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

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Disclosures

- Seres Therapeutics LLC (consultant)

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Overview

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

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Terminology Primer

RESISTANCE LEVELS

- MDR: Multi-drug resistant
  - Non-susceptible to ≥1 agent in ≥3 antimicrobial categories
- XDR: Extensively drug resistant
  - Susceptible to only 1–2 remaining antibiotic categories
- PDR: Pan-drug resistant
  - No in vitro susceptibility to any antibiotic agent
- DTR: Difficult-to-treat resistance
  - Non-susceptible to all first-line agents for that organism
  - Often used to describe *Pseudomonas aeruginosa*

KEY ORGANISMS

- GNR: Gram-negative rod
  - Bacteria with outer membrane; often harder to treat
- ESBL-E: ESBL-producing Enterobacterales
  - Resistant to 3rd-gen cephalosporins (e.g., ceftriaxone)
- CRE: Carbapenem-resistant Enterobacterales
  - Resistant to last-resort carbapenem antibiotics
- CPE: Carbapenemase-producing Enterobacterales
  - CRE subset that produces enzyme (e.g., KPC, NDM)
- CRAB: Carbapenem-resistant Acinetobacter baumannii
  - Environmental non-fermenter; high environmental persistence

KEY TERMS & CONCEPTS

- Colonization vs. Infection
  - Colonization: organism present, no symptoms, patient is a carrier
  - Infection: organism invades tissue, produces clinical signs/symptoms
  - Critical: colonized patients need IC precautions but NOT treatment

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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
- Impacts all aspects of modern medicine
  - Surgery
  - Oncology
  - Transplantation

Require effective antibiotics for their existence

Murray CJL et al. Lancet 2022;399:629–655 • Isturiz. Int J Antimicrob Agents 2008;32:s201

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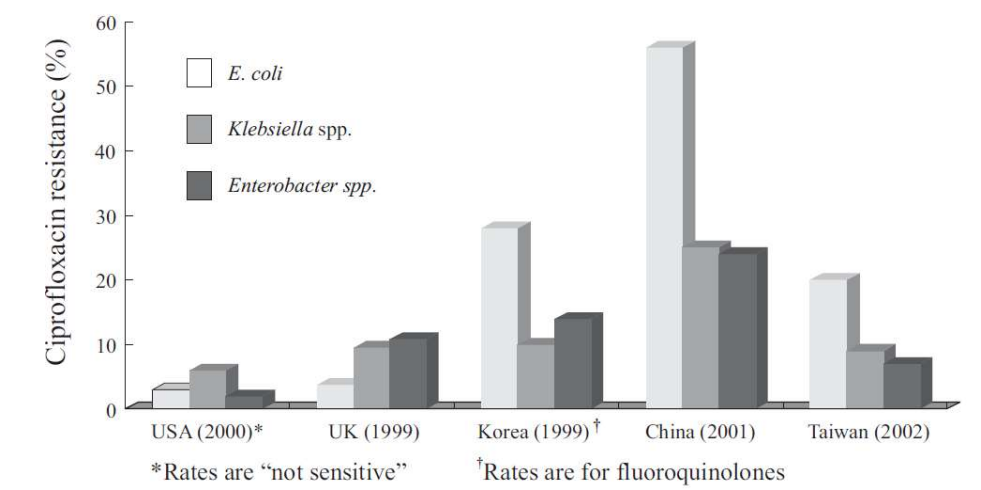
Resistance is Global



→*Antibiotic resistance is a global problem — no single country is unaffected*

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

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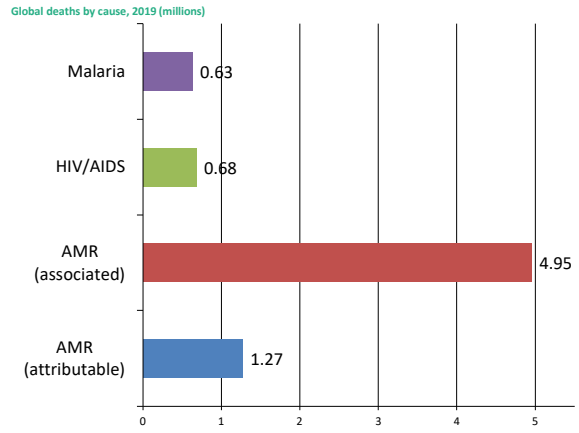
Global Burden of Antimicrobial Resistance

