

MDRO Colonization in the ICU: Initial Results from the DYNAMITE Cohort

Max A. Adelman, MD, MSc

Divisions of Infectious Diseases and Pulmonary/Critical Care Medicine
Houston Methodist Hospital



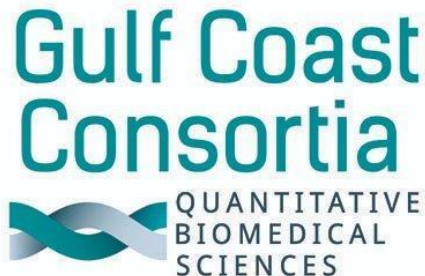
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The DYNAMITE Team

Cesar Arias & Arias lab

Rachel Atterstrom
Andie deTranaltes
Kirsten Bevan Rydell
Mary North Jones
Marissa Schettino
Husna Malikzad
Abigail Amaya
Hassan Virk
Giselle Ortiz
Subrha Singh
Asmita Ghosh
Alejandro de la Hoz
Rosi Arias Fernandez
Rodrigo De Paula Baptista
An Dinh
Haley Greenia
Georgeanne Llanes
Alex Deyanov
Blake Hanson
Hossaena Ayele



P01AI152999 (CAA, SAS,
TCS)

Sam Shelburne & Shelburne Lab



Tor Savidge & Savidge Lab



Tony Haag & Haag Lab

Kevin Garey & Garey Lab

Todd Treangen & Treangen Lab

David van Duin

Susan Xu



- None

- Background: MDRO infection and colonization in the ICU
- DYNAMITE results
 - Key Question 1: Impact of MDRO colonization
 - Key Question 2: Duration of colonization

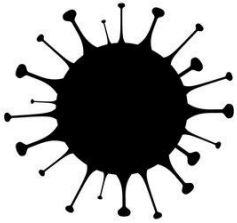
Background: Infection and colonization in the ICU

Infections are common in the ICU

EPIC I (1992)

EPIC II (2007)

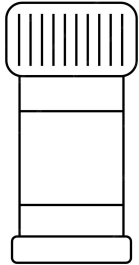
EPIC III (2017)



45%

51%

54%



62%

71%


70%

Key Question #1

What is the impact of MDRO colonization on ICU outcomes not limited to infection?

Relationship between immunosuppression and intensive care unit-acquired colonization and infection related to multidrug-resistant bacteria: a prospective multicenter cohort study



Louis Kreitmann^{1,2}, Margot Vasseur¹, Sonia Jermoumi¹, Juliette Perche³, Jean-Christophe Richard⁴, Florent Wallet^{5,6}, Myriam Chabani², Emilie Nourry², Pierre Garçon⁷, Yoann Zerbib⁸, Nicolas Van Grunderbeeck⁹, Christophe Vinsonneau¹⁰, Cristian Preda^{11,12}, Julien Labreuche¹³ and Saad Nseir^{1,14*} 

- 8 French ICUs
- Patients with ICU stay > 48h enrolled and followed for 4 weeks
- Screened for MDRO weekly (rectal/nasal swabs)
- 1^o outcome: ICU-MDRO colonization and/or infection

MDROs in the ICU

	Normal immune status <i>n</i> = 486	Immunocompromised status <i>n</i> = 264
MDR bacteria of first event (<i>n</i> , %)		
Methicillin-resistant <i>Staphylococcus aureus</i>	14/154 (9.1)	3/63 (4.8)
Carbapenem-resistant Enterobacteriaceae	13/154 (8.4)	8/63 (12.7)
MDR <i>Pseudomonas aeruginosa</i>	9/154 (5.9)	4/63 (6.3)
Carbapenem-resistant <i>Acinetobacter baumannii</i>	4/154 (2.6)	0/63 (0)
Vancomycin-resistant enterococci	0/154 (0)	1/63 (1.6)
3GC-resistant Enterobacteriaceae (including ESBL)	114/154 (74)	47/63 (74.6)

- No difference between rate of colonization or infection according to immunocompromised status
- No impact of MDRO on mortality
- Limitations: Little information on clinical outcomes

Colonization and infection with extended-spectrum β -lactamase-producing Enterobacteriaceae in ICU patients: what impact on outcomes and carbapenem exposure?

Journal of Antimicrobial Chemotherapy, Volume 71, Issue 4, April 2016, Pages 1088–1097,

<https://doi.org/10.1093/jac/dkv423>

Published: 10 January 2016 **Article history** ▾

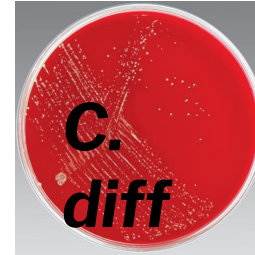
- >16000 patients in 17 European ICUs
- Admission and weekly ESBL rectal swabs
- 594 (3.5%) had ESBL (~1/2 on admission)
- ESBL colonization associated with decreased ICU discharge at d28 (HR 0.56, 95%CI 0.43-0.73) without increased mortality
- ESBL infection associated with increased mortality

- Determine the risk factors for and prevalence of MDRO colonization in the ICU, as well the impact of colonization on clinically important outcomes

- Dynamics of Colonization and Infection by Multidrug-resistant Pathogens in Immunocompromised and Critically Ill Patients (DYNAMITE, PI: Arias)
- Multicenter, prospective cohort study
- ICUs of referral centers in Houston, TX
- Target enrollment: 500 ICU patients
- Current analysis: Initial 200 ICU patients

- Patients consented on ICU admission
- Clinical data abstracted via chart review
 - Detailed clinical data for duration of ICU admission \leq 28 days
 - 30-day mortality
 - Clinical infections
 - Defined by CDC criteria or clinical team
- Colonization: Positive stool culture for ≥ 1 “target organism” (VRE, ESBL-E/CRE, *C. difficile*)

