The Threat of Multidrug Resistant Organisms (MDROs) in Hospitalized Patients

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Disclosures

- None

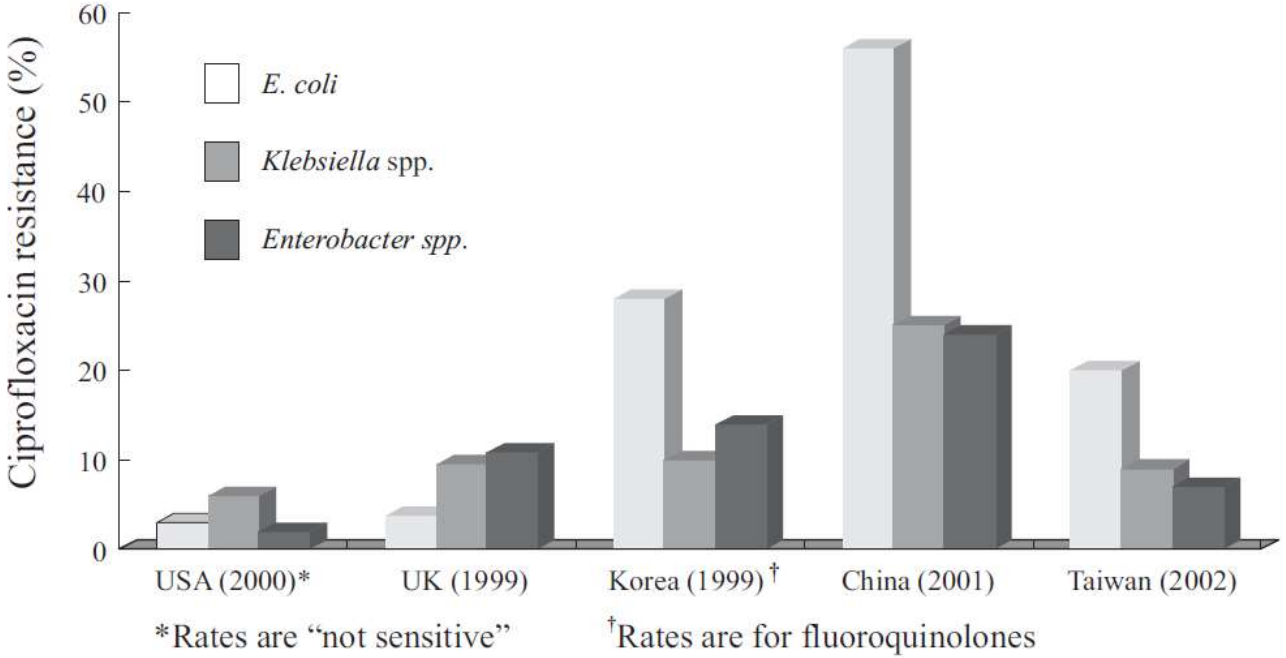
Overview

- Antimicrobial resistance (AMR)
- Drivers of AMR
- Risk factors for infection with MDROs
- Superbugs and super-resistance
  - ESBL-E, CRE/CPE, CRAB, DTR
- Consequences/costs of AMR

The Threat of Antibiotic Resistance

- WHO: “antibiotic resistance one of the three greatest threats to human health”
- US: annual additional costs of infections caused by resistant organisms $21-34 billion
- Impact on all aspects of modern medicine
  - Surgery
  - Oncology
  - Transplantation

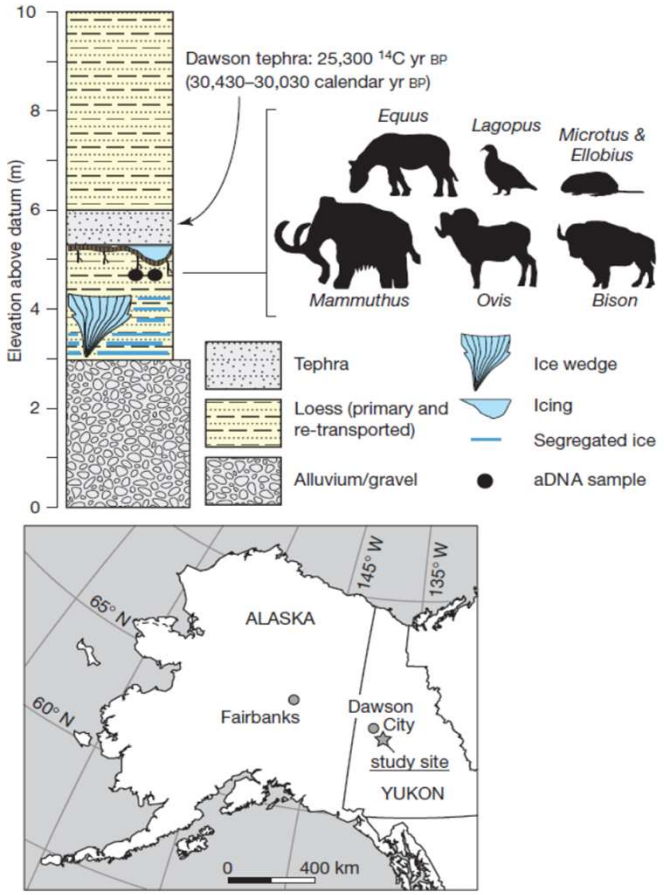
Resistance is Global

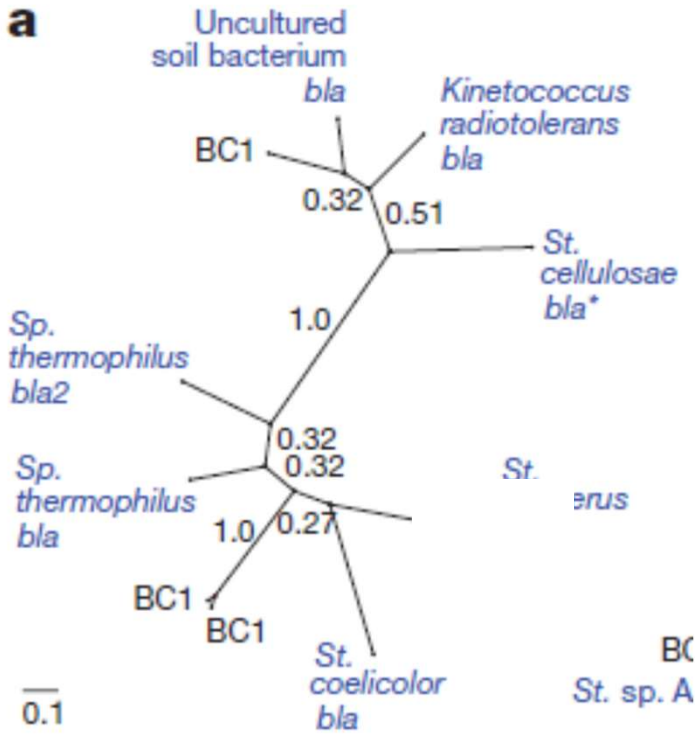


Isturiz. Int J of Antimicrob Agents 2008;32:s201

Where did antimicrobial resistance originate from?

Antibacterial Resistance is Ancient

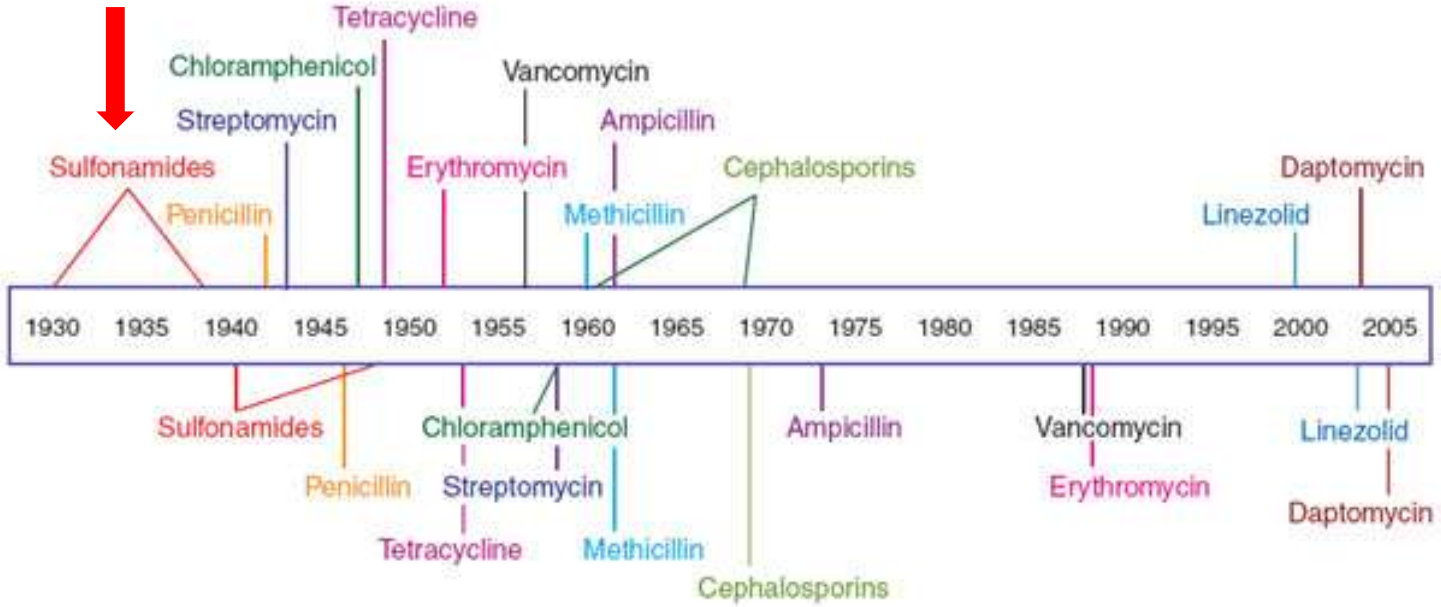




D'Costa et al. Nature 2011;477:457

Antibiotic Resistance Timeline

Antibiotic first used

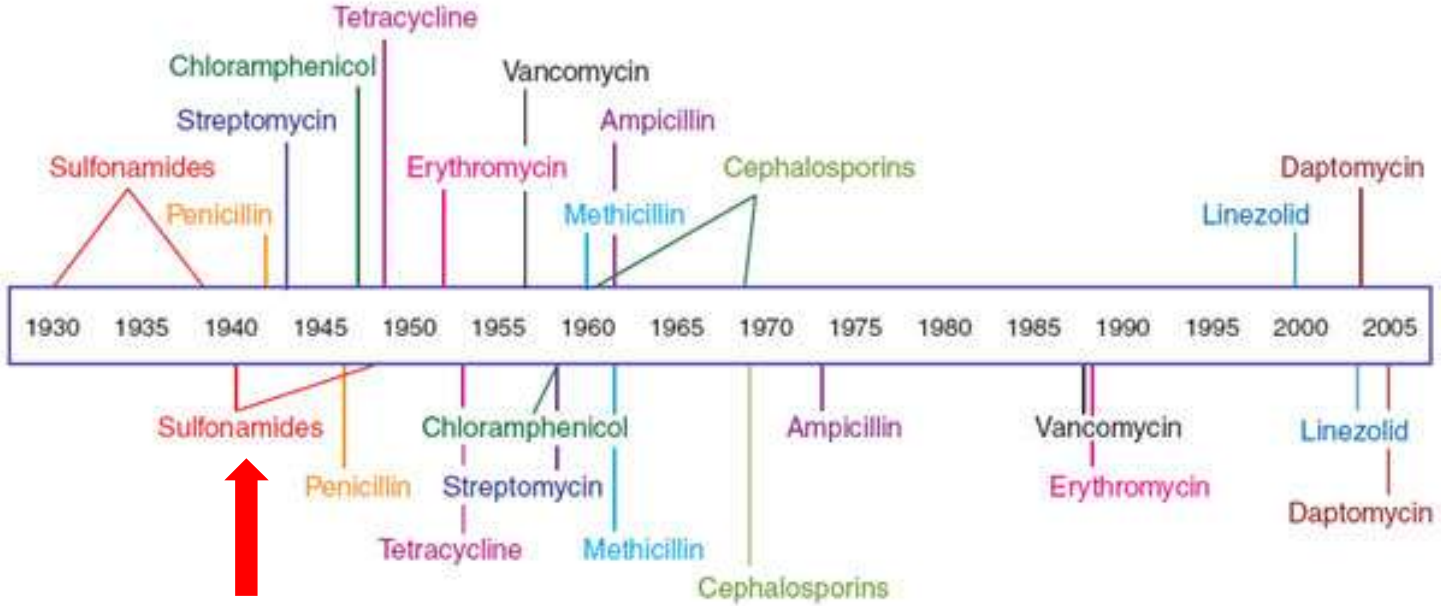


Resistance first observed

Clatworthy et al. Nature Chem Biol 2007:3;541

Antibiotic Resistance Timeline

Antibiotic first used



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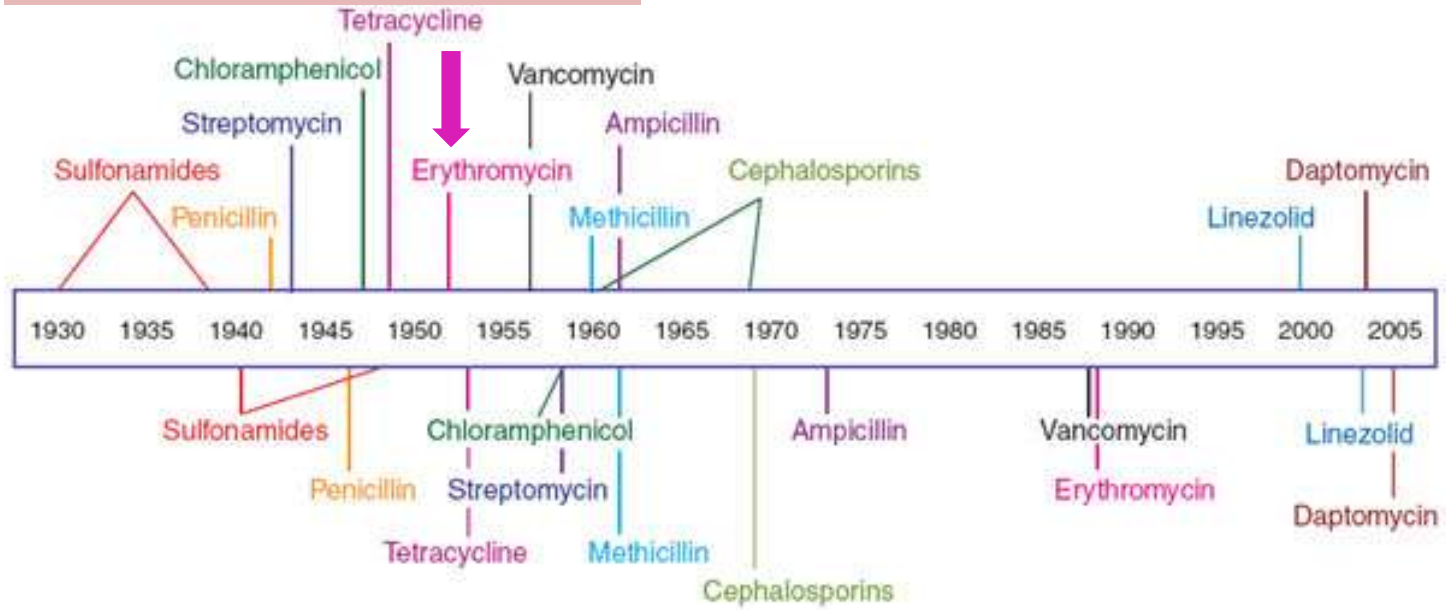

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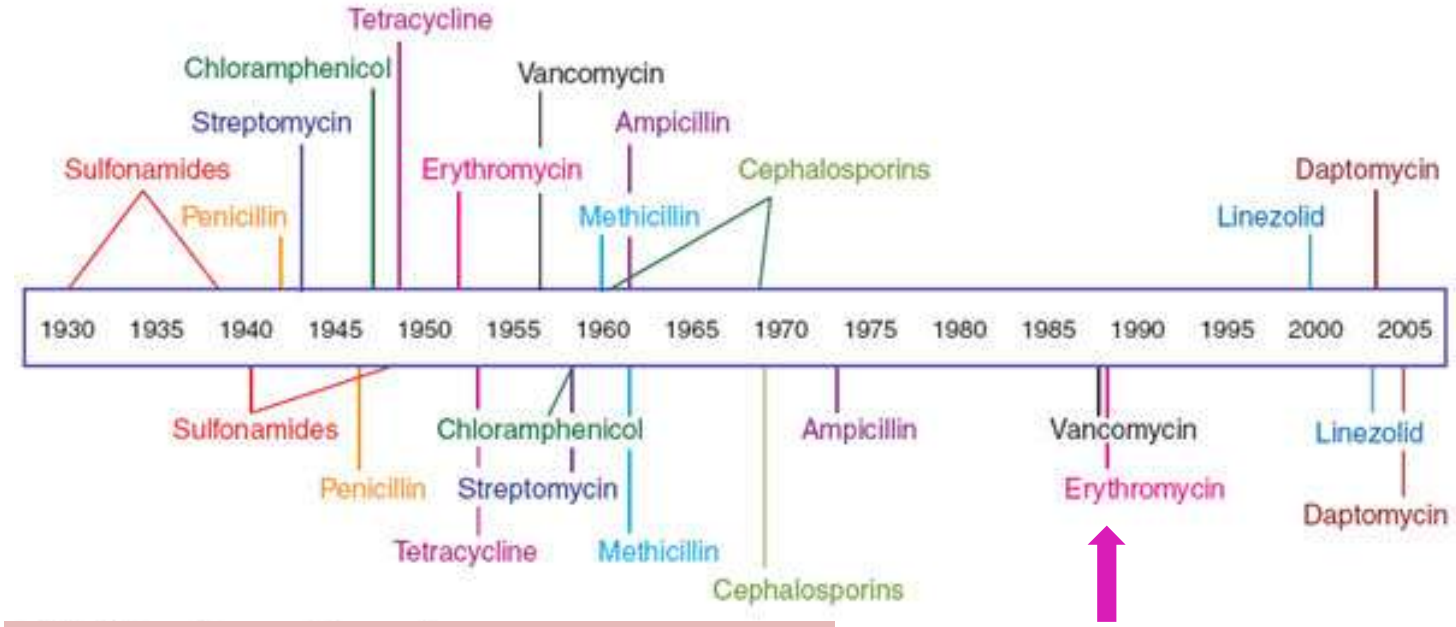
Antibiotic Resistance Timeline