1.27 million
deaths directly attributable to bacterial AMR (2019)

4.95 million
deaths associated with bacterial AMR (2019)

Ranked #1
infectious disease cause of death globally (surpassing HIV/AIDS & malaria)

1.91 million
projected annual attributable deaths by 2050 (2024 forecast)



- Leading syndrome: lower respiratory infections
  - >1.5 million deaths associated with AMR
- Top 6 pathogens account for 73% of attributable deaths
  - *E. coli, S. aureus, K. pneumoniae, S. pneumoniae, A. baumannii, P. aeruginosa*
- Geographic disparity: highest burden in sub-Saharan Africa
  - 27.3 deaths per 100,000 vs. 6.5 in Australasia
- 2050 projection: 39.1 million cumulative attributable deaths (2025–2050)
  - Sharpest rise in adults ≥70 years in all regions

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Where did antimicrobial resistance originate from?

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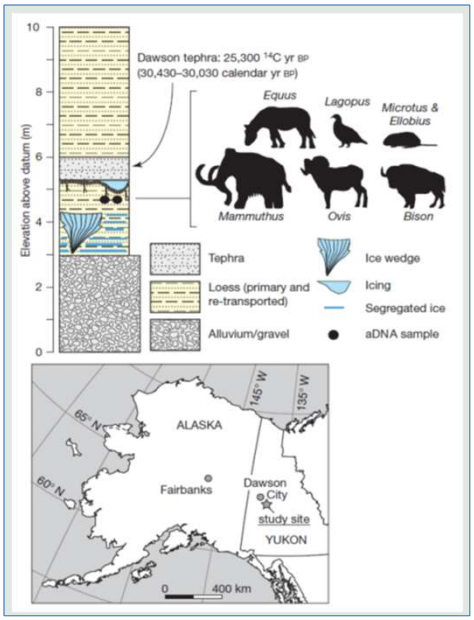
Antibacterial Resistance is Ancient

- Researchers analyzed DNA from 30,000-year-old permafrost
- Found beta-lactamase genes in ancient *Streptococcus* and *Streptomyces* bacteria
- Also found resistance genes for tetracyclines and glycopeptides (vancomycin)
- Bacteria produce antibiotics themselves in constant ecological warfare
  - Bacteria in ecosystems produce antibiotics; others develop resistance to survive
- Human medicine has selected for organisms already resistant to antibiotics



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

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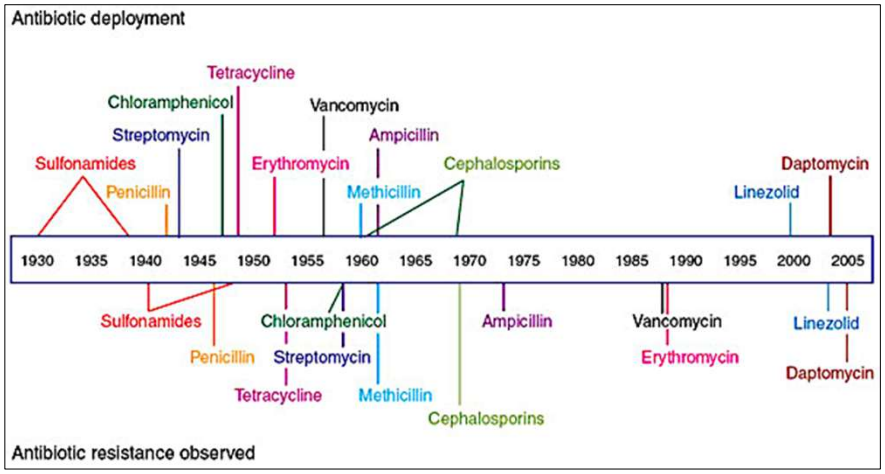
Antibiotic Resistance Timeline

- For every antibiotic developed, a resistance mechanism already exists and is selected for shortly after use
- This pattern holds from penicillin (1940s) to the most recent agents
- **Key takeaway**: we cannot outpace resistance through discovery alone



