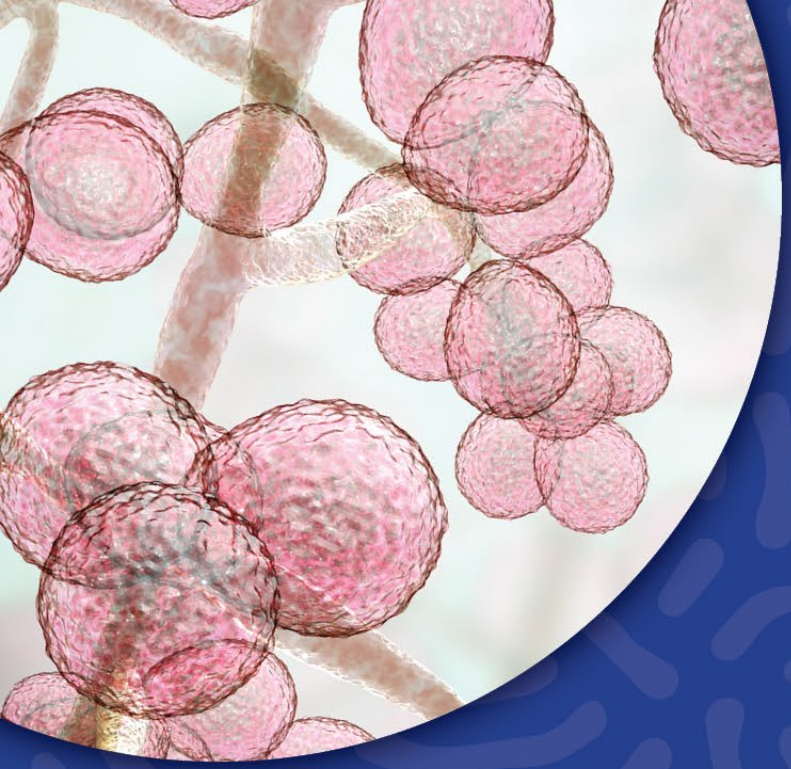

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APHL

2025

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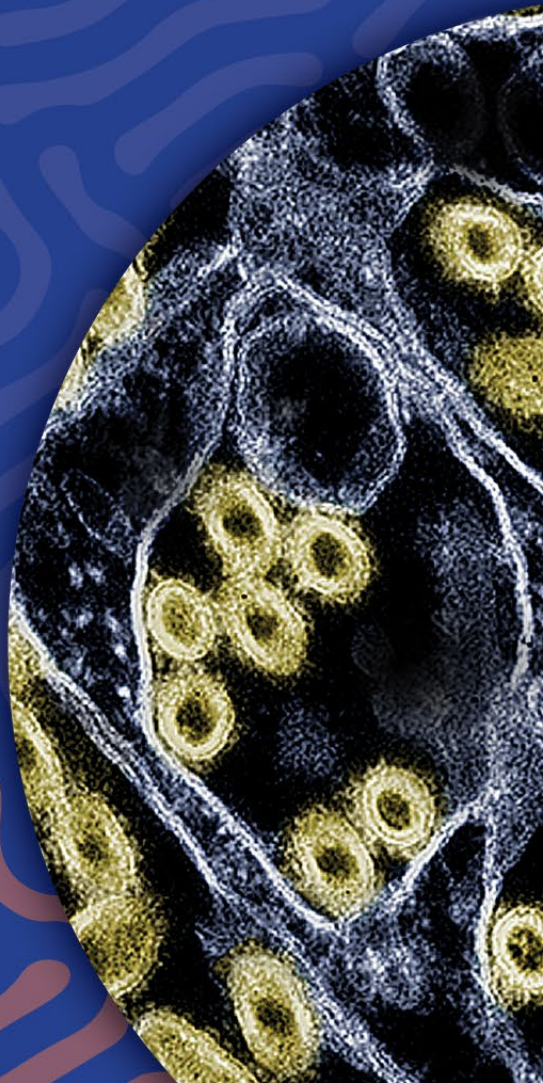


Carbapenem-resistant *Acinetobacter baumannii*

#IDLabCon

Robert Potter, PhD, D(ABMM)

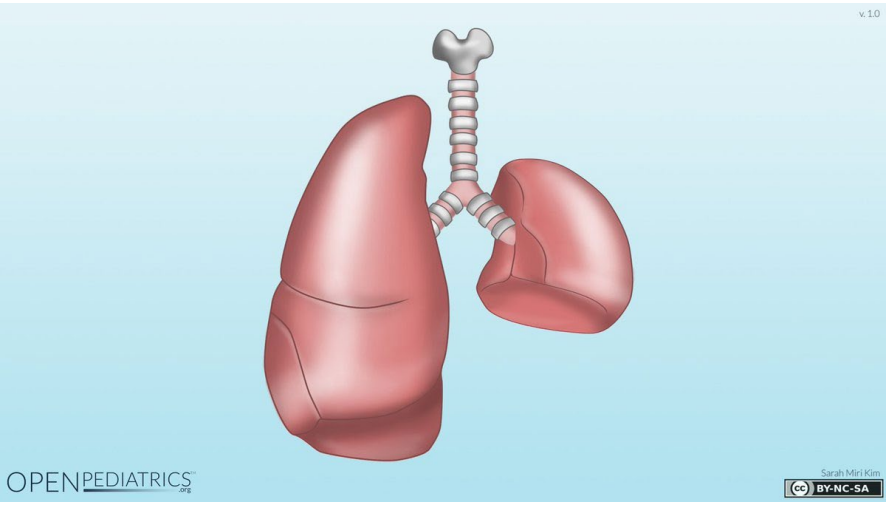
Assistant Director
Infectious Disease Diagnostics Laboratory
Children's Hospital of Philadelphia

Director, Outbreak Investigations
Center for Microbial Medicine
Children's Hospital of Philadelphia

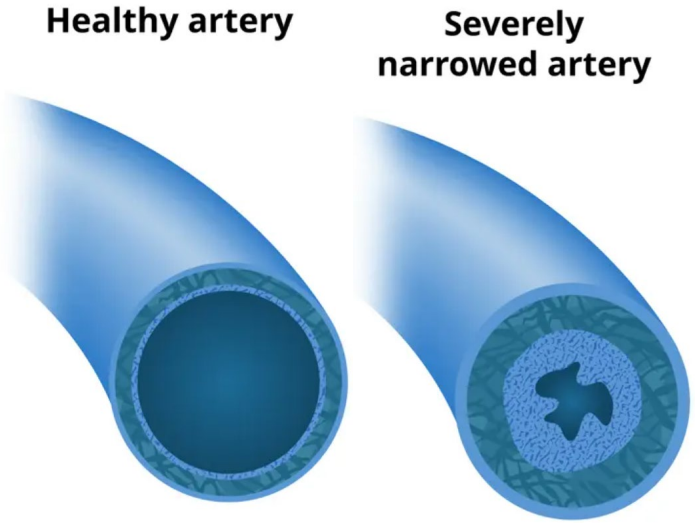
Assistant Professor
Department of Pathology & Laboratory Medicine
The Perelman School of Medicine at the University of Pennsylvania

Patient is a medically complicated four year old with pulmonary problems admitted to CHOP Fall 2024

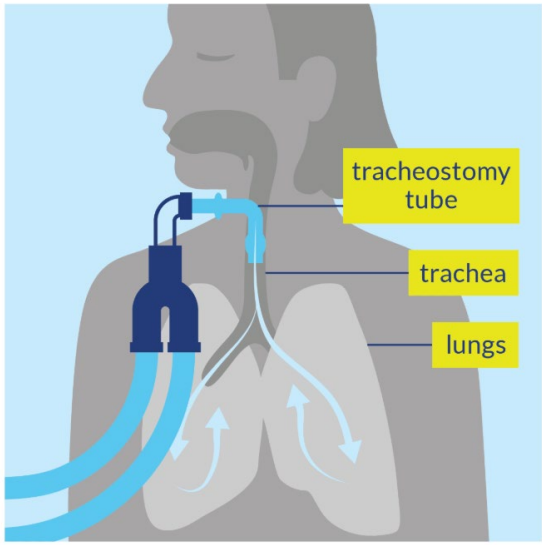
Pulmonary hypoplasia



Pulmonary hypertension

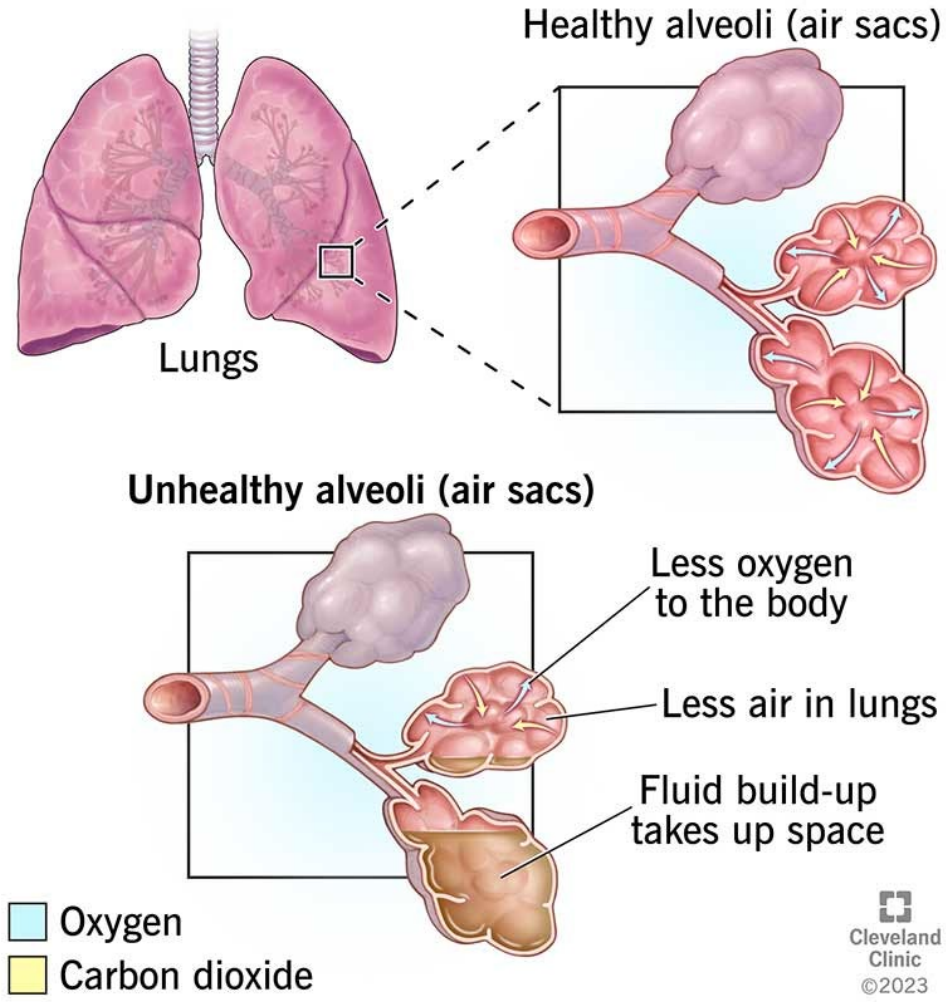


Tracheostomy



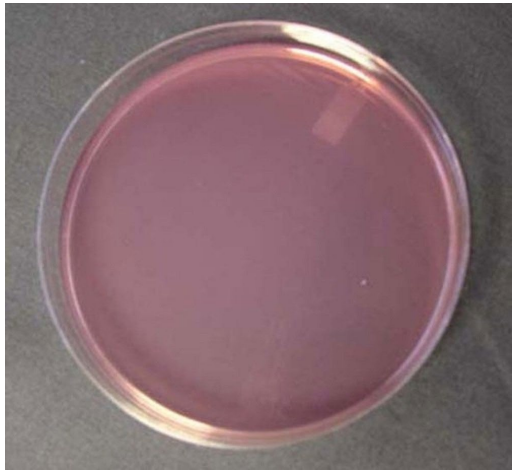
https://scireproject.com/wp-content/uploads/2023/10/MechVent.png
https://www.openpediatrics.org/assets/image/pulmonary-hypoplasia
https://www.gleneagles.com.sg/conditions-diseases/pulmonary-arterial-hypertension/symptoms-causes

Patient has an episode of acute respiratory distress syndrome (ARDS) and endotracheal cultures were obtained



Blood agar

MacConkey agar



Chocolate agar

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Carbapenem resistant *Acinetobacter baumannii* (CRAB) grew from endotracheal aspirate culture

Respiratory Culture

Status: **Final result** Visible to patient: **Yes (not seen)** Next appt: **None**

Specimen Information: Endotracheal aspirate; Respiratory

0 Result Notes

Respiratory culture	Normal respiratory flora present, except: Heavy Growth of Acinetobacter baumannii complex !
Gram Stain	Moderate White blood cells Many Gram negative coccobacilli

Susceptibility

	Acinetobacter baumannii complex MIC	
CEFTAZIDIME	>=64	Resistant
IMIPENEM	>=16	Resistant
AMPICILLIN/SULBACTAM	16.0	Intermediate
MEROPENEM	>=16	Resistant
LEVOFLOXACIN	>=8	Resistant
PIPERACILLIN/TAZOBACTAM	>=128	Resistant
MINOCYCLINE	8.0	Intermediate
DOXYCYCLINE	>=16	Resistant

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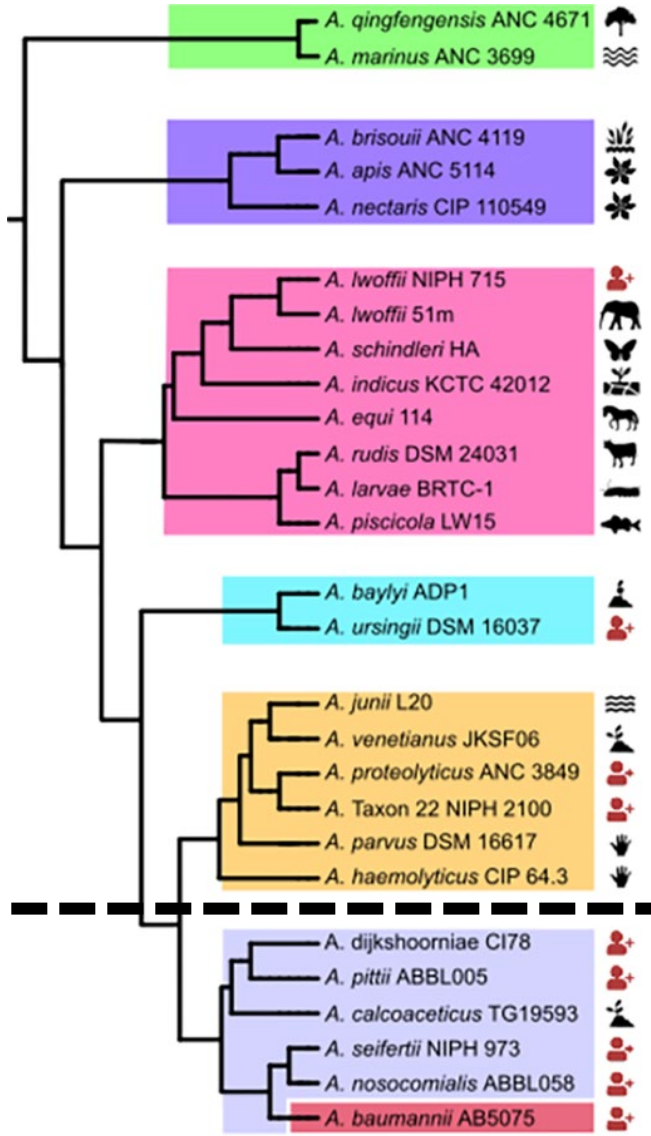
Carbapenem-resistant *Acinetobacter* is an urgent antimicrobial threat in the CDC 2019 AR Threat Report

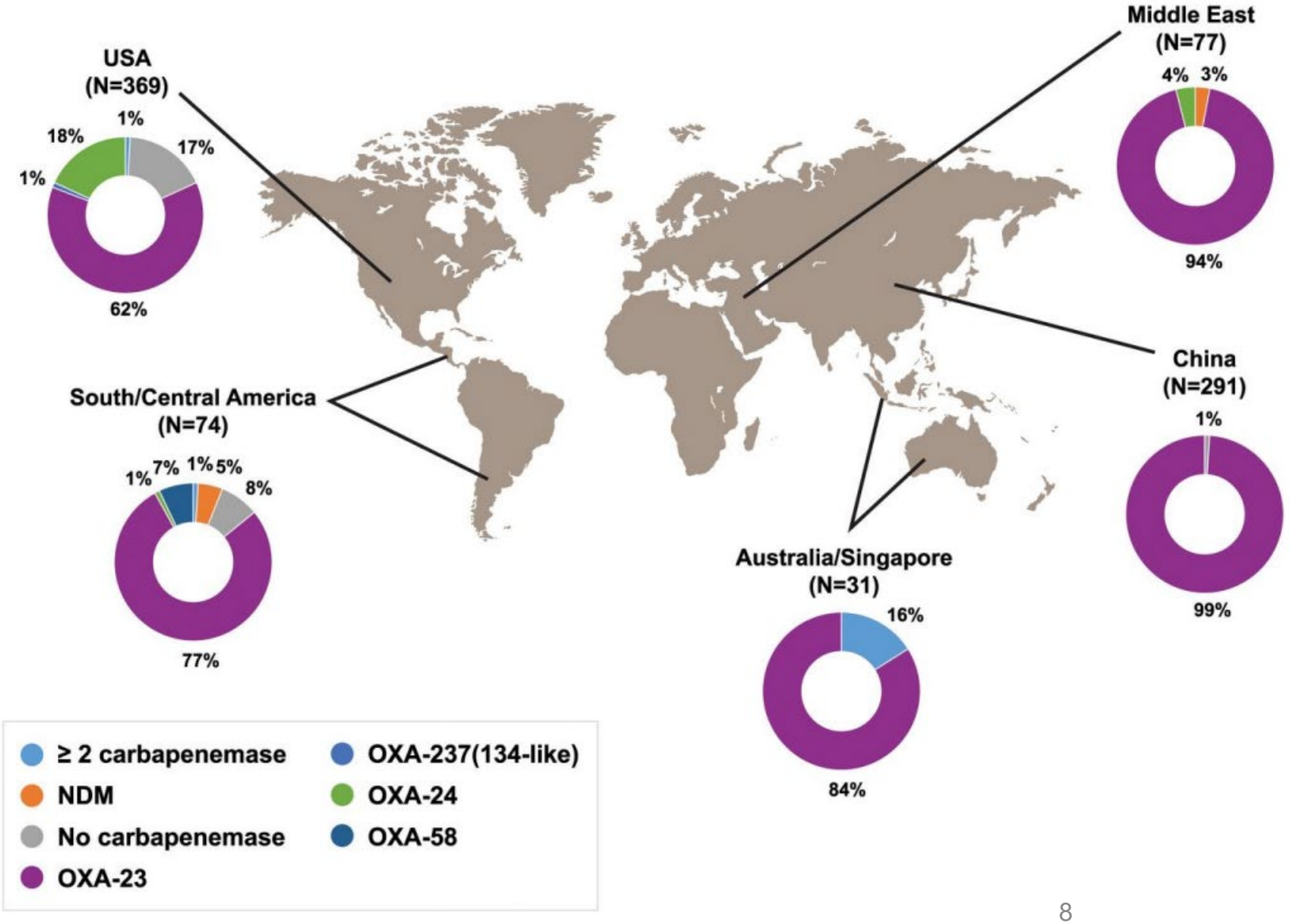
Clinically, species in the *A. baumannii* complex causes most of human disease



A. baumannii complex

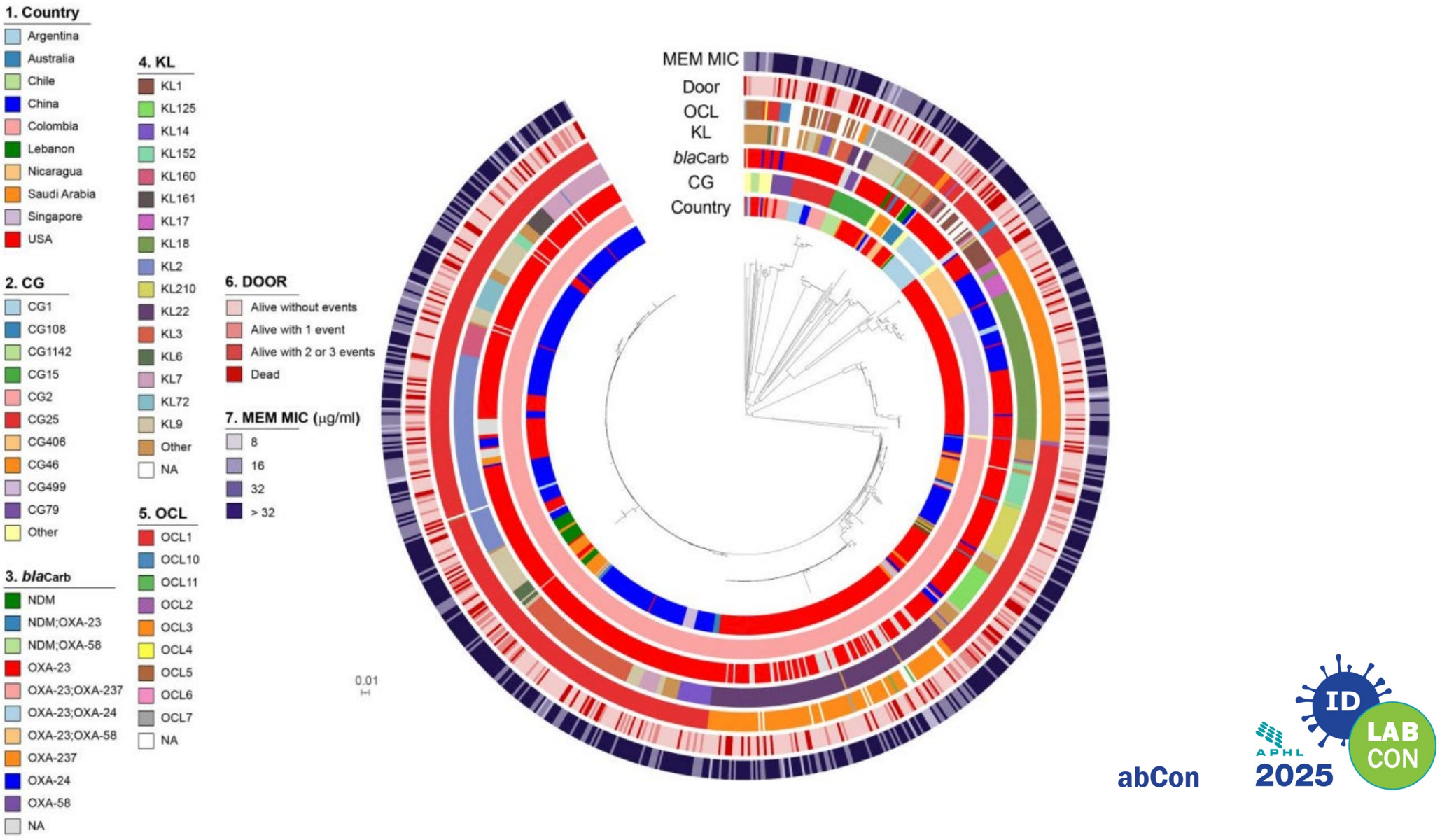
PMID: 35653398

*bla*OXA-23 is largely responsible for spread of CRAB around the globe.



PMID: 37738153

A. baumannii clonal group 2 (CG2) causes majority of CRAB infections in the USA and abroad

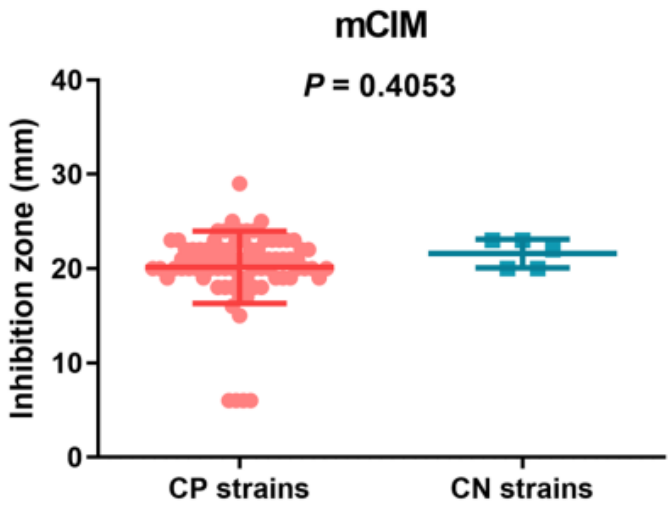


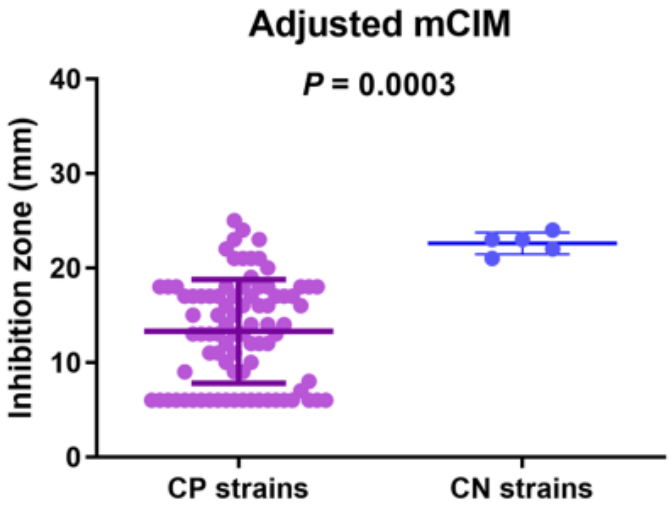
PMID: 37738153

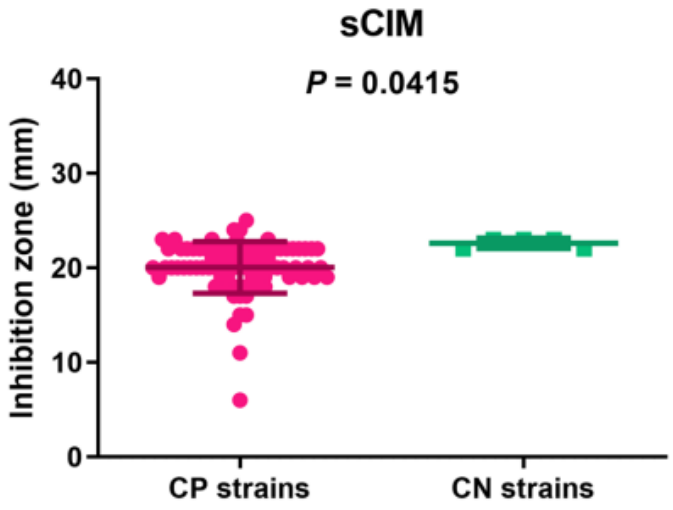
abCon

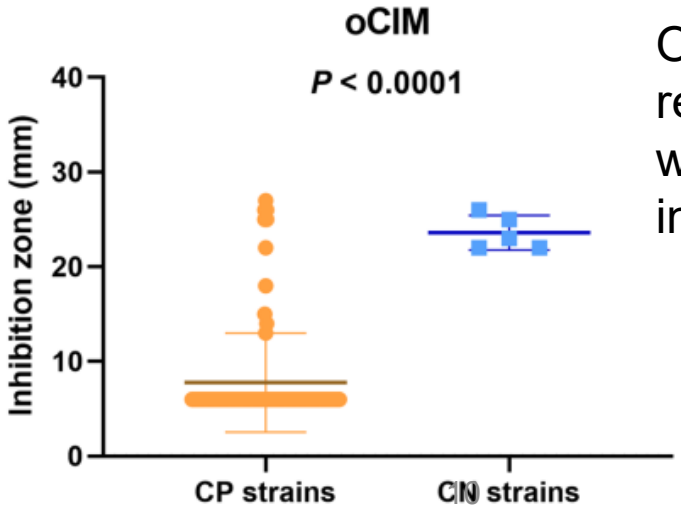
APHL ID LAB CON 2025

Carbapenem inactivation method (CIM) performs poorly against CRAB except the oCIM variation









OD600 of 8, then was resuspended in 200µL TSB, in which the 10µg MEM disk was incubated for 4h

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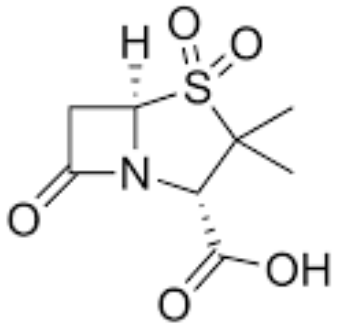
PMID: 37520356

Clinical outcomes from CRAB infections differ based on institutional location

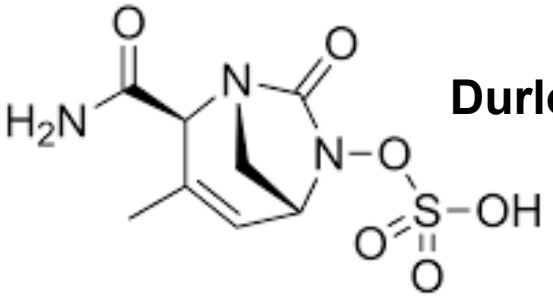
Characteristics	United States (n = 216)	China (n = 219)	South-Central America (n = 49)	Middle East (n = 34)	Australia-Singapore (n = 18)	Total (n = 536)	*P* Value[a]
Mortality[b]							
30-day (primary outcome)	54 (25)	43 (20)	24 (49)	6 (18)	1 (6)	128 (24)	.0001
Risk difference (vs United States, 95% CI)	…	−5 (−13 to 2)	24 (9–39)	−7 (−19 to 9)	−20 (−28 to 1)	…	…
90-day	65 (30)	49 (22)	26 (53)	10 (29)	6 (33)	156 (29)	.0009
Risk difference (vs United States, 95% CI)	…	−8 (−16 to 1)	23 (8–38)	−1 (−15 to 17)	3 (−15 to 27)	…	…
Length of hospital stay from index culture	9 (4–18)	15 (7–24)	15 (7–28)	34 (6–62)	33 (14–43)	12 (5–24)	<.0001
DOOR outcome at 30 d[c] (Supplementary Figure 3)							
Alive without events	74 (34)	79 (36)	9 (18)	7 (21)	2 (11)	171 (32)	…
Alive with 1 event	60 (28)	63 (28)	6 (12)	7 (21)	6 (33)	142 (26)	…
Alive with 2 or 3 events	28 (13)	35 (16)	10 (20)	14 (41)	9 (50)	96 (18)	…
Death	54 (25)	43 (20)	24 (49)	6 (18)	1 (6)	128 (24)	…
DOOR probability % (vs United States, 95% CI)	…	52 (47–57)	34 (26–43)	43 (34–52)	43 (34–53)	…	…
Disposition after discharge	…	…	…	…	…	…	<.0001
Home	31 (14)	72 (33)	17 (35)	21 (62)	9 (50)	150 (28)	…
Long-term care facility	64 (30)	3 (1)	0 (0)	0 (0)	2 (11)	69 (13)	…
Long-term acute care	46 (21)	2 (1)	1 (2)	0 (0)	1 (6)	50 (9)	…
Transfer to another hospital	8 (4)	72 (33)	3 (6)	1 (3)	1 (6)	85 (16)	…
Hospice	22 (10)	21 (10)	3 (6)	0 (0)	0 (0)	46 (9)	…
Death	44 (20)	49 (22)	25 (51)	11 (32)	4 (22)	133 (25)	…
Transfer to a foreign country	1 (0)	0 (0)	0 (0)	1 (3)	1 (6)	3 (1)	…
Clinical response	107 (50)	86 (39)	12 (24)	13 (38)	6 (33)	224 (42)	.013

