Dissecting The Epidemics of Multidrug-Resistant Organisms: A Focus on Carbapenem-Resistant *Klebsiella pneumoniae*

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@SuperBugDoc

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Disclosures

- **Grant Recipient**: MeMed diagnostics, Merck and Entasis Pharmaceuticals

AMR Latest Data

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

*Antimicrobial Resistance Collaborators**

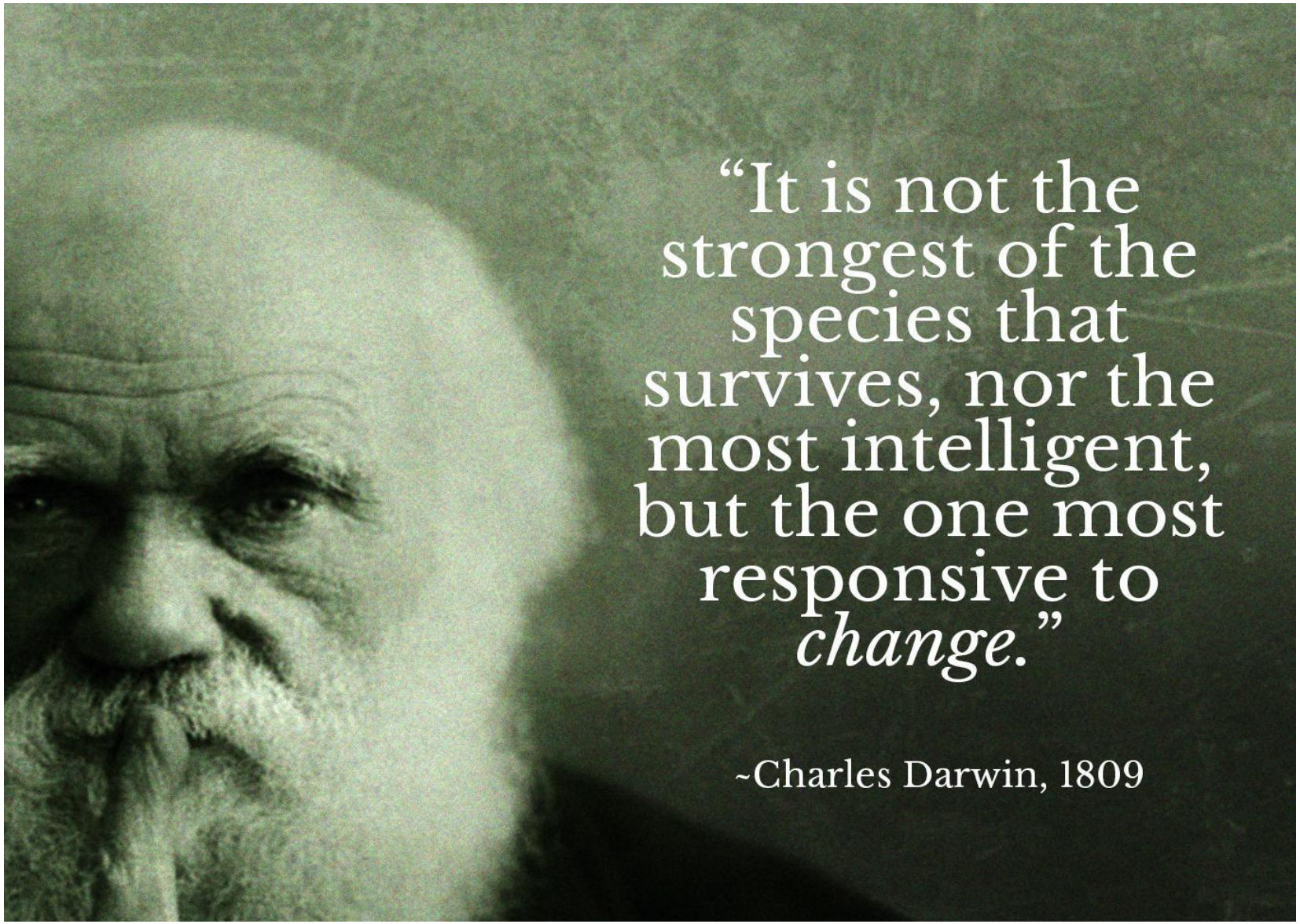
Findings On the basis of our predictive statistical models, there were an estimated 4·95 million (3·62–6·57) deaths associated with bacterial AMR in 2019, including 1·27 million (95% UI 0·911–1·71) deaths attributable to bacterial AMR.

Lancet, Feb 2022

Objectives

- Discuss the main mechanisms by which MDR bacteria can cause epidemics
- Dissect the epidemic of carbapenemase-producing *K. pneumoniae* in Houston, TX and in Colombia

Epidemics of MDR Organisms Is Evolution at Its peak



Resistance is Part of Evolution

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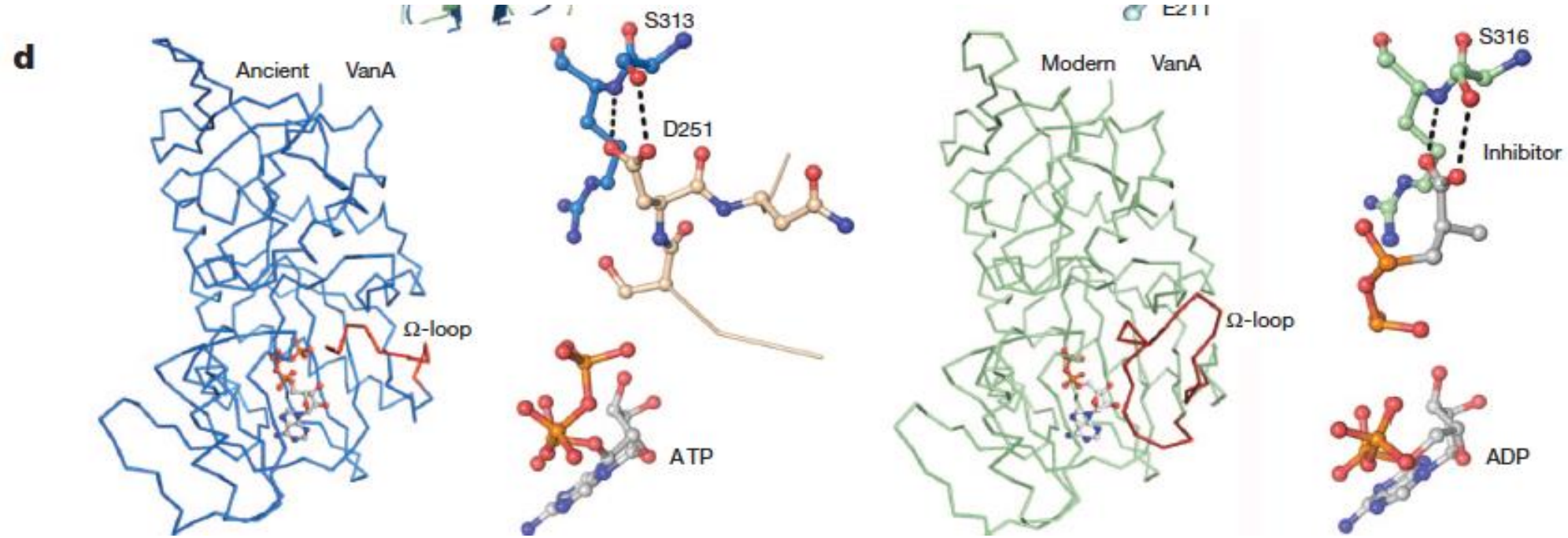
LETTER

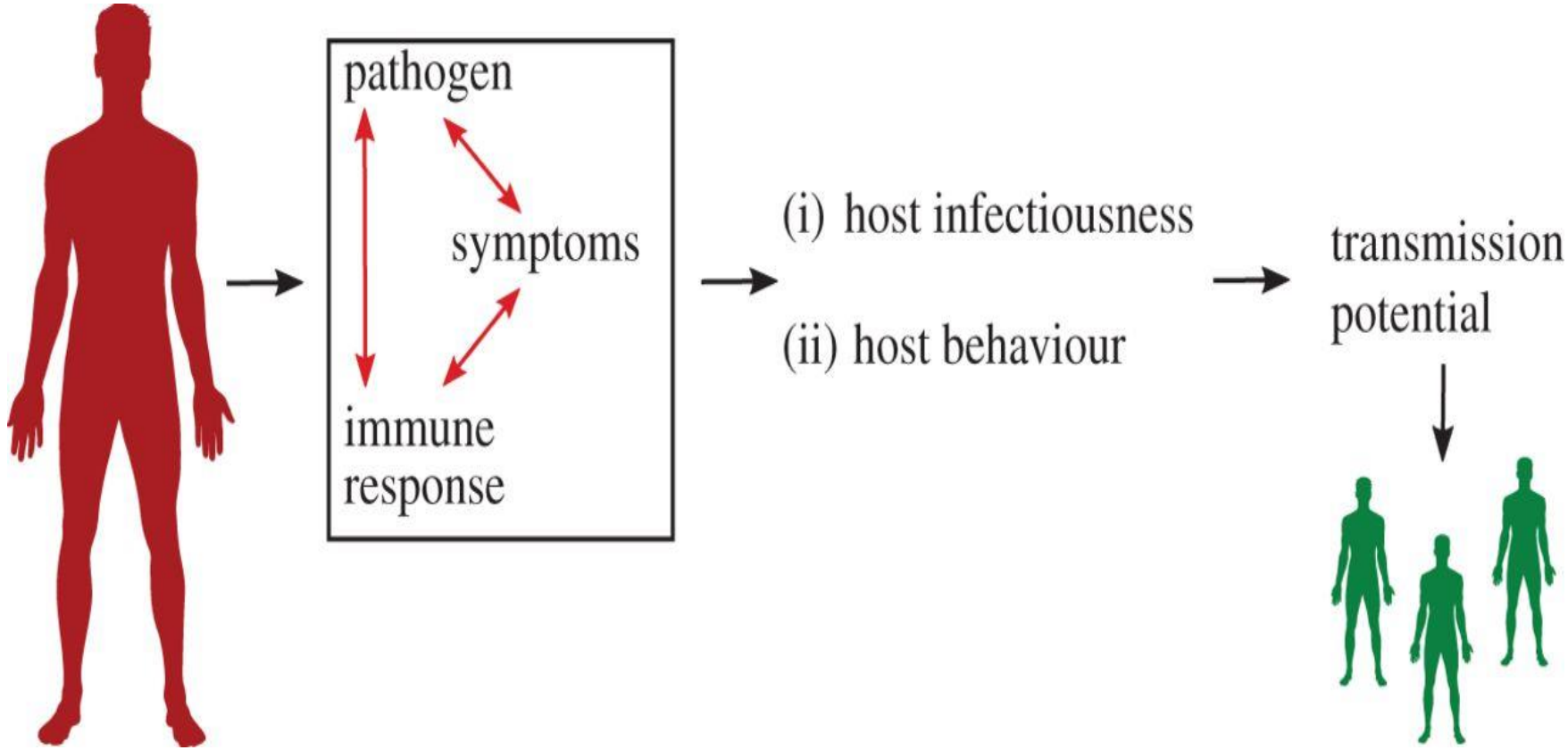
doi:10.1038/nature10388

Antibiotic resistance is ancient

Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]



