites across 10 countries



*Other countries to come onboard include USA, Chile, Malaysia, Japan, France, Spain

- NHMRC 1184238; 2014900; 2032628; 2032163; MRF 2017301
- NZ HRC 20/344; Te Niwha Infectious Disease Research Platform
- Canada CIHR 451092, 485083, 451092, RN539641 – 519177, RN537808 – 518432, RN536798 - 518016
- Singapore NMRC CTGIITnov-0002
- UK NIHR 133719
- US NIH 1R01AI173138-01A1
- Netherlands ZonMw 10140022110014 & UMC Utrecht
- ANRS-MIE (Agence Nationale de Recherche sur le SIDA et les Maladies Infectieuses Emergentes); PHRC-N (Protocole Hospitalier de Recherche Clinique - National)
- Ministerium für Wissenschaft, Energie, Klimaschutz und Umwelt des Landes Sachsen-Anhalt, Germany; Bundesministerium für Bildung und Forschung, Germany
- The Swedish Research Council; Stig and Ragna Gorthon's foundation
- Instituto de Salud Carlos III, Spain


SNAP Trial Enrolment
ALL PUBLISHED SAB TRIALS (2005-2024; N=4087)
4251
6,803 randomisations
ARREST
CAMERA2
ERADICATE
SABATO
DAPTOMYCIN
Cumulative enrolment
0
1000
2000
3000
4000
2022-02
2022-03
2022-04
2022-05
2022-06
2022-07
2022-08
2022-09
2022-10
2022-11
2022-12
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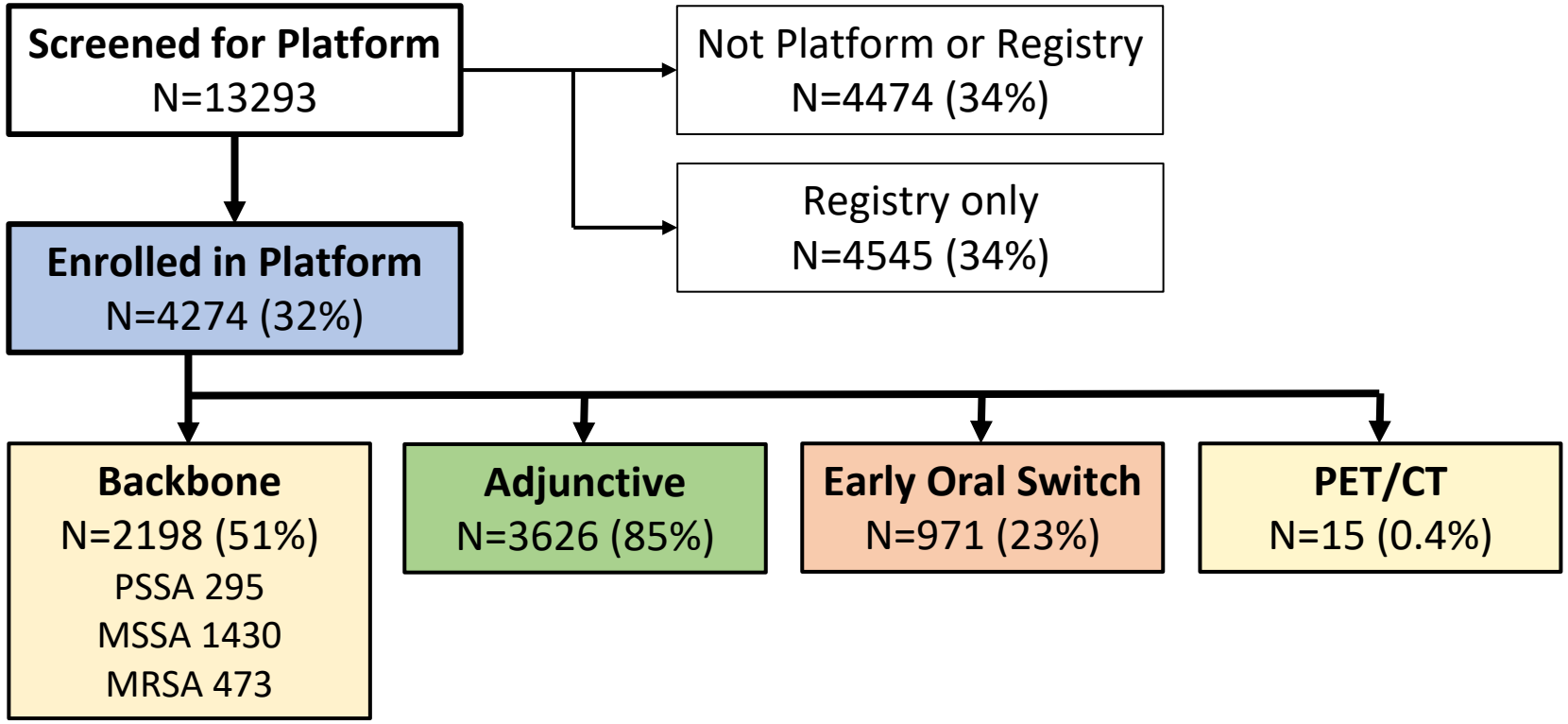
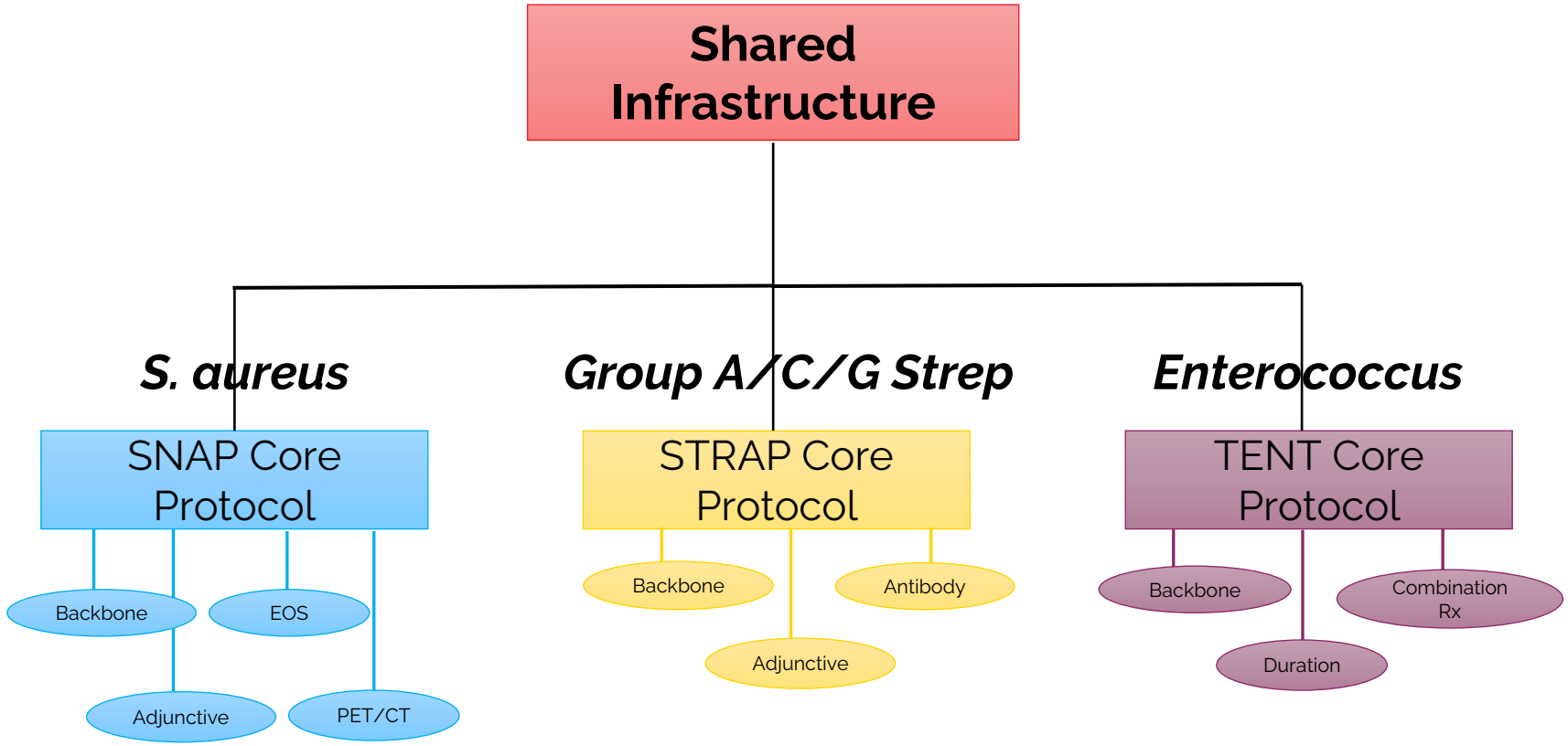
2024-11
2024-12
2025-01
2025-02
2025-03
Month

Platform consort



Platform of gram-positives



Joshua Davis

Communicable
by CMI Communications

Breakpoints
The SIDP Podcast

Coming Soon!

"SNAP Out of It: Rethinking Antistaphylococcal Penicillins for S. aureus Bacteremia – The SNAP Trial PSSA/MSSA Results"

With hosts, Drs. Erin McCreary and Angela Huttner, and SNAP trial investigators, Drs. Steven Tong and Joshua Davis

ESCMID

SIDP

NEJM Journal Watch

GENERAL MEDICINE | SPECIALTIES | TOPICS | VOICES | CME | GUIDELINE WATCH

HIV and ID Observations

An ongoing dialogue on HIV/AIDS, infectious diseases, all matters medical, and some not so medical.

APRIL 18TH, 2025

SNAP Trial Helps Resolve Long-Running Controversies Over Management of Staph Bacteremia

For those who do hospital-based patient care, the significance of *Staphylococcus aureus* bacteremia (SAB) cannot be overstated. It's one of the most frequent reasons for infectious disease consultations — and for good reason: when mismanaged or complicated, it can lead to high morbidity, a myriad of complications, and a disturbingly high mortality rate.