PMID: 37738153

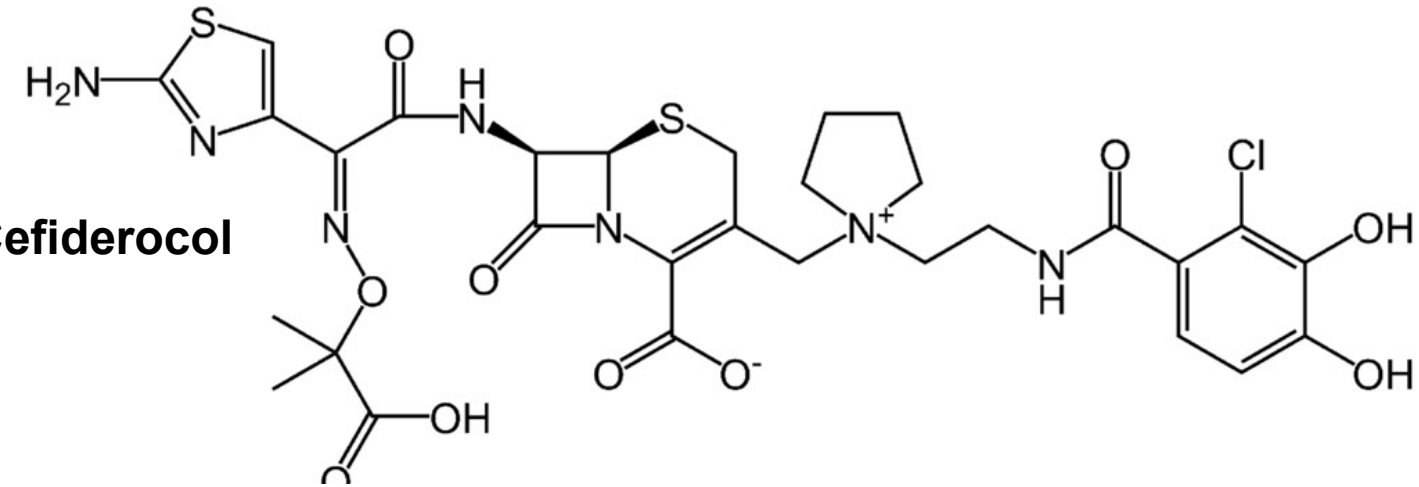
Sulbactam-Durlobactam and Cefiderocol are two options for treating CRAB infections, often compared to Colistin



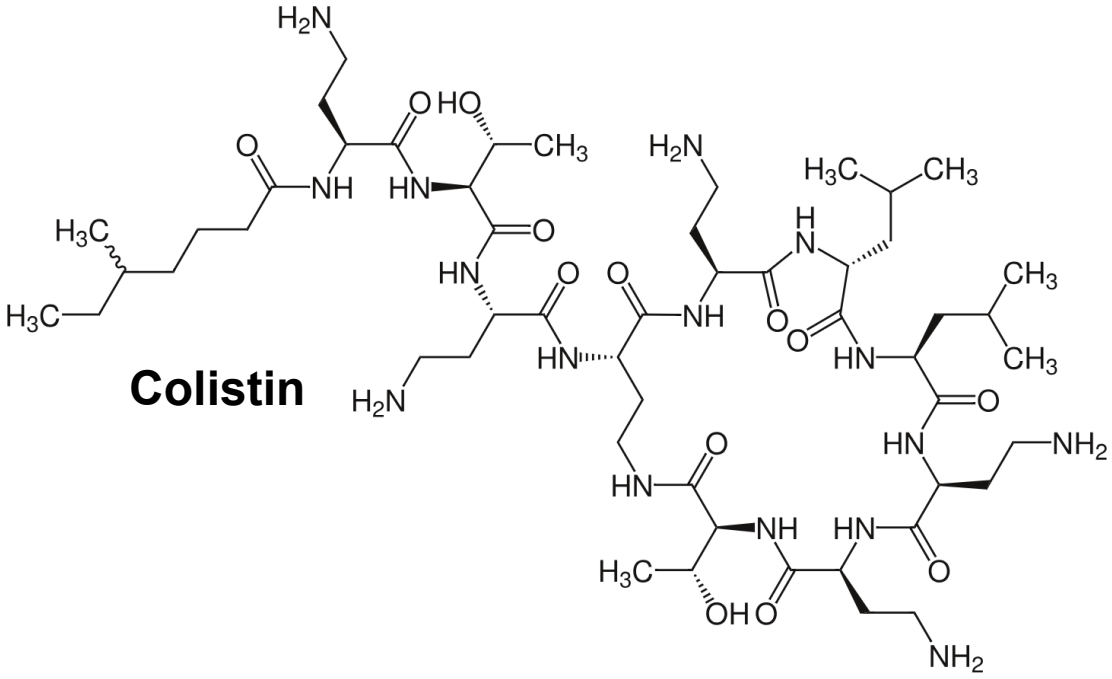
Sulbactam



Durlobactam



Cefiderocol



Colistin

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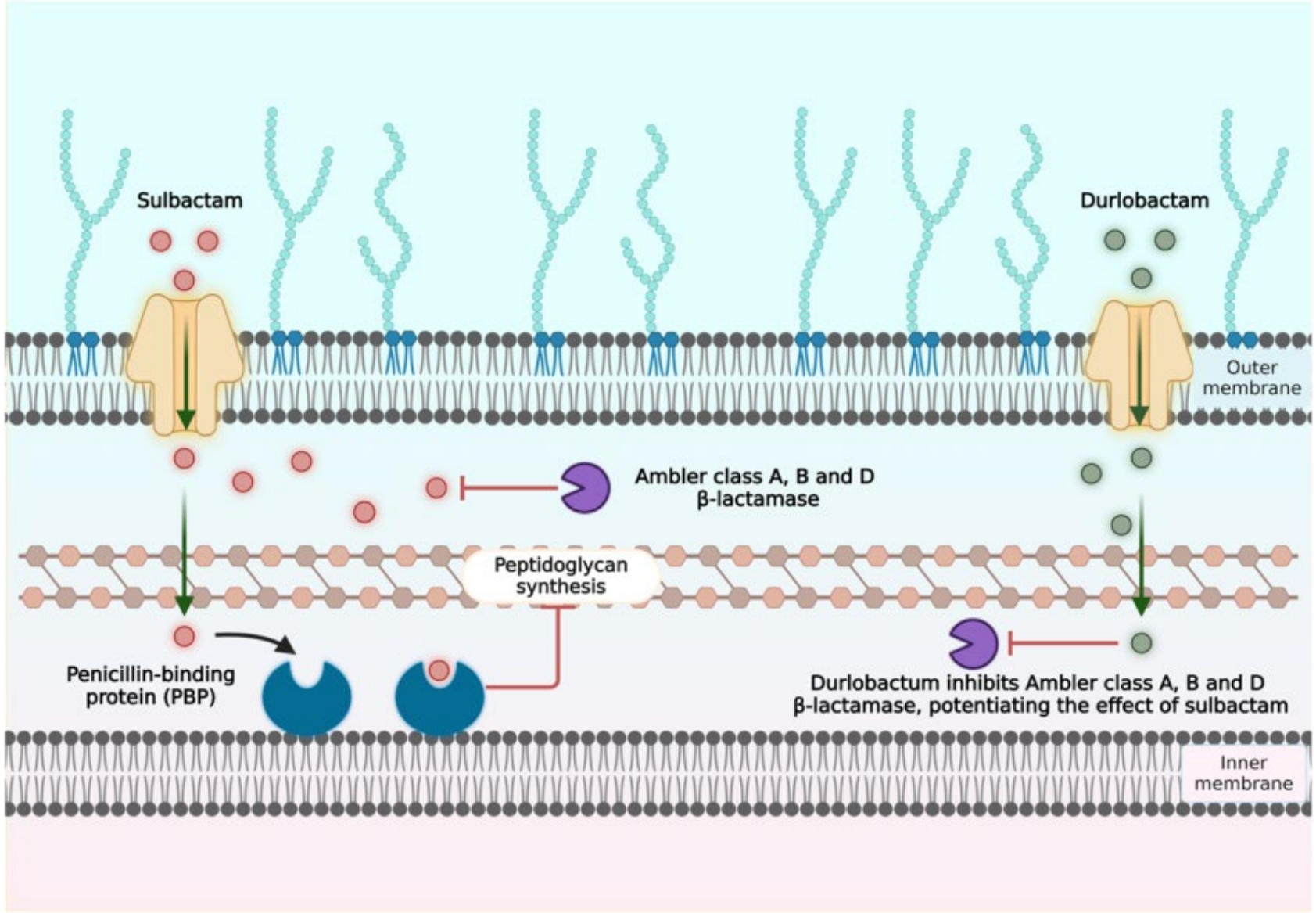
Sulbactam acts as a β-lactam antibiotic to inhibit PBPs while Durlobactam inhibits β-lactamase activity



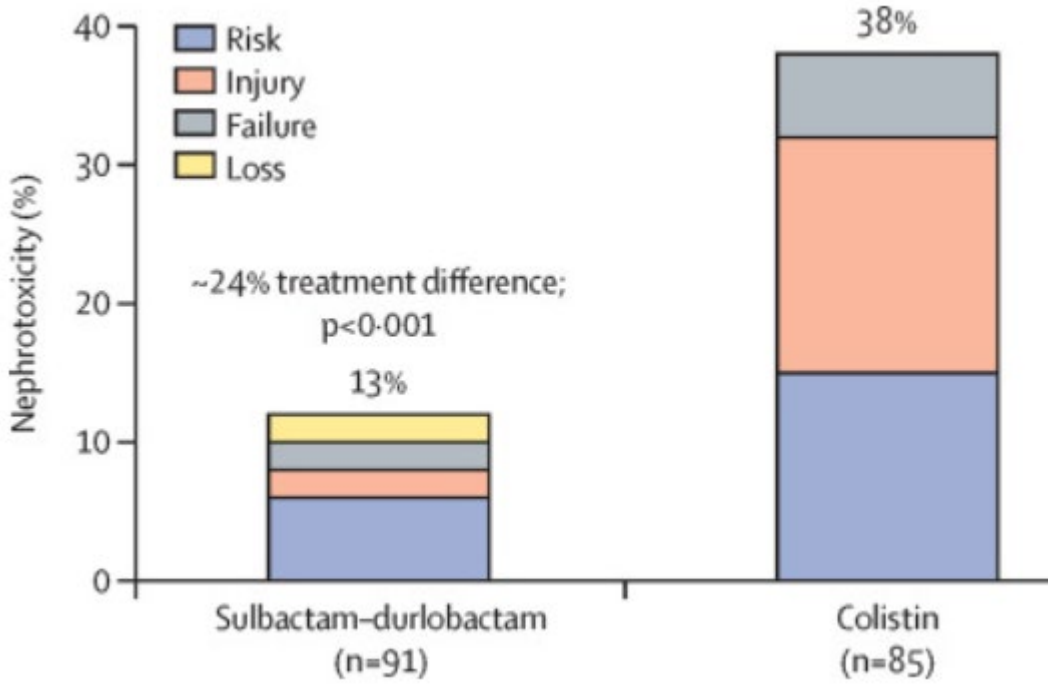
PMID: 39257909

ATTACK study found that Sulbactam-durlobactam had a lower incidence of nephrotoxicity compared to colistin

THE LANCET
Infectious Diseases

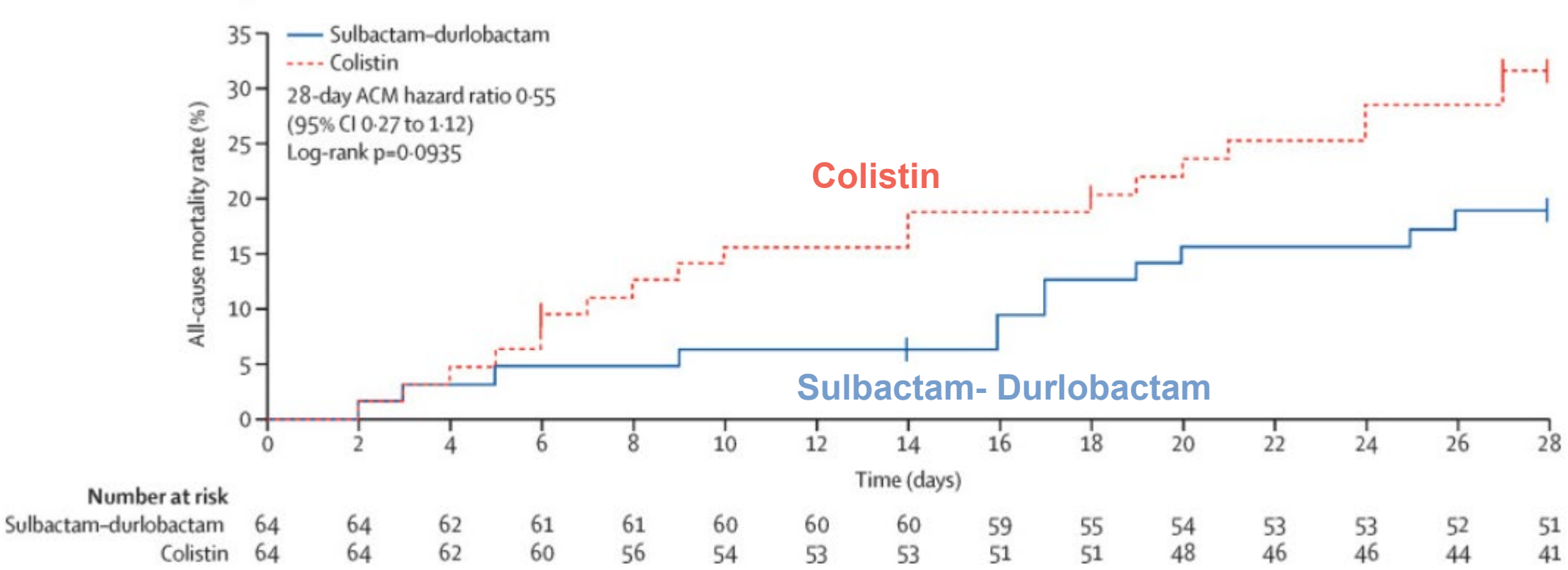
Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

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



PMID: 37182534

Sulbactam-durlobactam had a lower all-cause mortality compared to colistin in a multicenter CRAB study



PMID: 37182534

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January 2024 Clinical Laboratory Standards Institute (CLSI) released breakpoints for Sulbactam-durlobactam testing

AST News Update January 2024: Sulbactam-Durlobactam: The "double beta-lactamase inhibitor" drug

1/22/2024

MIC Breakpoints (µg/mL)			Disk Breakpoints (mm)		
S	I	R	S	I	R
≤4/4	8/4	≥16/4	≥17	14-16	≤13

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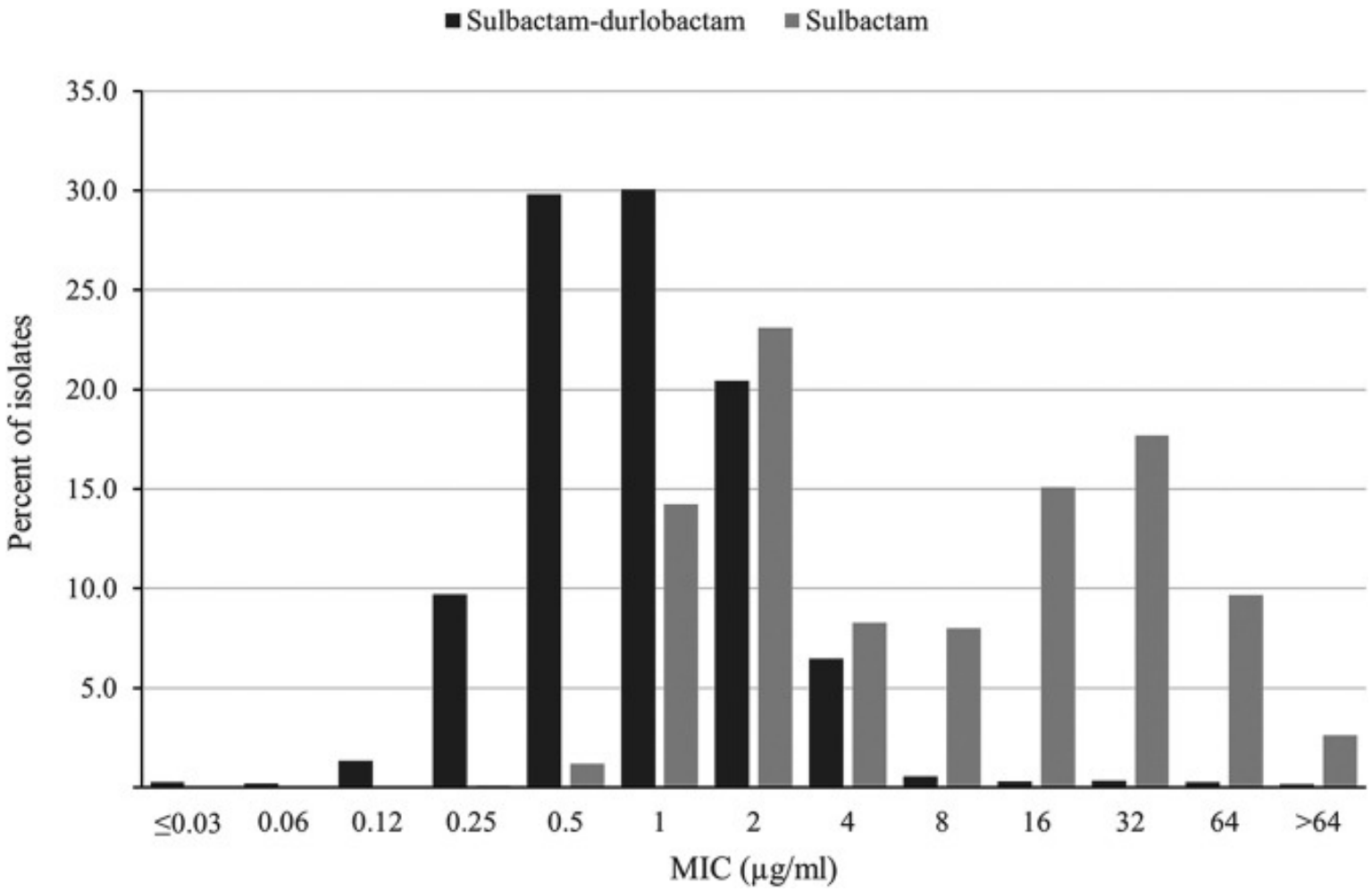
1.7% (84/5,032) *Acinetobacter* isolates showed resistance to sulbactam-durlobactam from a global cohort



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PMID: 36005804

86% (31/36) of *Acinetobacter* isolates are susceptible to meropenem at CHOP 2024 year

Organism	Number of isolates	Ampicillin	Ampicillin-sulbactam	Piperacillin-tazobactam[2]	Cefazolin	Ceftriaxone	Ceftazidime	Cefepime[2]	Ertapenem	Imipenem-cilastatin	Meropenem	Gentamicin	Tobramycin	Amikacin	Ciprofloxacin	Levofloxacin	Trimethoprim-sulfamethoxazole	Doxycycline	Minocycline	Nitrofurantoin[6]	Aztreonam
Acinetobacter spp.	36		91				75			84	86	84	88	93		81	91	87	93		

PMID: 36005804

Meta-analysis of resistance reports finds that *bla*NDM-1 harboring strains are resistant

Antimicrobial activity of sulbactam/durlobactam against *Acinetobacter* tested isolates.

Isolates Characteristics	Susceptible to SUL/DUR (%)	Resistant to SUL/DUR (%)
A. baumannii complex (n = 9754)	9530 (97.7%)	224 (2.3%)
CRAB (n = 5812)	5614 (96.6%)	198 (3.4%)
Colistin-resistant (n = 507)	488 (96.2%)	19 (3.7%)
NDM-1 producers (n = 28)	0 (0%)	28 (100%)

PMID: 36551450

IDSA guidelines support sulbactam containing treatment regimes for CRAB infection

Clinical Infectious Diseases

IDSA GUIDELINES

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1] Emily L. Heil,[2] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

[1]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Department of Practice, Sciences, and Health-Outcomes Research, University of Maryland School of Pharmacy, Baltimore, Maryland, USA; [3]Department of Pharmacy, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire, USA; [4]Departments of Medicine and Pathology, University of Virginia, Charlottesville, Virginia, USA; [5]Department of Medicine, Weill Cornell Medicine, New York, New York, USA; and [6]Medical Service and Center for Antimicrobial Resistance and Epidemiology, Louis Stokes Cleveland Veterans Affairs Medical Center, University Hospitals Cleveland Medical Center and Departments of Medicine, Pharmacology, Molecular Biology, and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA

Question 5.1: What is the general approach for the treatment of infections caused by CRAB?

Suggested approach: The use of an antibiotic regimen which includes a sulbactam-containing agent is suggested for the treatment of CRAB infections. The preferred regimen is sulbactam-durlobactam in combination with a carbapenem (i.e., imipenem-cilastatin or meropenem). An alternative regimen is high-dose ampicillin-sulbactam (total daily dose of 9 grams of the sulbactam component) in combination with at least one other agent (i.e., polymyxin B, minocycline > tigecycline, or cefiderocol), if sulbactam- durlobactam is not available.

Patient treated with intravenous sulbactam-durlobactam and meropenem for 10 days

Clinical Infectious Diseases

IDSA GUIDELINES

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1] Emily L. Heil,[2] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

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"600 mg (25 mg/kg/DOSE), Intravenous, EVERY 6 HOURS, 17 doses, Administer over 3 Hours"

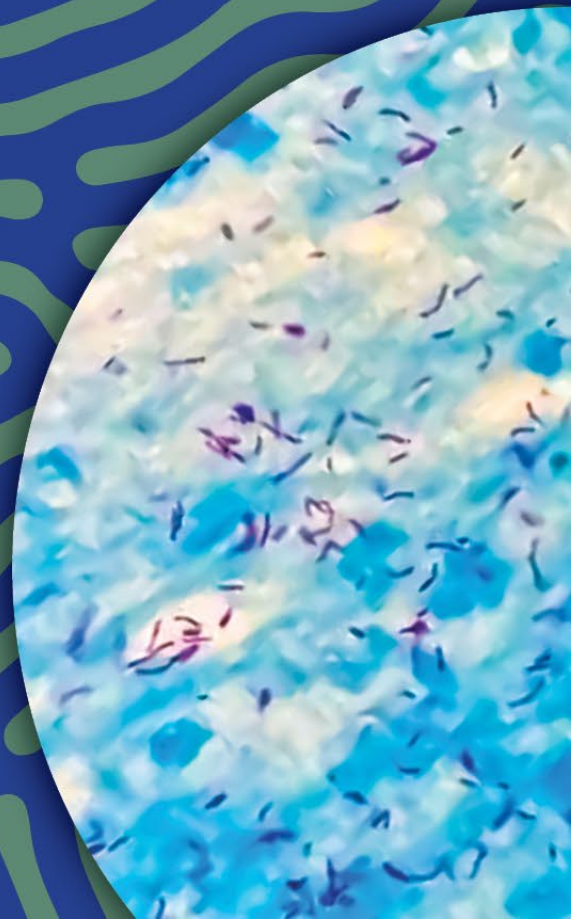
ARDS resolved and no new cultures have grown the CRAB

Question 5.1: What is the general approach for the treatment of infections caused by CRAB?

Suggested approach: The use of an antibiotic regimen which includes a sulbactam-containing agent is suggested for the treatment of CRAB infections. The preferred regimen is sulbactam-durlobactam in combination with a carbapenem (i.e., imipenem-cilastatin or meropenem). An alternative regimen is high-dose ampicillin-sulbactam (total daily dose of 9 grams of the sulbactam component) in combination with at least one other agent (i.e., polymyxin B, minocycline > tigecycline, or cefiderocol), if sulbactam- durlobactam is not available.

Conclusions

-CRAB is an urgent antimicrobial threat
-primarily mediated by blaOXA-23
-may phenotypically test CIA negative
-Sulbactam containing regimes are recommended by IDSA
-Sulbactam/Durlobactam shows strong *in vitro* activity against *A. baumannii*



Shigella spp.

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Robert Potter, PhD, D(ABMM)

Assistant Director
Infectious Disease Diagnostics Laboratory
Children's Hospital of Philadelphia

Director, Outbreak Investigations
Center for Microbial Medicine
Children's Hospital of Philadelphia

Assistant Professor
Department of Pathology & Laboratory Medicine
The Perelman School of Medicine at the University of Pennsylvania

Patient is a previously healthy 6 year old

- Presents to CHOP ED with vomiting, diarrhea, fever, headache, abdominal pain
- Previous travel to Guatemala (1 week ago) where several cousins were confirmed to have Dengue
- ID consulted in ED and recommended infectious stool testing

Stool Culture

No Aeromonas or Plesiomonas isolated

Growth of Shigella sonnei !

Sent to reference lab for further testing: Philadelphia Department of Health Bureau of Laboratory Services. Phone: 215-685-6748. See Miscellaneous Sendout Order (MSO) for additional results.

Resulting Agency: Children's Hospital of Philadelphia UC Laboratory

Susceptibility

	Shigella sonnei MIC	
CIPROFLOXACIN	0.5	Intermediate
CEFTRIAXONE	<=0.25	**Sensitive**
TRIMETHOPRIM/SULFA		Resistant
AMPICILLIN	<=2	**Sensitive**

CDC defines four demographics at risk for shigellosis

Who is at risk

Some groups of people are more likely to get sick with shigellosis than others.

- Children younger than 5 years old are the most likely to get shigellosis, but people of all ages can get the disease. Many outbreaks occur in early care and education settings and schools.
- Travelers to places where water and food may be unsafe and sanitation is poor are more likely to get a *Shigella* infection. They are also more likely to become sick with types of *Shigella* that are more difficult to treat.
- Gay, bisexual, and other men who have sex with men* (GBMSM) have factors that put them at increased risk for *Shigella* infection. Although rates are higher among GBMSM, the risk is present for any sexual activity involving stool exposure.
- People who are experiencing homelessness are at high risk for *Shigella* infection when there is shigellosis spread in the community. They may face challenges in their living situations that increase the risk for disease transmission, which can result in outbreaks.

Shigella (and other causes of bacterial gastroenteritis) can be diagnosed by culture or nucleic acid testing

Etiologic Agent	Diagnostic Procedures	Optimal Specimen
Clostridium difficile	NAAT	Stool
	GDH antigen with or without toxin detection followed by cytotoxin or *Clostridium difficile* toxin or toxigenic *C. difficile* strain	
Salmonella enterica, *Shigella* spp, *Campylobacter* spp	Routine stool enteric pathogen culture[a] or NAAT	Stool
Salmonella enterica serovars Typhi and Paratyphi (enteric fever)	Routine culture	Stool, blood, bone marrow, and duodenal fluid
Shiga toxin–producing *Escherichia coli*	Culture for *E. coli* O157:H7[b] and Shiga toxin immunoassay or NAAT for Shiga toxin genes	Stool
Yersinia spp, *Plesiomonas* spp, *Edwardsiella tarda*, *Staphylococcus aureus*, *E. coli* (enterotoxigenic, enteroinvasive, enteropathogenic, enteroaggregative)	Specialized stool culture or molecular assays[c] or NAAT	Stool

Children's Hospital of Philadelphia
Pathology & Laboratory Medicine

GI bacterial panel/Stool culture

Methodology

Amplification and detection of Salmonella, Shigella, Campylobacter and Shiga-like toxin 1 & 2 (includes *E.coli* 0157) DNA by Real-Time PCR; detection of *Aeromonas* and *Plesiomonas* by conventional culture.

