The Role of the Built Environment as a Reservoir for Human Infection

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Washington University in St. Louis
SCHOOL OF MEDICINE

Kwon Lab

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  - CDC SHEPheRD 2024 Domain 2-B001
  - ICTS CTRFP1717

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  - None

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  - None

- **Board/Committee/Advisory Board Membership**
  - Centers for Disease Control and Prevention
  - US Department of Health & Human Services
  - National Academy of Medicine

- **Intellectual Property/Royalty Income**
  - None

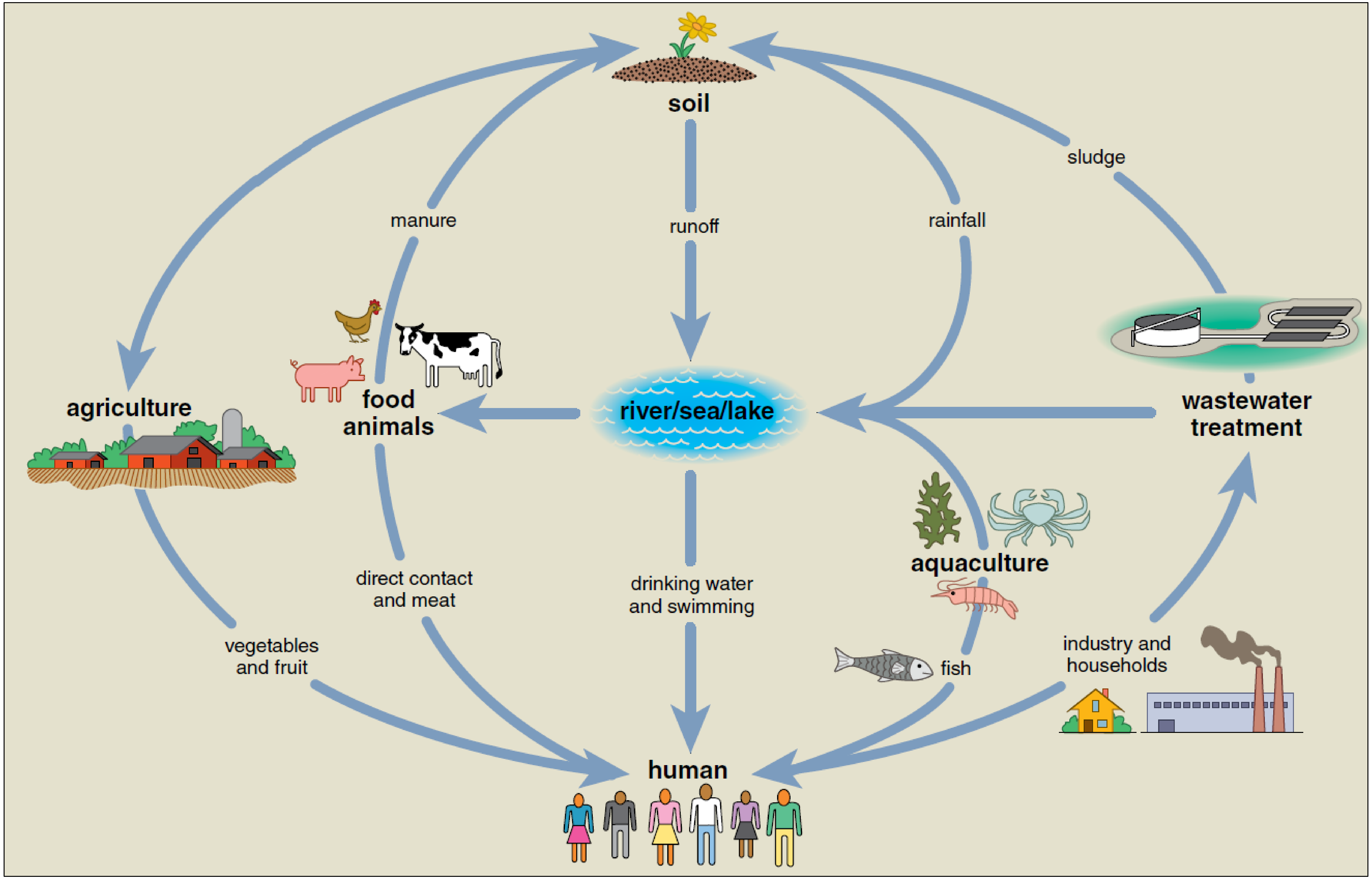
Objectives

- Discuss role of the human gut microbiome as a reservoir for potentially pathogenic microbes

- Discuss the link between the environment and human infections

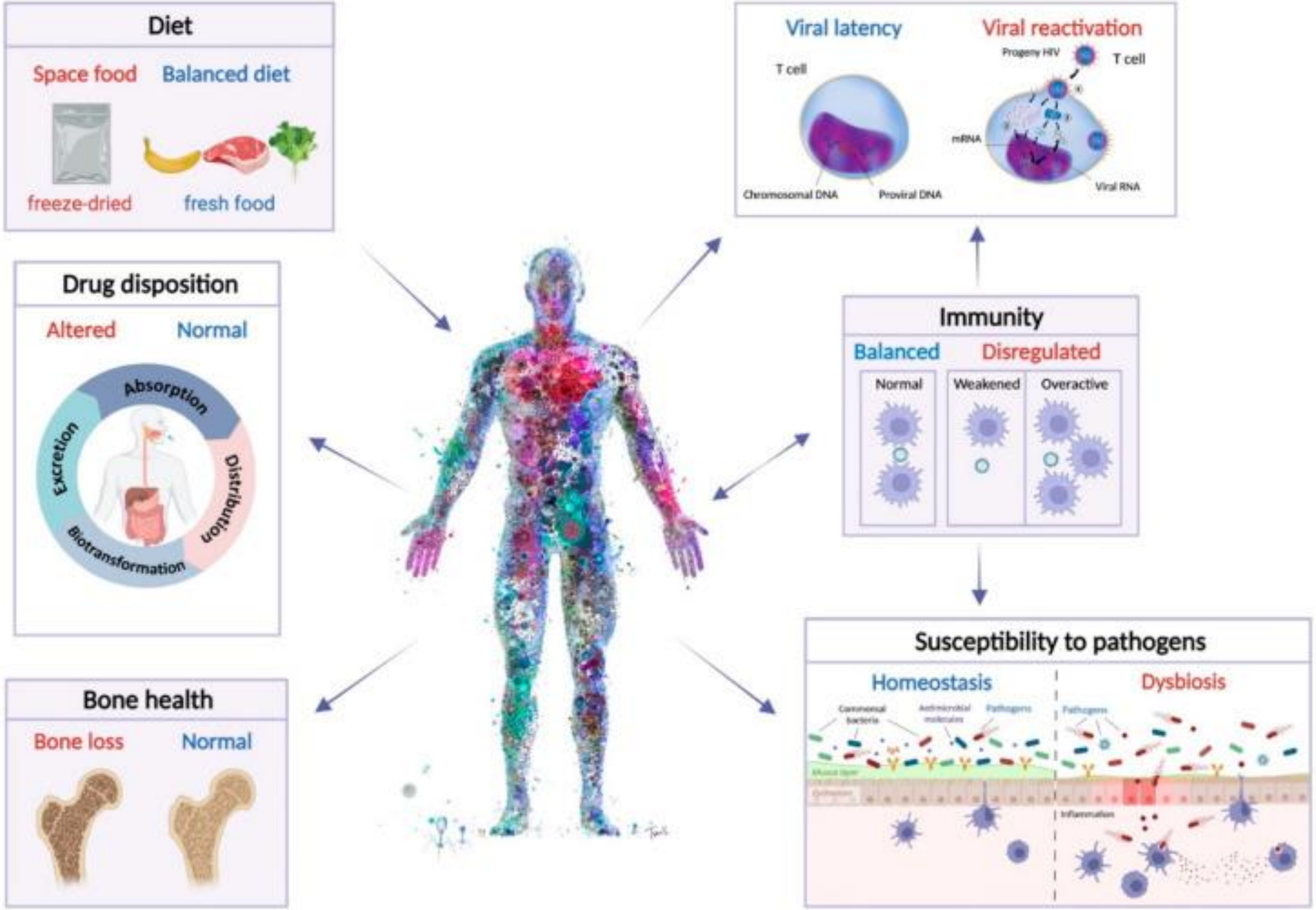
- Discuss future directions to detect and prevent infections

People, animals, and the environment are interconnected



Dantas, Sommer. American Scientist. 2014.

Spaceflight can impact host susceptibility to pathogens



Tesei D, et al, MDPI March 2022

Cell Reports

CellPress
OPEN ACCESS

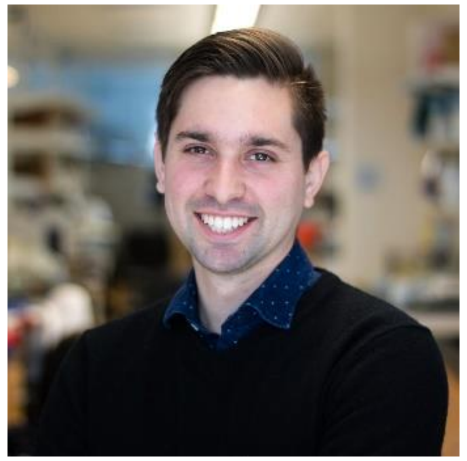
Article

Acute and persistent effects of commonly used antibiotics on the gut microbiome and resistome in healthy adults

Winston E. Anthony,[1] Bin Wang,[1,2] Kimberley V. Sukhum,[1,2] Alaric W. D'Souza,[1] Tiffany Hink,[4] Candice Cass,[4]
Sondra Seiler,[4] Kimberly A. Reske,[4] Christopher Coon,[4] Erik R. Dubberke,[4] Carey-Ann D. Burnham,[2,3,4,*]
Gautam Dantas,[1,2,3,5,*] and Jennie H. Kwon[4,6,*]

Carey-Ann Burnham

Erik Dubberke



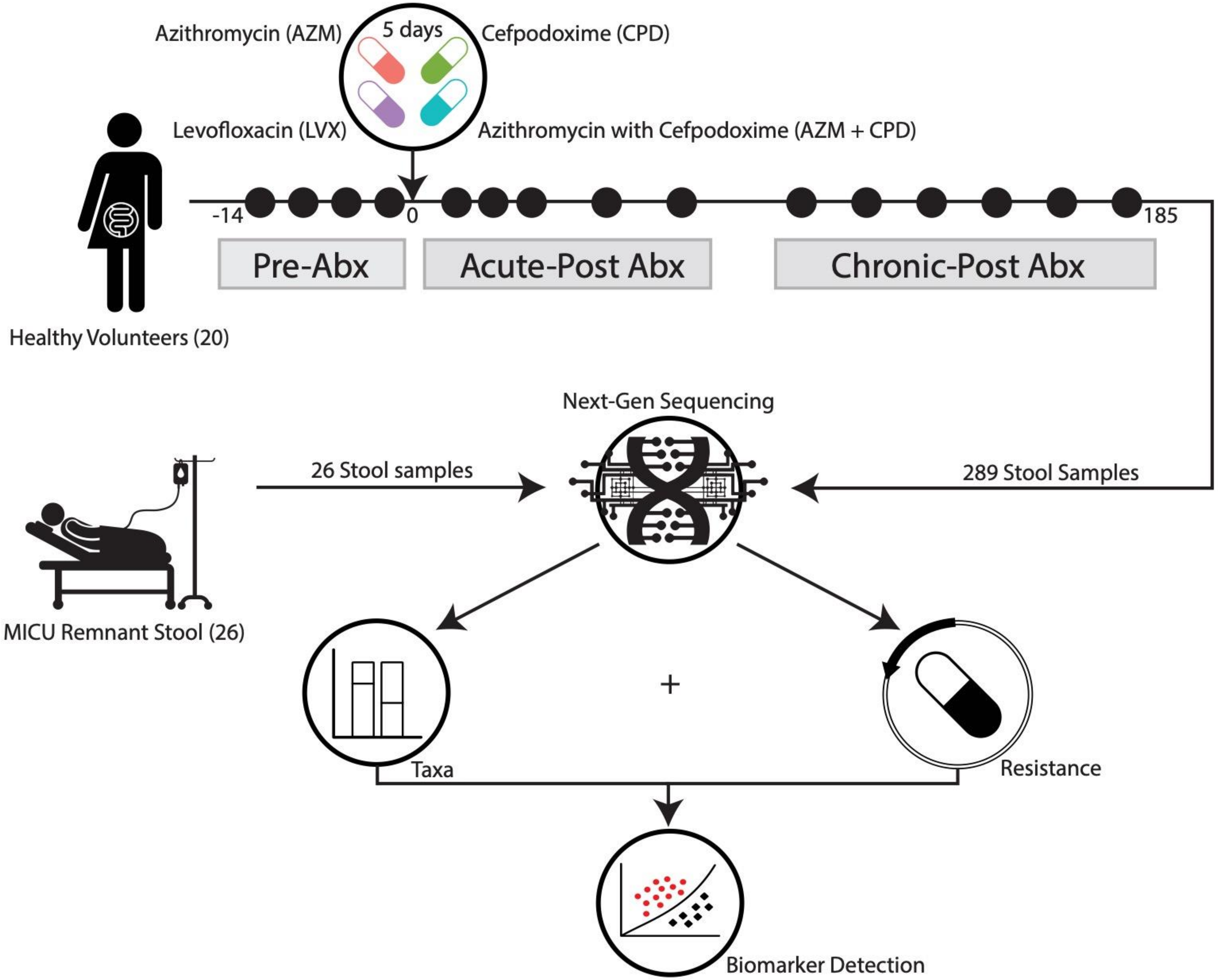
Winston Anthony

Gautam Dantas

Study Objective

- What is the impact of a short course of oral antimicrobials on the human gut microbiome and resistome?
- Resistome
  - Compendium of antibiotic resistance genes (ARG) within the microbiota
- Disruption
  - A statistically significant change from the pre-antibiotic state

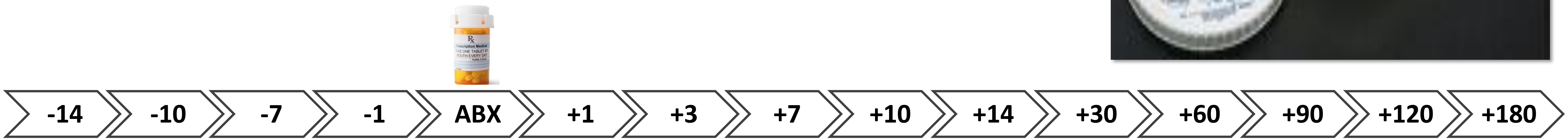
Study Overview



Anthony, et al, Cell Reports, 2022

Study Protocol

- Written, informed consent
- In-person enrollment interview, clinical evaluation, physical exam
- Antibiotics (5 per group)
    - Azithromycin 500 mg on day 1, then 250 daily for 4 days
    - Cefpodoxime 200 mg PO BID x 5 days
    - Levofloxacin 750 mg PO QD x 5 days
    - Azithromycin + Cefpodoxime
- Subject remuneration
- Investigators blinded to study group assignments



Anthony, et al, Cell Reports, 2022

Stool and Data Analysis

Microbiologic Culture

- Selective culture for antibiotic resistant organisms

Whole metagenome shotgun sequencing

- DNA extracted using PowerLyzer PowerSoil DNA Isolation Kit
- DNA sequencing library preparation using Nextera-XT tagmentation protocol (Illumina)

Metagenomic data analysis

- MetaPhlAn: estimate relative abundance of bacterial taxa

Resistome characterization

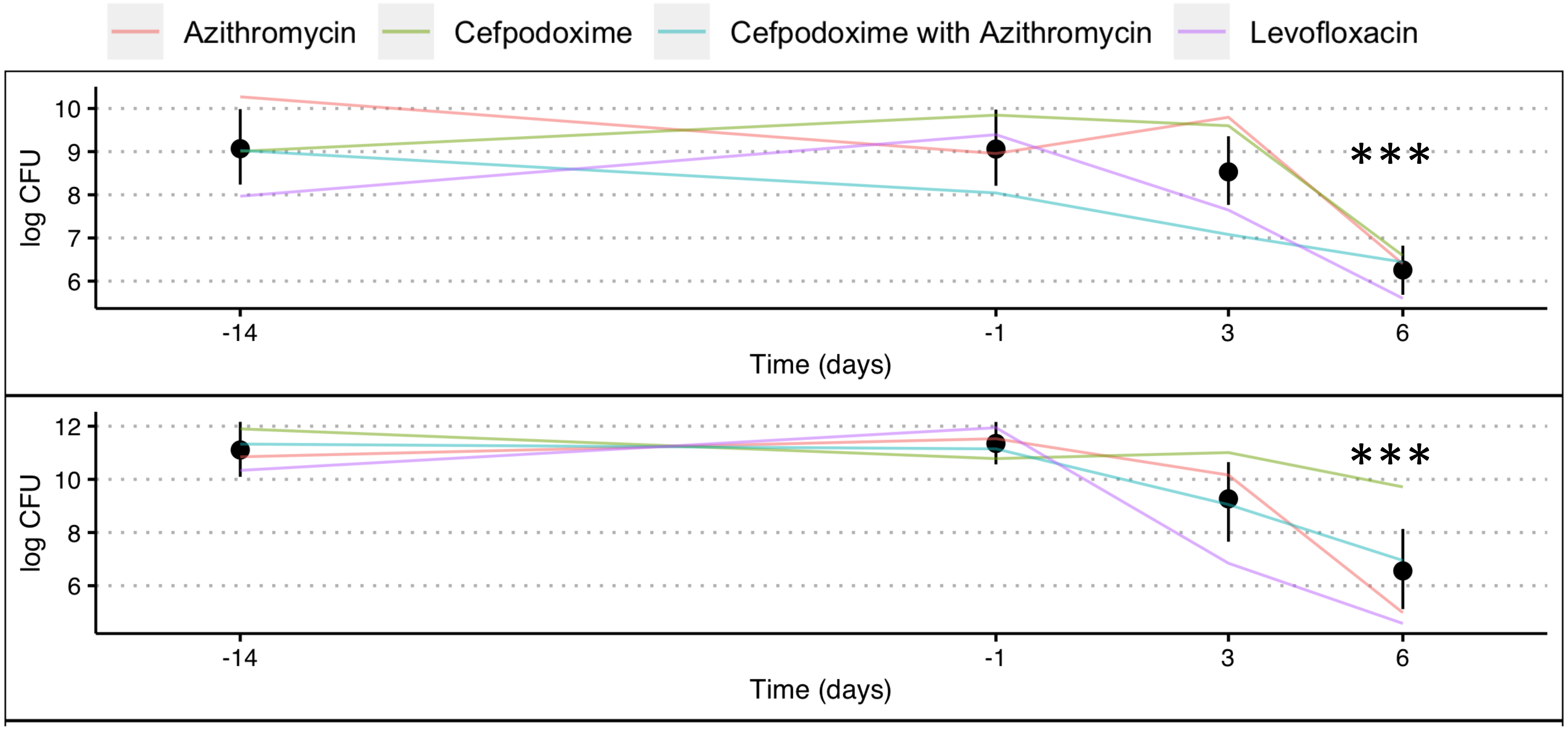
- Comprehensive Antibiotic Resistance Database (CARD): reference database of resistance genes
- ShortBRED: estimate ARG composition