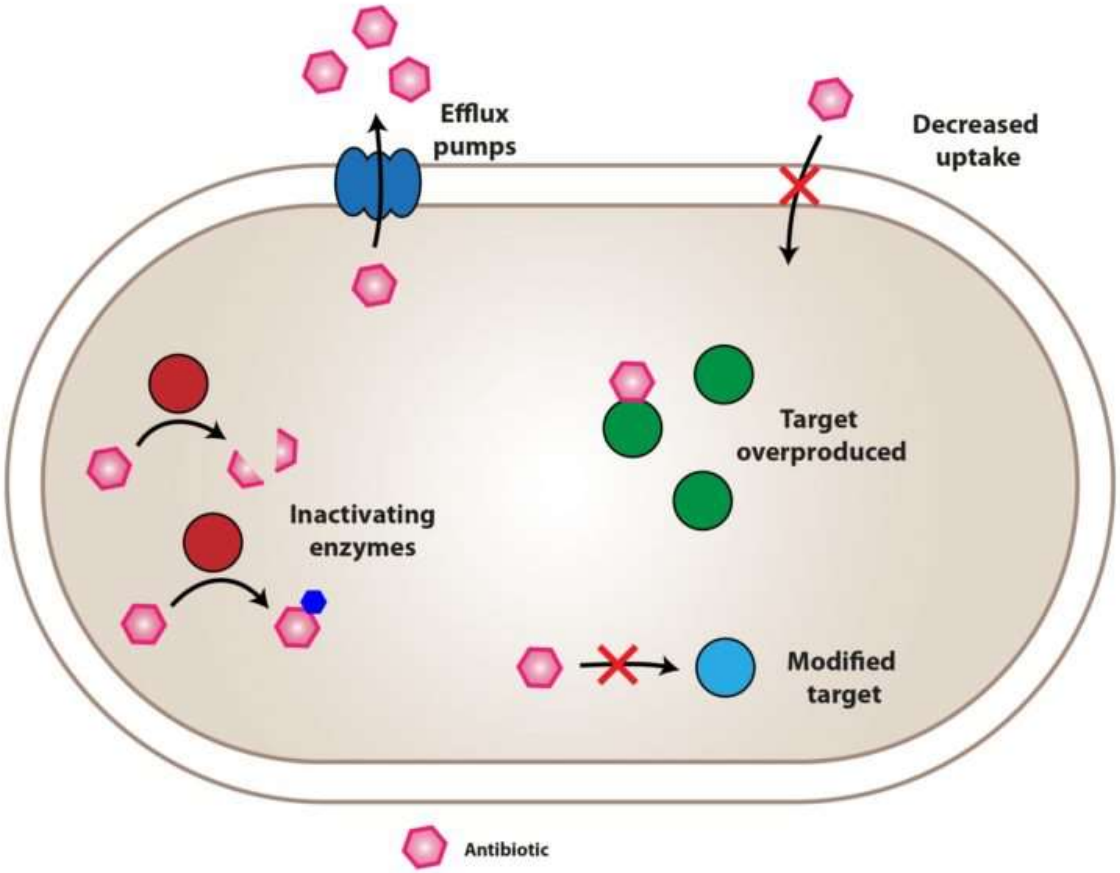
Antibiotic first used



Resistance first observed

Clatworthy et al. Nature Chem Biol 2007:3;541

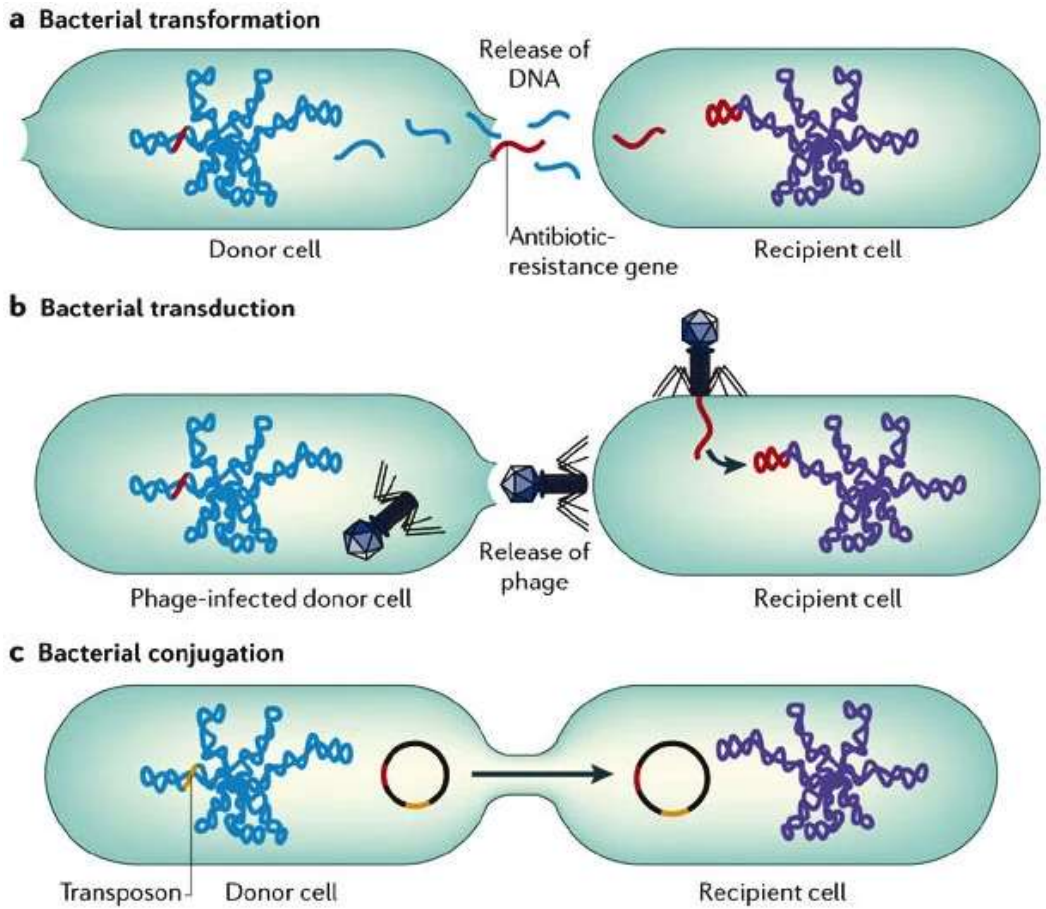
Mechanisms of Resistance in Bacteria



https://www.futurelearn.com/info/courses/introduction-to-bacterial-genomics/0/steps/45329

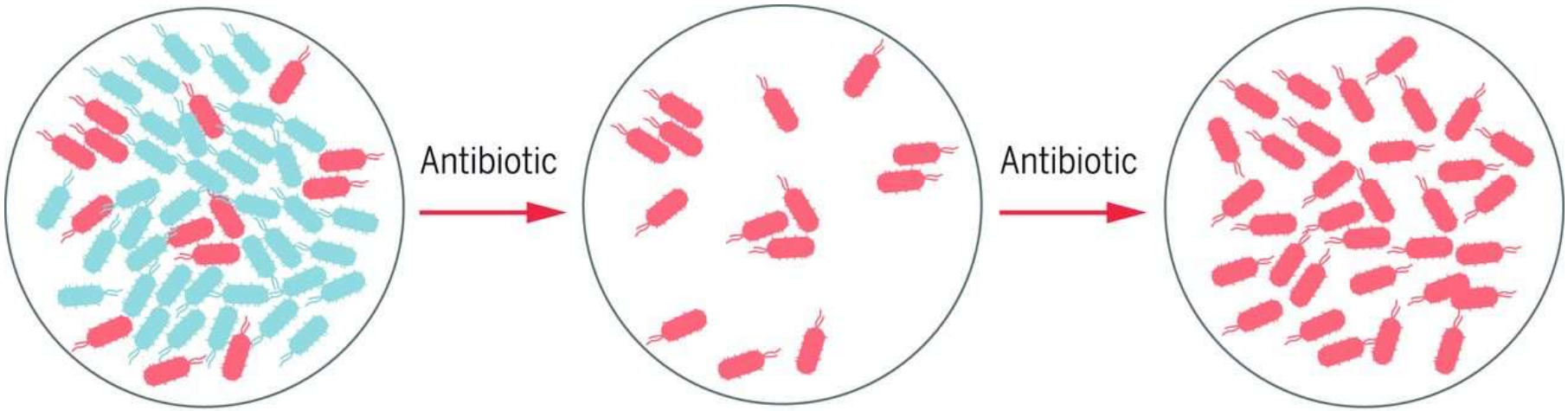
Mechanisms of AMR Gene Sharing in Bacteria

1. Transformation
2. Transduction
3. Conjugation



Furuya, E., Lowy, F. *Nat Rev Microbiol* **4**, 36–45 (2006).

Selection of Antimicrobial Resistance

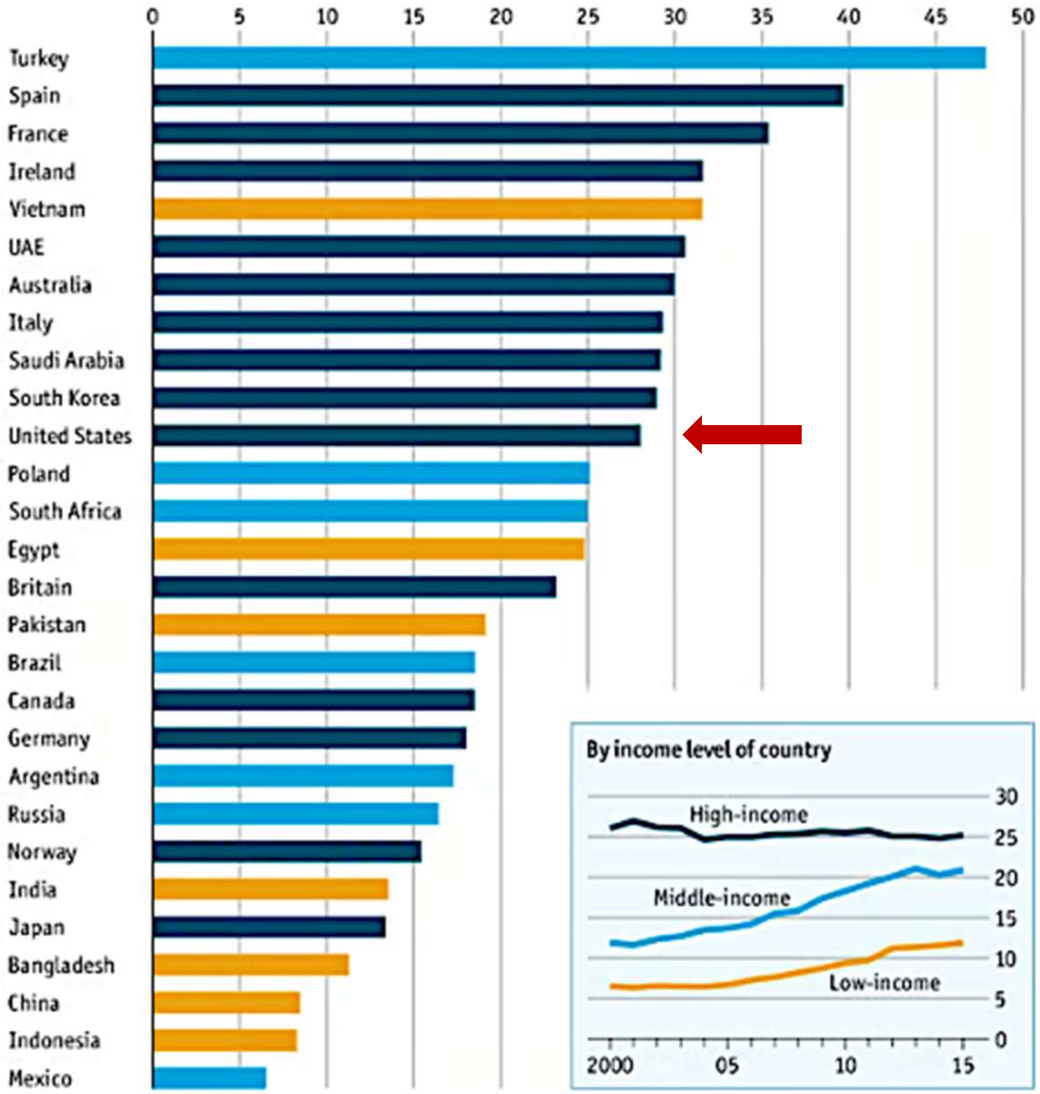


Baym et al. Science, 2016

Drivers of Antimicrobial Resistance

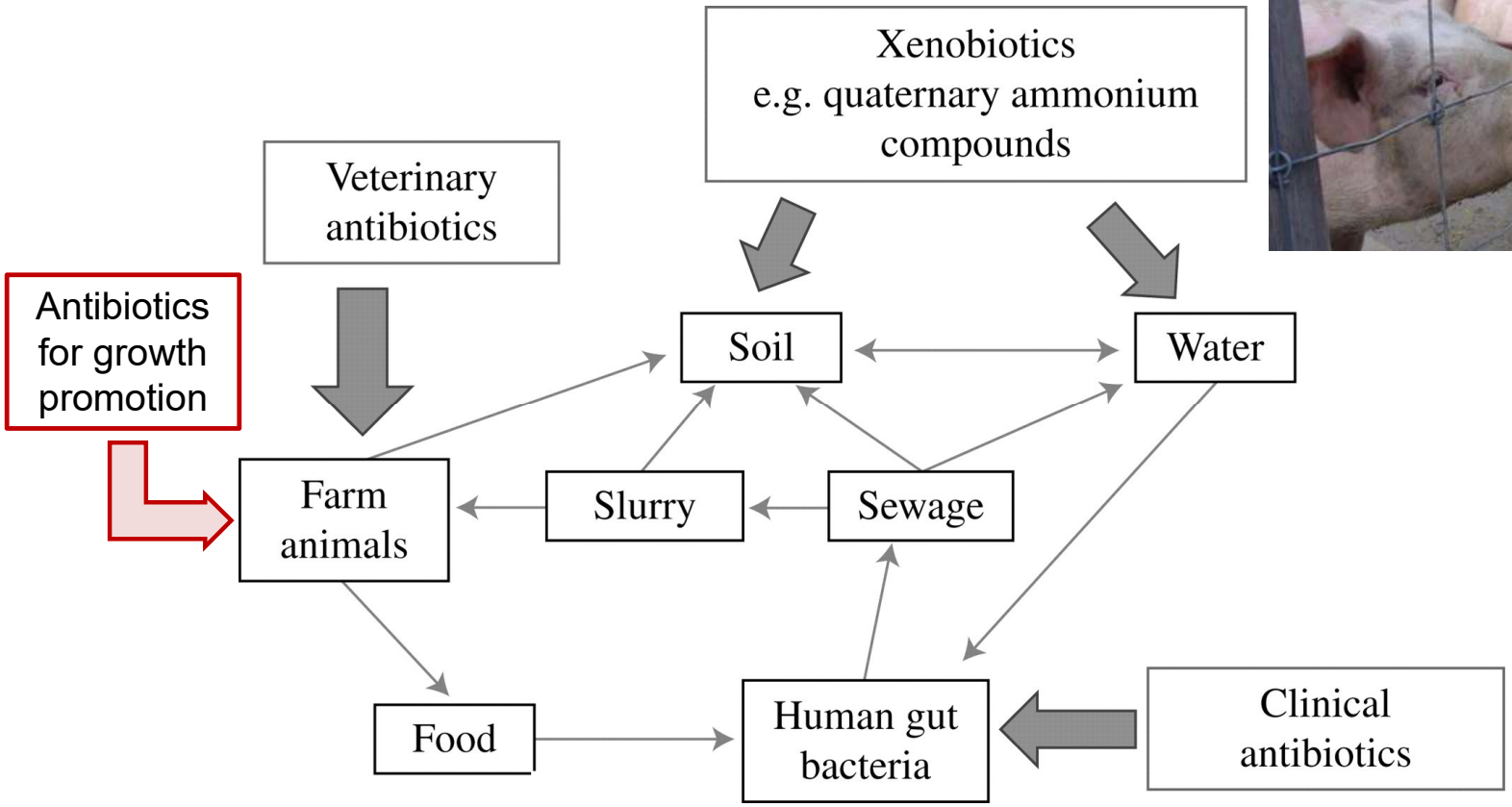
Antibiotic Usage is High Across the World