Despite its clinical importance, **pivotal questions about optimal management have lingered for decades** —

Paul E. Sax, MD

Contributing Editor

NEJM JOURNAL WATCH INFECTIOUS DISEASES

Biography | Disclosures | Summaries

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Review

April 7, 2025

Management of *Staphylococcus aureus* Bacteremia

A Review

Steven Y. C. Tong, MBBS, PhD[1,2]; Vance G. Fowler Jr, MD, MHS[3,4]; Lesley Skalla, PhD, MSLS[5]; Thomas L. Holland, MD, MSc[3,4]

Author Affiliations | Article Information

JAMA. Published online April 7, 2025. doi:10.1001/jama.2025.4288

REVIVE by GARDP

Patrick Harris

Patrick Harris is a staff Specialist in Microbiology at Pathology Queensland, Infectious Disease Physician at the Royal Brisbane and Women's Hospital and NHMRC Emerging Leadership Fellow at The University of Queensland Centre for Clinical Research (UQCCR). He leads a multidisciplinary research group at UQCCR with a focus on antibiotic resistance and the use of randomised trials to define optimal management for multi-drug resistant gram-negative bacteria. He has also been the clinical lead for the Queensland Genomics infection program, aiming to introduce the routine application of microbial genomics to clinical practice.

Trials for MDR Gram-negative bacteria

Patrick Harris

University of Queensland Centre for Clinical Research
Pathology Queensland
Herston Infectious Disease Institute

HERSTON INFECTIOUS DISEASES INSTITUTE

THE UNIVERSITY OF QUEENSLAND AUSTRALIA | UQCCR UQ Centre for Clinical Research

pathology queensland

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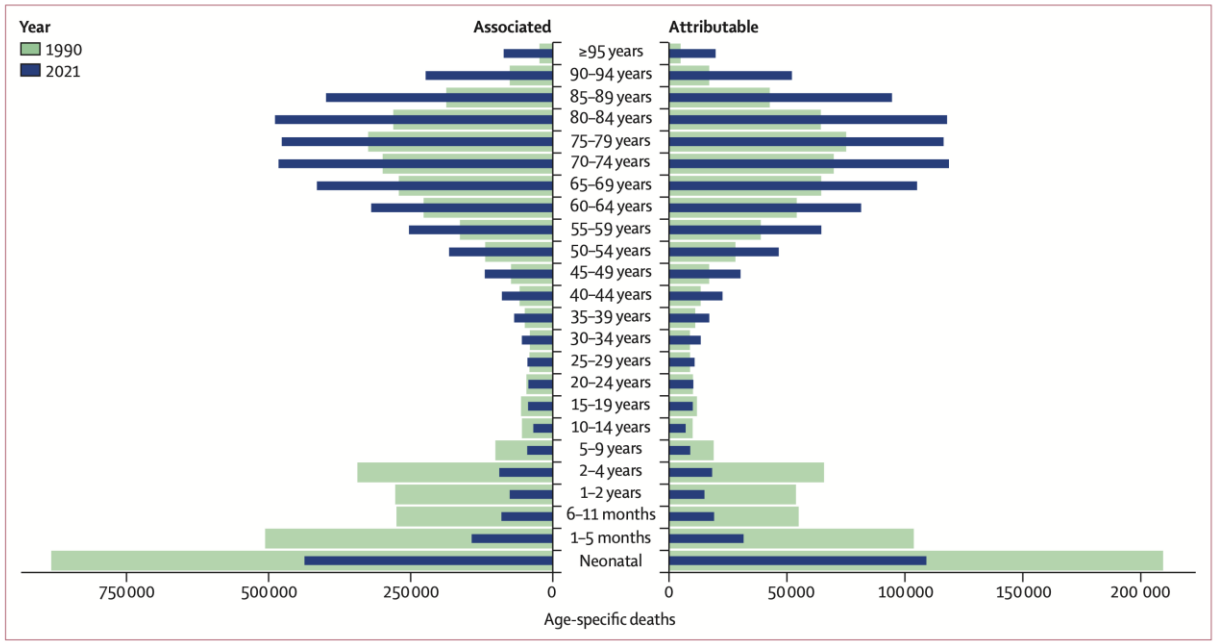
Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050

*GBD 2021 Antimicrobial Resistance Collaborators**

- Estimated 4.71M global deaths associated with AMR in 2019
- 1.14M attributable to bacterial AMR



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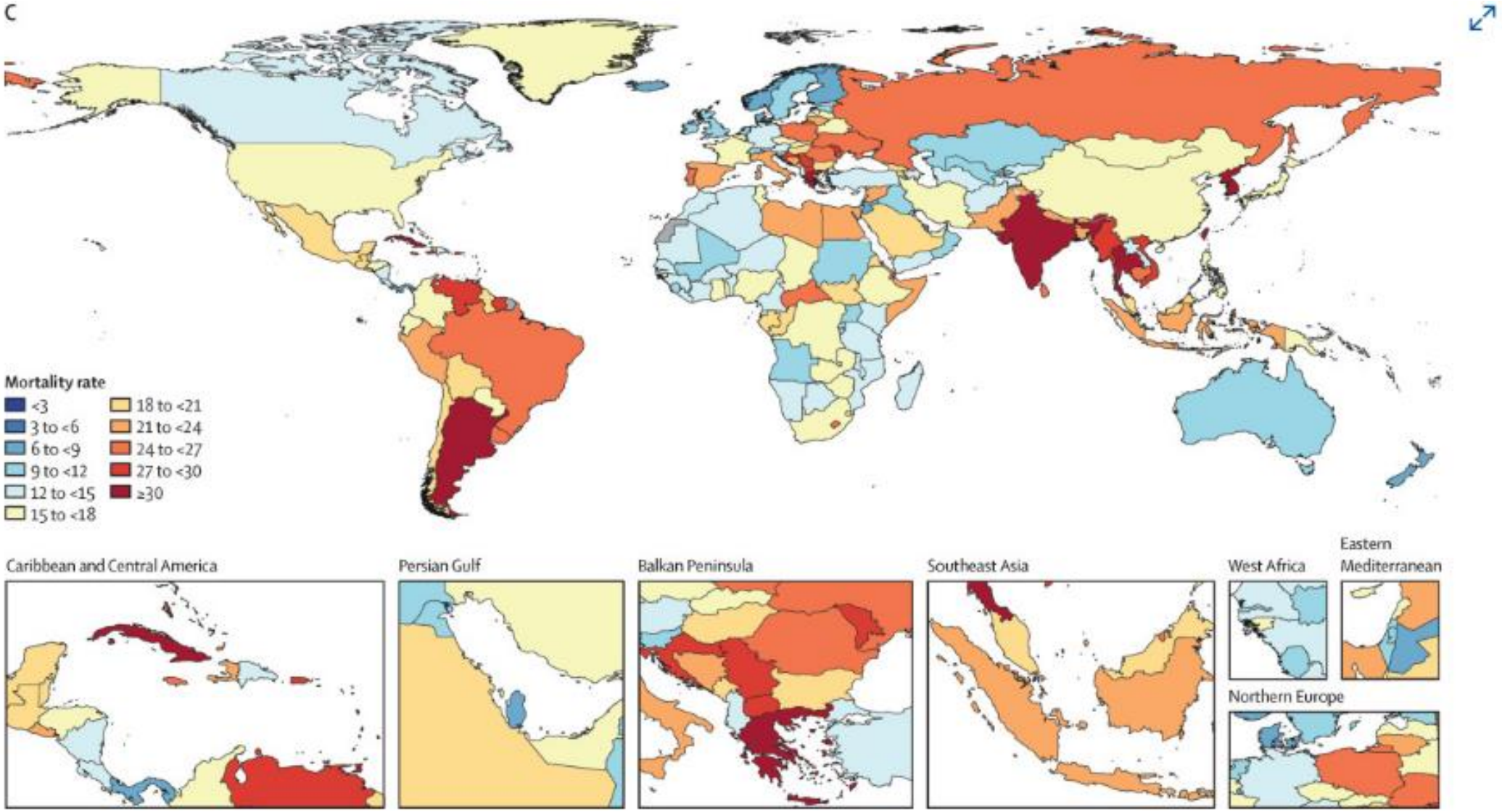
Lancet 2024; 404: 1199–226