Anthony, et al, Cell Reports, 2022

Short courses of antibiotics can perturb the gut microbiome acutely

Aerobic culture

Anaerobic culture



*** $p < 0.001$

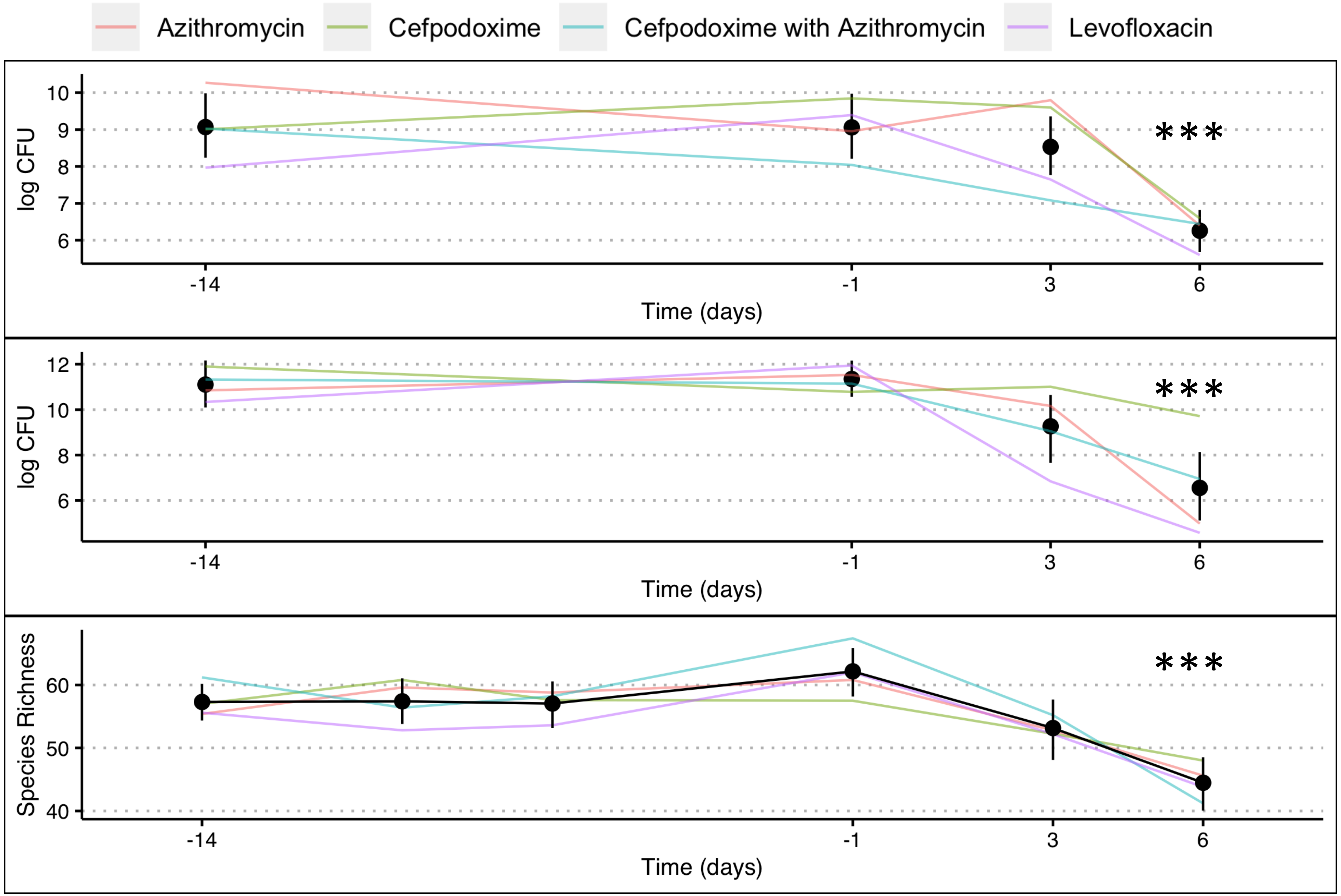
Anthony, et al, Cell Reports, 2022

Short courses of antibiotics can perturb the gut microbiome acutely

Aerobic culture

Anaerobic culture

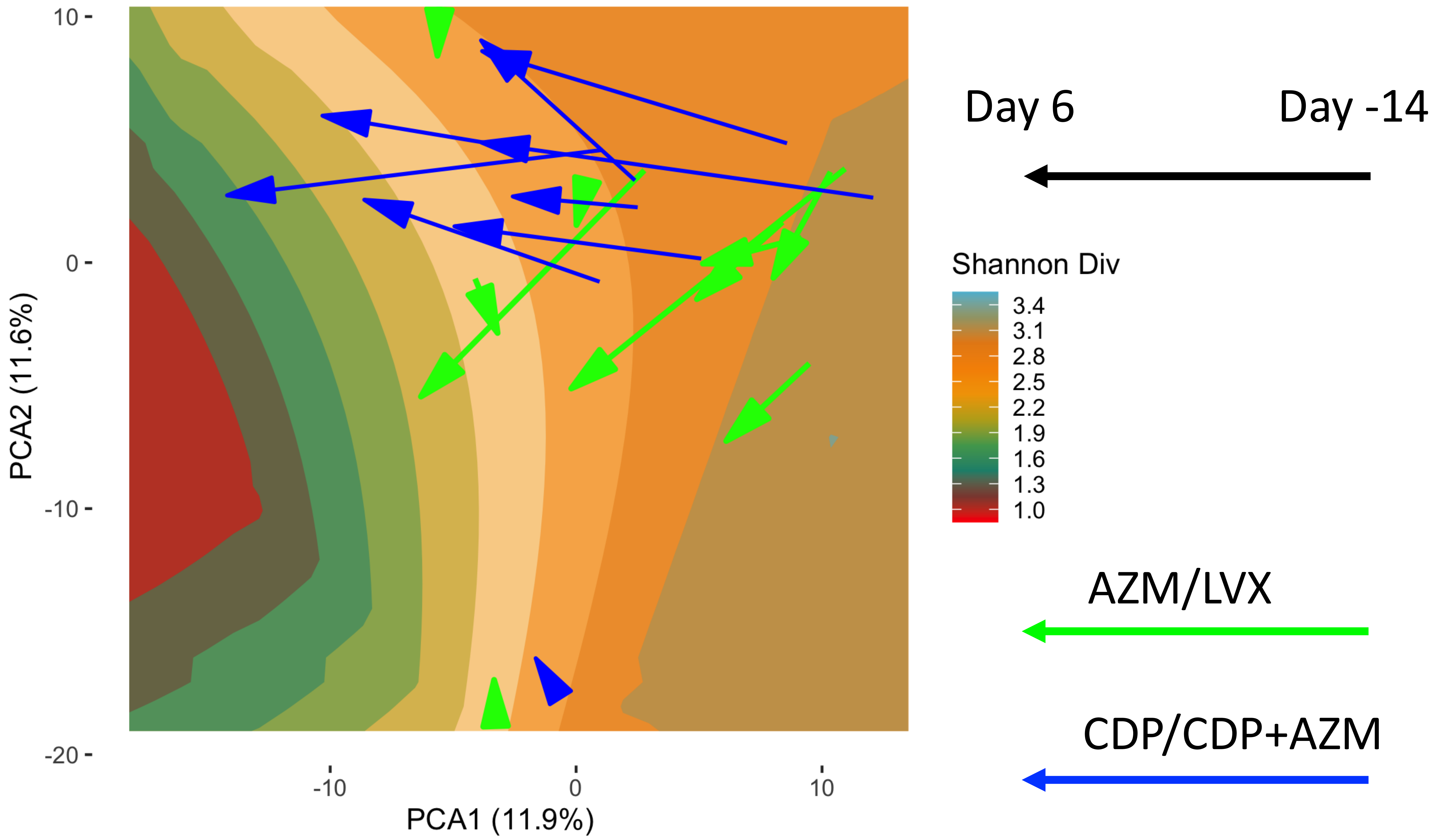
Stool metagenome



*** $p < 0.001$

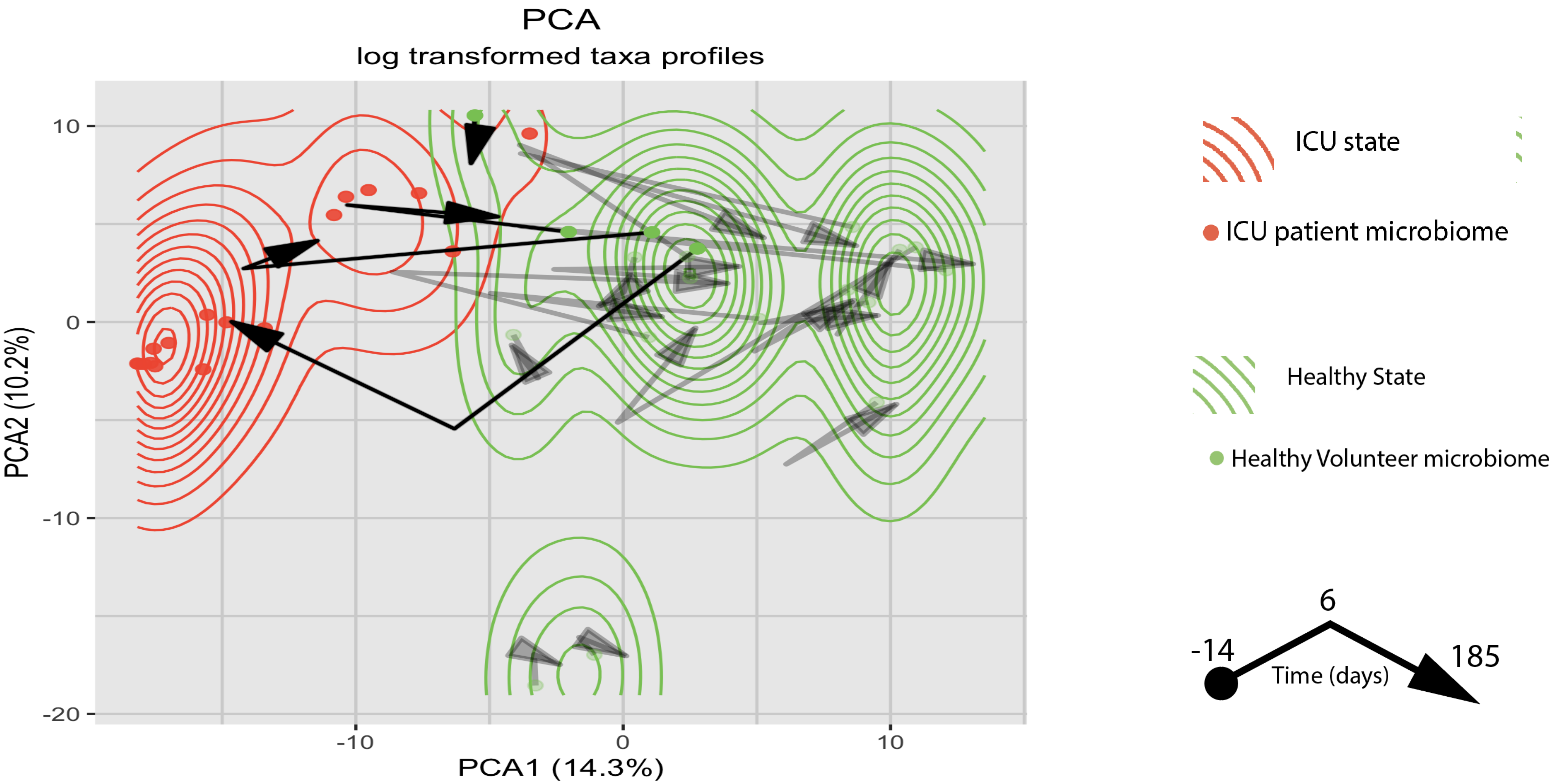
Anthony, et al, Cell Reports, 2022

The gut microbiome shifts acutely after antibiotics



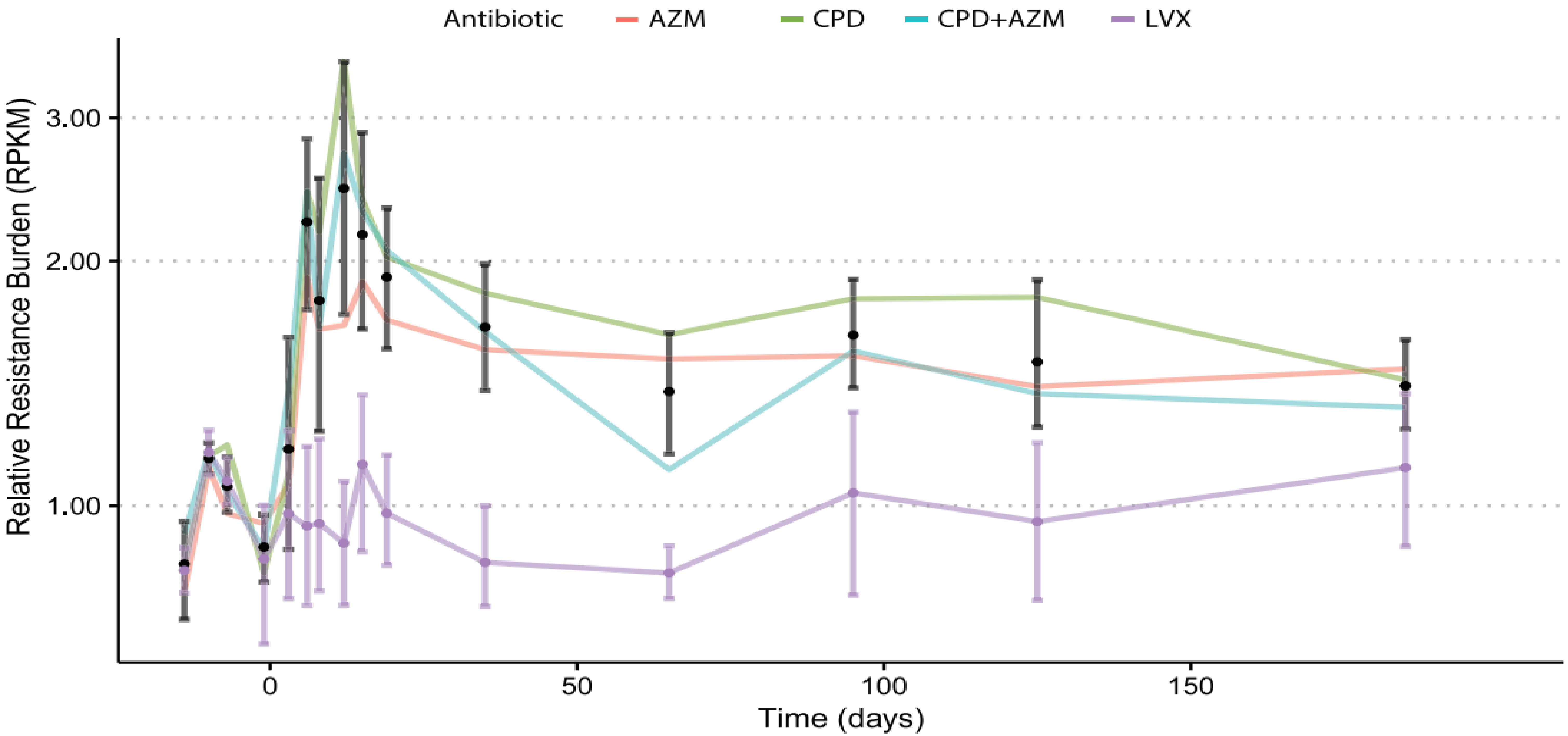
Anthony, et al, Cell Reports, 2022

HVs experience varying degrees of microbiome disruption



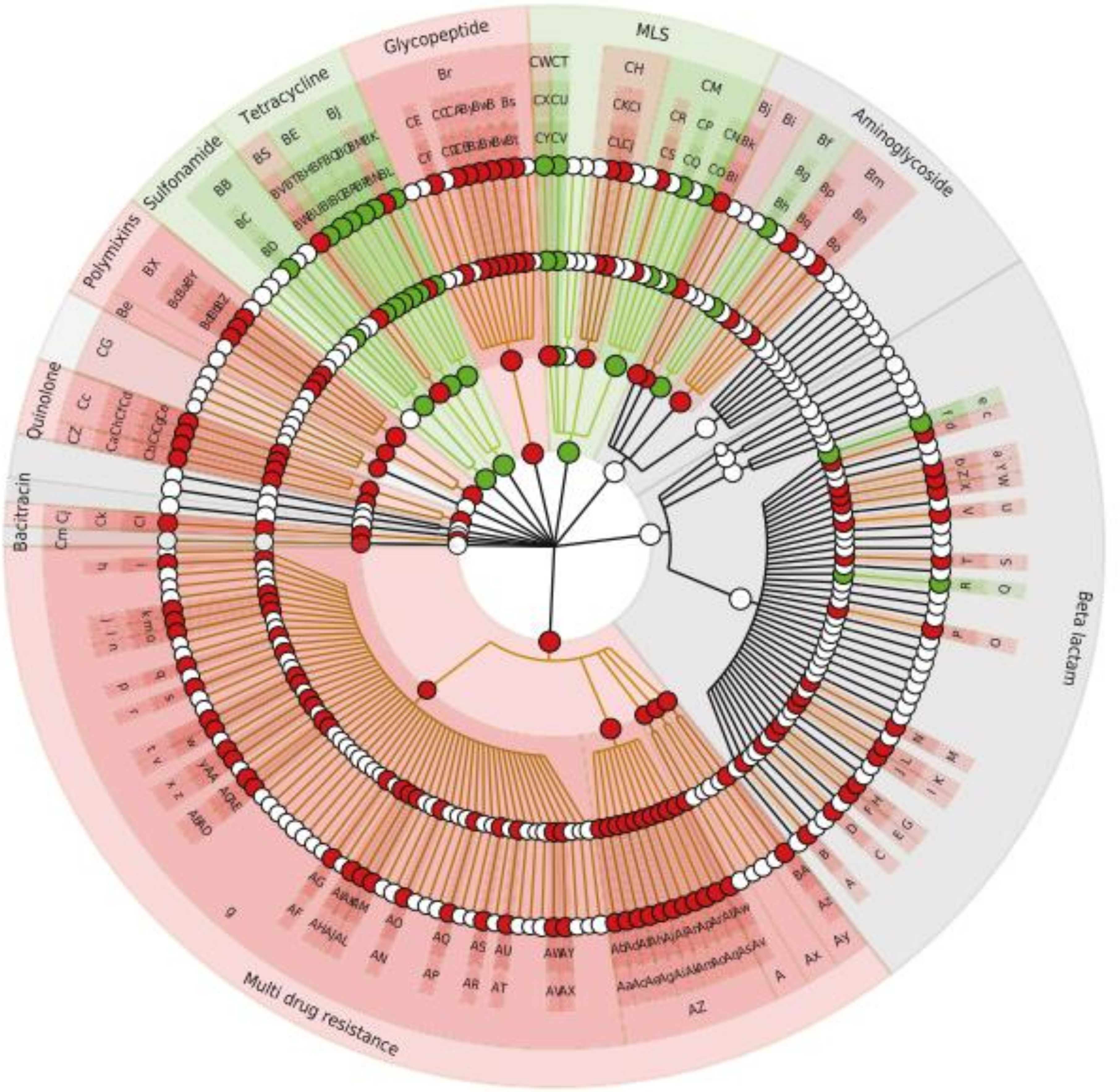
Anthony, et al, Cell Reports, 2022

ARGs can be increased up to 60 days after antibiotics



Anthony, et al, Cell Reports, 2022

The HV resistome is distinct from the ICU patient resistome



● Healthy Volunteer
● ICU

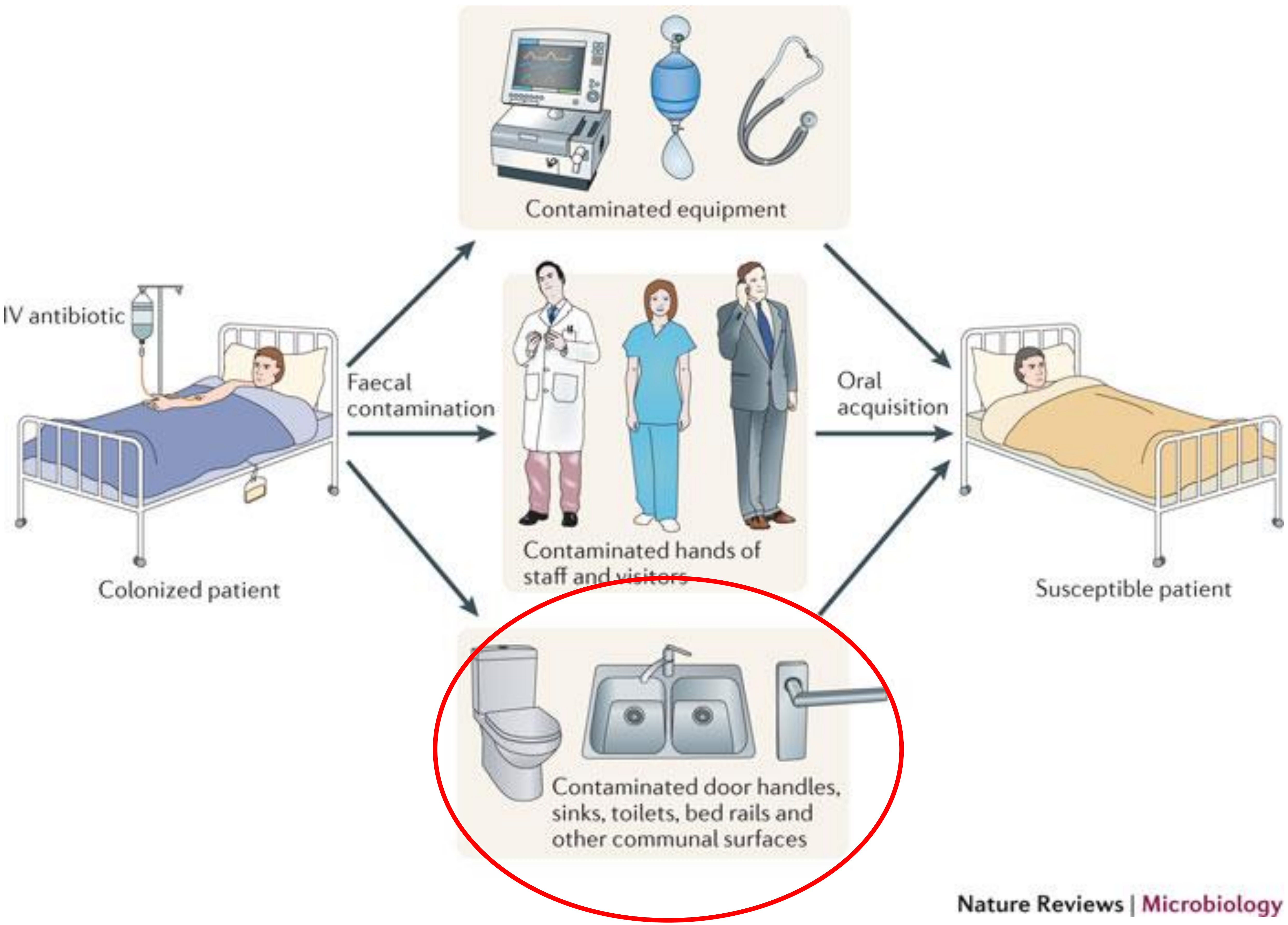
A: Other EffluComplex Subunit
B: MFS Antibiotic Efflux Pump
C: ABC Antibiotic Efflux Pump
D: SMR Antibiotic Efflux
E: 23S ribosomal RNA methyltransferase
F: ABC Antibiotic Efflux Pump
G: MFS Antibiotic Efflux Pump
H: Chloramphenicol
I: Chloramphenicol AcetyltransferasCAT
J: Trimethoprim Resistant Dihydrofolate Reductase dfr
K: Tetracycline Inactivation Enzyme
L: MFS Antibiotic Efflux Pump
M: ABC Antibiotic Efflux Pump
N: Tetracycline Resistant Ribosomal Protection Protein
O: Othepolymixins
P: Gene Altering Cell Wall Charge
Q: Other EffluComplex Subunit
R: Aminoglycoside NucleotidyltransferasANT
S: Other EffluComplex Subunit
T: RND Antibiotic Efflux
U: Aminoglycoside AcetyltransferasAAC
V: Other EffluComplex Subunit
W: Quinolone
X: Quinolone Resistance Proteiqnr
Y: Other EffluComplex Subunit
Z: Othebacitracin
a: Gene Conferring Resistance via Molecular Bypass
b: ABC Antibiotic Efflux Pump

Anthony, et al, Cell Reports, 2022

Key findings

- Short courses of antibiotics can cause acute and chronic microbiome disruptions in healthy volunteers
  - Decreased microbiome diversity
  - Acute decreases in the taxonomic composition
  - ARGs enriched post-antimicrobials
  - This impact can vary by antimicrobial type and by individual
- Thoughtful utilization of antibiotics, even PO and short courses
- Gut microbiome is a reservoir for antimicrobial resistance

Is the ICU environment a reservoir for antimicrobial resistance?