Syndromic PCR panels for gastrointestinal disease have increased presence within clinical laboratories

BIOMÉRIEUX

BIOFIRE® FILMARRAY®

Gastrointestinal (GI) Panel

BACTERIA

Campylobacter (C. jejuni / C. coli / C. upsaliensis)

Clostridioides (Clostridium) difficile (toxin A/B)

Plesiomonas shigelloides

Salmonella

Yersinia enterocolitica

Vibrio (V. parahaemolyticus / V. vulnificus / V. cholerae)

Vibrio cholerae

DIARRHEAGENIC ESCHERICHIA COLI/SHIGELLA

Enteroaggregative E. coli (EAEC)

Enteropathogenic E. coli (EPEC)

Enterotoxigenic E. coli (ETEC) *lt/st*

Shiga-like toxin-producing E. coli (STEC) *stx1/stx2*

E. coli O157

Shigella/Enteroinvasive E. coli (EIEC)

PARASITES

Cryptosporidium

Cyclospora cayetanensis

Entamoeba histolytica

Giardia lamblia

VIRUSES

Adenovirus F40/41

Astrovirus

Norovirus GI/GII

Rotavirus A

Sapovirus (I, II, IV, and V

BD

BD MAX™ Enteric Bacterial Panel

Salmonella spp., *Shigella* spp./EIEC, *Campylobacter* spp. (*jejuni* and *coli*)
Shiga toxin-producing organisms (STEC, *Shigella dysenteriae*)

QIAGEN

Bacteria

- *Campylobacter (C. jejuni, C. coli and C. upsaliensis)*
- *Shigella*/Enteroinvasive *Escherichia coli* (EIEC)
- Enteropathogenic *Escherichia coli* (EPEC)*
- Enterotoxigenic *Escherichia coli* (ETEC) lt/st
- Shiga-like toxin-producing Escherichia *coli* (STEC) stx1/stx2 (including specific identification of *E. coli* O157 serogroup within STEC)*
- *Salmonella*
- *Plesiomonas shigelloides*
- *Yersinia enterocolitica*

Viruses

Parasites

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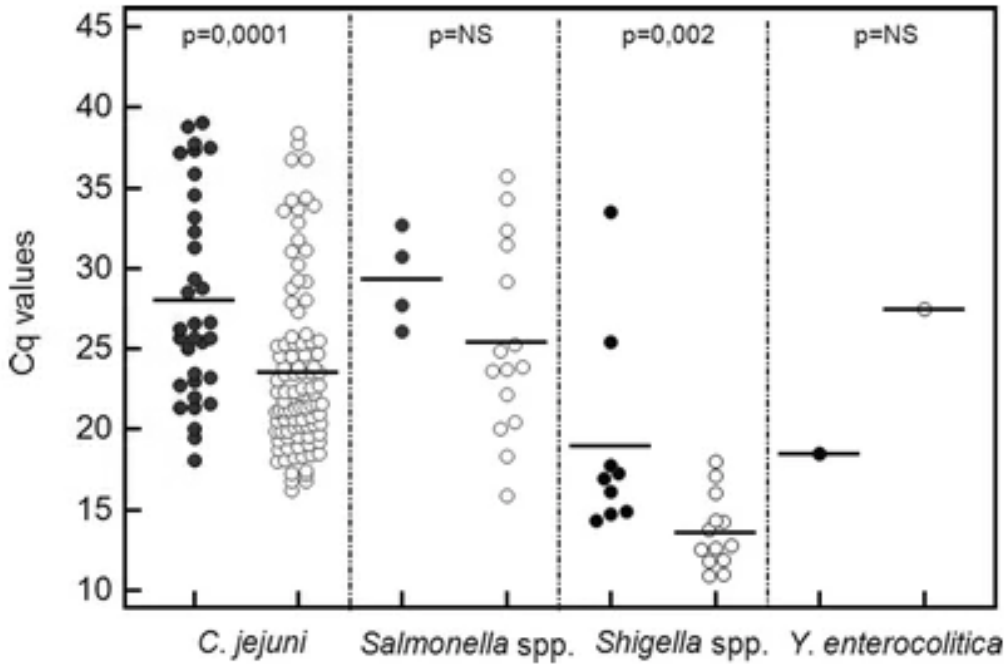
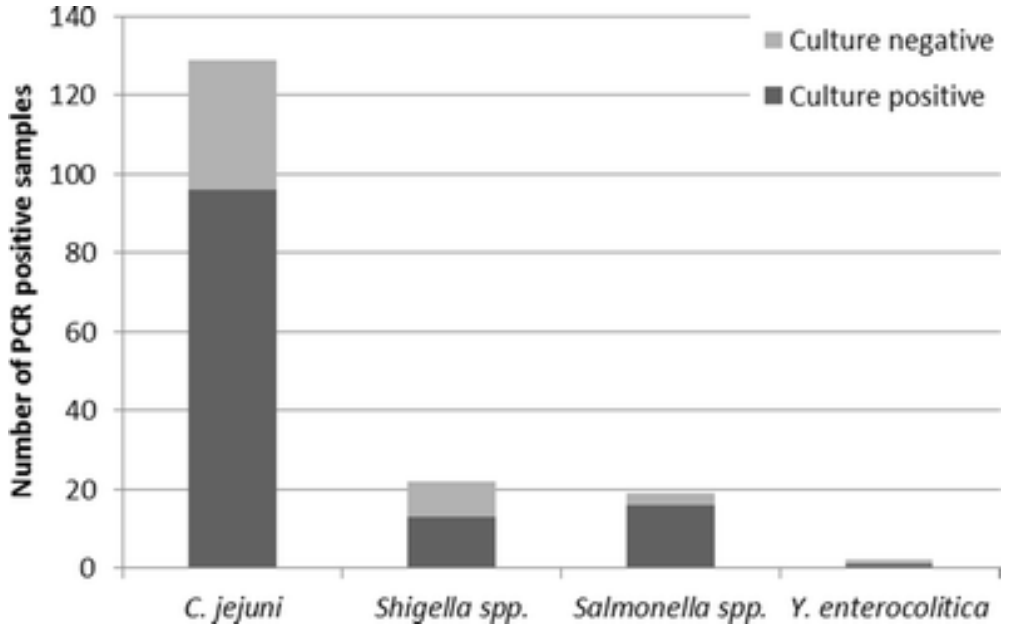
IDDL laboratory developed test (LDT) assay targets the *ipaH* gene from *Shigella* and had higher sensitivity over culture

Shigella	5' CCT TTT CCG CGT TCC TTG A -3'	5' CGG AAT CCG GAG GTA TTG C -3'	5' - (FAM)- CGC CTT TCC GAT ACC GTC TCT GCA- (BHQ-1) – 3'	ipaH Gene 64 bp	Van Lint P, et al. Eur J Clin Microbiol Infect Dis. 2015;34:535-542





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PMID: 25326870

Culture on positive specimens is important for sending isolate to local public health laboratory for typing

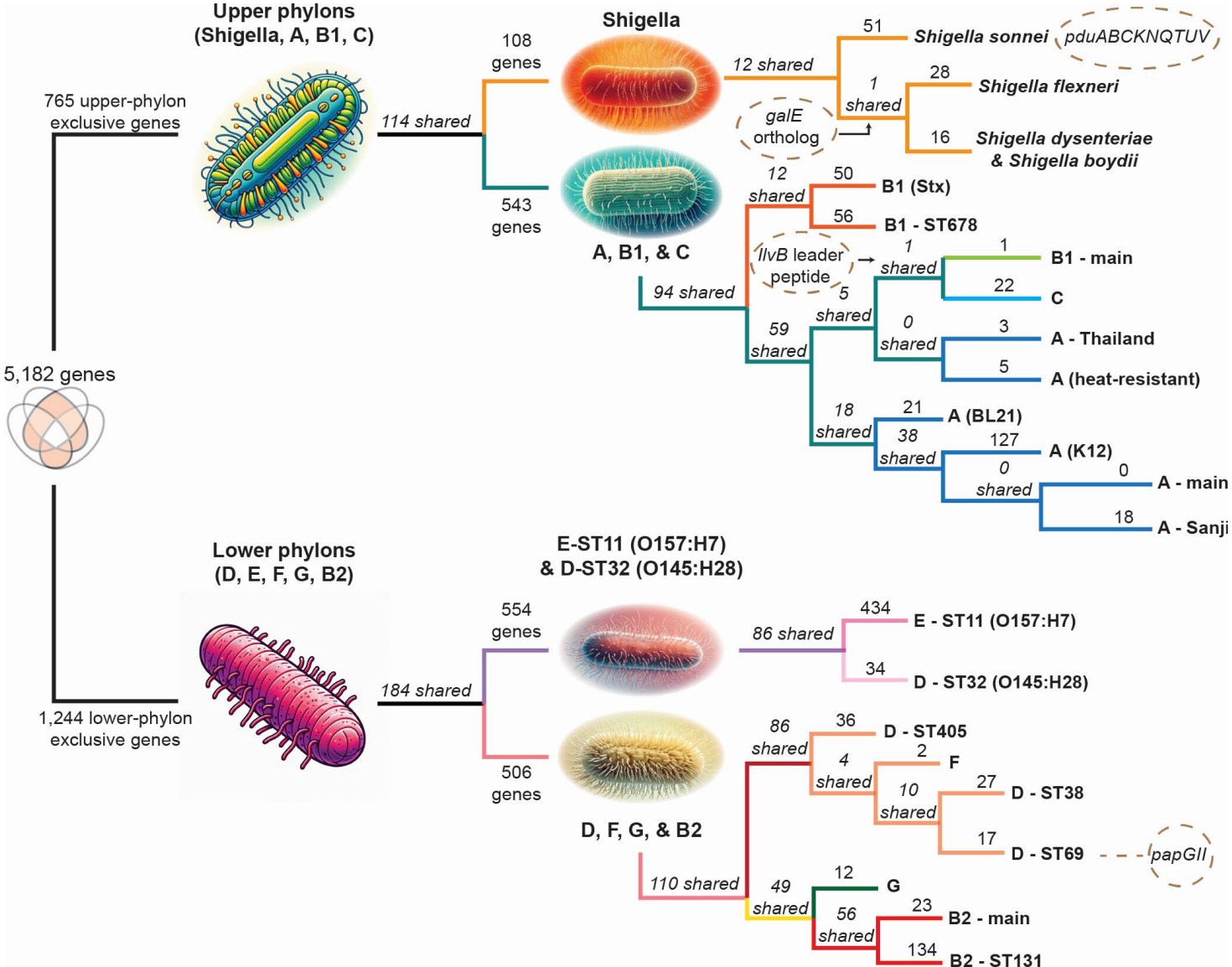
***Shigella* sp.**

***Salmonella* sp.**

Normal Flora

https://www.medical-labs.net/hektoen-enteric-agar-2204

Four recognized *Shigella spp*, genomically are best characterized as a phylogroup within *Escherichia coli*



PMID: 39745367

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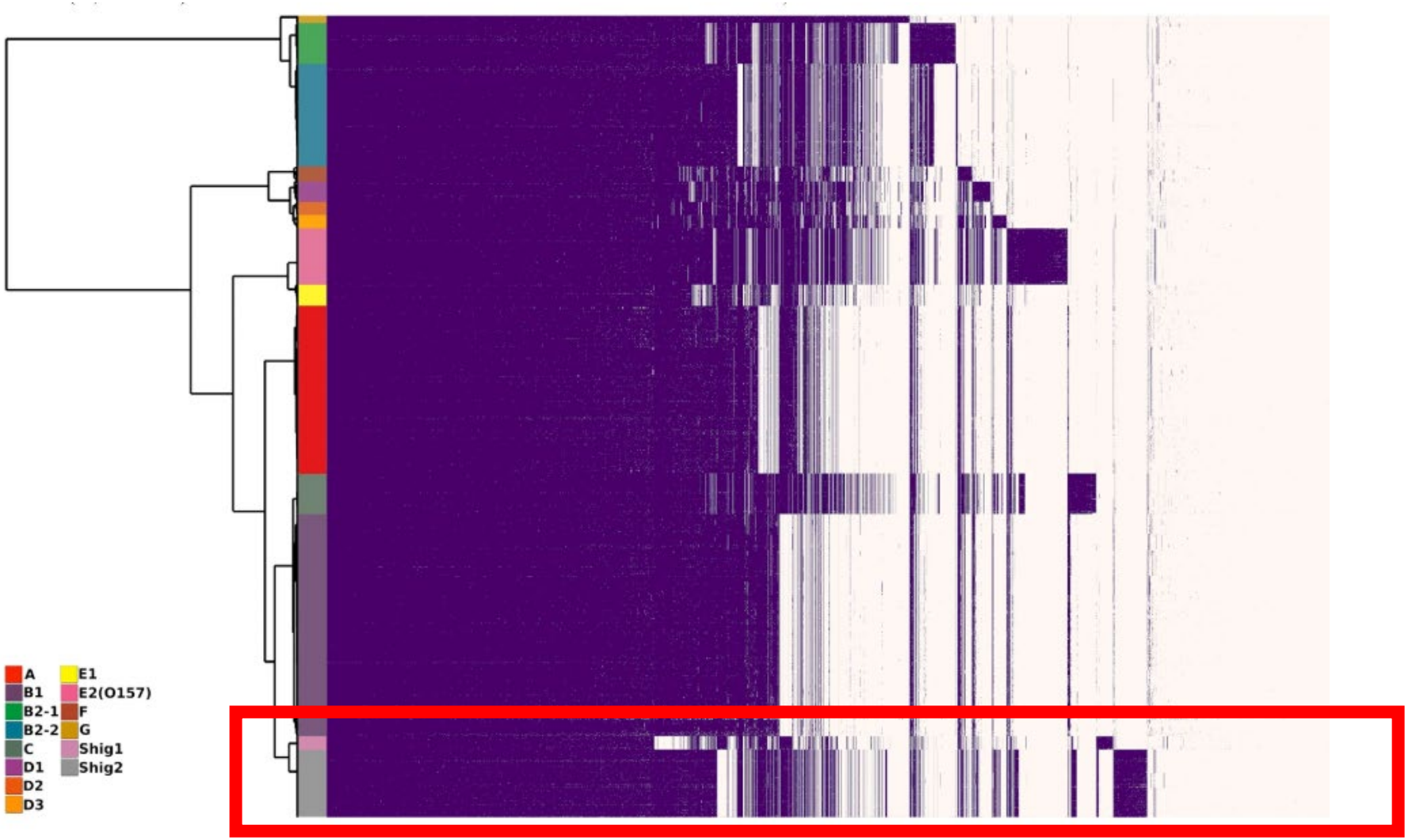
Further evidence *Shigella* species are a distinct phylogroup compared to *E. coli* isolates via pan-genome distribution



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PMID: 33500552

Shigella species can be differentiated from *E. coli* via biochemical testing

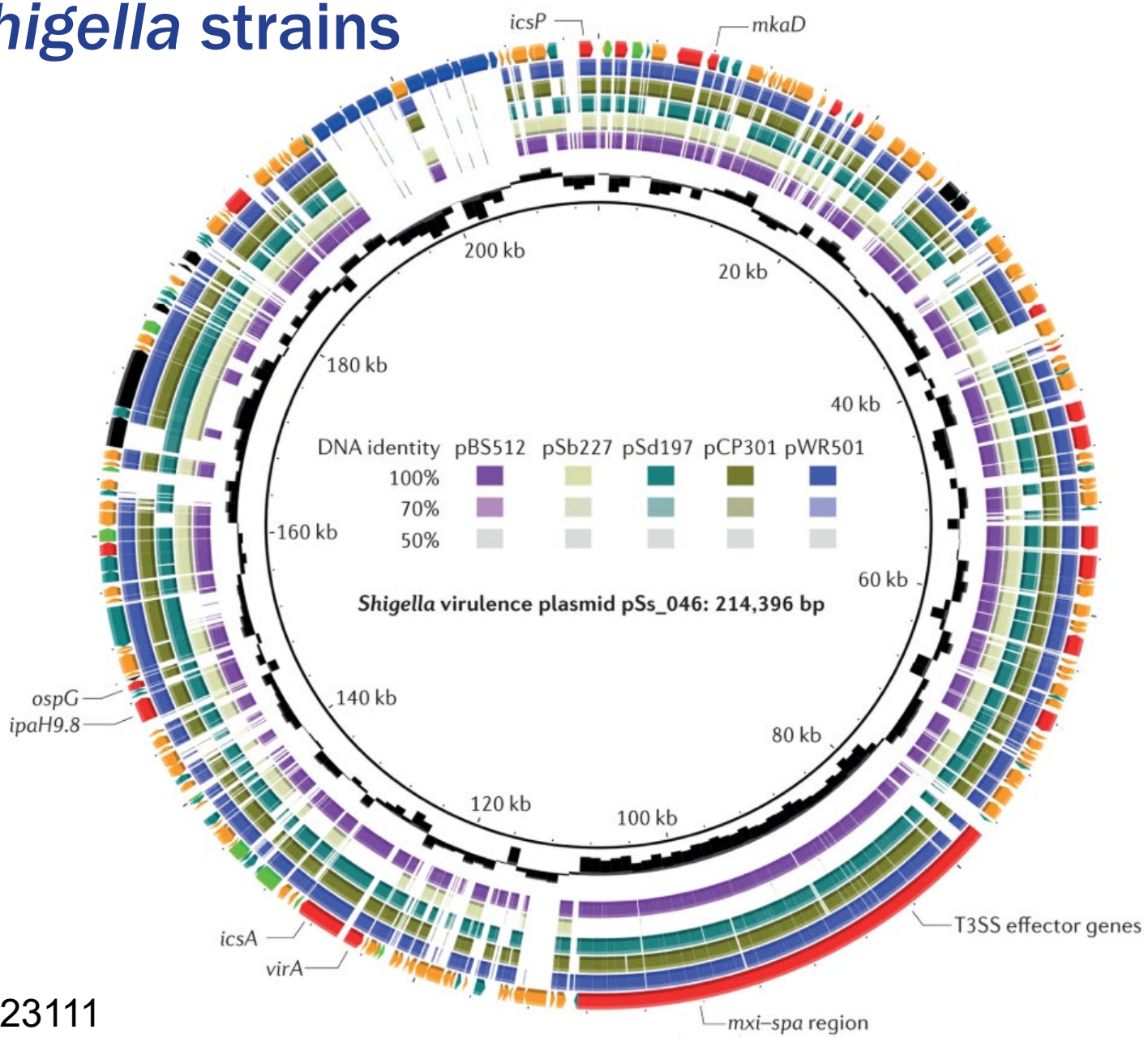
Table 2: Biochemical characteristics of bacteria

Citrate	Urease	Indole	MR	VP	Catalase	Oxidase	Motility	TSI	Gas/ H_2S	Results
+	-	-	-	+	+	-	+	A/A	+/-	*Enterobacter* spp
+	+	-	-	+	+	-	-	A/A	+/-	*Klebsiella* spp
-	-	+	+	-	+	-	+	A/A	+/-	*E. coli*
+	-	-	+	-	+	-	+	A/A or K/A	+/+	*Citrobacter* spp
-	+	+			+	-	+		-	*Yersinia* spp
-	-	-	+	-	+	-	-	K/A	-/-	*Shigella* spp

+ represents Positive test, - represents Negative test, while D denotes Variable result (either positive or negative), A and K signify Acidic and Alkaline respectively.

ISSN: 2091-2854

A large virulence plasmid confers enteroinvasiveness of *Shigella* strains

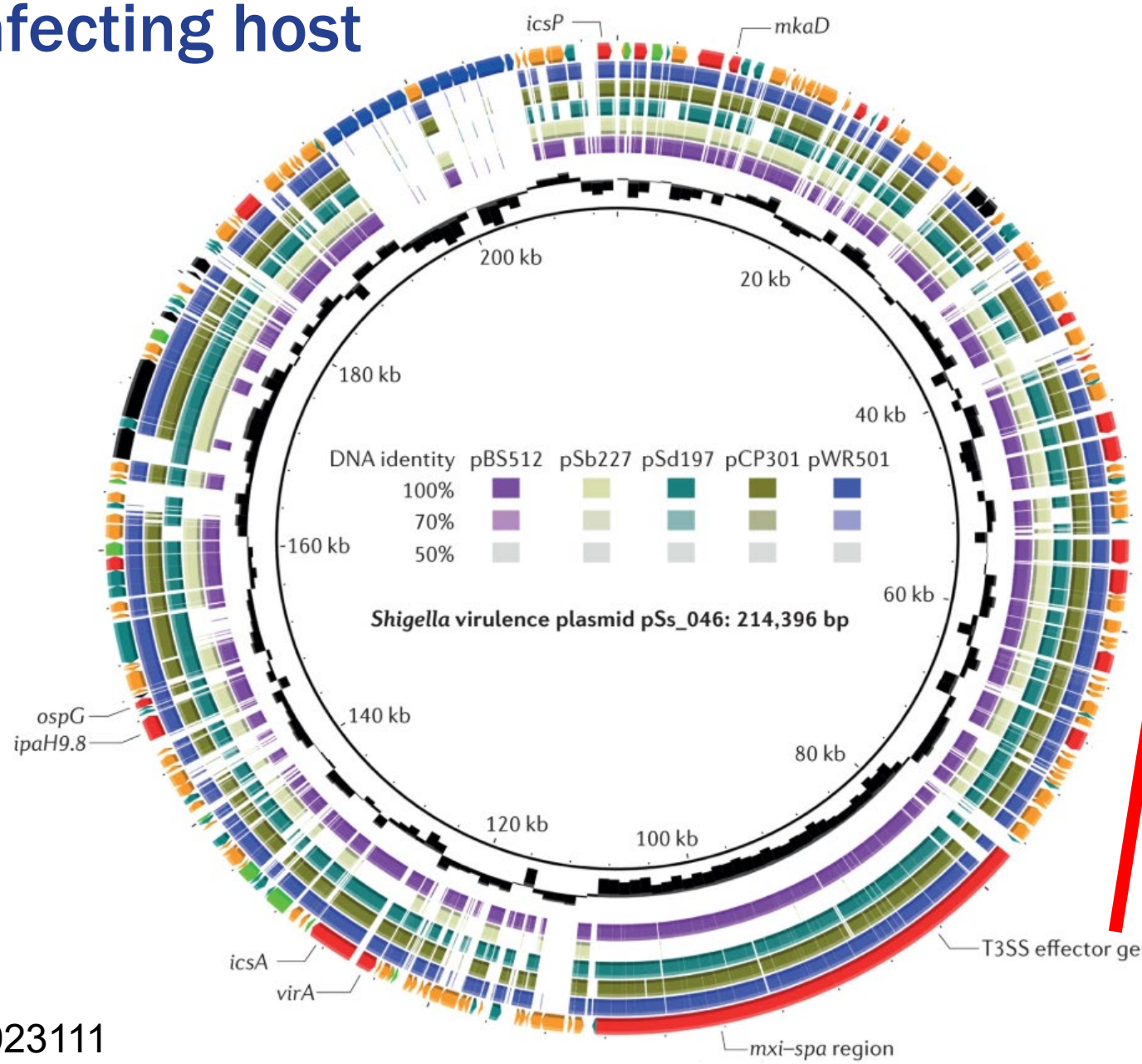


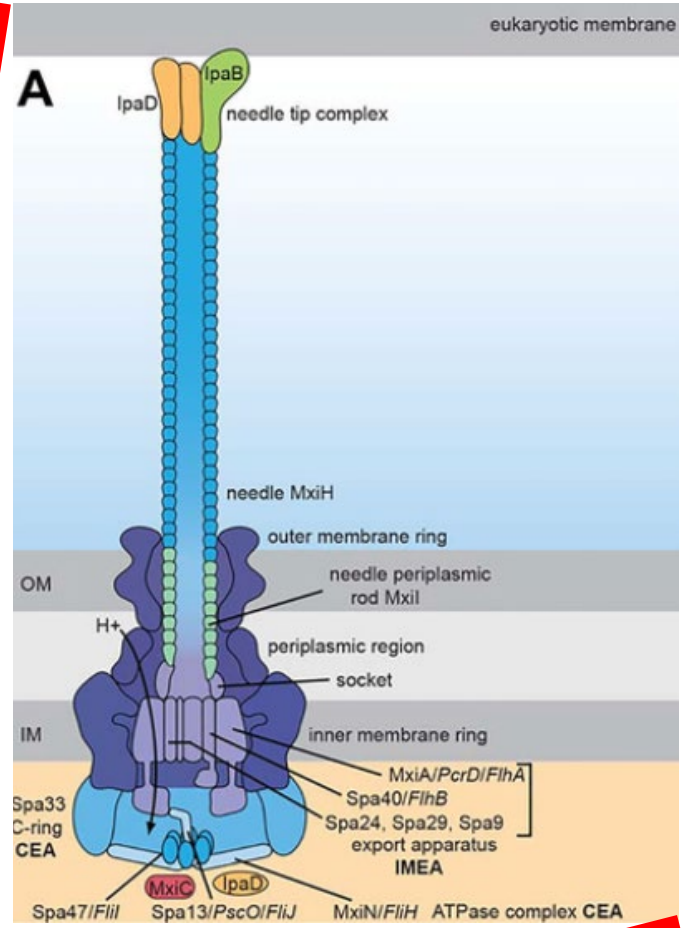
PMID: 26923111

#IDLabCon

APHL 2025 ID LAB CON

Type 3 Secretion system is a “reverse” flagella used for infecting host



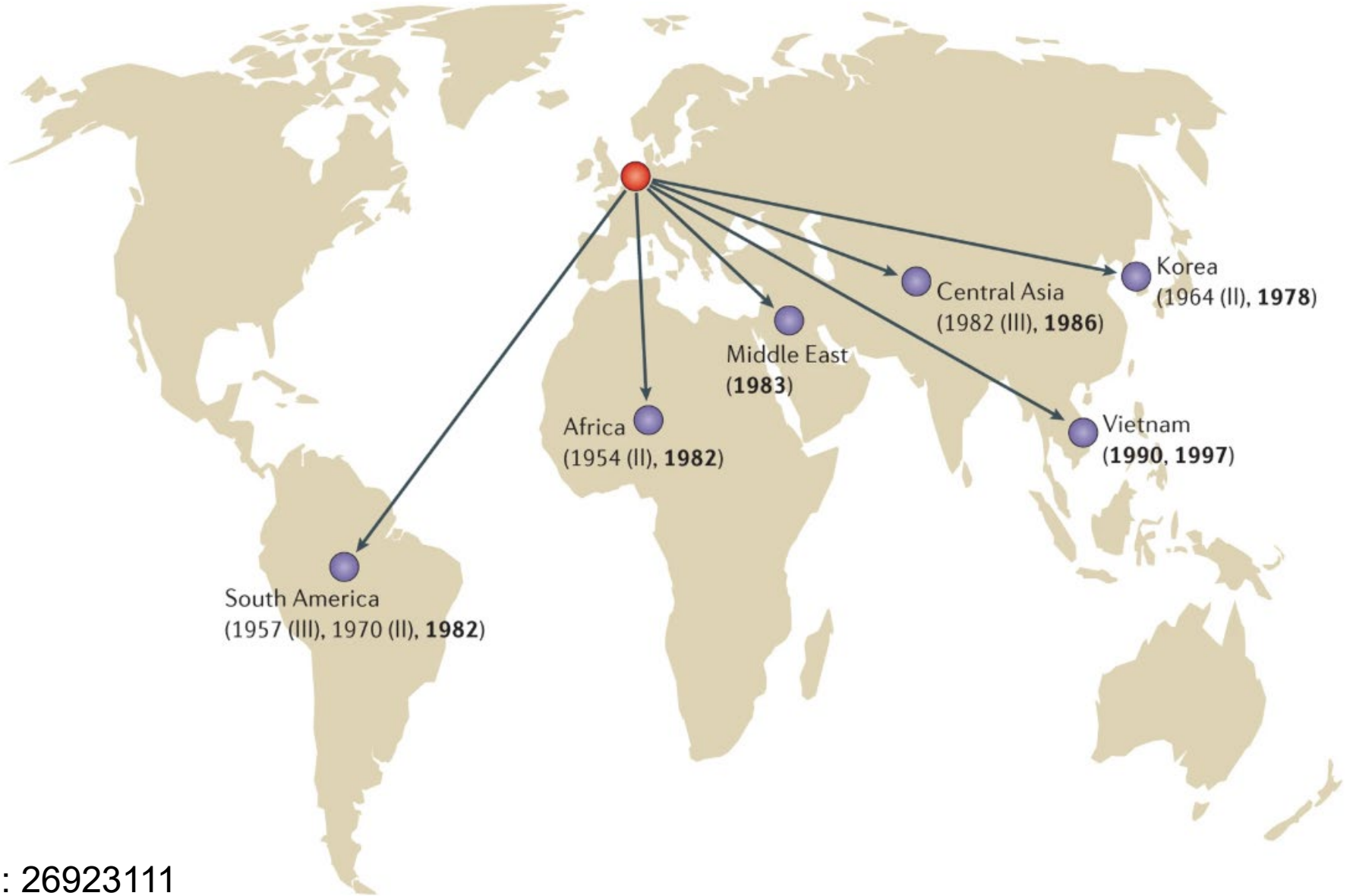


PMID: 26923111

#IDLabCon

APHL 2025 ID LAB CON

Shigella sonnei emerged relatively recent in Europe (~400 ya) and then spread throughout the world



#IDLabCon

PMID: 26923111

Antibiotic resistant *Shigella* spp. is a serious antimicrobial threat in the CDC 2019 AR Threat Report

Azithromycin, ciprofloxacin, and ceftriaxone are first choice treatments for shigellosis

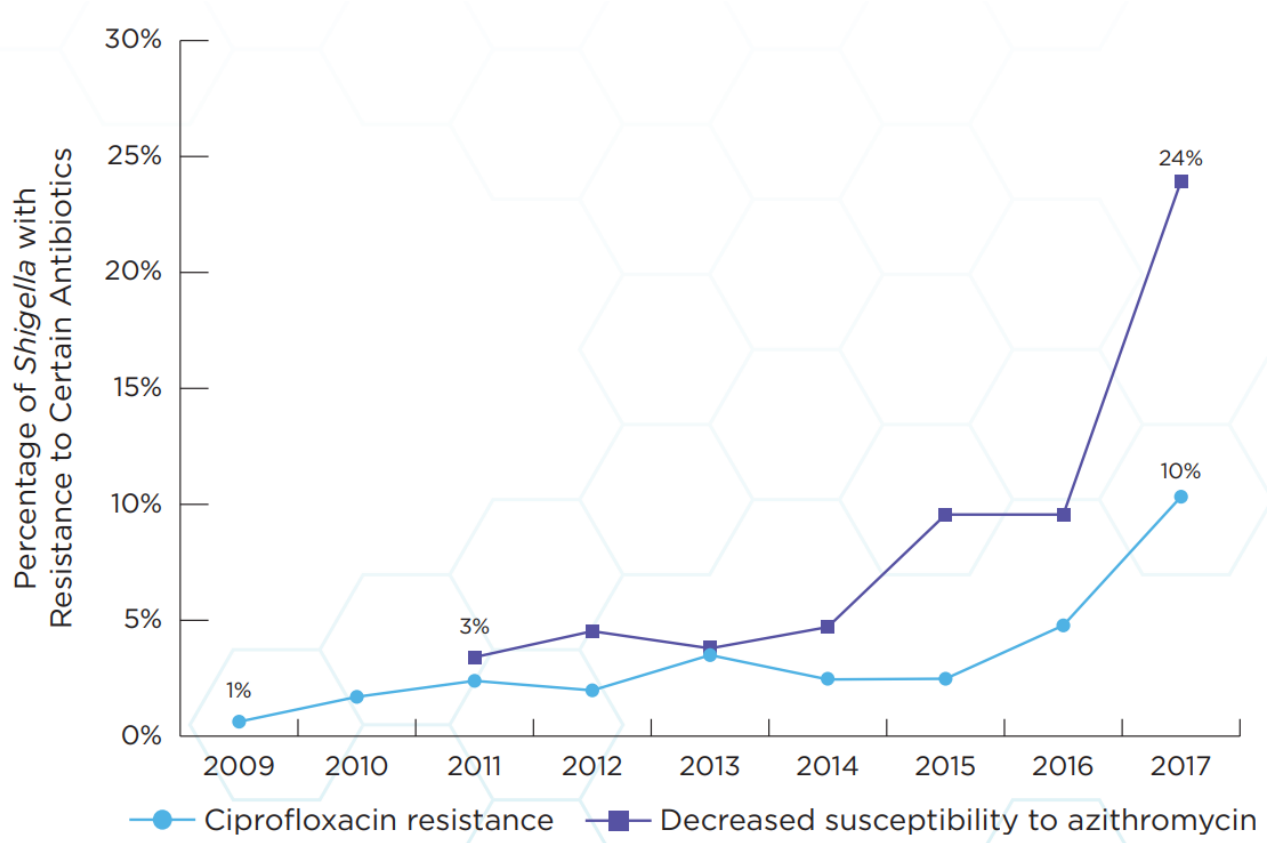
Indication	First Choice	Alternative	Comments/Considerations
Shigella [a]	Azithromycin[c] or ciprofloxacin[a], or ceftriaxone	TMP-SMX or ampicillin if susceptible	Clinicians treating people with shigellosis for whom antibiotic treatment is indicated should avoid prescribing fluoroquinolones if the ciprofloxacin MIC is 0.12 µg/ mL or higher even if the laboratory report identifies the isolate as susceptible. See https://emergency.cdc.gov/han/han00401.asp

Major concern is increase in phenotypic ciprofloxacin and azithromycin resistance

RESISTANCE SNAPSHOT

Among *Shigella*, emerging resistance to important drugs threatens available treatment options.