- Defined daily dose per 1,000 inhabitants per day, 2015 data
- High-income countries have the most antibiotic use
- Largest increases are in low-income countries



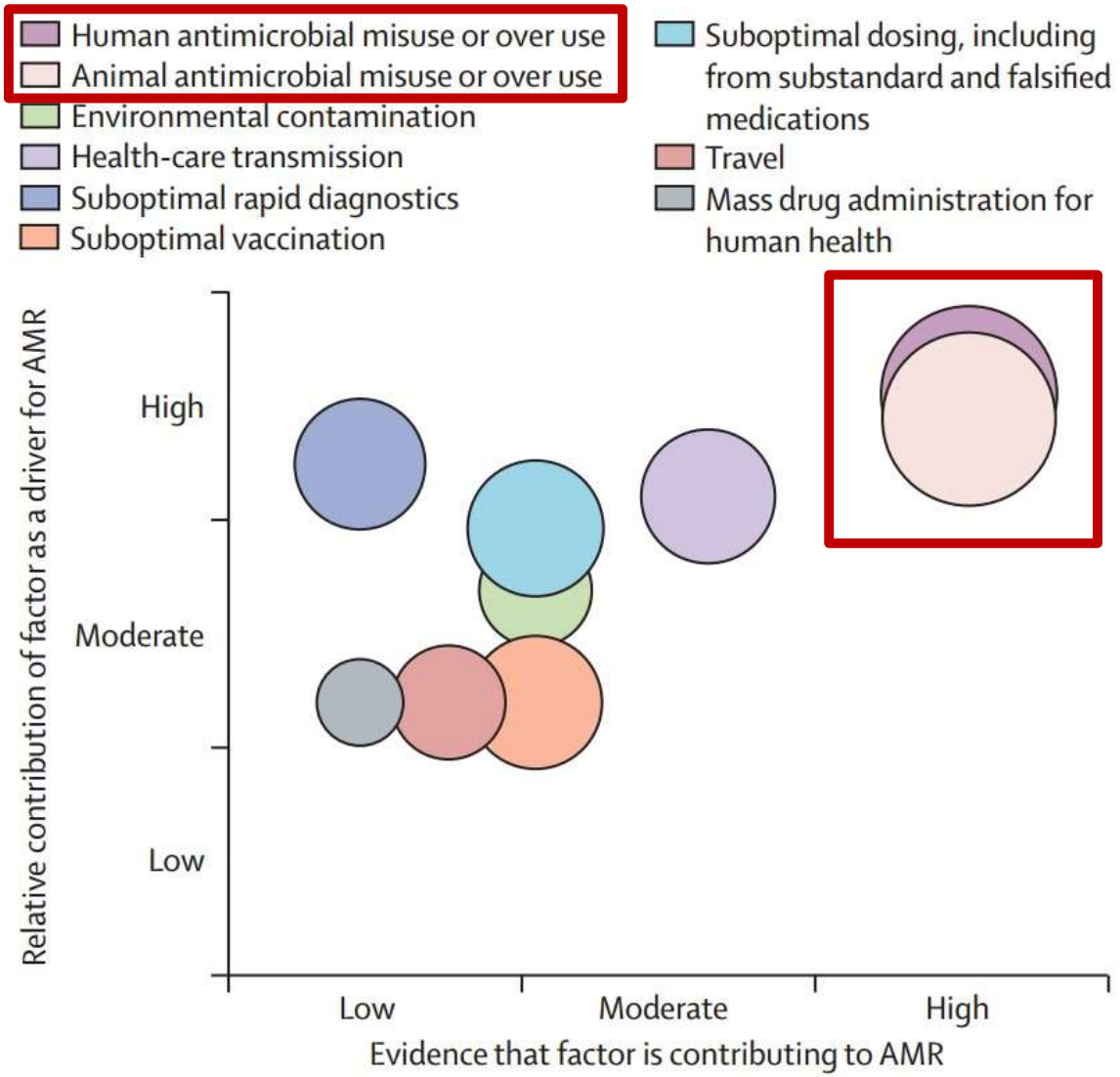
Klein et al. PNAS 2016

Drivers of Resistance



Hawkey et al. JAC 2009;64:i3

Modifiable drivers of antimicrobial resistance



Holmes et al. Lancet, 2016

Risk Factors for Infections with Multidrug-Resistant Organisms (MDROs)

World Health Organization

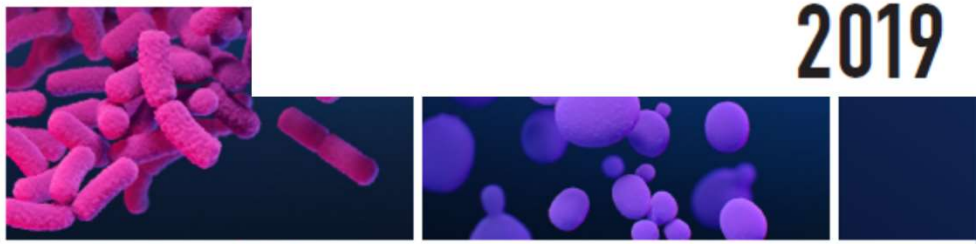
GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

Priority 1: CRITICAL[#]

- ***Acinetobacter baumannii***, carbapenem-resistant *
- ***Pseudomonas aeruginosa***, carbapenem-resistant *
- ***Enterobacteriaceae****, carbapenem-resistant, 3rd generation cephalosporin-resistant *

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES

2019



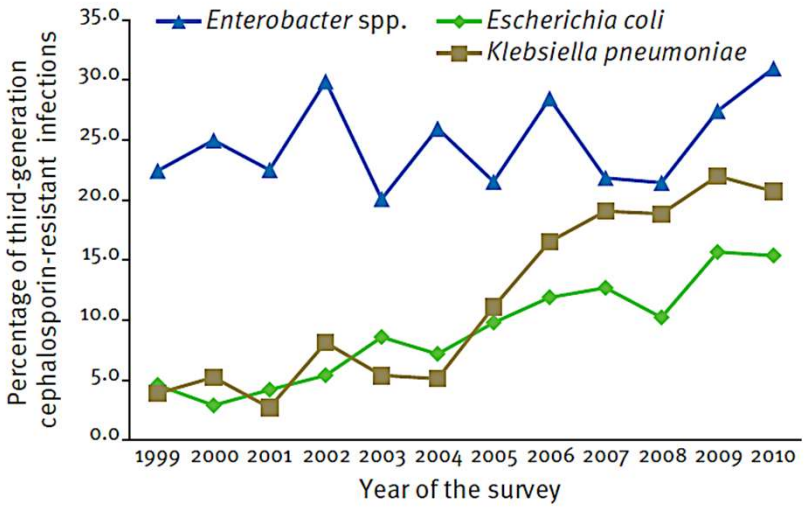
Urgent Threats

- *Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- *Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

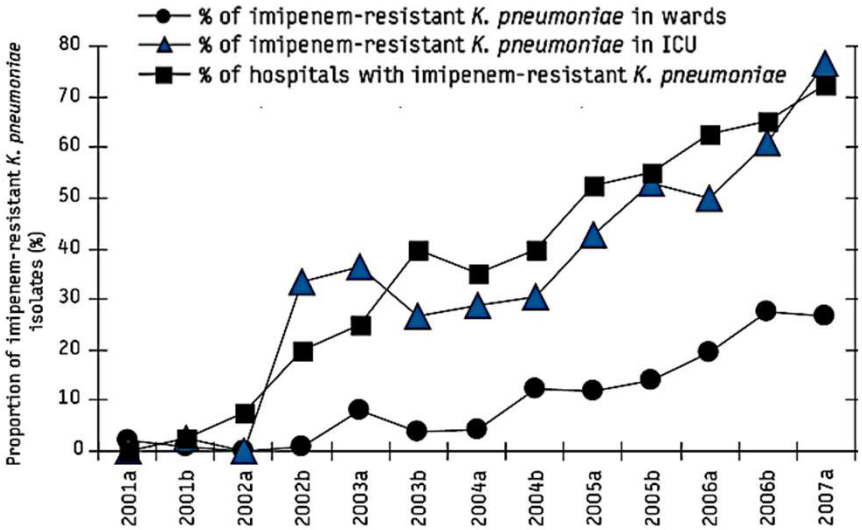
Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- *Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae

Trends in Resistant Enterobacteriaceae



Spain (ESBL)

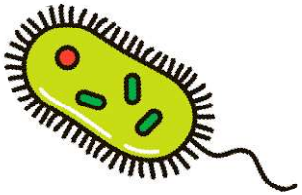


Greece (CRE)

Asensio et al. Eurosurveillance 2011;16:1
Vatopoulos. Eurosurveillance 2008;1-3:1

Risk Factors for Infections with Multidrug-Resistant Organisms (MDROs)

HOST (patient) → procedures, immune suppression, etc



ENVIRONMENT

1. Community
2. Acute care facilities
3. Long-term care facilities

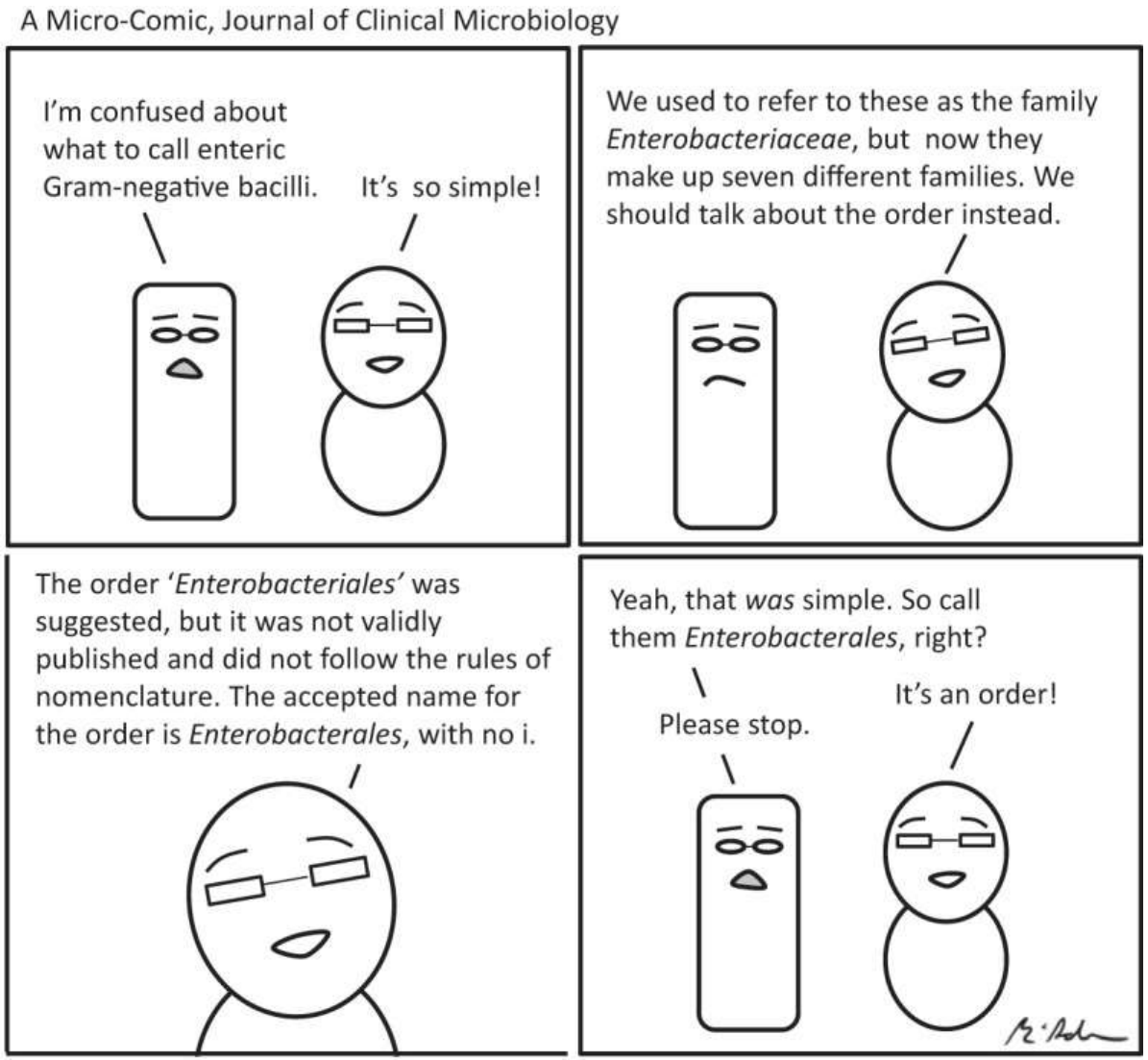
ORGANISM

1. Antimicrobial resistance
2. Virulence
3. Persistence

But first some definitions…

Focus of AMR Lecture: GNRs

- Two primary types of GNRs
  - Fermenters: Enterobacteriaceae/Enterobacterales* (gut-associated)
  - Non-fermenters: Environment-associated organisms (water, surfaces, etc)



J Clin Microbiol. 2020 Feb; 58(2): e01888-19.

Focus of AMR Lecture: GNRs

- Two primary types of GNRs
  - Fermenters: Enterobacteriaceae/Enterobacterales (gut-associated)
  - Non-fermenters: Environment-associated organisms (water, surfaces, etc)

- Two primary resistance types discussed today
  - Extended-spectrum beta-lactamases (ESBL)
    - Define by resistance to 3rd-generation cephalosporins
  - Carbapenem resistance
    - Carbapenem resistant Enterobacterales/Enterobacteriaceae (CRE)
    - Some produce carbapenemases (NDM, KPC)
      - Carbapenemase producing Enterobacterales (CPE)
    - Others result from the combination of multiple drug-resistance mechanisms

ESBL… What's in a Name?

Genotypic ESBL

-presence of ESBL gene

- Whole genome sequencing
- Targeted PCR

Phenotypic "ESBL"

-often a synonym for resistance to extended-spectrum cephalosporins (e.g. ceftriaxone)

-sometimes other phenotypic testing

-NOTE: remember AmpC enzymes

- Chromosomal, inducible (e.g. *Enterobacter cloacae*) vs. plasmid-mediated (e.g. *E. coli*)

ESBL Families

Family	Nomenclature	Characteristics
TEM	Temoneira, the patient infected with the first isolate expressing TEM-1	Point mutation variants of TEM-1 or TEM-2
SHV	Sulfhydryl reagent variable	Point mutation variants of SHV-1
IRT	Inhibitor-resistant TEM	TEM variants that are resistant to inhibition by clavulanate and sulbactam, but do not have ESBL phenotype
CMT	Complex mutant derived from TEM-1	TEM variants that are resistant to inhibition by clavulanate and sulbactam and also have ESBL phenotype
CTX-M	Cefotaxime-hydrolysing β-lactamase isolated in Munich	Derived from the chromosomal β-lactamase from *Kluyvera* spp. Preferentially hydrolyses cefotaxime
GES	Guiana-extended spectrum	More prevalent in *P. aeruginosa* than Enterobacterales Some variants also hydrolyse carbapenems
PER	*Pseudomonas* extended resistant	More prevalent in *P. aeruginosa* and *A. baumannii* than Enterobacterales Inhibition by newer β-lactamase inhibitors is variable
VEB	Vietnam extended-spectrum β-lactamase	Preferentially hydrolyses ceftazidime and aztreonam compared with cefotaxime Inhibition by newer β-lactamase inhibitors is variable
BEL	Belgium extended β-lactamase	Preferentially hydrolyses ceftazidime and aztreonam compared with cefotaxime
TLA	Named after the Tlahuica Indians (Mexico), from whom the first isolate was obtained	Preferentially hydrolyses ceftazidime and aztreonam compared with cefotaxime
SFO	From *Serratia fonticola*	Inducible
OXY	From *Klebsiella oxytoca*	Chromosomally encoded

Castanheira et al. JAC-Antimicrobial Resistance 2021:3(3) https://doi.org/10.1093/jacamr/dla

CDC-Defined CRE

US Centers for Disease Control and Prevention (CDC)