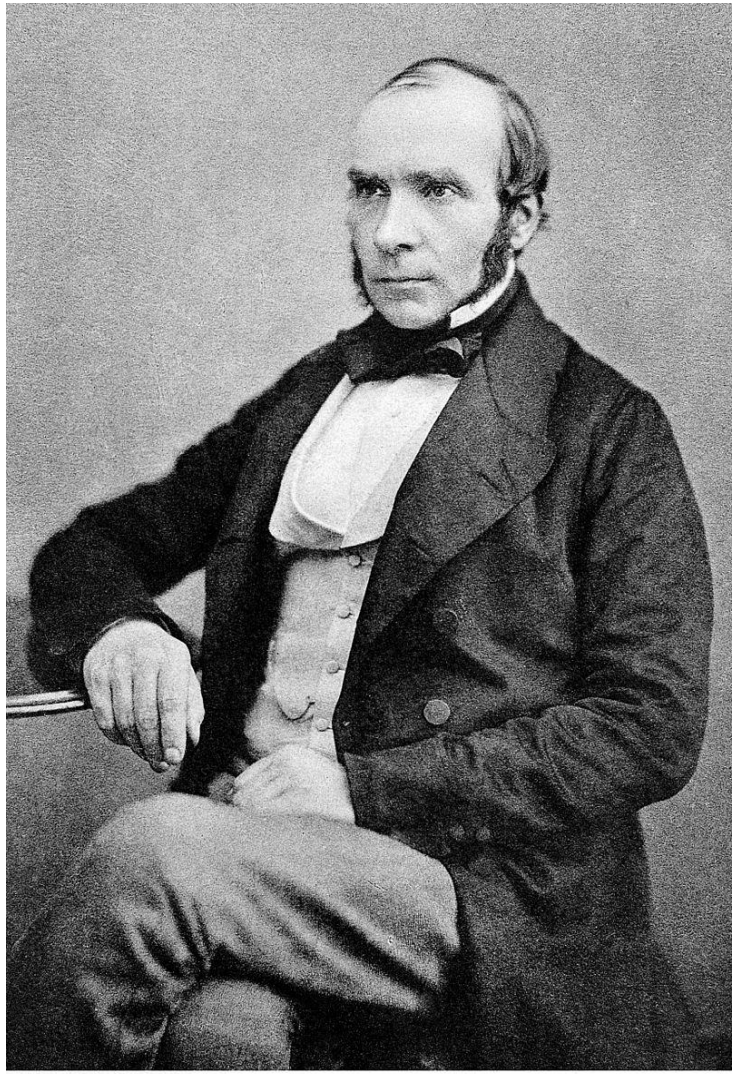
The Dynamics of Epidemics and Pandemics



Handel & Rohani, Philosophical Transactions of the Royal Society, 2016

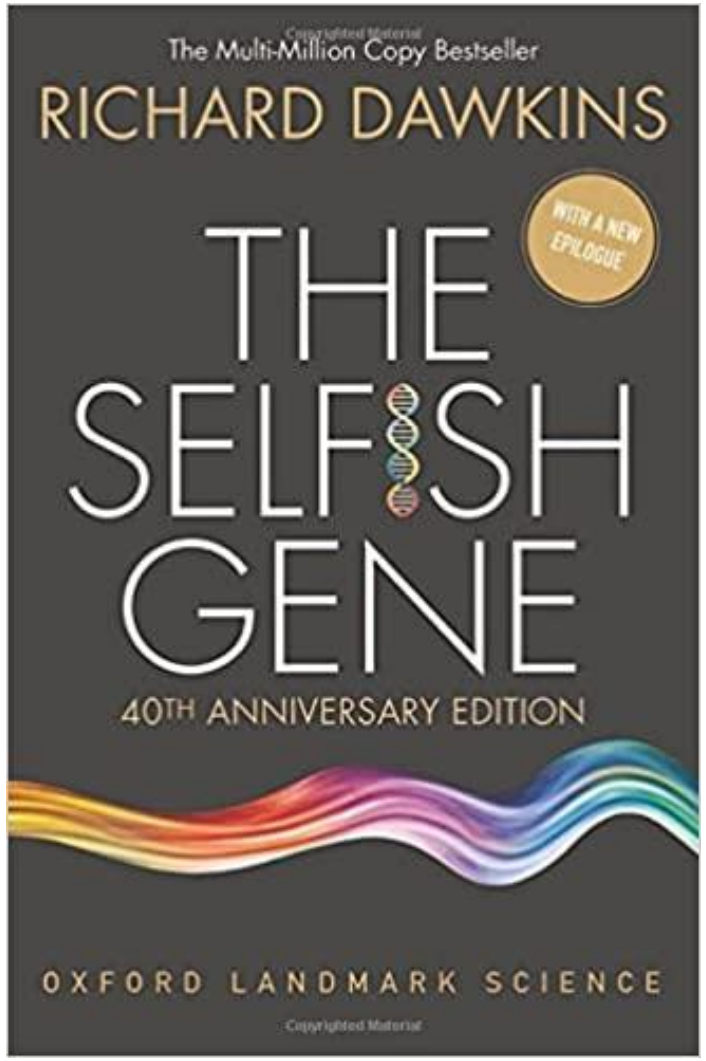
Bubonic Plague

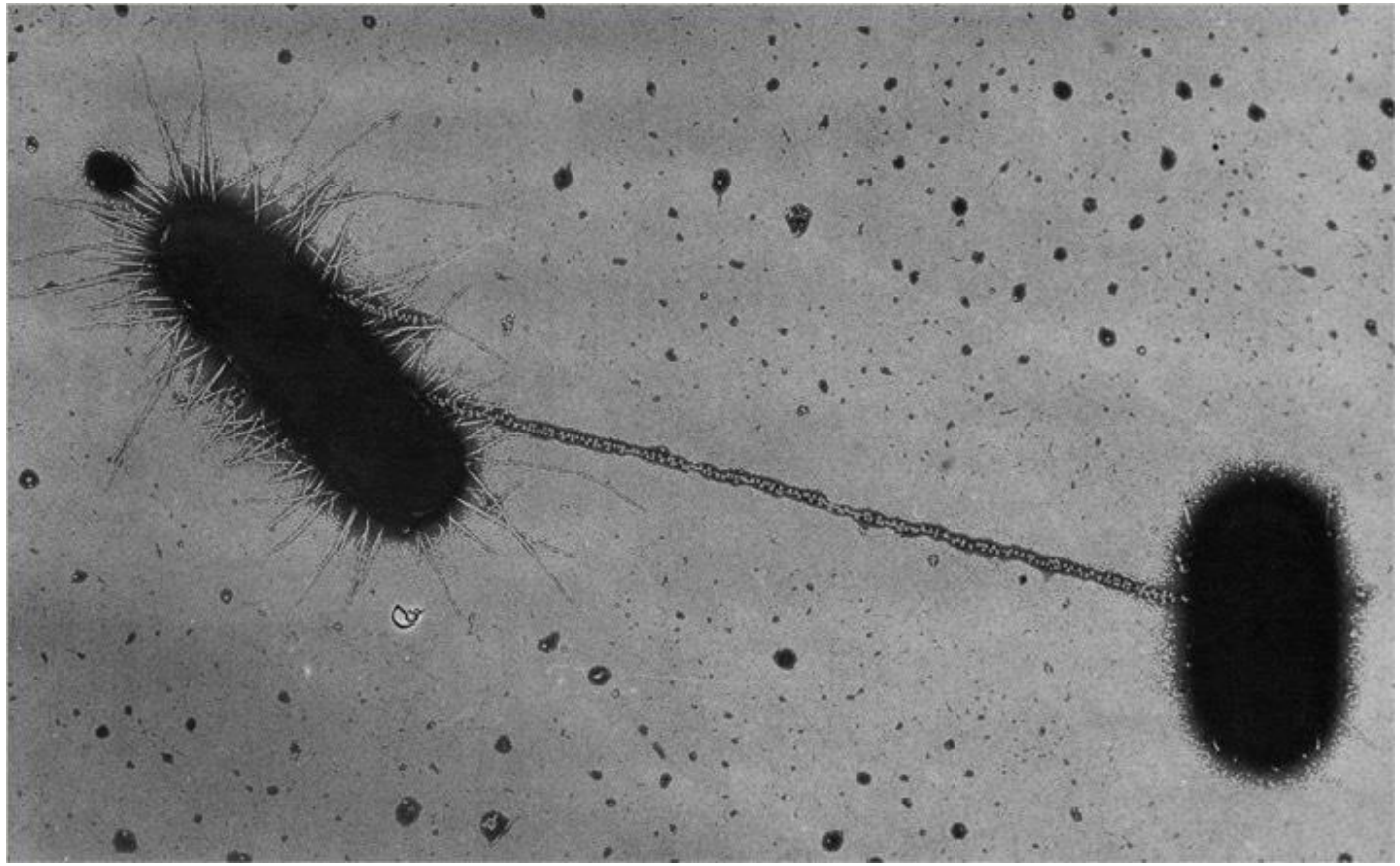
John Snow and Public Health Epidemiology of Pandemics



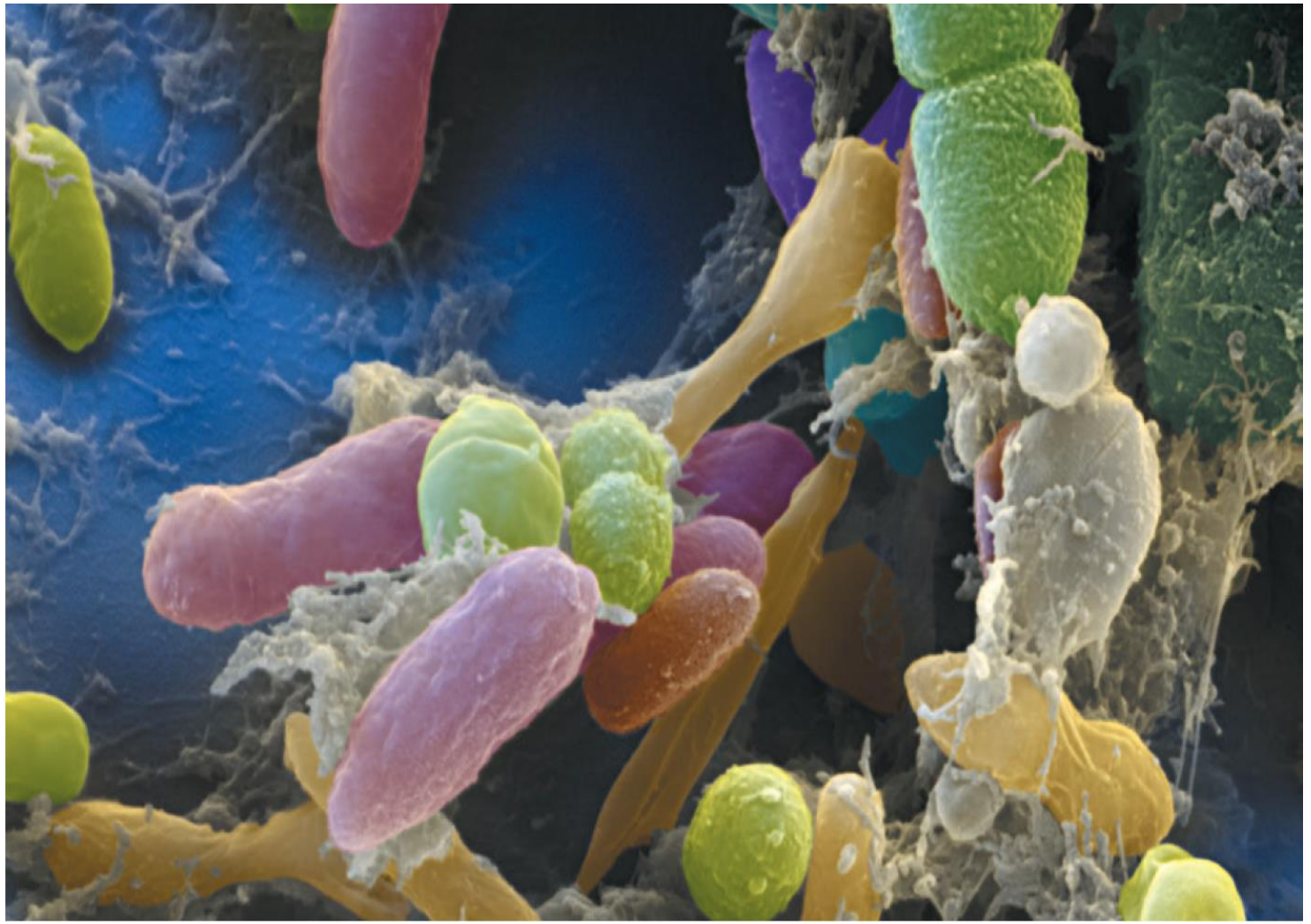
https://commons.wikimedia.org/w/index.php?curid=357998

