ARLG
Antibacterial Resistance Leadership Group

6th Annual Texas Medical Center Antimicrobial Resistance Conference

Carbapenemases in XDR *Pseudomonas*

Michael Satlin; Weill Cornell Medicine; 19 Jan 2023

Financial Disclosures (last 3 years)

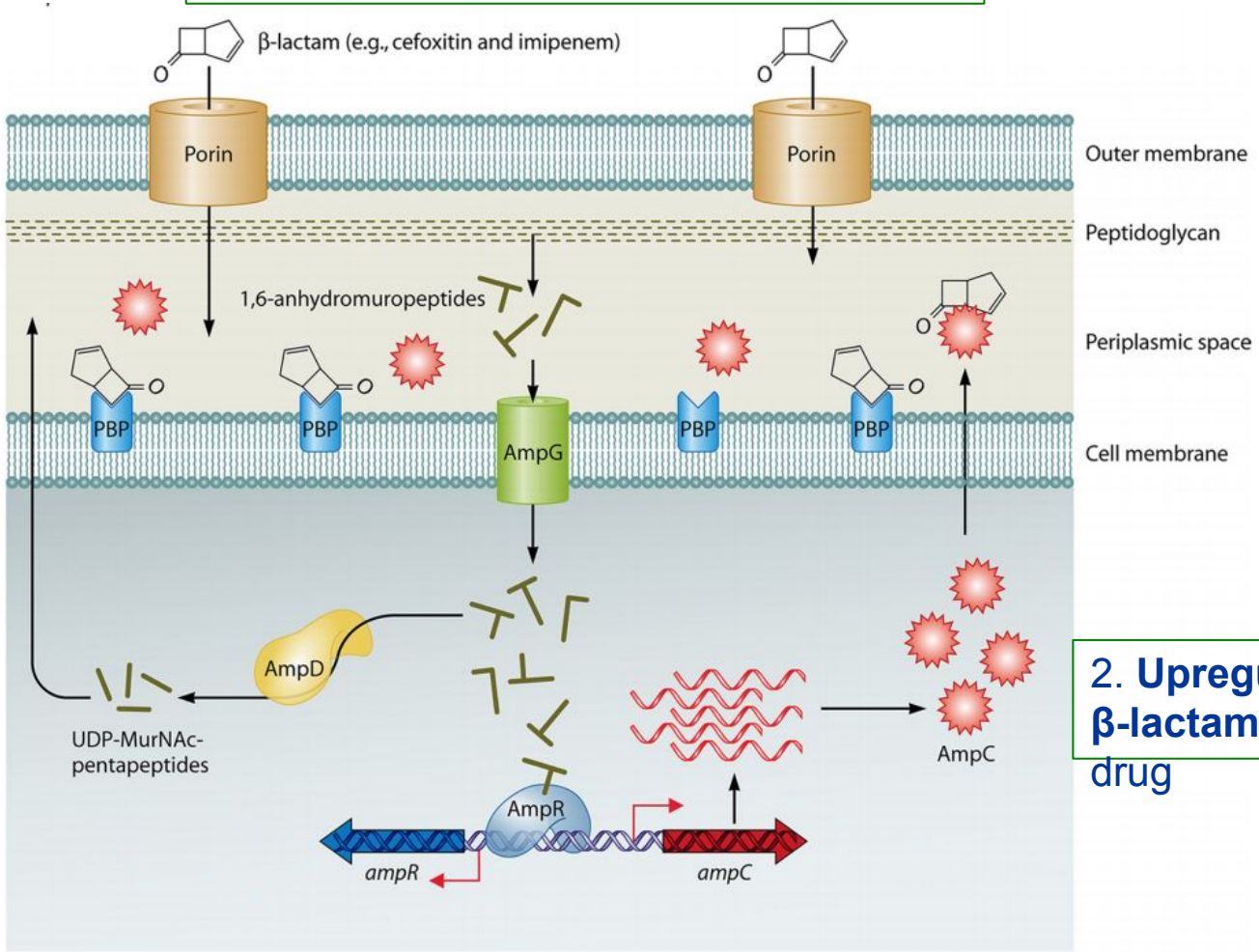
- Consulting: Shionogi
- Data Safety Monitoring Board: Spero Therapeutics, AbbVie
- Research grants/contracts: Merck, bioMérieux, Hardy Diagnostics, Affinity Biosensors, SNIPRBiome

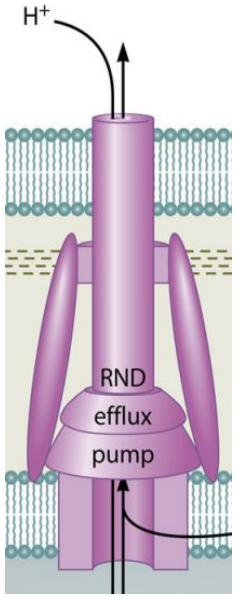
- POP is funded by NIAID through ARLG (UM1AI140681)

- POP results are In Press

P. aeruginosa: Multiple mechanisms of β-lactam resistance

1. **Porin mutation**: Drug can't get in





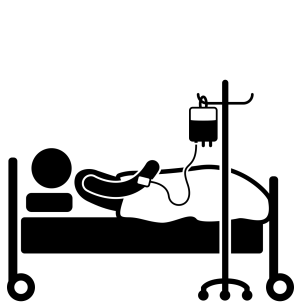
3. **Efflux pumps** shoots drug out

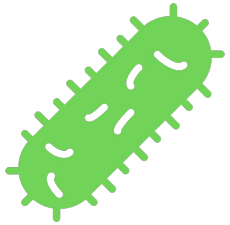
2. **Upregulation of AmpC β-lactamase** to inactivate drug

4. Carbapenemases

Lister PD, et al. Clin Microbiol Rev 2009. PMID: 19822890.

What's different about carbapenemases that make them unique as a mechanism of resistance in *P. aeruginosa*?