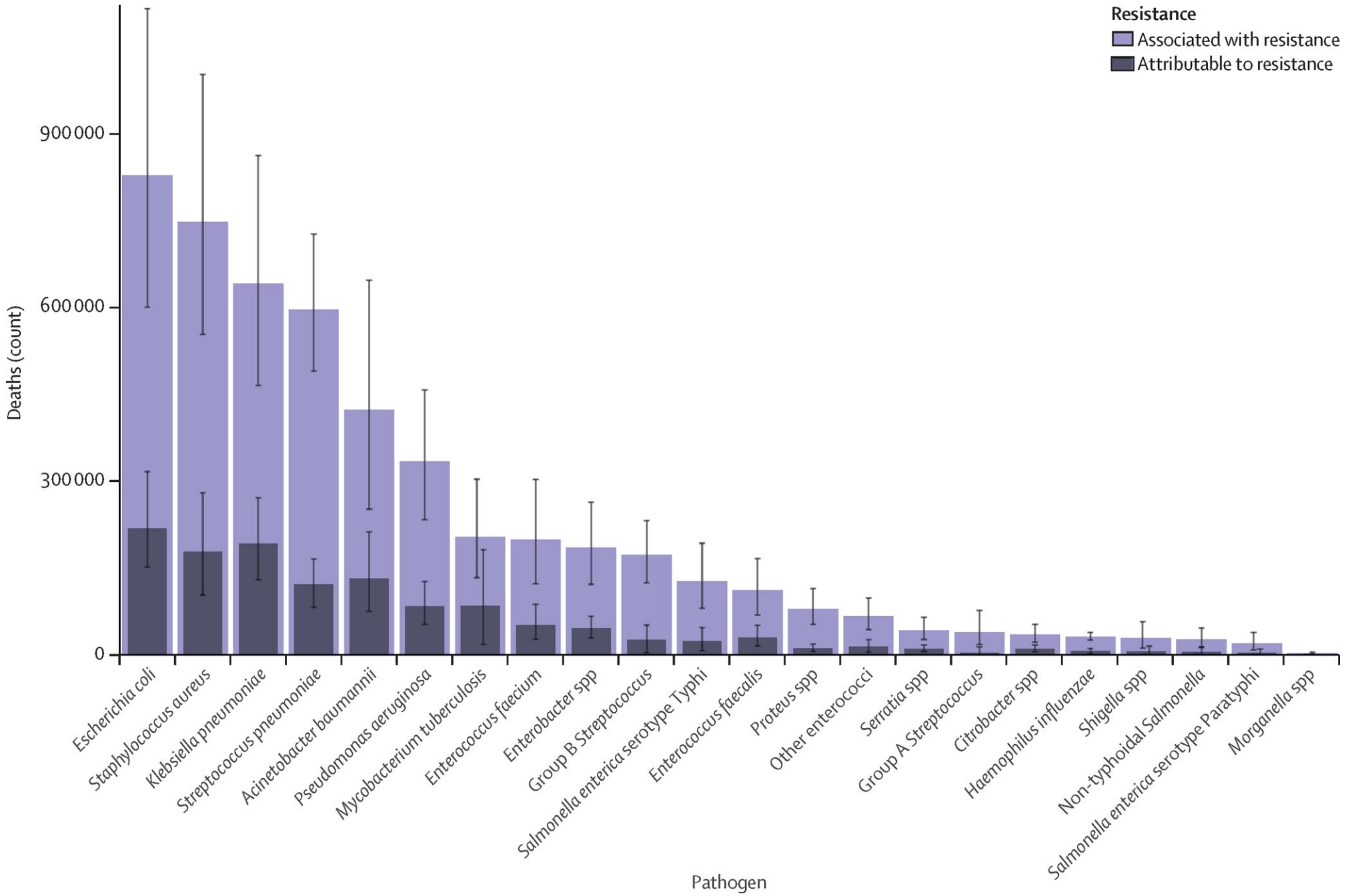
Forecast AMR mortality in 2050



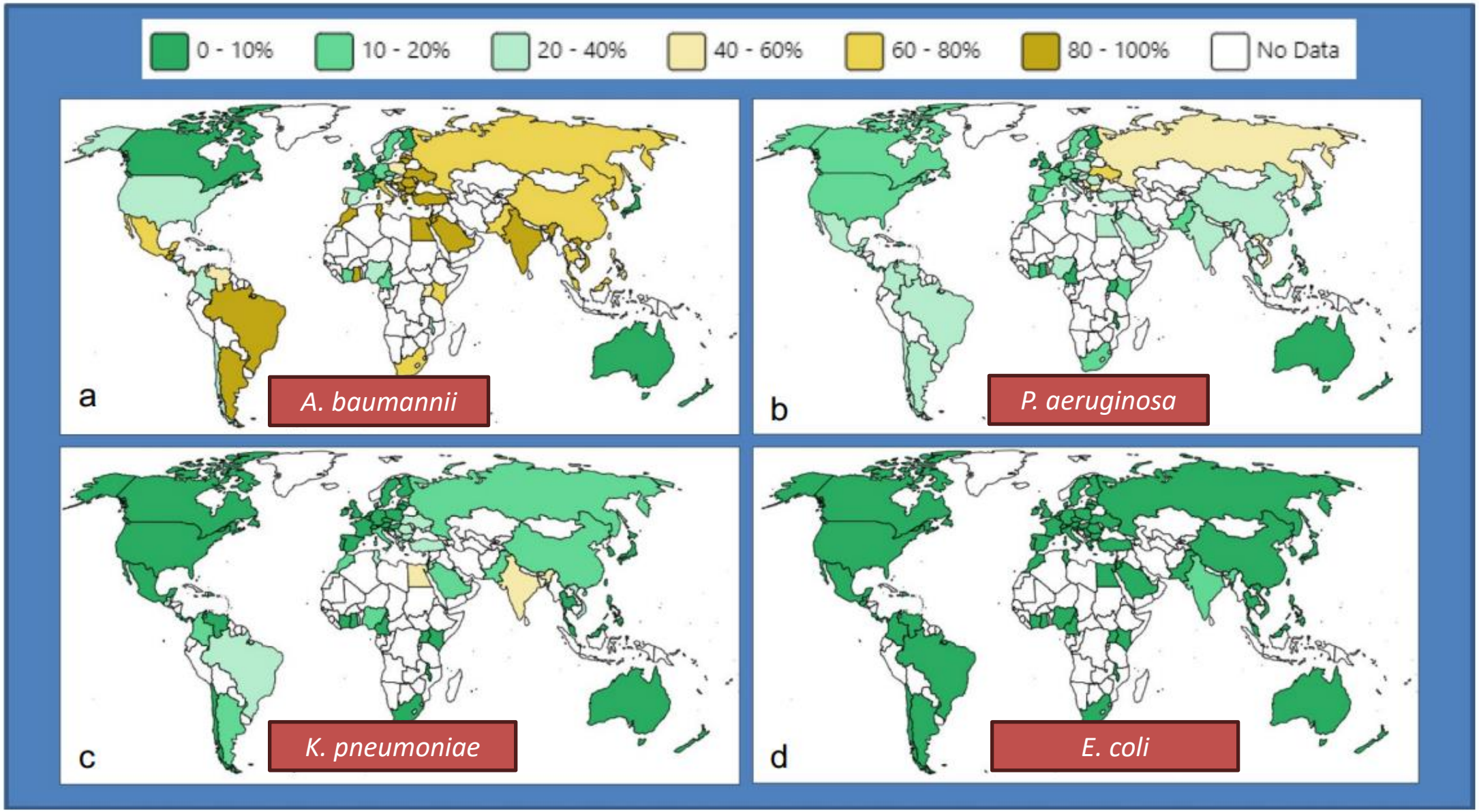
Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050 Naghavi, Mohsen et al. The Lancet, Volume 404, Issue 10459, 1199 - 1226

Gram-negative bacteria

- Carbapenem resistance increased more than any other antibiotic class
  - 619,000 associated deaths in 1990, to 1.03 million in 2021
  - 127,000 attributable deaths in 1990, to 216,000 in 2021
- **11.1 million AMR deaths could be averted through the development of better Gram-negative drug treatments**

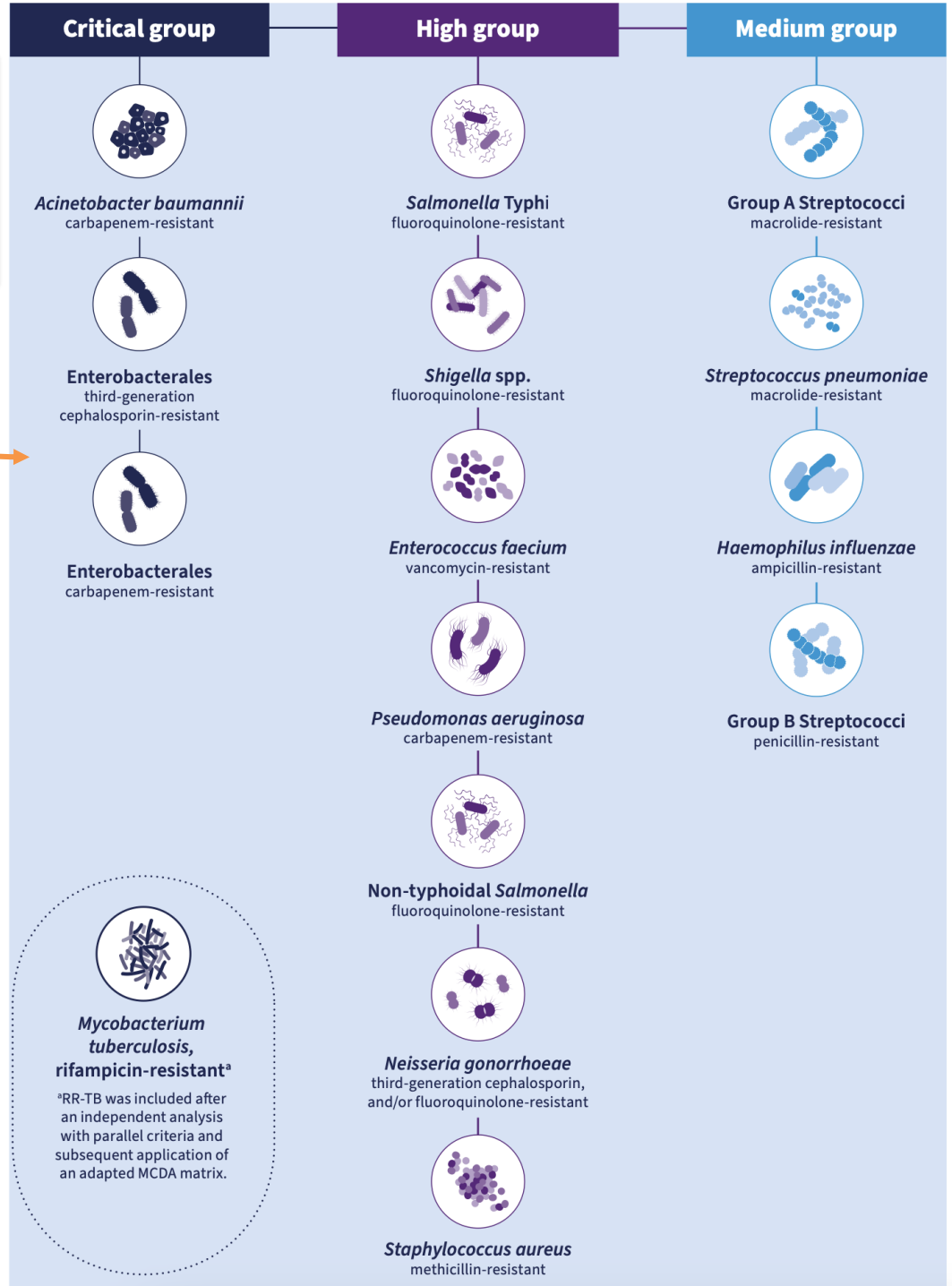

Resistance
Associated with resistance
Attributable to resistance
Deaths (count)
900 000
600 000
300 000
0
Escherichia coli
Staphylococcus aureus
Klebsiella pneumoniae
Streptococcus pneumoniae
Acinetobacter baumannii
Pseudomonas aeruginosa
Mycobacterium tuberculosis
Enterococcus faecium
Enterobacter spp
Group B Streptococcus
Salmonella enterica serotype Typhi
Enterococcus faecalis
Proteus spp
Other enterococci
Serratia spp
Group A Streptococcus
Citrobacter spp
Haemophilus influenzae
Shigella spp
Non-typhoidal Salmonella
Salmonella enterica serotype Paratyphi
Morganella spp
Pathogen

Carbapenem Resistant GNBs



Eur J Clin Microbiol Infect Dis (2025). https://doi.org/10.1007/s10096-025-05080-1