Gene Epidemic



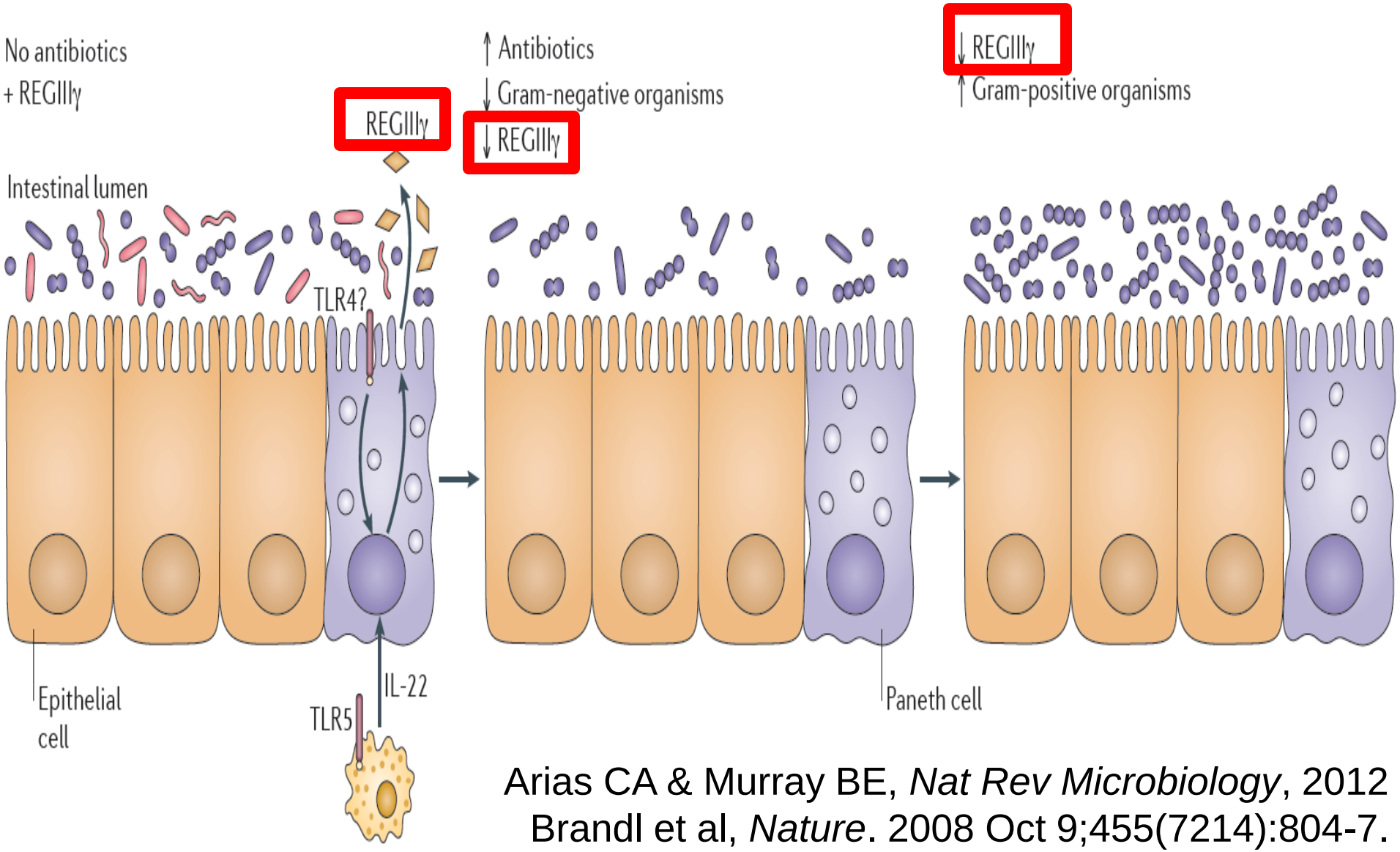


The Human Microbiome and AMR



21 AUGUST 2014 | VOL 512 | NATURE | 247

Antibiotics and The Gut



Arias CA & Murray BE, *Nat Rev Microbiology*, 2012
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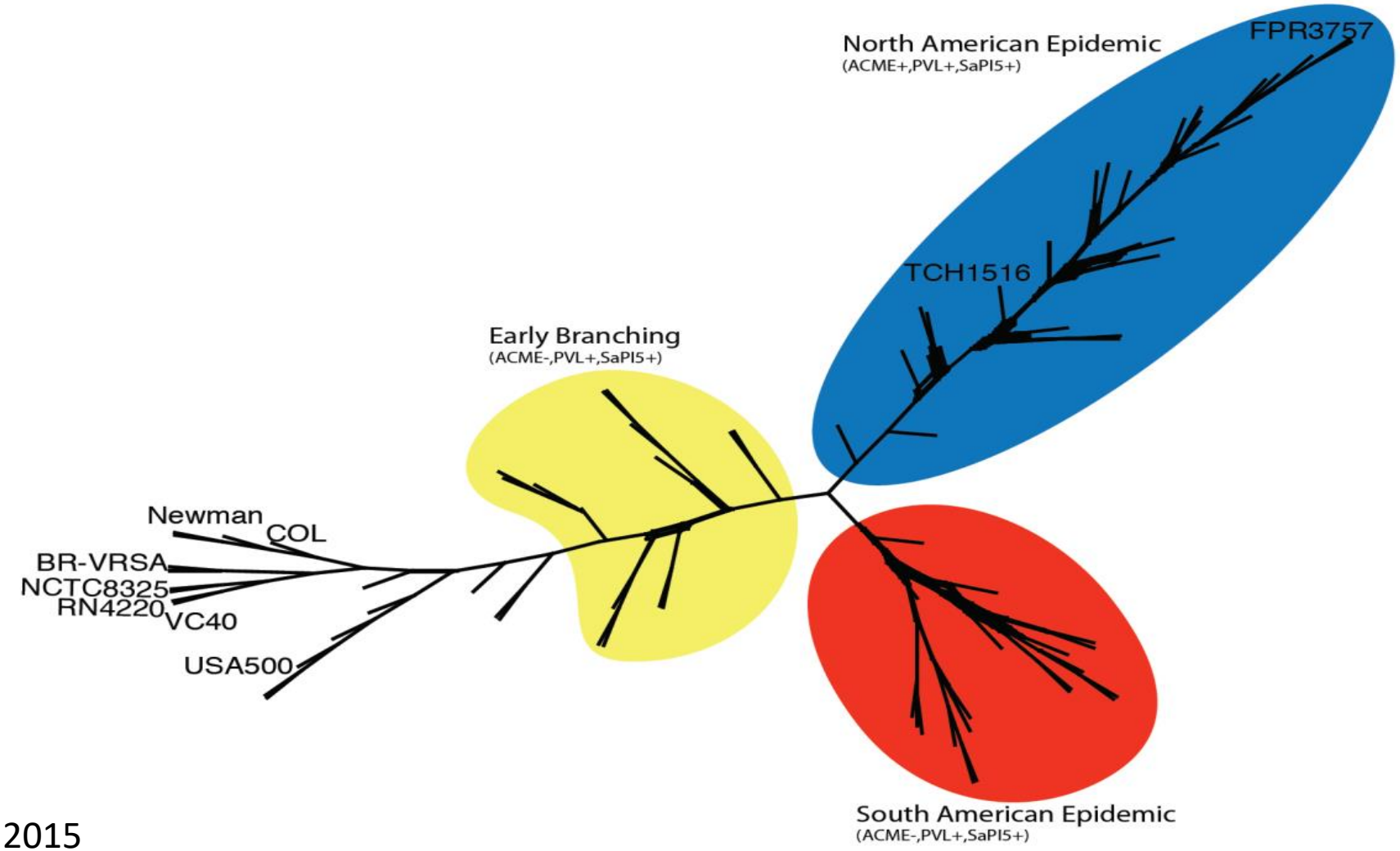
Phylogenetic Analyses of USA300 and USA300-LV

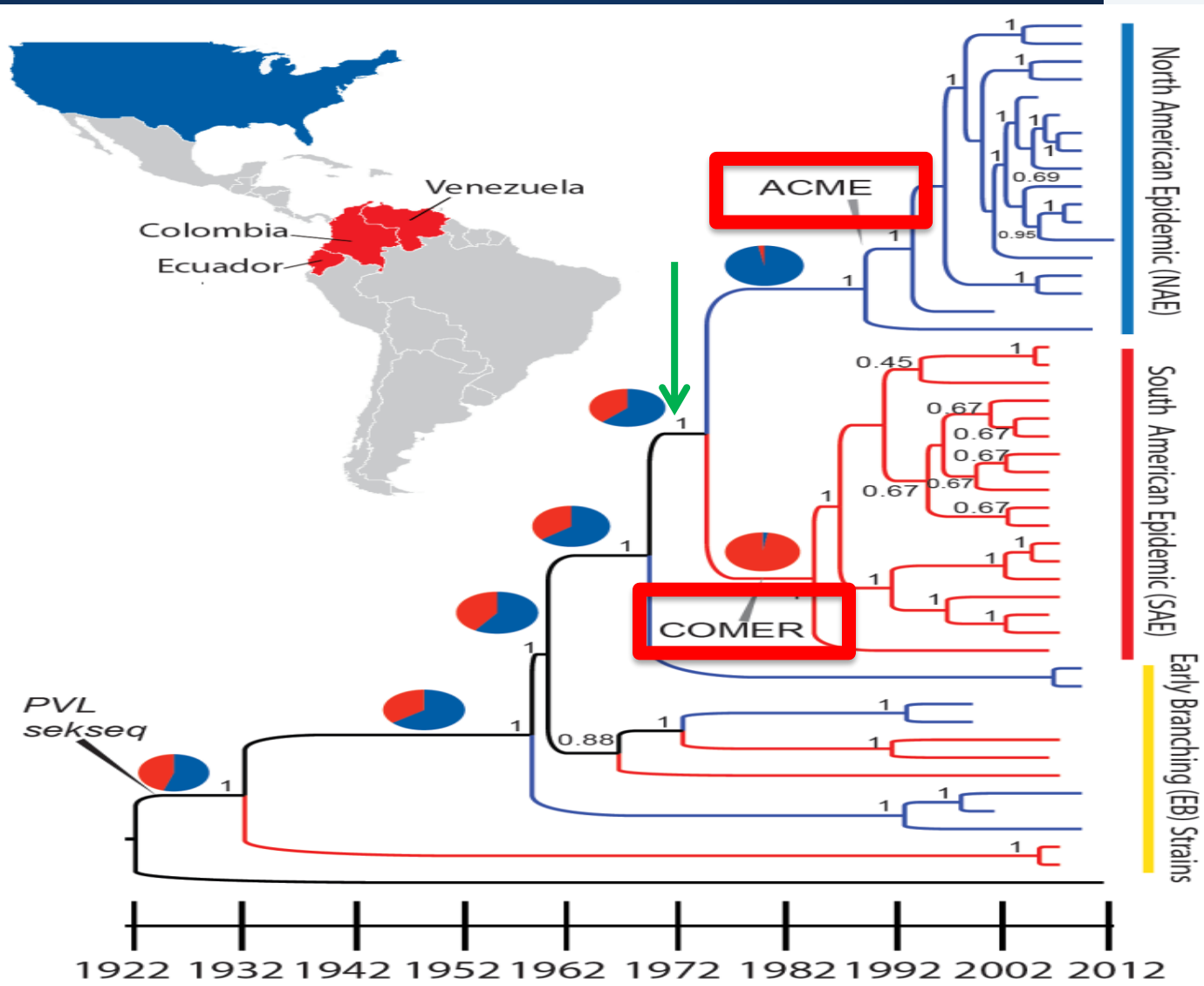
Paul Planet

George Weinstock

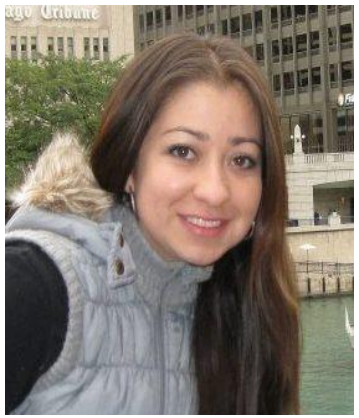


Planet et al., *J Infect Dis*. 2015
Arias et al. *NEJM*, 2009

Evolutionary History of CA-MRSA



Jinnethe Reyes



Lorena Diaz

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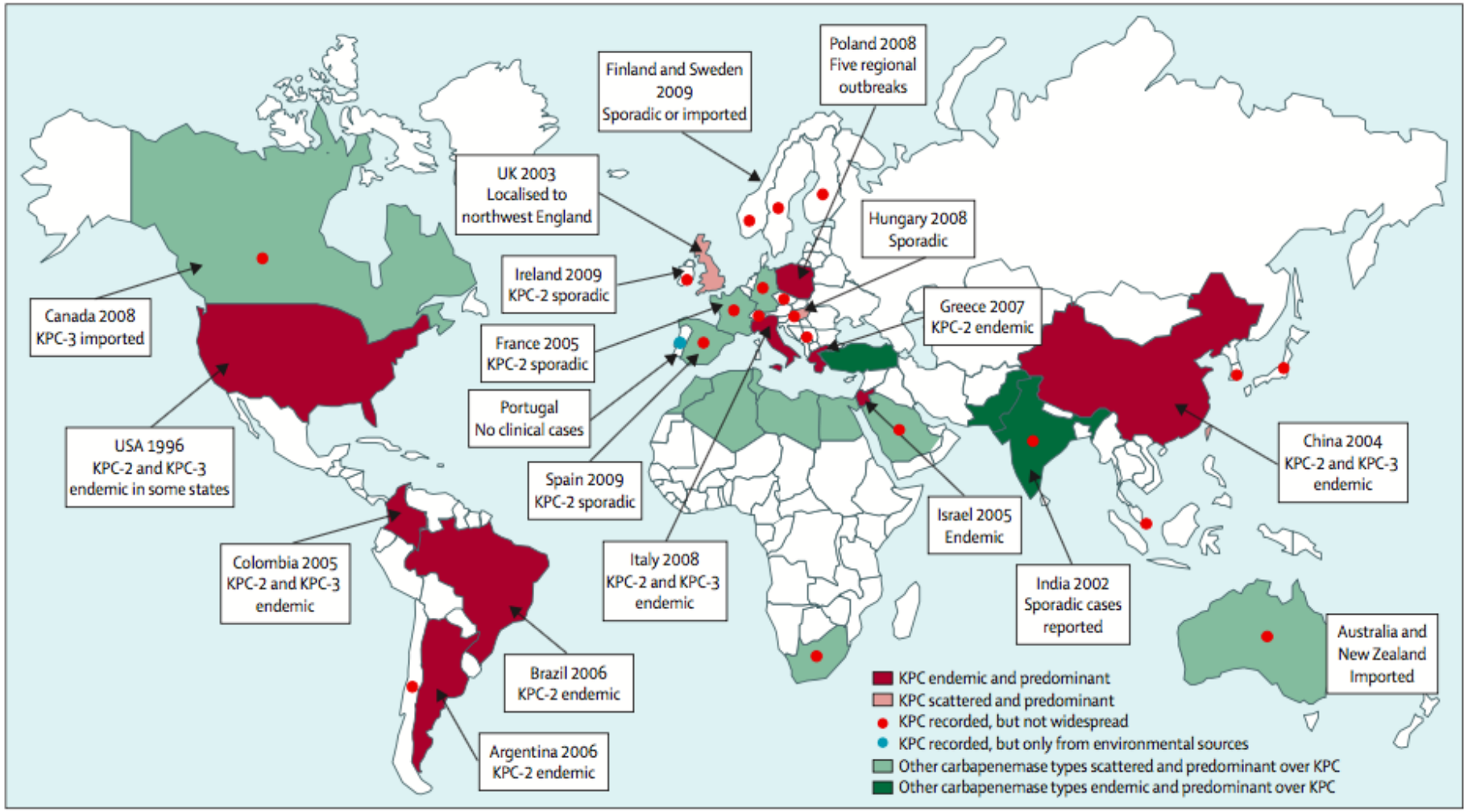
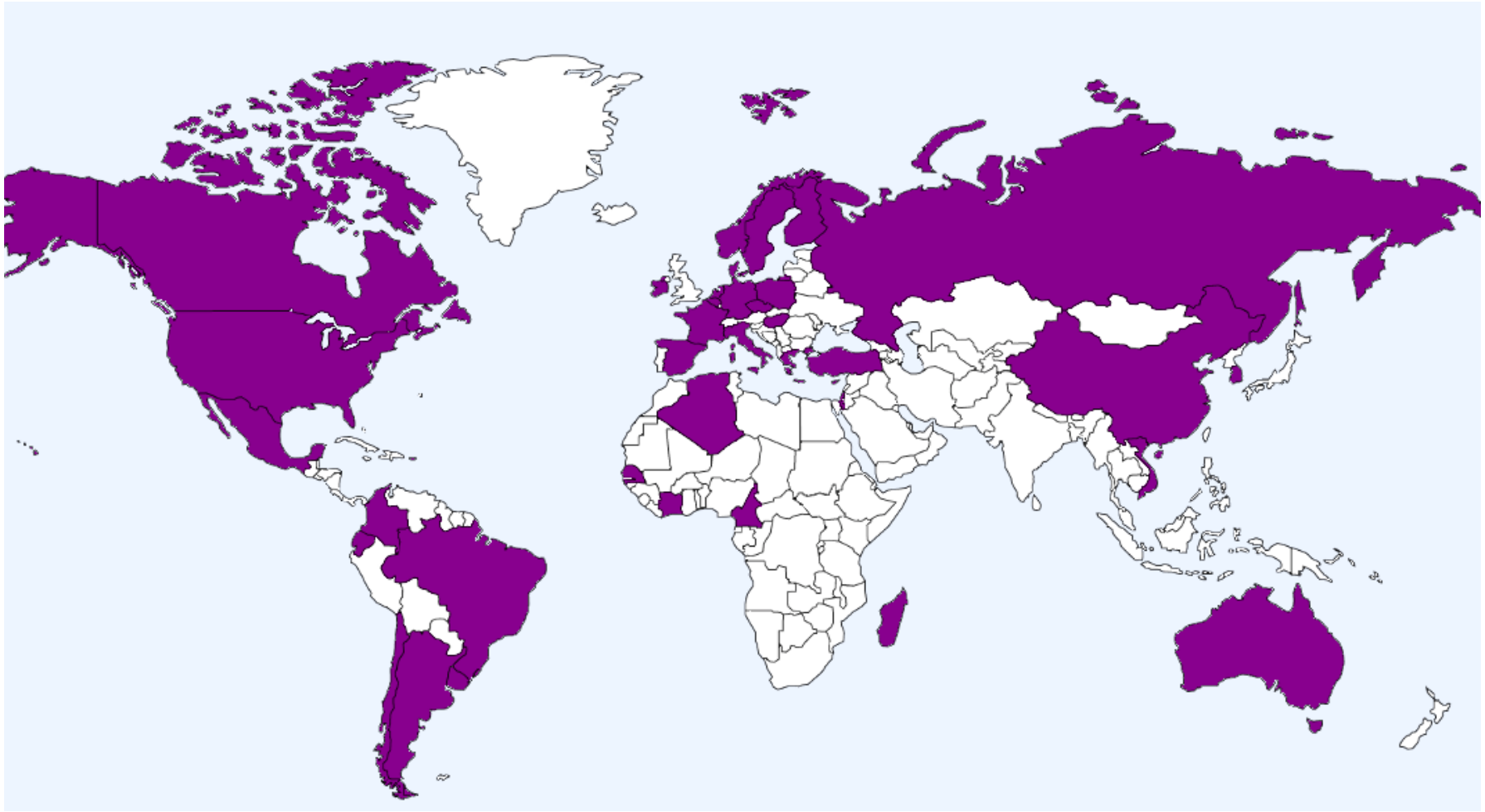
KPC-Carbapenemase Global Dissemination



Munoz-Price LS, et.al. 2013. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. The Lancet Infectious Diseases **13:**785-796.