Nature Reviews | Microbiology

Arias C et al. Nature Reviews Microbiology (2012)

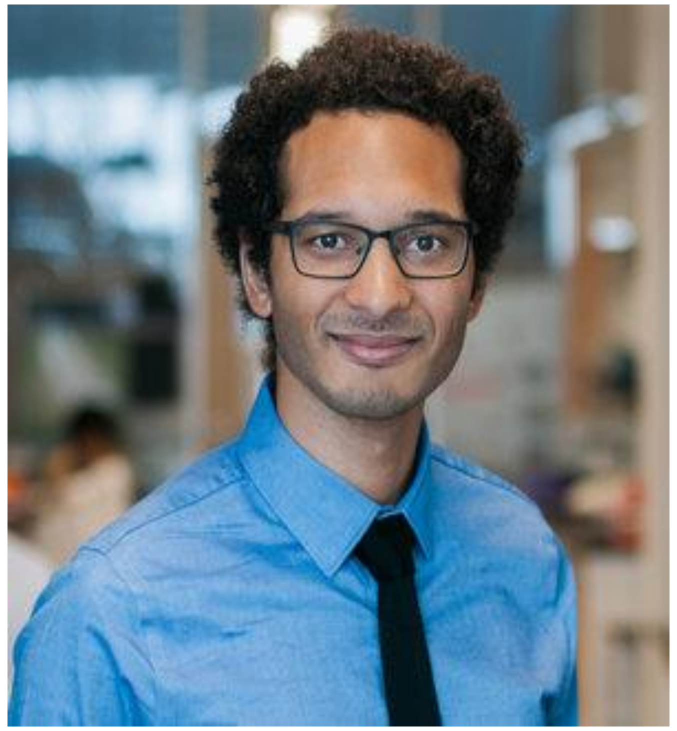
ARTICLE

https://doi.org/10.1038/s41467-019-12563-1 OPEN

Spatiotemporal dynamics of multidrug resistant bacteria on intensive care unit surfaces

Alaric W. D'Souza[1,8], Robert F. Potter[1,8], Meghan Wallace[2], Angela Shupe[2], Sanket Patel[1,2], Xiaoqing Sun[1,2], Danish Gul[3], Jennie H. Kwon[4], Saadia Andleeb[3*], Carey-Ann D. Burnham[2,4,5,6*] & Gautam Dantas[1,2,5,7*]

Gautam Dantas



Alaric D'Souza

Carey-Ann Burnham

Robert Potter

Saadia Andleeb

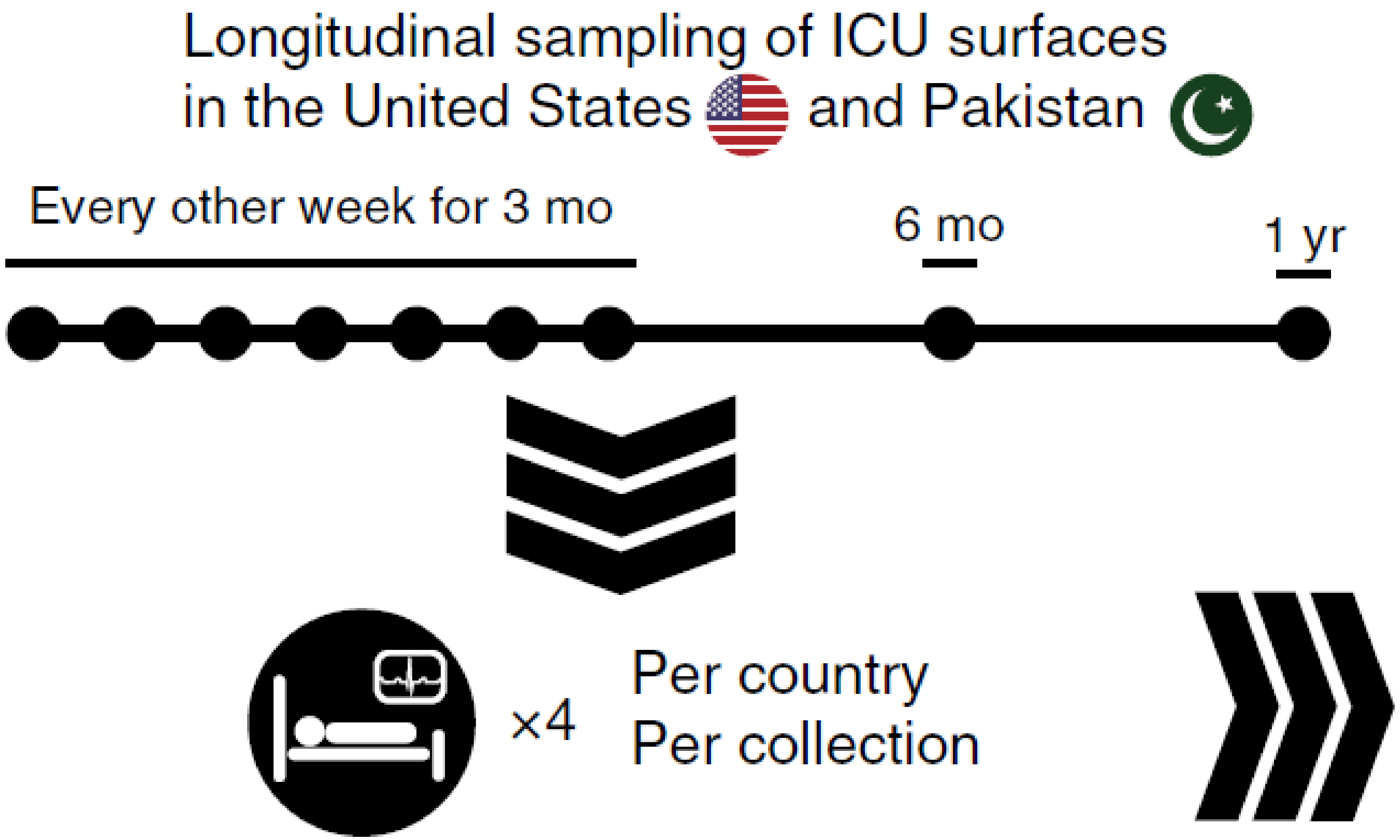
D'Souza, Potter, et al. Nature Comm. 2019.

Study Objectives

- Evaluate the natural history of ARO contamination of surfaces in intensive care units (ICU)
  - US hospital and a Pakistani hospital over the course of one year
  - Characterization of the microbes and resistance determinants

D'Souza, Potter, et al. Nature Comm. 2019.

Longitudinal study design



Longitudinal sampling of ICU surfaces
in the United States and Pakistan

Every other week for 3 mo

6 mo

1 yr

×4

Per country
Per collection

Tertiary care hospital
Pakistan

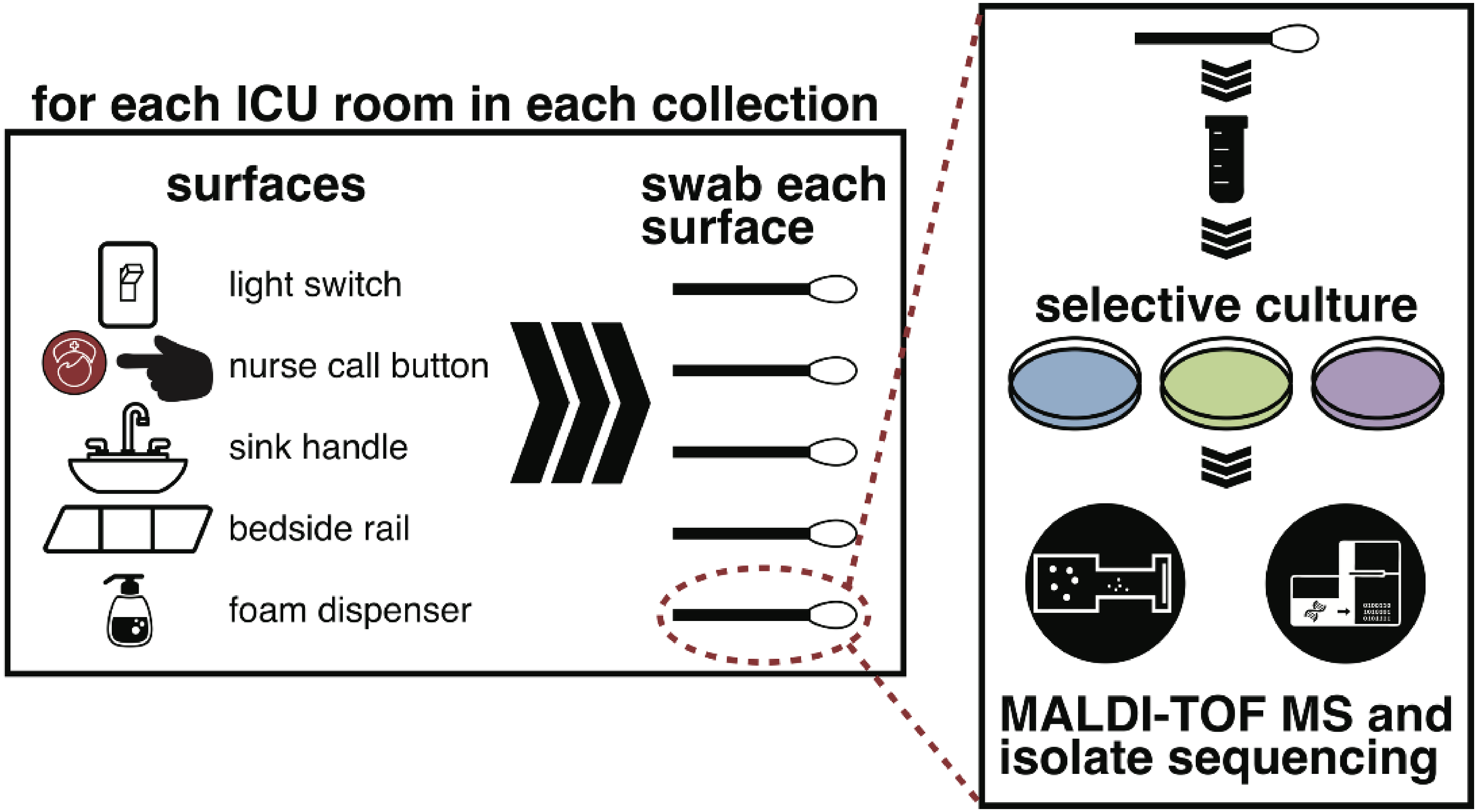
1,200 beds

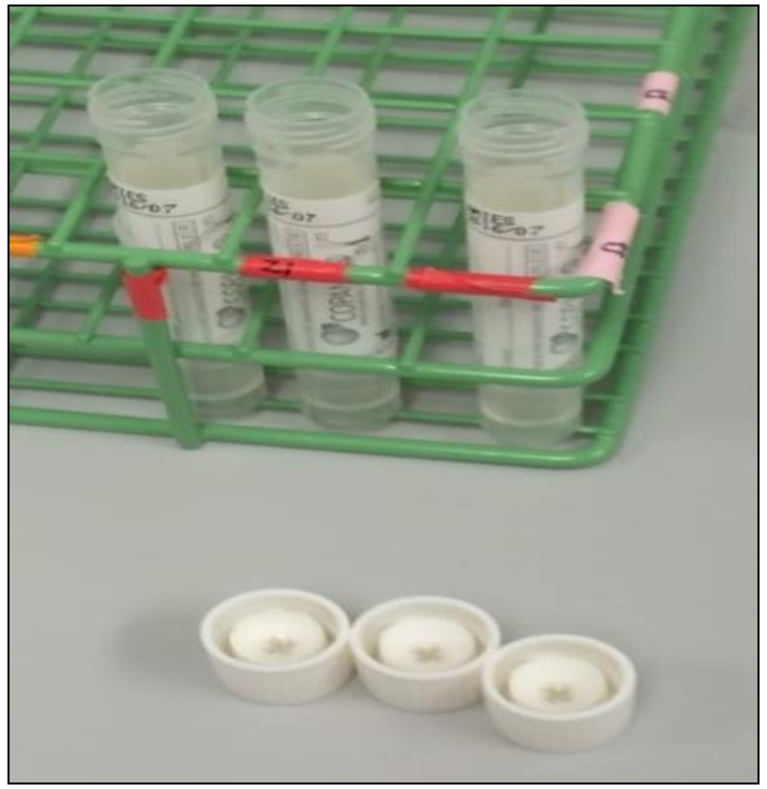
Barnes Jewish Hospital
St. Louis, United States

1,252 beds

D’Souza, Potter, et al. Nature Comm. 2019.

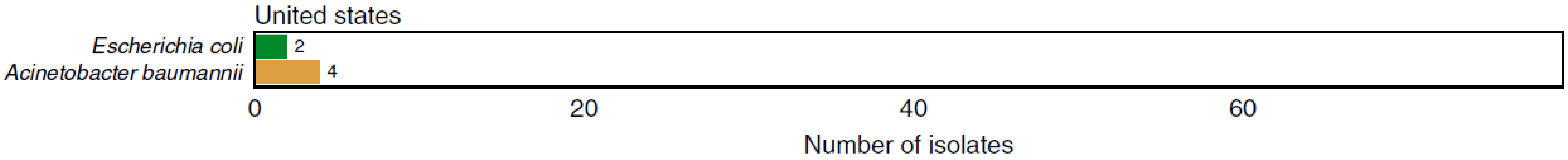
Samples underwent selective microbiologic culture and isolate sequencing





D’Souza, Potter, et al. Nature Comm. 2019.

Microbes were recovered from hospital surfaces



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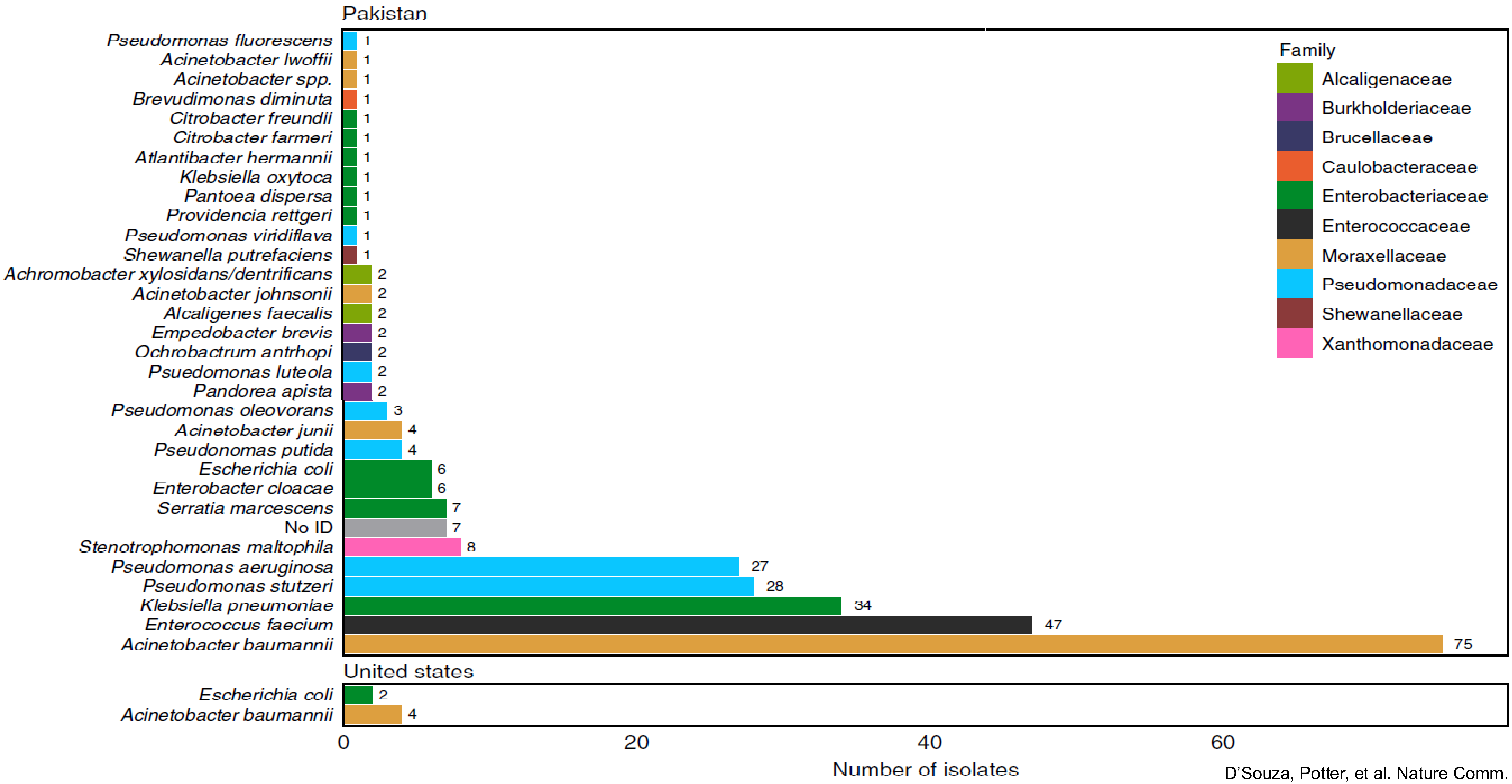
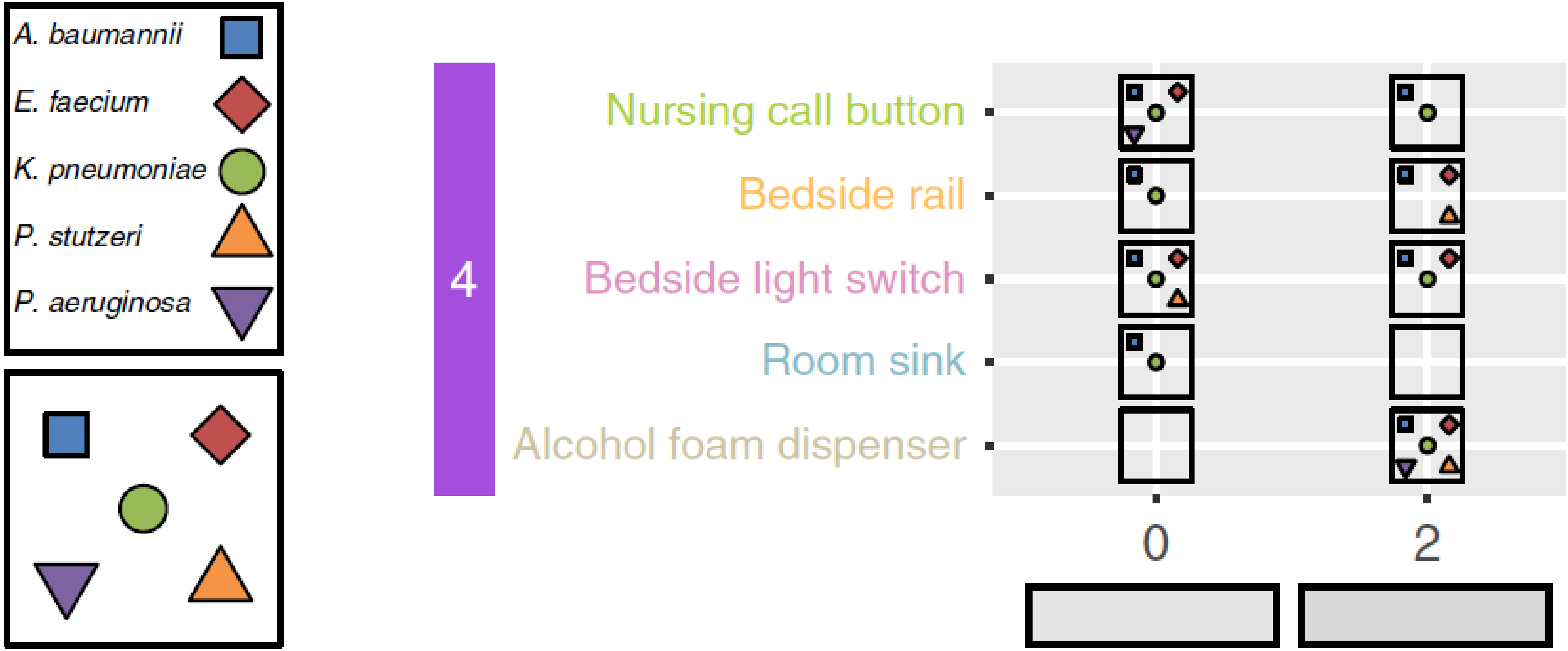