	PERCENTAGE OF ALL *SHIGELLA**	ESTIMATED NUMBER OF INFECTIONS PER YEAR	ESTIMATED INFECTIONS PER 100,000 U.S. POPULATION
CIPROFLOXACIN RESISTANCE	6%	26,300	10
DECREASED SUSCEPTIBILITY TO CIPROFLOXACIN	17%	74,100	20
DECREASED SUSCEPTIBILITY TO AZITHROMYCIN (DSA)	14%	64,500	20
CIPROFLOXACIN RESISTANCE **OR** DSA	17%	77,000	20
CIPROFLOXACIN RESISTANCE **AND** DSA	3%	13,900	Less than 5



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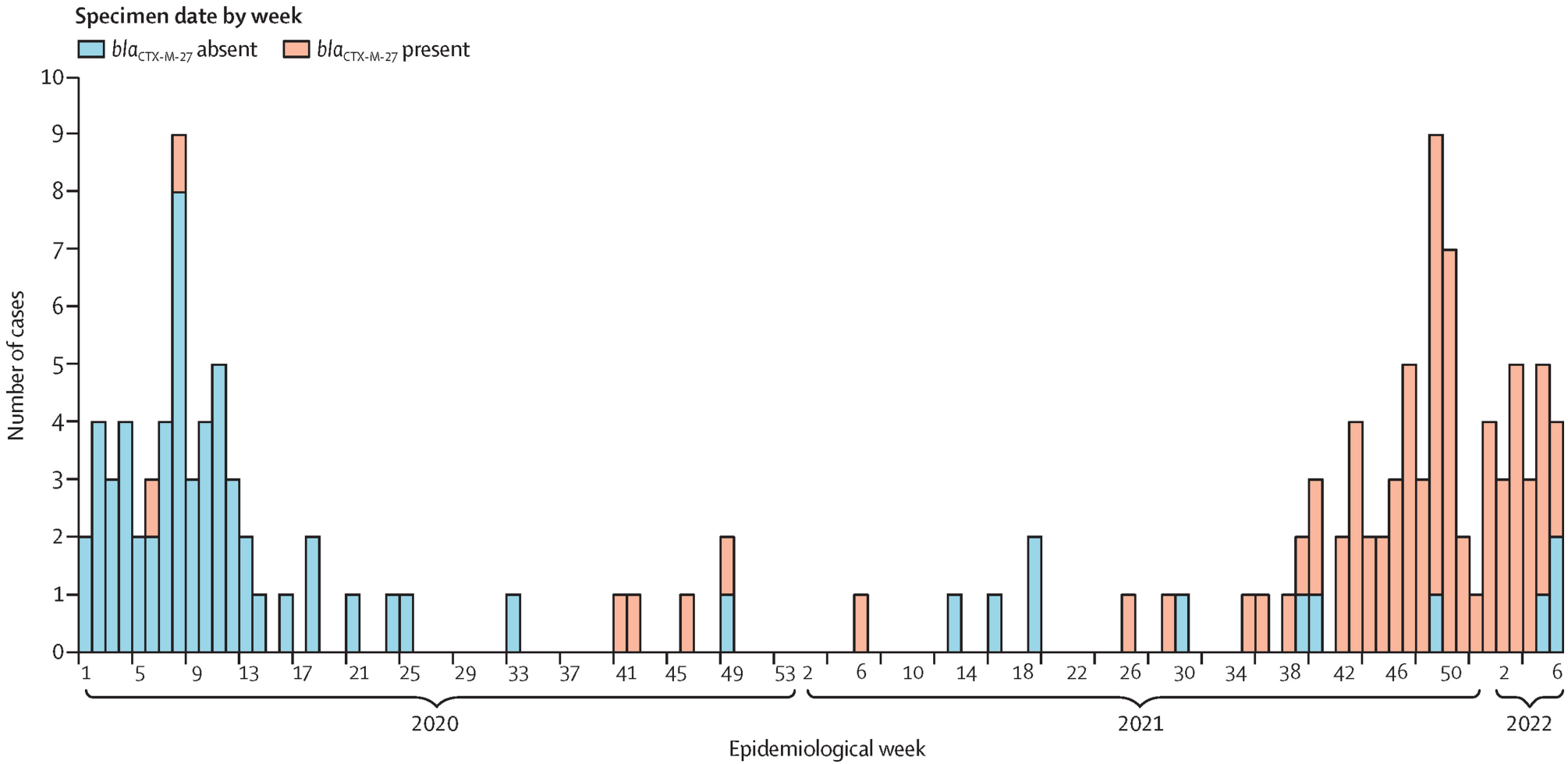
CDC AR Threat Report 2019

ESBL producing *Shigella* spp. cause an outbreak of gastroenteritis in the United Kingdom



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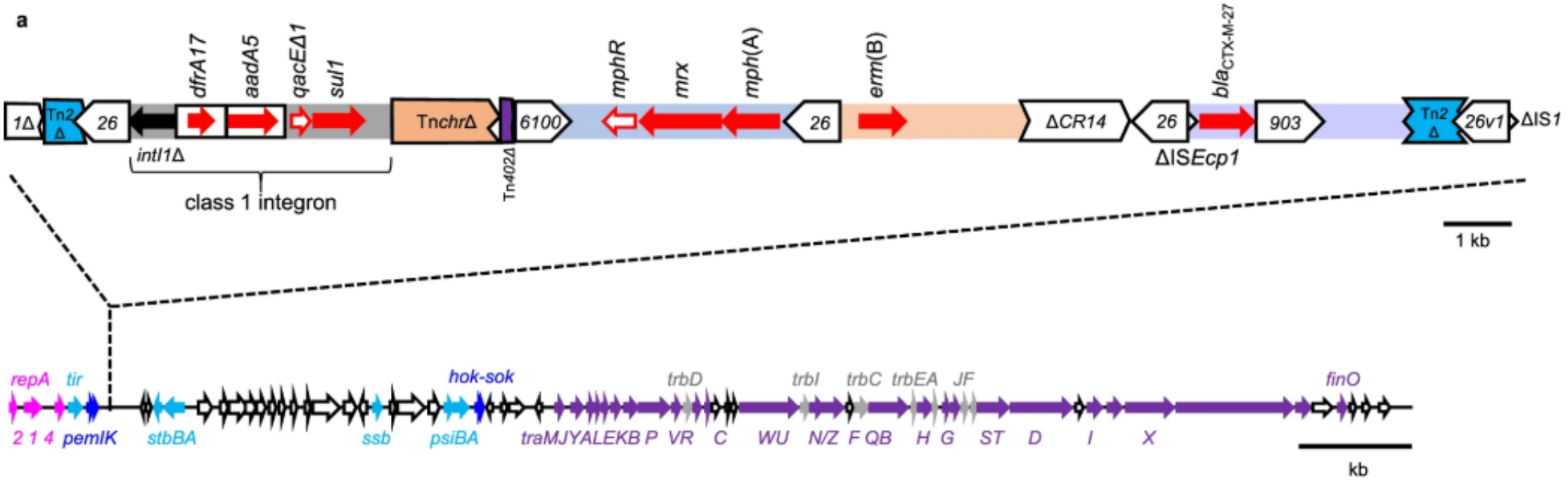
PMID: 35809593

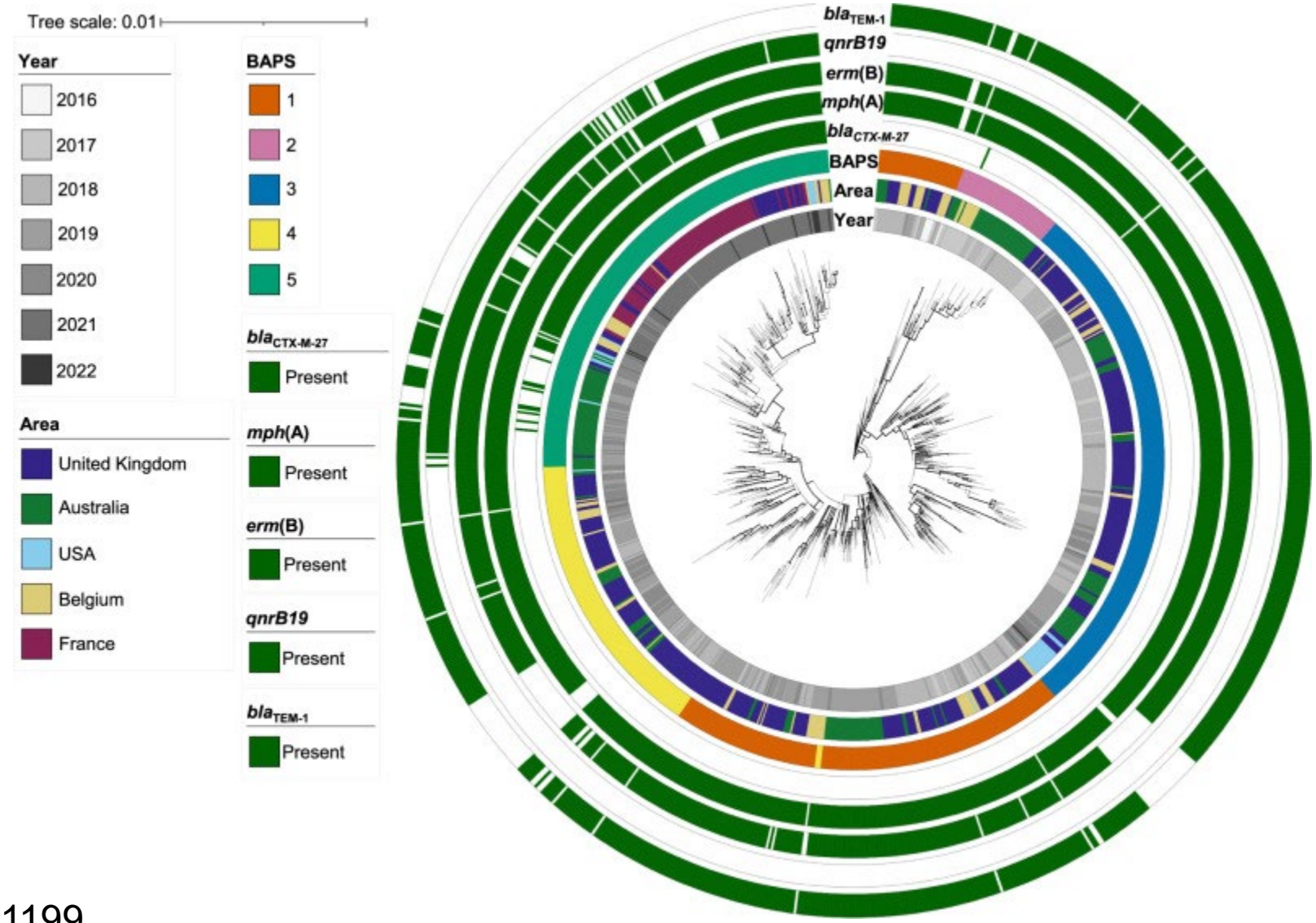
Integrons containing multiple acquired antibiotic resistance genes are on self transmissible plasmids in *Shigella* spp.



PMID: 37031199

#IDLabCon

Integrons containing multiple acquired antibiotic resistance genes are on self transmissible plasmids in *Shigella* spp.



#IDLabCon

APHL ID LAB CON 2025

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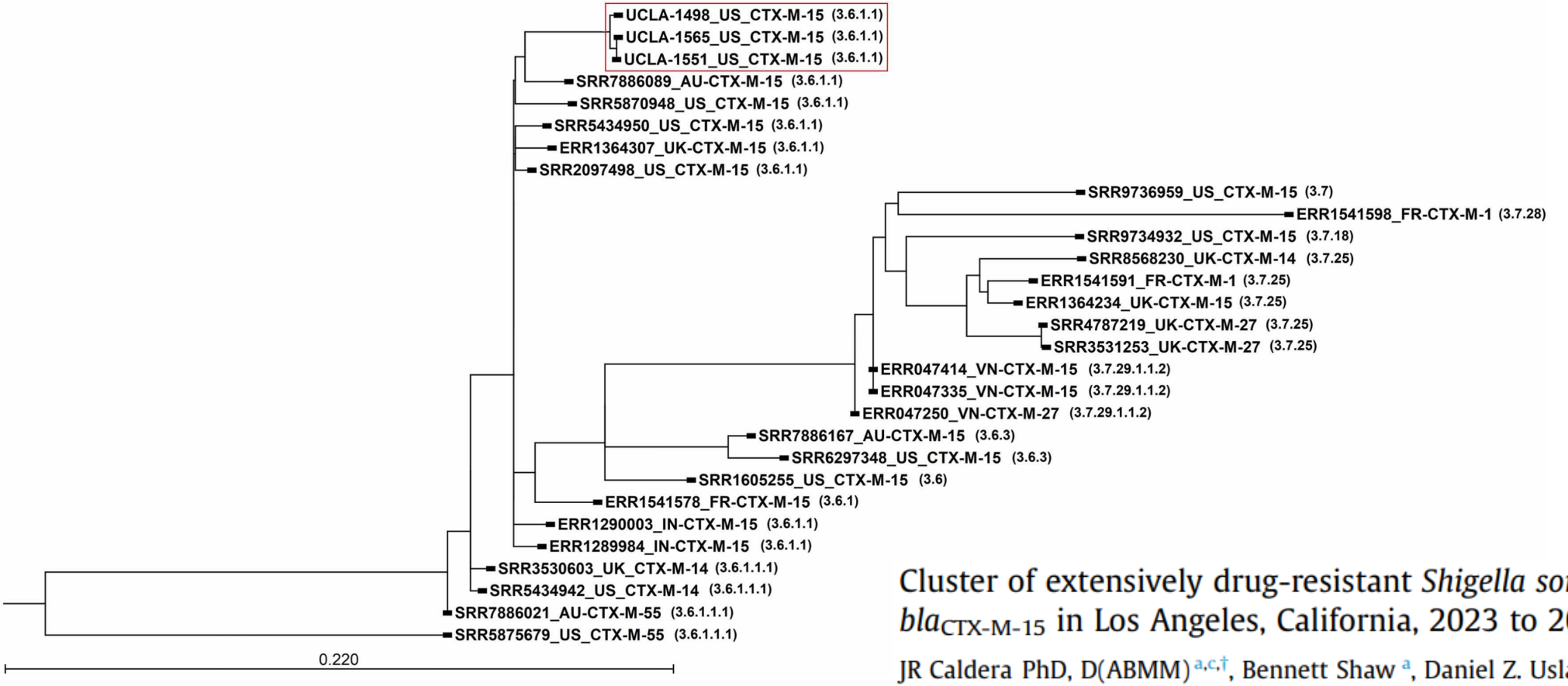
*bla*CTX-M-15 harboring *S. sonnei* in Los Angeles were determined to be closely related to one another



Cluster of extensively drug-resistant *Shigella sonnei* carrying $bla_{CTX\text{-}M\text{-}15}$ in Los Angeles, California, 2023 to 2024

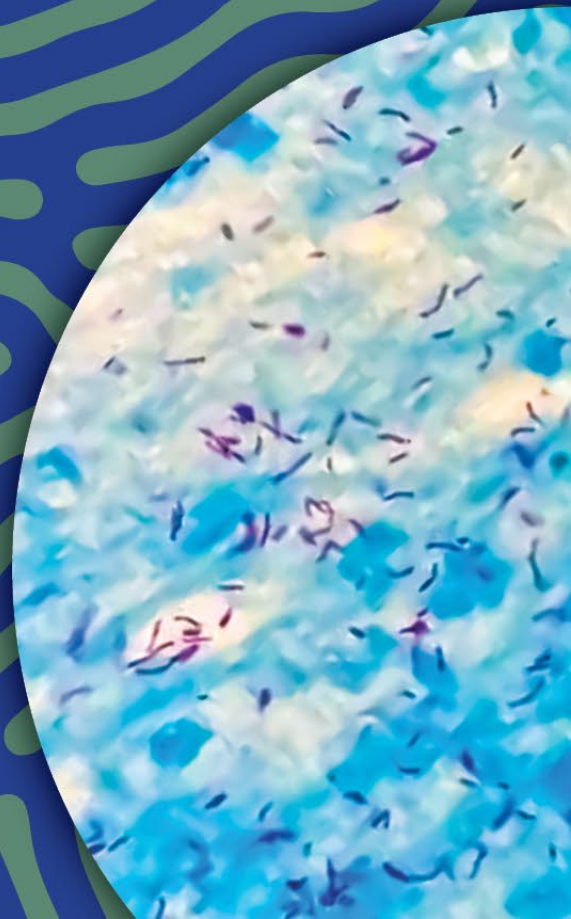
JR Caldera PhD, D(ABMM) [a,c,†], Bennett Shaw [a], Daniel Z. Uslan MD, MBA, FIDSA, FSHEA [b], Shangxin Yang PhD, D(ABMM) [a,*]

[a] *Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA*
[b] *Division of Infectious Diseases, David Geffen School of Medicine, University of California, Los Angeles, CA*
[c] *Infectious Disease, Quest Diagnostics, San Juan Capistrano, CA*

PMID: 39667596

Conclusions

–Shigella is a phylogroup of E. coli that causes gastroenteritis
-Frontline treatment includes ciprofloxacin and azithromycin
-Resistance to these agents and ceftriaxone is increasing
-Resistance is primarily mediated by horizontal gene transfer



Stenotrophomonas maltophilia.

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Robert Potter, PhD, D(ABMM)

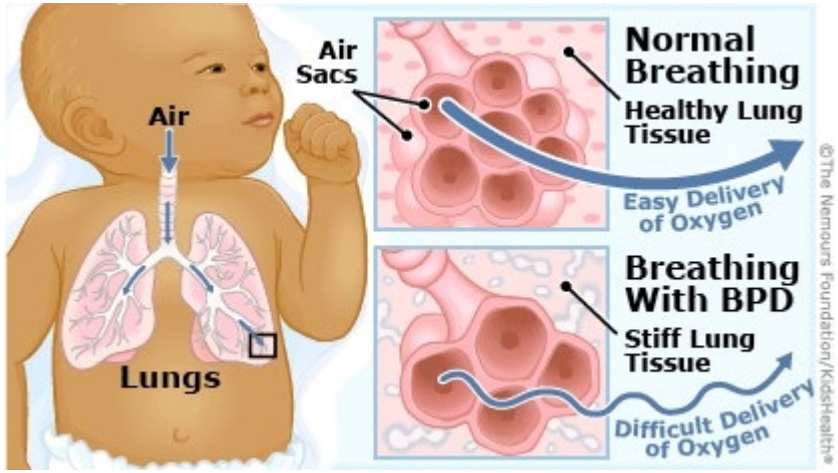
Assistant Director
Infectious Disease Diagnostics Laboratory
Children's Hospital of Philadelphia

Director, Outbreak Investigations
Center for Microbial Medicine
Children's Hospital of Philadelphia

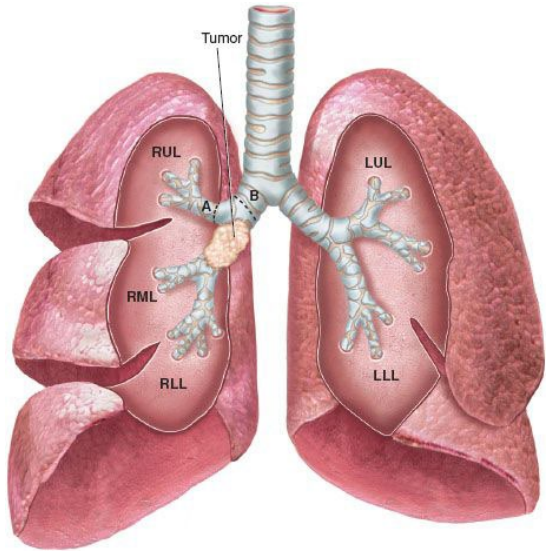
Assistant Professor
Department of Pathology & Laboratory Medicine
The Perelman School of Medicine at the University of Pennsylvania

Patient is a medically complicated 1 year old with a surgical site infection

- Bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD)



- LLL lobectomy



Specimen Information: Abscess; Aspirate

0 Result Notes

Aerobic Culture	Moderate Growth of Escherichia coli !
	Please contact the Infectious Disease Diagnostics Laboratory at ext. 42050 if Cefazolin susceptibility testing is required.
	Moderate Growth of Stenotrophomonas maltophilia !
	Sent to reference lab for further testing: ARUP Laboratories (Associated Regional & University Pathologists). Phone 800-522-2787. See Microbiology Susceptibilities ARUP for additional results. - Cefiderocol.

Much less options for treating *S. maltophilia* compared to E. coli but thankfully both relatively susceptible

Susceptibility

	Escherichia coli MIC		Stenotrophomonas maltophilia KB
AZTREONAM	<=1	**Sensitive**	
CEFTAZIDIME	<=1	**Sensitive**	
CIPROFLOXACIN	<=0.06	**Sensitive**	
GENTAMICIN	<=1	**Sensitive**	
AMPICILLIN/SULBACTAM	>=32	Resistant	
CEFTRIAXONE	<=0.25	**Sensitive**	
MEROPENEM	<=0.25	**Sensitive**	
TRIMETHOPRIM/SULFA		**Sensitive**	**Sensitive**
LEVOFLOXACIN	<=0.12	**Sensitive**	**Sensitive**
PIPERACILLIN/TAZOBACTAM	<=4	**Sensitive**	
AMPICILLIN	>=32	Resistant	
CEFEPIME	<=0.12	**Sensitive**	
MINOCYCLINE			**Sensitive**
ERTAPENEM	<=0.12	**Sensitive**	
AMOXICILLIN/CA	16.0	Intermediate	

Comment: Stenotrophomonas maltophilia
Organism identified by client
INTERPRETIVE INFORMATION: Susceptibility Not Specified

Units = ug/mL
SMICCefiderocol <=0.03 Suscept
Performed By: ARUP Laboratories
500 Chipeta Way
Salt Lake City, UT 84108

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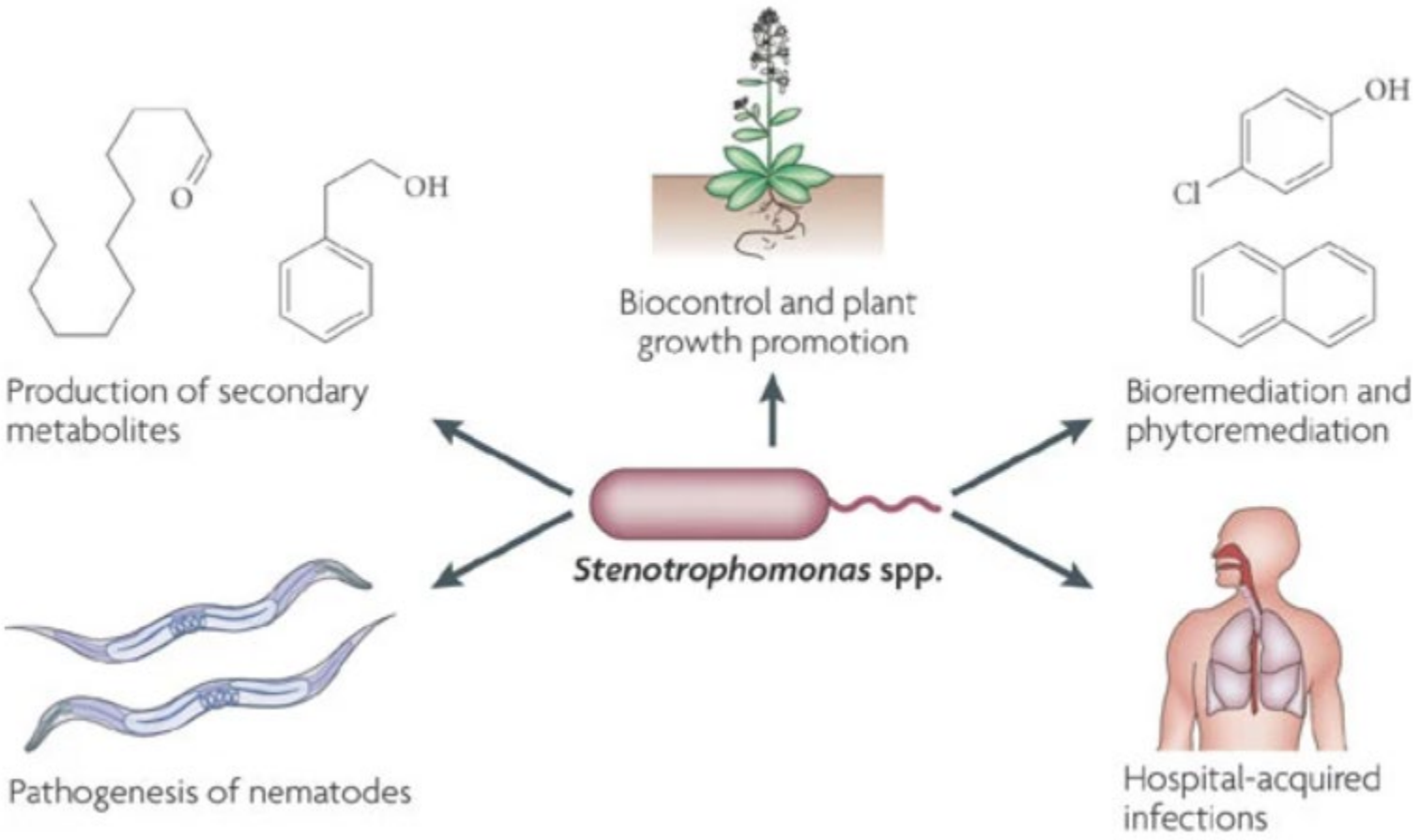
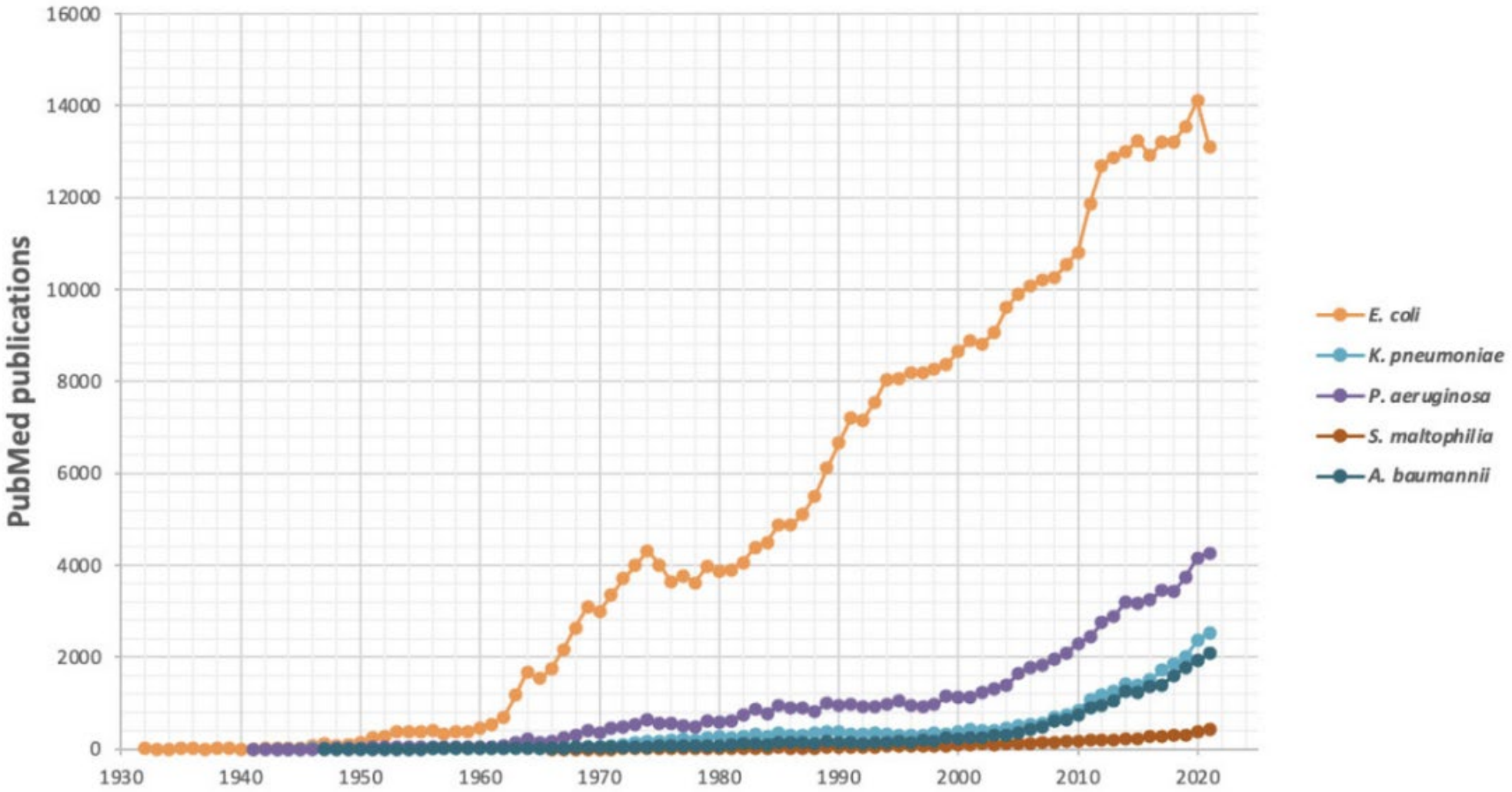
S. maltophilia is a common environmental bacterial that can cause opportunistic infections