> 290,000 ESBLs and > 30,000 CRE occur in patients in the US each year



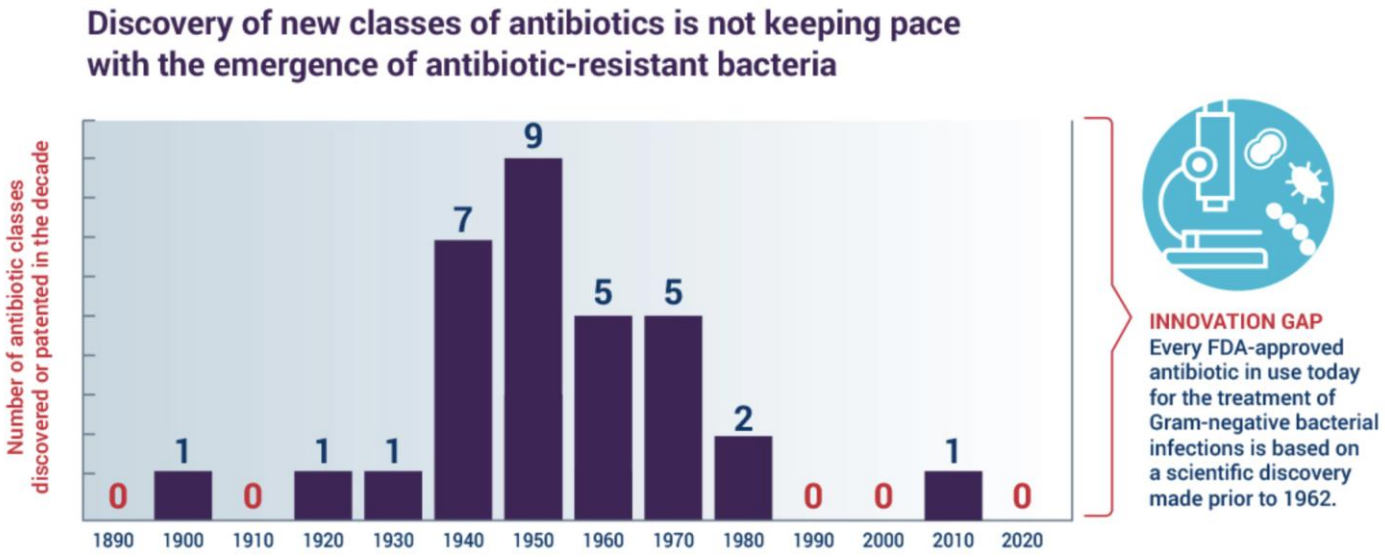
Gupta V, Ye G, Olesky M, et al. Int J Infect Dis 2019; 85:203–211

ANTIBACTERIAL AGENTS IN CLINICAL DEVELOPMENT

An analysis of the antibacterial clinical development pipeline, including tuberculosis

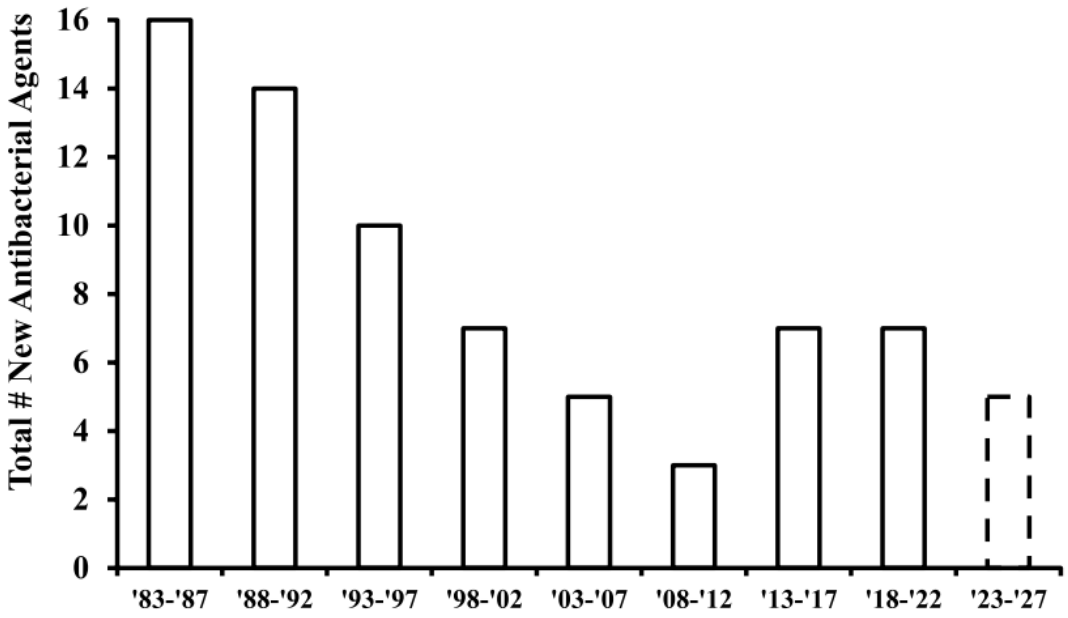
World Health Organization

http://www.who.int/medicines/en/



The antibiotic 'pipeline' lacks true innovation…

But… is not entirely dry



https://carb-x.org/

Health Affairs Scholar, 2025, 3(2), qxaf012

New agents against MDR-GNBs

New BL-BLIs

New BLs

	ESBL	KPC	OXA-48	MBL	CRPA	CRAB	Phase
β-lactam/β-lactamase inhibitors							
Meropenem/vaborbactam	✓	✓	–	–	–	–	Postmarket
Meropenem/nacubactam	✓	✓	✓	–	–	–	Phase I
Meropenem/QPX7728	✓	✓	✓	✓	±	✓	Preclinical
Imipenem/relebactam	✓	✓	–	–	✓	–	Postmarket
Ceftazidime/avibactam	✓	✓	✓	–	✓	–	Postmarket
Ceftolozane/tazobactam	✓	–	–	–	✓	–	Postmarket
Cefepime/tazobactam (2 g/2 g)	✓	–	✓	–	–	–	Phase III[a]
Cefepime/enmetazobactam	✓	–	–	–	–	–	Phase III
Cefepime/zidebactam	✓	✓	✓	✓	±	±	Phase I
Cefepime/VNRX5133	✓	✓	✓	±	±	–	Phase III
Cefepime/QPX7728	✓	✓	✓	✓	±	–	Preclinical
Ceftibuten/VNRX-7145	✓	–	–	–	–	–	Phase I
Ceftibuten/QPX7728	✓	✓	✓	–	–	–	Preclinical
Cefpodoxime/ETX-0282	✓	–	–	–	–	–	Phase I
Aztreonam/avibactam	✓	✓	✓	✓	–	–	Phase III[b]
Sulbactam/durlobactam	✓	✓	✓	✓	–	✓	Phase III
β-lactams							
Cefiderocol	✓	✓	✓	±	✓	±	Phase III
Tebipenem	✓	–	–	–	–	–	Phase III
Sulopenem	✓	–	–	–	–	–	Phase III
Aminoglycosides							
Plazomicin	✓	✓	✓	±	–	–	Postmarket
Tetracyclines							
Eravacycline	✓	✓	✓	✓	–	±	Postmarket
Polymyxins							
SPR741 plus beta-lactams	✓	±[c]	±[c]	–	–	✓	Phase I
SPR206	✓	✓	✓	✓	✓	✓	Phase I
QPX9003	✓	✓	✓	✓	✓	✓	Preclinical

Paterson DL, Isler B, Stewart A.. Curr Opin Infect Dis, 33(2), 214-223 (2020)

Spectrum of activity against MDR-GNBs

Agent	Enterobacterales					*DTR Pseudo. aeruginosa*	*CR-Acineto. baumannii*	*Stenotroph. maltophilia*	Pathogen – directed RCTs?
	ESBL-producers	AmpC-producers	Class A CPE (e.g. KPC)	Class B CPE (e.g. NDM)	Class D CPE (OXA-48)				
CAZ-AVI									No
TOL-TAZ									No
MER-VAB									Yes
IMI-REL									Yes
SUL-DUR									Yes
CAZ-AVI + ATM									No
ATM-AVI									Yes
Cefepime-enmetazobactam									No
Cefiderocol									Yes
Eravacycline									No

Adapted from: Macesic, et al. The Lancet, Volume 405, Issue 10474, 257 - 272

Pathogen-directed trials

- AMR landscape increasingly complex and dynamic - new genes, new drugs, emerging pathogens …
  - AMR burden and patterns highly variable across the world
  - Urgent need for new drugs, reassessment of existing drugs, evidence-based strategies (e.g. combination therapy, duration, adjunctive treatment etc)
  - Several new agents in pipeline with very-targeted activity (e.g. only *Acinetobacter,* or specific CPE genes, phage, CRISPR, mAbs, etc)
  - Trials designed for regulatory approvals rarely address the specific infections / pathogens or AMR profiles for which we see the greatest clinical need..
    - Usually syndromic rather than pathogen specific

Regulatory trials rarely answer the AMR questions that we see as important

- **Ceftaroline** approved from two ABSSSI trials
  - only a third of cases due to MRSA
- Two trials in patients with CAP ***where MRSA was an exclusion criterion*** (comparator had no-MRSA activity)

J Antimicrob Chemother 2011; **66** Suppl 3: iii19–iii32
doi:10.1093/jac/dkr096

Journal of Antimicrobial Chemotherapy

FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia

Thomas M. File Jr[1]*, Donald E. Low[2], Paul B. Eckburg[3], George H. Talbot[4], H. David Friedland[3], Jon Lee[3], Lily Llorens[3], Ian A. Critchley[3] and Dirk A. Thye[3] on behalf of the FOCUS 1 investigators†

The struggle to recruit patients with AMR

- Four new AMR pathogen-directed RCTs in recent years for new MDR-GNB active drugs..
  - CARE [plazomicin]
  - CREDIBLE [cefiderocol]
  - TANGO II [meropenem-varborbactam]
  - RESTORE-IMI [imipenem-relebactam])