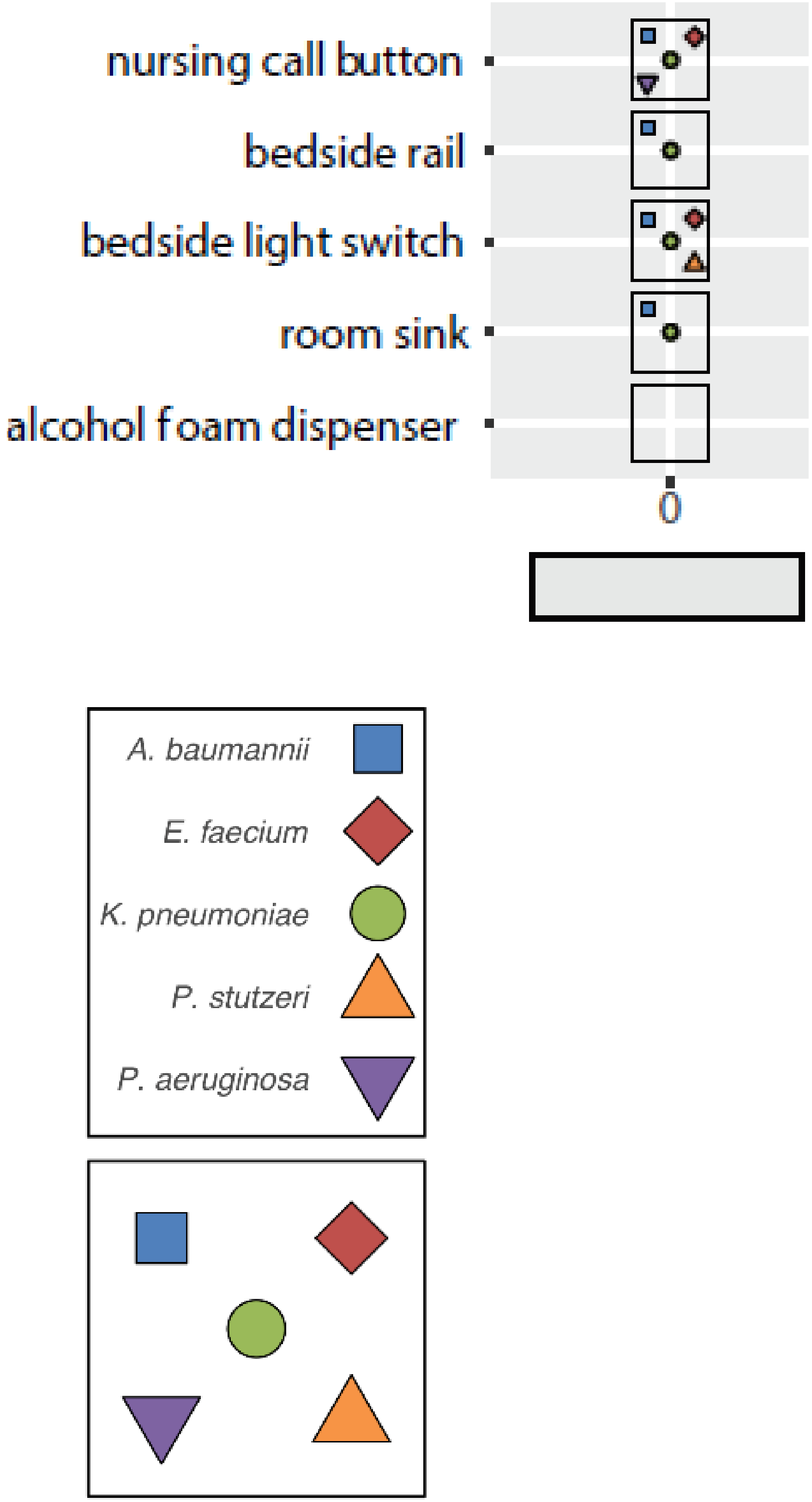
D’Souza, Potter, et al. Nature Comm. 2019.

Pakistan: Antibiotic resistant organisms were recovered from multiple surfaces



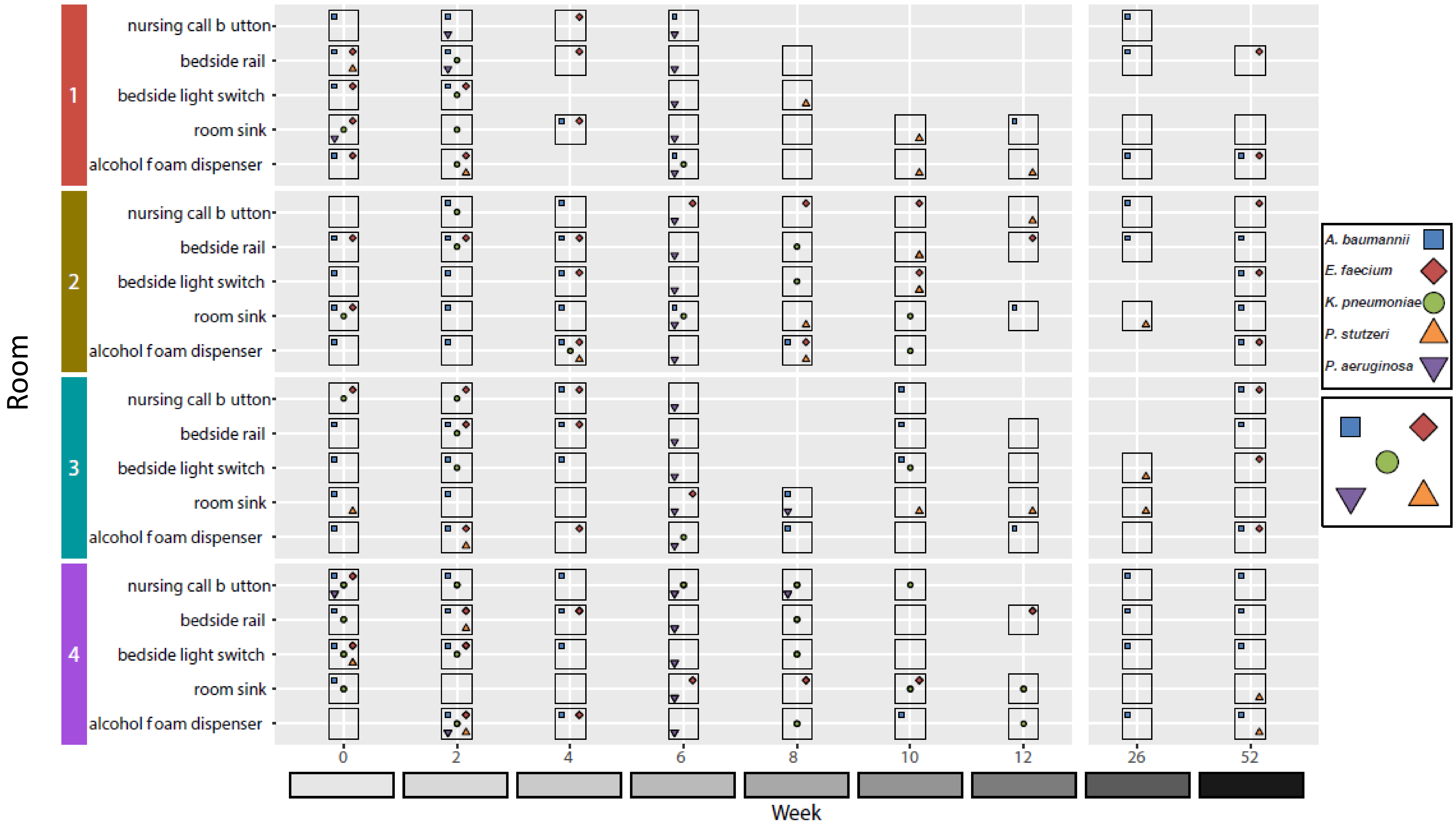
D'Souza, Potter, et al. Nature Comm. 2019.

Pakistan: The same antibiotic resistant organisms are found across multiple surfaces over a year.



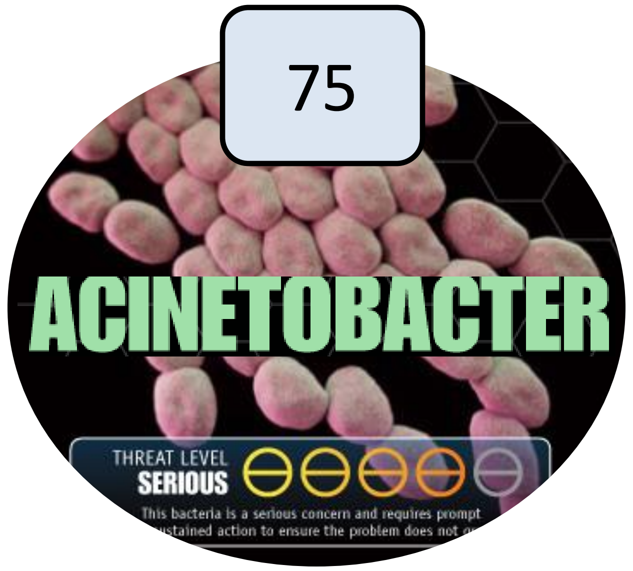
D’Souza, Potter, et al. Nature Comm. 2019.

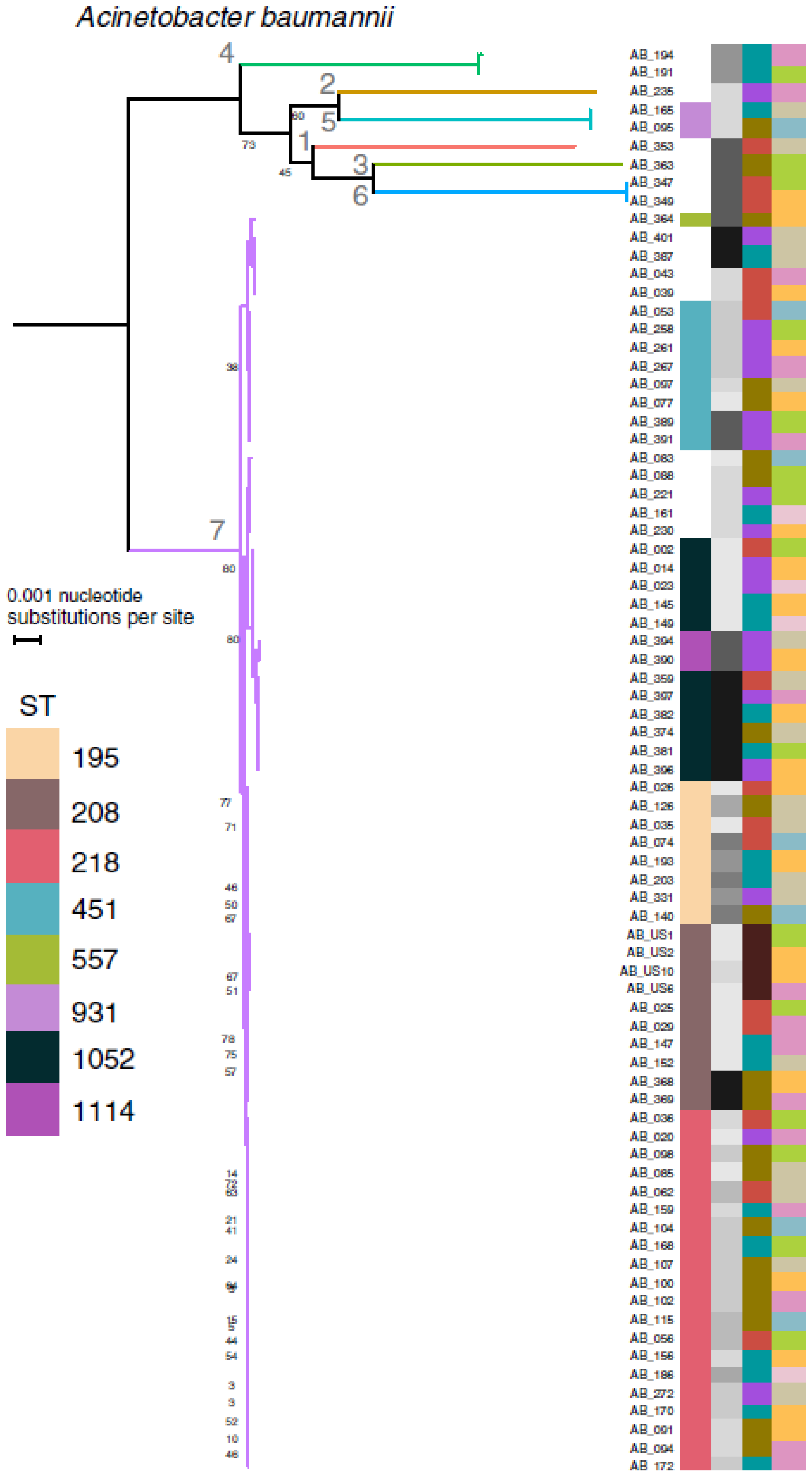
Pakistan: Antibiotic resistant organisms are persistently found across space and time

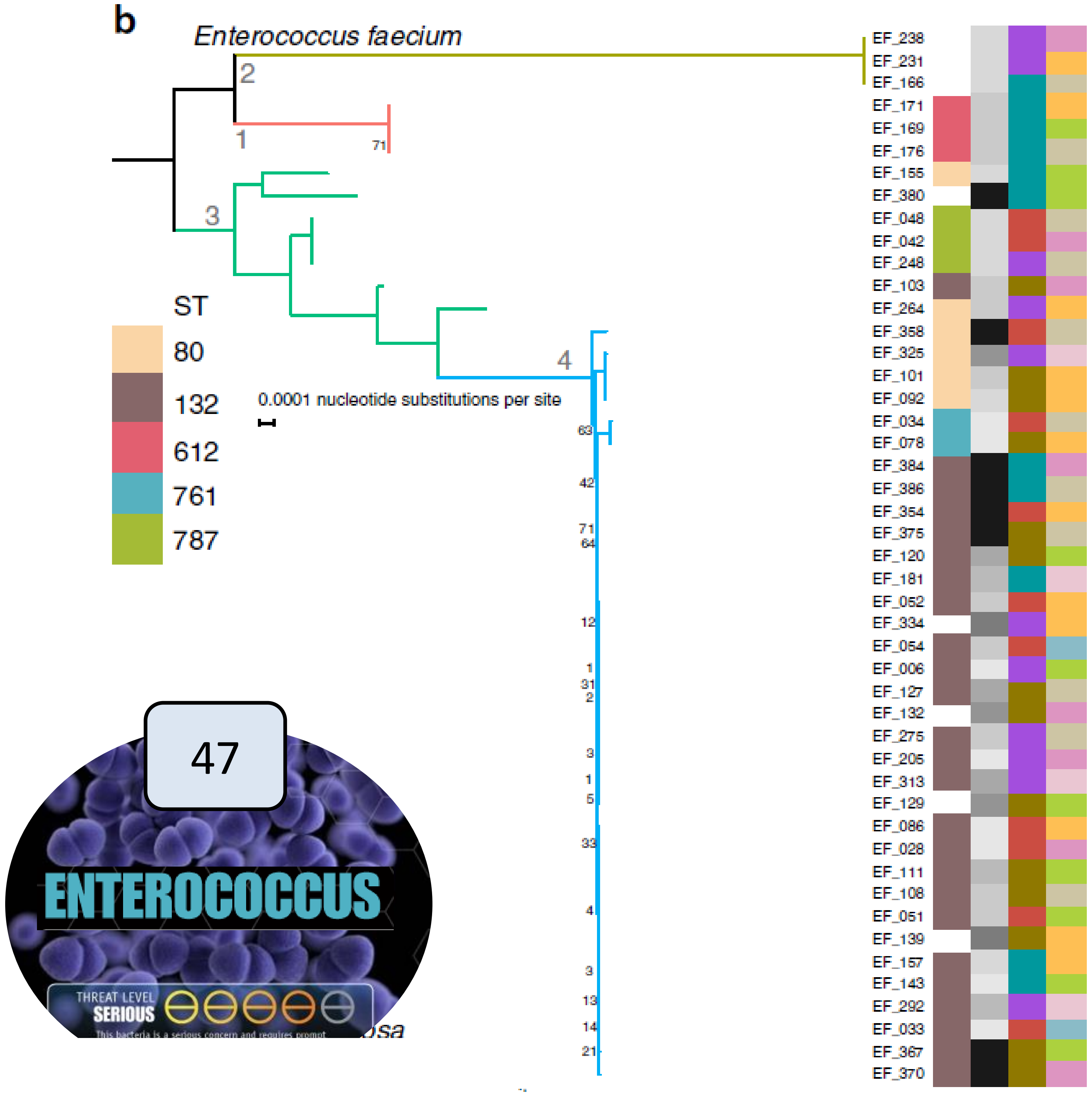


D'Souza, Potter, et al. Nature Comm. 2019.