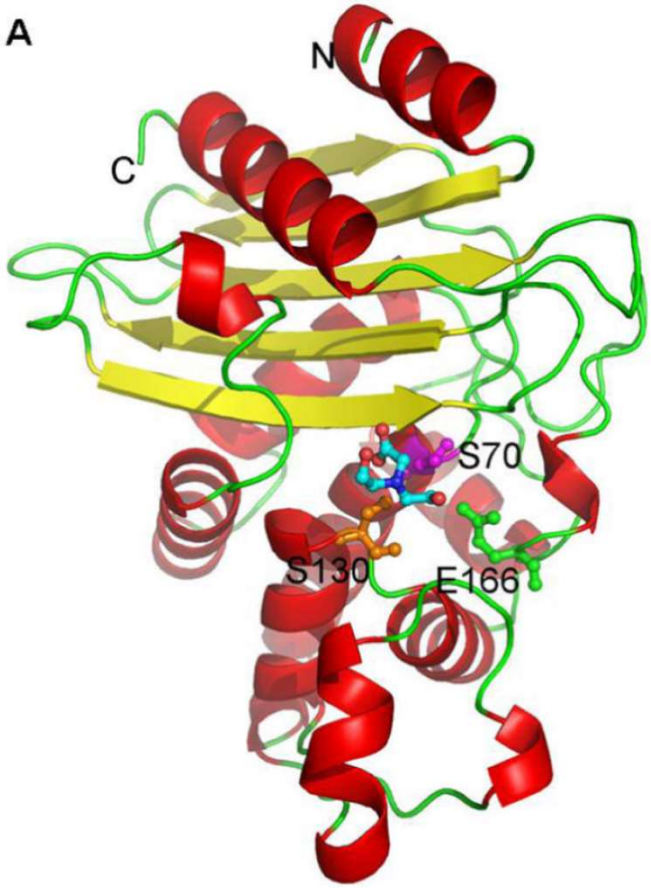
- 2012 CRE definition:
  - *Non-susceptible* to imipenem, meropenem, OR doripenem (MIC > 1 mcg/ml), AND
  - resistant to all 3rd gen. cephalosporins tested

- 2015 (current) CRE definition:
  - *Resistant* to imipenem, meropenem, doripenem (MIC ≥4 mcg/ml), AND/OR *ertapenem* (MIC ≥2 mcg/ml) AND/*OR*
  - Documented to produce carbapenemase

"CRE" ≠ Carbapenemase Production (CPE)

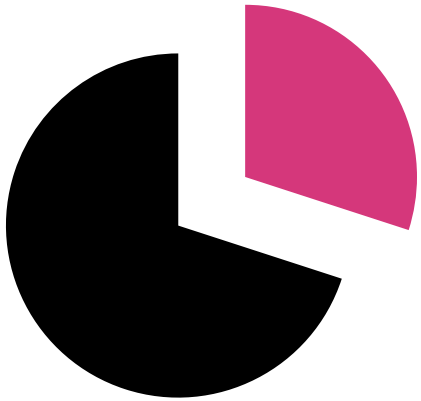
Carbapenemases

- KPC: Most common carbapenemase encountered in Enterobacterales in US
  - 13 variants; KPC-2 and KPC-3 most common
  - Class A serine-carbapenemase
  - Hydrolyzes carbapenems, cephalosporins, penicillins, aztreonam
- Other carbapenemases much less common in US
  - NDM, OXA, VIM, etc
  - Serine- and metallo-carbapenemases



Ke et al. Biochem 2007;46:5732

Rising threat from multidrug-resistant Gram-negative bacteria (MDR-GNR) in the hospital



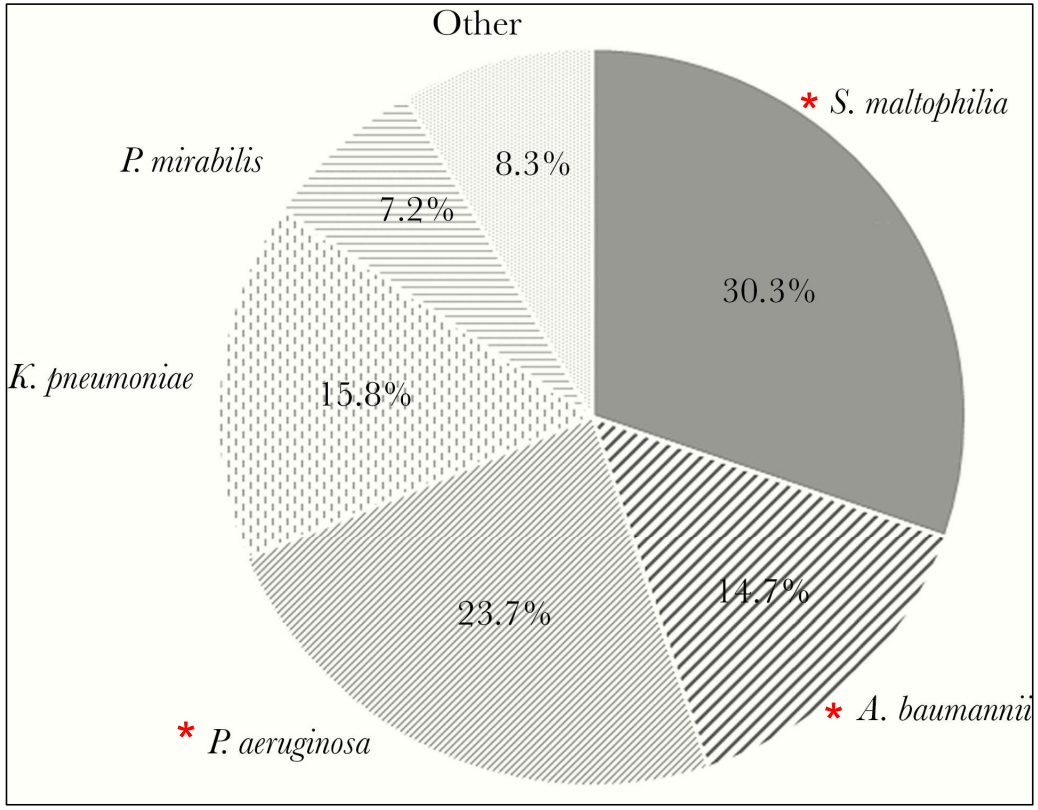
% of all HAI caused by GNBs

% of ICU HAI caused by GNBs

Non-fermenters	***Acinetobacter baumannii*** ***Pseudomonas aeruginosa*** ***Stenotrophomonas maltophilia***
Enterobacteriaceae	*Klebsiella pneumoniae* *Escherichia coli* *Enterobacter cloacae*

Hidron et al. *Infect Control Hosp Epidemiol* 2008;29:966-1011.
Peleg & Hooper. *N Engl J Med* 2010;362:1804-1813.

Carbapenem-resistant (CR), gram-negative pathogens causing bacteremia in the United States



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Risk factors & at-risk population

	Enterobacteriaceae	Non-fermenters
Risk factors	LOS ICU stay Catheters / devices Ventilation Prior antibiotics **Travel**	LOS ICU stay Catheters / devices Ventilation Prior antibiotics **Trauma (esp. burns)**
At-risk population	Acute settings Recent travel to areas of high prevalence Potential for community spread	High-risk patients Esp in ICU and burn units Rarely community-acquired infection.

ECDC CPE risk assessment, 2011.
Peleg *et al. Clin Microbiol Rev* 2008;21:538-582.

Risk factors are common across many MDR-pathogens

Risk Factors	Odds Ratio or Relative Risk (References)			
	Methicillin-Resistant *Staphylococcus aureus* (11, 12, 16–26)	**Vancomycin-Resistant Enterococcus (27–48)**	**Extended-Spectrum β-Lactamase–Producing Gram-Negative Bacilli (49–57)**	***Clostridium difficile* (58–77)**
Advanced age	1.2 to 1.3 (17, 23)	2.6 (45)	NS (49, 51, 54, 56)	1.0 to 14.1 (60, 69, 74, 77)
Underlying disease			† (51), NS (49, 56, 57)	
Renal failure	† (12, 17, 18, 22, 23, 26)	4.4 to 6.98 (35, 42)		1.71 to 6.7 (66, 76)
Hematologic cancer	† (12, 17, 23, 26), NS (22)	8.4 (33)		
Hepatic failure	† (12, 17, 23, 26)			
Severity of illness‡	1.9 (24)	2.3 to 6.1 (29, 30, 32, 47)	11.6 (53)	2.0 (63)
Interhospital transfer of a patient; patient from a nursing home	6.9 (24)	4.1 to 2.9 (32, 45)	3.6 (52)	3.1 (66)
Extended length of stay	1.7 to 17.5 (16–19, 21–23, 25, 26)	1.1 to 2.9 (28, 31–34, 38, 44)	1.1 to 9.0 (49, 50, 57)	1.3 to 3.6 (62, 67, 75)

Safdar & Maki. Ann Intern Med 2002;136:834

Endoscope-related outbreaks

EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Gastrointestinal Endoscopes
A Need to Shift From Disinfection to Sterilization?

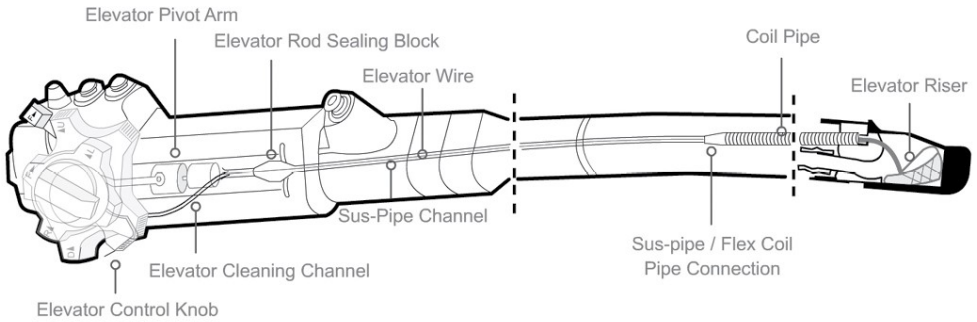
William A. Rutala, PhD, MPH; David J. Weber, MD, MPH

Several outbreaks featuring carbapenemase-producing Enterobacteriaceae

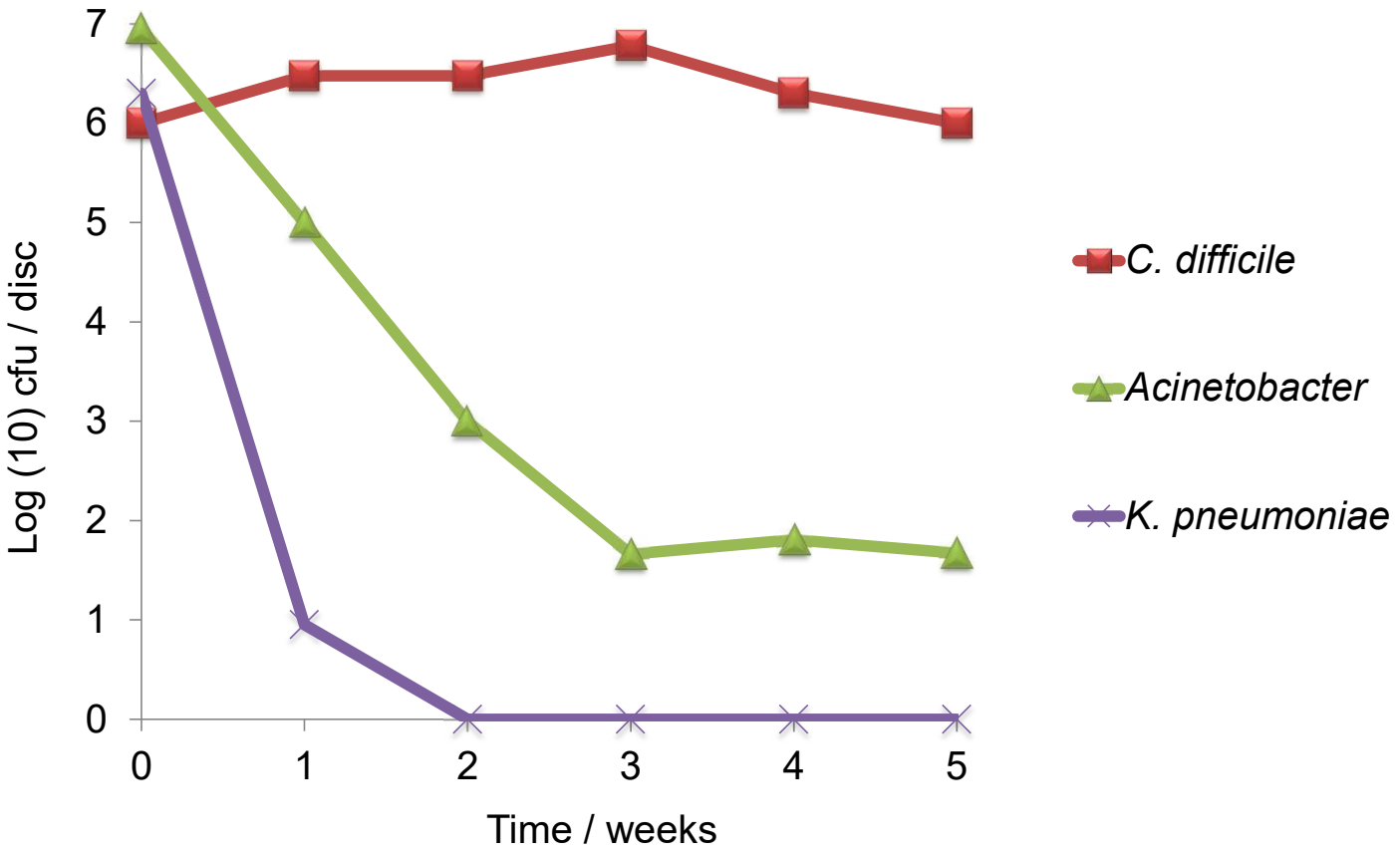
-NDM and KPC carbapenemase genes

-possibly related to elevator channel in scopes

-likely “tip of the iceberg”

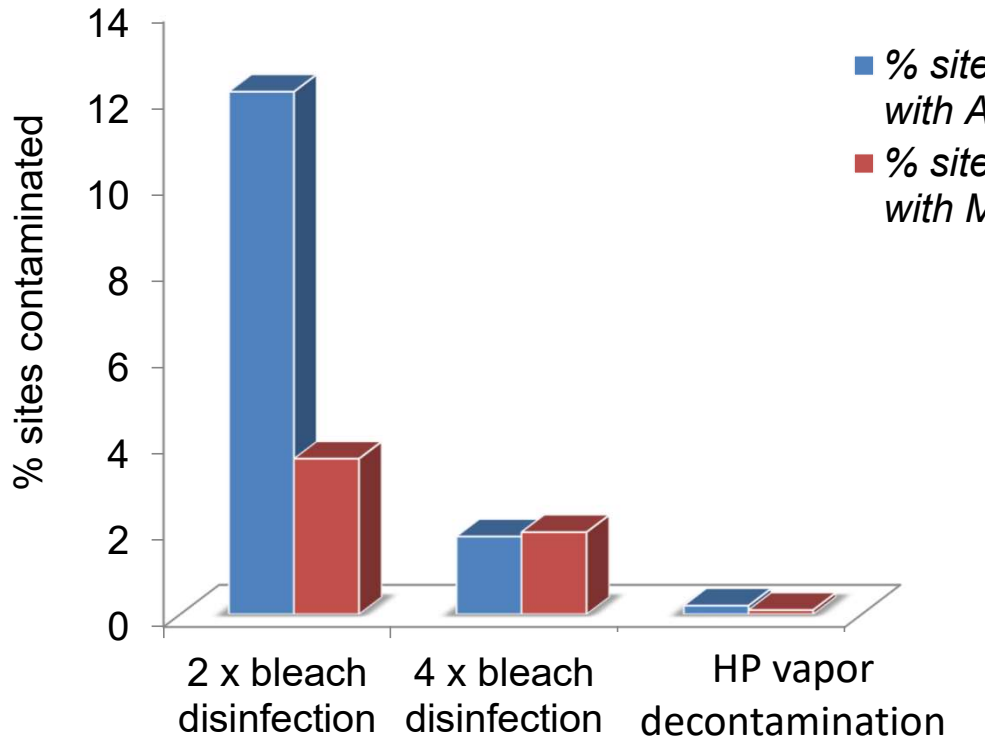


Organisms and persistent contamination: Surface survival



Otter & French. *J Clin Microbiol* 2009;47:205-207.