- Stool samples collected twice weekly



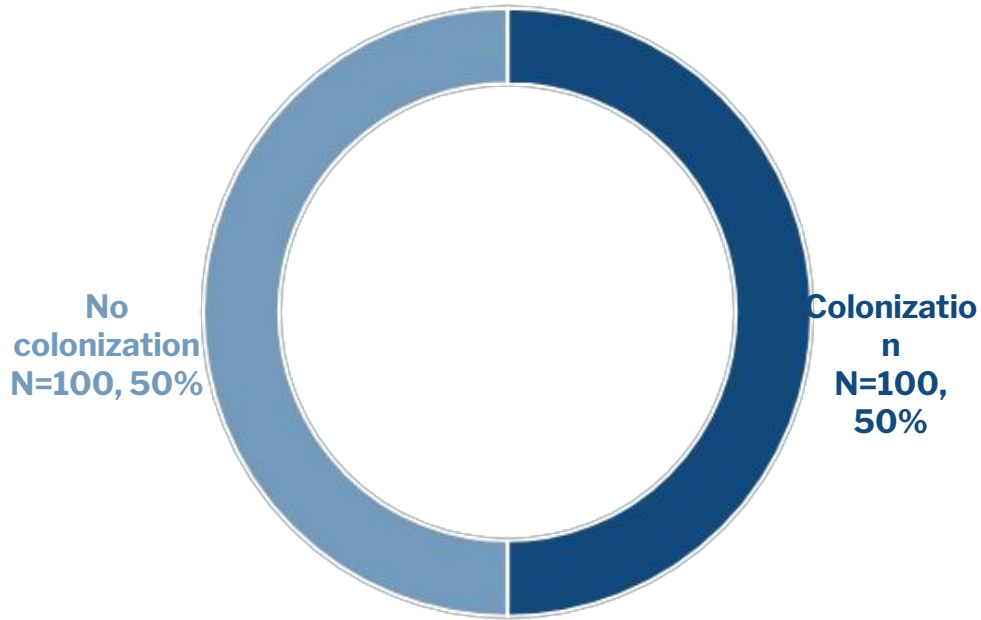
MALDI-ToF
Sequenced

- Target organisms recovered from any clinical sample sequenced and banked

- Compared baseline characteristics of patients with vs. without colonization
- Compared outcomes of patients with vs. without colonization using a desirability of outcomes ranking (DOOR) analysis
 - Unadjusted
 - Inverse probability weighted