For *A. baumannii* and *E. faecium*, a single lineage accounts for >70% of isolates recovered over 1 year

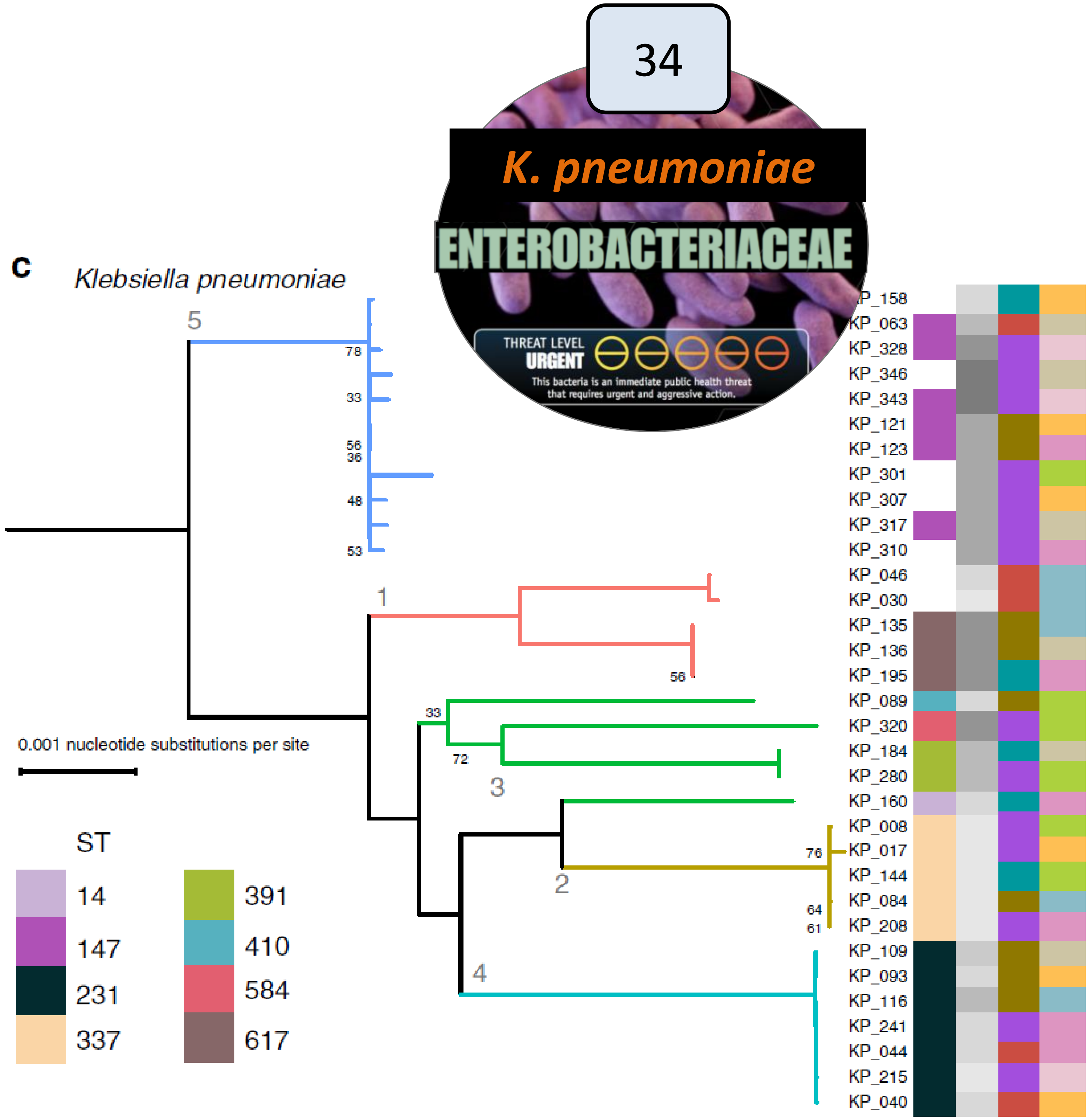


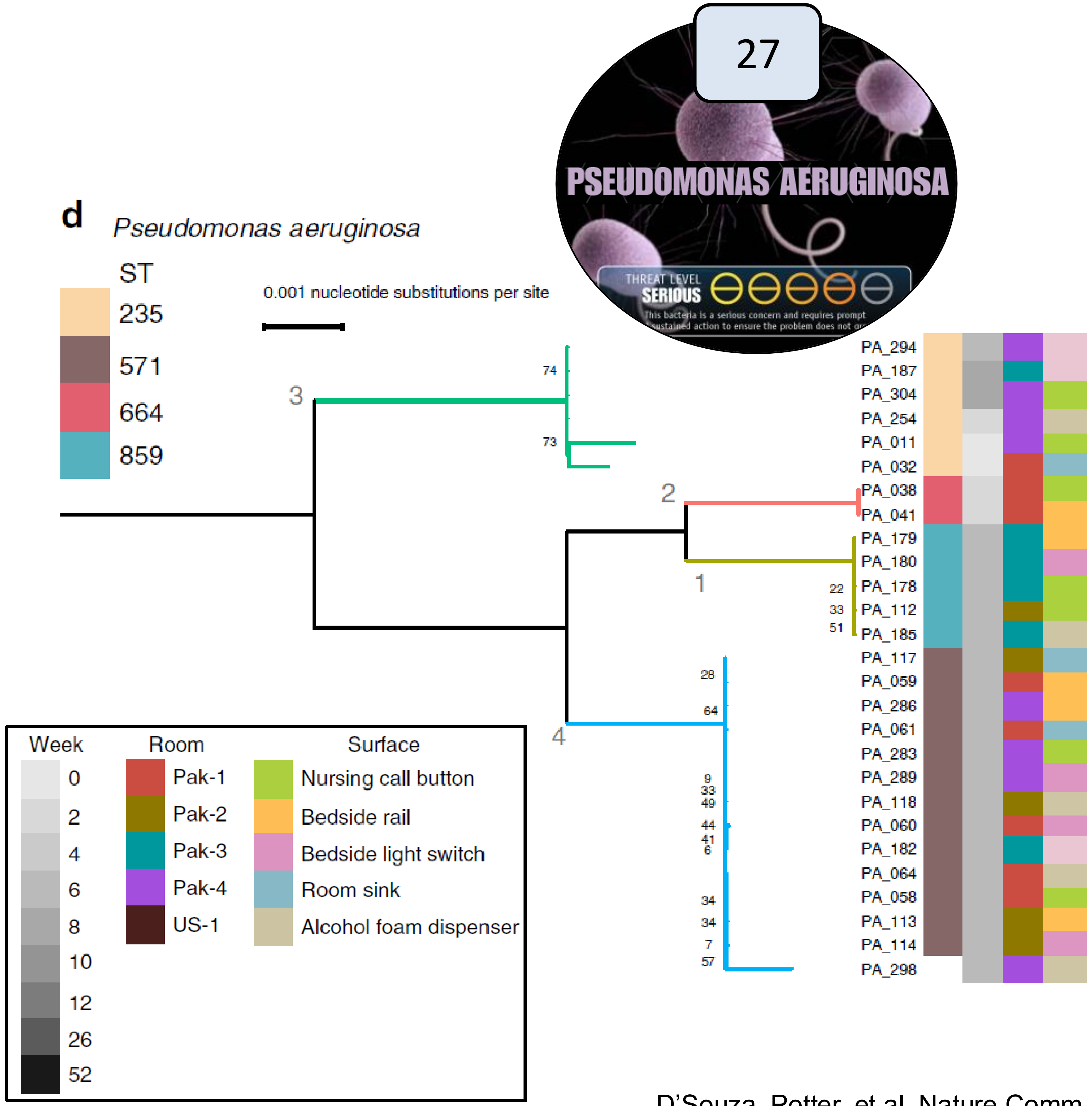




D'Souza, Potter, et al. Nature Comm. 2019.

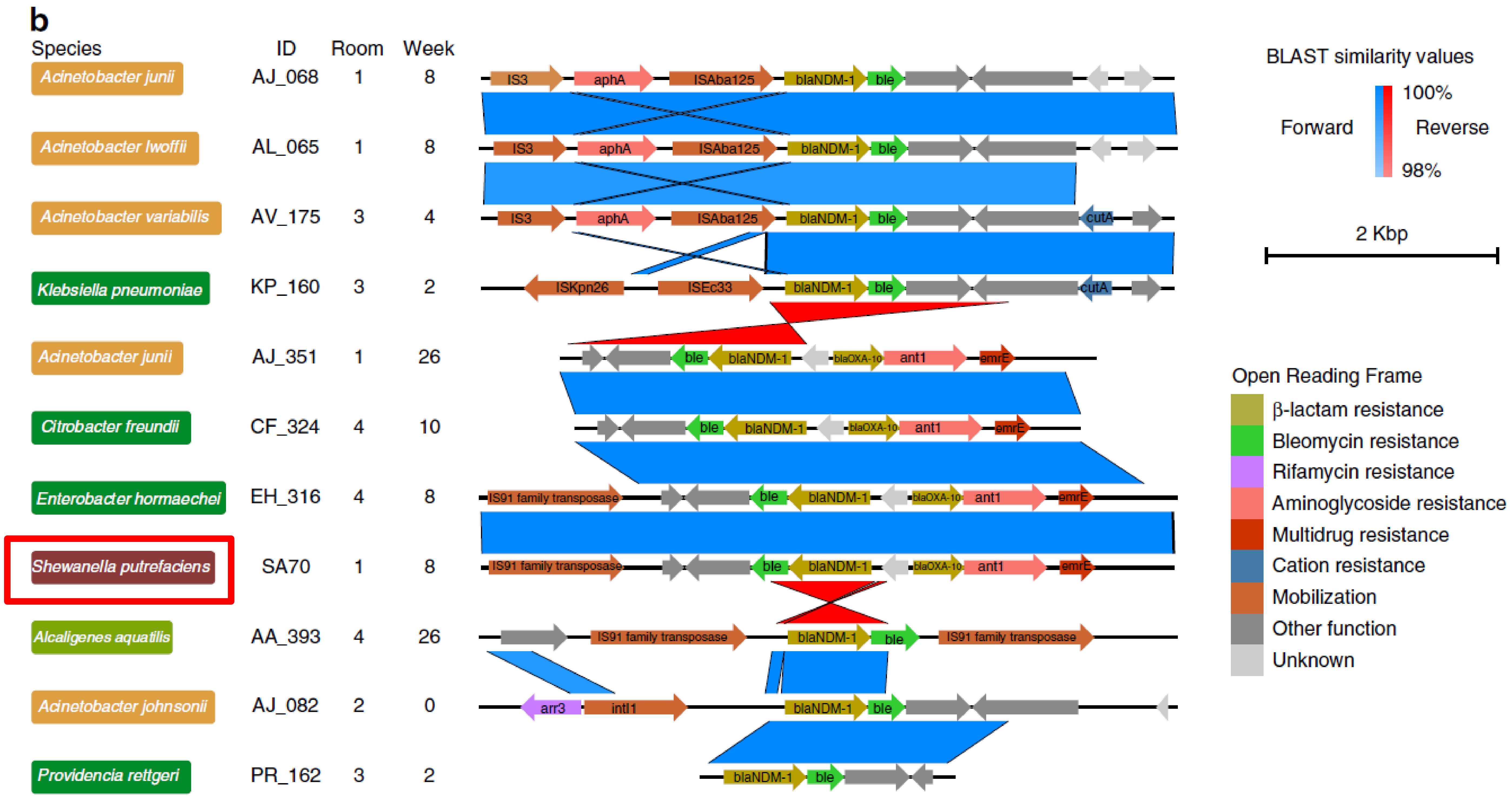
K. pneumoniae and *P. aeruginosa* strain types were heterogeneous





D'Souza, Potter, et al. Nature Comm. 2019.

Oxford NanoPore Sequencing of *bla*$_{\text{NDM-1}}$ strains



Species	ID	Room	Week
Acinetobacter junii	AJ_068	1	8
Acinetobacter lwoffii	AL_065	1	8
Acinetobacter variabilis	AV_175	3	4
Klebsiella pneumoniae	KP_160	3	2
Acinetobacter junii	AJ_351	1	26
Citrobacter freundii	CF_324	4	10
Enterobacter hormaechei	EH_316	4	8
Shewanella putrefaciens	SA70	1	8
Alcaligenes aquatilis	AA_393	4	26
Acinetobacter johnsonii	AJ_082	2	0
Providencia rettgeri	PR_162	3	2

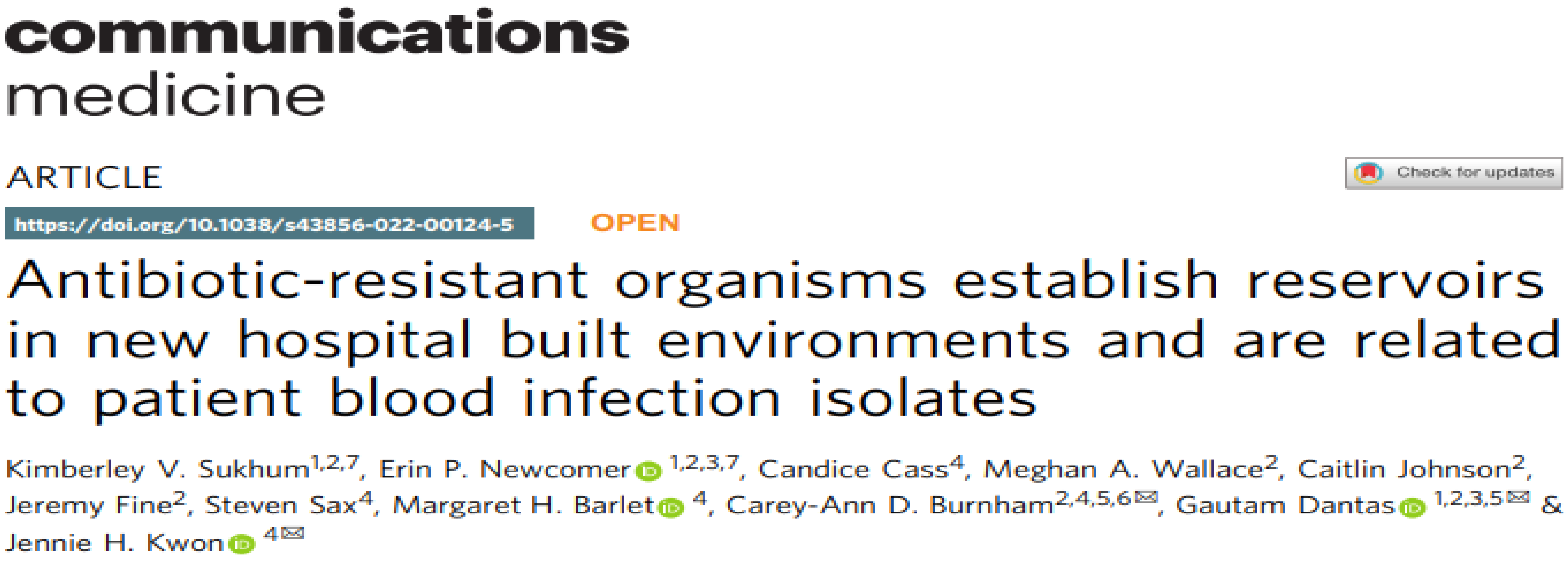
- 9/11 isolates: co-localized with a transposase
- Similar genetic context across diverse taxonomic groups; suggests horizontal gene transfer
- Environmental organisms can be a source of ARGs

D'Souza, Potter…..Burnham, Dantas. 2019. Nature Comm. 10: 4569. PMID: 31594927.

Key Findings

- AROs can be persistently recovered on surfaces across space and time
- The 4 most abundant organisms in our cohort are CDC threats
  - *A. baumannii*, *E. faecium*, *K. pneumoniae*, *Pseudomonas species*
  - Potential for horizontal gene transfer between environmental organisms and clinically significant organisms
  - Potential for clonal spread
- Need for further investigation on ICU reservoirs for AROs
  - Relationship to clinical infections

D’Souza, Potter, et al. Nature Comm. 2019.



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ARTICLE

Check for updates

https://doi.org/10.1038/s43856-022-00124-5

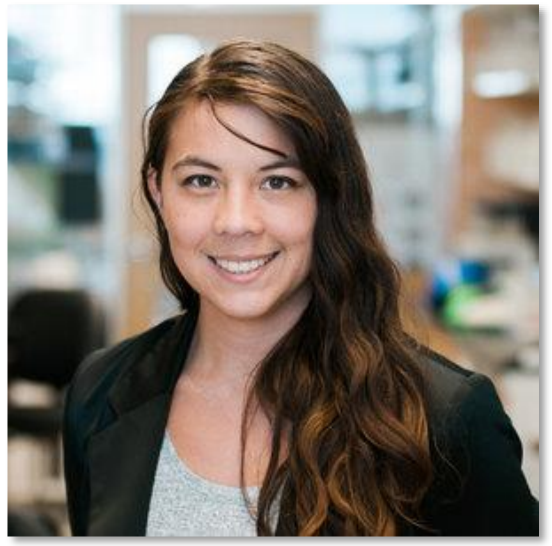
OPEN

Antibiotic-resistant organisms establish reservoirs in new hospital built environments and are related to patient blood infection isolates

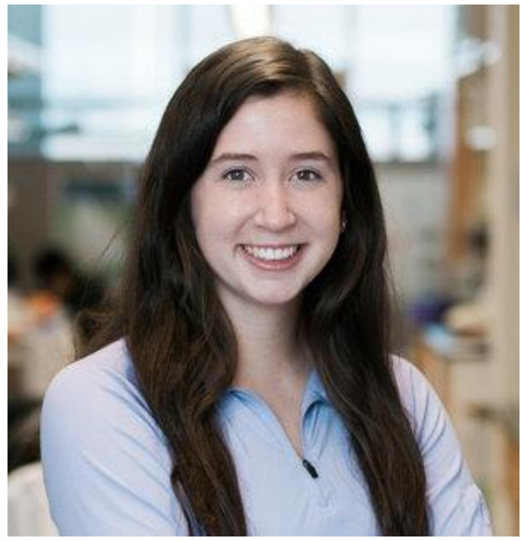
Kimberley V. Sukhum[1,2,7], Erin P. Newcomer[1,2,3,7], Candice Cass[4], Meghan A. Wallace[2], Caitlin Johnson[2], Jeremy Fine[2], Steven Sax[4], Margaret H. Barlet[4], Carey-Ann D. Burnham[2,4,5,6]✉, Gautam Dantas[1,2,3,5]✉ & Jennie H. Kwon[4]✉

Gautam Dantas

Carey-Ann Burnham



Kimberley Sukhum



Erin Newcomer

Characterize antibiotic resistant organism (ARO) transmission dynamics

- Key goals
  - Characterize ARO transmission dynamics to determine future interventions
  - Improve environmental hygiene and decrease transmission

- Key questions
  - When do AROs become established in ICU environments?
  - What areas in the ICU have the greatest burden of AROs?

Bone marrow transplant (BMT) patient population at high risk for infection from AROs

- Cancer
- Suppressed immune system
- Cancer chemotherapy
- Antibiotics
- High risk of infection

Down on the construction site!

Unique opportunity with the construction of a new BJH tower

Old versus new ICU

Room site samples

- 6 different ICU rooms
- 13 collection sites

Swab room areas that are frequently contacted by patients, visitors, and workers

Unique opportunity with the construction of a new BJH tower

Old versus new ICU

Communal areas

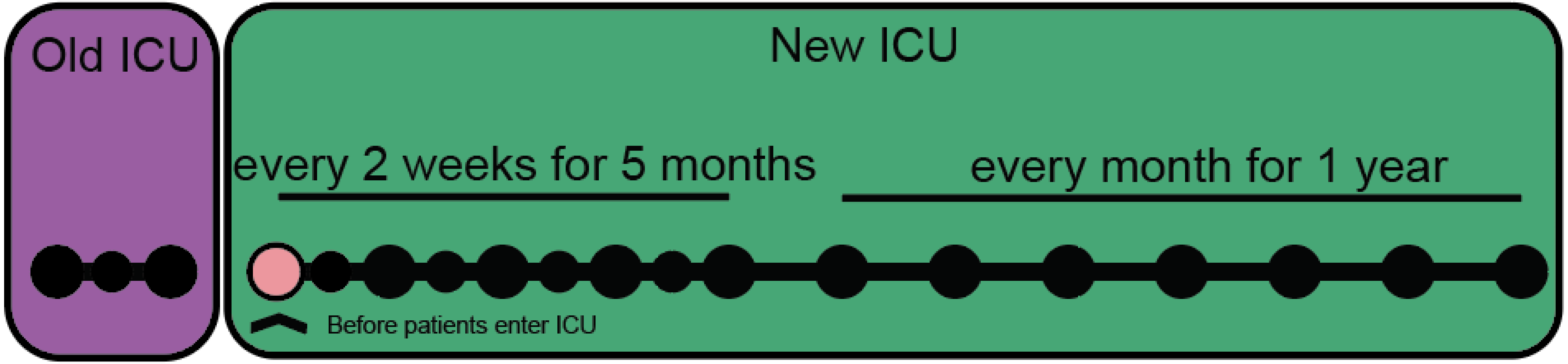
Soiled utility room sink drain

Vending machine

Housekeeping closet room drain

Family room floor

Longitudinal sampling of surfaces and patient samples



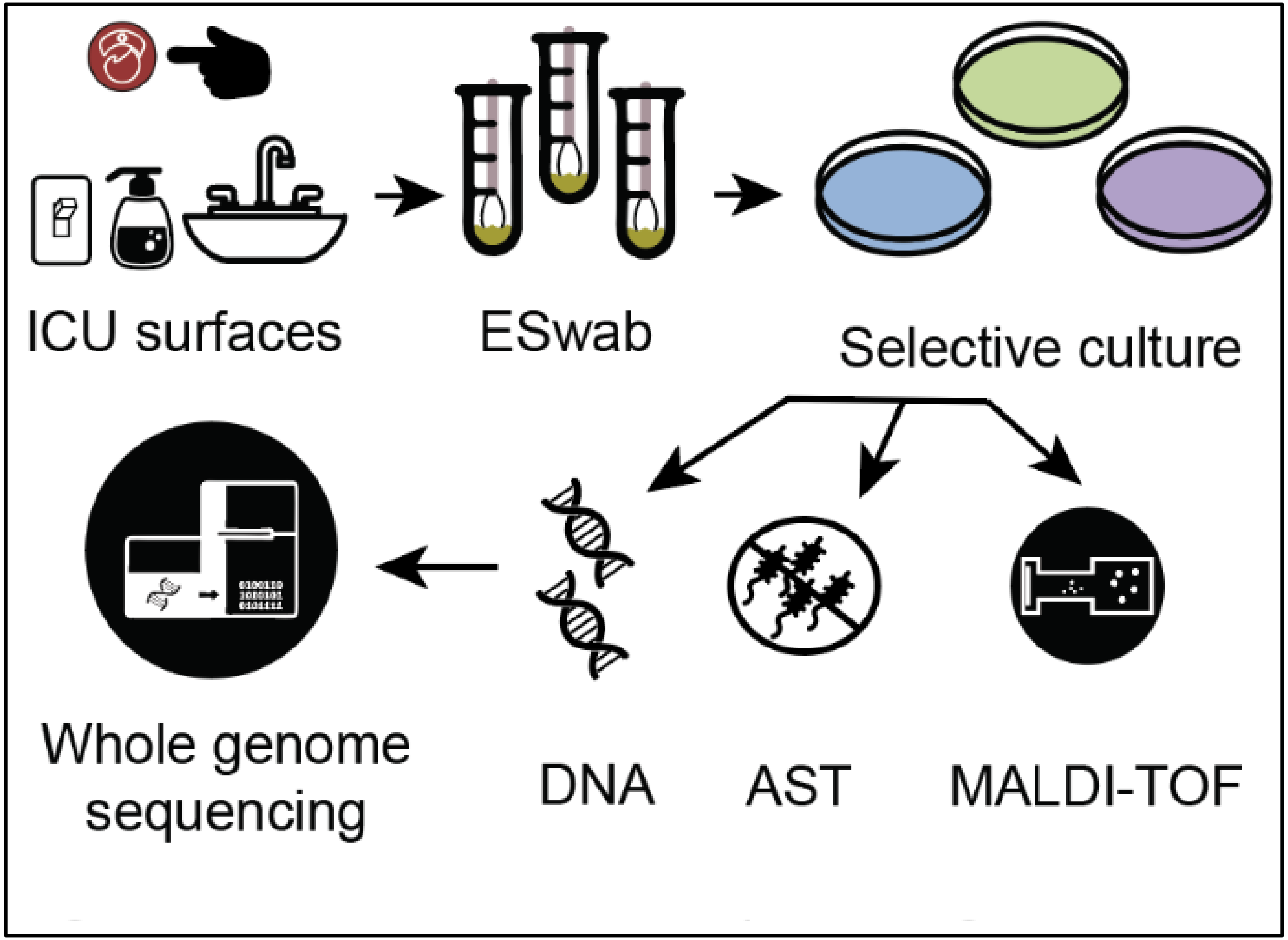
1666 samples collected

ICU Room
(n=1525)