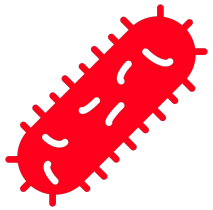




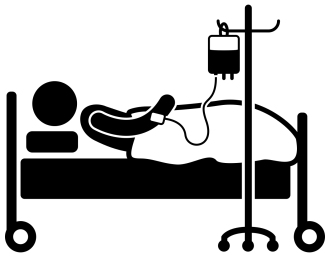
Susceptible *Pa*

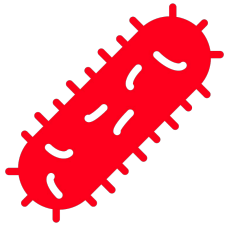
β-lactam exposure

1. Porin mutations
2. AmpC β-lactamases
3. Efflux pumps



Resistant *Pa*



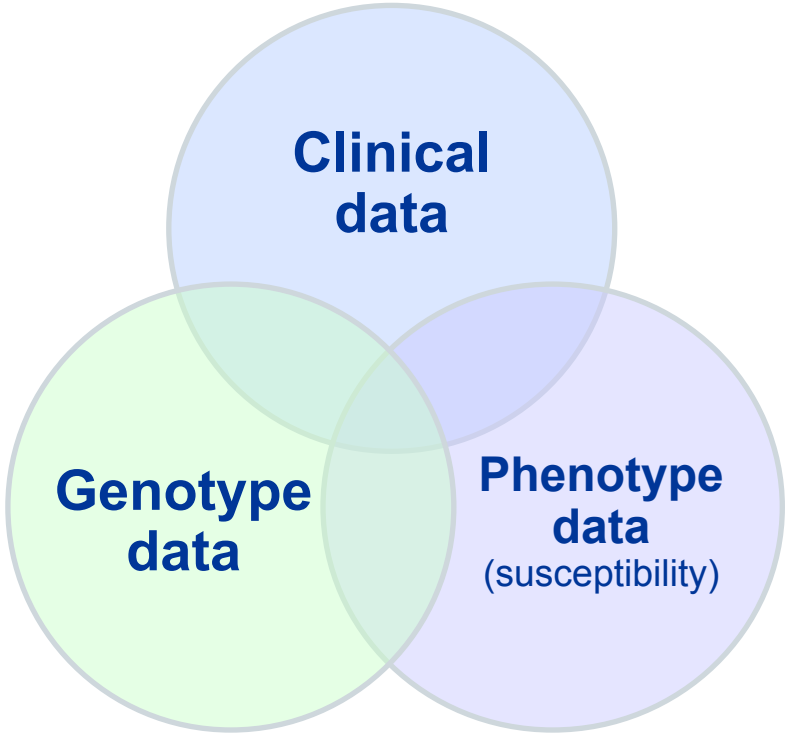


Carbapenemase-producing *Pa*

1. The patient's **first** *Pa* infection can be pan-resistant (not from mutations after antibiotic exposure)
2. Carbapenemase genes typically harbored on **plasmids** that have genes that confer **resistance to aminoglycosides, fluoroquinolones**, etc.
3. More easily spread to other patients

POP investigated the global epidemiology of carbapenemases in carbapenem-resistant *P. aeruginosa*

- Prospective Observational *Pseudomonas* Study
- Sample size: 1443 subjects (Dec 2018 – Nov 2019)
  - 44 hospitals, 10 countries, 4 continents