PMID: 19528958

S. maltophilia is understudied compared to other Gram-negative bacteria



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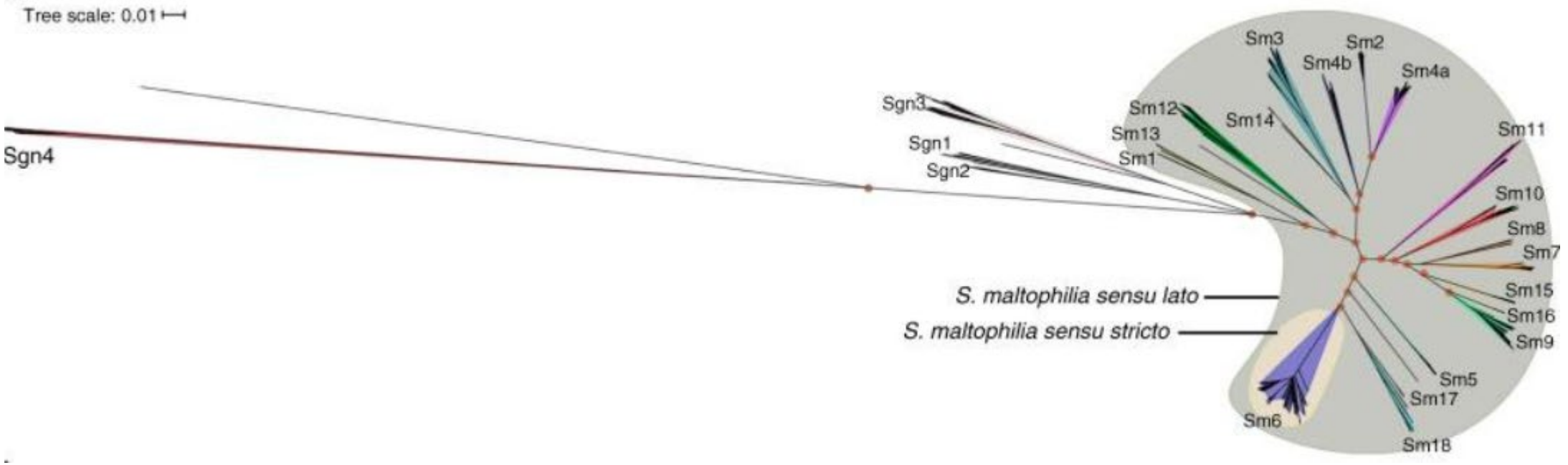
PMID: 35529051

S. maltophilia is composed of 23 phylogenetic lineages of 13 putative species



PMID: 19528958

S. maltophilia has intrinsic resistance to many antibiotics via core-genome antibiotic resistance genes

Antibiotic class	Antimicrobial agents	Intrinsic resistance?
β-lactams	Ampicillin, amoxicillin	Yes
	Piperacillin	Yes
	Ticarcillin	Yes
	Ampicillin-sulbactam	Yes
	Amoxicillin/clavulanate	Yes
	Piperacillin/tazobactam	Yes
	Cefotaxime	Yes
	Ceftriaxone	Yes
	Ceftazidime	No
	Cefepime	No
	Aztreonam	Yes
	Imipenem	Yes
	Meropenem	Yes
	Ertapenem	Yes
Polymyxins	Polymyxin B, colistin	No
Aminoglycosides		Yes
Other	Tetracycline, tigecycline	[b]
	Trimethoprim	Yes
	Trimethoprim/ sulfamethoxazole	No
	Chloramphenicol	No
	Fosfomycin	Yes

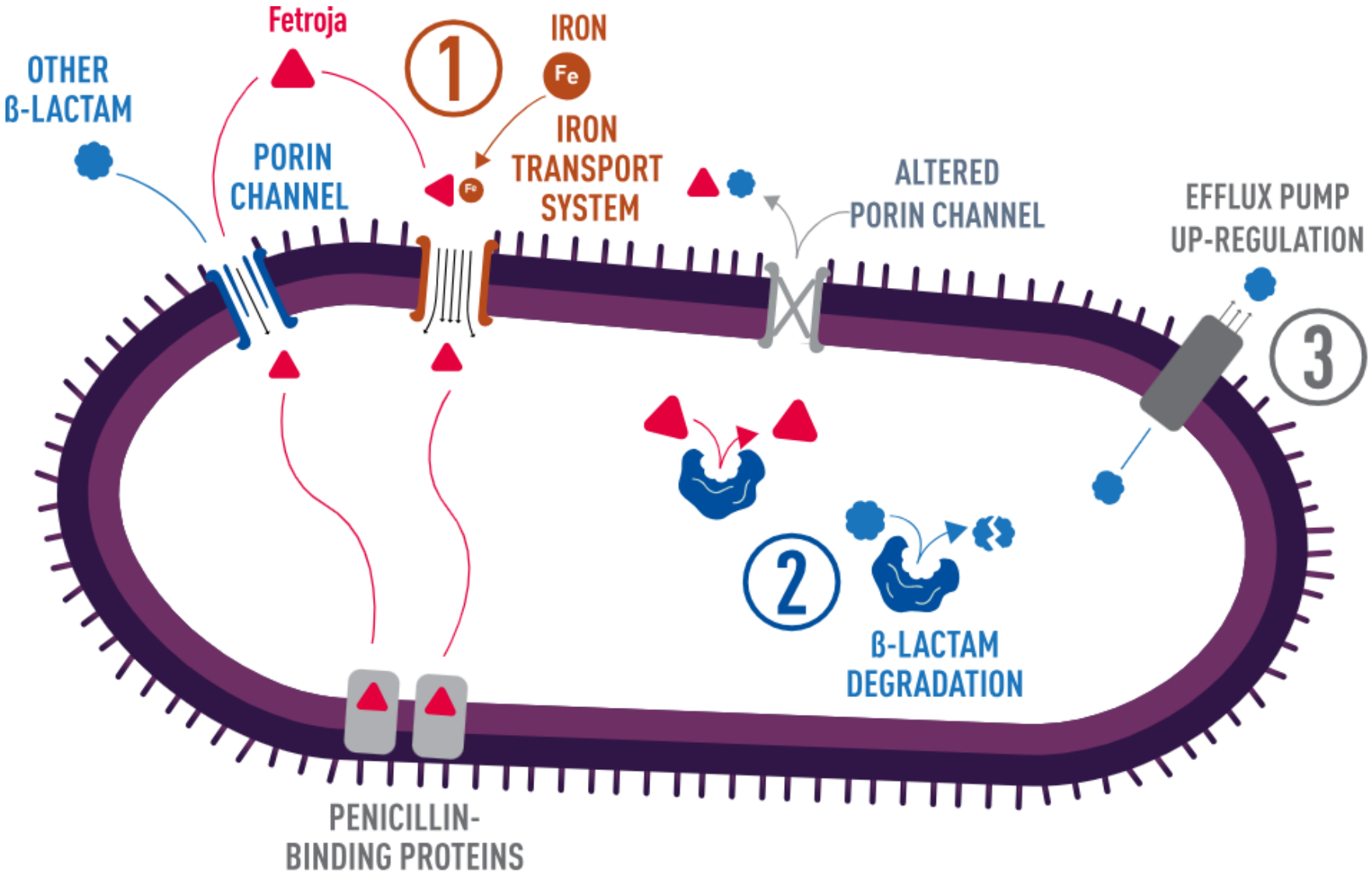
PMID: 35529051

S. maltophilia has intrinsic resistance to many antibiotics via core-genome antibiotic resistance genes

Mechanisms	Resistance mechanisms	Spectrum	Resistance
Efflux pumps	SmeABC	AMG, β-lactams, FLQ	Acq
	SmeDEF	TET, CHL, Macrolides, FLQ, SMX, TMP, SXT, TGC	Int*
	SmeGH	FLQ, β-lactams, TET, PMB	Int*
	SmeIJK	AMG, TET, MIN, CIP, LVX	Int*
	SmeVWZ	FLQ, CHL, SXT	Int*
	SmeYZ	AMG, TET, SXT	Int*
	SmrA	FLQ, TET	Int*
	OqxAB	FLQ	Acq
β-lactamases	L1 Class B3	β-Lactams (except monobactams)	Int
	L2 Class A	Penicillins, cephalosporins	Int
	TEM-2, CTX-M-1	Penicillins, cephalosporins	Acq
Aminoglycoside modifying enzymes	AAC(6′)-Iz	AMK, TOB	Int
	APH (3′)-Iic	KAN, NEO	Int
	AAC (6′)-Iak	NEO, TOB	Acq
Other	Sm*qnr*	Quinolones	Int*
	SUL1, SUL2, DfrA	SXT	Acq
	CatB	CHL	Acq
	tonB[a]	CAZ, FDC	Acq

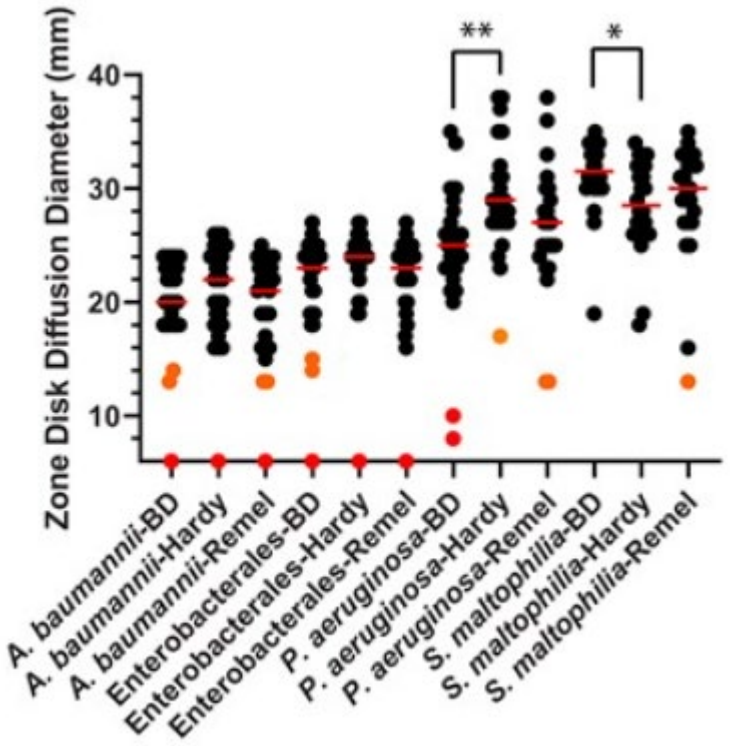
PMID: 35529051

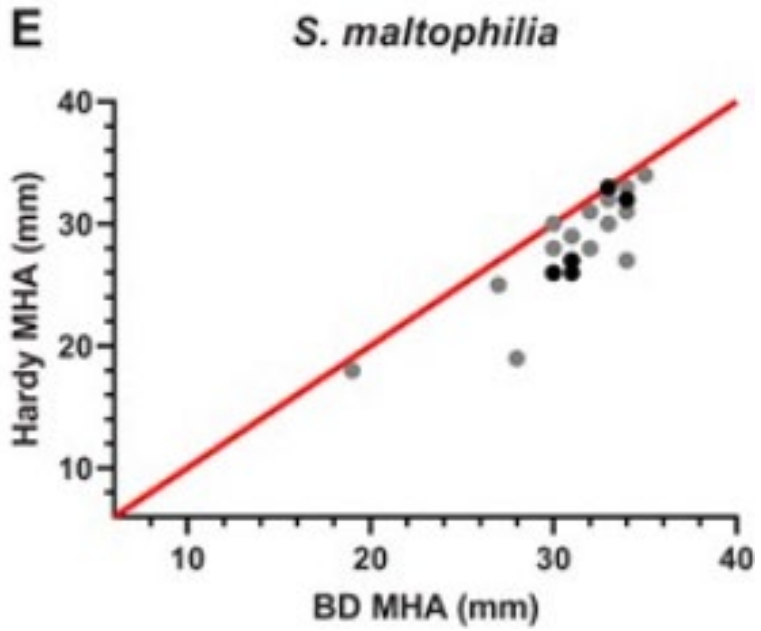
Cefiderocol (brand name Fetroja) binds to iron and mimics a siderophore so that it is actively uploaded into periplasm



https://www.fetroja.com/mechanism-of-action

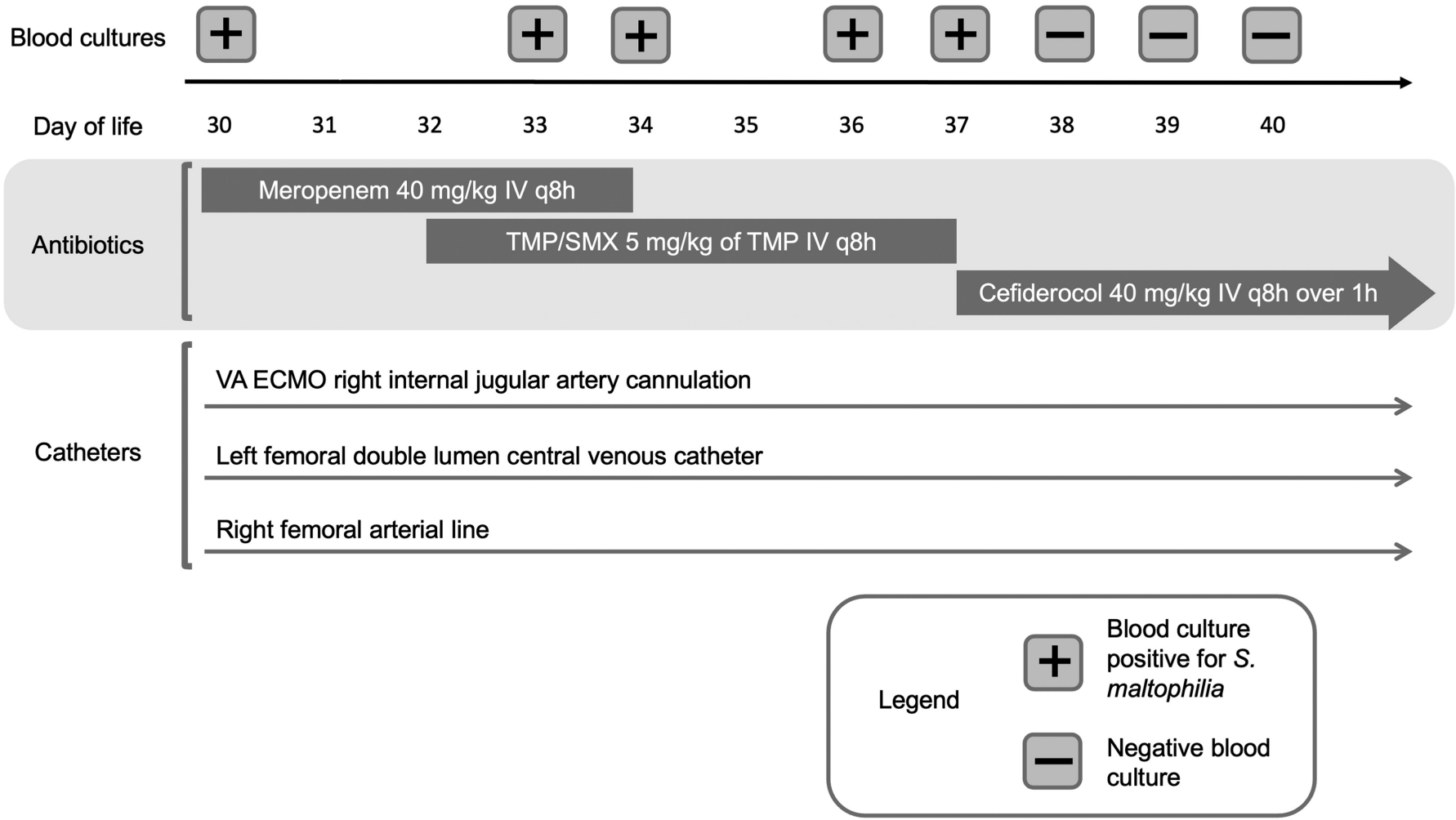
Statistically significant difference between Cefiderocol zone diffusion diameter for *S. maltophilia* on BD and Hardy MHA





PMID: 32571820

Cefiderocol used to successfully treat *S. maltophilia* bloodstream infection at Johns Hopkins children hospital



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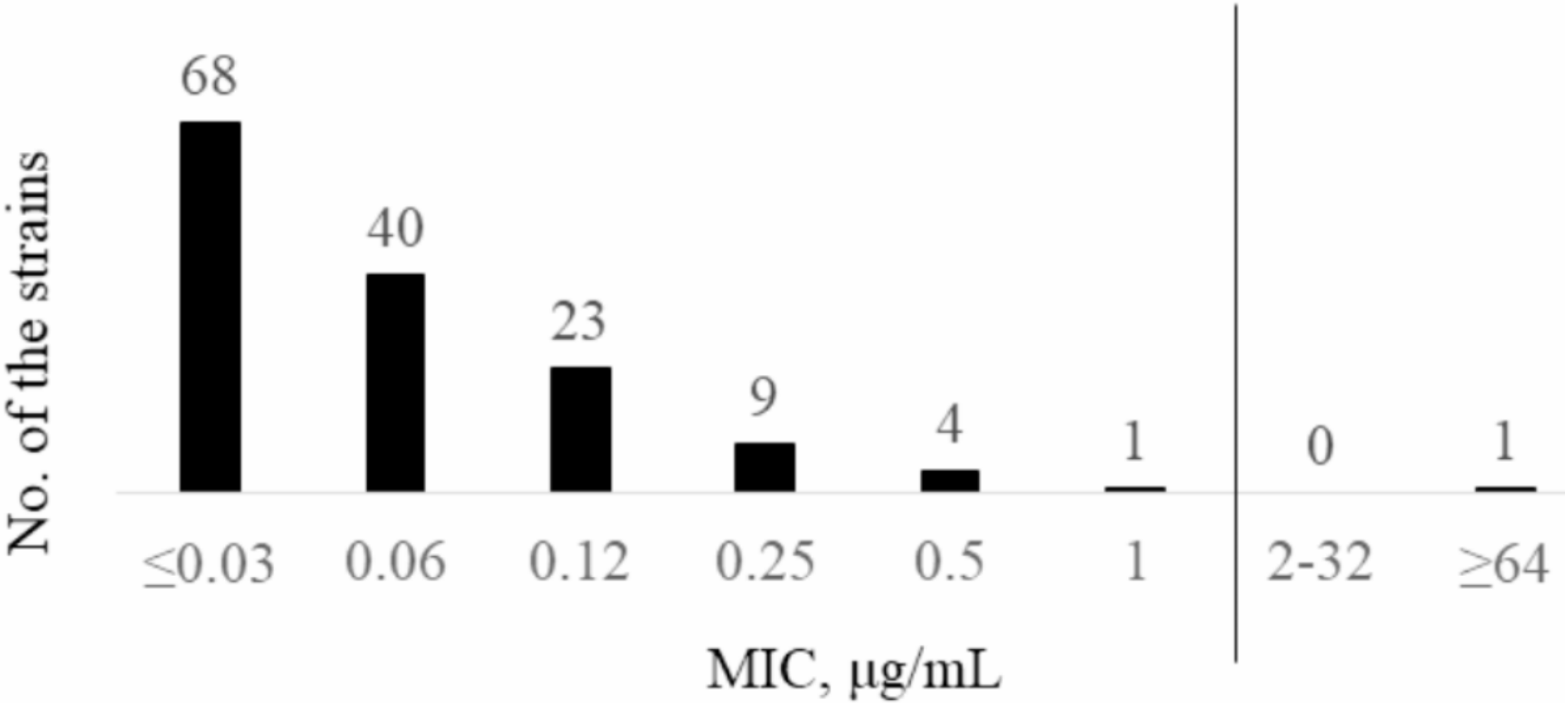
PMID: 32571820

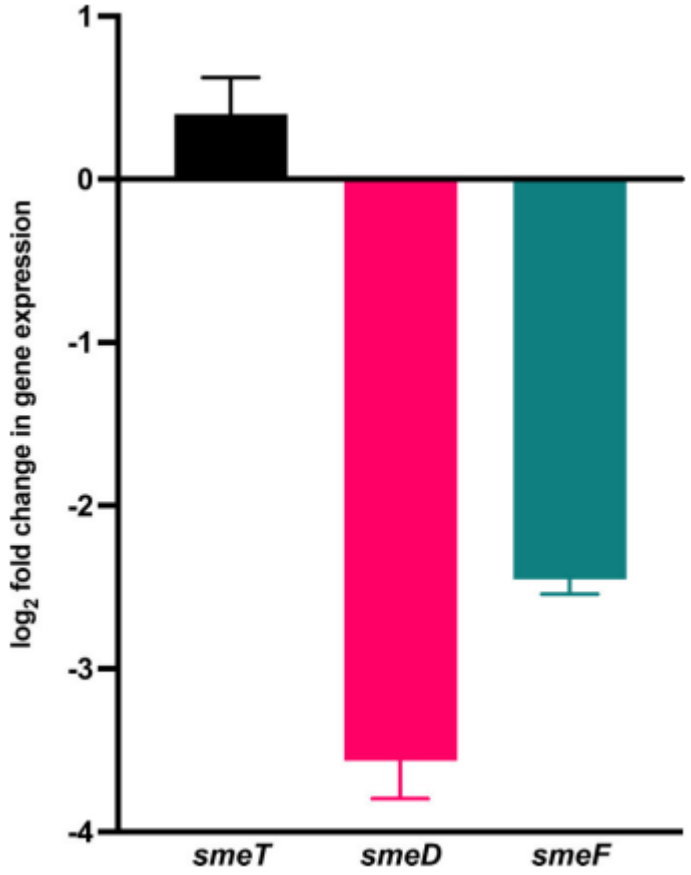
146 *S. maltophilia* strains from Japan tested over a 10 year period identified only one case of elevated resistance



PMID: 39392554

Mutations in promoter sequence of *sme* efflux operon led to lower expression in an evolved cefiderocol resistant isolate

Strain	Time to isolate emergence (days)	FDC	CAZ/AVI	CAZ	MIN	TMP/SMX	FDC stability: no. of drug-free passes			
							2	3	4	gene
W357-Parent	—	0.03125	4	128	4	0.5/9.5	0.03125	0.0625	0.03125	—
W357-2-10	15	32	≥256	256	2	0.125/2.375	8	4.0–8.0	4.0–8.0	*smeT*
W358-Parent	—	0.125	64	≥256	0.5	0.125/2.375	0.0625	0.0625	0.03125	—
W358-1-25	21	32	≥256	≥256	0.5	0.25/4.75	16	16	8.0–16.0	*smlt1148* *tesB* *panD* *smlt3318* *cysK1* *cirA*
W358-2-2	12	8	≥256	≥256	0.5	0.125/2.375	1.0–2.0	1	1	*smf-1*
W358-2-15	18	16	≥256	≥256	0.5	0.25/4.75	0.0625	0.0625	0.0625	*tolQ*
W364-Parent	—	0.03125	48	64–128	1	1/19	0.03125	0.03125	0.03125	—
W364-8	16	8	≥256	256	1	0.25/4.75	8	2.0–4.0	2	*tonB*



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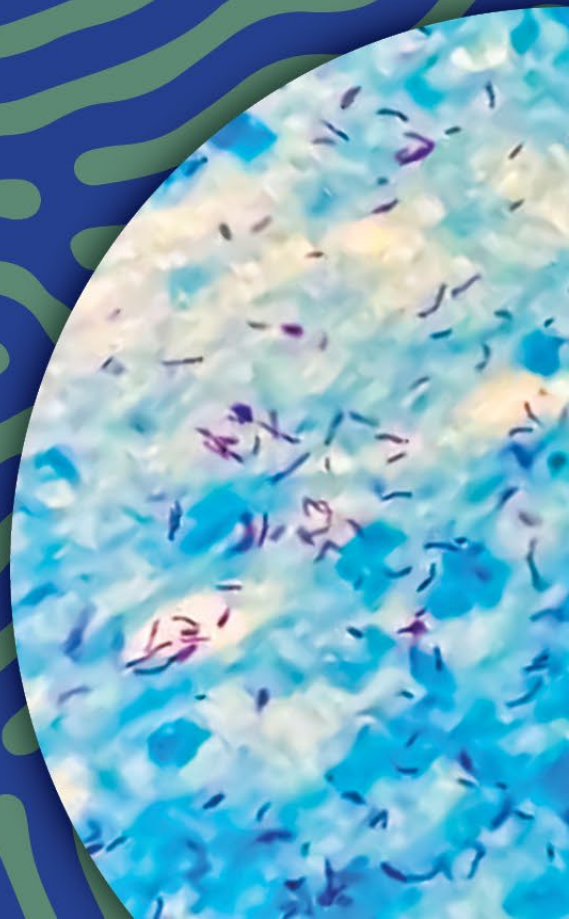
APHL ID LAB CON 2025

PMID: 35156034

Conclusions

-*S. maltophilia* is an environmental bacteria that can cause sever infections
-It has intrinsic resistance to many commonly used antibiotics
-Cefiderocol is a promising candidate for treatment but may have testing issues



Carbapenem Resistant Enterobacterales

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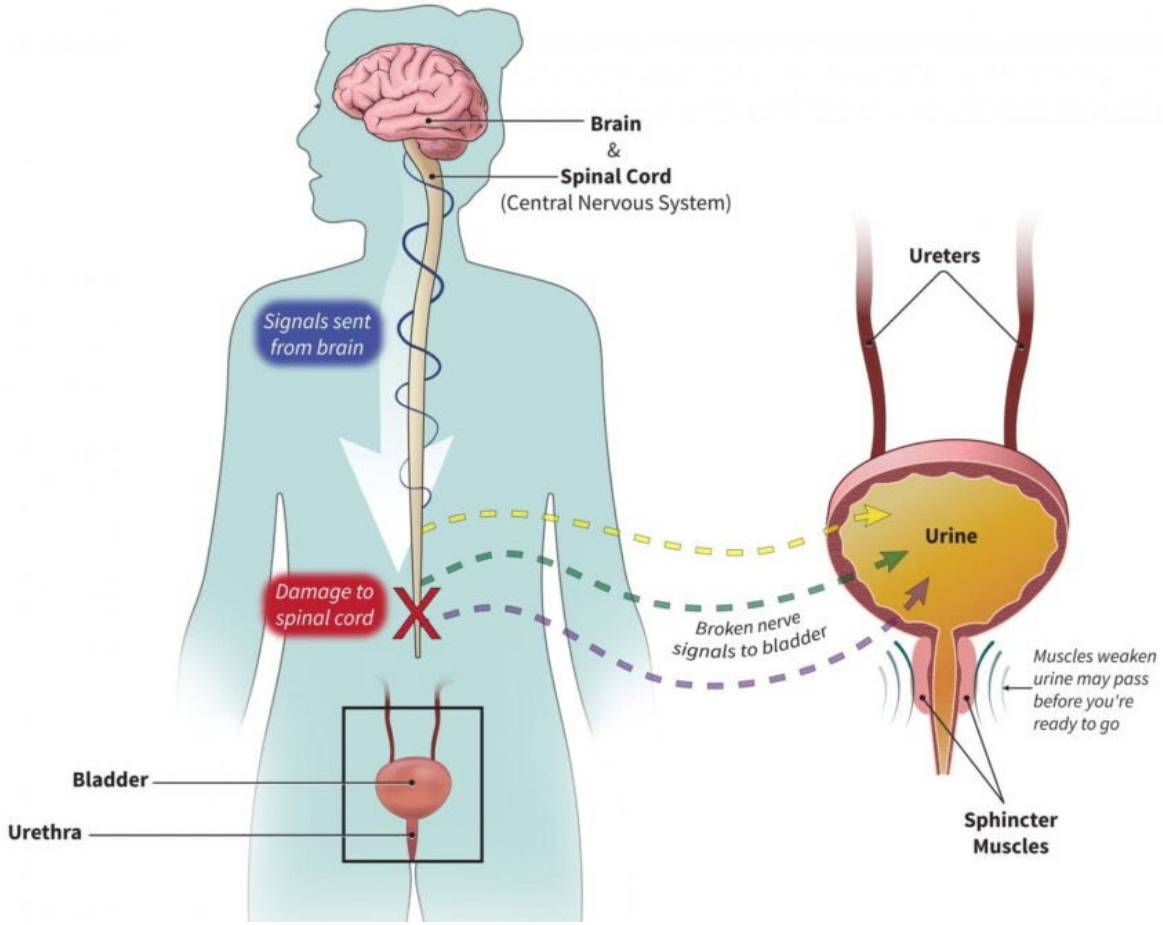
Robert Potter, PhD, D(ABMM)

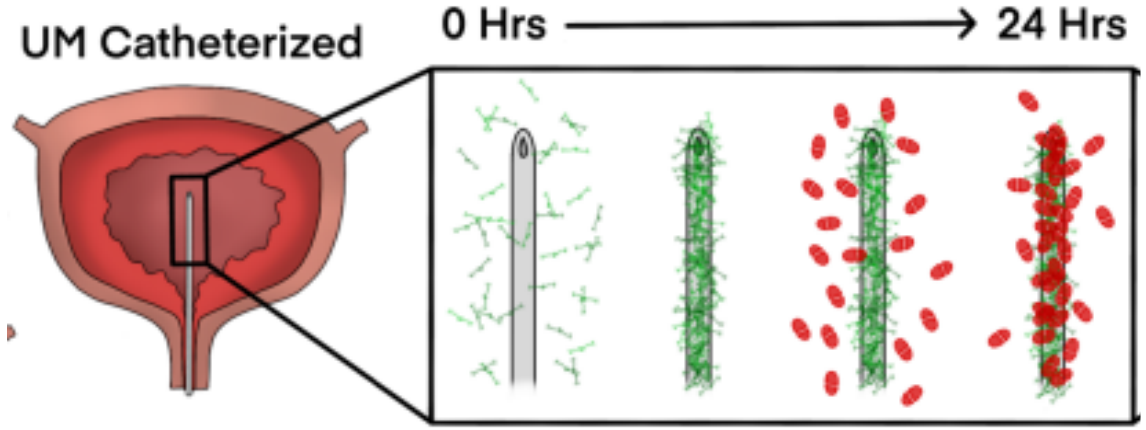
Assistant Director
Infectious Disease Diagnostics Laboratory
Children's Hospital of Philadelphia

Director, Outbreak Investigations
Center for Microbial Medicine
Children's Hospital of Philadelphia

Assistant Professor
Department of Pathology & Laboratory Medicine
The Perelman School of Medicine at the University of Pennsylvania