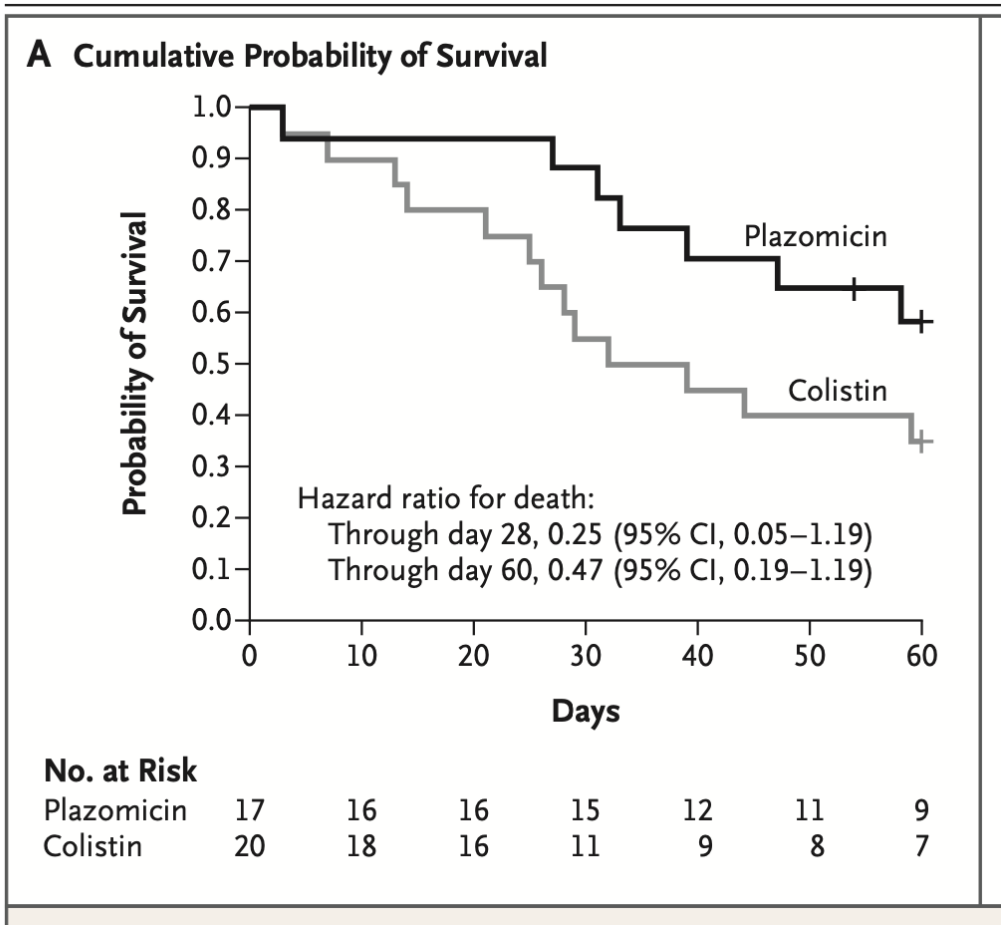
- included **<u>only 315 patients in total</u>**

Wunderink RG, al. ***TANGO II .*** *Infect Dis Ther 2018; 7: 439–55. 10.1007/s40121-018-0214-1*
Wagenlehner FME, ***Plazomicin****. N Engl J Med 2019; 380: 729–40. 10.1056/NEJMoa1801467*
Bassetti M, et al.. ***CREDIBLE-CR*** *Lancet Infect Dis 2021; 21*
Motsch J, et al. ***RESTORE-IMI 1****. Clin Infect Dis 2020; 70: 1799–808. 10.1093/cid/ciz530*

Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae

N Engl J Med 2019;380:791-793

- **CARE trial** (plazomicin)
- Total recruitment **N=37 across 68 sites**
  - Screened 2000..
- Only 17 patients received plazomicin
- Alongside UTI Phase 3 trial -> FDA approval
- 15 years and $1 Billion investment.... BUT



DEADLY GERMS, LOST CURES

Crisis Looms in Antibiotics as Drug Makers Go Bankrupt

First Big Pharma fled the field, and now start-ups are going belly up, threatening to stifle the development of new drugs.

The New York Times

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Investigator initiated pathogen-directed trials

- Investigator-initiated trials for Carb-R GNBs have been more successful than industry trials in recruiting into RCTs
  - **AIDA** (colistin combination) N=**406**, N=312 CR-*Acinetobacter* (6 sites)
  - **OVERCOME** (colistin combination) N=**464** (21 sites) pneumonia / BSI with CRAB, CRE, XDR-Psa

*Kaye et al **OVERCOME**. NEJM 2022; 2(1)*
Paul M, et al. JAC Antimicrob Resist. 2023

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Cefiderocol

Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial

Richard G Wunderink, Yuko Matsunaga, Mari Ariyasu, Philippe Clevenbergh, Roger Echols, Keith S Kaye, Marin Kollef, Anju Menon, Jason M Pogue, Andrew F Shorr, Jean-Francois Timsit, Markus Zeitlinger, Tsutae D Nagata

- **APEKS-cUTI:** n=452 patients, cefiderocol vs imipenem for cUTI
  - Composite endpoint of clinical / micro resolution @ TOC
  - 72.6% vs 54.5% met primary endpoint, within -15% NI margin
- **APEKS-NP:** non-inferior to meropenem for 14-day mortality in patients with Gram-negative nosocomial pneumonia
  - N=292; d14 mortality 12.4% cefiderocol vs. 11.6% meropenem
- **Both RCTs Specifically excluded carbapenem-R isolates ….**

Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial

Matteo Bassetti, Roger Echols, Yuko Matsunaga, Mari Ariyasu, Yohei Doi, Ricard Ferrer, Thomas P Lodise, Thierry Naas, Yoshihito Niki, David L Paterson, Simon Portsmouth, Julian Torre-Cisneros, Kiichiro Toyoizumi, Richard G Wunderink, Tsutae D Nagata

	Cefiderocol (n=101)	Best available therapy (n=49)
Acinetobacter spp*	21/42 (50%)	3/17 (18%)
Acinetobacter baumannii	19/39 (49%)	3/17 (18%)
Klebsiella pneumoniae	8/34 (24%)	4/16 (25%)
Without *Acinetobacter* spp	6/28 (21%)	4/15 (27%)
Pseudomonas aeruginosa	6/17 (35%)	2/12 (17%)
Without *Acinetobacter* spp	2/11 (18%)	2/11 (18%)
Escherichia coli	1/6 (17%)	0/3

	Nosocomial pneumonia		Bloodstream infections or sepsis		Complicated urinary tract infections		Overall	
	Cefiderocol (n=45)	Best available therapy (n=22)	Cefiderocol (n=30)	Best available therapy (n=17)	Cefiderocol (n=26)	Best available therapy (n=10)	Cefiderocol (n=101)	Best available therapy (n=49)
Day 14	11 (24%; 12·9—39·5)	3 (14%; 2·9–34·9)	5 (17%; 5·6–34·7)	1 (6%; 0·1–28·7)	3 (12%; 2·4–30·2)	2 (20%; 2·5–55·6)	19 (19%; 11·7–27·8)	6 (12%; 4·6–24·8)
Day 28	14 (31%; 18·2–46·6)	4 (18%; 5·2–40·3)	7 (23%; 9·9–42·3)	3 (18%; 3·8–43·4)	4 (15%; 4·4–34·9)	2 (20%; 2·5–55·6)	25 (25%; 16·7–34·3)	9 (18%; 8·8–32·0)
End of study	19 (42%; 27·7–57·8)	4 (18%; 5·2–40·3)	11 (37%; 19·9–56·1)	3 (18%; 3·8–43·4)	4 (15%; 4·4–34·9)	2 (20%; 2·5–55·6)	34 (34%; 24·6–43·8)	9 (18%; 8·8–32·0)

Data are n (%; 95% CI) by clinical diagnosis and overall. Percentages were calculated using n as the denominator, where n was the number of patients in the safety population who had the specified clinical diagnosis and known vital status at each timepoint.

Table 5: **All-cause mortality in the safety population**

GAME CHANGER Trial

STUDY PROTOCOL Open Access

Investigator-Driven Randomised Controlled Trial of Cefiderocol versus Standard Therapy for Healthcare-Associated and Hospital-Acquired Gram-negative Bloodstream Infection: Study protocol (the GAME CHANGER trial): study protocol for an open-label, randomised controlled trial

Hugh Wright[1,2*], Patrick N. A. Harris[1,3], Mark D. Chatfield[1], David Lye[4,5,6,7], Andrew Henderson[1,8], Tiffany Harris-Brown[1], Anna Donaldson[1] and David L. Paterson[1,2]

- Cefiderocol for treatment of healthcare associated Gram-negative bacteraemia
- Recruitment in areas with high rates of AMR (aiming to enrich for CRE, CRAB etc)
  - 17 Hospitals: Malaysia, Singapore, Taiwan, Thailand, Australia and Turkey
  - Enrolled **N=504** (of which **127 had carbapenem-resistant GNBs)**
- Cefiderocol 2g q8h over 3h vs “standard of care” (including combination therapy)
  - 5-14 days duration
- Primary outcome – all cause mortality at 14 days
  - NI margin of 10%

Primary outcome 14 days ACM

Cefiderocol: 20/250 (8%)
SOC: 17/254 (7%)