Communal
(n=69)

Patient Stool
(n=72)

Specimens



ICU surfaces

ESwab

Selective culture

DNA

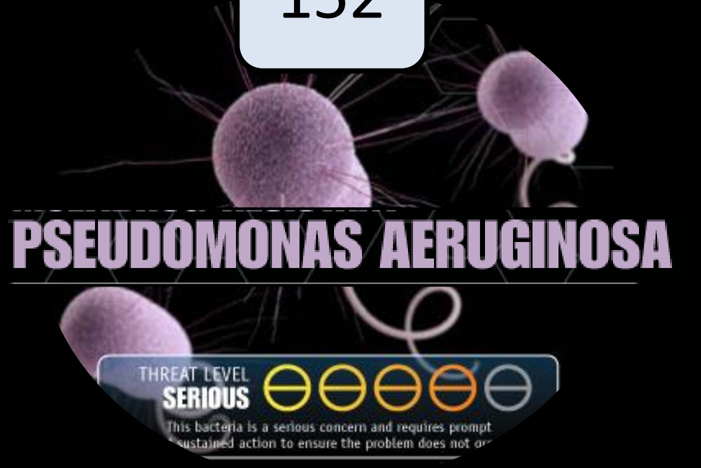
AST

MALDI-TOF

Whole genome sequencing

Results: 746 antibiotic resistant organisms were cultured from collections

152



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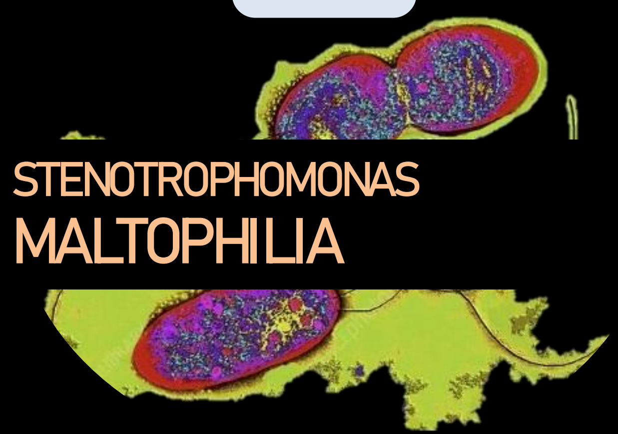

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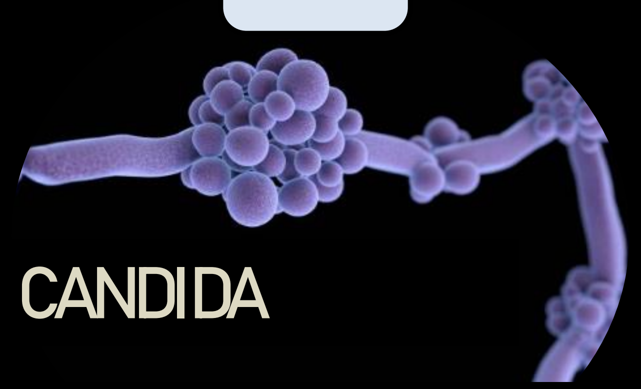

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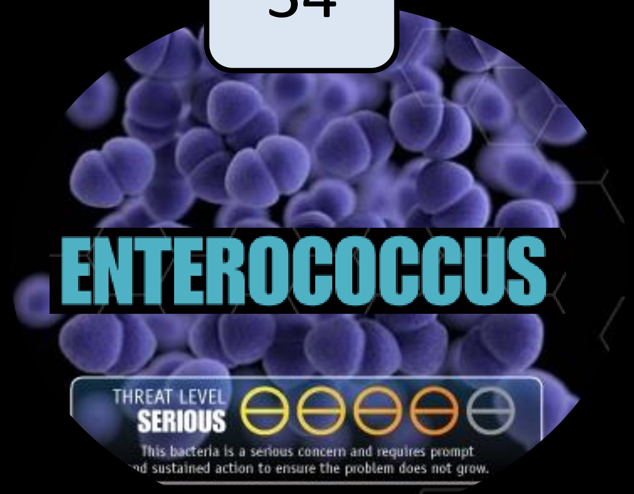

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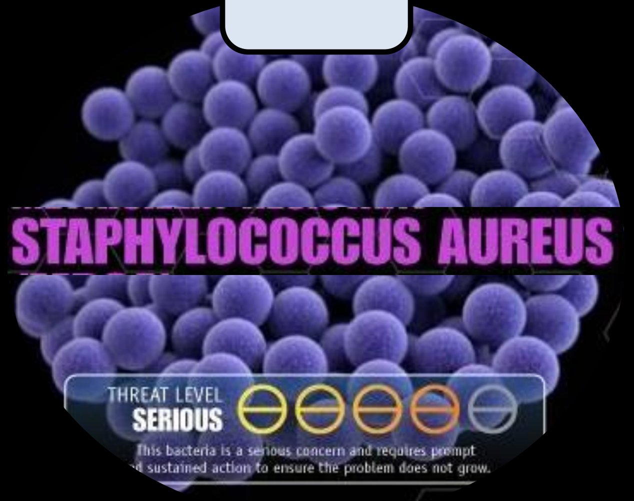


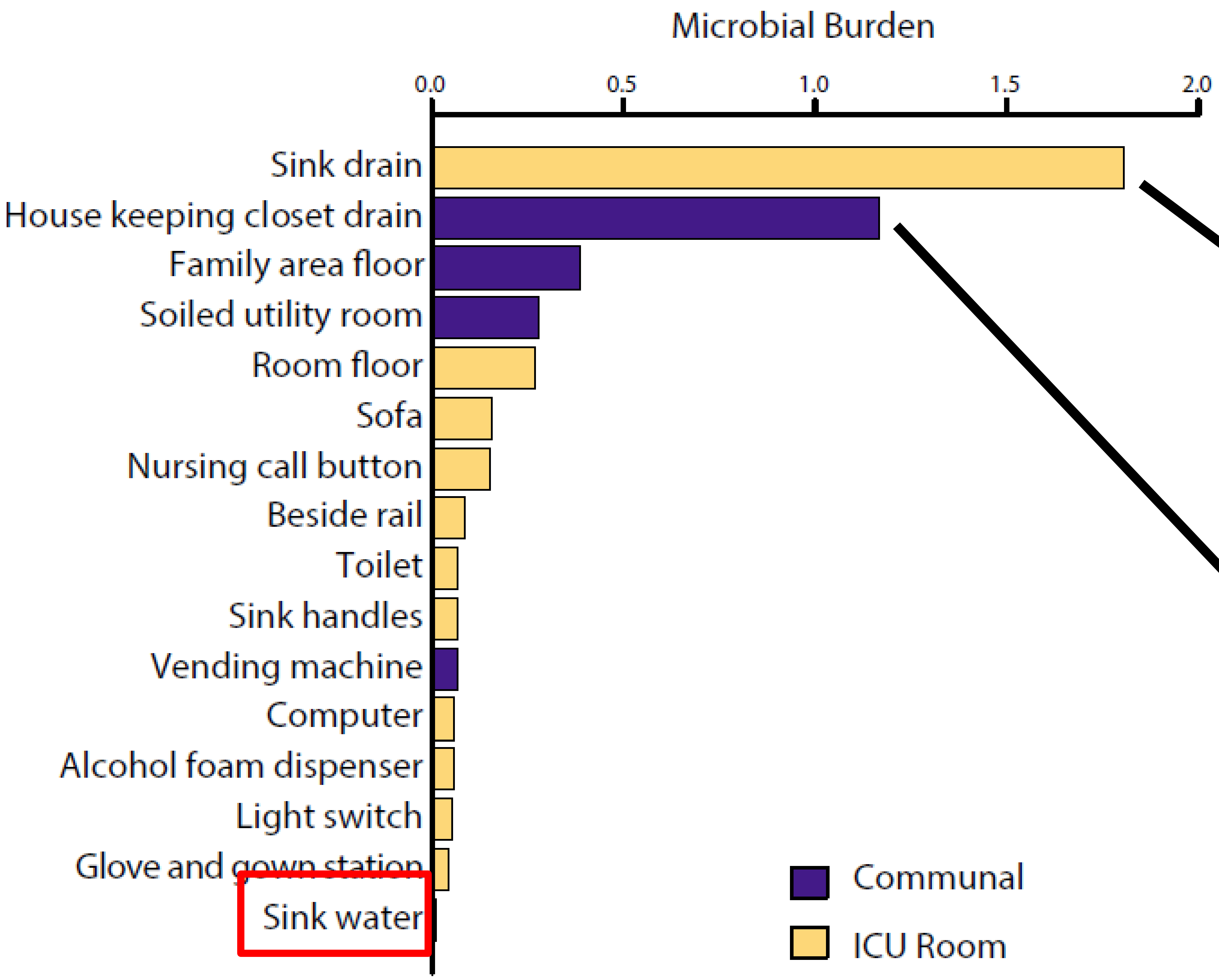
Results: 746 antibiotic resistant organisms were cultured from collections

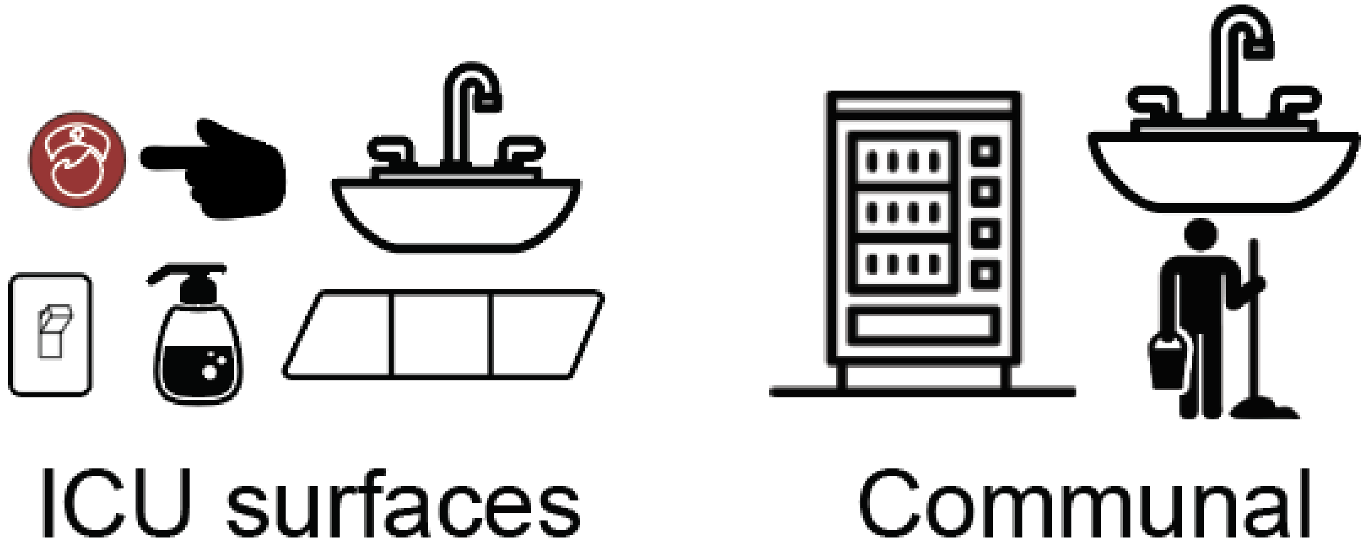
100% of BMT ICU rooms yielded AROs

4 of 4 communal collection sites yielded AROs

Communal Collection Sites

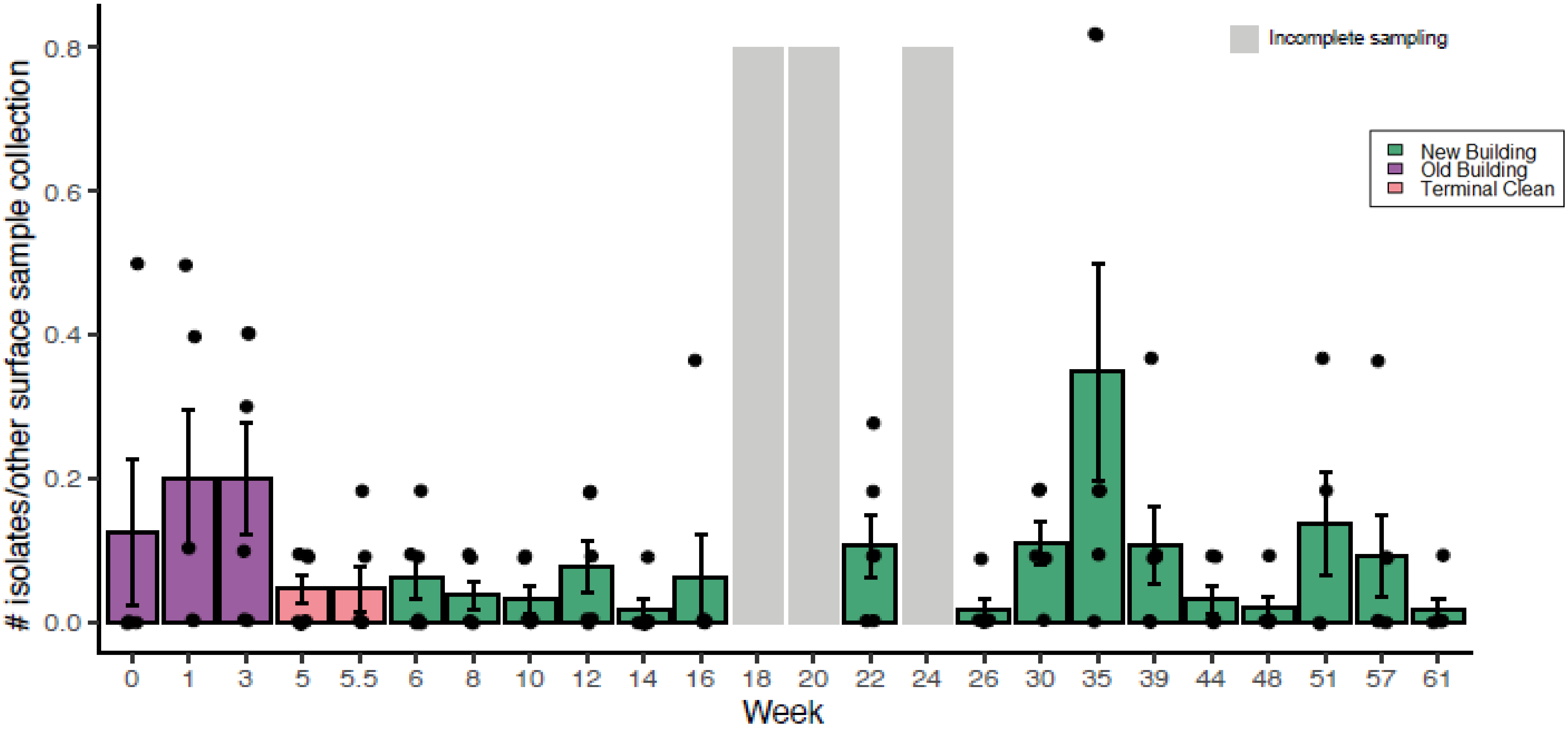
Sink drains were a major source of antibiotic resistant organisms.