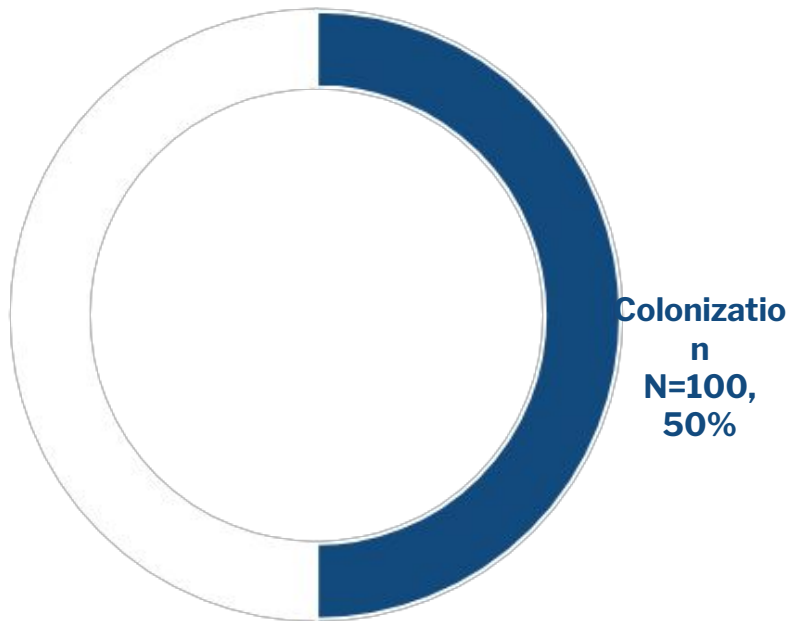
Results: Colonization

Any MDRO colonization

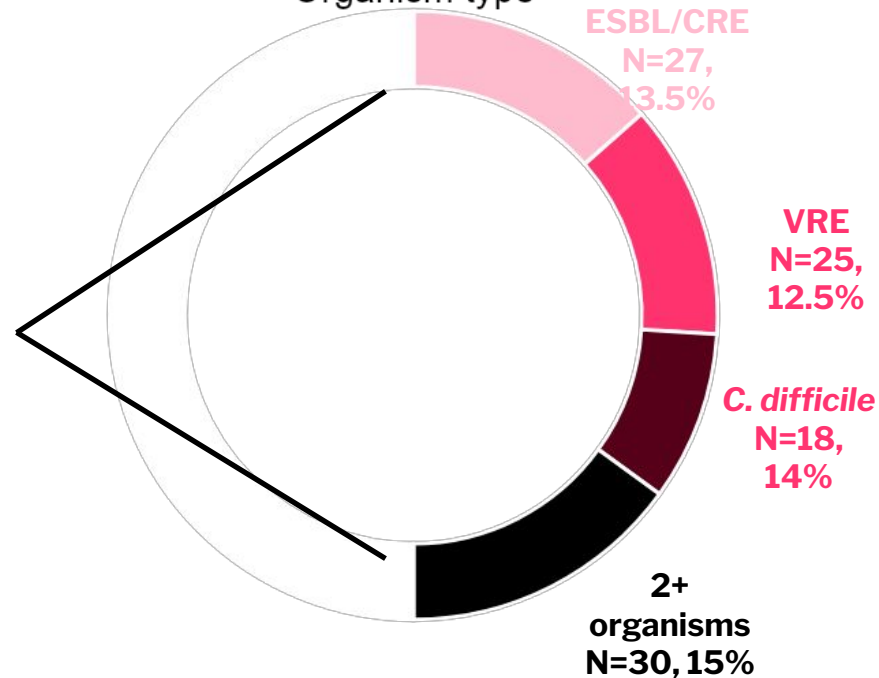


Results: Colonization

Any MDRO colonization

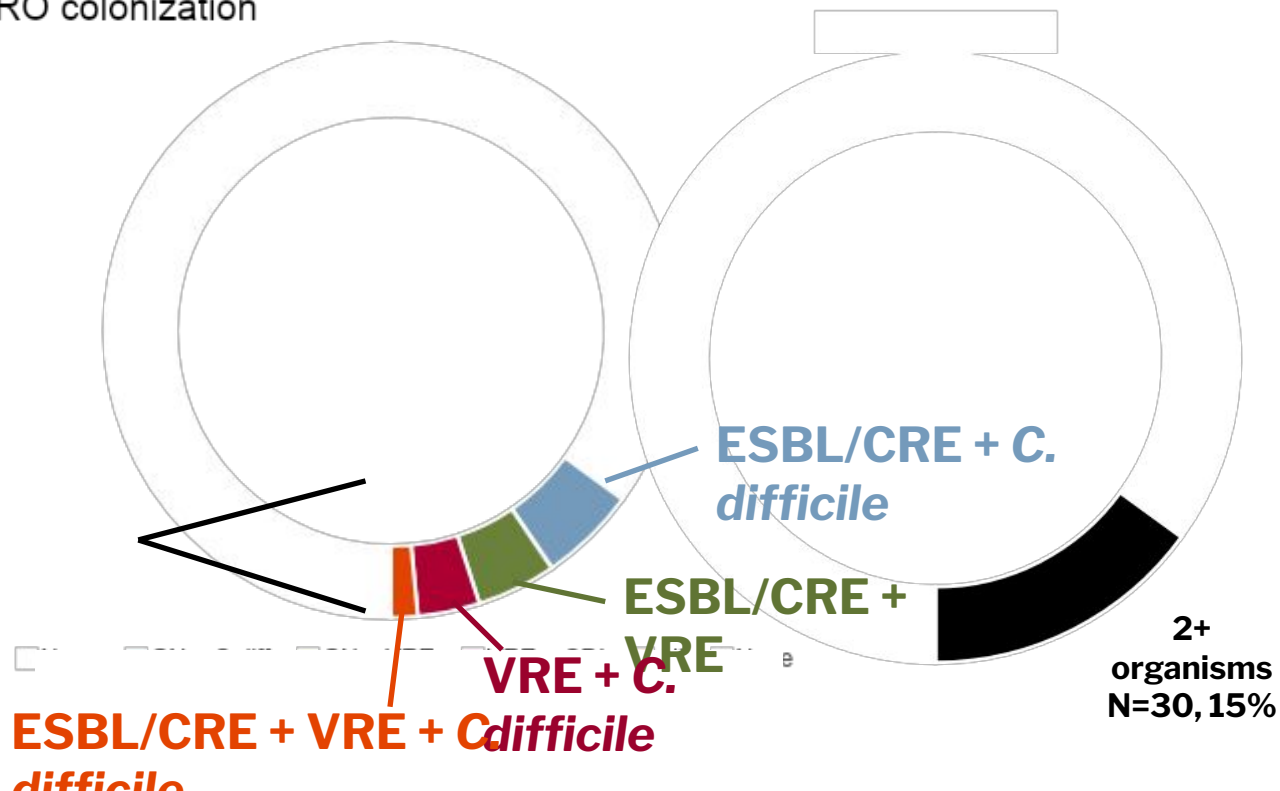


Organism type



Results: Colonization

Any MDRO colonization



Results: Colonization

Organism type

ESBL		CRE		VRE	
Genus	N (%)	Genus	N (%)	Species	N (%)
<i>Klebsiella</i>	32 (35%)	<i>Klebsiella</i>	20 (67%)	<i>E. faecium</i>	78 (87%)
<i>Escherichia</i>	29 (32%)	<i>Escherichia</i>	8 (27%)	<i>E. gallinarum</i>	6 (7%)
<i>Citrobacter</i>	15 (17%)	<i>Citrobacter</i>	1 (3%)	<i>E. faecalis</i>	3 (3%)
<i>Enterobacter</i>	10 (11%)	<i>Morganella</i>	1 (3%)	<i>E. casseliflavus</i>	3 (3%)

2+
organisms
N=30, 15%

Results: Colonization

	Colonization		
Characteristic	No (N=100, 50%)	Yes (N=100, 50%)	P
Age , years, mean (SD)	58 (16)	60 (15)	0.36
Female sex	44 (44%)	52 (52%)	0.32
Race			0.24
White	69 (69%)	67 (67%)	
Black	16 (16%)	24 (24%)	
Other	15 (15%)	9 (9%)	
Hispanic/Latinx	16 (16%)	20 (20%)	0.58
Charlson Index , mean (SD)	4.5 (3.0)	5.3 (3.0)	0.06
Origin			0.91
Home	65 (65%)	63 (63%)	
Other hospital	24 (24%)	27 (27%)	
Other	11 (11%)	10 (10%)	

Results: Colonization

Characteristic	Colonization		P
	No (N=100, 50%)	Yes (N=100, 50%)	
Antibiotic use , 90d prior to hospitalization	30 (30%)	35 (35%)	0.61
ICU			0.36
Medical	31 (31%)	29 (29%)	
Cardiac	22 (23%)	20 (20%)	
Surgical/Transplant	23 (22%)	20 (20%)	
Cardiovascular	13 (13%)	16 (16%)	
Neurological	11 (11%)	15 (15%)	
Solid organ transplant	20 (20%)	35 (35%)	0.03
Shock on admission	36 (36%)	35 (35%)	1
Mechanical ventilation (any)	71 (71%)	71 (71%)	1
ICU length of stay , days, mean (SD)	14.6 (17.6)	23.2 (21.9)	0.002

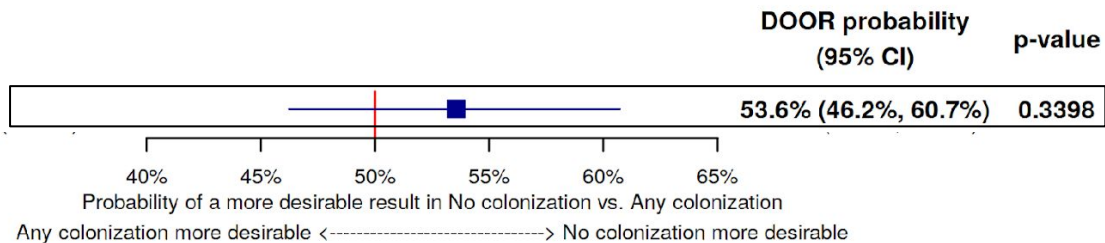
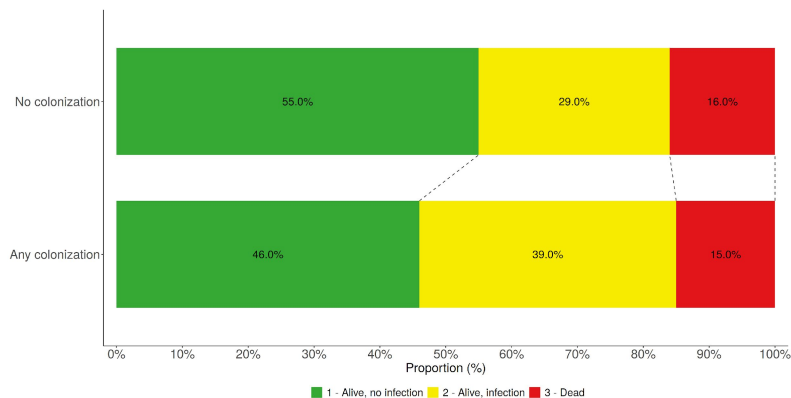
- Difference in outcomes according to colonization
- Desirability of outcome ranking (DOOR)
 - Ranking of all trial participants with respect to outcomes, including positive and negative outcomes
 - Summary statistic: Probability that a non-colonized patient has a better outcome than a colonized patient

	Not Colonized	Colonized
Level 1 – alive, no infection		
Level 2 – alive, + infection		
Level 3 - dead		