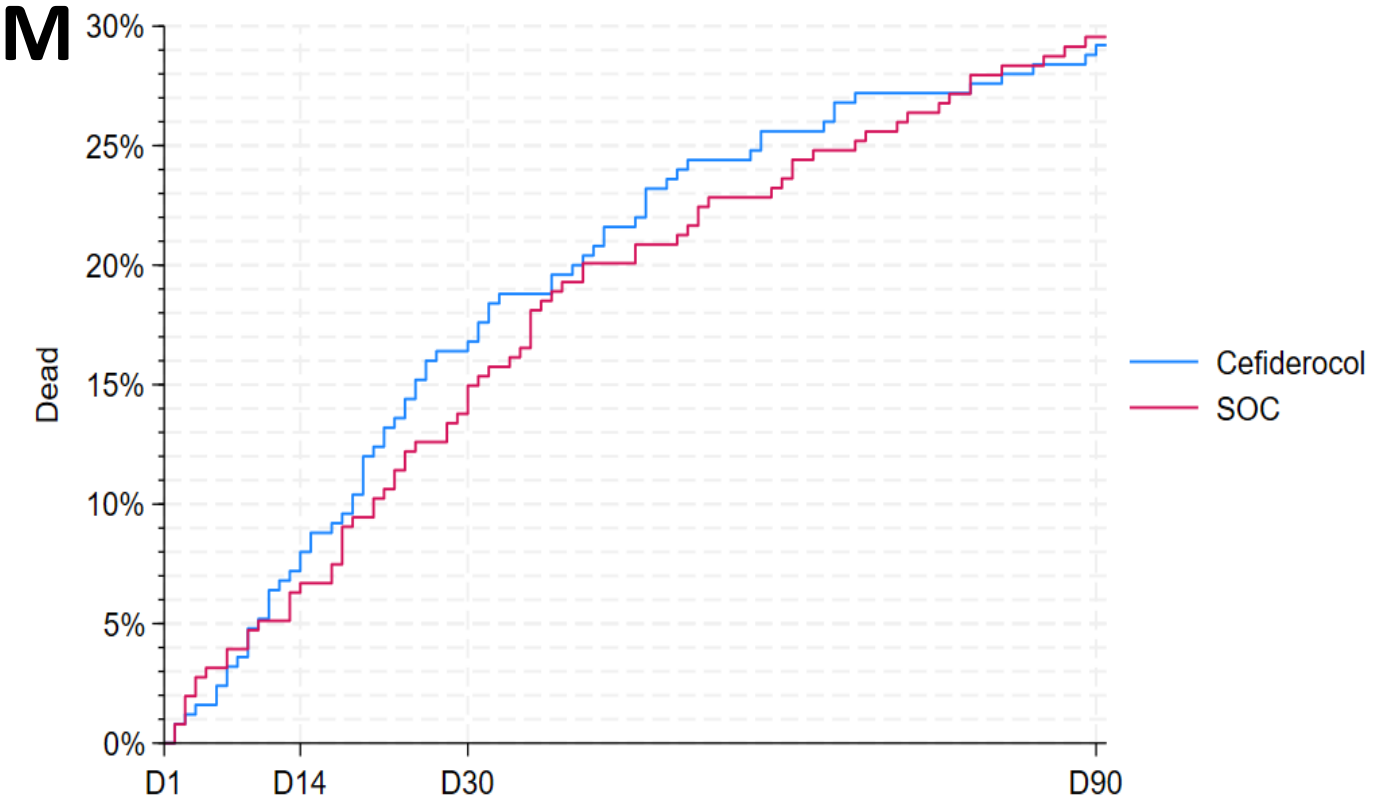
Risk difference 1%

(95% CIs: - 3% to 6%)

Relative Risk 1.20

(95% CIs: 0.64 to 2.23)

Non-inferiority met
Superiority not achieved



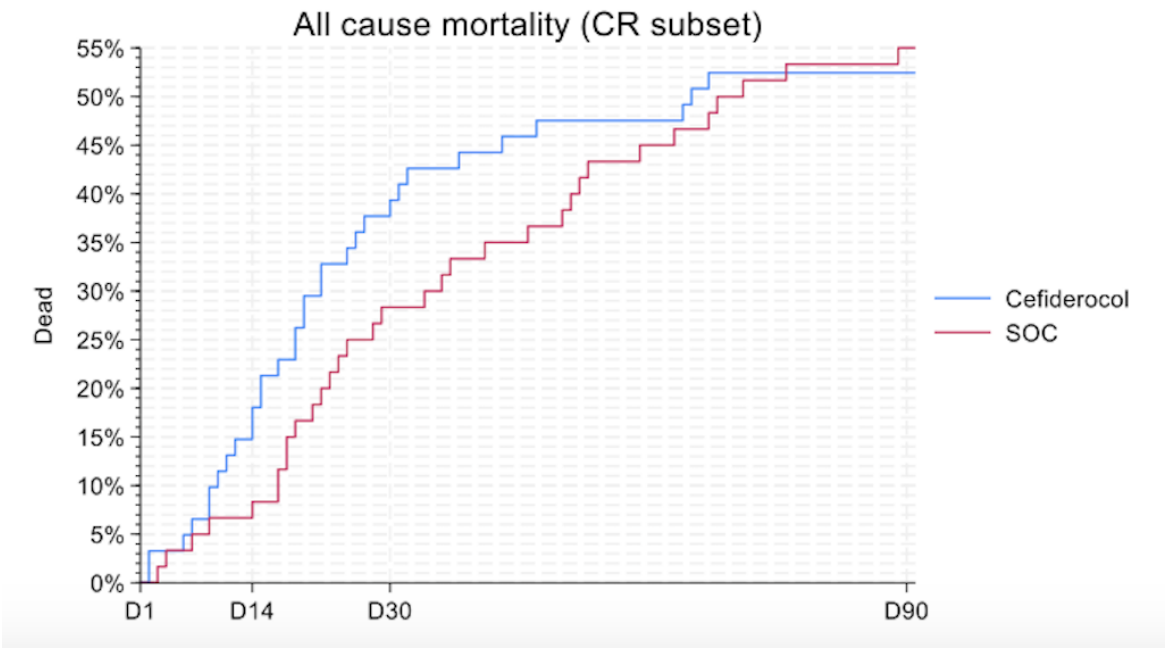
No signal of inferiority for *A. baumannii*
2/18 (11%) [FDC] vs 5/25 (20%) [SOC]
RD = -9 (-30 to 12)
RR = 0.56 (0.12 to 2.55)

Primary Endpoint – carbapenem-R only

	Cefiderocol	SOC
14-day ACM	9 / 64 (14%)	6 / 63 (10%)

Risk difference 4% (95% CI -7% to 16%)

Risk Ratio 1.5 (95% CI 0.6 to 3.9)



- 62% (21/34) index isolates with acquired MBL had cefiderocol MICs ≥4 mg/L
- All with intrinsic MBLs (e.g. *Stenotrophomonas*) h had MICs <4

Aztreonam/avibactam

- Big treatment ‘hole’ for CRE are MBLs, esp. NDM-producers
- Aztreonam stable to MBLs, but usually strains co-express other beta-lactamases which compromises its effect
- Addition of avibactam reduces MICs for most Enterobacterales
  - less so for *Pseudomonas*, *A. baumannii*
- Study from 2012 to 2015 in 40 countries 51,352 Enterobacterales isolates and 11,842 *P. aeruginosa* isolates.
  - ATM–AVI MIC_{90} of 0.12 µg/mL, compared to 64 µg/mL for ATM alone

Aztreonam–avibactam versus meropenem for the treatment of serious infections caused by Gram-negative bacteria (REVISIT): a descriptive, multinational, open-label, phase 3, randomised trial

Yehuda Carmeli, José Miguel Cisneros*, Mical Paul, George L Daikos, Minggui Wang, Julian Torre-Cisneros, George Singer, Ivan Titov, Illia Gumenchuk, Yongjie Zhao, Rosa-María Jiménez-Rodríguez, Lu Liang, Gang Chen, Oleksandr Pyptiuk, Firdevs Aksoy, Halley Rogers, Michele Wible, Francis F Arhin, Alison Luckey, Joanne L Leaney, Rienk Pypstra†, Joseph W Chow, for the COMBACTE-CARE consortium REVISIT study group‡*

Only 10 patients had confirmed MBL!

- "Descriptive" RCT – no formal sample size / power / hypothesis testing
- cIAI or HAP/VAP caused by GNB -> randomised 2:1 ATM-AVI (+/-MTZ) vs MEM (+/- colistin)
- Primary endpoint: clinical cure at TOC (day 28)
- 422 enrolled
- 68.4% ATM-AVI vs 65.7% MEM clinical cure at TOC (Diff: 2.7% [95% CI –6.6 to 12.4])
- 28-day mortality rates 4% ATM-AVI vs. 7% for MEM

	cIAI			HAP–VAP			Overall		
	Aztreonam–avibactam group	Meropenem group	Difference, % (95% CI)	Aztreonam–avibactam group	Meropenem group	Difference, % (95% CI)	Aztreonam–avibactam group	Meropenem group	Difference, % (95% CI)
ITT analysis set	159/208 (76·4%, 70·3 to 81·8)	77/104 (74·0%, 65·0 to 81·7)	2·4% (–7·4 to 13·0)	34/74 (45·9%, 34·9 to 57·3)	15/36 (41·7%, 26·7 to 57·9)	4·3% (–15·5 to 23·1)	193/282 (68·4%, 62·8 to 73·7)	92/140 (65·7%, 57·6 to 73·2)	2·7% (–6·6 to 12·4)
CE analysis set	143/168 (85·1%, 79·2 to 89·9)	66/83 (79·5%, 69·9 to 87·1)	5·6% (–4·0 to 16·6)	21/45 (46·7%, 32·7 to 61·1)	12/22 (54·5%, 34·3 to 73·7)	–7·9% (–31·9 to 17·3)	164/213 (77·0%, 71·0 to 82·3)	78/105 (74·3%, 65·3 to 81·9)	2·7% (–7·0 to 13·2)

Data are n/N (%, 95% CI) unless otherwise stated. 95% CIs for clinical cure rates were computed using Jeffreys method. CE=clinically evaluable. cIAI=complicated intra-abdominal infection. HAP–VAP=hospital-acquired pneumonia or ventilator-associated pneumonia. ITT=intention-to-treat.

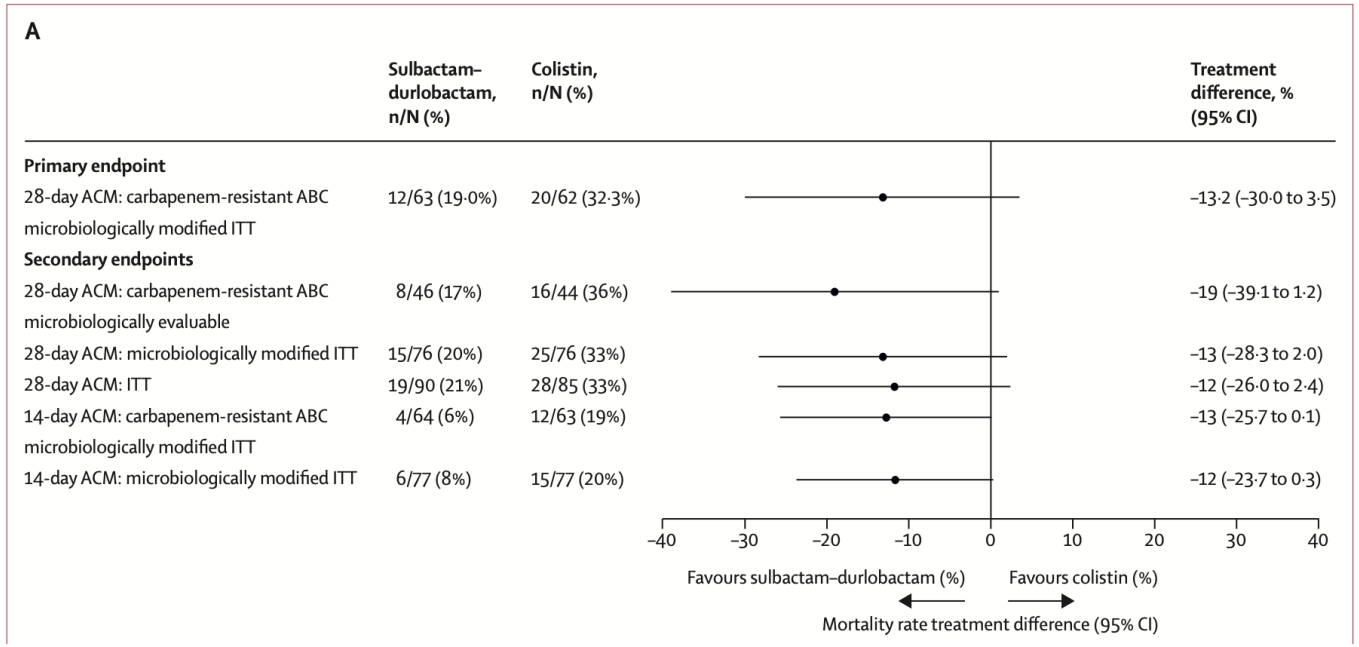
Table 3: **Adjudicated clinical response at the test-of-cure visit**