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

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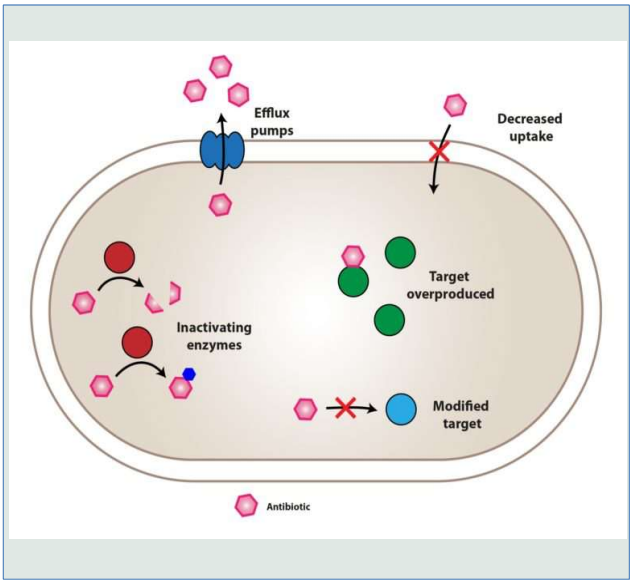
Mechanisms of Resistance in Bacteria

- Enzymatic degradation of antibiotic (e.g., beta-lactamases)
- Target site modification (e.g., altered penicillin-binding proteins)
- Efflux pumps: active export of antibiotic from cell
- Reduced outer membrane permeability (porin loss in GNRs)



futurelearn.com/info/courses/introduction-to-bacterial-genomics

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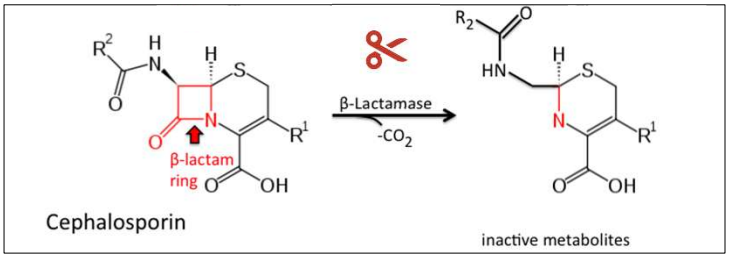
Beta-lactamases in AMR



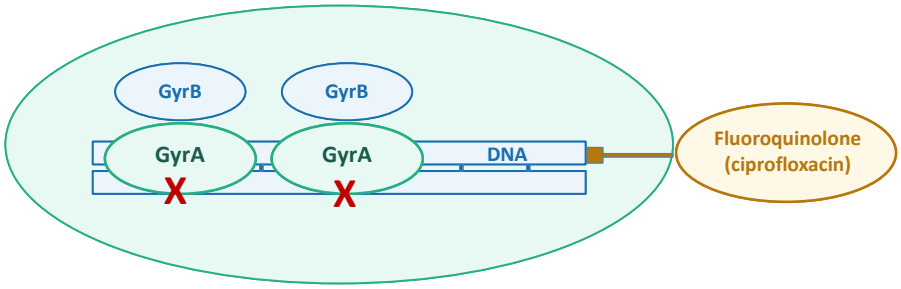
Key clinically important families

Enzyme	Class	Substrates hydrolyzed	Clinical relevance
TEM / SHV	A	Penicillins, early cephalosporins	Common nosocomial ESBLs
CTX-M	A	3rd-gen cephalosporins (CTX)	Dominant ESBL worldwide
KPC	A	Carbapenems + all β-lactams	Most common carbapenemase in US
NDM	B	Carbapenems (metallo-enzyme)	South Asia; travelers
OXA-48	D	Carbapenems (weakly)	Europe, Middle East, Africa
AmpC	C	Cephalosporins (not carbapenems)	Inducible in Enterobacter spp.

Bush K & Jacoby GA. Antimicrob Agents Chemother 2010;54:969–976 • Ke W et al. Biochemistry 2007;46:5732 • Castanheira M et al. JAC-Antimicrob Resist 2021;3(3)

DNA Gyrase Mutations in Fluoroquinolone Resistance

FQs trap gyrase on DNA → irreversible double-strand breaks → cell death



QRDR Mutations that confer fluoroquinolone resistance

Position	Wild-type	Common mutant	Resistance impact
GyrA Ser83	Serine	Leu / Trp	Primary; disrupts FQ–Mg^{2+} chelation at active site
GyrA Asp87	Aspartate	Asn / Gly	Additive with Ser83; step-wise MIC increase
GyrB Asp426	Aspartate	Asn	Less common; quinolone resistance
ParC Ser80 (Topo IV)	Serine	Ile / Arg	Second target; compounds GyrA resistance