DOOR: Any colonization

- Desirability of outcome ranking (DOOR) for any colonization

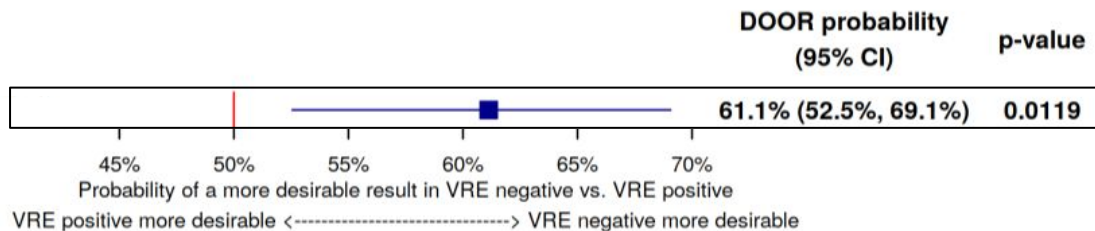
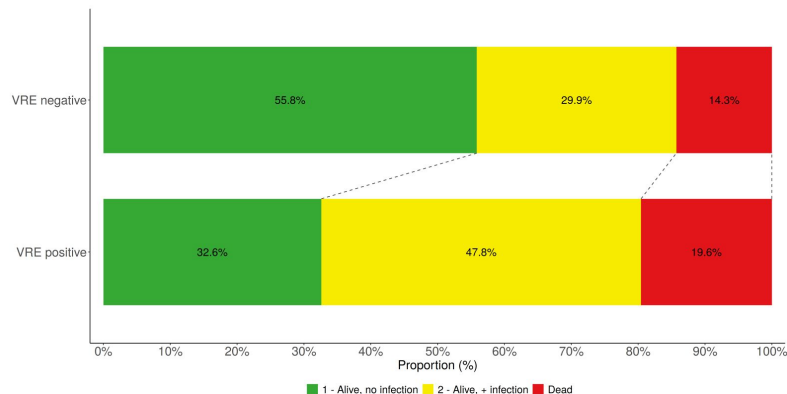
	No colonization (N=100, 50%)	Any colonization (N=100, 50%)
Level 1 – alive, no infection	55 (55%)	46 (46%)
Level 2 – alive, + infection	29 (29%)	39 (39%)
Level 3 - dead	16 (16%)	15 (15%)



DOOR: VRE colonization

- Desirability of outcome ranking (DOOR) for VRE colonization

	No VRE colonization (N=154, 77%)	VRE colonization (N=46, 23%)
Level 1 – alive, no infection	86 (56%)	15 (33%)
Level 2 – alive, + infection	46 (30%)	22 (48%)
Level 3 - dead	22 (14%)	9 (20%)



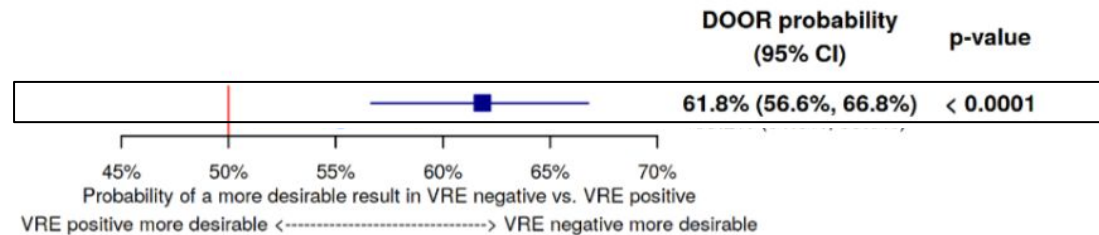
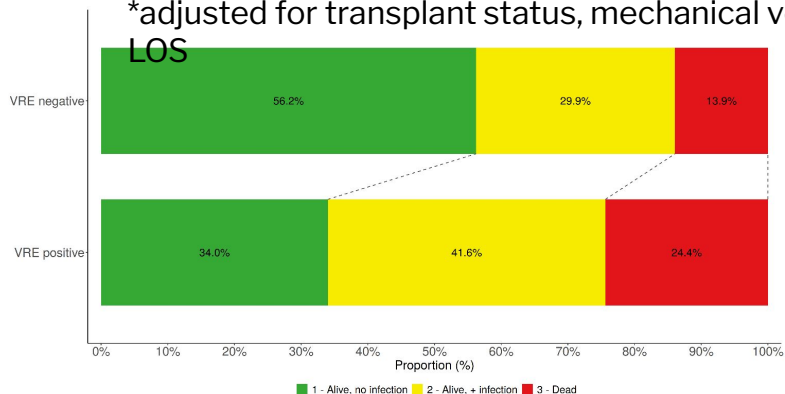
DOOR: VRE colonization – IPW*

- Desirability of outcome ranking (DOOR) for VRE colonization

	VRE not colonized (N=201)	VRE colonized (N=197)
Level 1 – alive, no infection	113 (56.0%)	67 (34.0%)
Level 2 – alive, + infection	60 (29.8%)	82 (41.6%)
Level 3 - dead	28 (14.1%)	48 (24.3%)