Persistent contamination with *Acinetobacter baumanii*

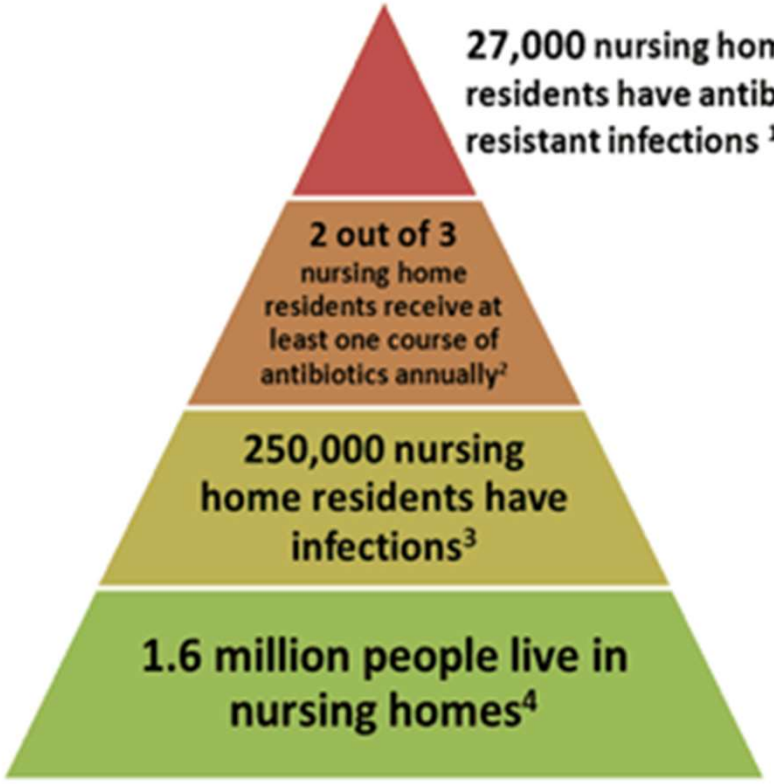


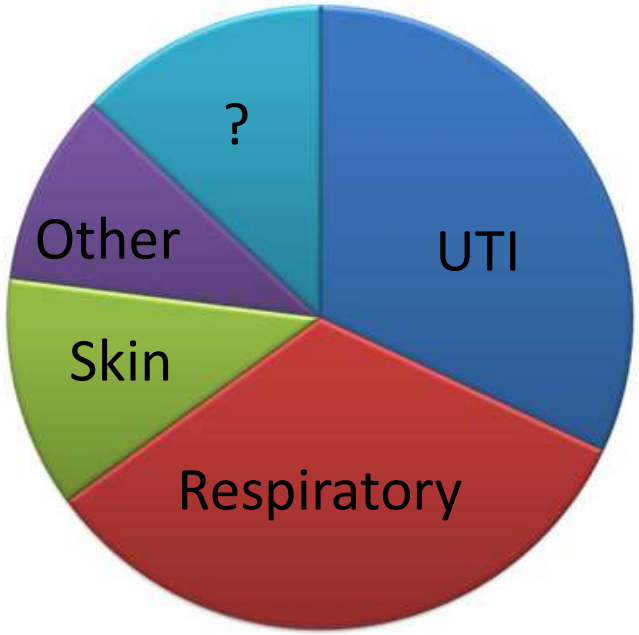
- 140 samples, 9 rooms after 2xbleach
- 5705 samples, 312 rooms after 4xbleach
- 2680 samples, 134 rooms after HP vapor

26.6% of rooms remained contaminated with either MRSA or *A. baumannii* following 4 rounds of bleach disinfection

Manian *et al. Infect Control Hosp Epidemiol* 2011;32:667-672.

The Nursing Home Pyramid

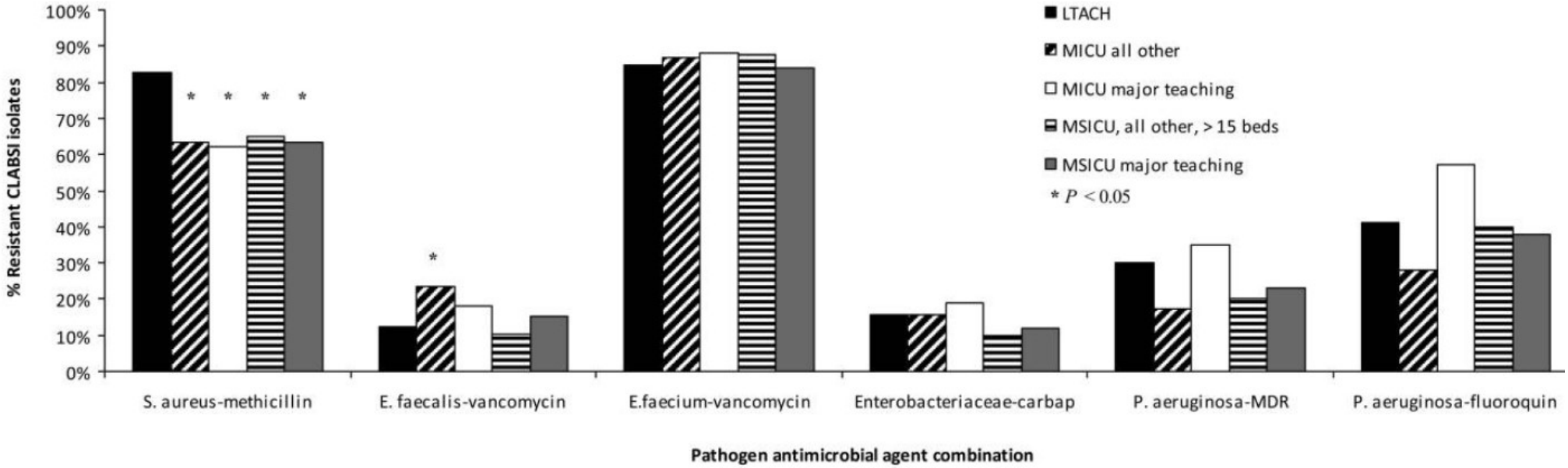




Most commonly-treated infections in NHs

Source: cdc.gov

Prevalence of MDROs in Long Term Acute Care Facilities Similar to ICUs



Chitnis et al. ICHE 2012;33:993

ESBL-producing Enterobacterales/ Enterobacteriaceae

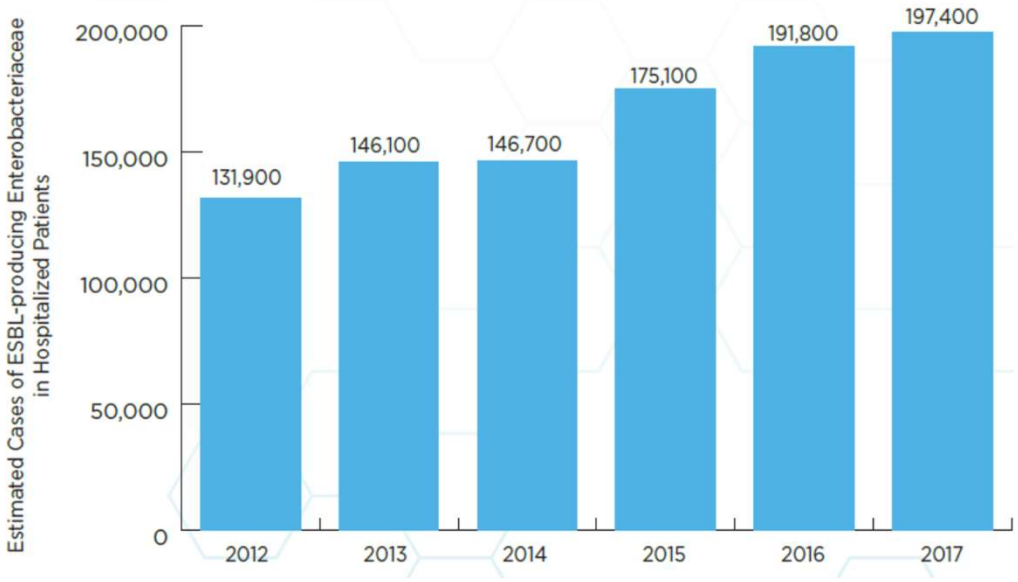
EXTENDED-SPECTRUM BETA-LACTAMASE (ESBL) PRODUCING ENTEROBACTERIACEAE

THREAT LEVEL **SERIOUS**

197,400 Estimated cases in hospitalized patients in 2017

9,100 Estimated deaths in 2017

$1.2B Estimated attributable healthcare costs in 2017



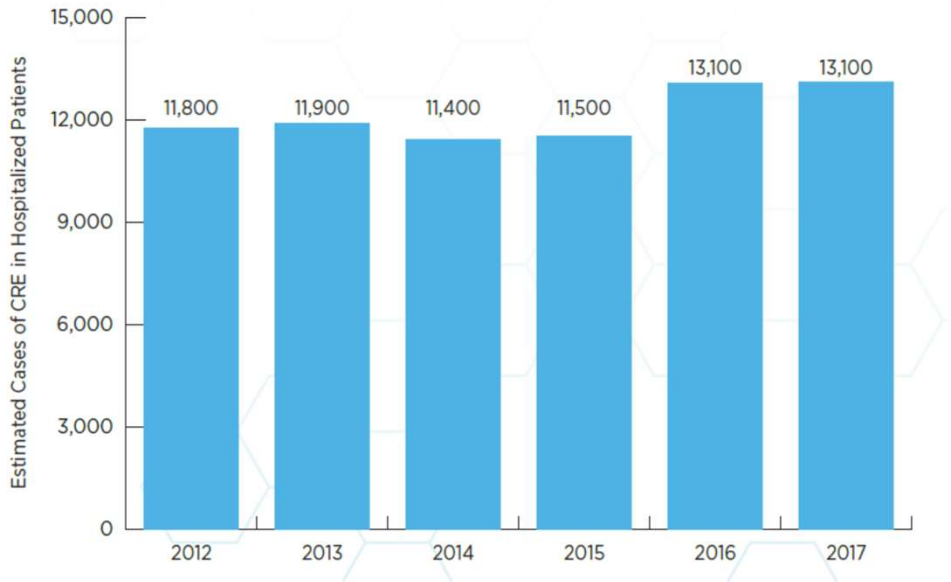
CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

THREAT LEVEL **URGENT**

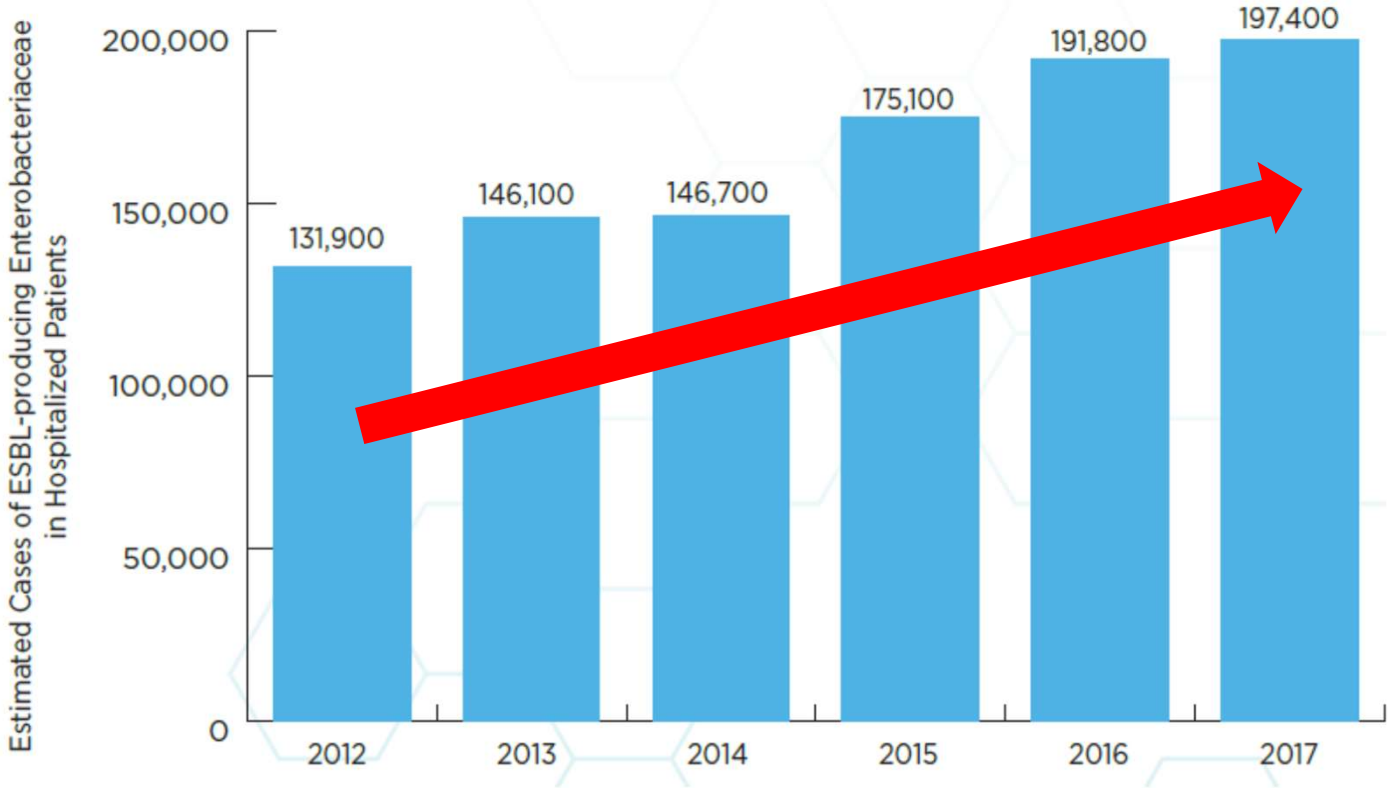
13,100 Estimated cases in hospitalized patients in 2017

1,100 Estimated deaths in 2017

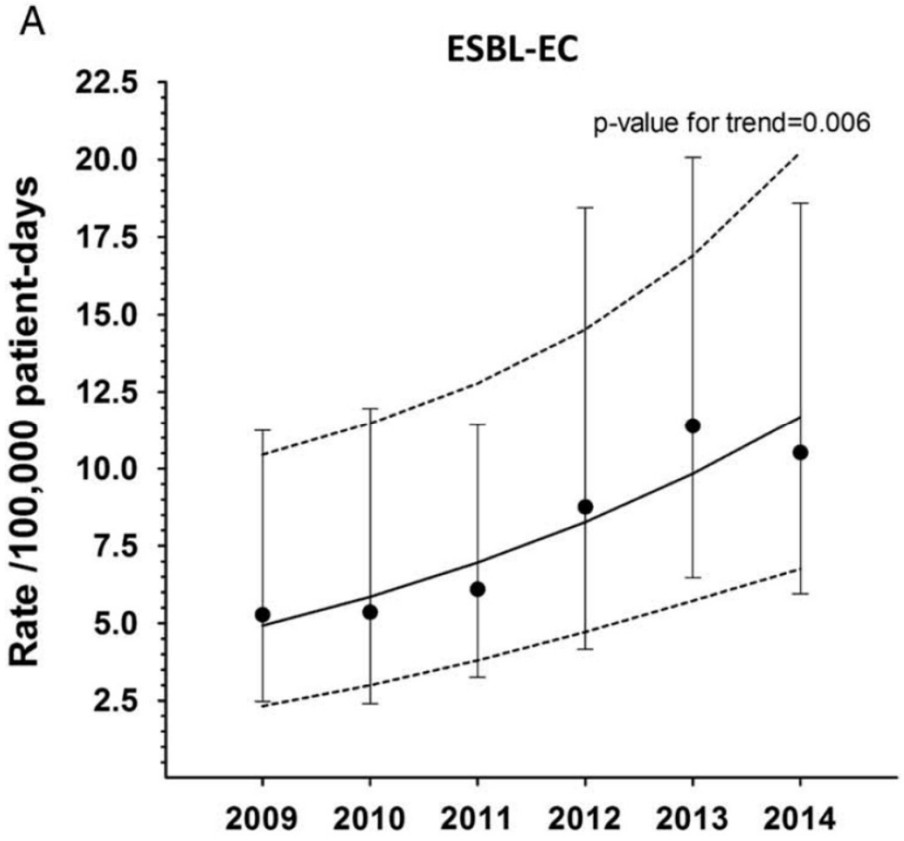
$130M Estimated attributable healthcare costs in 2017



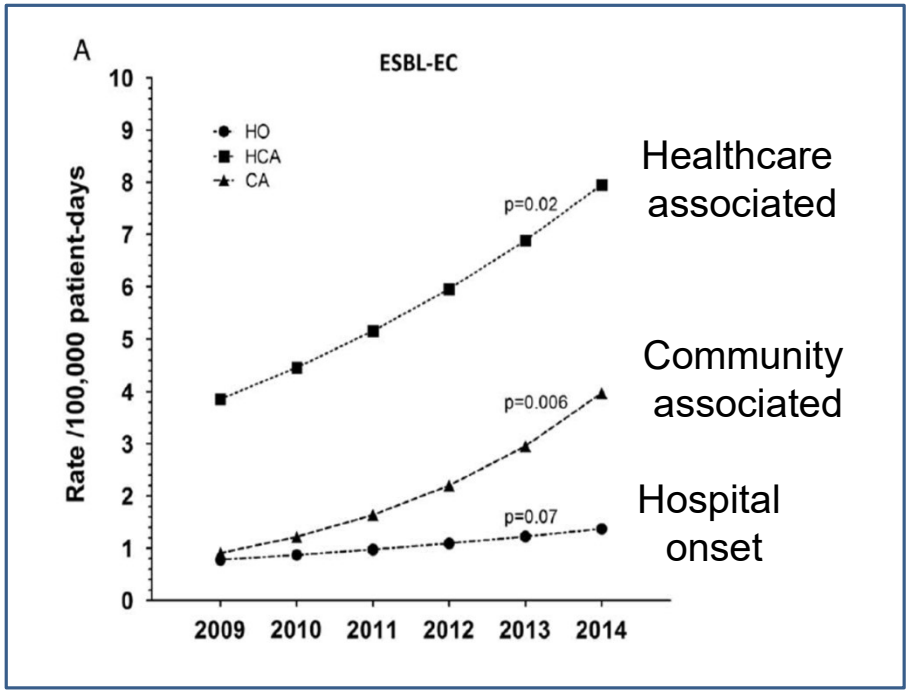
CDC estimate of “ESBL-producing Enterobacterales”