Hooper DC & Jacoby GA. Cold Spring Harb Perspect Med 2016;6:a025320 • Robicsek A et al. Nat Med 2006;12:83–88 • Jacoby GA. Clin Infect Dis 2005;41(Suppl 2):S120–S126

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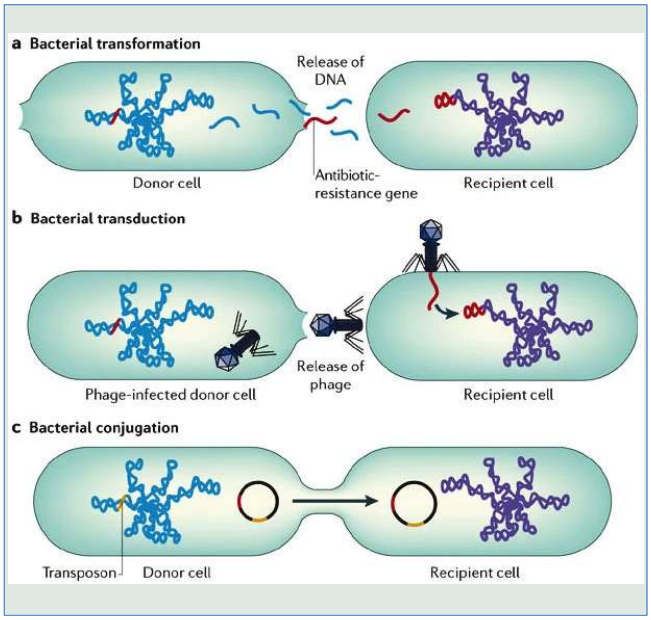
Mechanisms of AMR Gene Sharing in Bacteria

Horizontal gene transfer explains rapid spread of resistance across species

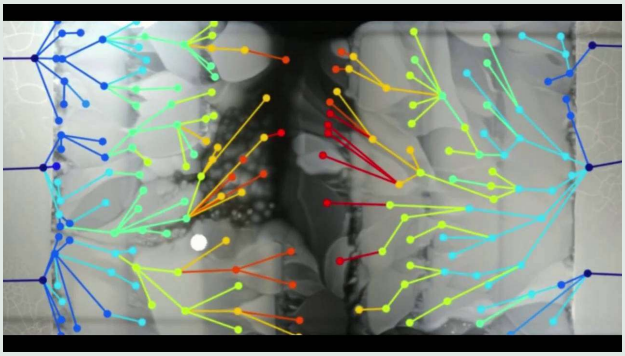
- **Transformation**: uptake of naked DNA from environment
- **Transduction**: bacteriophage-mediated gene transfer
- **Conjugation**: direct cell-to-cell plasmid transfer
  - Most clinically important mechanism for resistance spread



Furuya E, Lowy F. Nat Rev Microbiol 2006;4:36–45

Selection of Antimicrobial Resistance

- Classic MEGA-plate experiment with stepwise resistance selection
- Bacteria migrate from abx-free zones into progressively higher abx concentrations
- Sub-therapeutic abx are particularly effective at selecting resistance
- Mirrors real-world agricultural and clinical antibiotic exposure patterns



Baym et al. Science 2016

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Drivers of Antimicrobial Resistance

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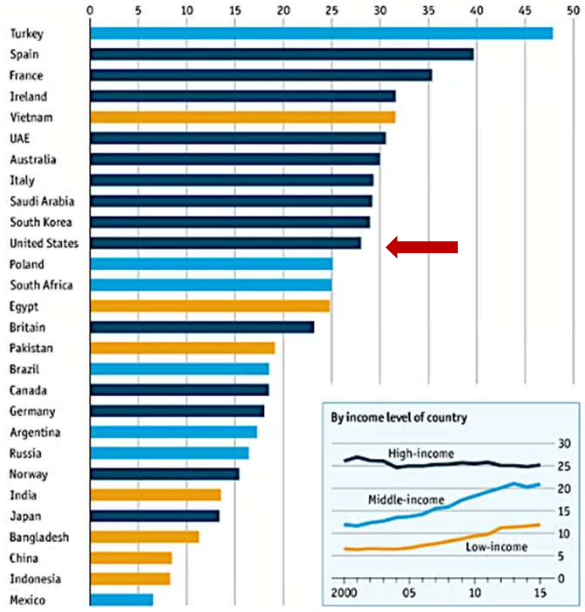
Antibiotic Usage Is High Across the World