Klebsiella pneumoniae Clonal (CG) 258



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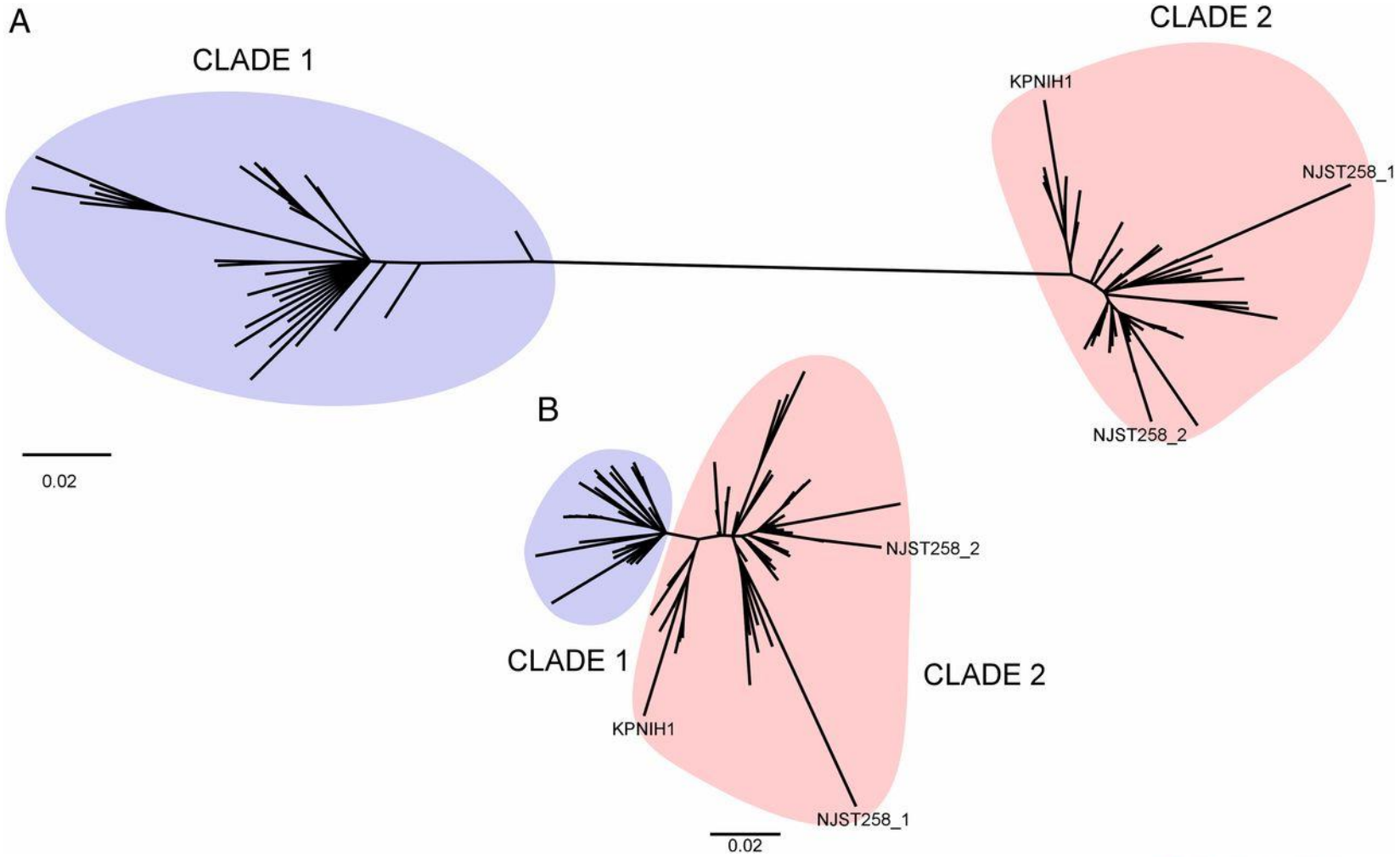
Phylogenetic analysis of *K. pneumoniae* ST258 clinical isolates in The USA



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Global Emergence of CG307

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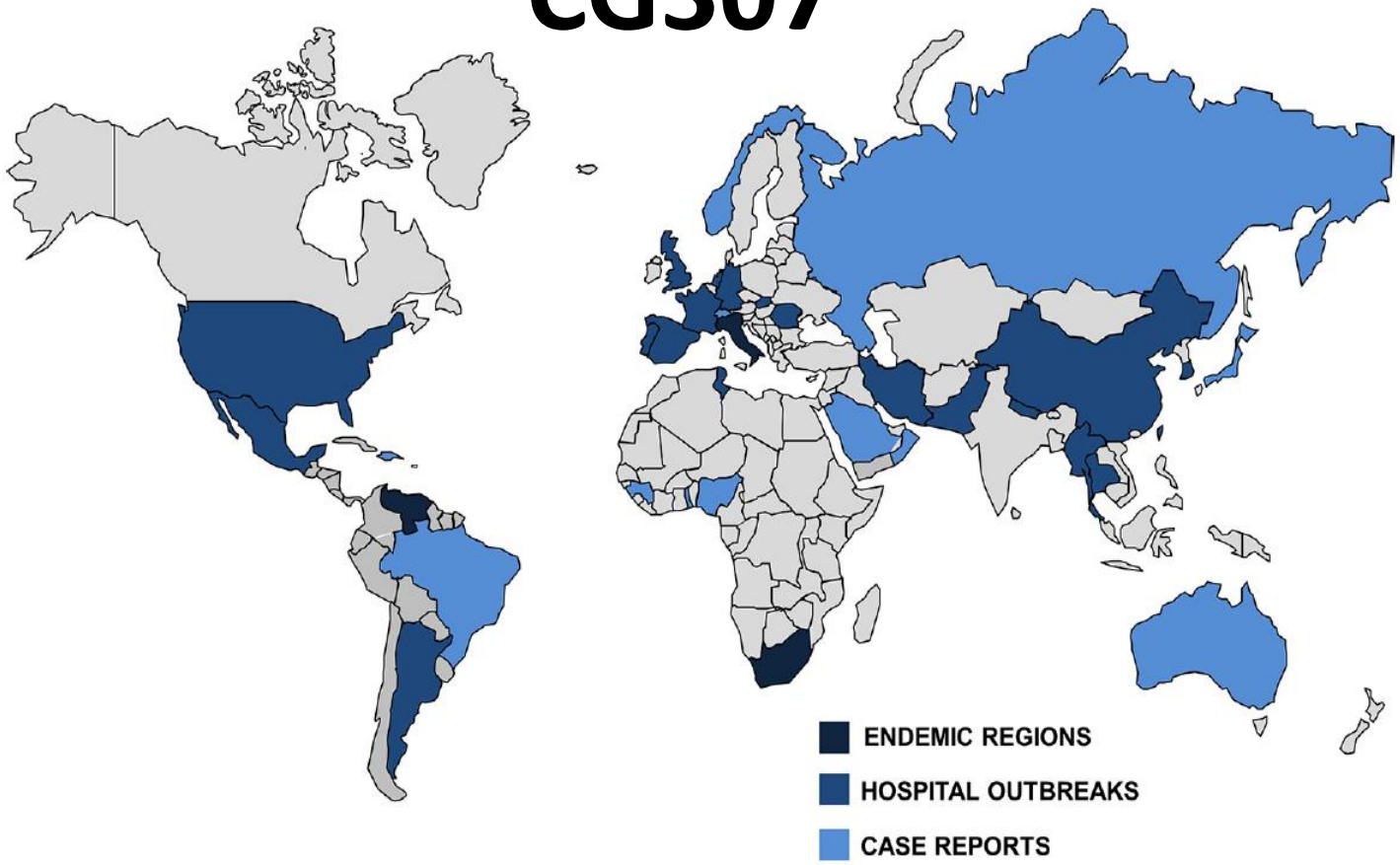
Emerging Antimicrobial-Resistant High-Risk *Klebsiella pneumoniae* Clones ST307 and ST147

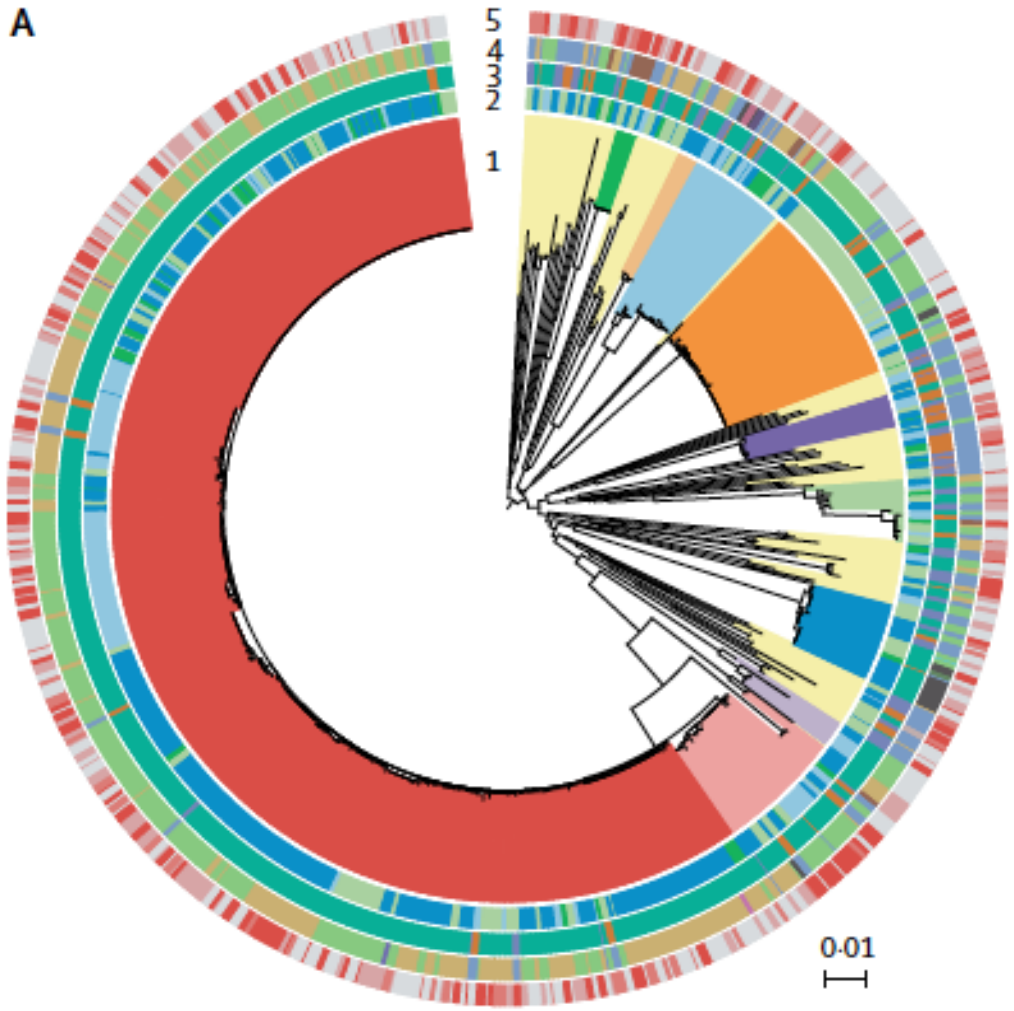
Gisele Peirano,[a,b] Liang Chen,[c,d] Barry N. Kreiswirth,[c,d] Johann D. D. Pitout[a,b,e]

[a]Alberta Precision Laboratories, Calgary, Alberta, Canada
[b]University of Calgary, Calgary, Alberta, Canada
[c]Hackensack Meridian Health Center for Discovery and Innovation, Nutley, New Jersey, USA
[d]Hackensack Meridian School of Medicine at Seton Hall University, Nutley, New Jersey, USA
[e]University of Pretoria, Pretoria, Gauteng, South Africa

CG307



Carbapenem-Resistant *K. pneumoniae* in USA



Molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in the USA (CRACKLE-2): a prospective cohort study

David van Duin*, Cesar A Arias*, Lauren Komarow, Liang Chen, Blake M Hanson, Gregory Weston, Eric Cober, Omai B Garner, Jesse T Jacob, Michael J Satlin, Bettina C Fries, Julia Garcia-Diaz, Yohei Doi, Sorabh Dhar, Keith S Kaye, Michelle Earley, Andrea M Hujer, Kristine M Hujer, T Nicholas Domitrovic, William C Shropshire, An Dinh, Claudia Manca, Courtney L Luterbach, Minggui Wang, David L Paterson, Ritu Banerjee, Robin Patel, Scott Evans, Carol Hill, Rebekka Arias, Henry F Chambers, Vance G Fowler Jr, Barry N Kreiswirth†, Robert A Bonomo†, for the Multi-Drug Resistant Organism Network Investigators

Houston was the only major city in the participating centers where *K. pneumoniae* CG307 was as frequent as CG258