Patient is a 3 year old with neurogenic bladder presenting with UTI symptons



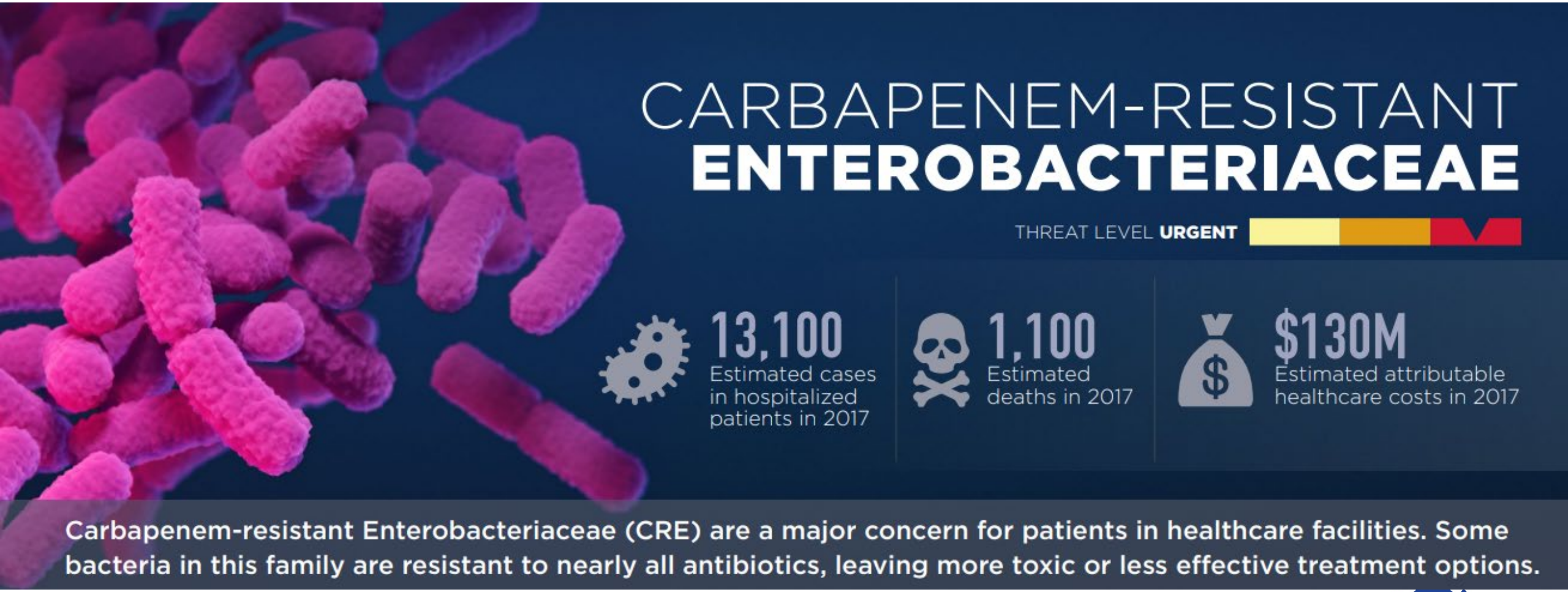


Patient grew at *bla*OXA-48 positive *E. coli*

Susceptibility

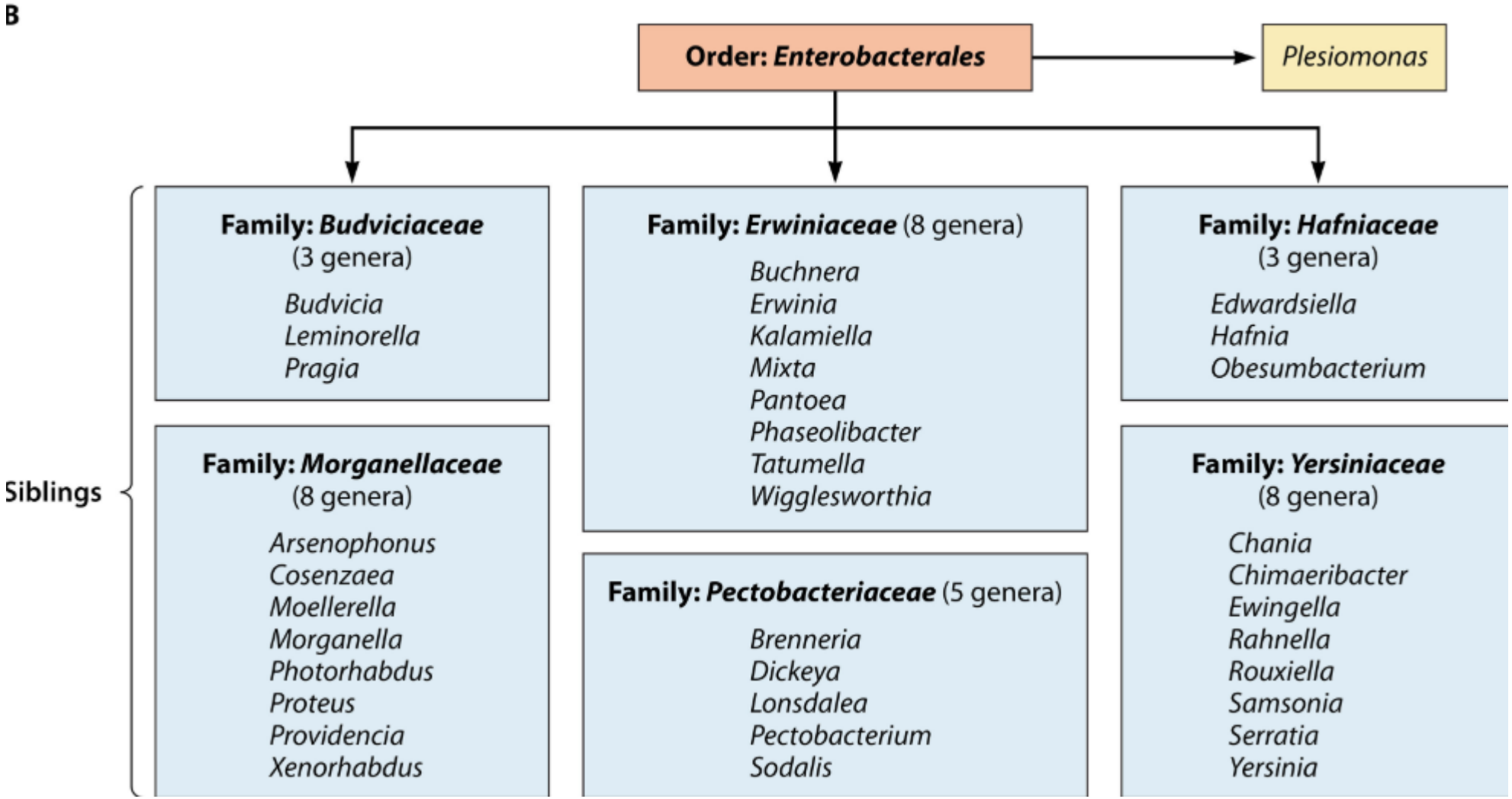
	Escherichia coli			
	MIC		MIC	
AZTREONAM	4.0	**Sensitive**		
CEFTAZIDIME	>=64	Resistant		
CIPROFLOXACIN	0.5	Intermediate		
GENTAMICIN	>=16	Resistant		
IMIPENEM			32.0	Resistant
AMPICILLIN/SULBACTAM	>=32	Resistant		
CEFAZOLIN	>=64	Resistant		
CEFTRIAXONE	>=64	Resistant		
NITROFURANTOIN	32.0	**Sensitive**		
MEROPENEM			>=32	Resistant
TRIMETHOPRIM/SULFA	>=320	Resistant		
LEVOFLOXACIN	1.0	Intermediate		
PIPERACILLIN/TAZOBACTAM	>=128	Resistant		
AMPICILLIN	>=32	Resistant		
CEFEPIME	8.0	Susceptible-Dose Dependent [1]		
ERTAPENEM			>32	Resistant
AMOXICILLIN/CA	16.0	Intermediate		
CEFTAZIDIME/ AVIBACTAM	>=16	Resistant		
MEROPENEM/VABORBACTAM	8.0	Intermediate		

Carbapenem-resistant Enterobacteriaceae are an urgent antimicrobial resistant threat



2019 CDC AR Threat Report

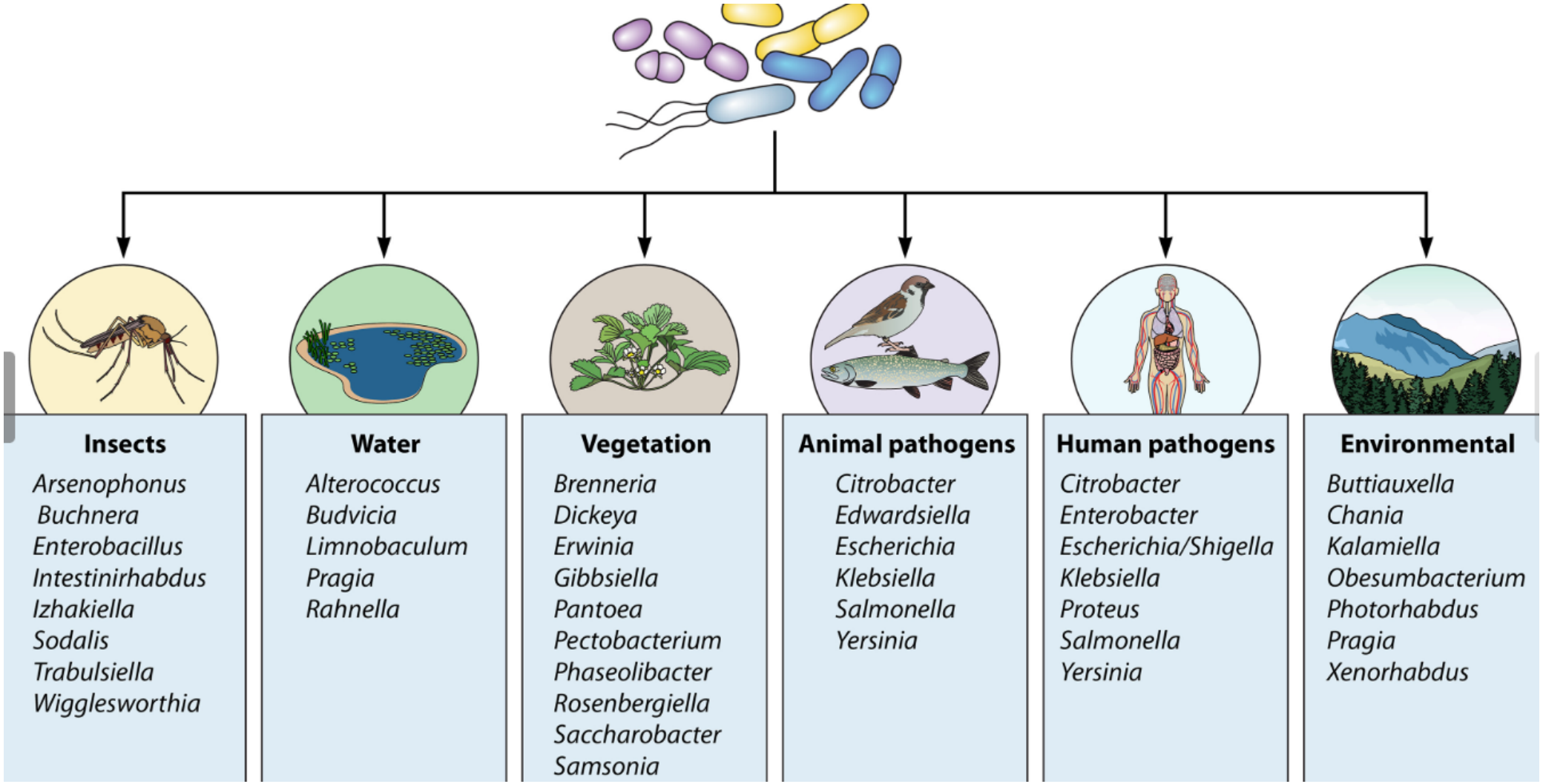
Enterobacterales is an order that includes many important human pathogens



#IDLabCon

PMID: 33627443

Enterobacterales is an order that includes many important human pathogens



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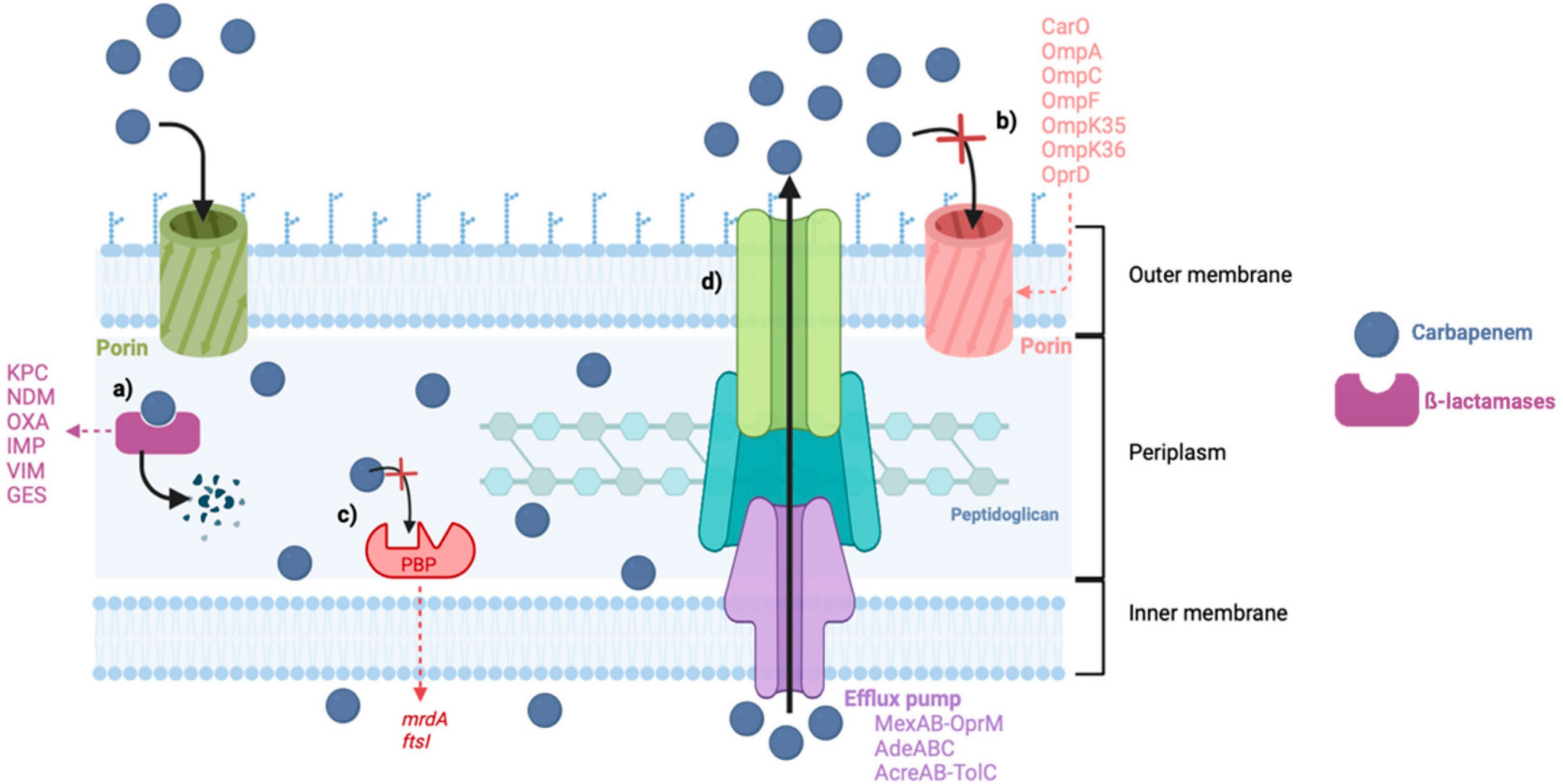
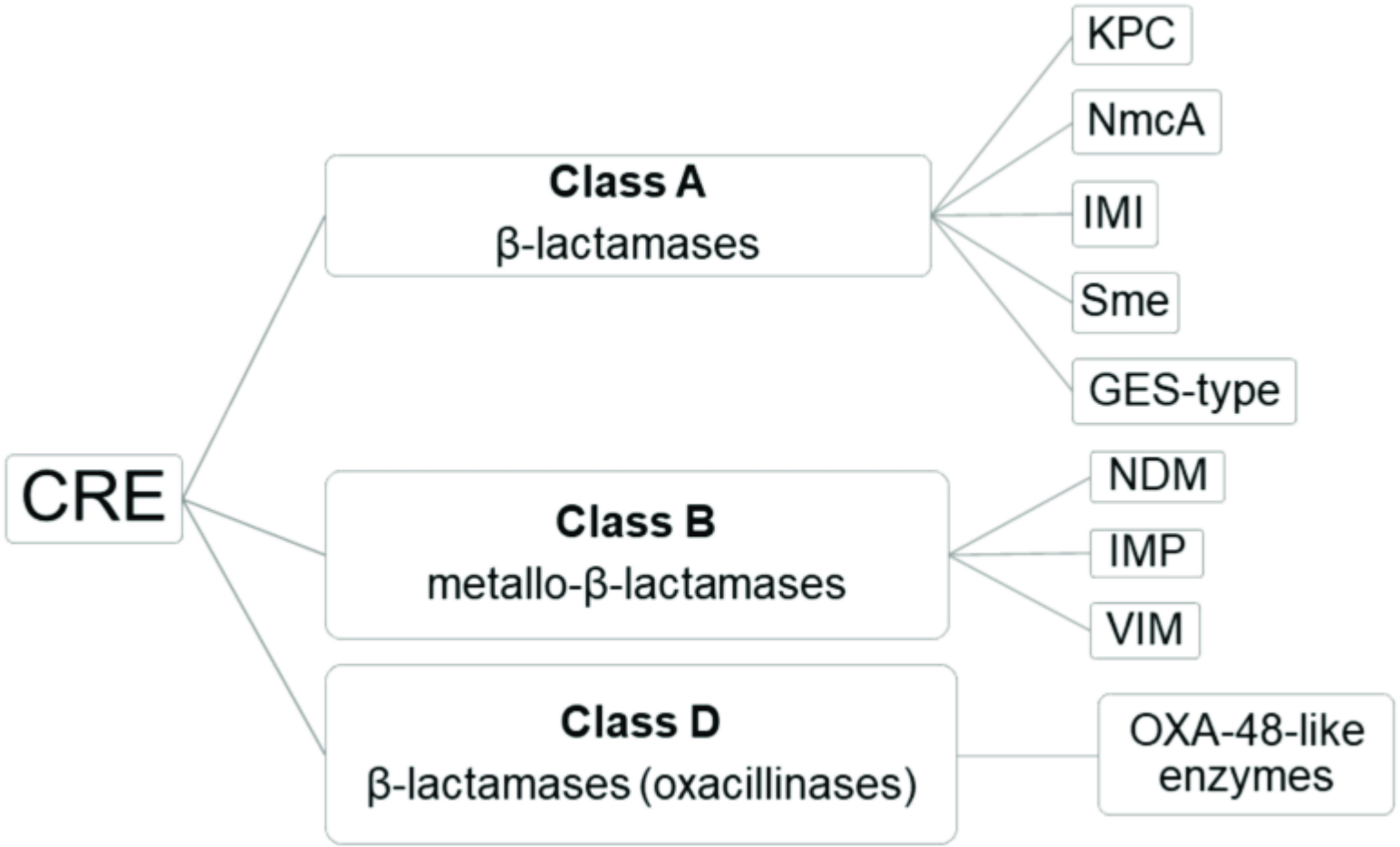
PMID: 33627443

High level carbapenem resistance is multifactorial but largely driven by carbapenemases



PMID: 38927223

Carbapenemases fall into Ambler Classes A, B, and D but not Class C



PMID: 28013264

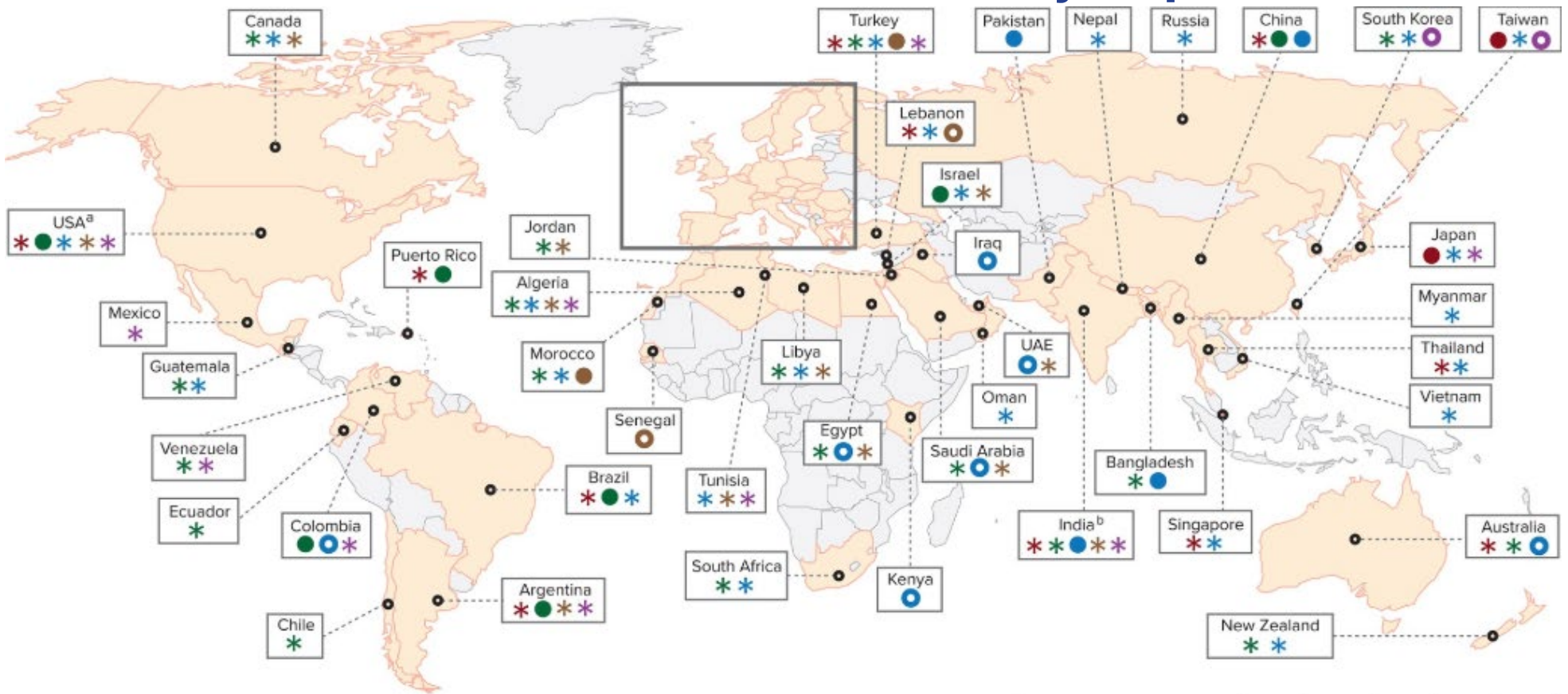
Infections with CP-CRE have a higher 14 day mortality rate compared to infections with non-CP-CRE

Fourteen-Day Mortality for Patients With Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* (CP-CRE) Compared With non-CP-CRE Bacteremia

Covariate	Odds Ratio (95% CI)	*P* Value	Adjusted Odds Ratio [a] (95% CI)	*P* Value
Carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* bacteremia	3.20 (1.06–9.61)	.04	4.92 (1.01–24.81)	.05
Pitt bacteremia score ≥4	9.13 (2.39–34.86)	.001	11.89 (2.38–59.30)	.005
Active empiric antibiotic therapy	.79 (0.27–2.29)	.67	2.46 (0.53–11.48)	.25
Active directed antibiotic therapy	.17 (0.04–0.72)	.01	0.10 (0.004–2.22)	.14
Days of combination antibiotic therapy	.89 (0.79–1.00)	.07	0.73 (0.59–0.93)	.01
Polymixin therapy administered	4.61 (1.16–18.3)	.03	5.57 (1.07–28.96)	.04
Diabetes	3.12 (0.99–9.84)	.05	3.42 (0.62–19.07)	.16
Immunocompromised	.45 (0.14–1.40)	.17	--	--
Carbapenem therapy administered	.82 (0.27–2.52)	.74	--	--
Meropenem minimum inhibitory concentration ≥16 µg/mL	1.40 (0.38–5.01)	.61	--	--

PMID: 28013264

The major carbapenem resistance genes are regionally endemic but due to travel can always spread



	IMP	KPC	NDM	OXA	VIM
Endemic/nationwide distribution	●	●	●	●	●
Significant outbreaks/ regional spread	○	○	○	○	○
Sporadic outbreak/ occurences	*	*	*	*	*

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PMID: 33627443

Large analysis of US CRE infections found that *K. pneumoniae* is most common CRE

	CPE (n=618)	Non-CP-CRE (n=194)	U-CRE (n=228)	All (n=1,040)	*P* value
Species					<0·001
K. pneumoniae	493 (80)	52 (27)	48 (21)	593 (57)	
ST258 *K. pneumoniae*	334 (54)	6 (3)	4 (2)	344 (33)	
Enterobacter spp.	46 (7)	73 (38)	73 (32)	192 (18)	
E. coli	38 (6)	33 (17)	51 (22)	122 (12)	
ST131 *E. coli*	22 (4)	13 (7)	24 (11)	59 (6)	
non-*K. pneumoniae Klebsiella* spp.	14 (2)	26 (13)	16 (7)	56 (5)	
other	27 (4)	10 (5)	40 (18)	77 (7)	
Meets 2012 CDC criteria for CRE	520 (84)	97 (50)	65 (29)	682 (66)	<0·001
Carbapenemases[a]					
bla_{KPC-2}	313 (51)			313 (30)	
bla_{KPC-3}	253 (41)			253 (24)	
other bla_{KPC}[b]	7 (1)			7 (1)	
bla_{NDM-1}	15 (2)			15 (1)	
other bla_{NDM}[c]	7 (1)			7 (1)	
bla_{OXA-48}	6 (1)			6 (1)	
Other $bla_{OXA-48-like}$[d]	15 (2)			15 (1)	
Other[e]	10 (2)			10 (1)	
Extended spectrum β-lactamase					
bla_{CTX-M}	121 (20)	59 (30)	45 (20)	225 (22)	0·004
bla_{SHV}[f]	217 (35)	19 (10)	14 (6)	250 (24)	<0·001
bla_{TEM}[g]	0 (0)	0 (0)	1 (<1)	1 (<1)	0·41
bla_{AmpC}	116 (19)	112 (58)	141 (62)	369 (35)	<0·001

PMID: 32151332

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Thankfully carbapenem resistance overall is relatively rare at CHOP

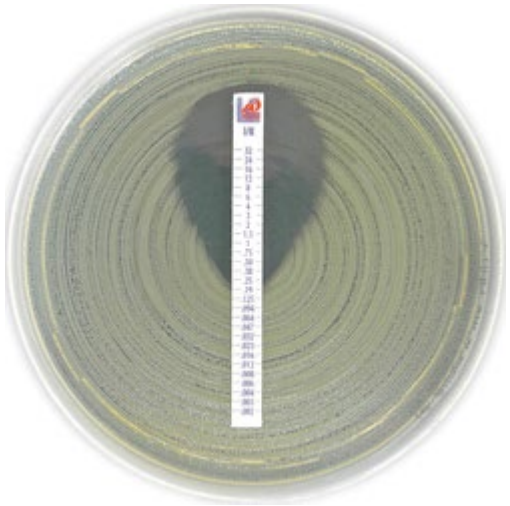
Gram-negative bacteria

Key:
Number of isolates = total number of isolates of that organism included in the antibiogram
Numbers in cells = percent of isolates susceptible to each antibiotic; unless otherwise specified, the denominator is the number found in the "number of isolates" column
Dark gray = intrinsic resistance/no breakpoint established
Light gray = antibiotic not recommended
White = no CHOP data/insufficient data to report percent susceptible

Organism	Number of isolates	Ampicillin	Ampicillin-sulbactam	Piperacillin-tazobactam[2]	Cefazolin	Ceftriaxone	Ceftazidime	Cefepime[2]	Ertapenem	Imipenem-cilastatin	Meropenem	Gentamicin	Tobramycin	Amikacin	Ciprofloxacin	Levofloxacin	Trimethoprim-sulfamethoxazole	Doxycycline	Minocycline	Nitrofurantoin[6]	Aztreonam
***Acinetobacter* spp.**	36		91				75			84	86	84	88	93		81	91	87	93		
Citrobacter freundii	35							97	100	100	100	88	88	100	80	82	74	73	83	88	77
Enterobacter cloacae	104							97	94	98	98	95	96	100	88	88	78	84	86	53	82
Escherichia coli	1100	50	60	96	Urine[3]: 88 (876/988)	91	94	94	99	100	99	88	89	99	74	75	71	78	91	98	93
Klebsiella aerogenes[1]	26							88	90	90		96	100	100	100	95	92	100	100	12	76
Klebsiella oxytoca	68		64	88		91	100	100	100	100	100	95	94	100	89	91	88	93	91	88	95
Klebsiella pneumoniae	211		70	90	Urine[3]: 81 (129/158)	81	86	87	98	98	98	91	88	99	78	77	79	73	82	25	85
Proteus mirabilis	147	84	91	100	Urine[3]: 92 (108/117)	93	97	95	100		98	91	96	100	85	86	79				97
Pseudomonas aeruginosa[5]	445			88			93	91		86	93		96	100[4]	87	84					
***Pseudomonas aeruginosa* – mucoid + nonmucoid**[4]	45			84			95	84		80	88		93		80	71					88
***Salmonella*, non-typhoid**	36	88				100									83		97				
Serratia marcescens	79					88	100	100	100	96	100	89	89	97	77	83	97	95	95		98

Multiple methods are used to identify CRE/CPE

Phenotypic



AST

CIA

Protein

NG-Carba 5

Genetic

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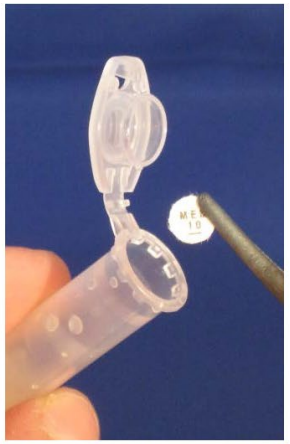
Carbapenemase activity can be detected by CIM/CIA assay