*adjusted for transplant status, mechanical ventilation, and ICU

LOS

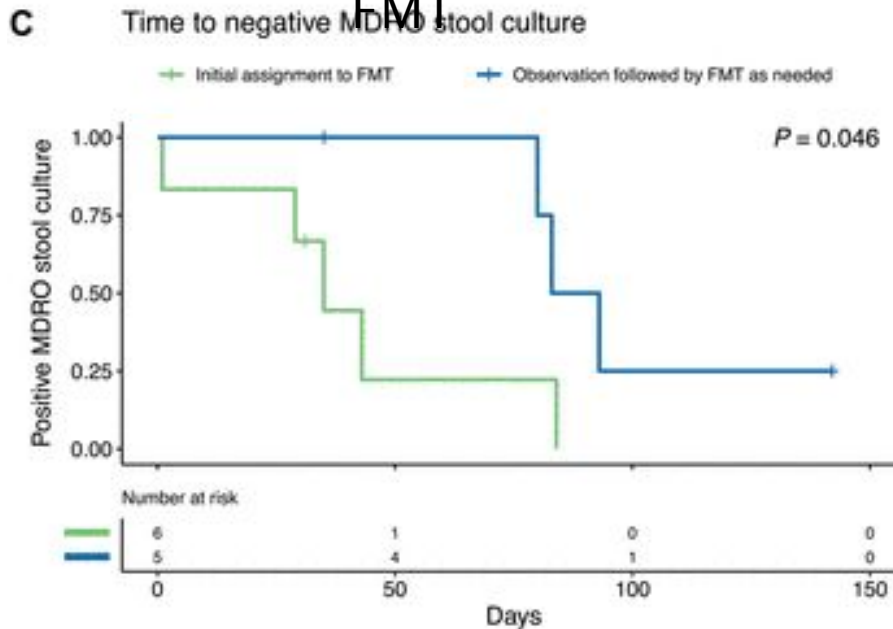


Key Question #2

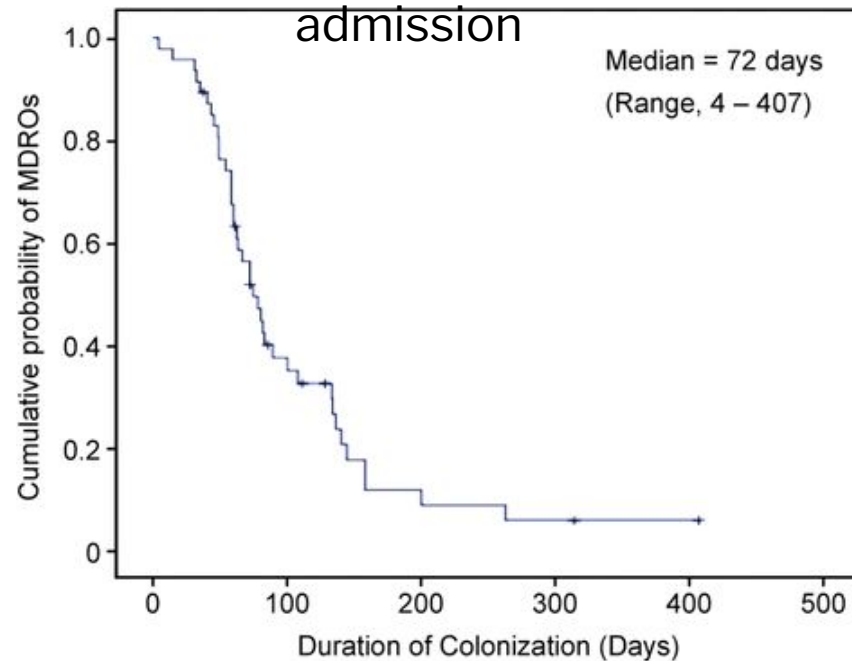
What is the duration of MDRO colonization in the ICU?