Community Spread of ESBL-*E.coli*

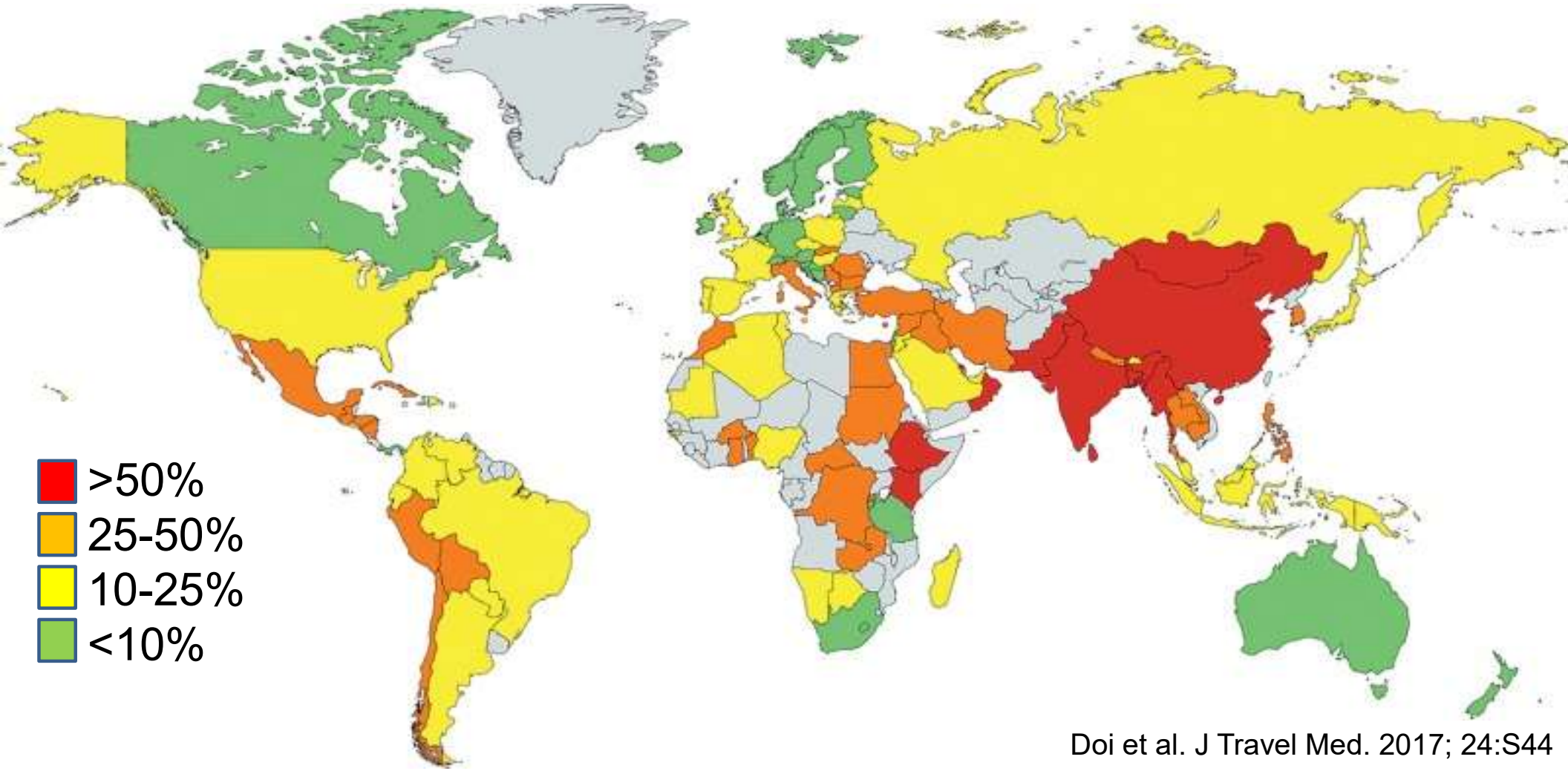


- 26 community hospitals
- Southeastern US



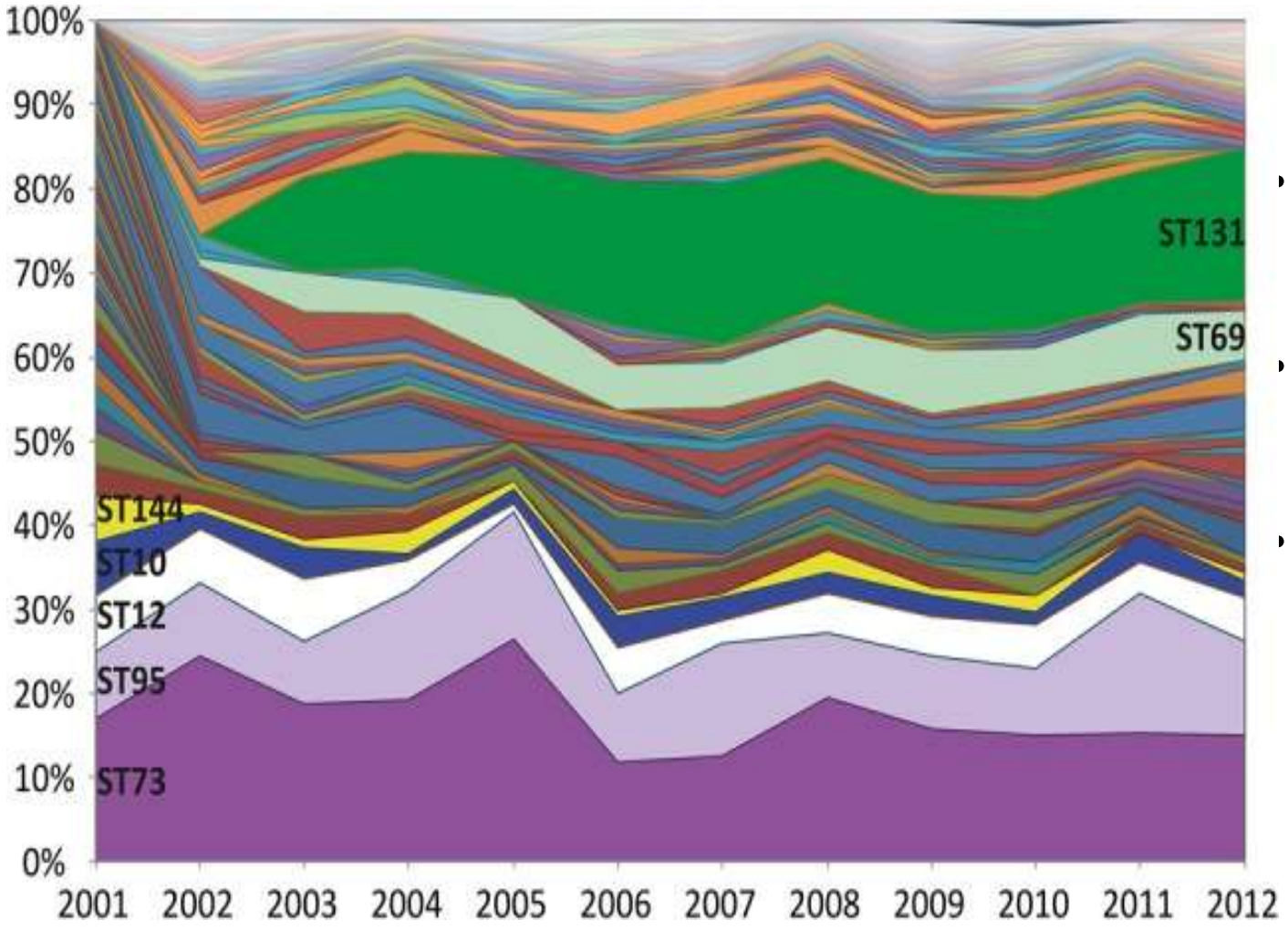
Thaden et al. ICHE 2016:37(1);49

Rates of ESBL producers among clinical *E. coli* isolates (2014 WHO data)



Doi et al. J Travel Med. 2017; 24:S44

Sequence Type (ST) 131 *E. coli*



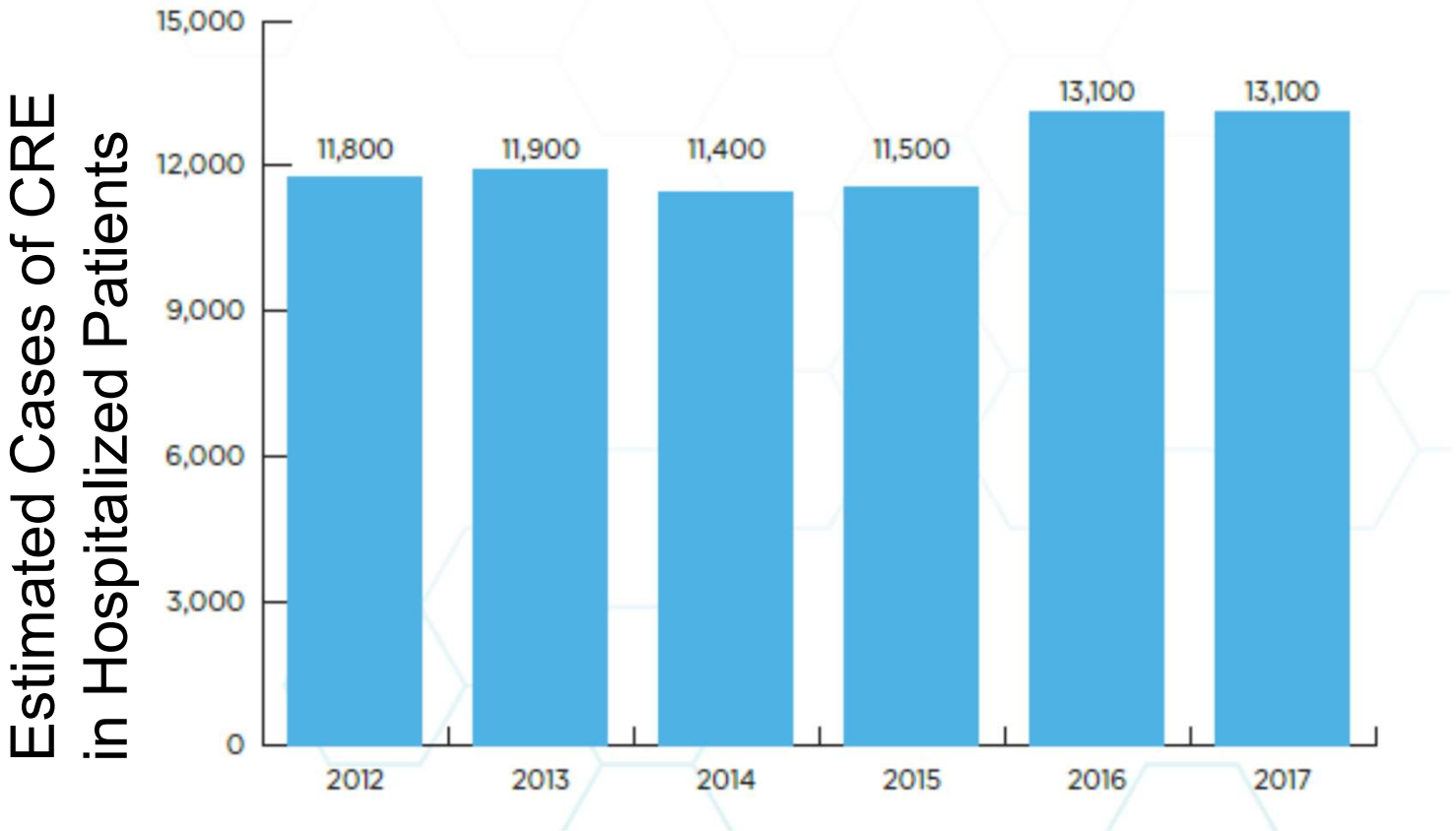
Triple Threat

- Resistance
  - Fluoroquinolones
  - ESBL (CTX-M-15)
- Virulence
  - 10 commonly shared virulence genes
- Transmissibility
  - Many documented community transmission cases
  - Animal/food sources

Nicolas-Chanoine et al. CMR 2014;27(3):543
Kallonen et al. Genome Res 2017;27(8):1437

Carbapenem-Resistant Enterobacterales/Enterobacteriaceae

CDC Estimates of CRE in US

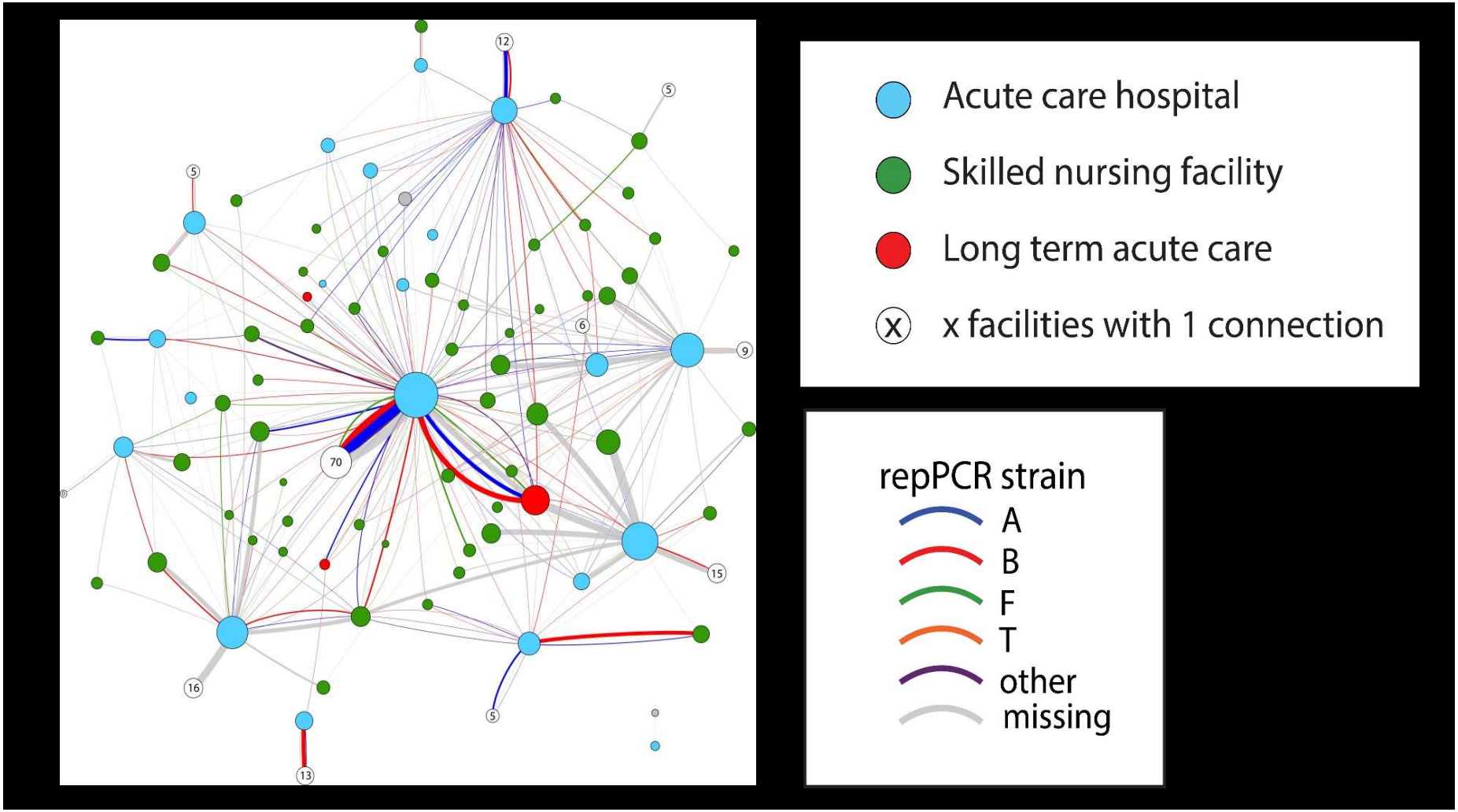


High Connectivity of Facilities with CRE Patients

CRACKLE-1: Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae.