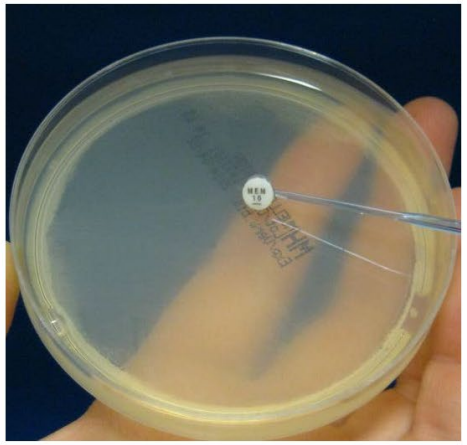
Suspend full loop of bacteria in H_2O



Add 10 µg meropenem disk

+/-EDTA

Incubate for 2 hours 35°C



Place on Mueller Hinton agar inoculated *with E. coli* ATCC 25922

Incubate for at least 6 hours 35°C

Read presence or absence of inhibition zone

+

Carbapenemase activity

-

No carbapenemase activity

PMID: 25798828

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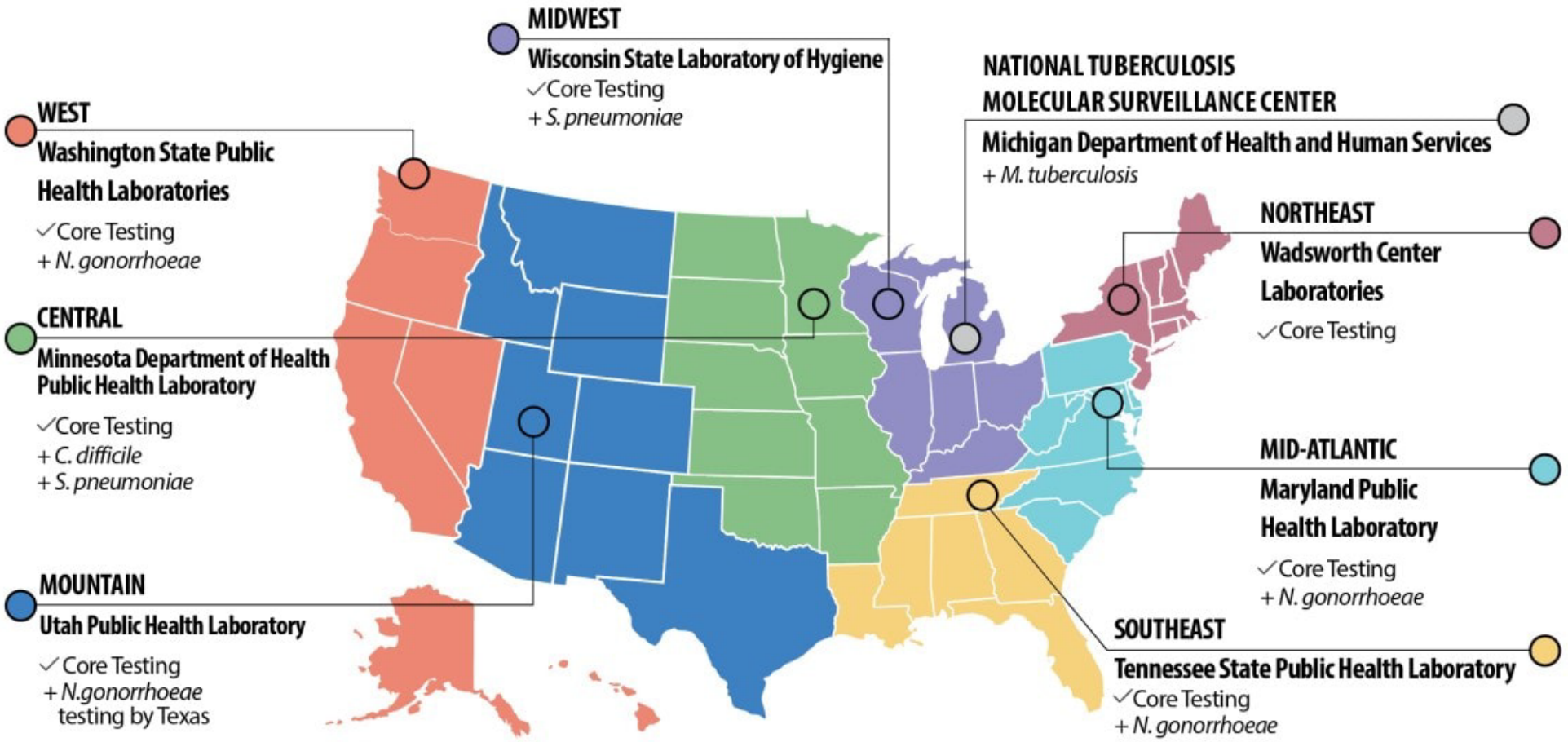
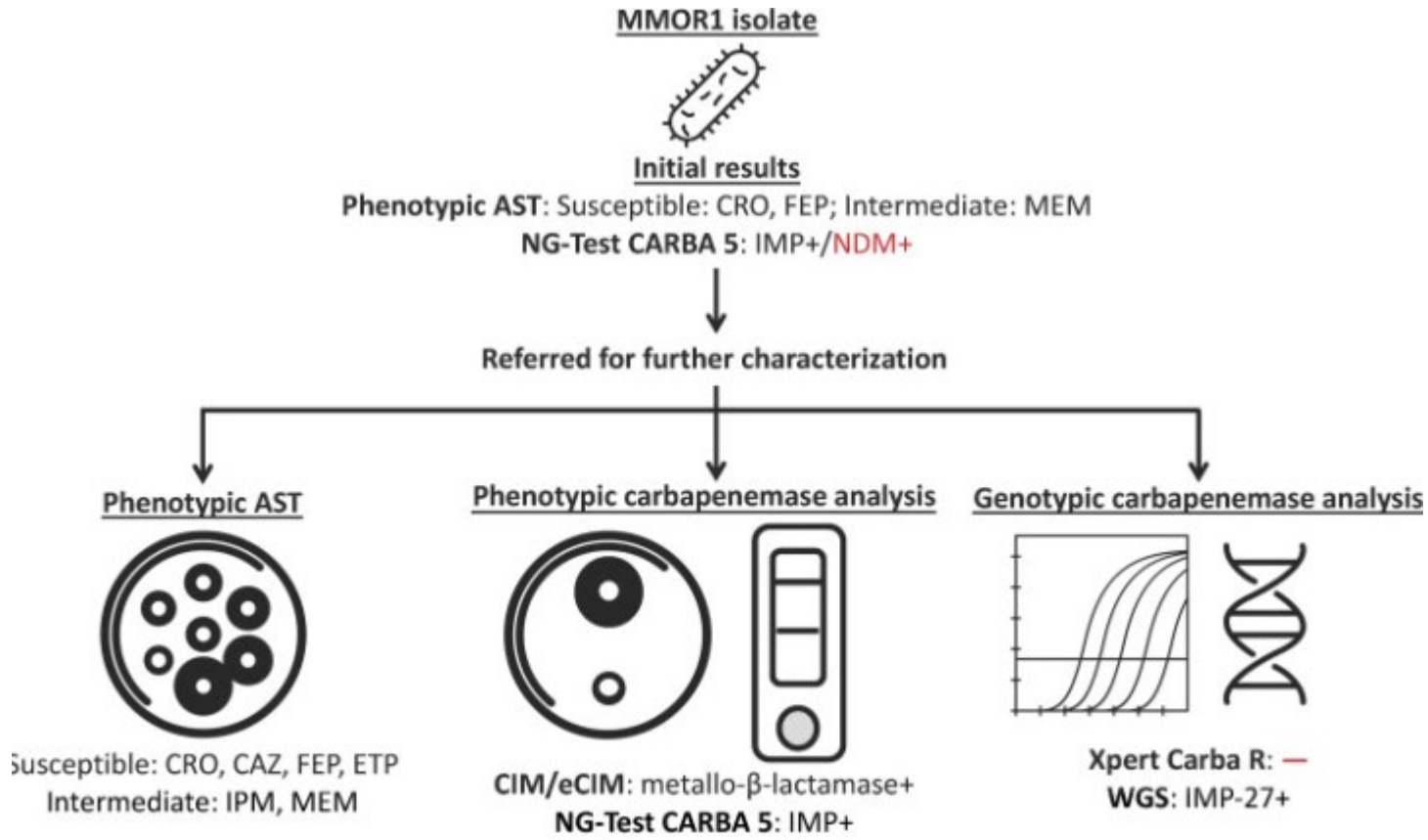
APHL ID LAB CON 2025

Isolate submission to Antimicrobial Resistance Laboratory Network laboratory is helpful for national surviellance

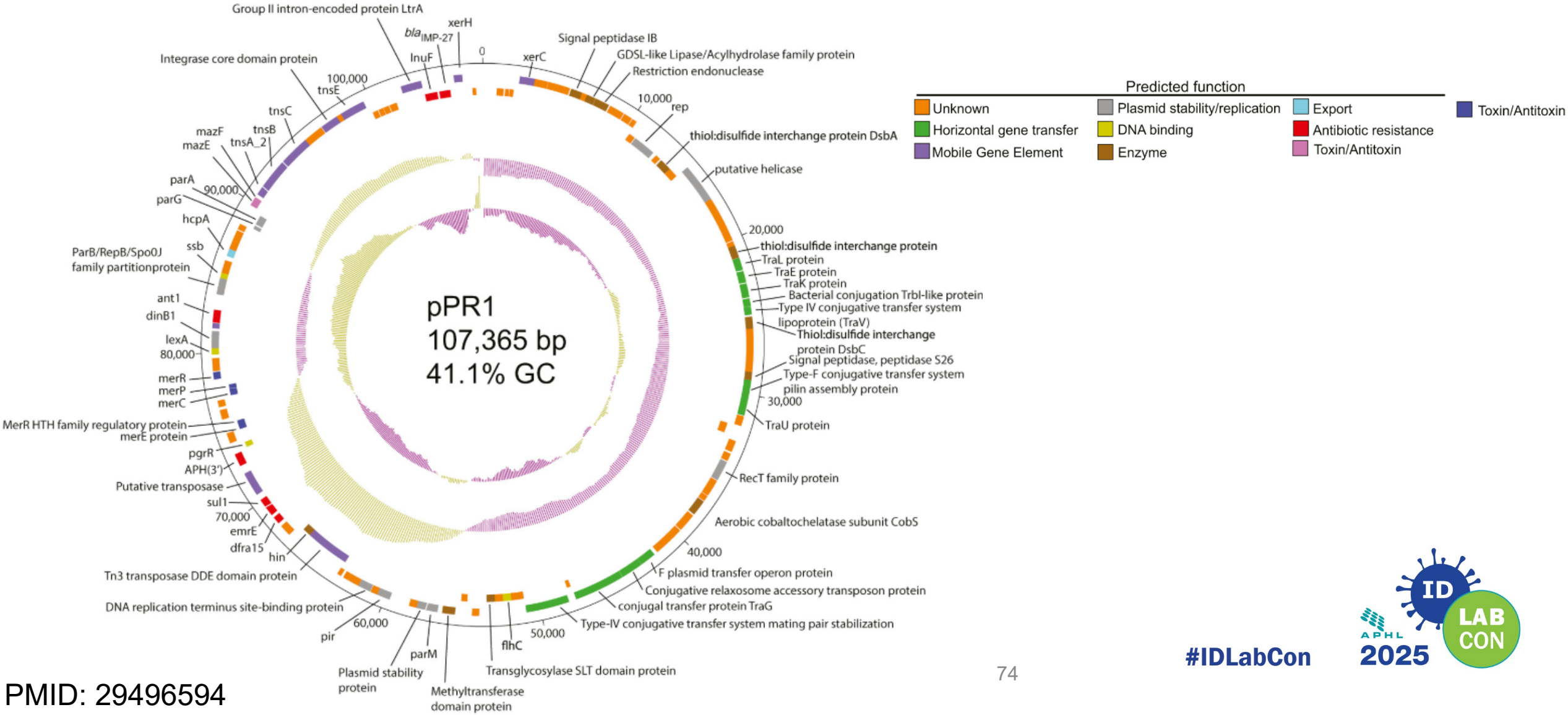


IMP-27 is a carbapenemase gene that was undetected by GeneXpert but identified on NG-test Carba 5



PMID: 25798828

Carbapenemase genes are on large mobilizable plasmids that contain other antibiotic resistance genes



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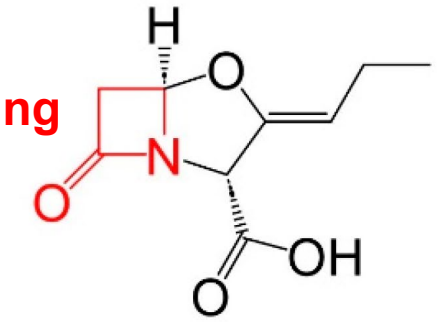
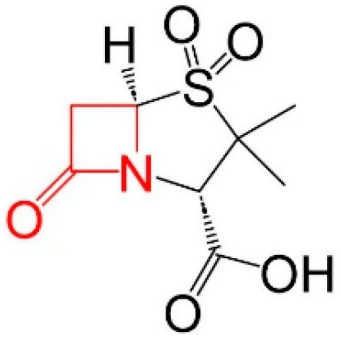
Non β-lactam β-lactamase inhibitors restore efficacy of carbapenems against CRE

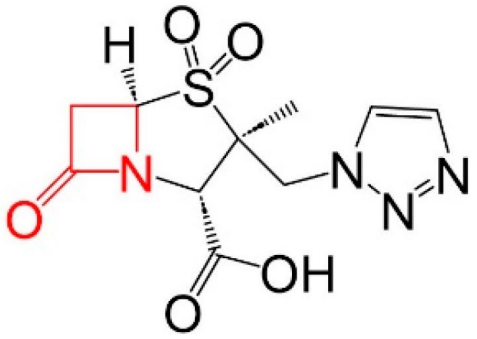
β-lactam ring



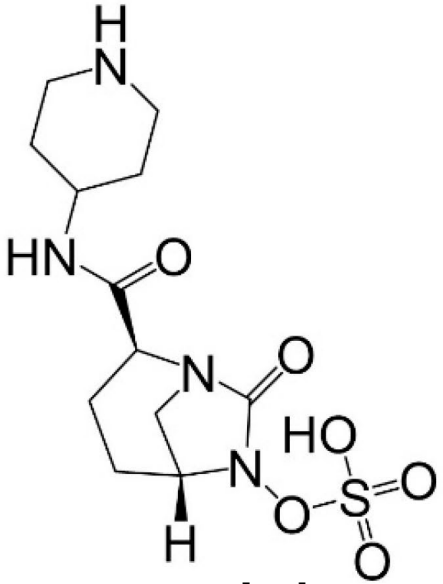
Clavulanate



Sulbactam

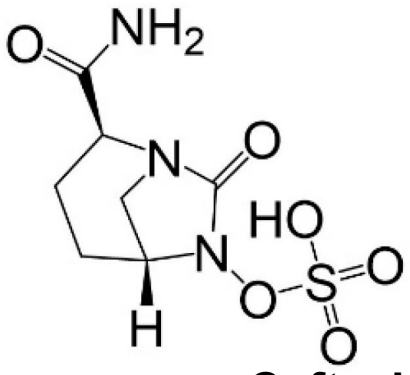


Tazobactam



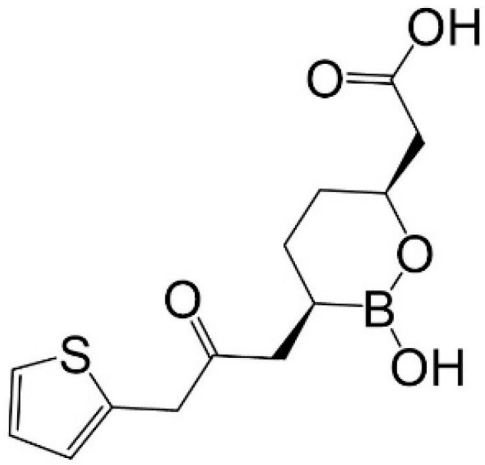
+Imipenem

Relebactam



+Ceftazidine

Avibactam



+Meropenem

Vaborbactam

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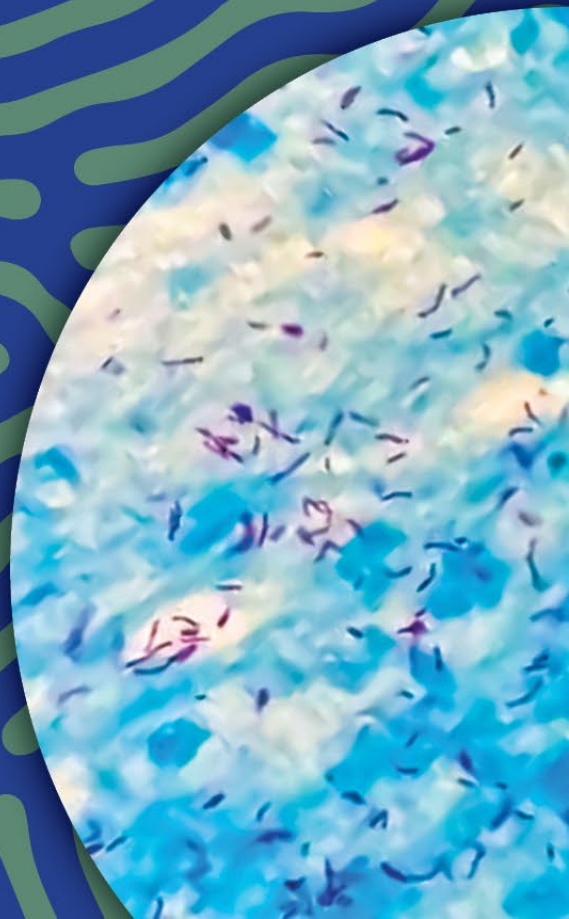
Conclusions

-CRE can be CP or non-CP
-K. pneumoniae and E. coli are most common CP-CRE
-Carbapenemase genes are regionally associated by can spread
-Multiple methods can be used to identify CRE carriage



Limitations of Antibiotic Susceptibility Testing (ft. GPCs)

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Robert Potter, PhD, D(ABMM)

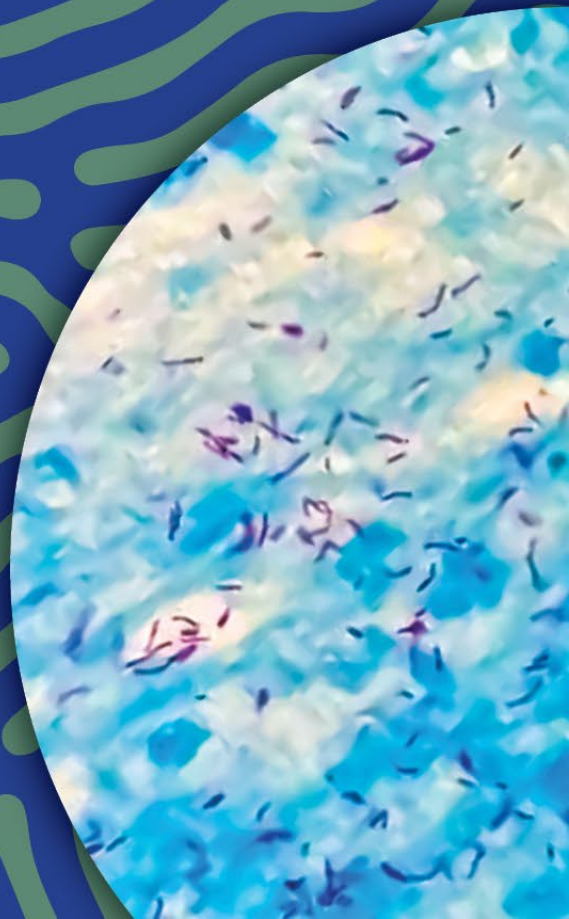
Assistant Director
Infectious Disease Diagnostics Laboratory
Children's Hospital of Philadelphia

Director, Outbreak Investigations
Center for Microbial Medicine
Children's Hospital of Philadelphia

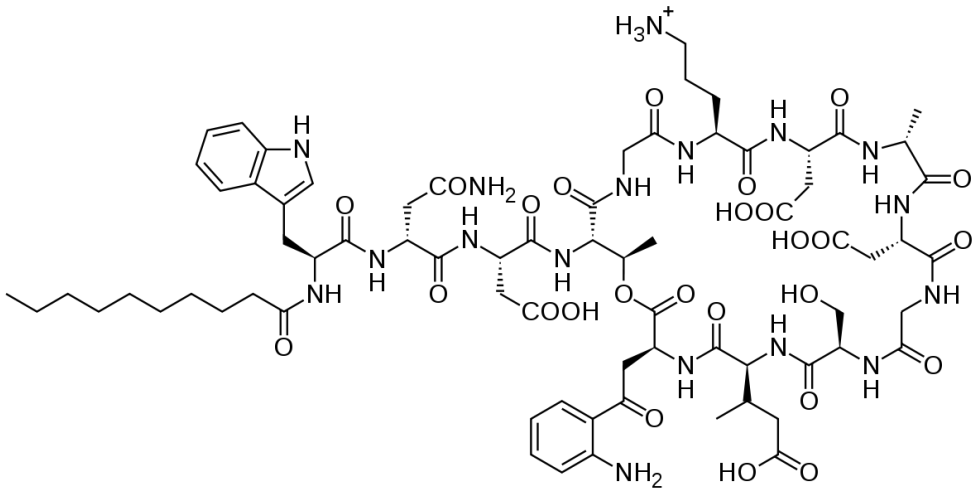
Assistant Professor
Department of Pathology & Laboratory Medicine
The Perelman School of Medicine at the University of Pennsylvania

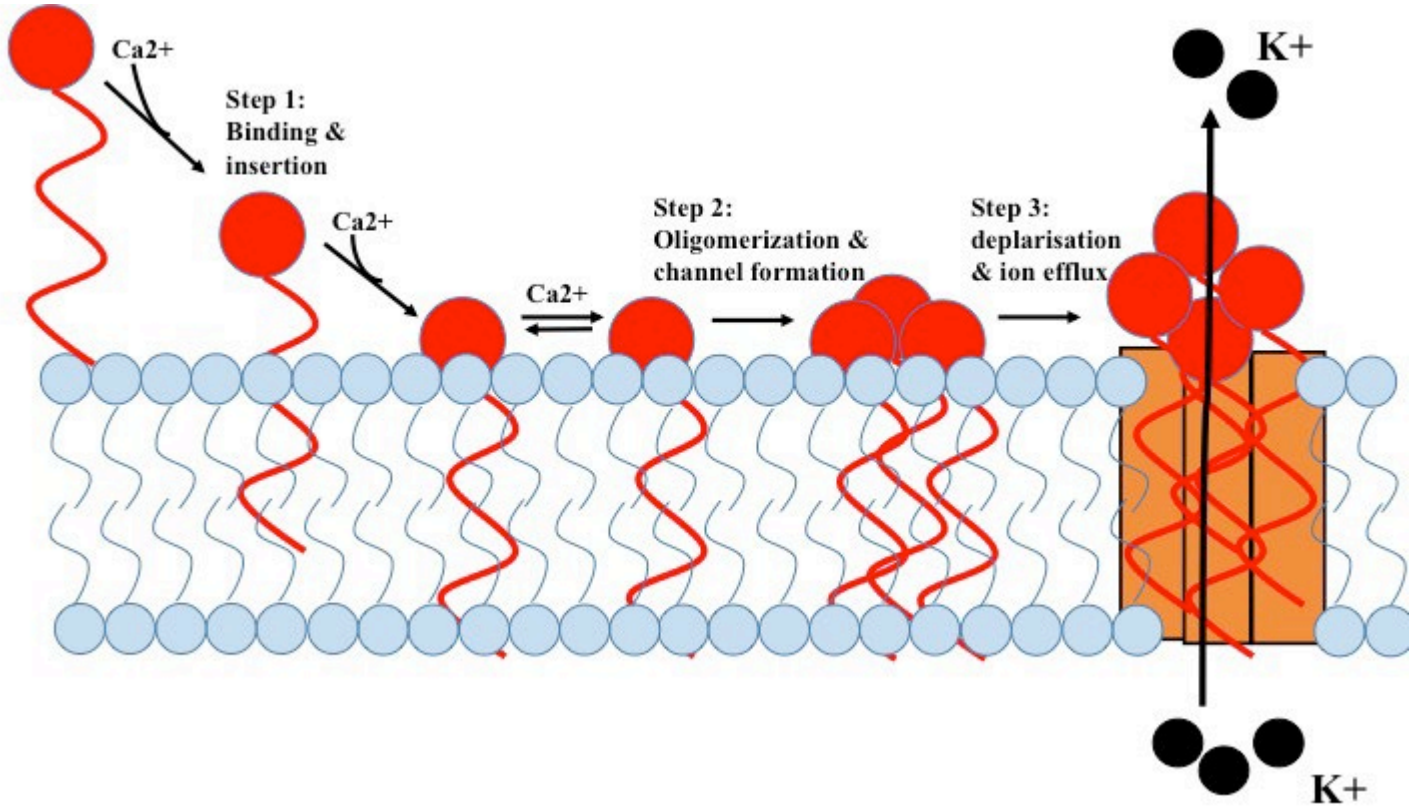
-Daptomycin and *Enterococcus* spp.

-Inoculum effect in *Staphylococcus aureus*



Daptomycin is a bactericidal lipopeptide antibiotic that causes pore formation in Gram-Positive cell membranes





PMID: 31504338

Enterococcus spp. Have elevated baseline daptomycin MICs compared to *S. aureus*

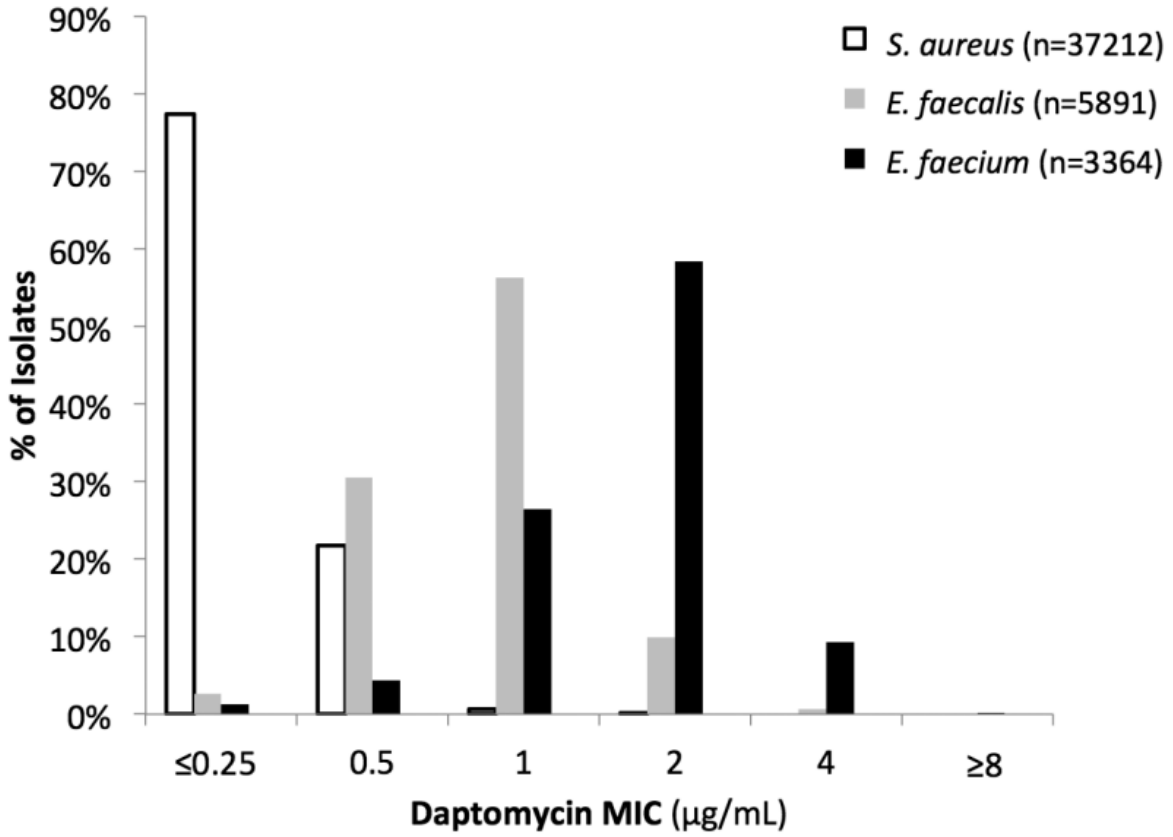


Figure 1. Daptomycin MIC distributions for *Staphylococcus aureus*, *Enterococcus faecalis*, and *Enterococcus faecium* for more than 46 000 isolates from 212 European and US medical centers from 2009–2013 by broth microdilution [19]. Abbreviation: MIC, minimum inhibitory concentration.

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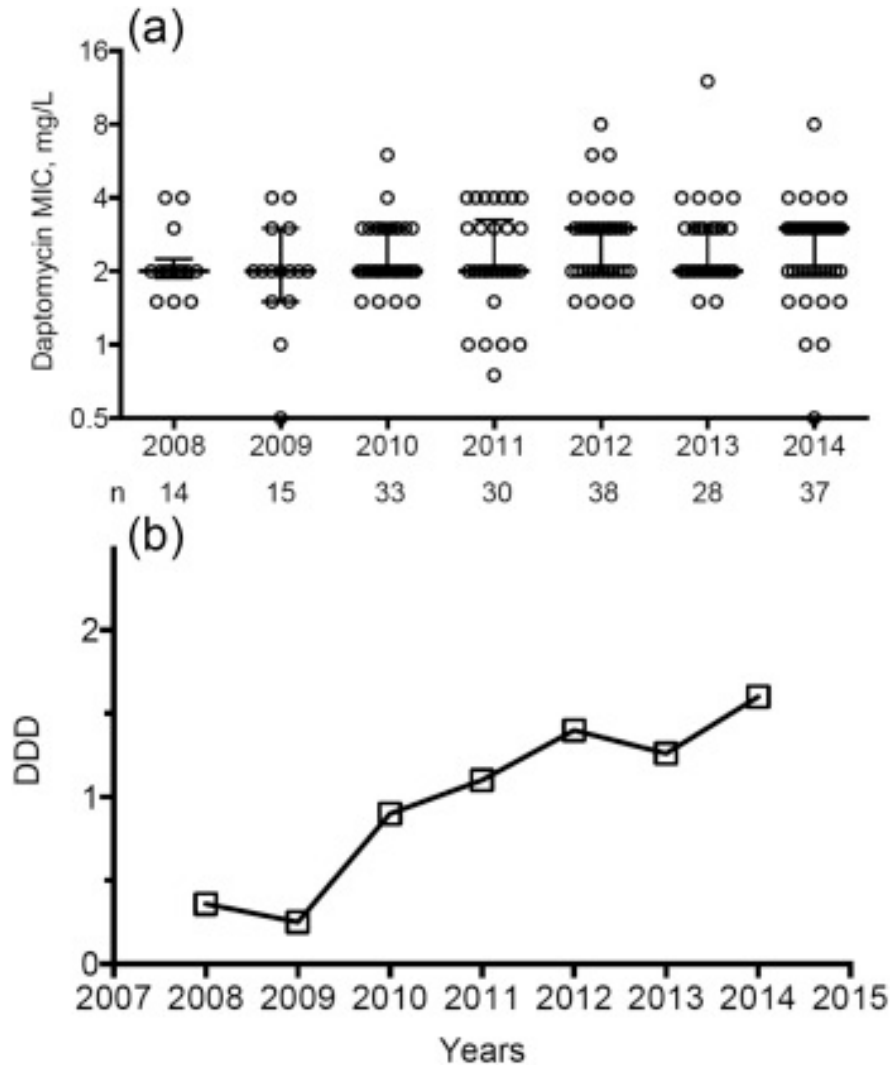
Daptomycin consumption (*b*) has increased since 2009-2015 but resistance has (so far) not increased (*a*)



PMID: 27746397

Daptomycin breakpoints have gone through changes since M100 28th Ed

Table 1. Comparison of Revised With Previous Clinical and Laboratory Standards Institute Breakpoints for Daptomycin and Enterococci

Version of Breakpoints	Susceptible (S), μg/mL	Susceptible Dose-Dependent (SDD), μg/mL	Intermediate (I), μg/mL	Resistant (R), μg/mL
M100, 28th ed. (previous)	≤4	…	…	…
M100, 29th ed. (revised 2019)	≤1[a]	2–4[b]	…	≥8
M100, 30th ed. (revised 2020—*Enterococcus faecium*)	…	≤4[b]	…	≥8
M100, 30th ed. (revised 2020—other species)	≤2[a]	…	4	≥8

[a]The breakpoint for susceptible is based on a dosage regimen of 6 mg/kg/day in adults.