ESBL-Producing *K. pneumoniae*, Houston ,TX

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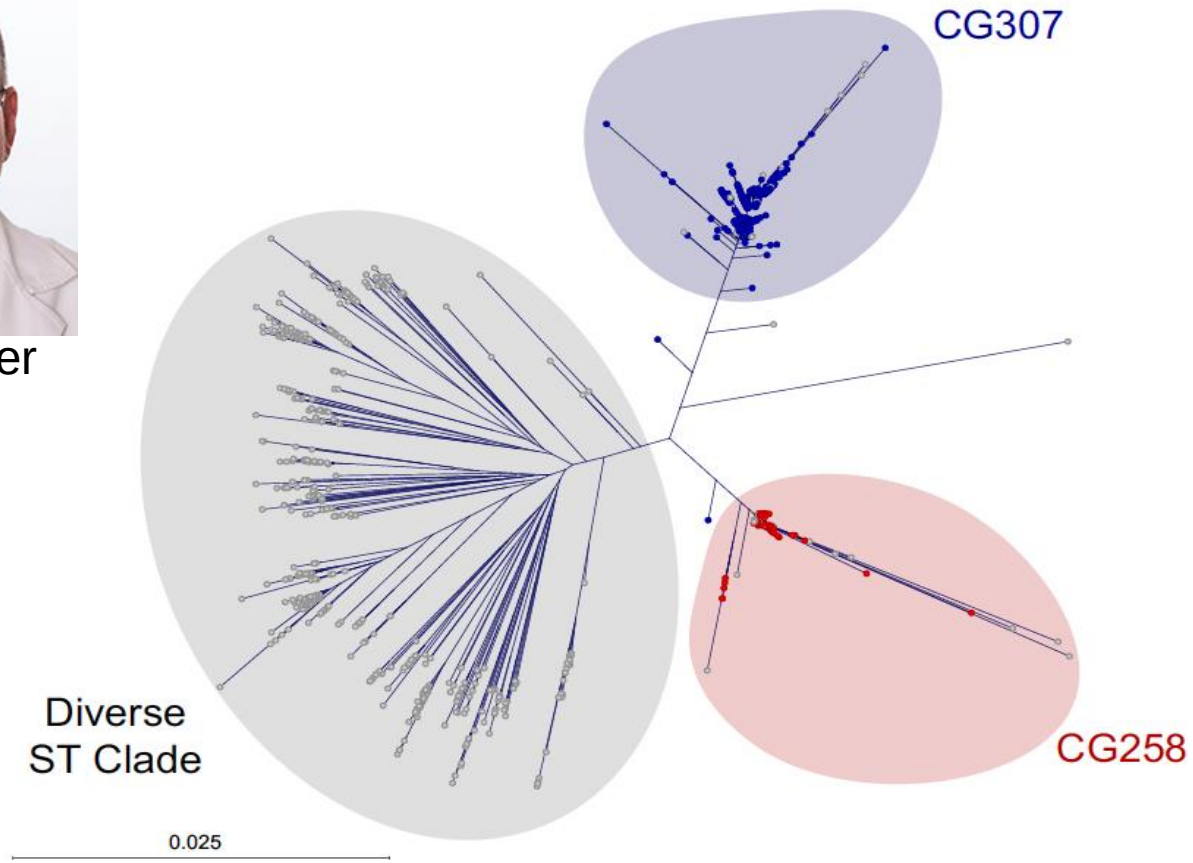
Wesley Long

Jim Musser

Population Genomic Analysis of 1,777 Extended-Spectrum Beta-Lactamase-Producing *Klebsiella pneumoniae* Isolates, Houston, Texas: Unexpected Abundance of Clonal Group 307

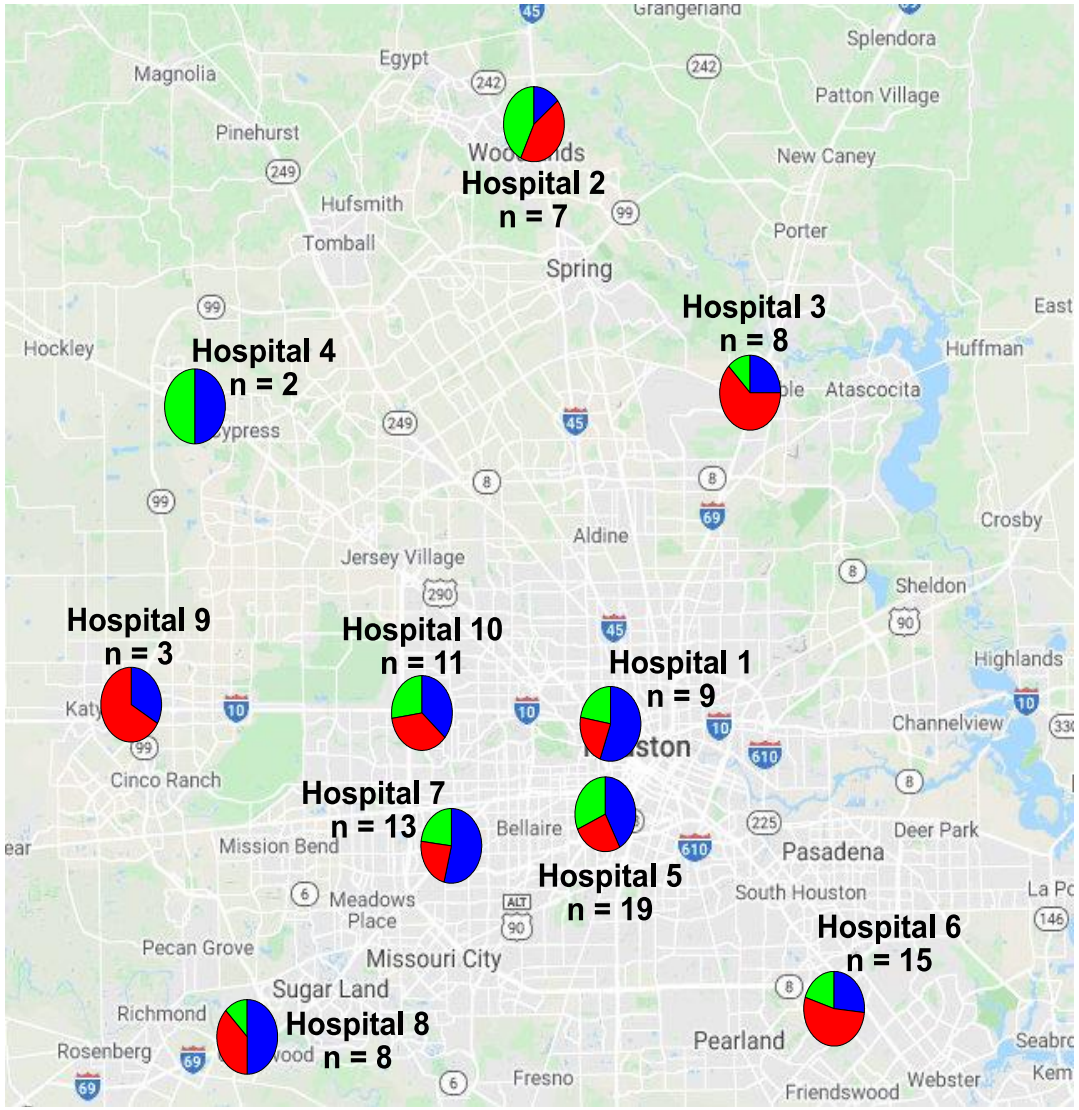
S. Wesley Long,[a,b] Randall J. Olsen,[a,b] Todd N. Eagar,[a] Stephen B. Beres,[a] Picheng Zhao,[a] James J. Davis,[c,d] Thomas Brettin,[c,d] Fangfang Xia,[c,d] James M. Musser[a,b]



***bla*$_{\text{CTX-M-15}}$**

Long et al., *mBio*, 2017

Carbapenem-Resistant *K. pneumoniae*, Houston, TX



Clonal Group

- CG258
- CG307
- Other CG

Will Shropshire

Blake Hanson

Population Structure of *K. pneumoniae* CG258 vs CG307, Houston TX

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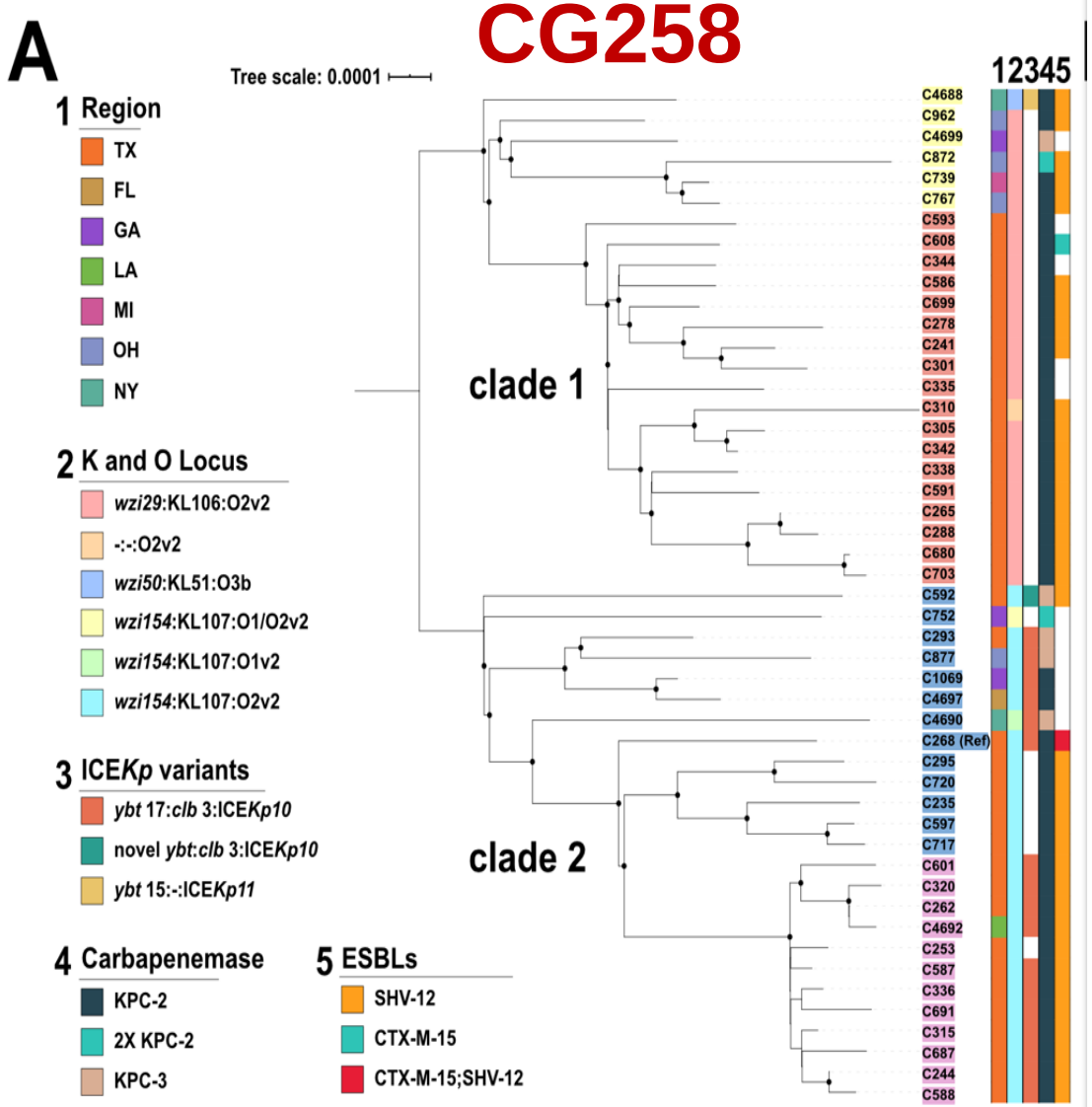
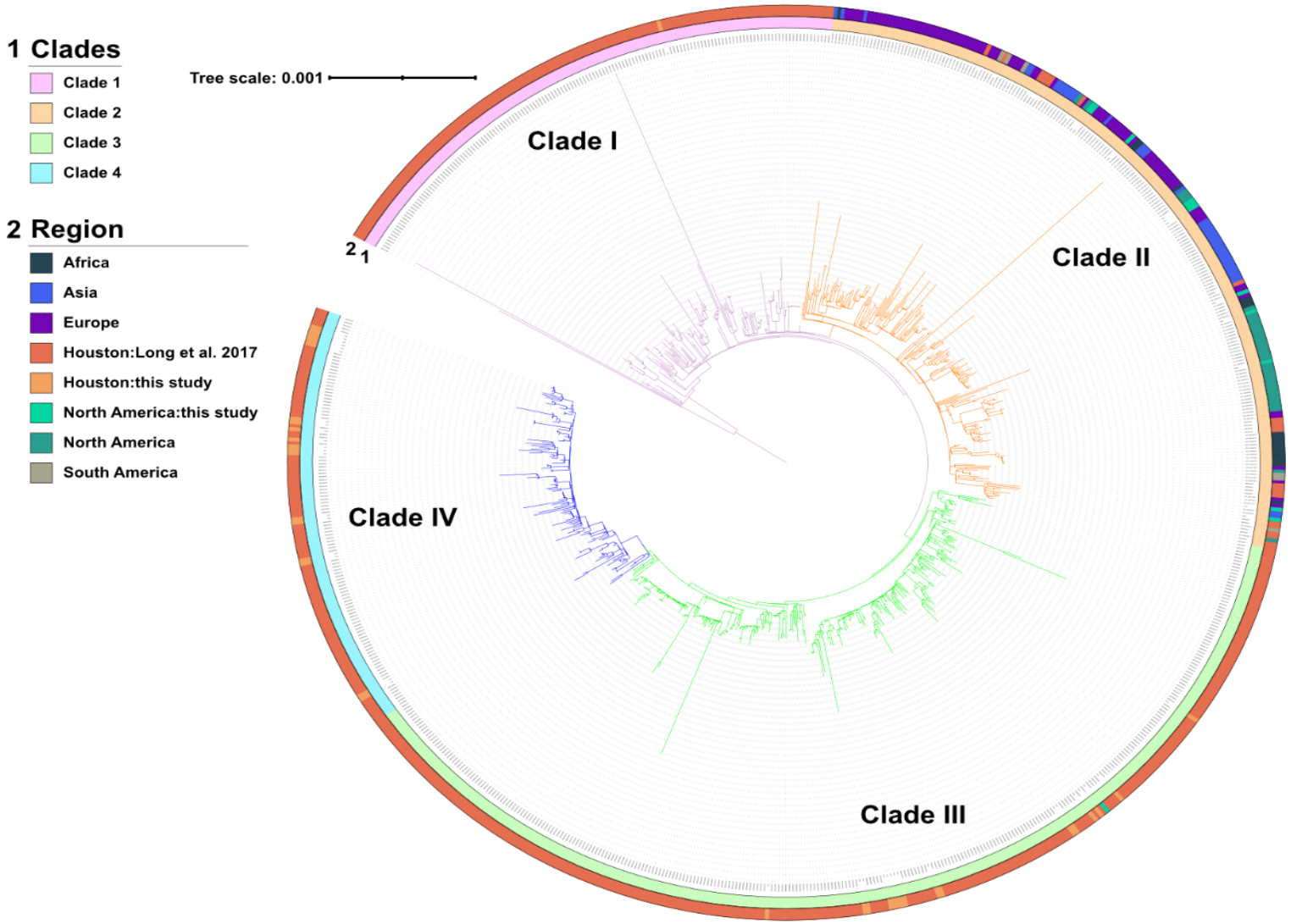