- High-income countries have the highest total antibiotic use
- Largest relative increases in use are in low- and middle-income countries
- Global antibiotic consumption increased 65% from 2000 to 2015



Klein et al. PNAS 2016

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Drivers of Resistance

- Inappropriate antibiotic prescribing in clinical settings
  - Antibiotics prescribed for viral infections; pressure from patients and performance metrics
- Antibiotic use in companion animals
- Agricultural antibiotic use for growth promotion
  - Sub-therapeutic doses highly effective at selecting resistance
  - Although banned in many countries, practice continues globally
- Poor infection control in healthcare settings
  - Facilitates transmission of already-resistant organisms between patients
- Limited access to clean water and sanitation in low-income settings
- Environmental contamination with antibiotic residues

Hawkey et al. JAC 2009;64:i3 • Holmes et al. Lancet 2016

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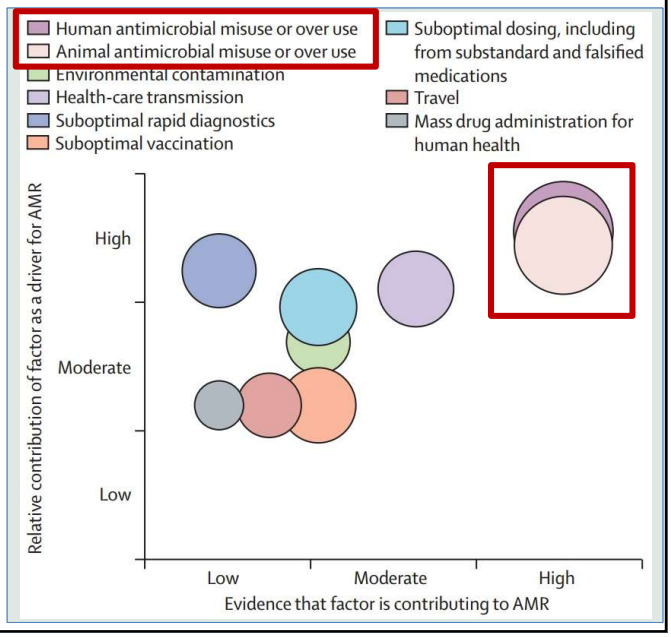
Modifiable Drivers of Antimicrobial Resistance

- **Human antibiotic consumption (hospital and community)**
- **Veterinary and agricultural antibiotic use**
- Sanitation and water quality
- Infection prevention and control practices
- Travel and population movement



Holmes et al. Lancet 2016

Focus of This Lecture: GNRs — Key Resistance Types

- Extended-spectrum beta-lactamases (ESBL)
  - Defined by resistance to 3rd-generation cephalosporins
- Carbapenem resistance
  - Carbapenem-resistant Enterobacterales (CRE)
  - Some produce carbapenemases (NDM, KPC) → CPE: Carbapenemase-producing Enterobacterales
  - Others result from combination of multiple drug-resistance mechanisms