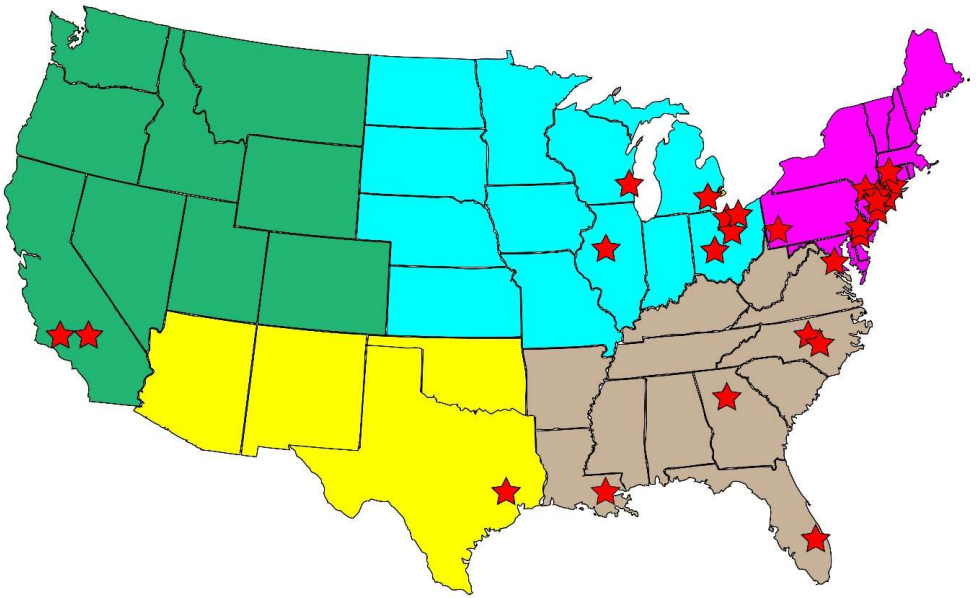
- Study sites in Ohio, Pennsylvania, Michigan, and North Carolina.
- Study period 12/24/2011 until 6/30/2016
- All hospitalized patients with clinical culture positive for carbapenem-resistant *K. pneumoniae* (CRKP) were included
- Rep-PCR for molecular strain typing on all available isolates
- Network analyses at the facility and individual level were performed

Network: Facilities



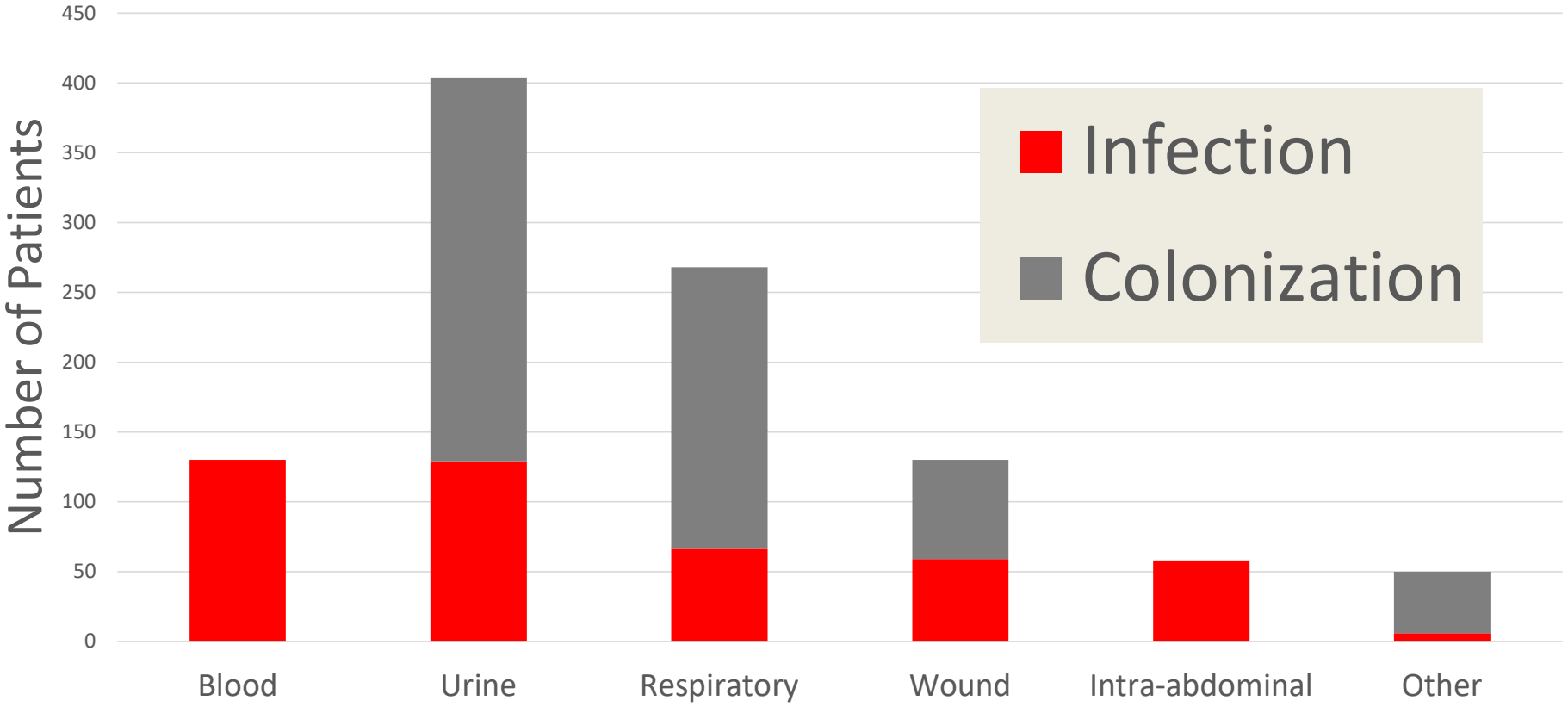
CRE in US (CRACKLE-2 data)

- Prospective, observational, multi-center, cohort study
- 2016-2017
- Consecutive hospitalized patients with CDC-defined CRE
- Analysis of first unique 1,040 patients from 49 US medical centers



van Duin et al. Lancet ID 2020; 20(6):731-741.

Distribution of Culture Sources



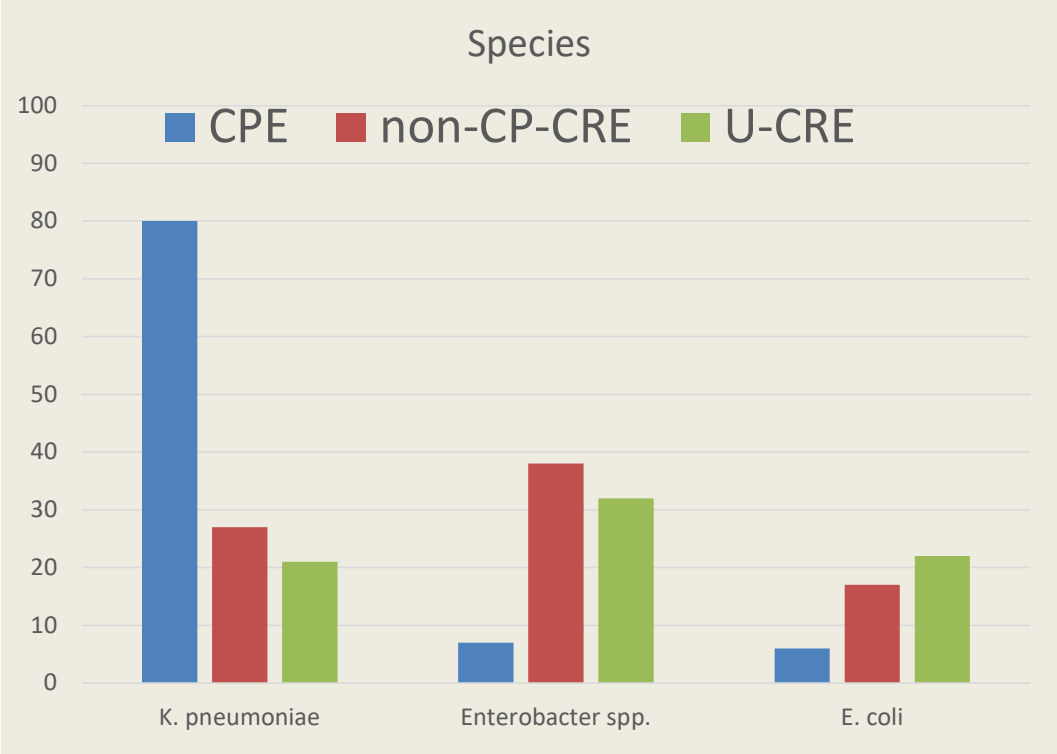
CDC-CRE: 3 subsets

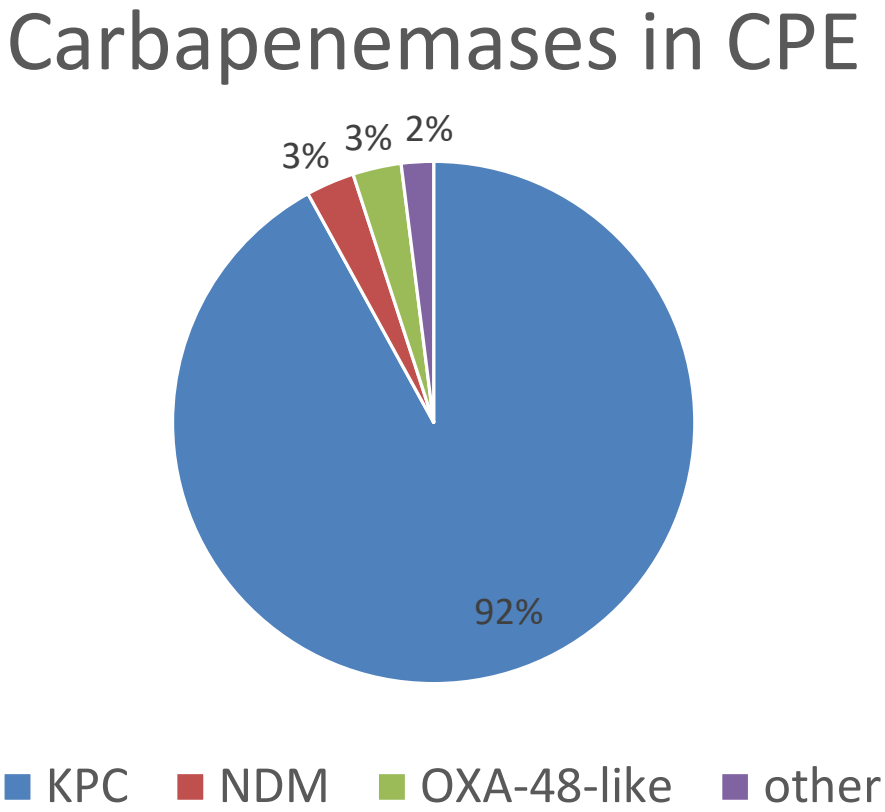
All isolates met CDC criteria for CRE at local micro lab

- **CPE**: Carbapenemase-producing Enterobacterales
  - Carbapenemase gene present on whole genome sequencing and/or targeted PCR
- **Non-CP-CRE**: Non-carbapenemase-producing CRE
  - No carbapenemase gene present
  - Carbapenem resistance confirmed in central laboratory
- **U-CRE**: "Unconfirmed" CRE
  - No carbapenemase gene present
  - Carbapenem susceptible in central laboratory (resistant by local testing)

van Duin et al. Lancet ID 2020; 20(6):731-741.

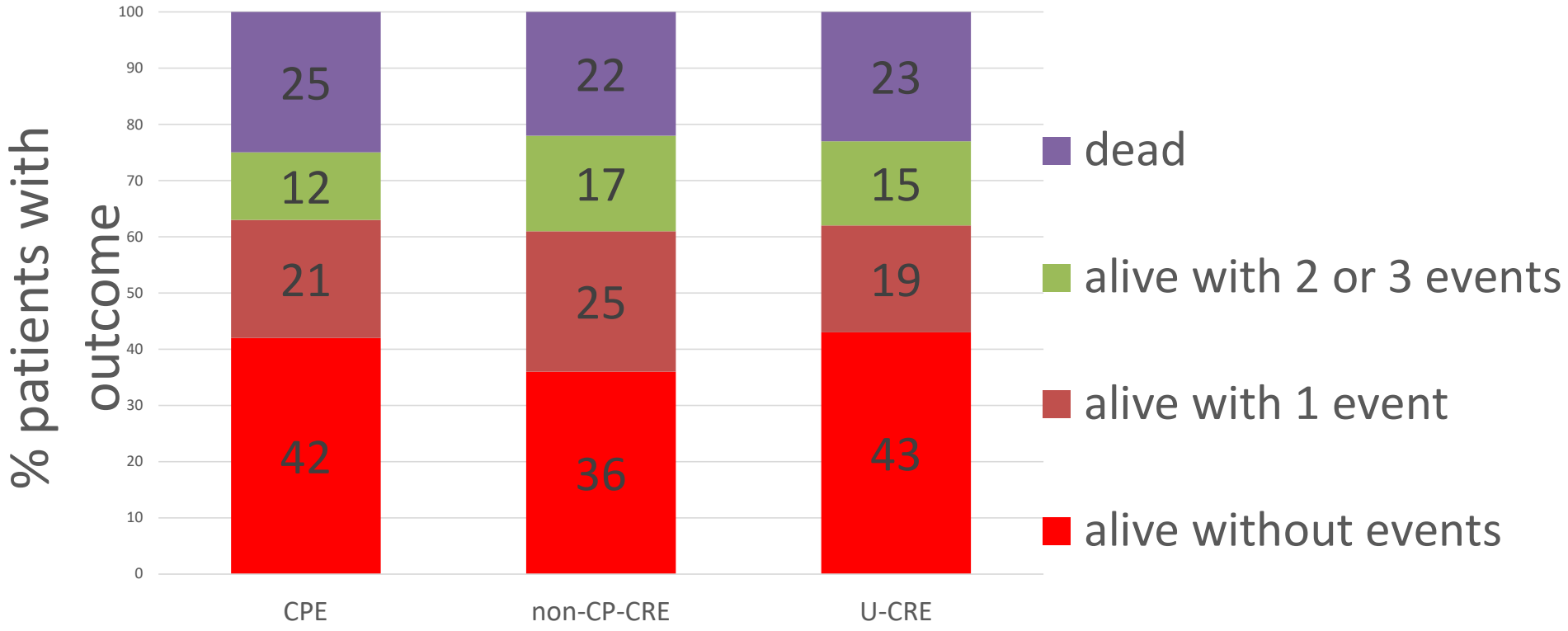
Species with Carbapenemases





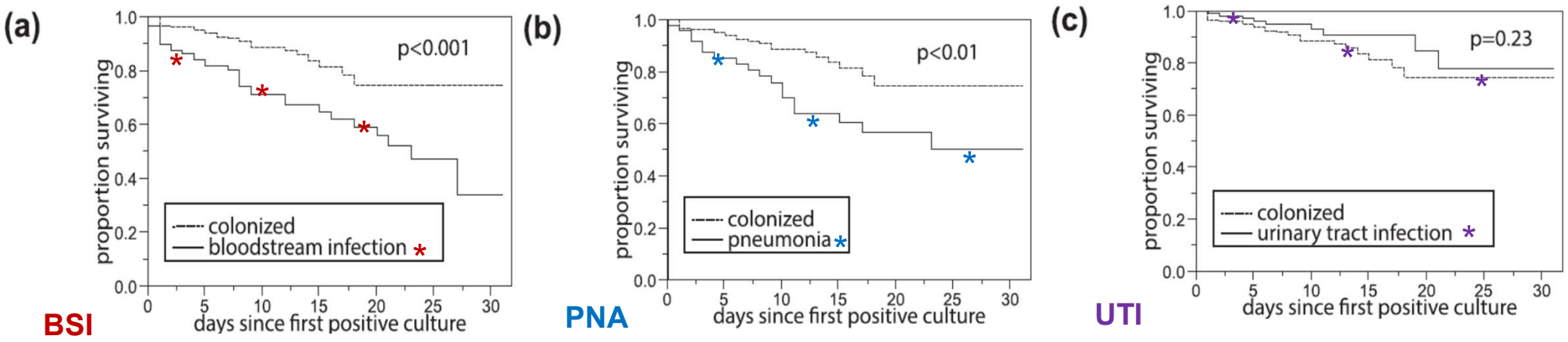
van Duin et al. Lancet ID 2020; 20(6):731-741.