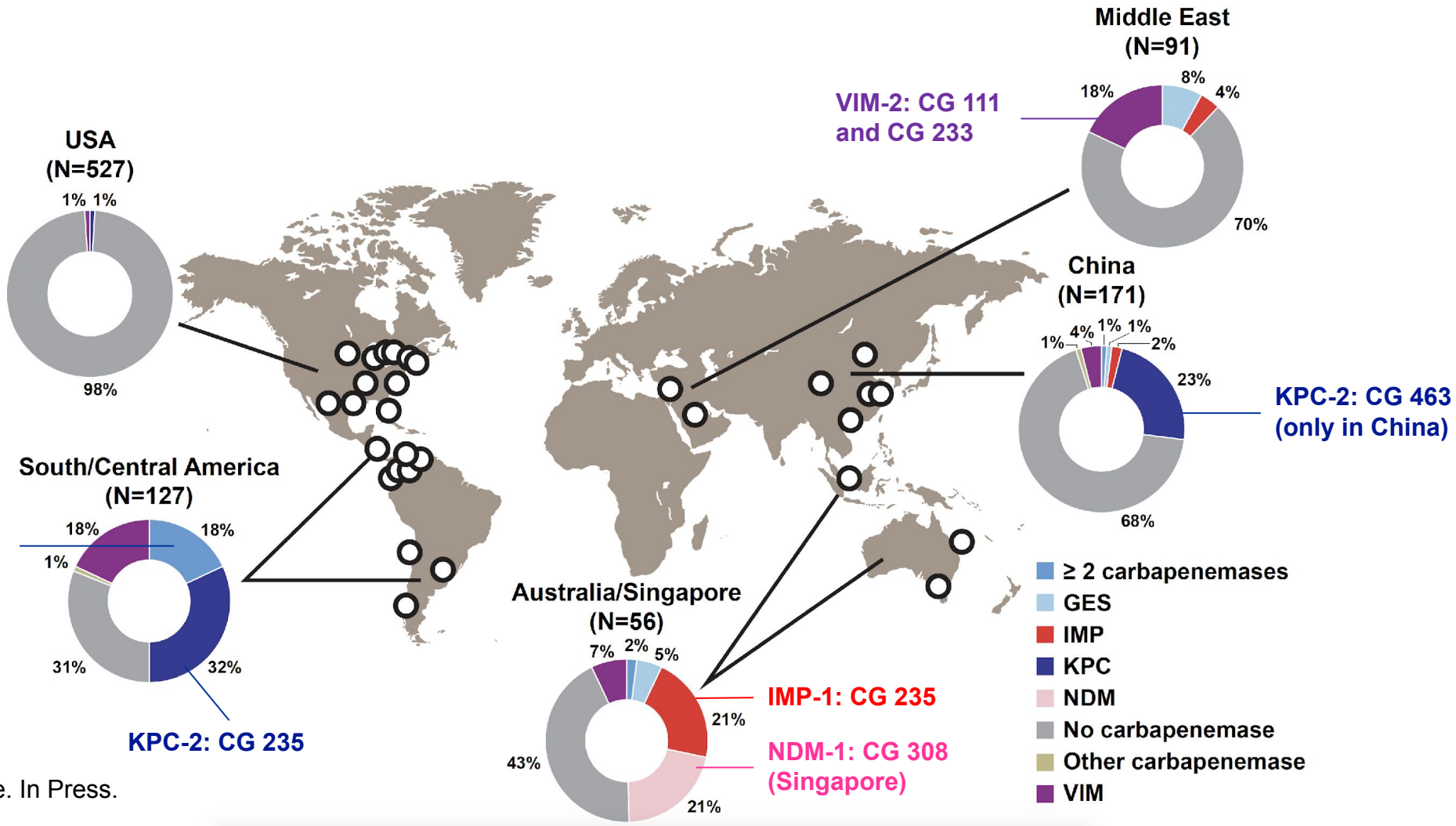


Inclusion criteria:

- Hospitalized patients with CRPA isolated from blood, respiratory, urine or wound culture
- First eligible CRPA culture episode per patient
- Meropenem resistant by broth microdilution testing (MIC ≥8 µg/mL) at central lab
- Whole-genome sequencing performed on isolate and confirmed to be *P. aeruginosa*
- 30-day outcome data available

Carbapenemases are rare in the USA, but certain clonal groups have acquired carbapenemases in other regions

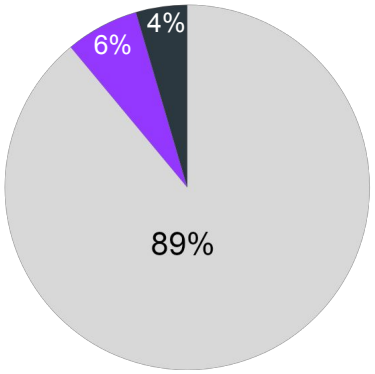
Only a matter of time until a clonal group in the USA acquires a carbapenemase



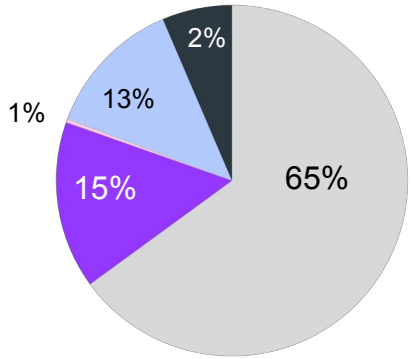
Reyes et al. Lancet Microbe. In Press.

Other global studies have also identified the emergence of carbapenemases in *P. aeruginosa* in other regions

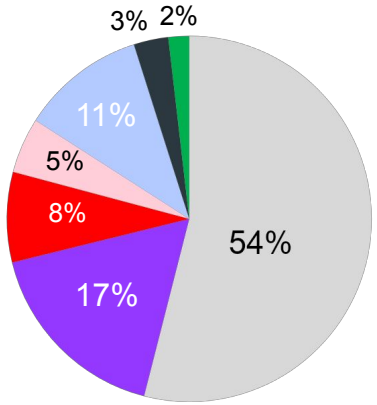
USA (n=154)



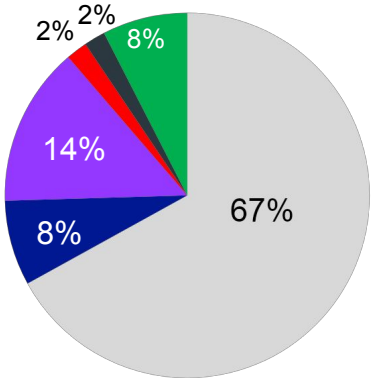
Europe (n=311)



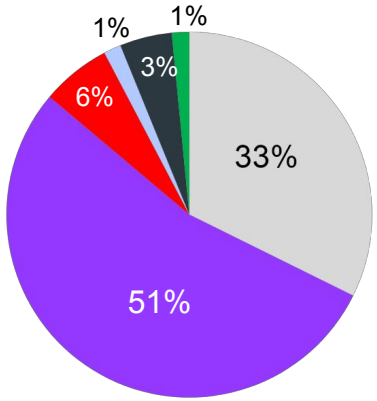
Middle East (n=163)

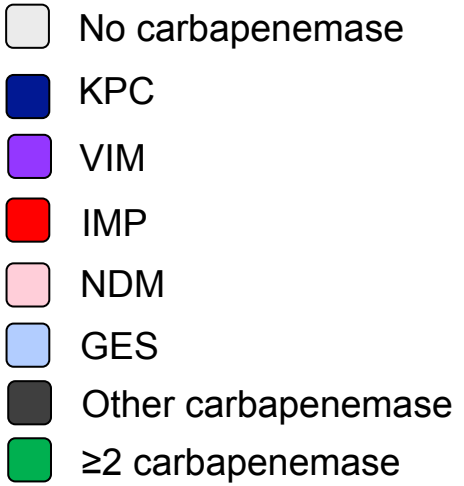


S. America (n=106)



Africa (n=65)