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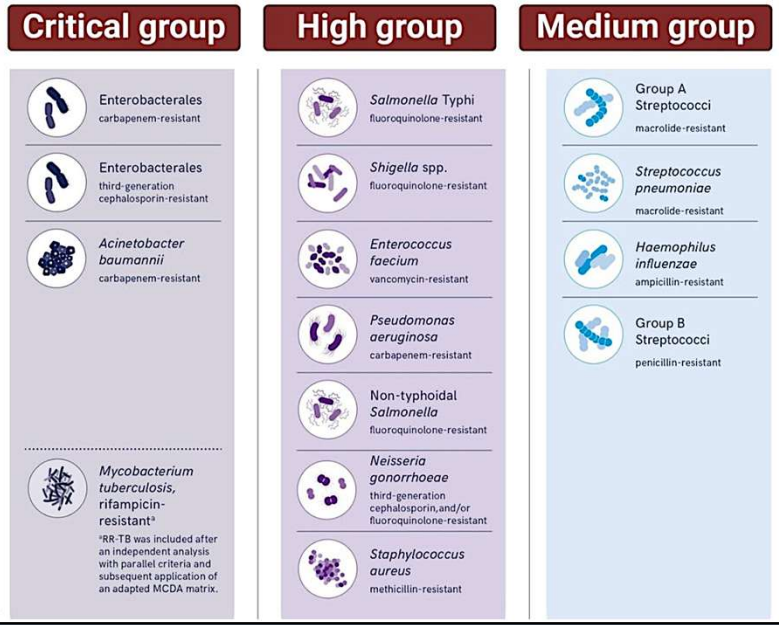
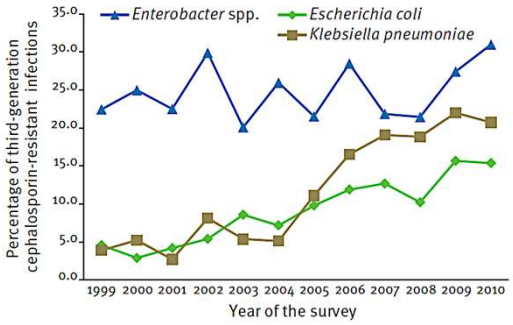
WHO Priority Pathogens 2024



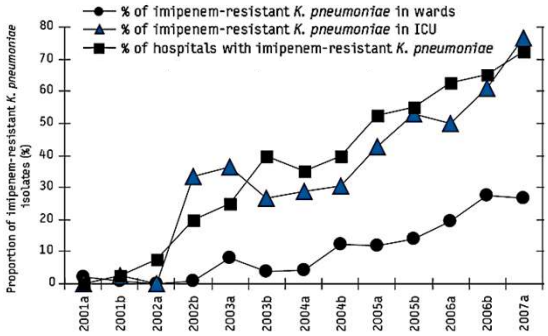
WHO Priority Pathogens List 20

Trends in Resistant Enterobacterales

- Spain: rapid rise in ESBL-producing Enterobacterales since early 2000s
- Greece: emergence and dramatic increase in CRE (carbapenem-resistant Enterobacterales)
- **Trends mirror global pattern: ESBL first, then carbapenem resistance emerging**



Spain (ESBL)



Greece (CRE)

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

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What's in a Name? Phenotypic vs. Genotypic Definitions

Phenotypic "ESBL"

- **Resistance to 3rd-gen cephalosporins on susceptibility testing**
  - e.g., ceftriaxone non-susceptible
  - May NOT reflect a true ESBL gene
- **Inducible AmpC ≠ ESBL: same phenotype, different mechanism**
  - Inducible: *Enterobacter cloacae*
  - Inducible R can look susceptible in micro lab

Genotypic ESBL

- **ESBL gene detected by:**
  - Whole genome sequencing (WGS) or
  - Targeted PCR for ESBL gene families
- **Key families: CTX-M, TEM, SHV**
  - CTX-M-15 dominates globally
- **Definitive: identifies the actual mechanism**
  - Not routinely reported by clinical labs

Why the Distinction Matters

- **Treatment: cephalosporins fail for ESBLs**
  - Carbapenems are first-line for serious infections
- **AmpC: inducible resistance can emerge on therapy**
  - Avoid cephalosporins with *Enterobacter* and other AmpC-inducible bacteria

CRE: CDC 2015 Phenotypic Definition

- **Resistant to imipenem, meropenem, or doripenem**
  - MIC ≥4 mcg/mL
  - AND/OR ertapenem MIC ≥2 mcg/mL
  - AND/OR documented carbapenemase (CPE)
- **CRE ≠ CPE: not all CRE produce a carbapenemase**
  - Porin loss + AmpC can also confer carbapenem resistance

CPE: Carbapenemase-Producing (genotypic)

- **A subset of CRE: enzyme-mediated carbapenem resistance**
  - Confirmed by WGS or targeted PCR
- **Key enzymes by Ambler class:**
  - KPC (Class A) —>90% of CPE in US
  - NDM, VIM, IMP (Class B, metallo) — South Asia, travelers
  - OXA-48 (Class D) — Europe, Middle East
- **Horizontally transferable on plasmids between species**

Implications: CRE vs. CPE

- **Both CRE/CPE require contact precautions**
  - Outcomes similarly poor across all CRE subtypes
- **CPE is notifiable in many US states**
  - Triggers regional outbreak investigation
- **Determines treatment options**
  - Example: Ceftazidime-avibactam is active vs. KPC and OXA-48; NOT active vs. NDM (metallo-enzyme)