[b]The breakpoint for S-DD is based on a dosage regimen of 8–12 mg/kg/day in adults and is intended for serious infections due to *Enterococcus* species. Consultation with an infectious diseases specialist is recommended.

PMID: 31504338

FDA breakpoints also exist for *E. faecalis*

		Minimum Inhibitory Concentrations (mcg/mL)			
		S	SDD[a]	I	R
Current CLSI breakpoints, (published in M100, 29 ed. in March 2019)	*E. faecium* only	-	≤4	-	≥8
	Enterococcus spp. other than *E. faecium*	≤2	-	4	≥8
Current FDA breakpoints (published in Sep 2020)	*E. faecalis* (including vancomycin-resistant isolates)	≤2	-	4	≥8

Monte Carlo simulations were used to estimate the probabilities of achieving pharmacodynamic thresholds

Daptomycin MIC (μg/mL)	30-Day Survival[a] *f*AUC/MIC >27.4	Microbiologic Response[a] *f*AUC/MIC >20.0	1-Log Kill in the Murine Neutropenic Thigh Model *f*AUC/MIC >12.9[b]
Daptomycin 6 mg/kg/day (US FDA-approved dosage)			
1	91–98[c]	99–100[c]	100[c]
2	32–54	63–83	94–99[c]
4	2–6	8–20	38–60
8	0	0	2–7
Daptomycin 8 mg/kg/day			
1	99–100[c]	100[c]	100[c]
2	61–80	87–96[c]	99–100[c]
4	7–18	25–45	66–85
8	0	0	10–23
Daptomycin 10 mg/kg/day			
1	100[c]	100[c]	100[c]
2	80–93	96–99[c]	100[c]
4	18–36	45–67	85–95[c]
8	0–2	3–10	23–42
Daptomycin 12 mg/kg/day			
1	100[c]	100[c]	100[c]
2	91–98[c]	99–100[c]	100[c]
4	32–54	63–83	94–99[c]
8	2–6	8–20	38–60

Data are presented as percentages. Monte Carlo simulations with adjustments for inflated variance were used to derive these probabilities. Abbreviations: CLSI, Clinical and Laboratory Standards Institute; *f*AUC/MIC, area under the free drug concentration time curve to minimum inhibitory concentration ratio; FDA, Food and Drug Administration; MIC, minimum inhibitory concentration.

PMID: 31504338

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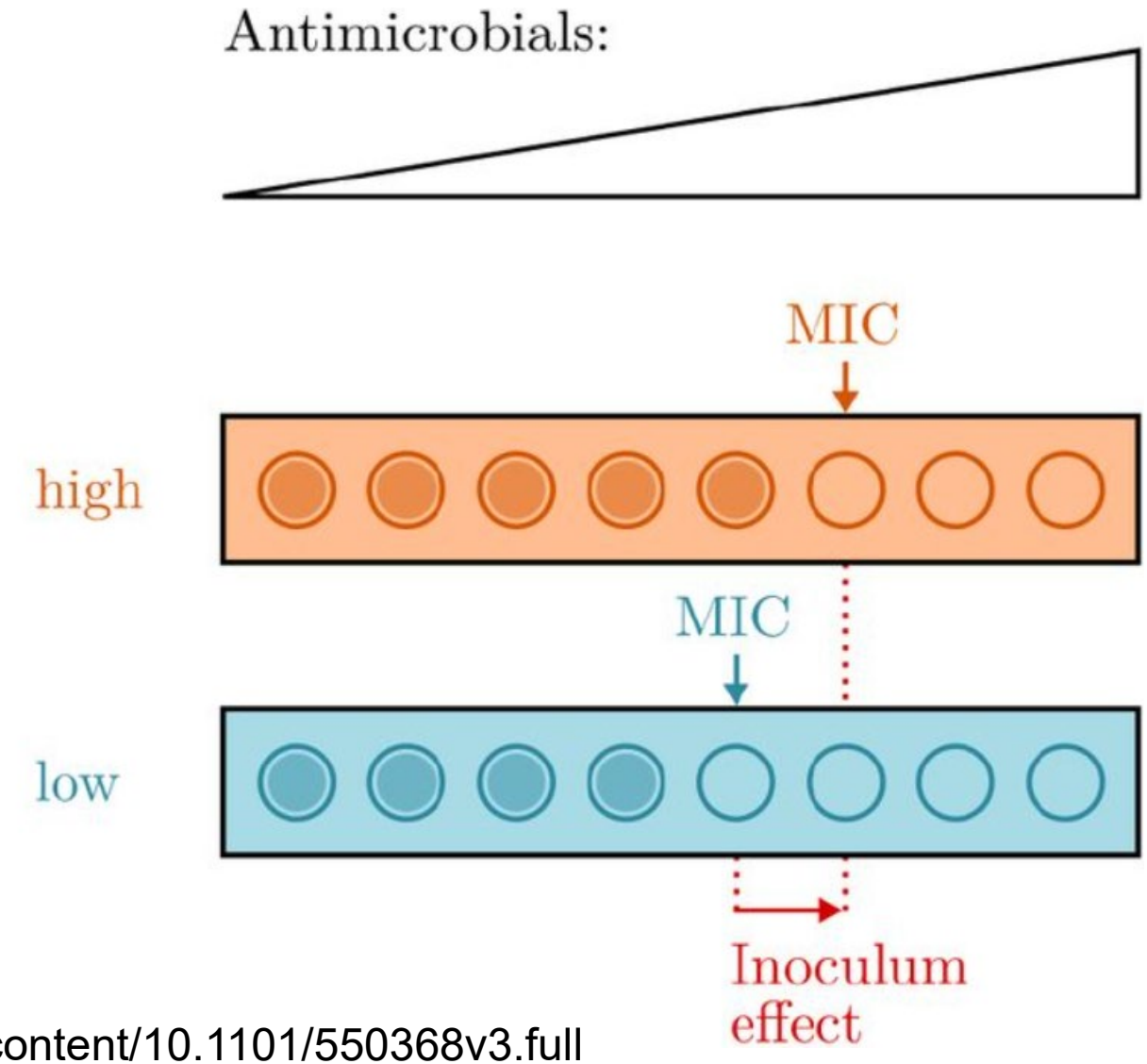
Inoculum effect is the observation of higher MICs with higher inoculums for certain bug-drug combinations



https://www.biorxiv.org/content/10.1101/550368v3.full

Cefazolin Inoculum Effect observed in certain in *S. aureus* strains and results in in higher MICs

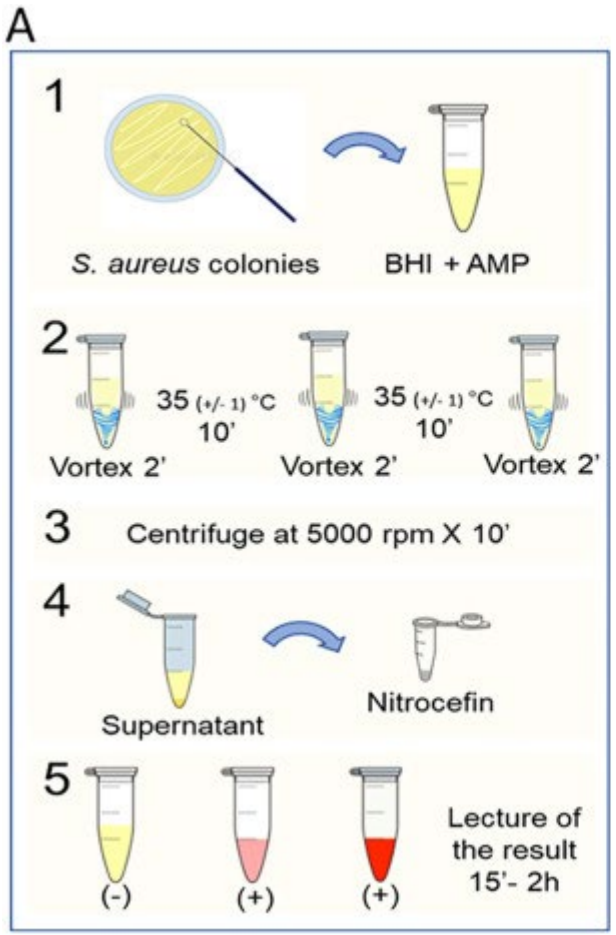
TABLE 2 MIC distributions of CzIE-positive and CzIE-negative isolates

MIC (μg/mL)	No. (%) of CzIE-positive isolates (n = 57) at:		No. (%) of CzIE-negative isolates (n = 248) at:	
	Standard inoculum	High inoculum	Standard inoculum	High inoculum
0.25	3 (5.3)[a]	NA[c]	98 (39.5)[a]	79 (31.9)
0.5	36 (63.2)	NA	142 (57.3)	29 (11.7)
1	17 (29.8)[b]	NA	8 (3.2)[b]	71 (28.6)
2	1 (1.8)	NA	0	25 (10.1)
4	0	NA	0	21 (8.5)
8	0	NA	0	23 (9.3)
16	0	17 (29.8)	0	NA
32	0	27 (47.4)	0	NA
>32	0	13 (22.8)	0	NA
Geometric mean MIC (μg/mL)	0.60	NA	0.39	0.87
Modal MIC (μg/mL)	0.5	32	0.5	1.0

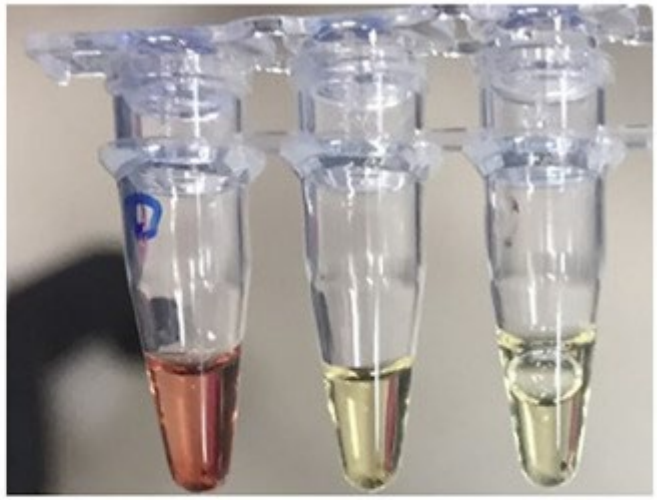
[a]$P < 0.0001$.
[b]$P < 0.0001$.
[c]NA, not applicable.

PMID: 35578988

Cefazolin Inoculum Effect can be observed via beta-lactamase hydrolysis of nitrocefin



B



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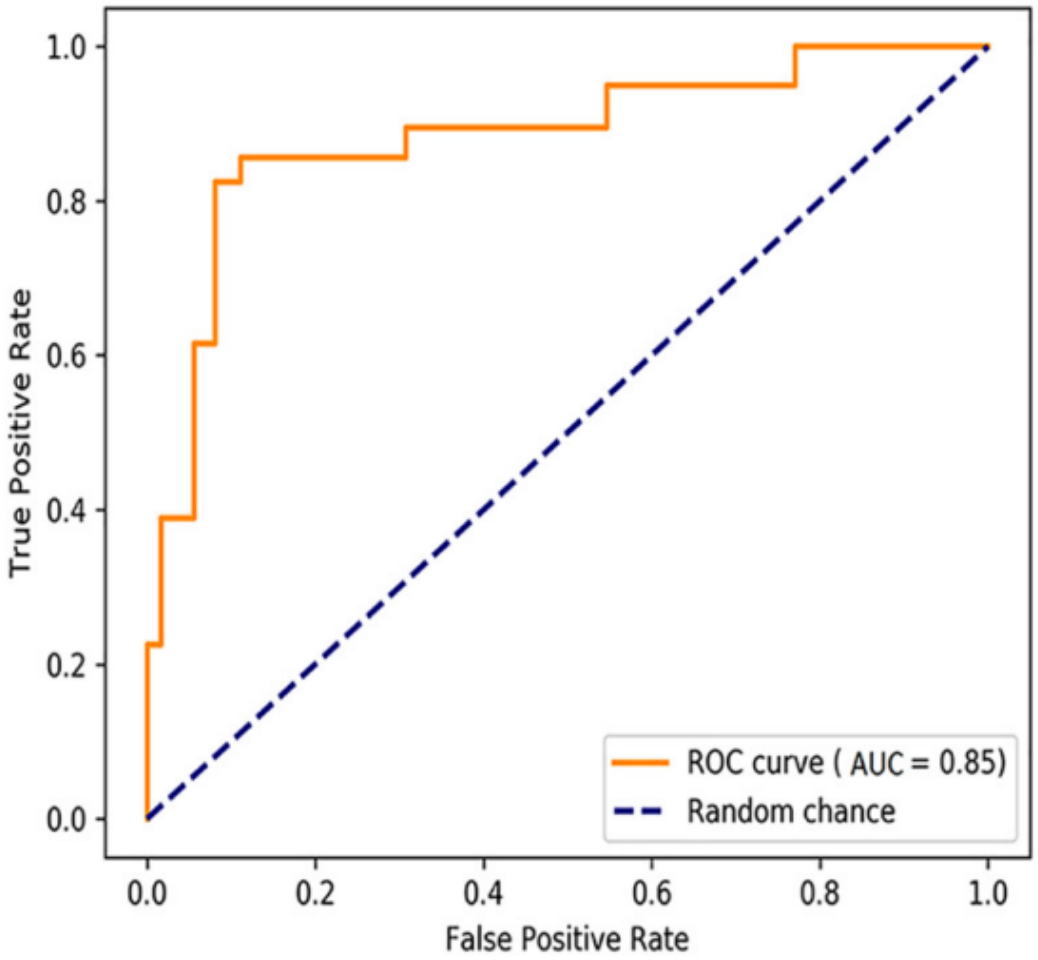
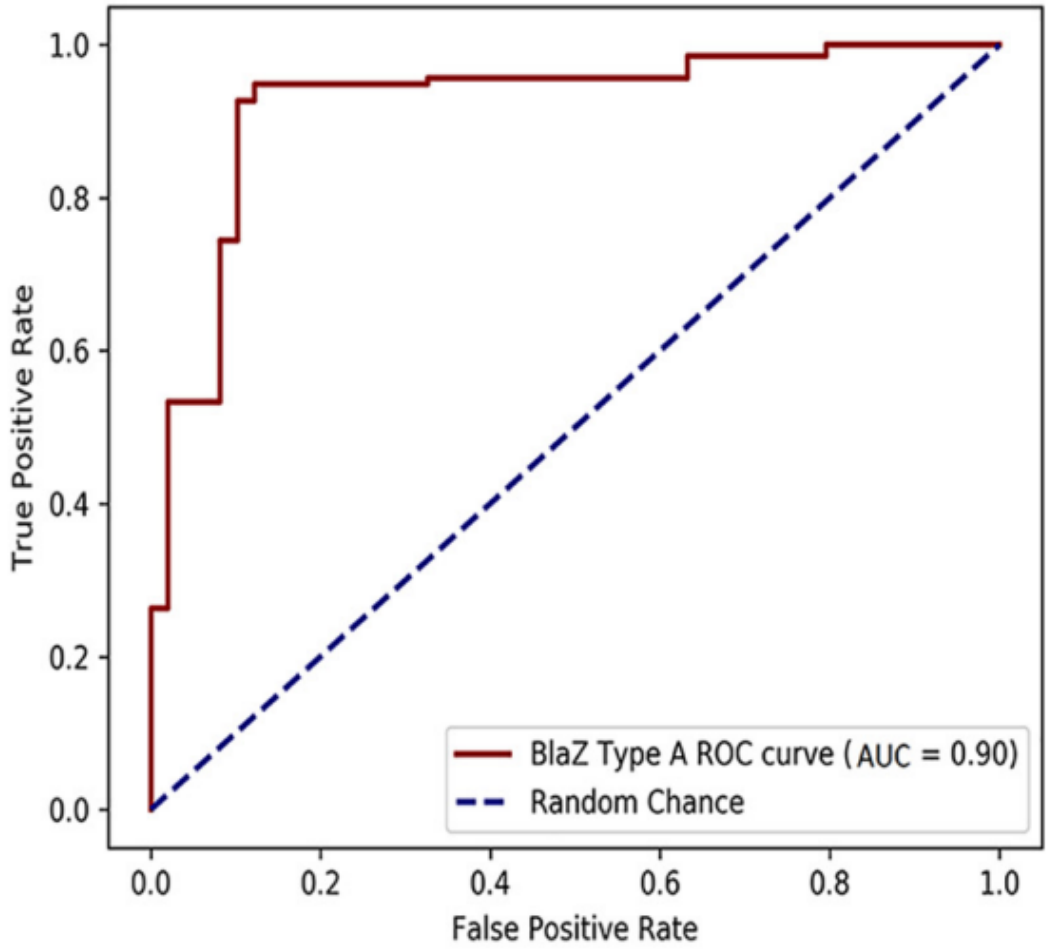
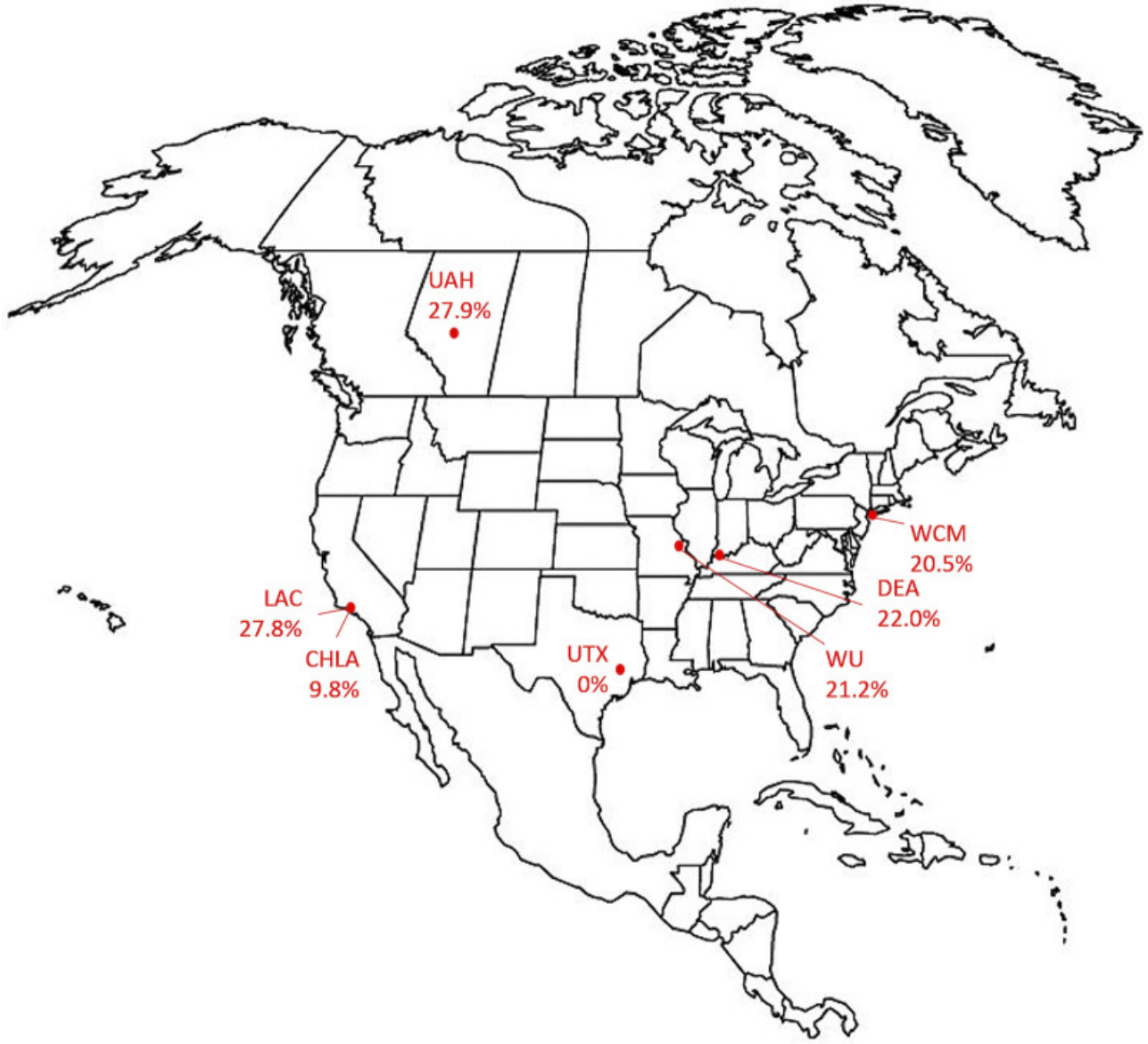
Area under the curve (AUC) analysis was good (.85) for all MSSA but better (.9) for BlaZ type A isolates (.9)





PMID: 33536292

Cefazolin Inoculum Effect in *S. aureus* varied by geography rom 0% in Texas (USA) to 28% in Alberta (Canada)



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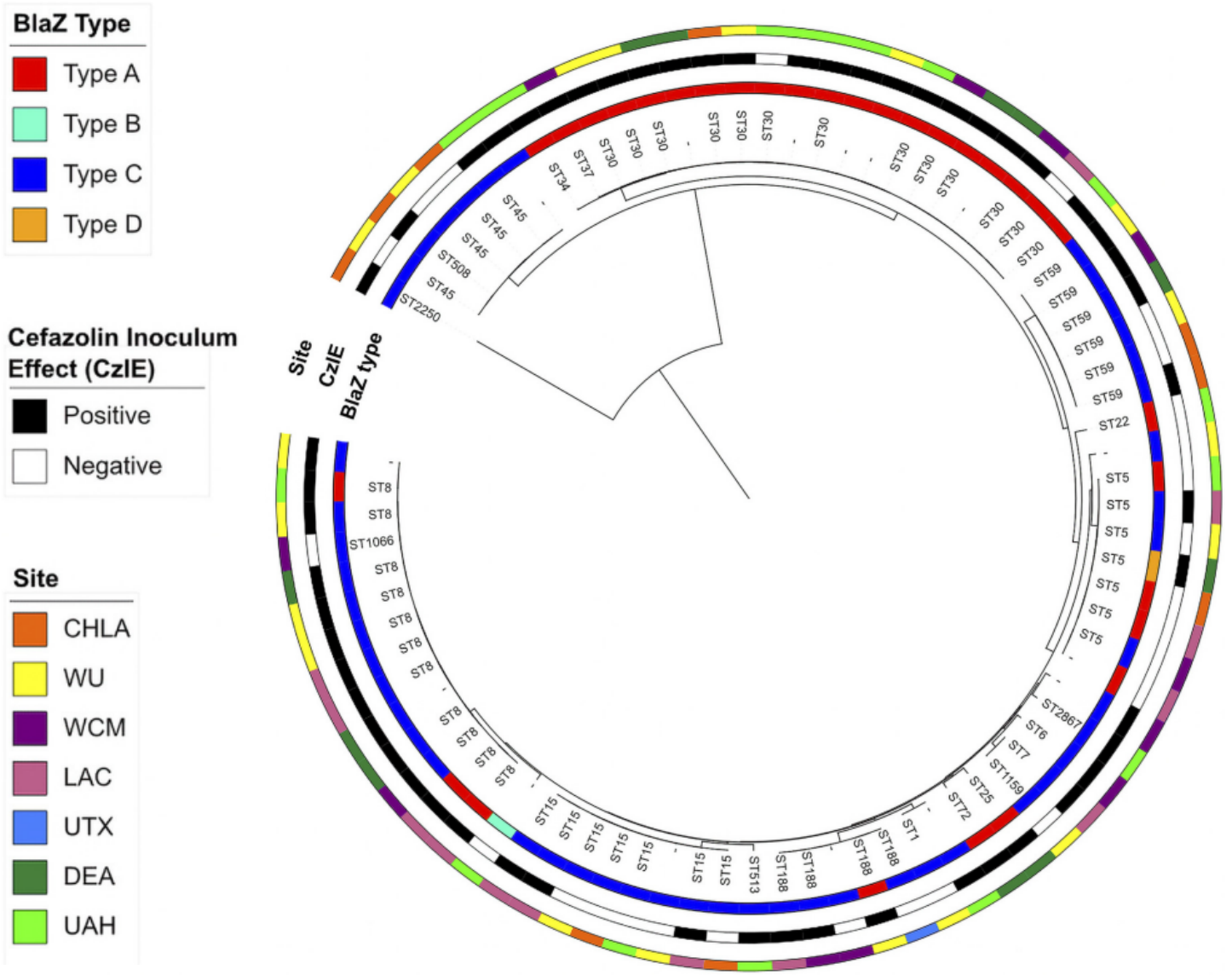
PMID: 35578988

Cefazolin Inoculum Effect in *S. aureus* is not constrained by phylogenomic strain background



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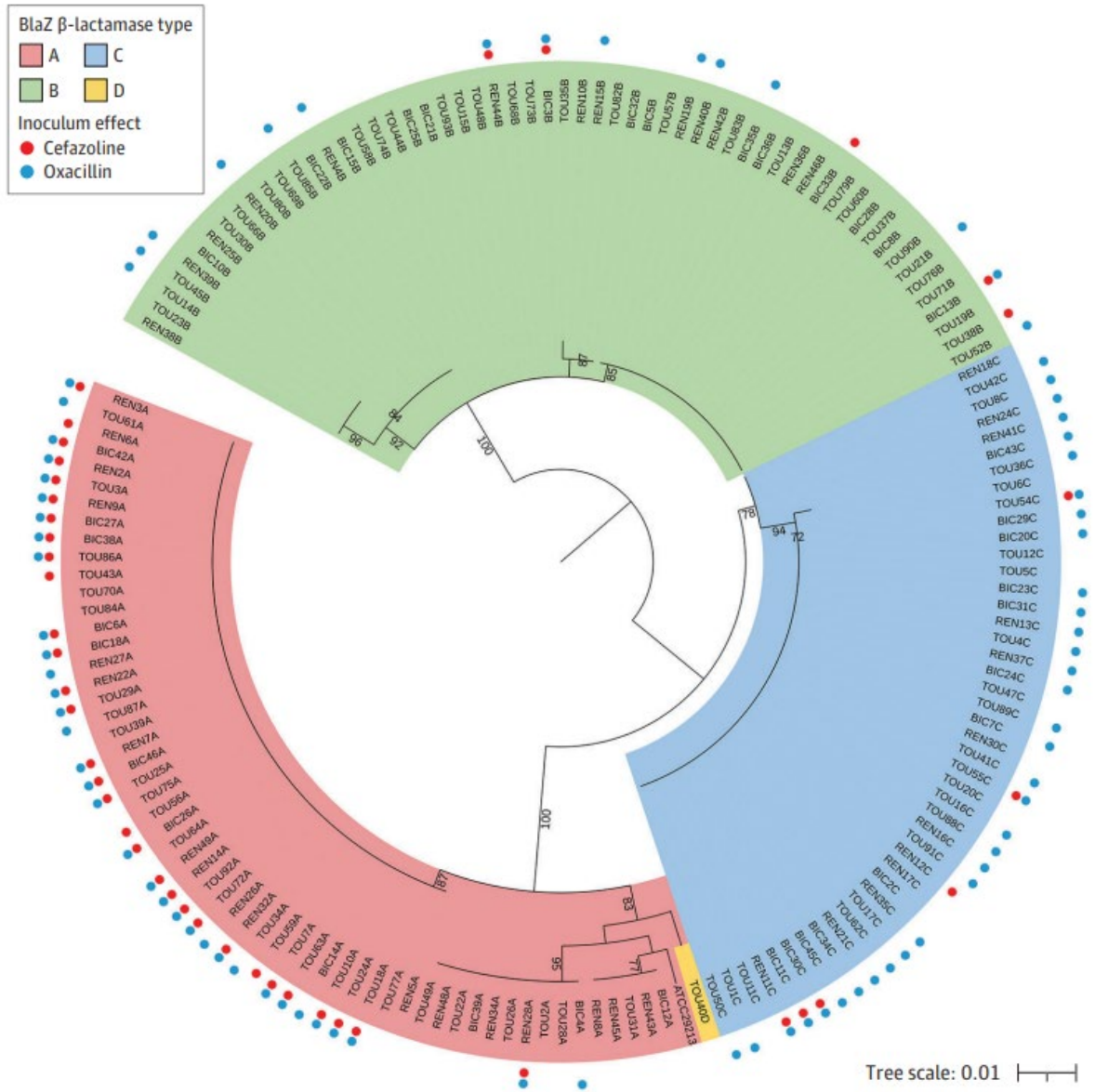
Cefazolin Inoculum Effect in *S. aureus* is not constrained by phylogenomic strain background



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-Daptomycin and *Enterococcus* spp. has encountered numerous changes to breakpoints

-Inoculum effect in *Staphylococcus aureus* occurs in many different strains across geography but has uncertain clinical impact