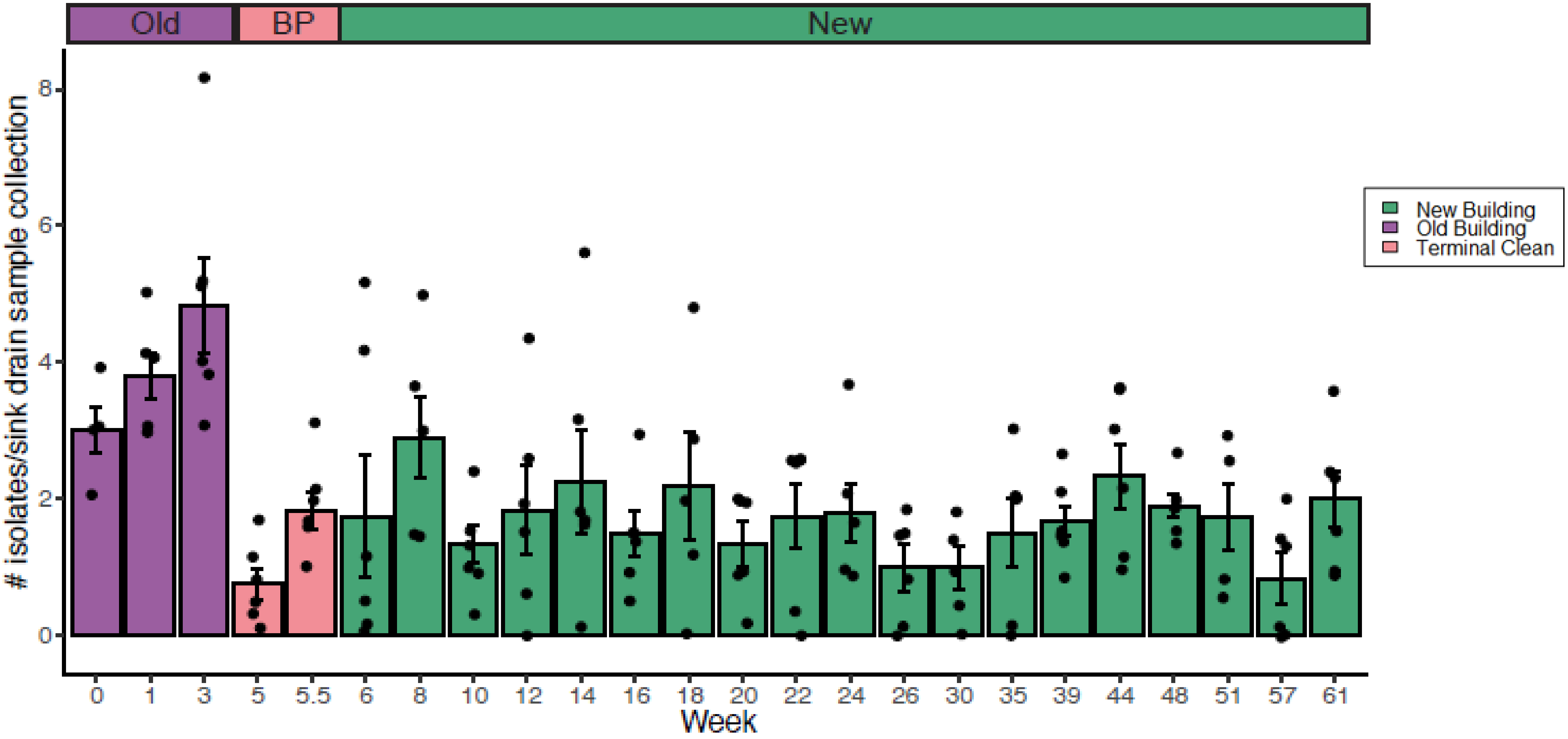


*Microbial Burden = # of AROs / # of collections

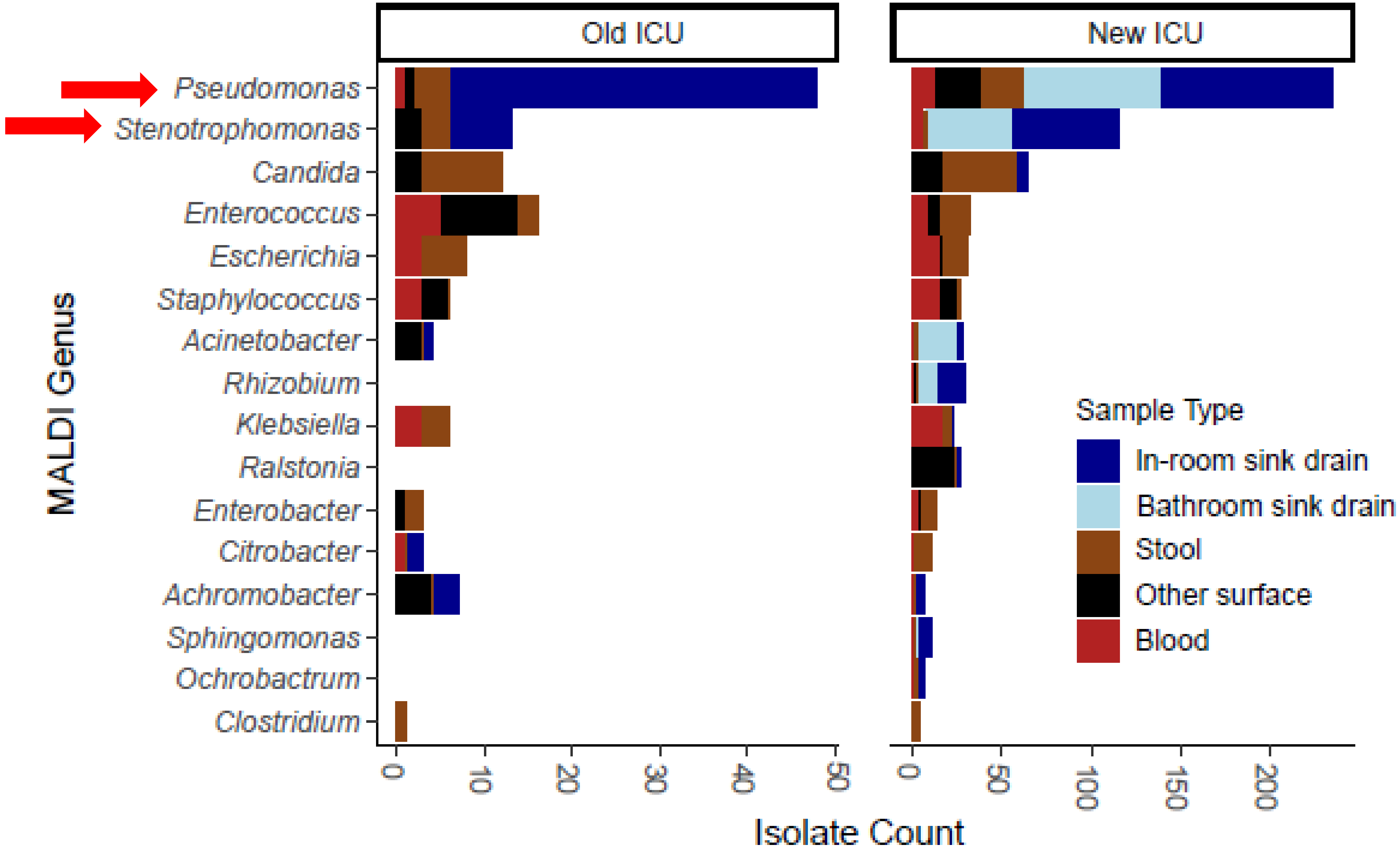
Antibiotic resistant organisms are present all time points



Antibiotic resistant organisms are present all time points in ICU sink drains

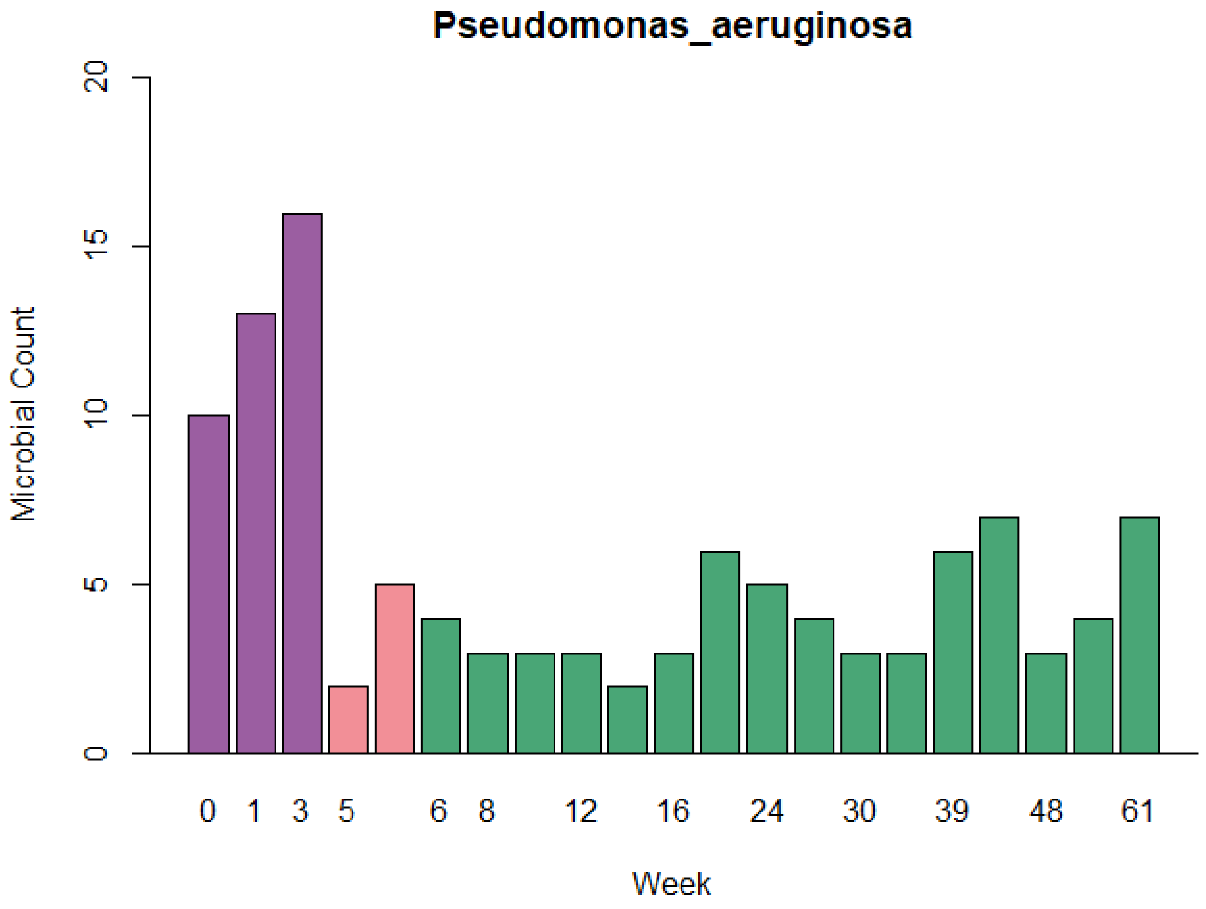


Pseudomonas species were abundant

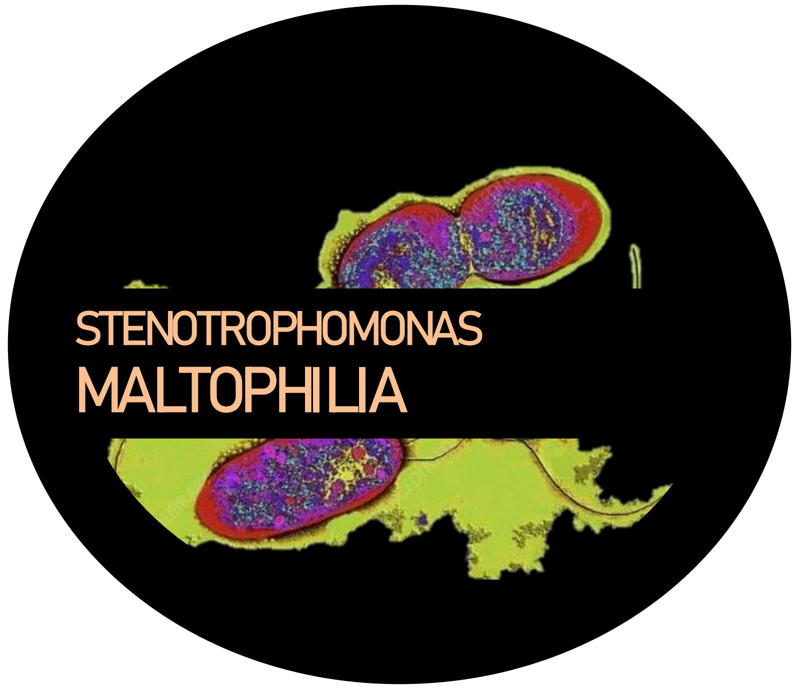


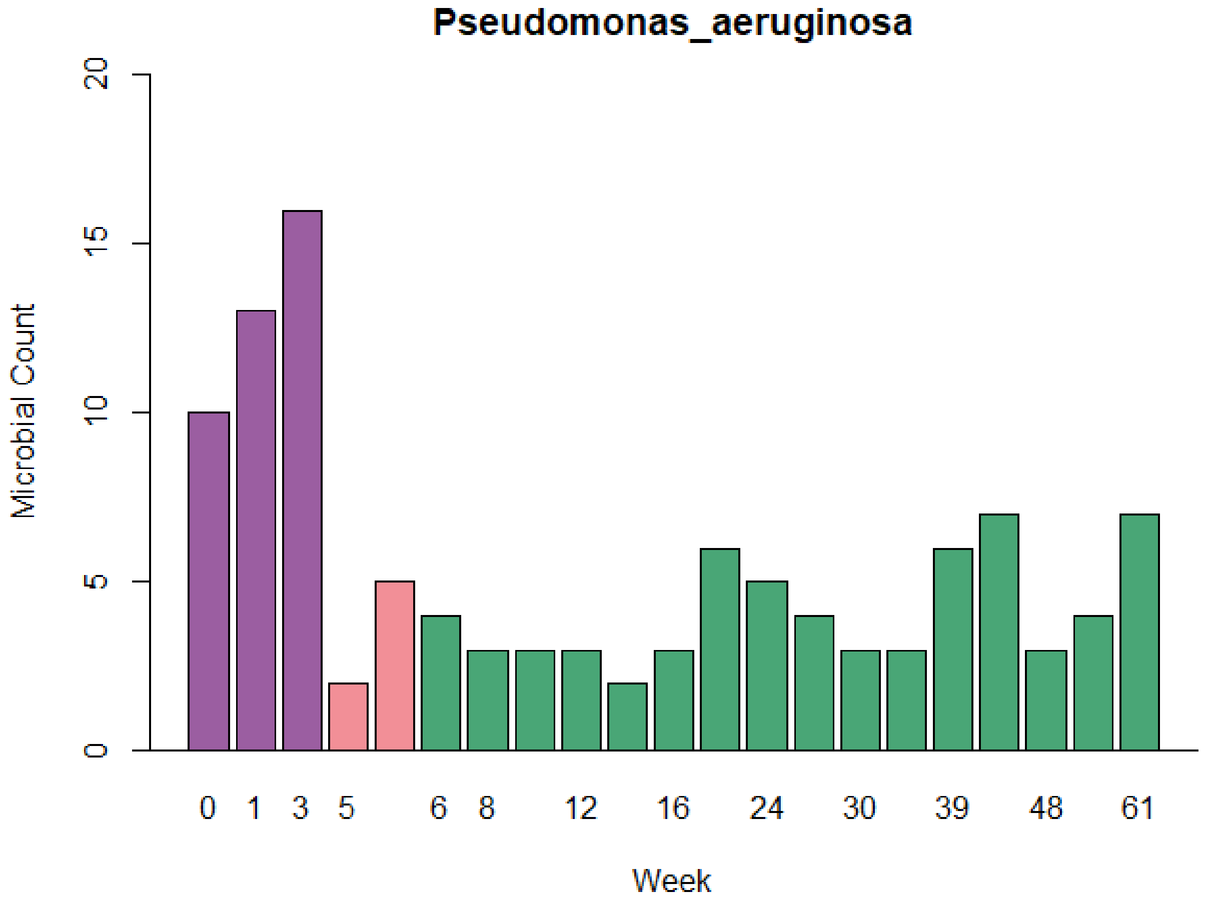
Sukhum, Newcomer et al., pending publication

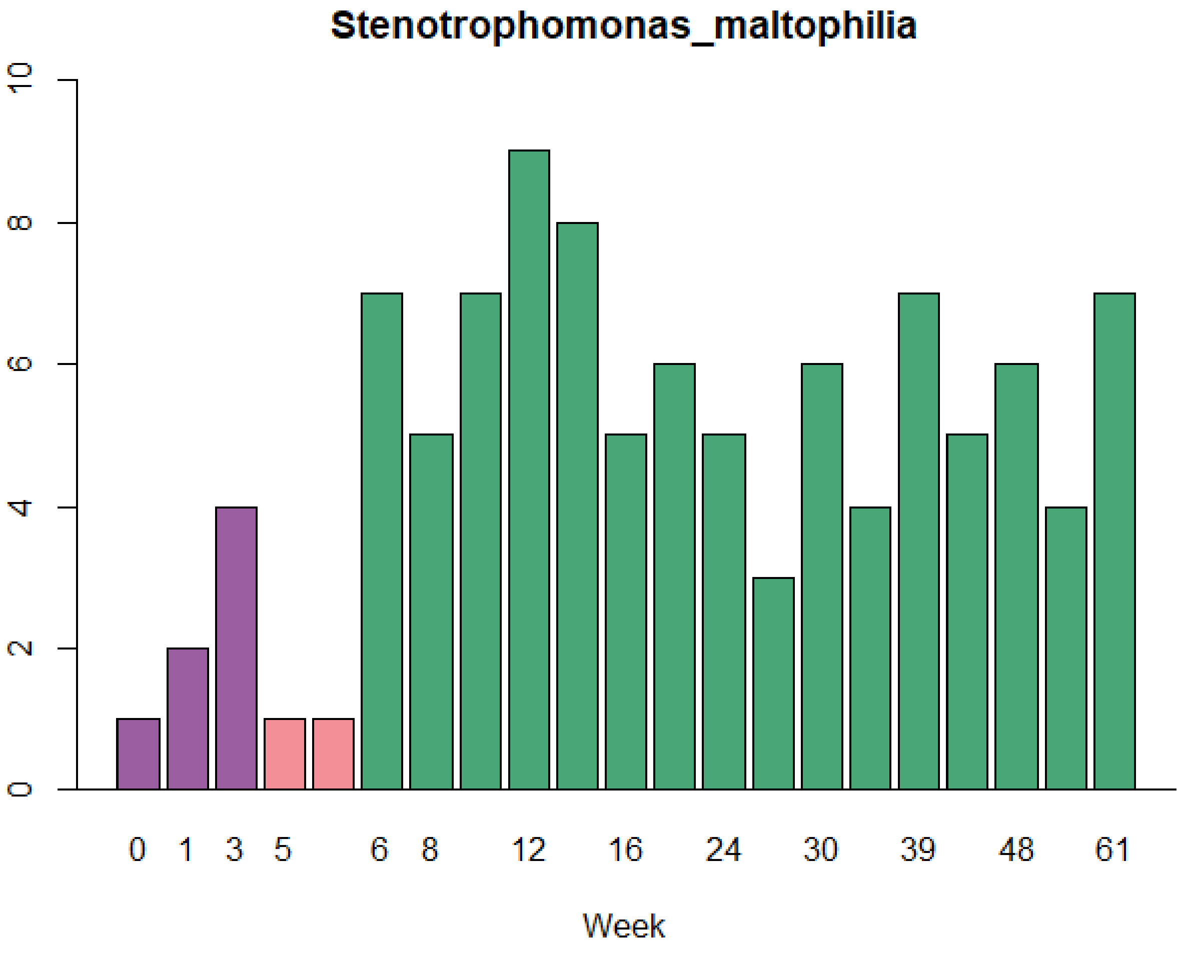
Antibiotic resistant organisms in sink drains vary in transition to new ICU



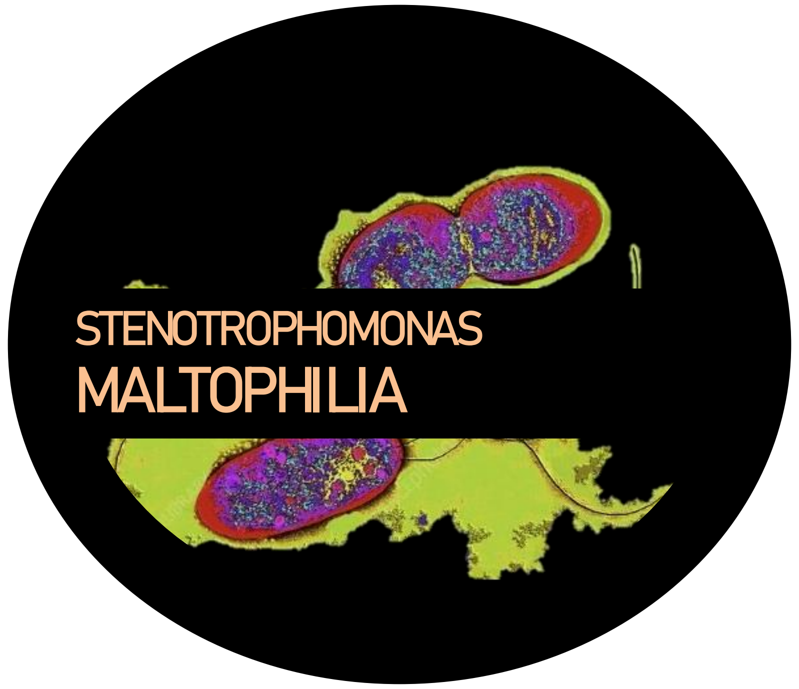
Antibiotic resistant organisms in sink drains vary in transition to new ICU