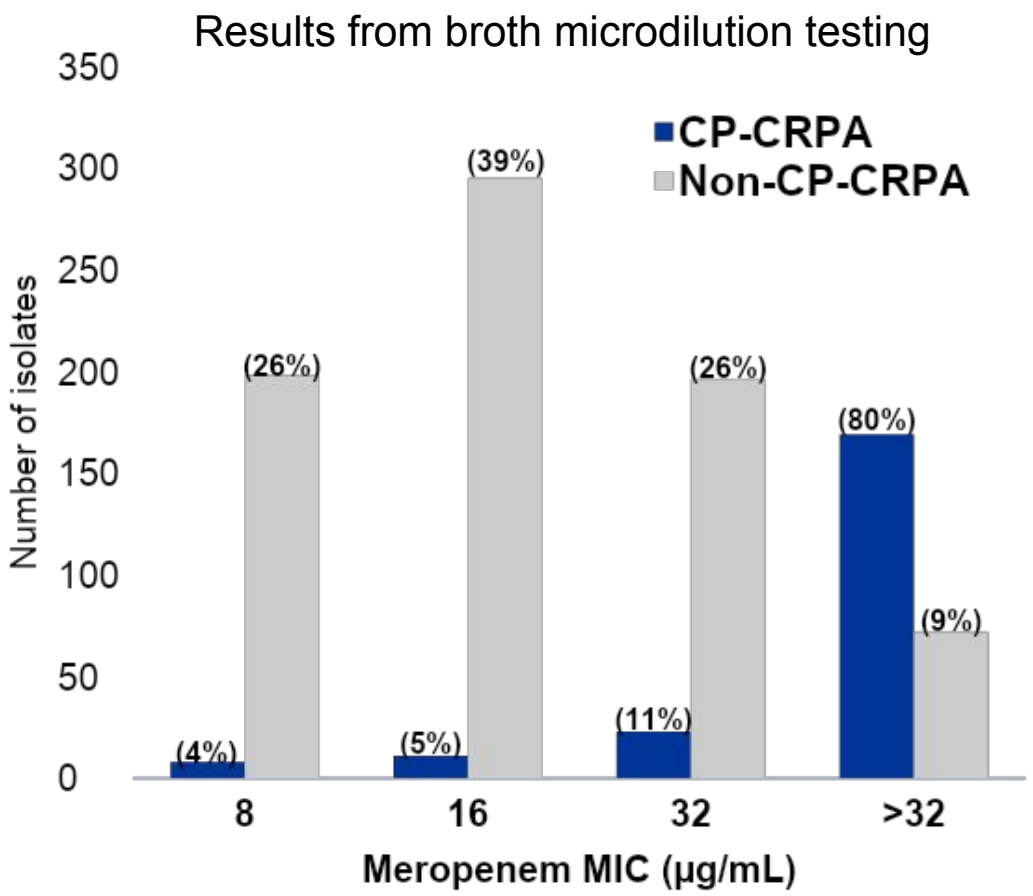




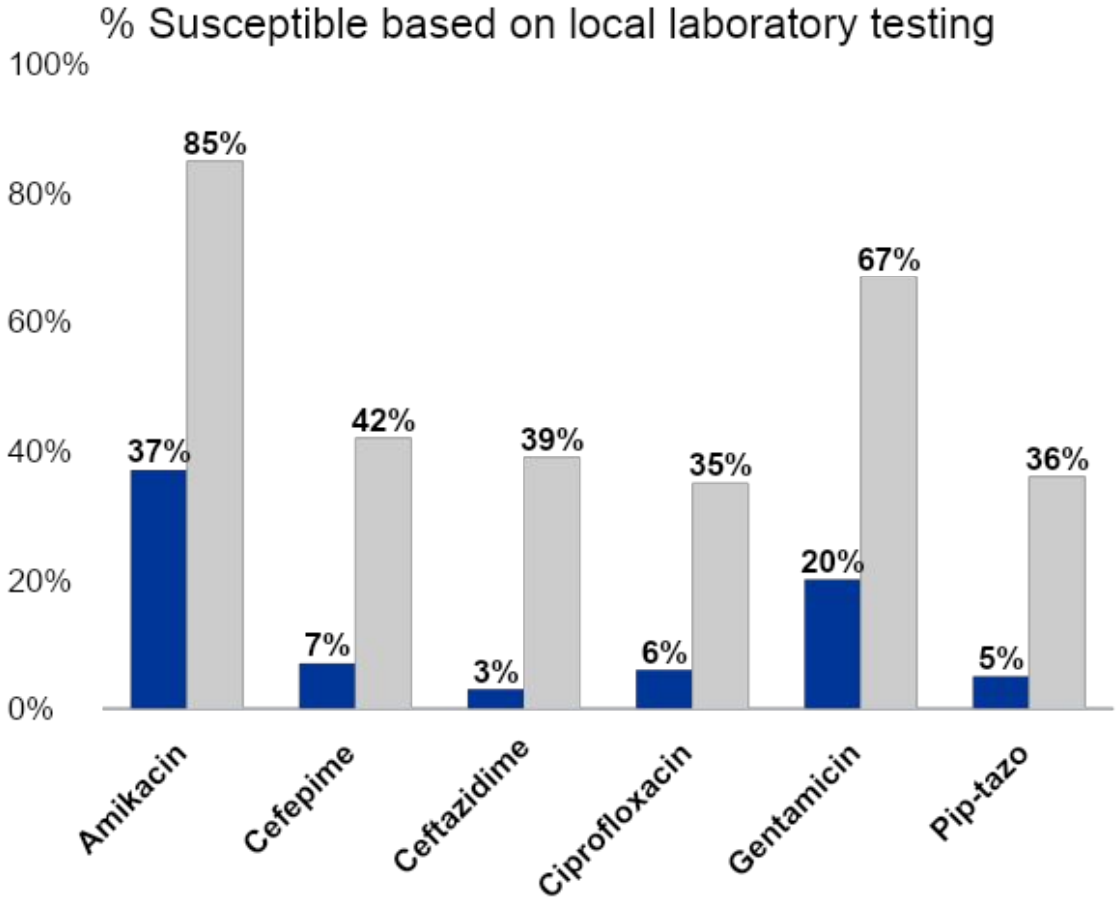
Gill et al. Eur J Clin Microl Infect Dis 2021. PMID: 34291323.