Duration of colonization

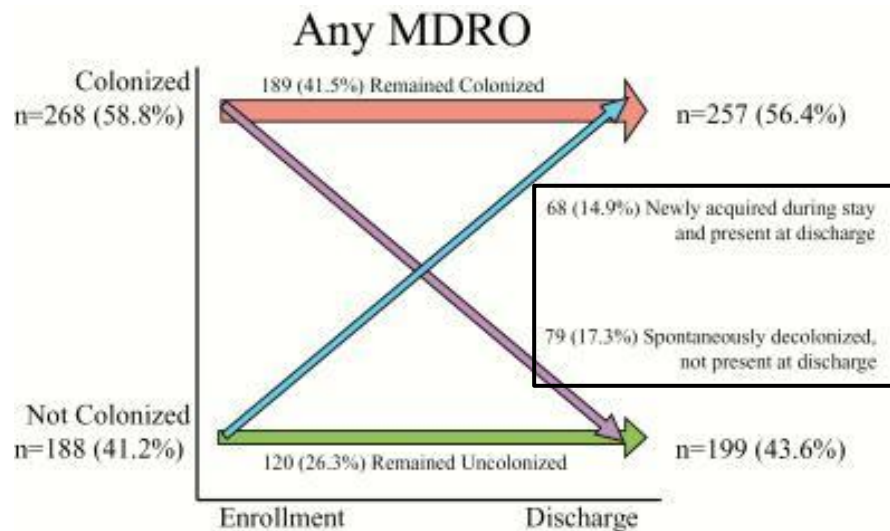
After
FMT



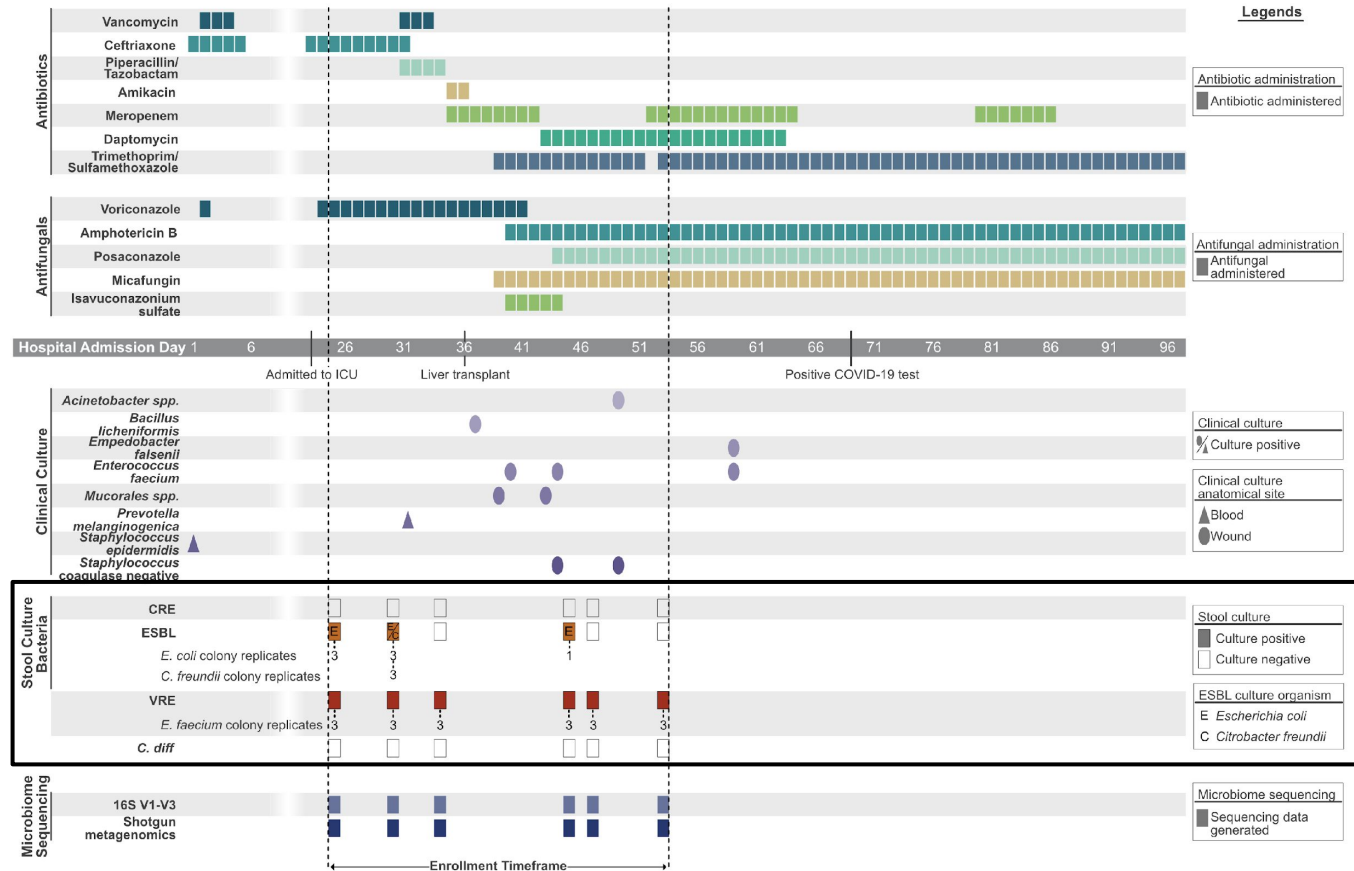
After LTAC
admission



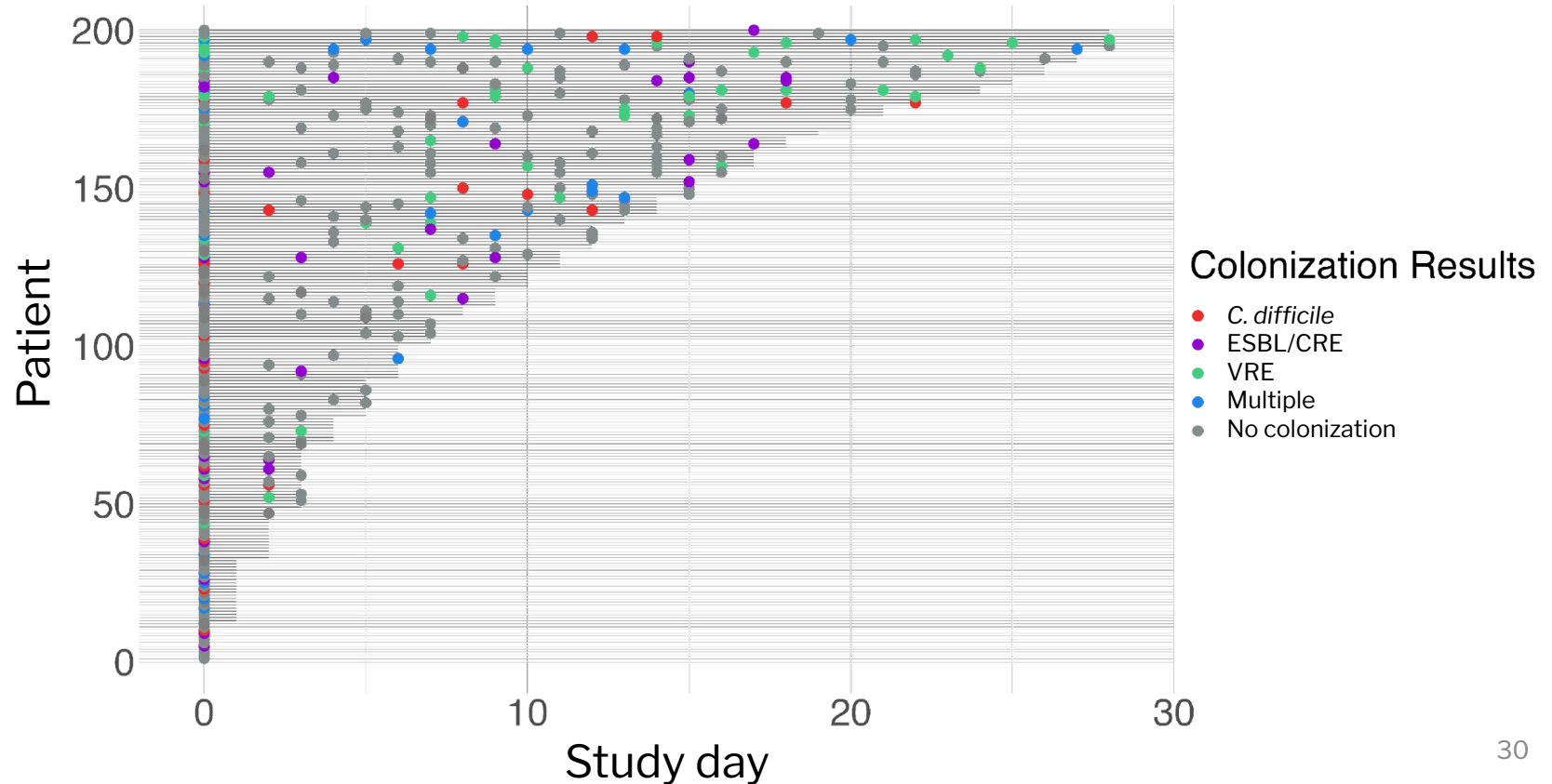
Duration of colonization



“Typical” ICU patient

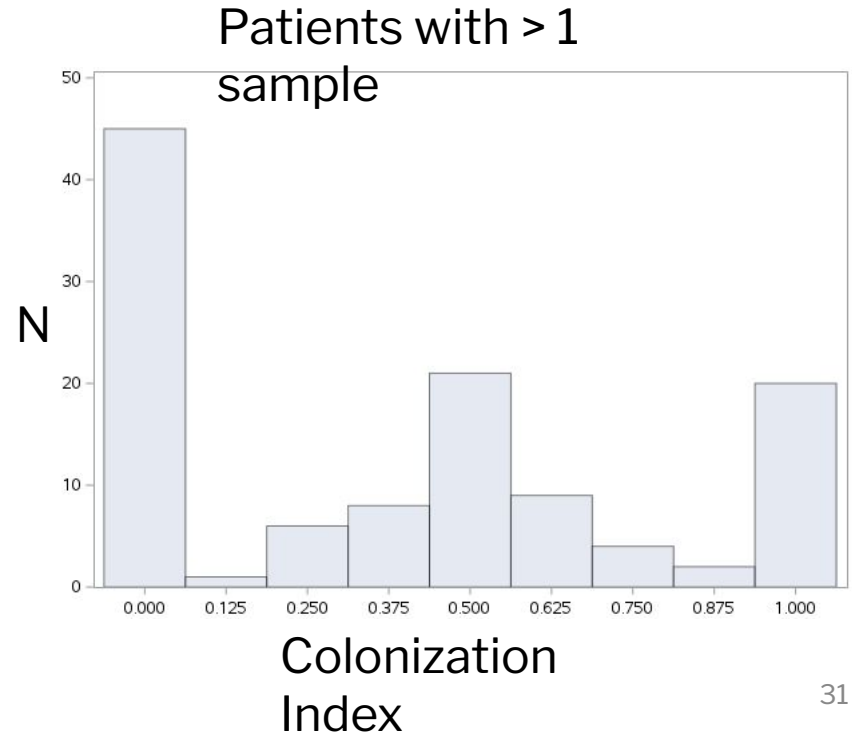
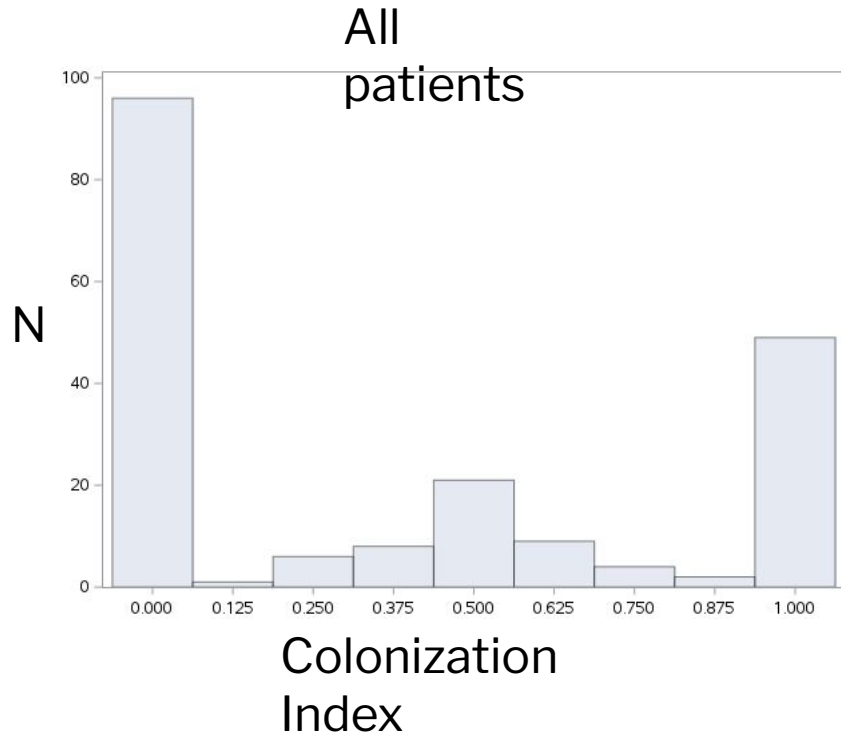