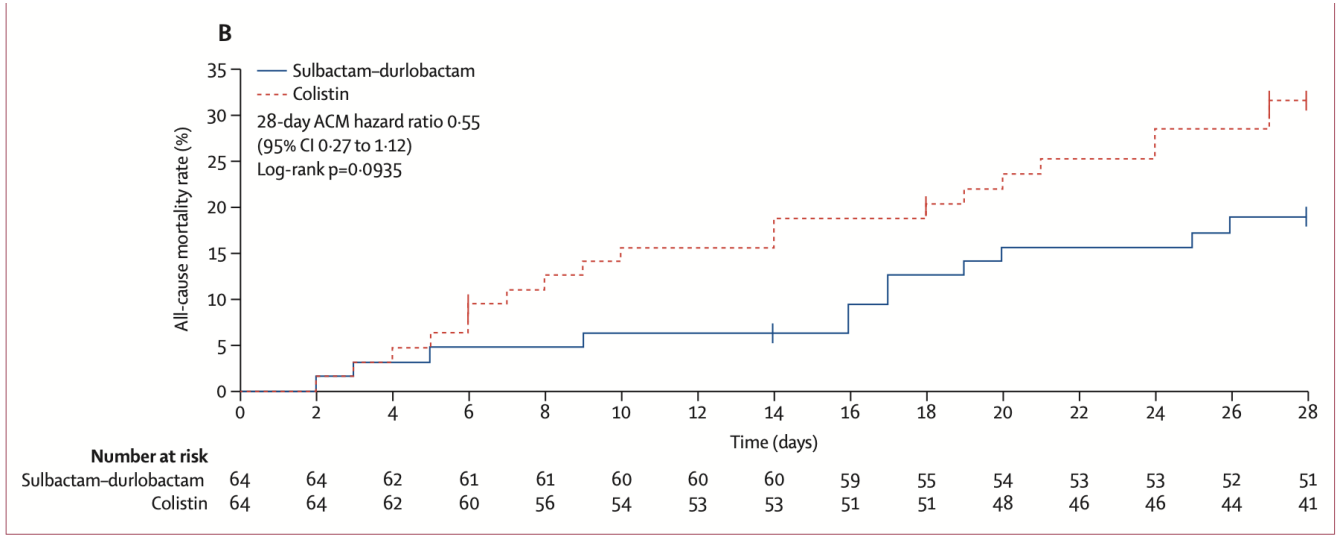
Lancet Infect Dis 2025; 25: 218–30

Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

Keith S Kaye, Andrew F Shorr, Richard G Wunderink, Bin Du, Gabrielle E Poirier, Khurram Rana, Alita Miller, Drew Lewis, John O'Donnell, Lan Chen, Harald Reinhart, Subasree Srinivasan, Robin Isaacs, David Altarac

- 59 sites in 16 countries
- HAP/VAP or BSI with CR-AB
- SUL-DUR vs COL
  - + Imipenem in all
- NI margin 20%
- N=186, 125 confirmed CR-AB
- 28-day mortality
  - 12/63 (19%) SUL-DUR vs. 20/62 (32%) COL
  - **RD –13% (95% CI –30 to 4)**
- Incidence of nephrotoxicity lower (p<0.001)





Lancet Infect Dis 2023; 23: 1072–84

Personalised randomised controlled trial designs—a new paradigm to define optimal treatments for carbapenem-resistant infections

A Sarah Walker, Ian R White*, Rebecca M Turner, Li Yang Hsu, Tsin Wen Yeo, Nicholas J White, Mike Sharland*, Guy E Thwaites**

- AMR trials are compromised by the lack of an agreed "standard of care" (e.g. for CRE, CRAB, *XDR-Pseudomonas* etc) and wide variation in practice
- "BAT" comparators are pragmatic, but highly heterogeneous
- Many reasons comparators can't be used
  - Co-morbidities, resistance / AMR gene profile, contraindications, local availability
- ***The PRACTical design addresses this problem***

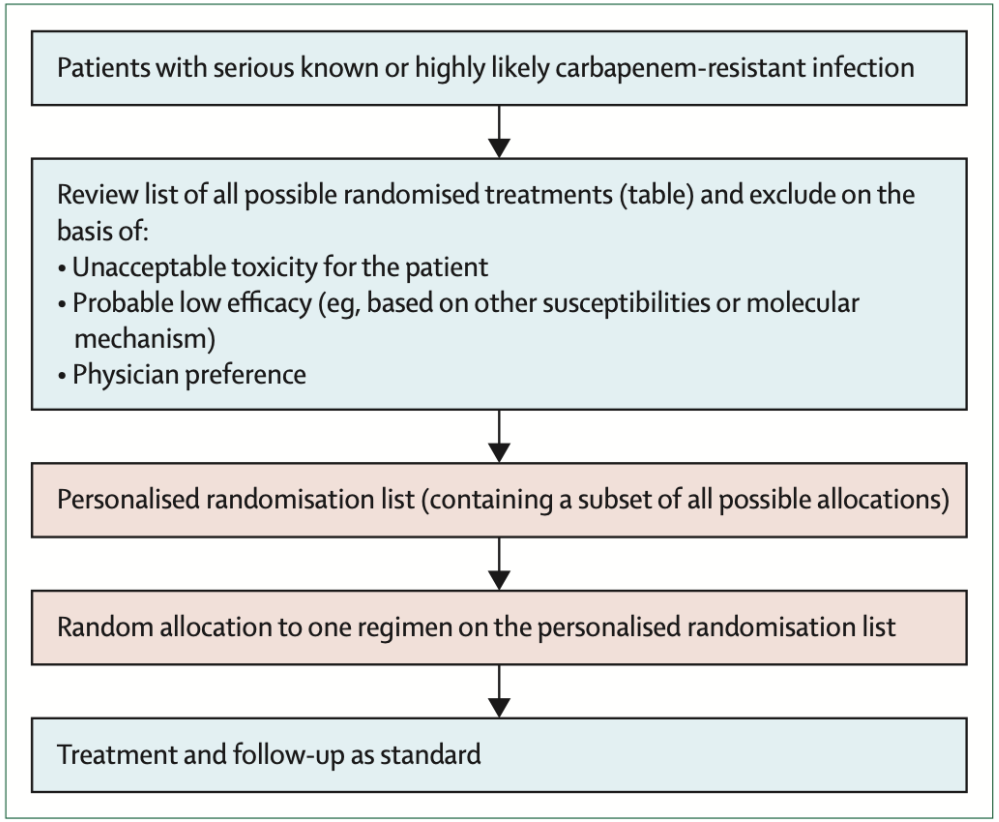


Figure 1: **Proposed flow diagram of participants through the trial**

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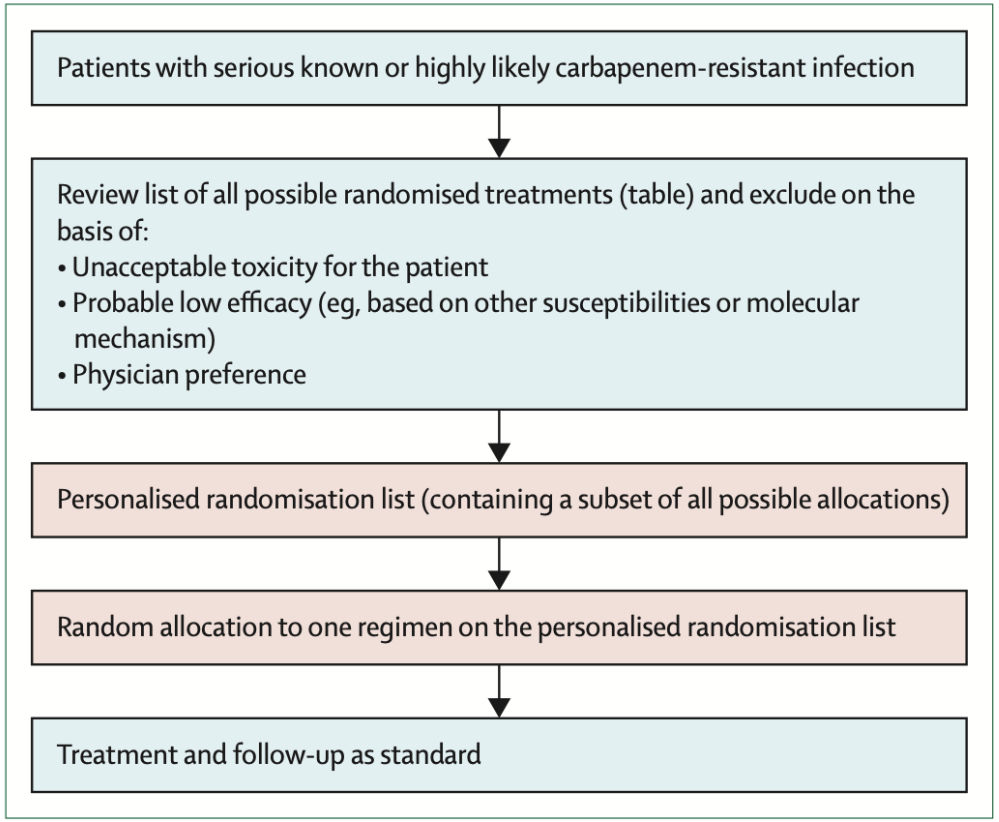