Consequences of carbapenemases in *Pa*: increased resistance

More carbapenem resistant

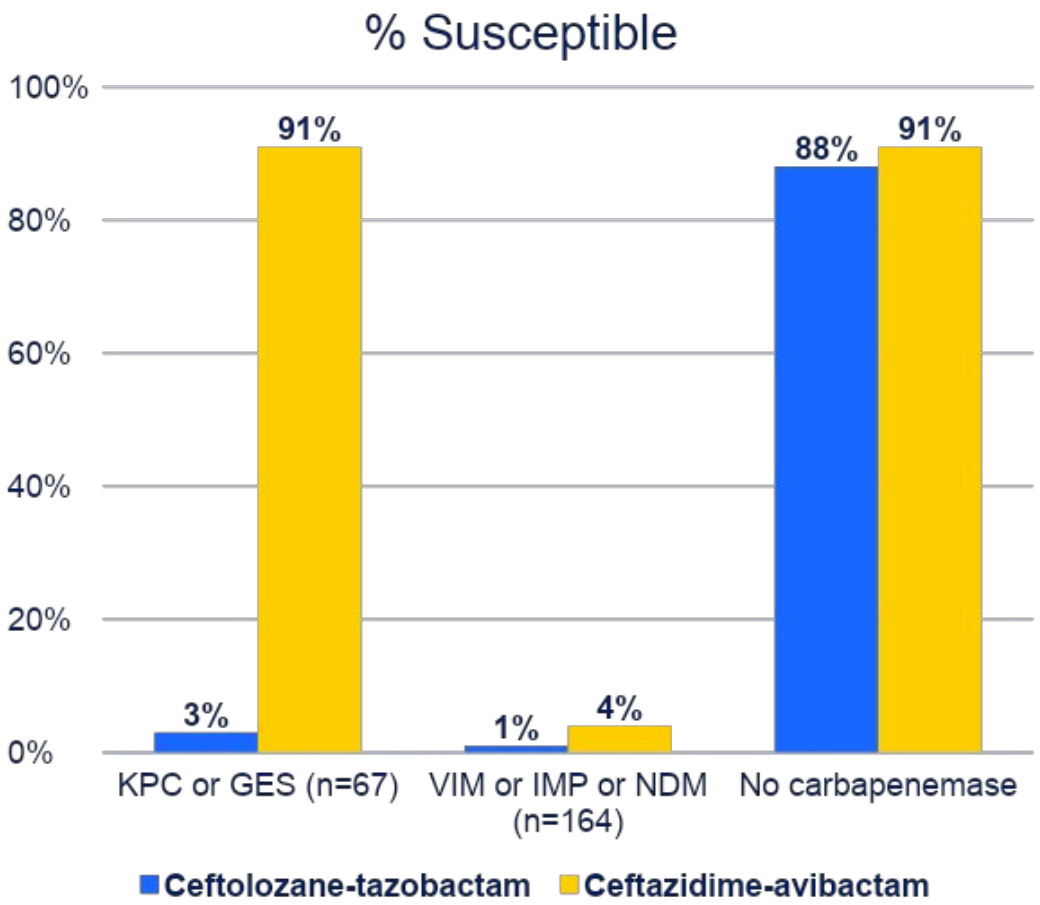


More resistant to other antibiotics



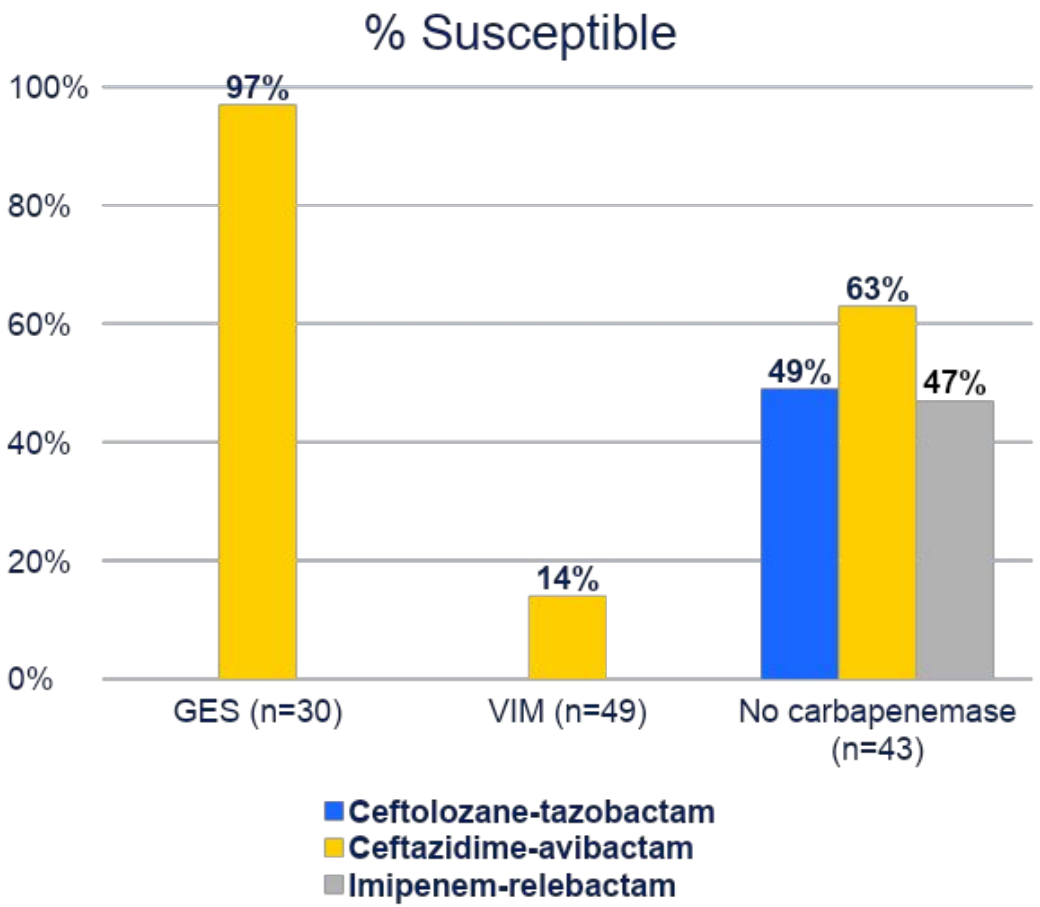
Carbapenemases lead to resistance to new β-lactam/β-lactamase inhibitors in *P. aeruginosa*