Longitudinal stool colonization



Persistent colonization

- Colonization Index = $\frac{\# \text{ samples colonized}}{\text{total } \# \text{ samples}}$

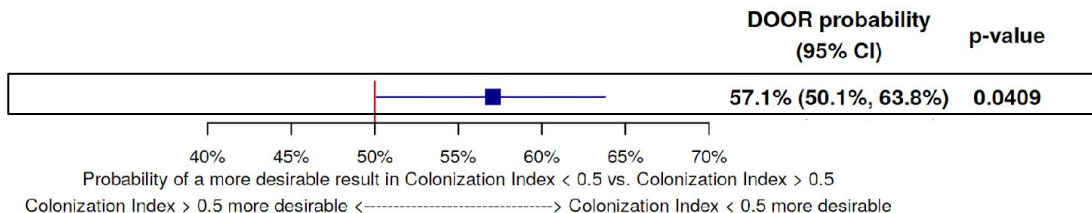
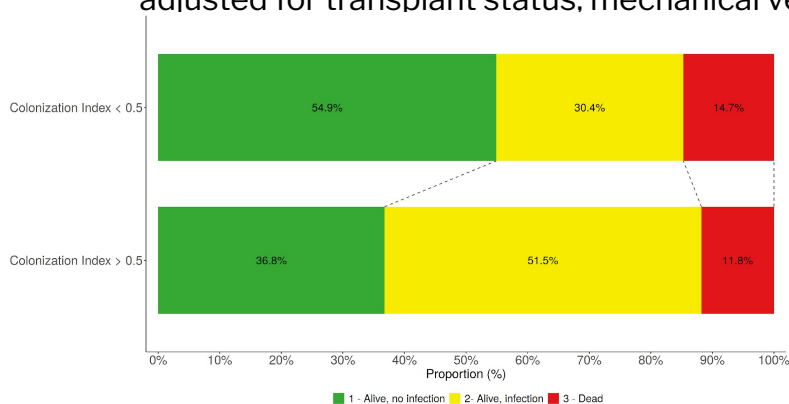


Persistent colonization

- Desirability of outcome ranking (DOOR) for “persistent colonization” (Colonization Index ≥ 0.5)*

	Colonization index < 0.5 (N=102)	Colonization index ≥ 0.5 (N=136)
Level 1 – alive, no infection	56 (55%)	50 (37%)
Level 2 – alive, + infection	31 (31%)	70 (52%)
Level 3 - dead	15 (14%)	16 (12%)

*adjusted for transplant status, mechanical ventilation, and ICU

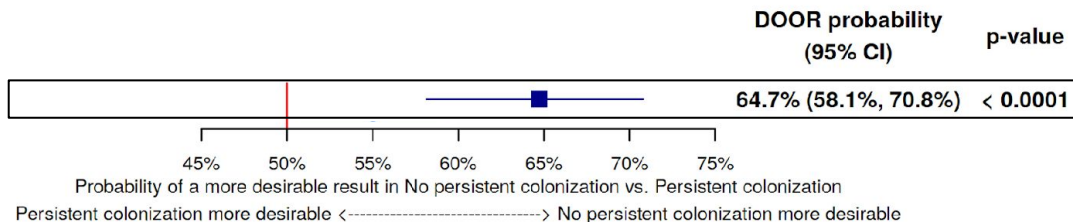
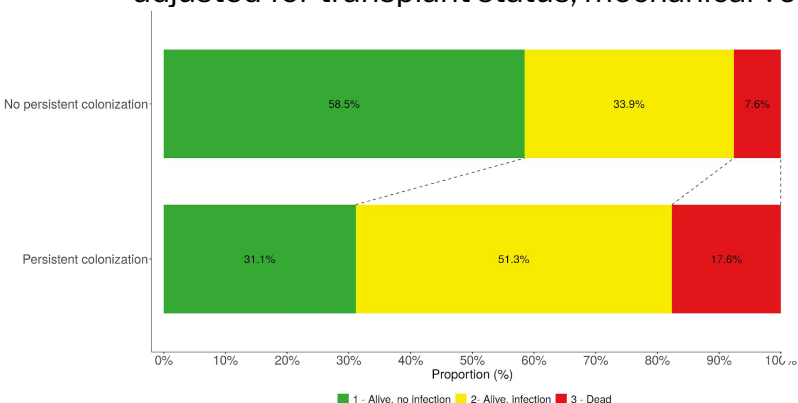