Outcomes are Similar in All Three Patient Groups



*** ”Events” include lack of clinical response, unsuccessful discharge, and adverse events**

Evaluating Outcomes in CRE Infections

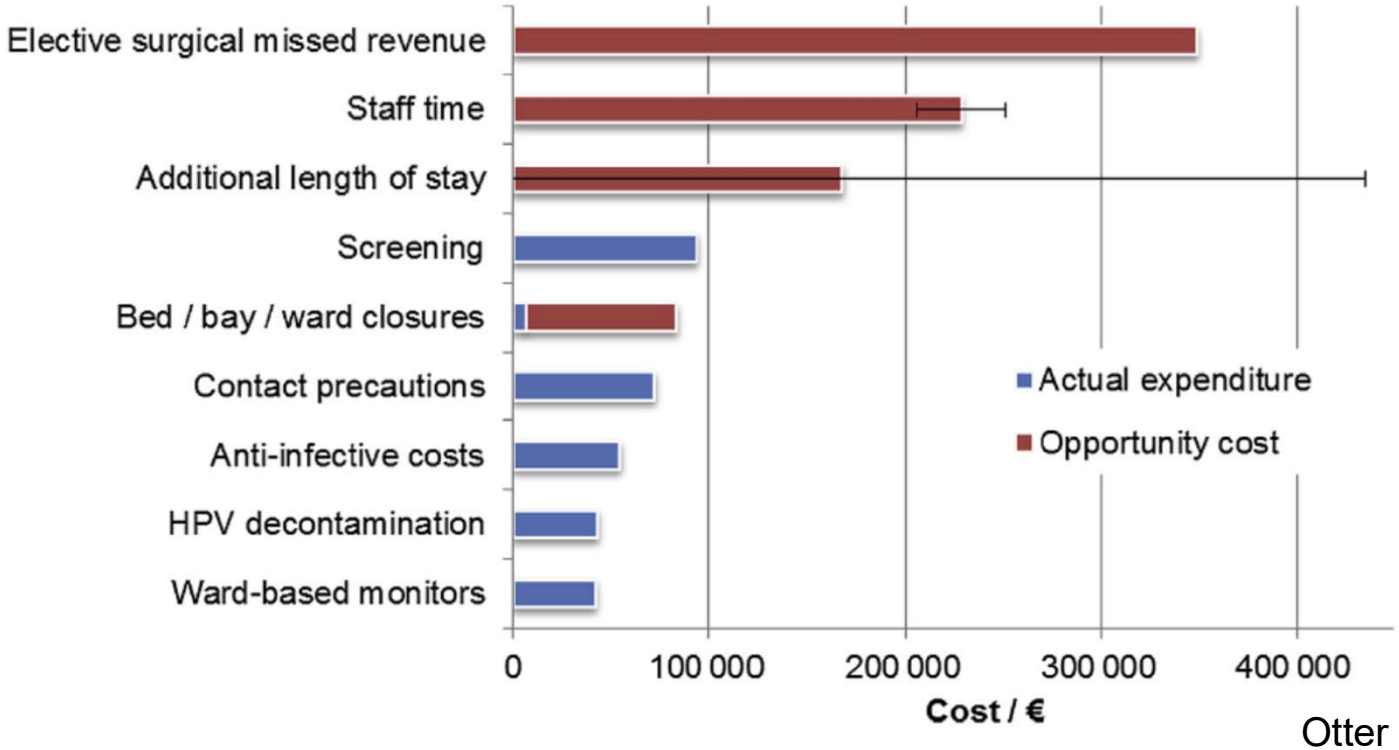


- BSI/pneumonia CRE infections
  - All-cause mortality 39%
- CRE-colonized
  - 12% all-cause mortality
- "Excess mortality" of 27% (no difference in UTI)

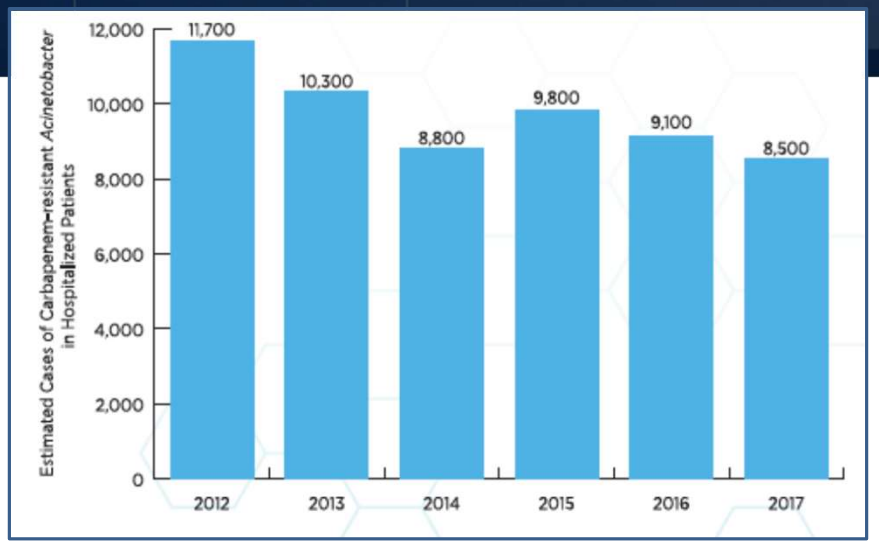
Hauck et al. CMI 2016;22:513

Financial cost of CRE

- NDM-producing CRE outbreak in UK
  - 40 patients in 5 hospitals
- Total costs €1,100,000 ($1,163,415)



Otter et al. CMI 2017;23:188



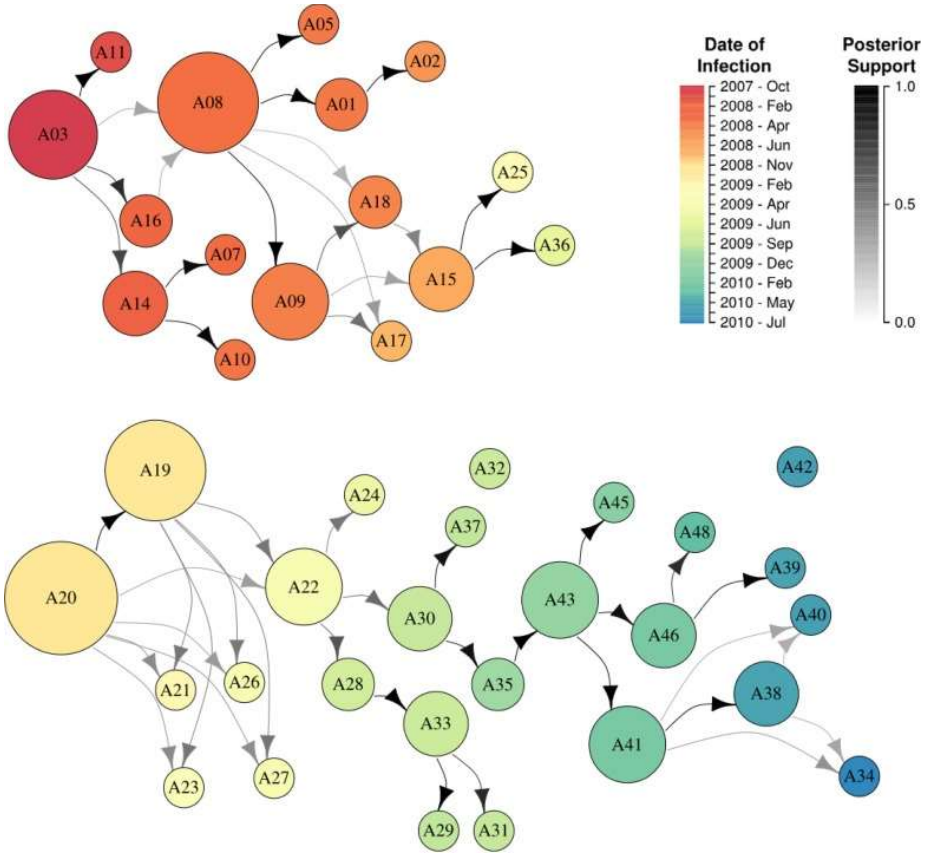
www.cdc.gov/DrugResistance/Biggest-Threats.html

Carbapenem-resistant *Acinetobacter baumanii* (CRAB) in the US

- Healthcare-associated, affects the most severely ill
- Sustained outbreaks
- Environmental persistence
- Commonly multidrug-resistant
- Rapid acquisition of AMR genes through horizontal, plasmid-mediated transfer
- Study Network of Acinetobacter as a Carbapenem-Resistant Pathogen (SNAP): all-cause 30-day mortality of 24%

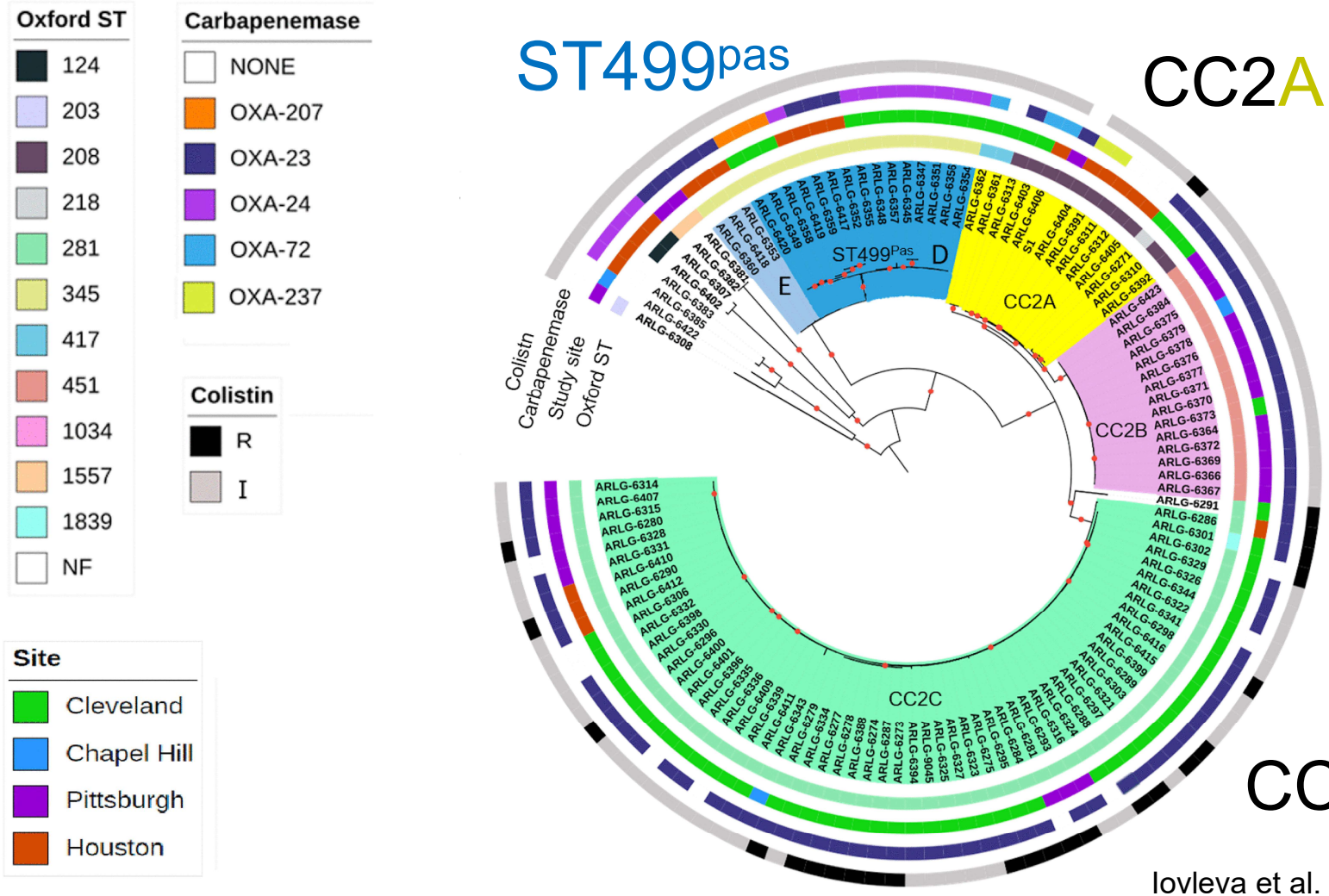
CRAB as nosocomial outbreak pathogen

- 46 clinical isolates from patients in burn unit at UNC (2007-2010)
- 3 separate clonal outbreaks identified (WGS)
- Extensive environmental contamination
- Primarily OXA carbapenemase genes identified

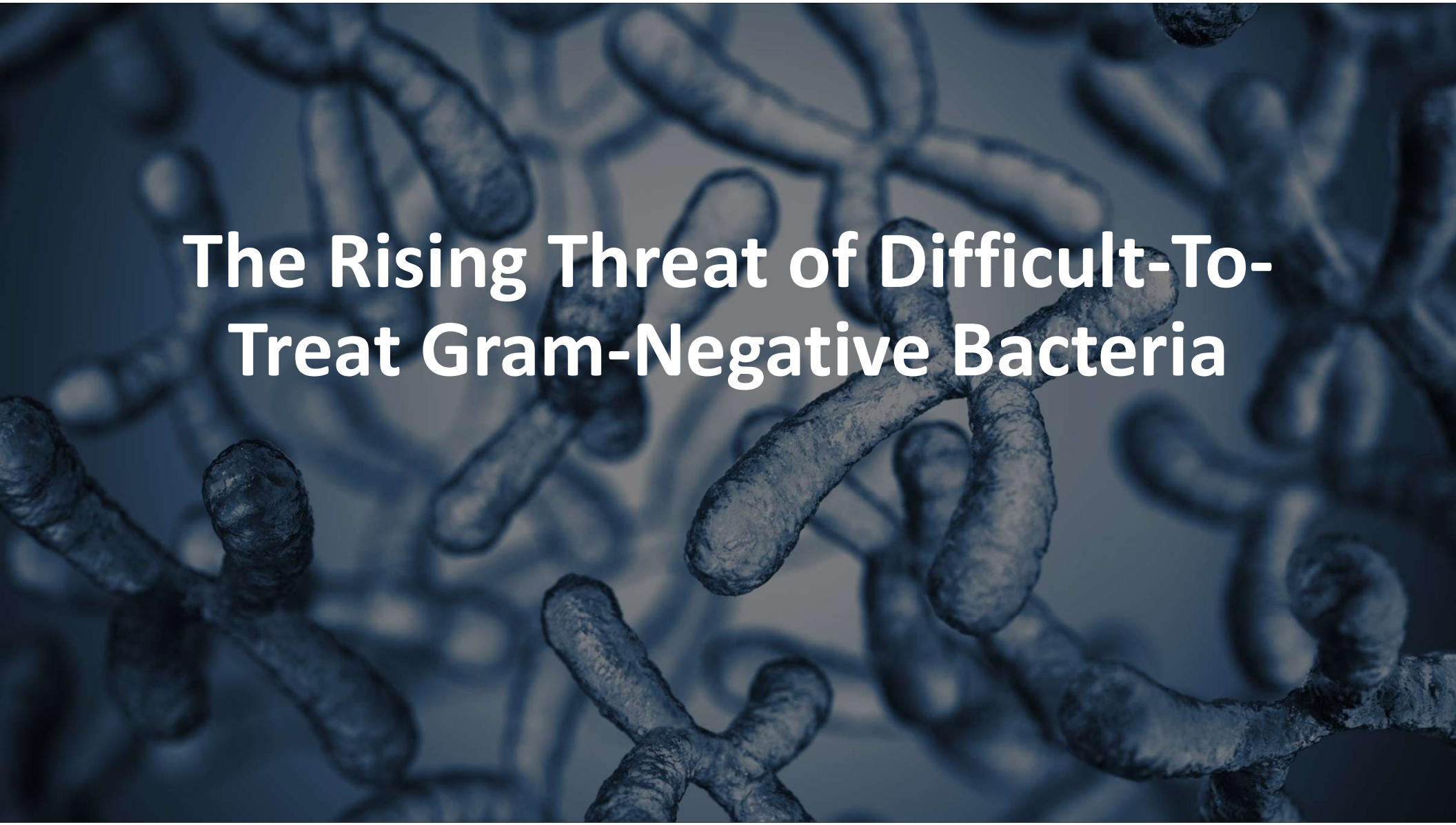


Kanamori et al. AAC 2016;60(3):1249

Acinetobacter baumannii in the US (n=115 isolates, WGS)



Iovleva et al. mBio 2022;13(2):e0275921.

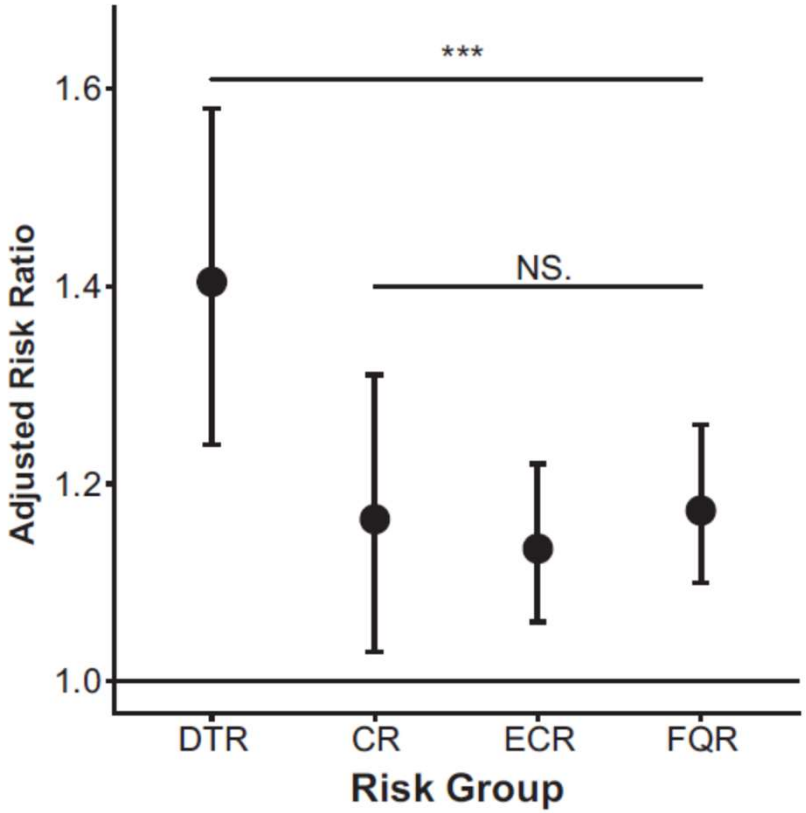


The Rising Threat of Difficult-To-Treat Gram-Negative Bacteria

Higher Mortality for All GNRs with Difficult-to-Treat Resistance

Difficult-to-Treat Resistance (DTR)

- **Non-susceptibility to all first-line agents:**
  - Piperacillin-tazobactam
  - Ceftazidime/Cefepime
  - Aztreonam
  - Meropenem/Imipenem-cilastatin
  - Ciprofloxacin/Levofloxacin



Kadri et al. Clin Infect Dis 2018;67(12):1803-1814

Summary

- MDROs are a growing threat to hospitalized patients
- Worse outcomes in patients with MDRO infections vs. susceptible organisms
- Carbapenem-resistant Gram-negative bacteria especially worrisome
  - Limited treatment options
  - Poor outcomes

Why did the dinosaur-killing-comet come to earth?

Why does the cat wake up one hour before he has to be fed?

Why is the sky blue?

What makes waterproof things waterproof?

Why does my brother always bother me?

How come we don't have wings and fly like birds?

Questions?

What kind of skulls do ant-eaters have?

What are we going to have for dinner?

Why do people cause pollution?

What is coldness made out of?

What is the smallest thing on earth?

What are electrons made of?

Why do people need to sleep?

How does electricity power technology?