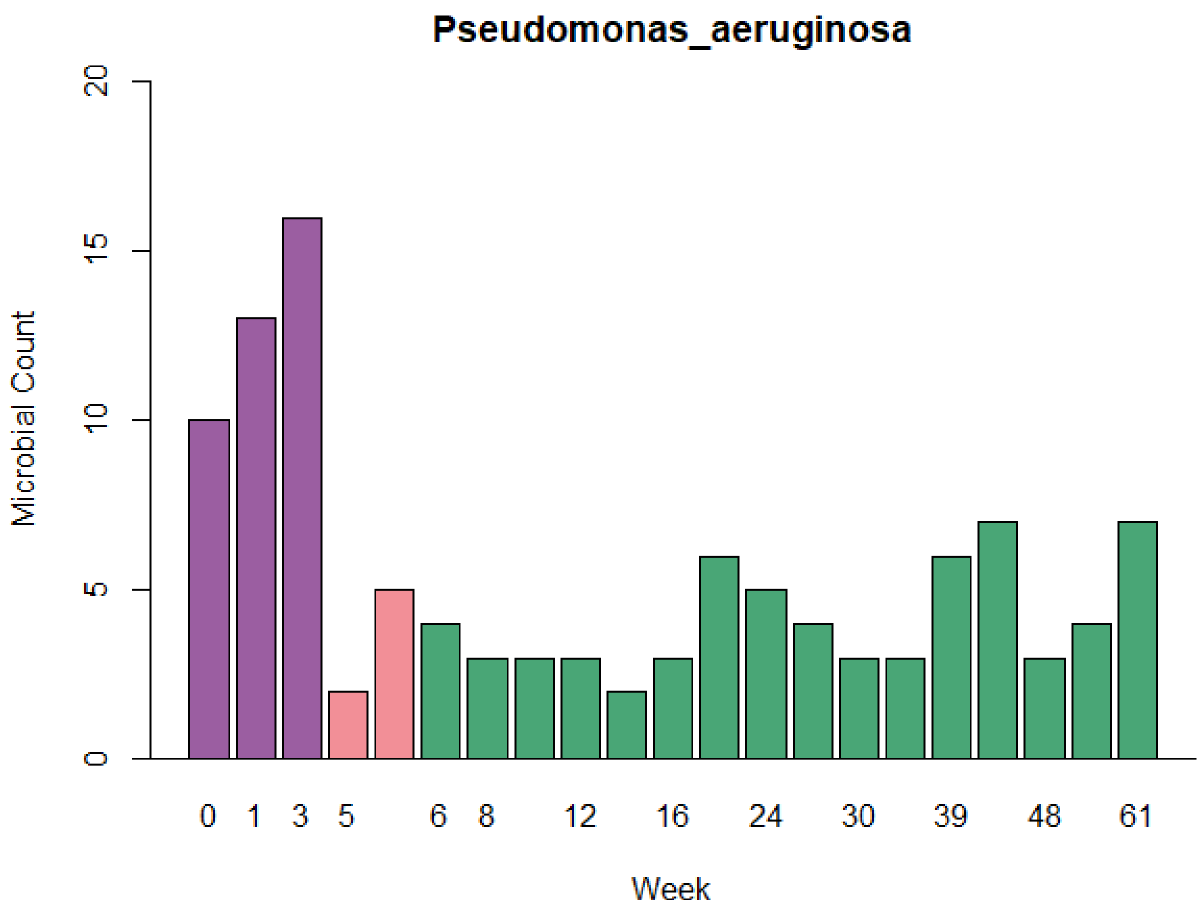


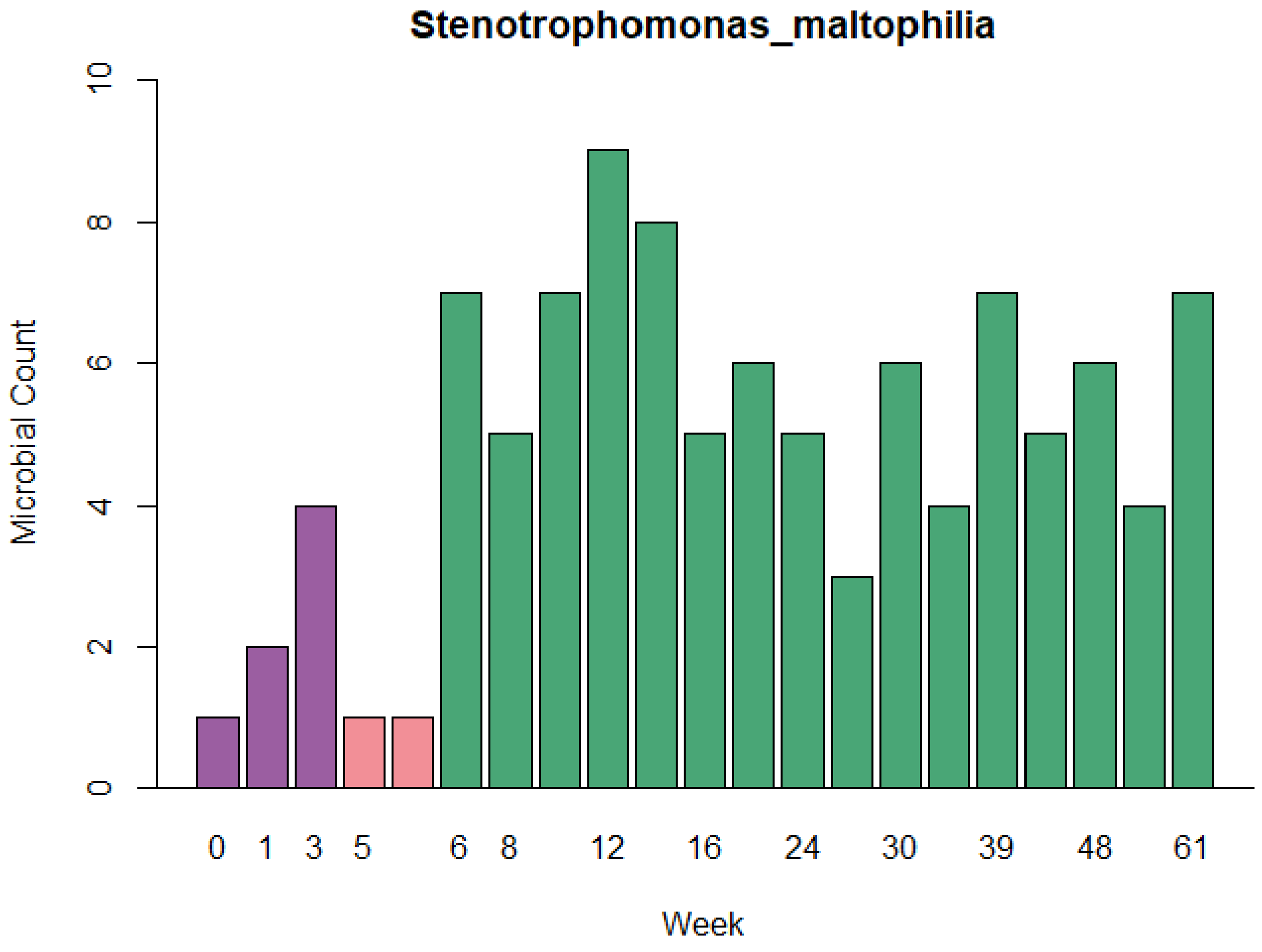


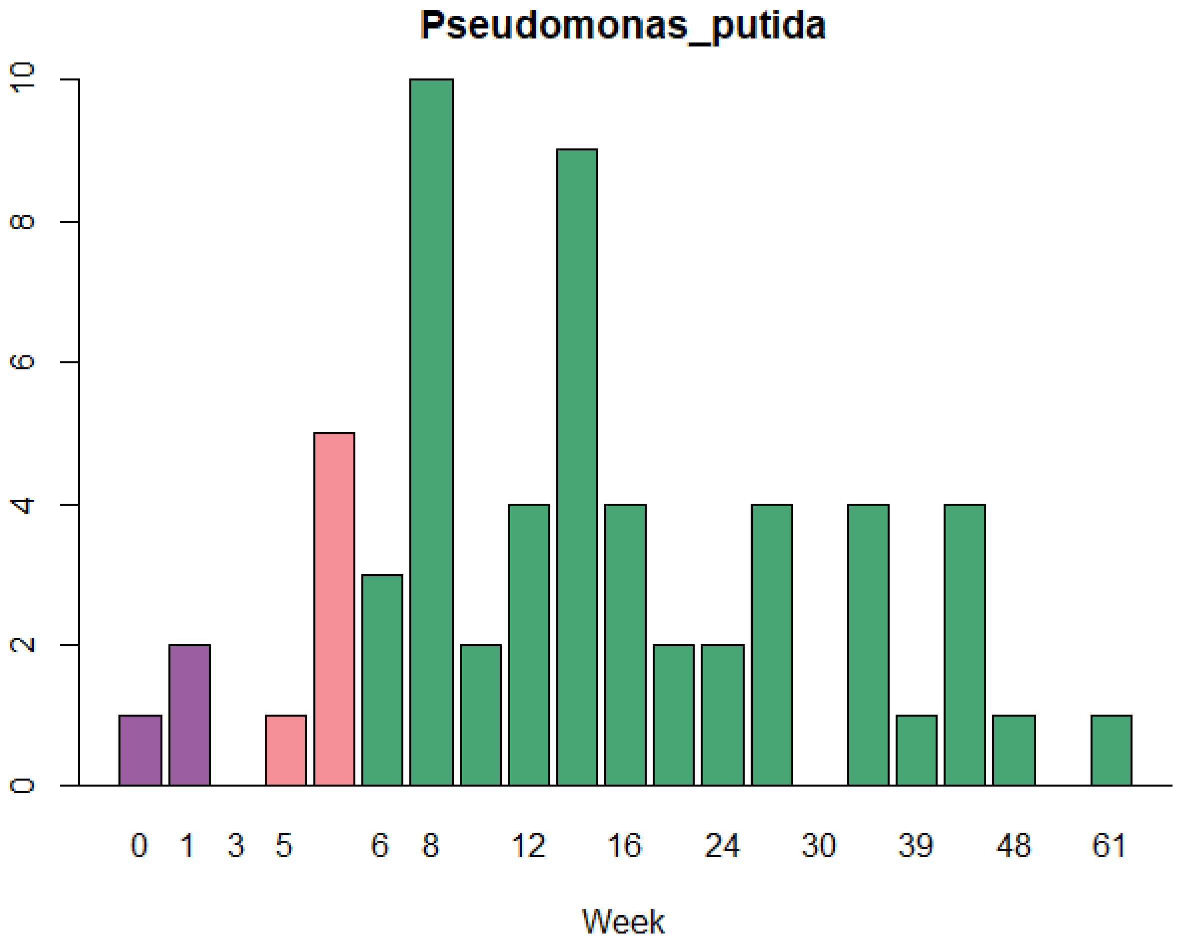


Antibiotic resistant organisms in sink drains vary in transition to new ICU

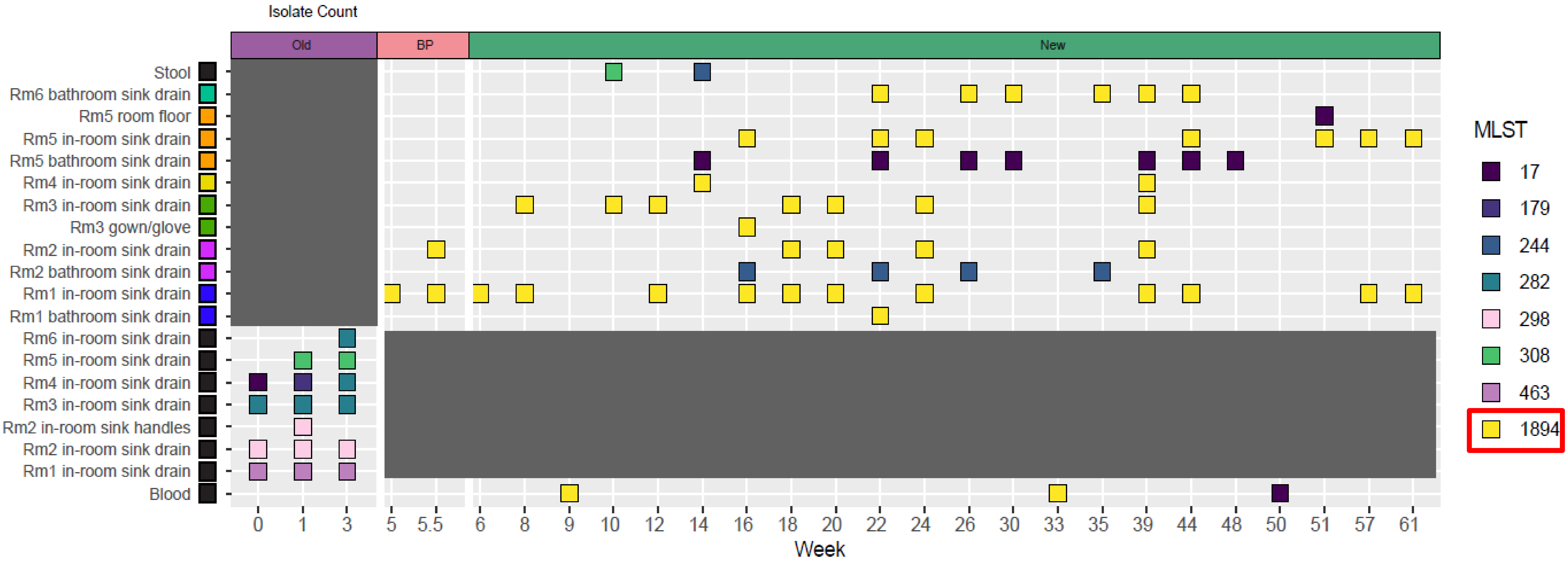




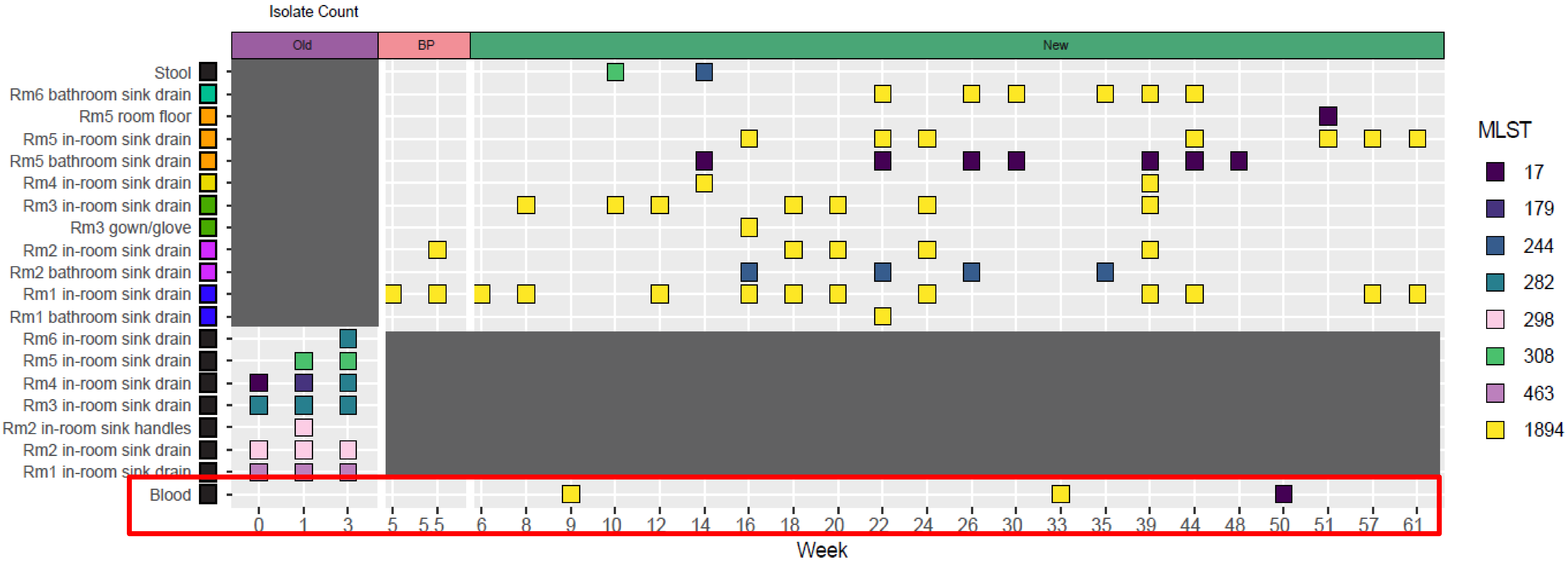




P. aeruginosa lineage ST1984 is found in the BMT ICU before patients arrive



P. aeruginosa lineage ST1984 is linked with isolates from blood cultures



In the news: outbreaks related to premise plumbing and sinks

UK outbreak probe points to Salmonella reservoir in faulty restaurant drains

Filed Under: Foodborne Disease; Salmonella
Lisa Schnirring | News Editor | CIDRAP News | Dec 07, 2017

SPLASHY OUTBREAK —

Freaky superbug poured out of NIH sinks for a decade, infecting patients

From 2006 to 2016, an aquatic bacterium creeped in clinic sinks, causing rare infections.

BETH MOLE - 1/2/2019, 11:37 AM

New HLM-designed hospital may have to be 'ripped down', warns union official

6 AUGUST 2019 - BY KATE YOUDE

Hospitals installed more sinks to stop infections. The sinks can make the problem worse

By HELEN BRANSWELL @HelenBranswell / OCTOBER 25, 2016

How can we reduce the burden of AROs in ICU sinks?

- No clear recommendations for sink drain environmental hygiene interventions
  - Disinfectant types
  - Frequency of cleaning
  - Needs to be affordable, practical, and scalable
- Clinical materials are kept near sink
- Hydrogen peroxide and peracetic acid-based disinfectant
  - Suppressed sink colonization for 3 days

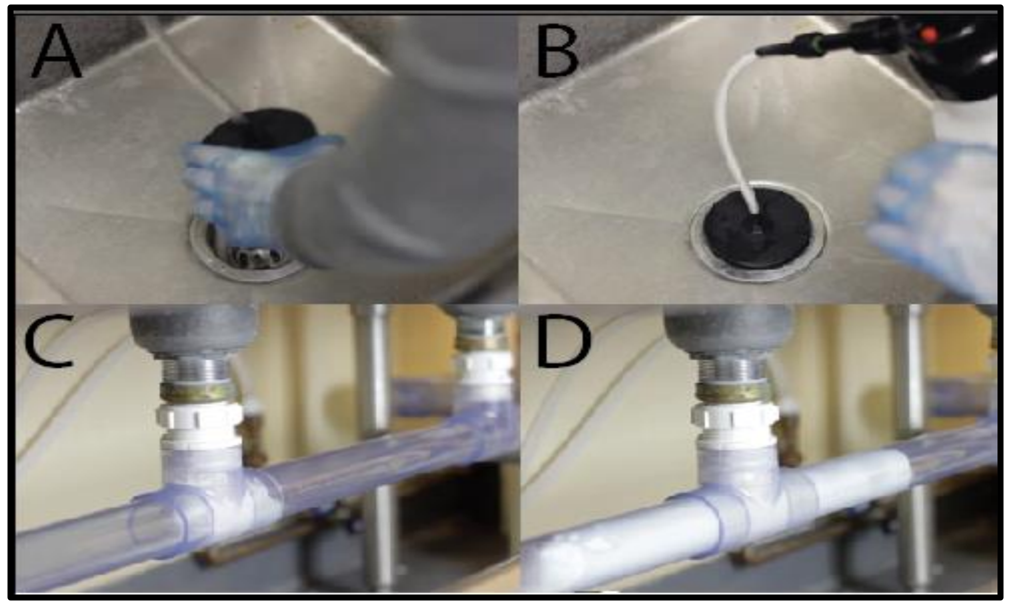


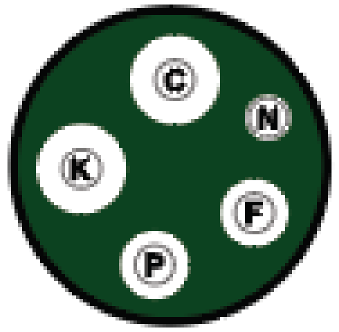
Photo credit: FOAM-iT.com. Buchan, ICHE 2019. Gestrich, ICHE 2018. Ramos-Castaneda, ICHE 2020. Jones, ICHE 2020.

Key Findings

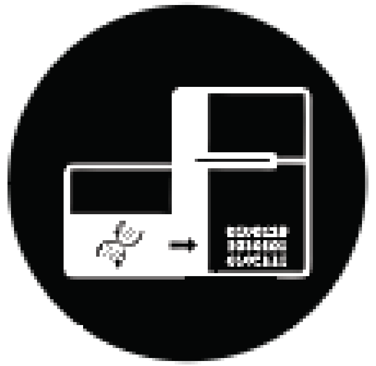
- Human gut is a reservoir for antibiotic resistant organisms and potentially pathogenic microbes
- The built environment can be a reservoir for potentially pathogenic microbes
    - Can be linked to clinically significant infections
- Limited data on surveillance and interventions
- Mixed methods of detection are key to progress
- Avenue for future investigation

Future Directions

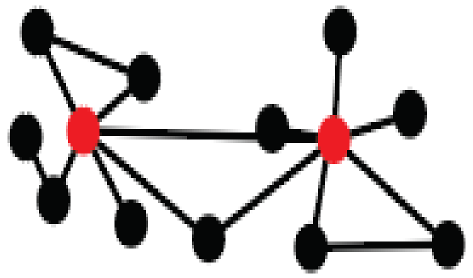
Goal	Benefit
Develop methods for the identification of reservoirs of potential pathogens	Identify areas of concern
	Application of next generation sequencing methods
Characterize and understand transmission	Understand microbe transmission, modeling
	Identify targets for interventions
Data driven interventions to disrupt cycle of transmission	Prevent infection
	Scalable, feasible, sustainable



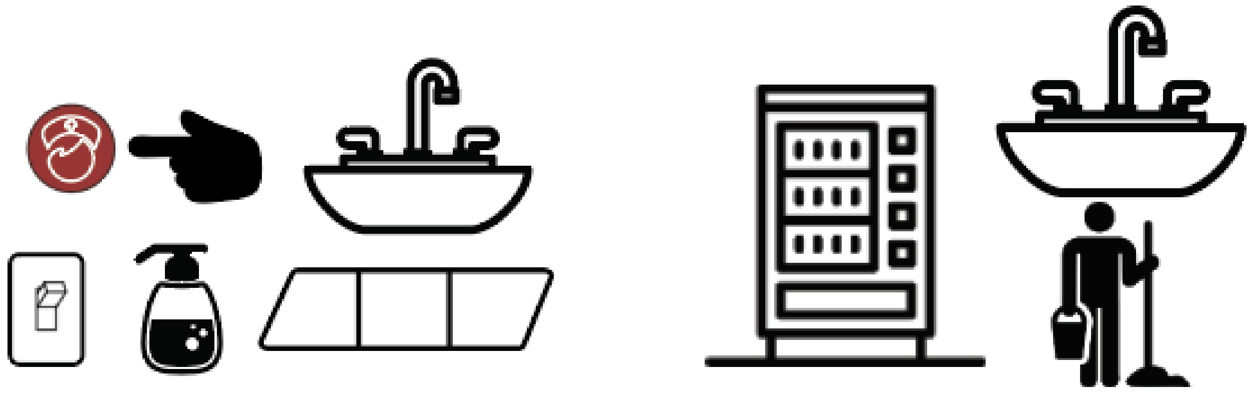
Microbiologic culture



Next generation sequencing



Transmission dynamics modeling



Infection prevention interventions

Acknowledgements

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BARNES-JEWISH
Hospital
BJC HealthCare

Institute of Clinical and Translational Sciences

AHRQ Agency for Healthcare Research and Quality

NIH National Institute of Allergy and Infectious Diseases

DD DORIS DUKE CHARITABLE FOUNDATION

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