Global collection of CRPA isolates



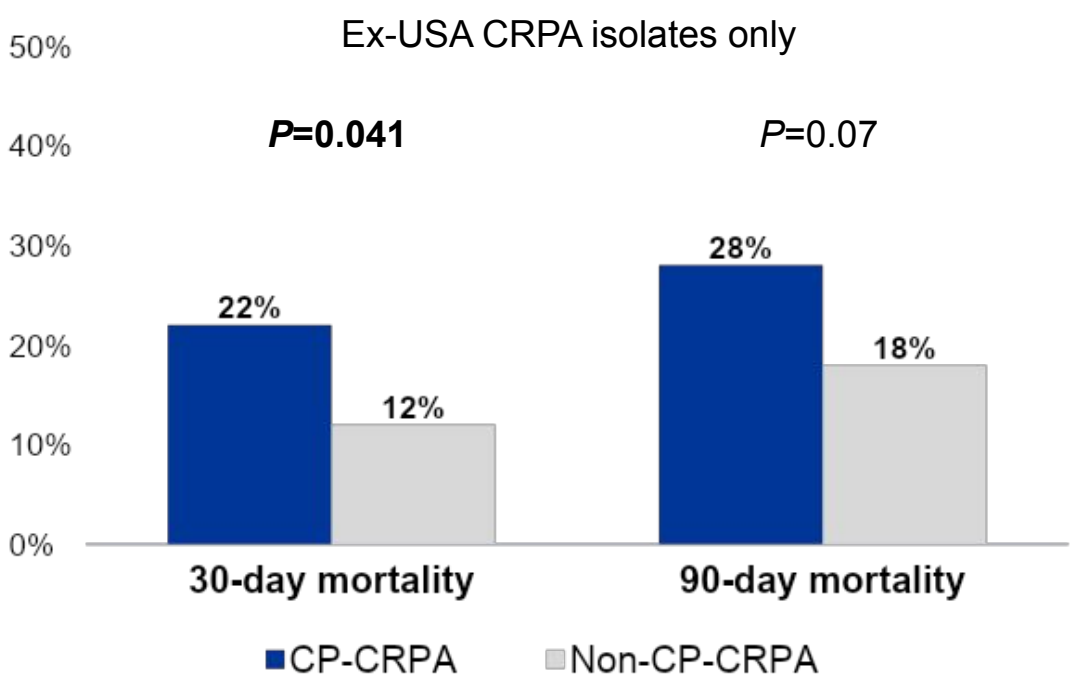
Gill et al. Eur J Clin Microl Infect Dis 2021. PMID: 34291323.

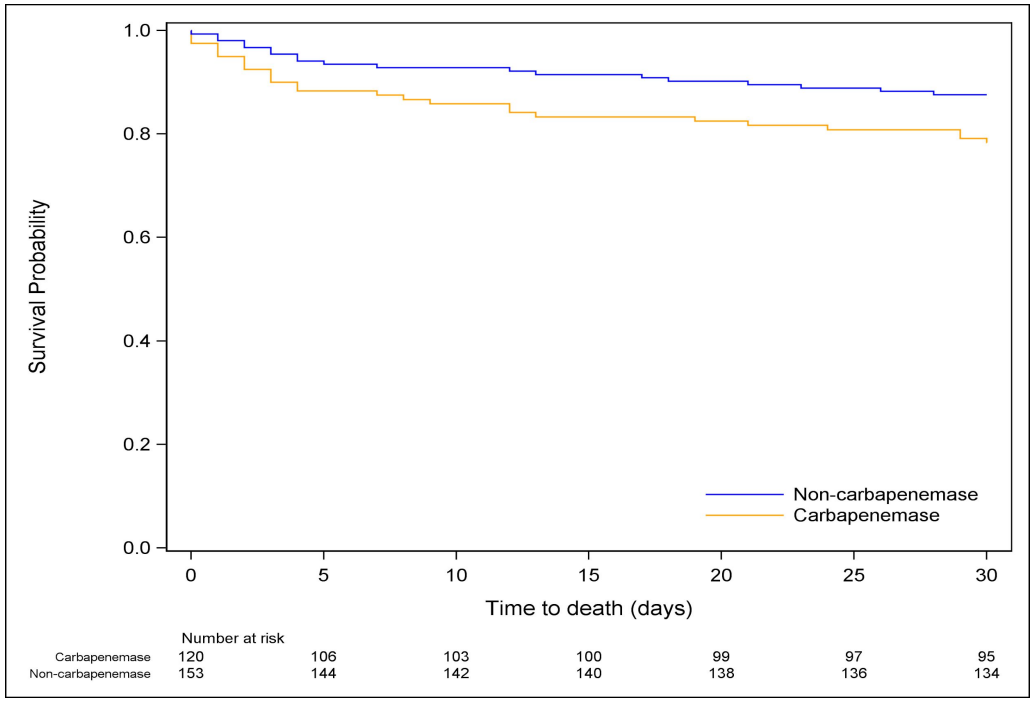
CRPA isolates from Spain



Hernández-Garcíá et al. Antimicrob Agents Chemother 2022. PMID: 35007130.