Persistent colonization

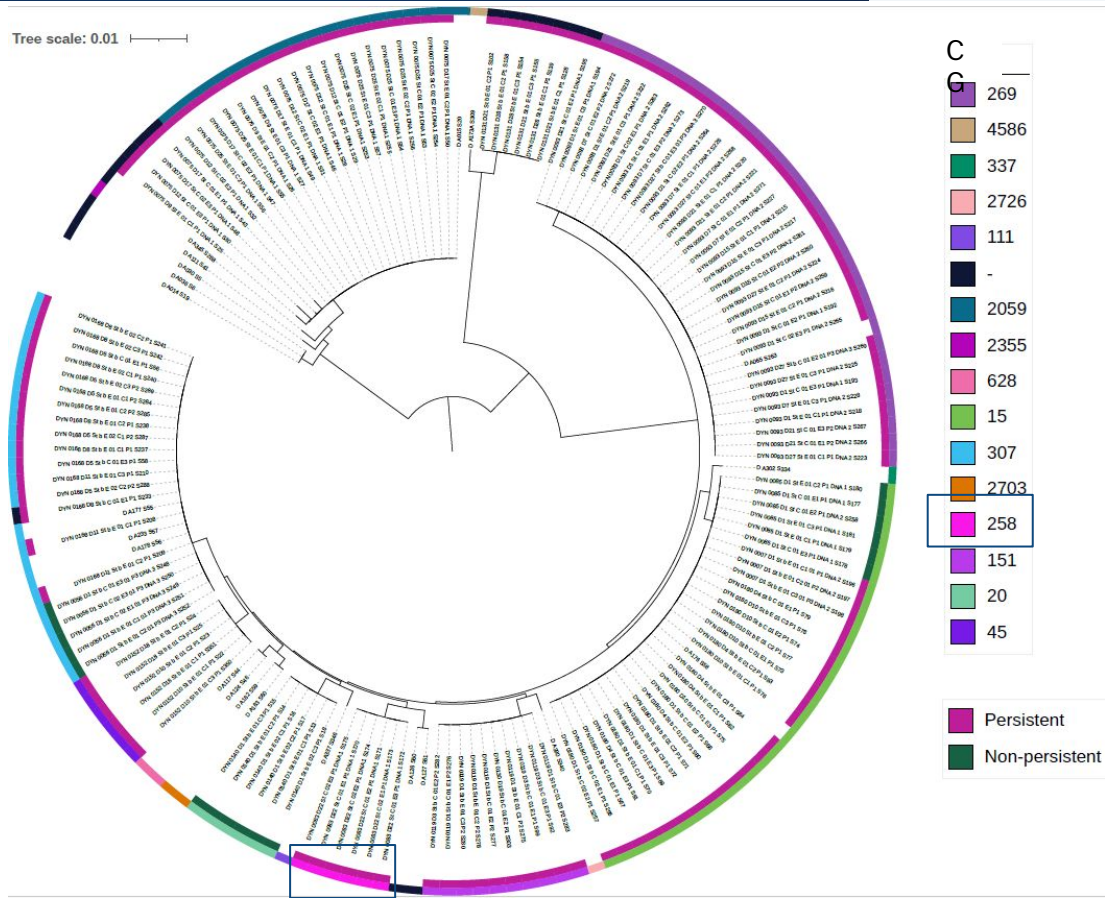
- Desirability of outcome ranking (DOOR) for “persistent colonization” (≥ 2 consecutive samples colonized)*

	No persistent colonization (N=118)	Persistent colonization (N=119)
Level 1 – alive, no infection	69 (58%)	37 (31%)
Level 2 – alive, + infection	40 (34%)	61 (52%)
Level 3 - dead	9 (8%)	21 (18%)

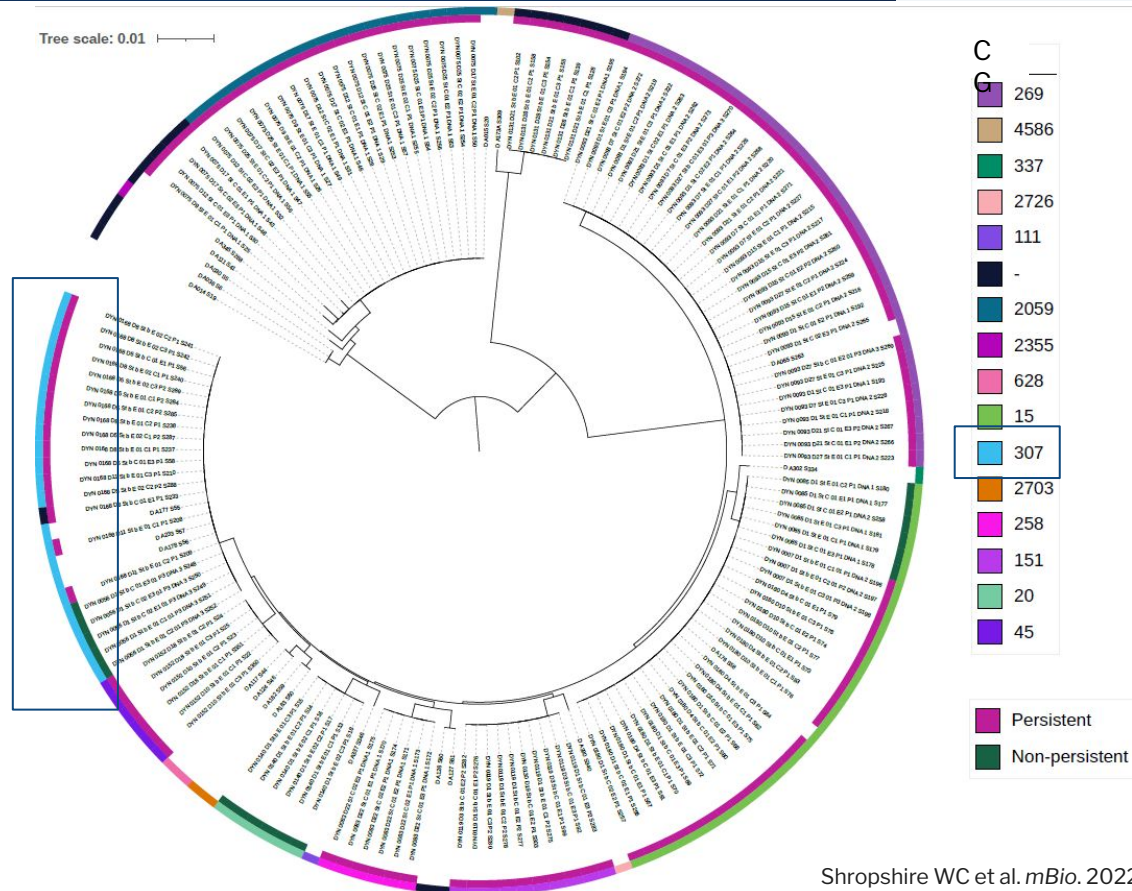
*adjusted for transplant status, mechanical ventilation, and ICU



K. pneumoniae phylogeny



K. pneumoniae phylogeny



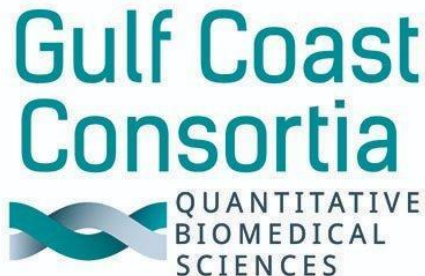
- What is the mechanism of colonization gain/loss?
 - Antibiotics?
 - Microbiome features?
 - Organism genomic features?
- What factors facilitate transition from colonization to infection? Why are patients with colonization at increased risk of infection?
- Can we modify any of the above factors to improve patient outcomes?

- A high proportion of ICU patients (50% in DYNAMITE) have stool colonization with MDRO organisms
- Colonization is highly dynamic, and patients rarely have persistent colonization
- VRE colonization and persistent colonization are associated with adverse outcomes, especially increased risk of infection

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