Phylogenetic Analyses of CG307 from Houston, TX vs Rest of The World



Accesory Genomes, Houston CG307 vs CG258

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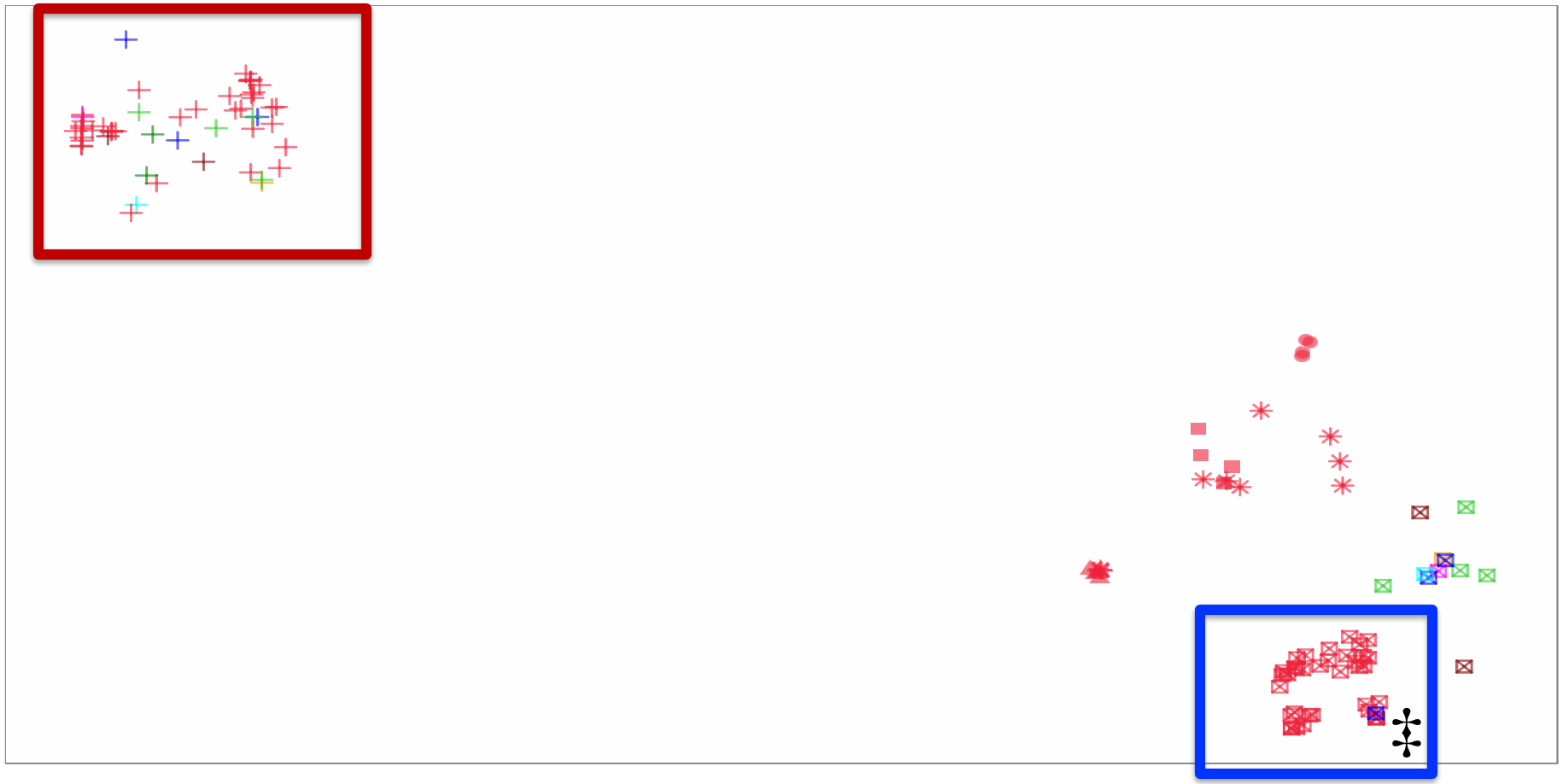
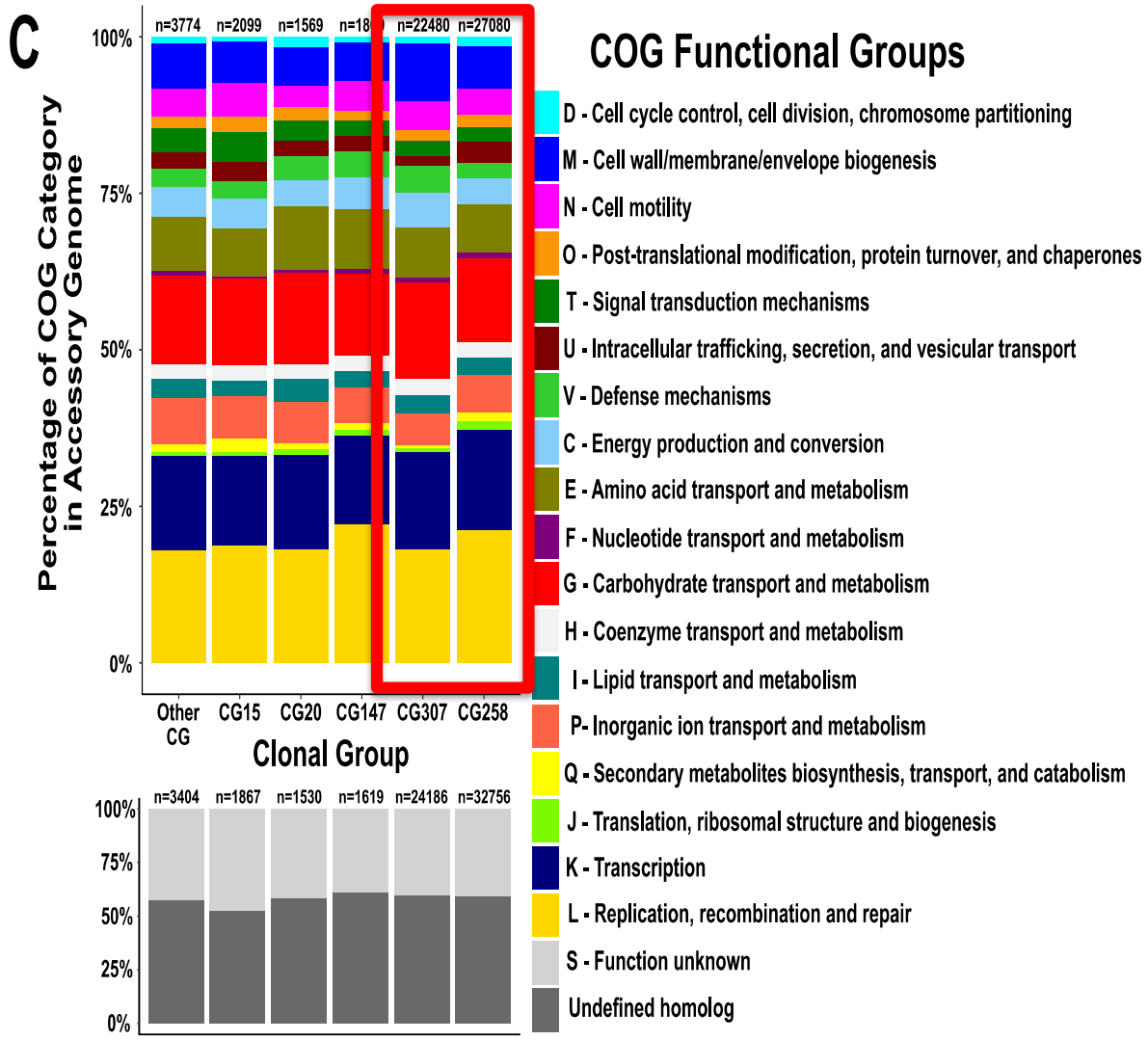
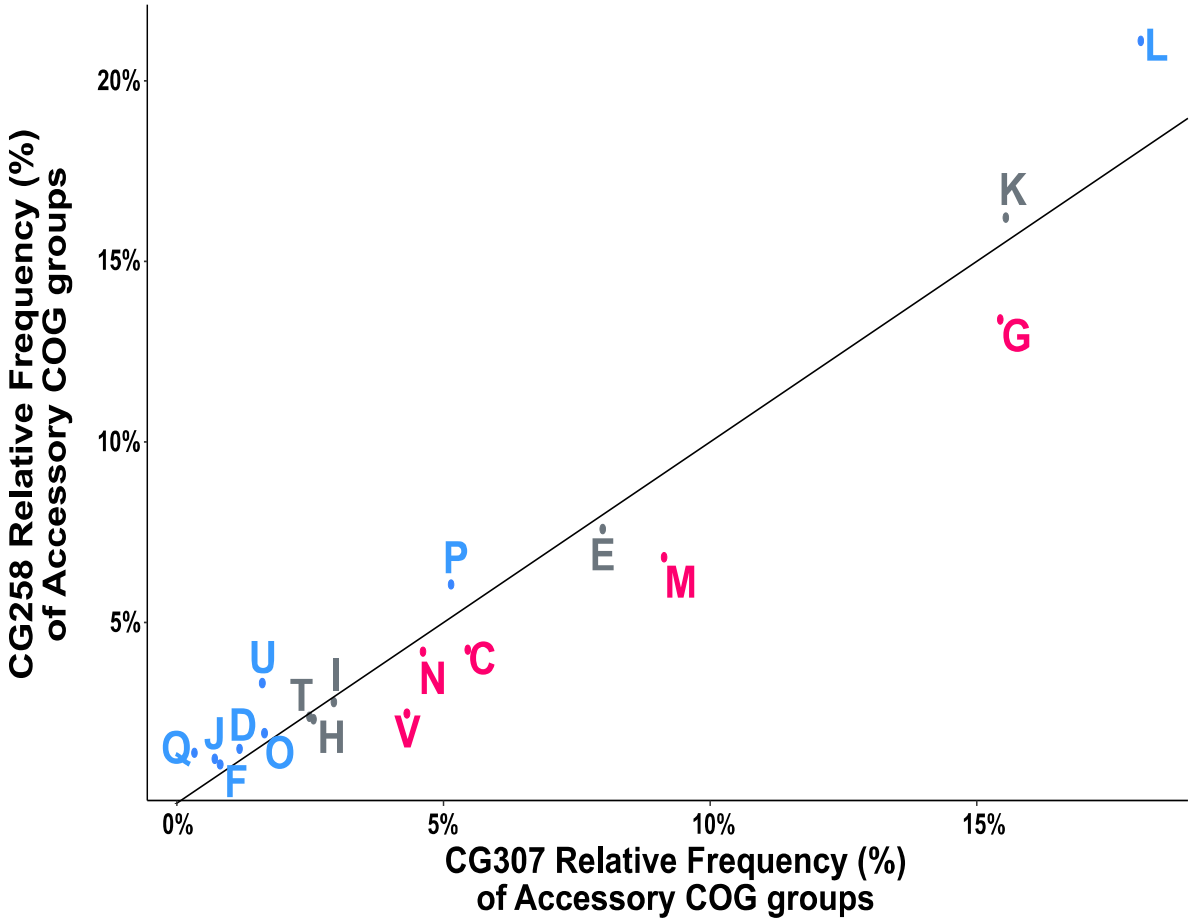