Carbapenemases associated with increased mortality in CRPA





Methods of adjustments for confounders for 30-day mortality:

1. Inverse probability weighting: 7% absolute increase in mortality with CP-CRPA (95% CI: 1-14%)
2. Multivariate logistic regression: adjusted odds ratio of 2.1 (95% CI: 0.9 – 4.7) with CP-CRPA
3. Multivariate Cox proportional hazards model: adjusted hazard ratio of 1.4 (95% CI: 0.7-2.8) w/ CP-CRPA

POP: Next Steps

1) Investigate reasons for increased mortality with CP-CRPA infections compared to non-CP-CRPA infections
   - Hypothesis: CP-CRPA infections associated with:
     - Prolonged time until receipt of active therapy
     - Use of polymyxins, aminoglycosides, and other agents that are less effective and more toxic than β-lactam agents
2) Comparison of outcomes of anti-pseudomonal β-lactams by MIC values -> provide clinical data to support breakpoints
3) Assessment of *in vitro* activity of new agents (e.g., ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam) against POP isolates that underwent whole-genome sequencing

Algorithm for treatment of DTR *P. aeruginosa*

Antibiotic	MIC (µg/mL)	S/I/R
Ceftazidime	>16	R
Cefepime	>16	R
Piperacillin-tazobactam	>64/4	R
Meropenem	>8	R
Levofloxacin	>4	R
Gentamicin	>8	R
Tobramycin	≤1	S

Carbapenemase-producing *Pa* rare in USA

Ceftolozane-tazobactam

If prior exposure to TOL-TAZ or CAZ-AVI

Imipenem-relebactam

If KPC detected

Ceftazidime-avibactam

If MBL detected

Cefiderocol

- Polymyxins only as a last resort
- Aminoglycosides: short courses for UTIs

Algorithm for treatment of DTR *P. aeruginosa*

Antibiotic	MIC (µg/mL)	S/I/R
Ceftazidime	>16	R
Cefepime	>16	R
Piperacillin-tazobactam	>64/4	R
Meropenem	>8	R
Levofloxacin	>4	R
Gentamicin	>8	R
Tobramycin	≤1	S

Carbapenemase-producers common in S. America

If prior exposure to TOL-TAZ or CAZ-AVI

Ceftolozane-tazobactam

Imipenem-relebactam

If KPC detected

Ceftazidime-avibactam

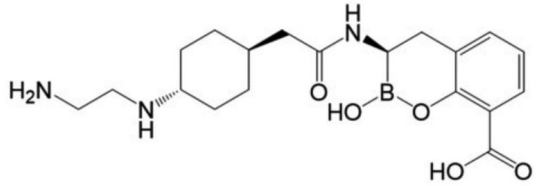
If MBL detected

Cefiderocol

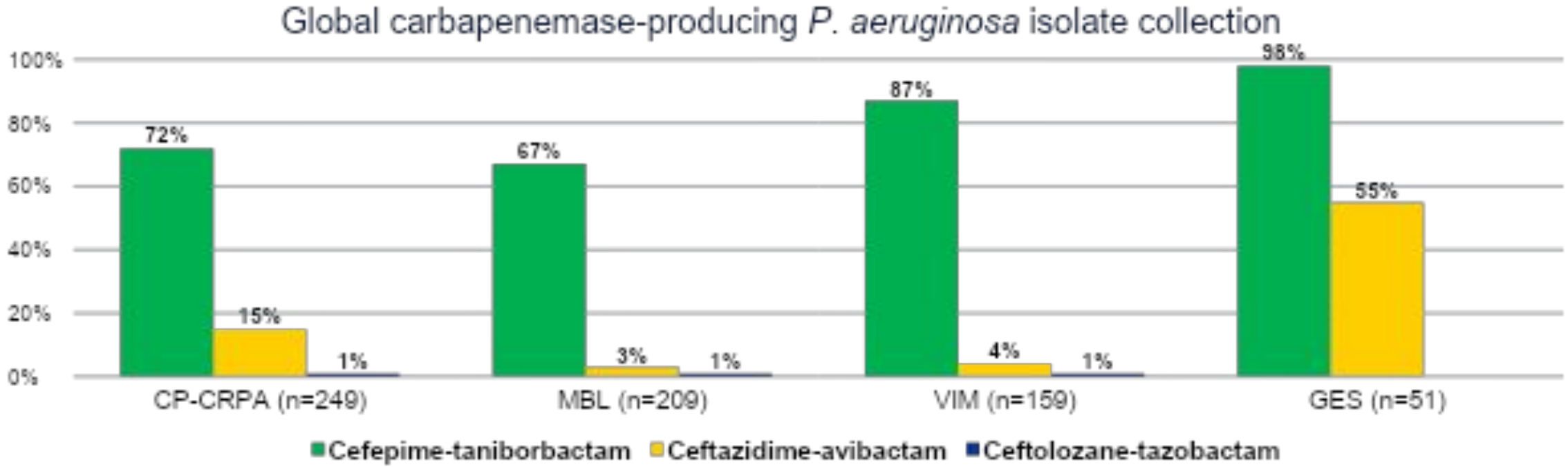
- Polymyxins only as a last resort
- Aminoglycosides: short courses for UTIs

Cefepime-taniborbactam: Hope for MBL-producing *Pa*

Positive Results for Phase 3 Clinical Trial (CERTAIN-1) for Treatment of cUTI



β-lactamase inhibitor that inhibits class A, B (except IMP), C, and D enzymes

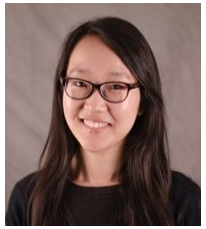


Karlowsky et al. Antimicrob Agents Chemother 2022. PMID: 36541767.