Figure 1: **Proposed flow diagram of participants through the trial**

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	Patient 1: moderate renal impairment (creatinine clearance <40mL/min)	Patient 2: history of myocardial infarction	Patient 3: meropenem MIC ≥64	Patient 4: ventilator-acquired or hospital-acquired pneumonia	Patient 5: *Pseudomonas aeruginosa* infection	Patient 6: known class B (NDM, IMP, VIM) infection	Patient 7: presence of 6S ribosomal RNA methyltransferases (encoding aminoglycoside resistance)*	Patient 8: history of moderate to severe allergy to cephalosporins
~~A: plazomicin~~	No or maybe†	Yes	Yes	Yes	Yes	No	No	Yes
~~B: ceftazidime plus avibactam~~	No or maybe†	Yes	Yes	Yes	Yes	No	Yes	No
C: cefiderocol	Maybe†	Yes	Yes	Yes	Yes	Yes	Yes	No
D: high-dose meropenem‡	Maybe†	Yes	No	Yes	Yes	Yes	Yes	Yes
~~E: polymyxin B with or without zidovudine~~	No or maybe†	Yes	Yes	No	Yes	Yes	Yes	Yes
F: high-dose meropenem‡ plus ertapenem	Maybe†	Yes	No	Yes	No	Yes	Yes	Yes
G: high-dose meropenem‡ plus imipenem	No or Maybe†	Yes	No	Yes	Yes	Yes	Yes	Yes
~~H: high-dose meropenem‡ plus polymyxin B with or without zidovudine~~	No or maybe†	Yes	No	No	Yes	Yes	Yes	Yes
I: high-dose meropenem‡ plus high-dose tigecycline	Maybe†	No	No	Yes	No	Yes	Yes	Yes
J: ~~high-dose meropenem‡ plus fosfomycin~~	Maybe†	Yes	No	Yes	Yes	Yes	Yes	Yes
~~K: high-dose tigecycline§ plus polymyxin B with or without zidovudine~~	No or maybe†	No	Yes	No	No	Yes	Yes	Yes
L: ~~high-dose tigecycline§ plus fosfomycin~~	Maybe†	No	Yes	Yes	No	Yes	Yes	Yes
~~M: fosfomycin plus polymyxin B with or without zidovudine~~	No or maybe†	Yes	Yes	No	Yes	Yes	Yes	Yes

72 yo, with AKI, IMP+ Enterobacter in BCs, UTI source, Mero MIC 8,

IV fosfomycin not available locally

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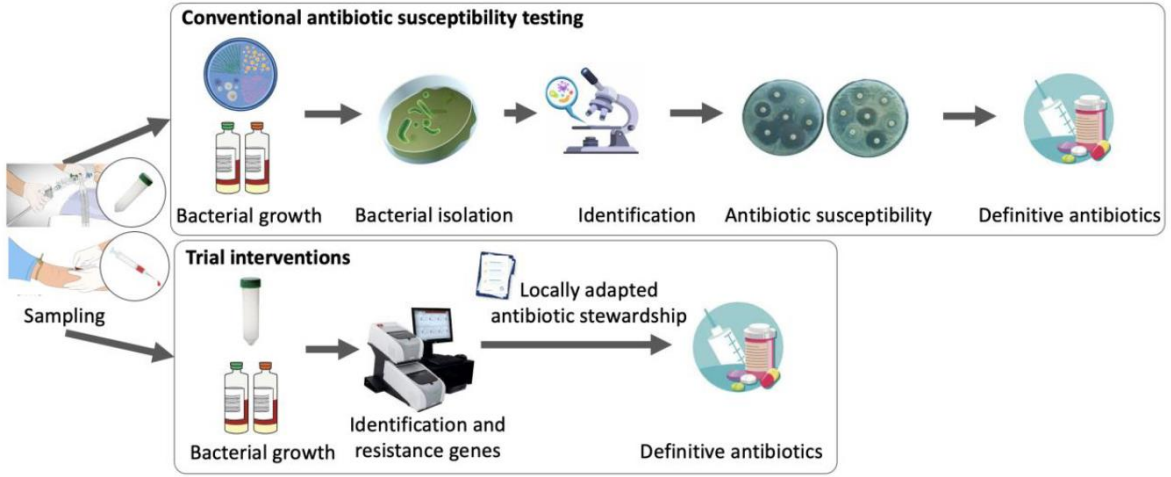
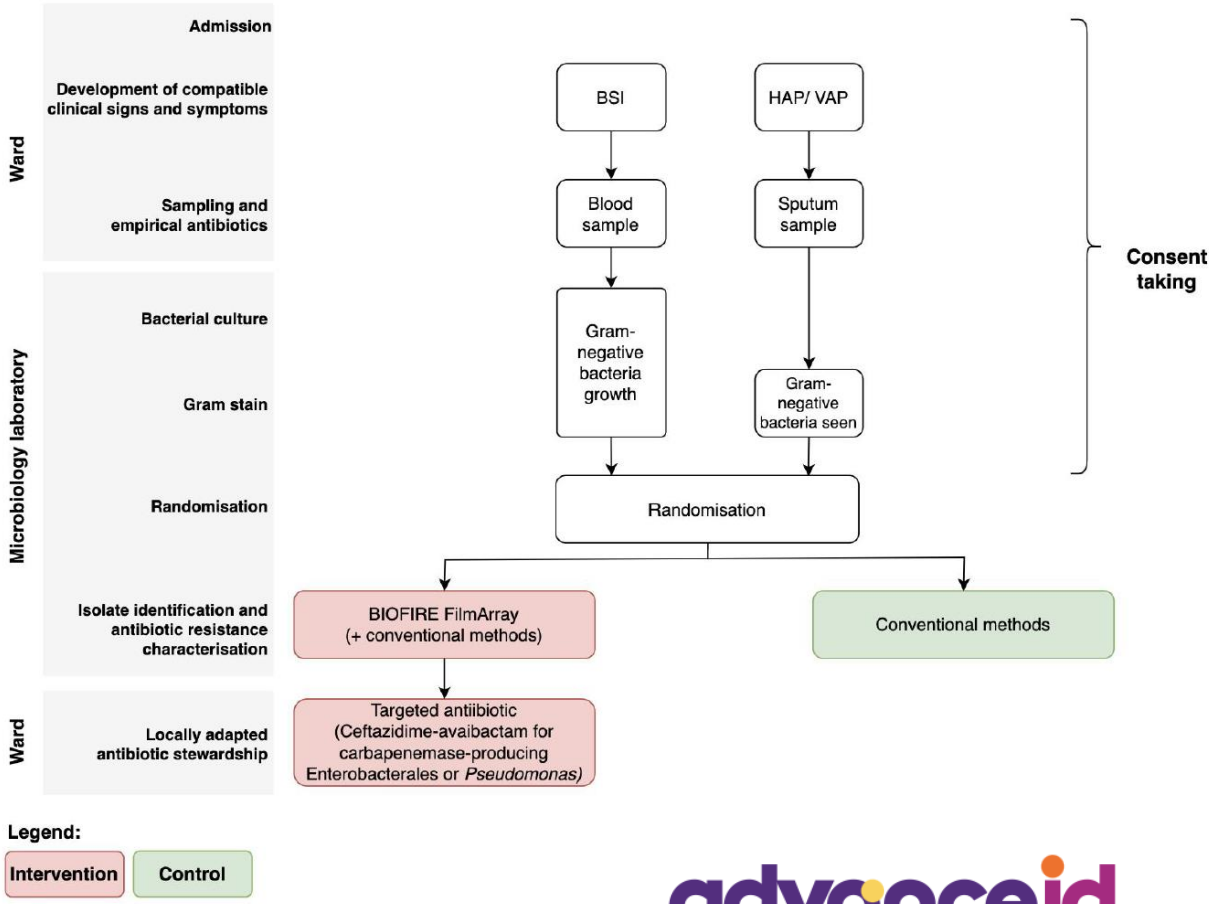
Using rapid diagnostics: RAPID Trial

- CAZ-AVI for OXA-48, KPC and MDR-*Pseudomonas* vs SOC
- Using rapid diagnostics to enhance enrolment for MDR-GNBs with suitable AMR profile
- Measure “bundle” effect of rapid testing and targeted treatment with new drugs





advanceid.

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Several new MDR-GNB trials… but

- Conventional industry trials are essential for registration but rarely (if ever) answer the clinical question for which the need is greatest
- Industry experience with trials specifically targeting AMR pathogens has been disappointing
- **Are more investigator-initiated trials, in the patient populations where these drugs are most useful, the answer?**

Thank you!

p.harris@uq.edu.au

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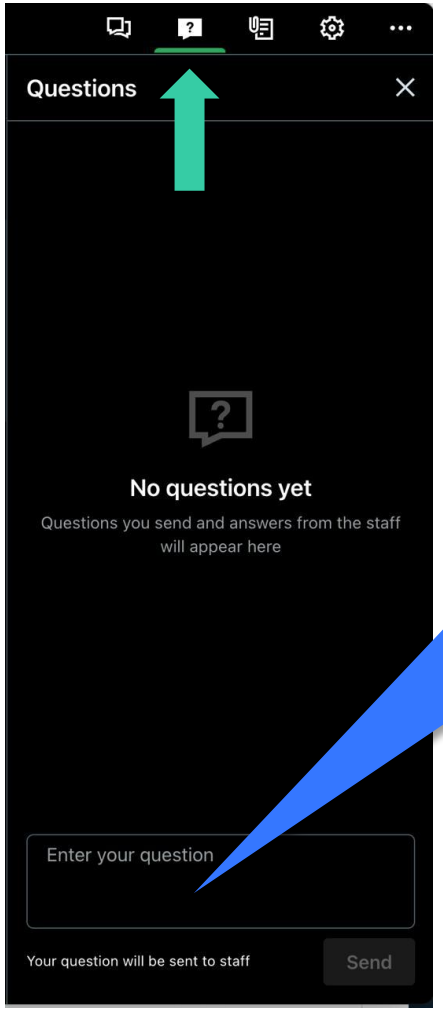
How to submit your questions

REVIVE by GARDP

If your question is addressed to a specific speaker, please include their name when submitting the question.



Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

The next REVIVE webinar will be announced soon!

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Conference

Global AMR Innovators' Conference (GAMRIC), co-organized by GARDP.
The conference organisers are glad to offer 10 travel grants to Early Career Researchers (ECR) and 10 to residents of low- or middle-income country (LMIC).
Registration open until 2nd of June via the website.

https://www.gamric.org/

Thank you for joining us