Region
- TX
- FL
- GA
- LA
- MI
- OH
- NJ
- NY

Clonal Group
- CG258
- CG307
- CG147
- CG15
- CG20
- Other CG

Accesory Genomes, Houston CG307 vs CG258

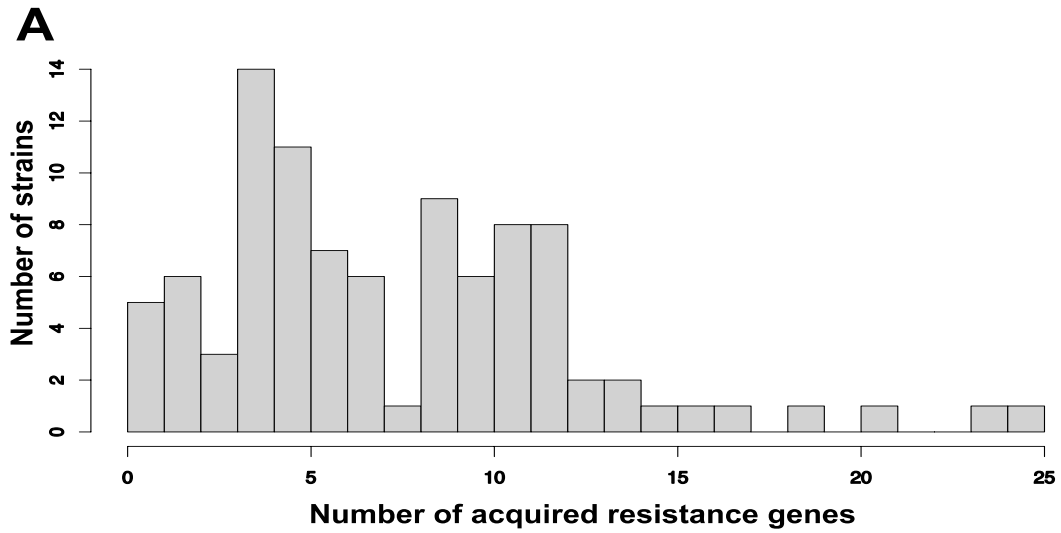


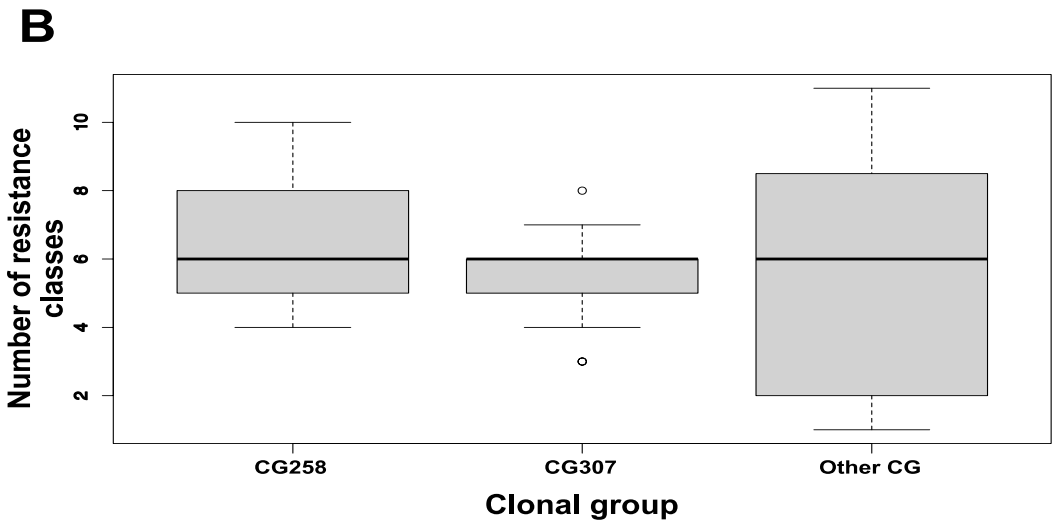


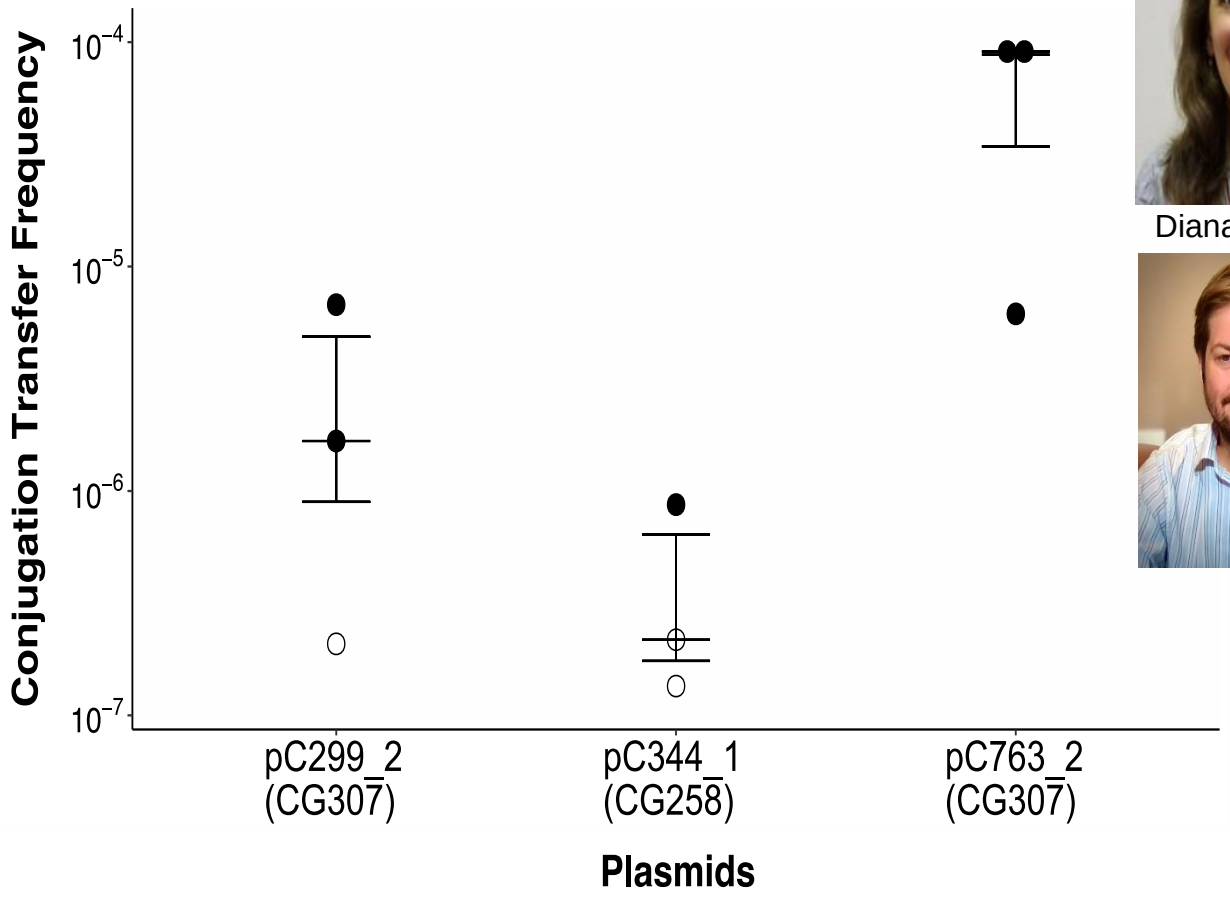
AMR Determinants CG258 vs CG307

- CG258 isolates harbored either ***bla***$_{KPC-2}$ (35/37; 94.6%) or *bla*$_{KPC-3}$ (2/37; 5.41 %) with the majority on **pKpQIL** plasmids (27/37; 73%),
- CG307 isolates (31/35; 88.6%) carried ***bla***$_{KPC-2}$ **on different vectors**, with one isolate (C678) carrying two *bla*$_{KPC-2}$ copies, one on the chromosome and the other on a FIIK/FIB (pKpQIL) plasmid
- All Houston CG307 harbored **more than one copy of *bla***$_{CTX-M-15}$ (2 [n=25], 3 [n=9] and 4 [n=1])

AMR Resistance and Plasmid Conjugation







Diana Panesso

Clinical Characteristics CG258 VS CG307

- The crude 30-day **mortality** for the full Houston cohort (n=73) was **17.8%**; (13/73 [95% CI: 7.8 – 22.6%]).
- Patients with **CG258** exhibited a **statistically significant higher 30-day mortality** compared with those infected/colonized with CG307, albeit with a small number of events
- Patients with **CG307** infection/colonization exhibited a higher proportion of samples isolated from **urine** (65.6%) compared to CG258 (37.0%) (p=0.068).
- Conversely, patients with **CG258** infection/colonization had a higher proportion of isolates from **blood** (14.8% vs 0%) and **respiratory cultures** (25.9% vs 12.5%) compared to the CG307 patient group.

Global Heterogenous Epidemiology of Carbapenem-Resistant *K. pneumoniae*

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Clinical outcomes and bacterial characteristics of carbapenem-resistant *Klebsiella pneumoniae* complex among patients from different global regions (CRACKLE-2): a prospective, multicentre, cohort study

Minggui Wang, Michelle Earley, Liang Chen, Blake M Hanson, Yunsong Yu, Zhengyin Liu, Soraya Salcedo, Eric Cober, Lanjuan Li, Souha S Kanj, Hainv Gao, Jose M Munita, Karen Ordoñez, Greg Weston, Michael J Satlin, Sandra L Valderrama-Beltrán, Kalisvar Marimuthu, Martin E Stryjewski, Lauren Komarow, Courtney Luterbach, Steve H Marshall, Susan D Rudin, Claudia Manca, David L Paterson, Jinnethe Reyes, Maria V Villegas, Scott Evans, Carol Hill, Rebekka Arias, Keri Baum, Bettina C Fries, Yohei Doi, Robin Patel, Barry N Kreiswirth, Robert A Bonomo, Henry F Chambers, Vance G Fowler Jr, Cesar A Arias, David van Duin, for the Multi-Drug Resistant Organism Network Investigators

Wang et al., *Lancet Infect Dis*, 2021

Global Heterogenous Epidemiology of Carbapenem-Resistant *K. pneumoniae*

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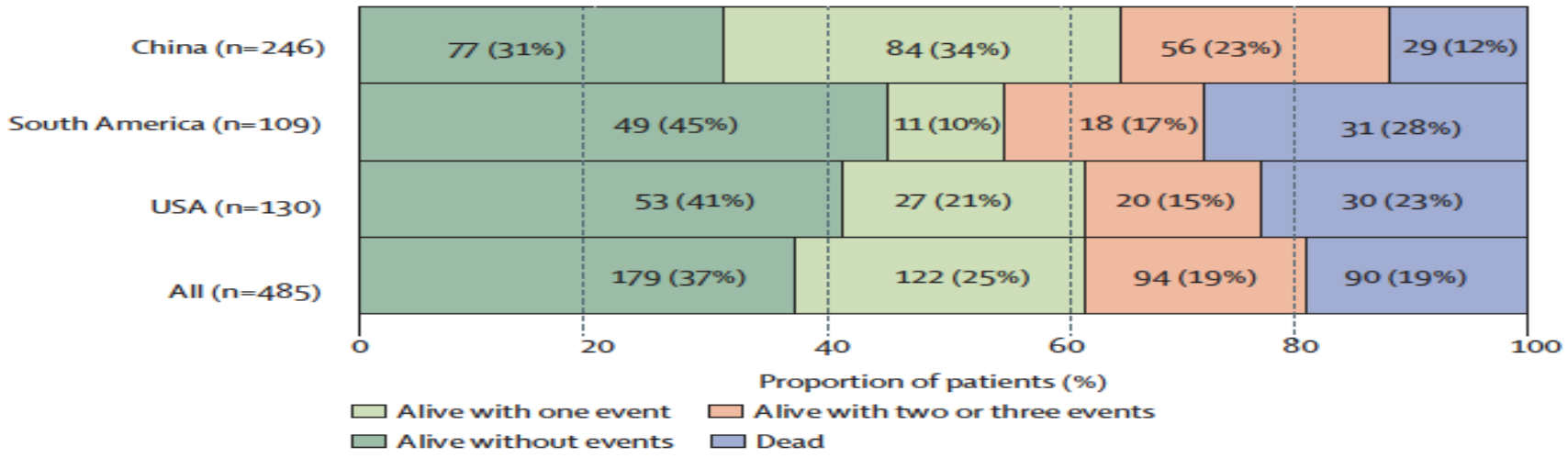
	China (n=485)	South America (n=170)	USA (n=284)	Australia, Lebanon, and Singapore (n=52)	All infected patients (n=502)	Total (n=991)	p value*
Carbapenemases†							
Carbapenemase(s) present	473 (98%)	127 (75%)	249 (88%)	39 (75%)	443 (88%)	888 (90%)	<0·0001
bla_{KPC-2}	454 (94%)	66 (39%)	124 (44%)	2 (4%)	324 (65%)	646 (65%)	<0·0001
bla_{KPC-3}	0	51 (30%)	105 (37%)	0	78 (16%)	156 (16%)	<0·0001
Other bla_{KPC}‡	2 (<1%)	0	3 (1%)	0	3 (1%)	5 (1%)	0·28
bla_{NDM-1}	8 (2%)	14 (8%)	6 (2%)	3 (6%)	16 (3%)	31 (3%)	<0·0001
Other bla_{NDM}§	4 (1%)	0	0	9 (17%)	7 (1%)	13 (1%)	0·15
bla_{OXA-48}	0	0	7 (2%)	25 (48%)	10 (2%)	32 (3%)	0·0003
Other $bla_{OXA-48-like}$¶	3 (1%)	1 (1%)	7 (2%)	5 (10%)	8 (2%)	16 (2%)	0·053
Other‖	4 (1%)	3 (2%)	0	1 (2%)	4 (1%)	8 (1%)	0·10
No carbapenemase detected	12 (2%)	43 (25%)	35 (12%)	13 (25%)	59 (12%)	103 (10%)	..



Wang et al., *Lancet Infect Dis*, 2021

Carbapenem-Producing *K. pneumoniae*

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The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

An Analysis of the Epidemic of *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae*: Convergence of Two Evolutionary Mechanisms Creates the "Perfect Storm"

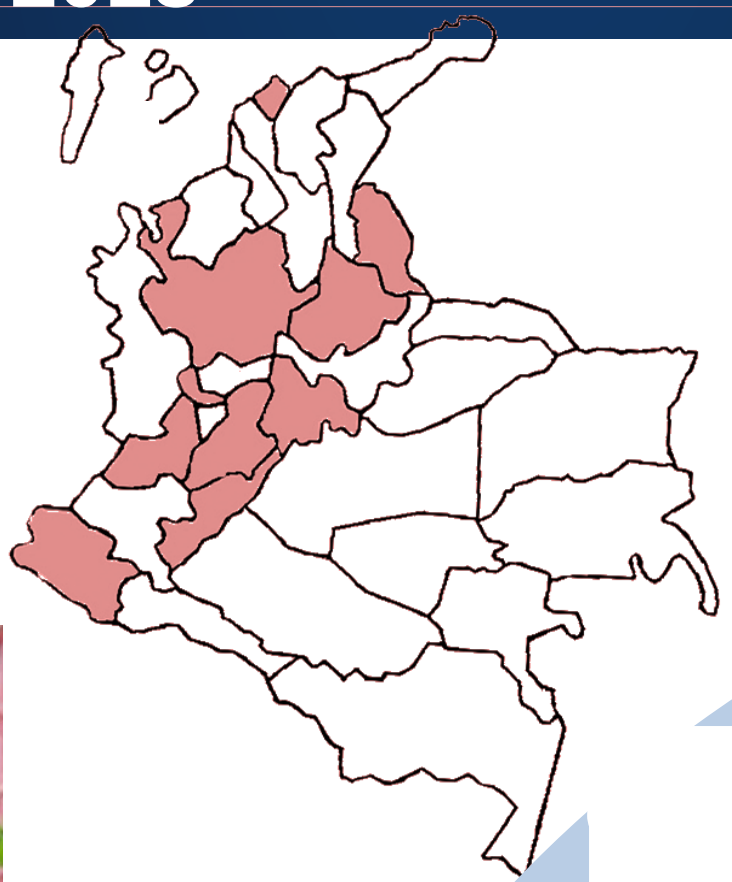
Laura J. Rojas,[2,7] George M. Weinstock,[9] Elsa De La Cadena,[10,11] Lorena Diaz,[11,12] Rafael Rios,[11] Blake M. Hanson,[9] Joseph S. Brown,[9] Purva Vats,[9] Daniel S. Phillips,[9] Hoan Nguyen,[9] Kristine M. Hujer,[1,7] Adriana Correa,[10] Mark D. Adams,[9] Federico Perez,[1,6,7] Erica Sodergren,[9] Apurva Narechania,[14] Paul J. Planet,[15–17] Maria V. Villegas,[10,11] Robert. A. Bonomo,[1–8,a] and Cesar A. Arias[11–14,a]