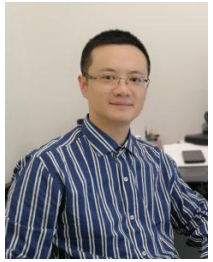
POP Acknowledgements

Jinnethe Reyes, PhD

Lauren Komarow, MS



Lizhao Ge, MAS



Liang Chen, PhD

Blake Hanson, PhD

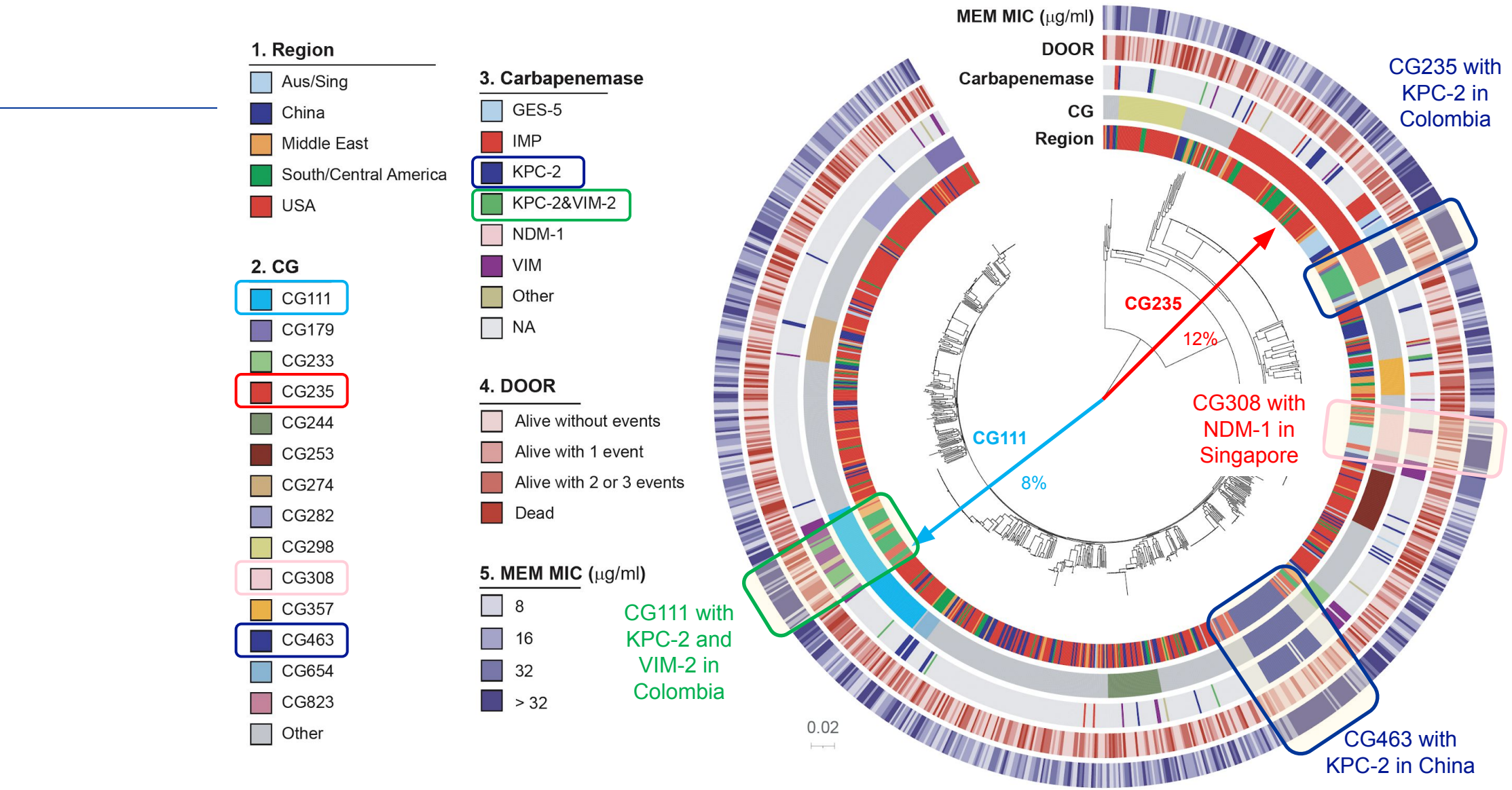
Keri Baum, BS

David van Duin, MD, PhD

Yohei Doi, MD, PhD

Robin Patel, MD

Co-Investigators		
Eric Cober	Soraya Salcedo	Sorabh Dhar
Erica Herc	Lillian Abbo	Jairo Figueroa
Thamer Alenazi	Qing Xie	Bettina Fries
Keith Kaye	Karen Ordoñez	Zhang Fujie
Julia Garcia-Diaz	Minggui Wang	Andrew Henderson
Lanjuan Li	Martin Stryjewski	Charles Huskins
Souha Kanj	Jose Munita	Marcel Leroi
Zhengyin Liu	David Paterson	Linghua Li
Jose Oñate	Scott Evans	Todd McCarty
Robert Salata	Carol Hill	Anton Peleg
Kalisvar Marimuthu	Robert Bonomo	Maria Rioseco
Hainv Gao	Barry Kreiswirth	Marisa Sanchez
Zhiyong Zong	Maria Virginia Villegas	Samuel Vilchez
Sandra Valderrama-Beltrán	Cesar Arias	
Yunsong Yu	Chip Chambers	
Paul Tambyah	Vance Fowler	
Gregory Weston	Deverick Anderson	


1. Region
Aus/Sing
China
Middle East
South/Central America
USA
2. CG
CG111
CG179
CG233
CG235
CG244
CG253
CG274
CG282
CG298
CG308
CG357
CG463
CG654
CG823
Other
3. Carbapenemase
GES-5
IMP
KPC-2
KPC-2&VIM-2
NDM-1
VIM
Other
NA
4. DOOR
Alive without events
Alive with 1 event
Alive with 2 or 3 events
Dead
5. MEM MIC (μg/ml)
8
16
32
> 32
MEM MIC (μg/ml)
DOOR
Carbapenemase
CG
Region
CG235
12%
CG111
8%
0.02
CG235 with KPC-2 in Colombia
CG308 with NDM-1 in Singapore
CG111 with KPC-2 and VIM-2 in Colombia
CG463 with KPC-2 in China