Rojas, LJ et al. *J Infect Dis*, 2017

Dissemination of KPC-2 in Colombia 2005 - 2013

Laura Rojas

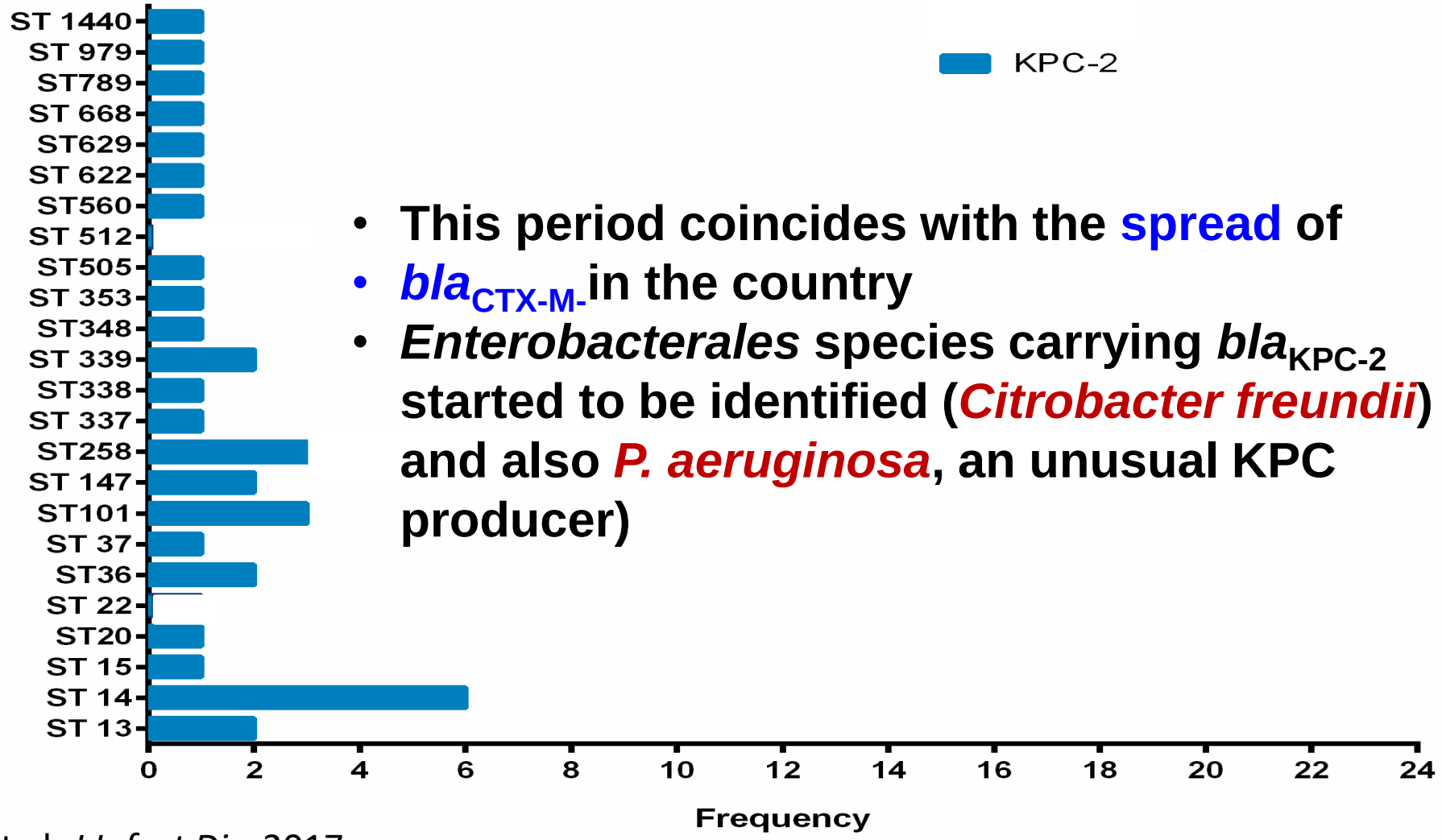
Maria V. Villegas



2005 : First KPC-2 on Kpn

Rojas, LJ et al. *J Infect Dis*, 2017.,[32]

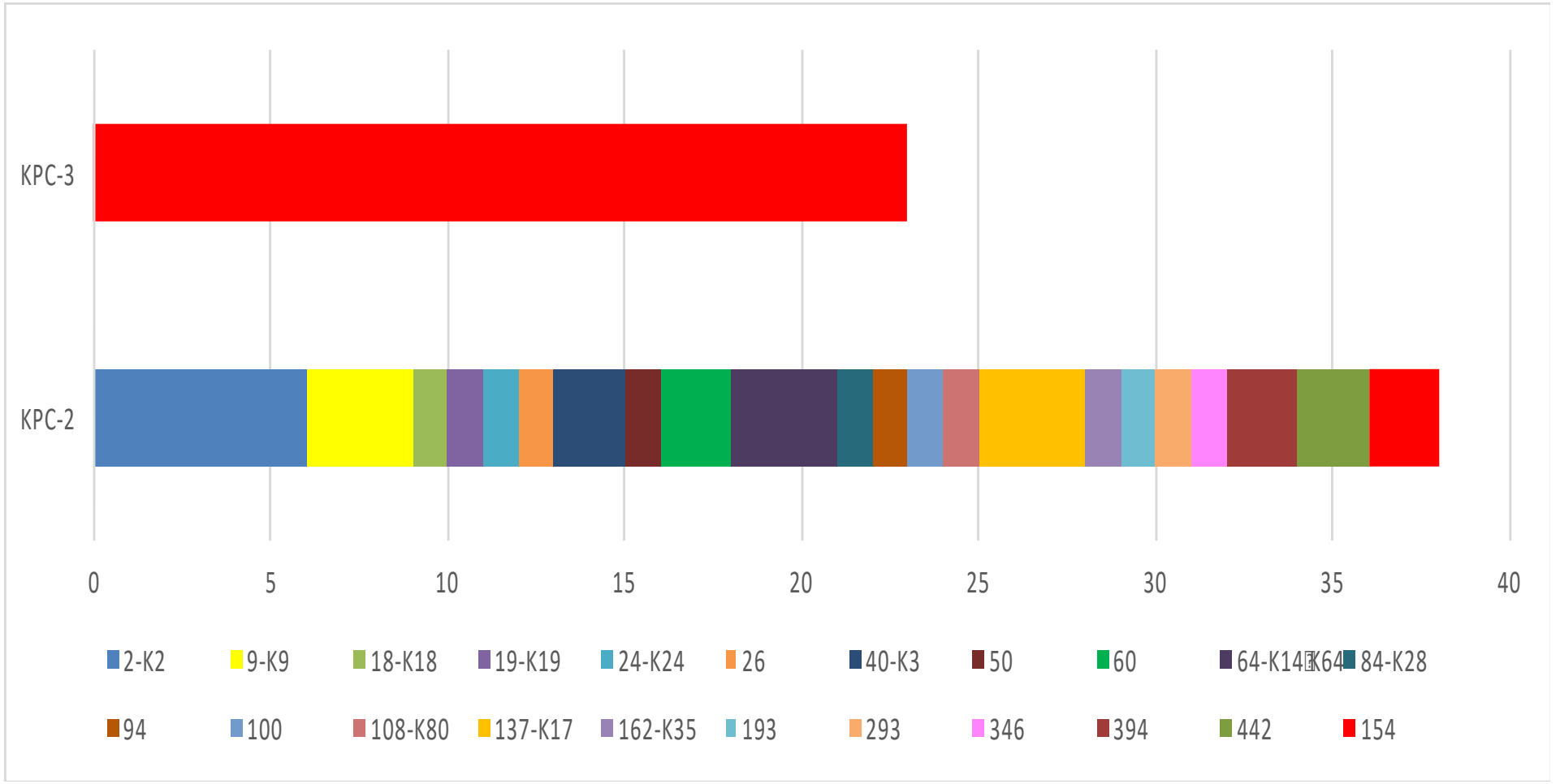
Dissemination of KPC-2 in Colombia 2005 - 2007



- This period coincides with the spread of
- *bla*$_{CTX-M-}$ in the country
- *Enterobacterales* species carrying *bla*$_{KPC-2}$ started to be identified (*Citrobacter freundii*) and also *P. aeruginosa*, an unusual KPC producer)

Rojas, LJ et al. *J Infect Dis*, 2017.,

Capsular Diversity *K. pneumoniae* in Colombia



The “Perfect Storm” In Colombia

- Before the emergence of KPC (“pre-KPC period,” 2002–2005), ESBLs were prevalent amongst *K. pneumoniae* circulating in Colombia
- After a sentinel event of acquisition of bla_{KPC-2}, circulationamong K. pneumoniae isolates with heterogeneous genetic backgrounds between 2005 and 2007 was rapidly documented
- In 2008 introduction of a CG258 isolate harboring IncI2 plasmids that have been circulating in the United States (New York/New Jersey area) seems to have occurred.
- Then, a monophyletic clade of the “high risk clone” CG258 K. pneumoniae carrying bla_{KPC-3} is expanded simultaneously

IncN Plasmids Disseminate KPC in A Colombian Region

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EPIDEMIOLOGY AND SURVEILLANCE

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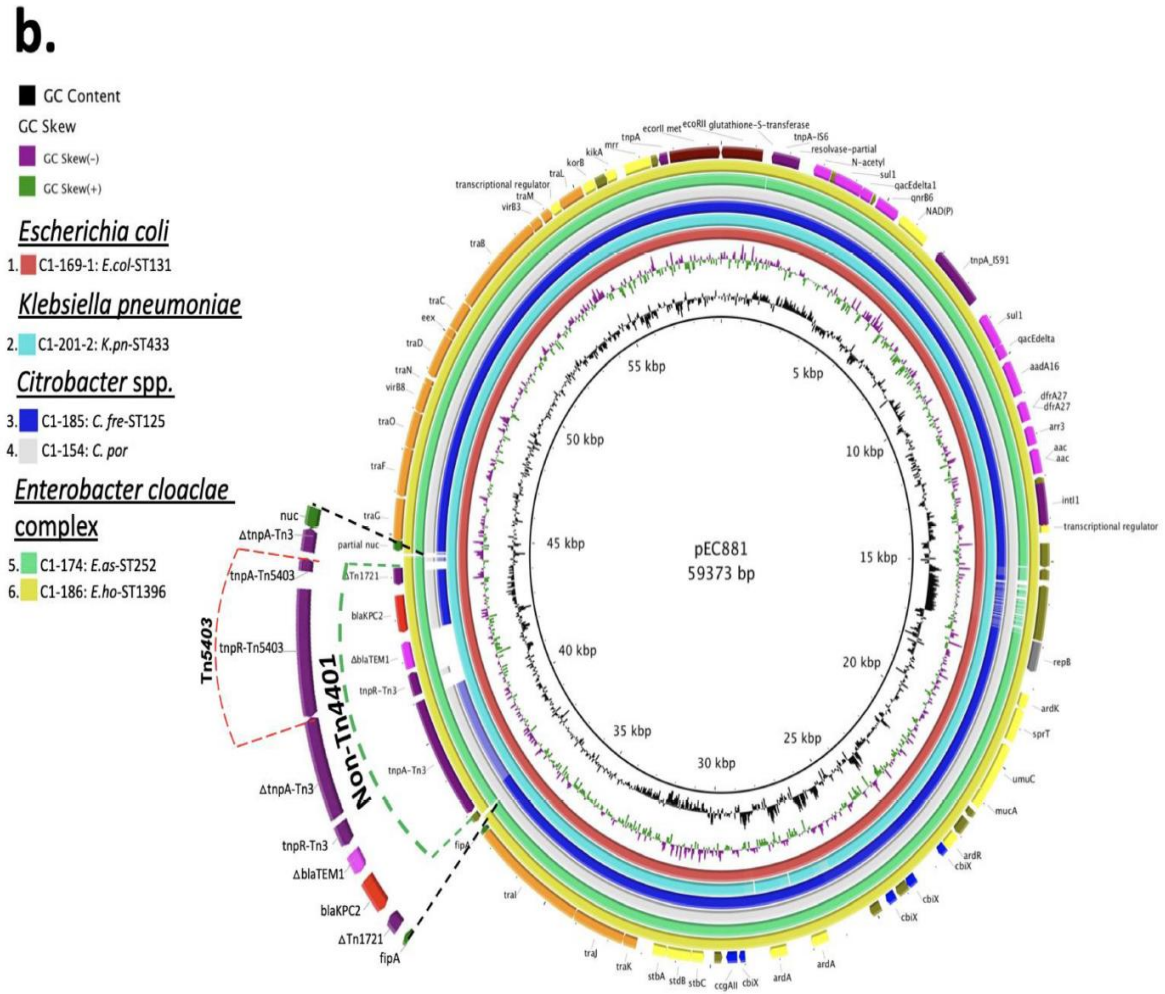
Ana Rada

Dynamics of *bla*$_{KPC-2}$ Dissemination from Non-CG258 *Klebsiella pneumoniae* to Other *Enterobacterales* via IncN Plasmids in an Area of High Endemicity

Ana M. Rada,[a,b] Elsa De La Cadena,[c] Carlos Agudelo,[d] Cesar Capataz,[e] Nataly Orozco,[a] Cristian Pallares,[c] An Q. Dinh,[f] Diana Panesso,[f,g] Rafael Ríos,[f,g] Lorena Diaz,[f,g] Adriana Correa,[h] Blake M. Hanson,[f] Maria V. Villegas,[c] Cesar A. Arias,[f,g,i] Eliana Restrepo[a]



Rada et al, *Antimicrob Agents Chemother*, 2022

Conclusions

- The silent pandemic of AMR is challenging and we need to understand the complexities of dissemination in order to have successful interventions
- Detailed analyses of how MDR bacteria spread is of paramount importance to detect emergence of new high-risk populations.
- In Houston, two major mechanisms within CG258 and CG307 lineages have evolved independently of one another and appear to be disseminating in parallel with limited evidence of inter-clade horizontal gene transfer between them.
- In Colombia, an initial plasmid epidemic was followed by introduction of a high-risk clone with both mechanisms acting independently that amplified the epidemic

Lab and Collaborators
Looking for postdocs!!

Rachel Atterstrom
Dierdre Axell-House, MD
German Contreras, MD
Haley Greenia
Andrea deTrantales
Alex Deyanov
An Dinh
Sara Gomez, MD
Kara Hood PhD
Karen Jacques-Palaz
Ayesha Khan, PhD
William Miller, MD
Mary North
Diana Panesso, PhD
Isabel Reyes
Kirsten Rydell MPH
Kavindra Singh, PhD
Shelby Simar, MPH
Cecilia Tran, PharmD
Hassan Virk MD

UTHealth
Blake Hanson

Universidad El Bosque
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