Doi Y et al. J Travel Med 2017;24:S44 • CDC CRE definitions 2015 • van Duin D et al. Lancet Infect Dis 2020;20:731–741 • Castanheira M et al. JAC-Antimicrob Resist 2021;3(3)

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

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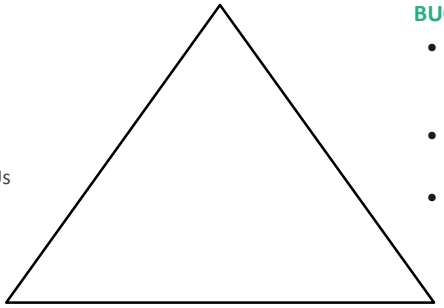
Risk Factors for Infections with MDROs

HOST (Patient)

- Invasive procedures and devices
  - Catheters, ventilators, lines
- Immune suppression
  - Chemotherapy, transplant, HIV
- Diabetes mellitus
- Prior antibiotic exposure
- Prolonged hospital stay

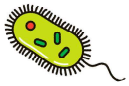
ENVIRONMENT

- Community exposure
  - Travel to high-prevalence regions
- Acute care facilities
  - ICU stays confer highest risk
- Long-term care facilities
  - LTACHs harbor MDRO rates ≃ ICUs
- Inter-facility patient transfers



BUG

- Antimicrobial resistance profile
  - Breadth of resistance determines treatment options
- Virulence factors
  - Toxin production, capsule, adhesins
- Environmental persistence
  - A. baumannii survives weeks on surfaces



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HOST: 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)

- Prior antibiotic use, device exposure, and healthcare contact are universal MDRO risk factors

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

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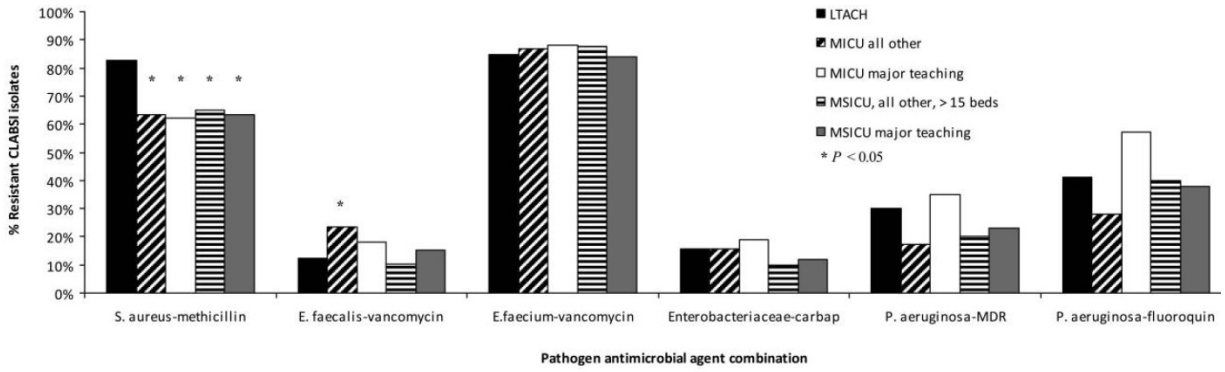
ENVIRONMENT: Prevalence of MDROs in LTACHs similar to ICUs



Chitnis et al. ICHE 2012;33:993 • Source: cdc.gov

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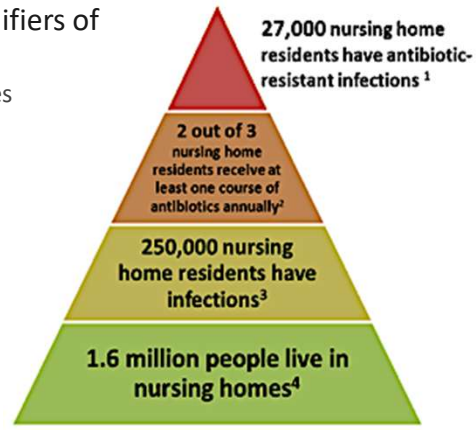
ENVIRONMENT: MDROs in Long-Term Care Settings

- Most common infections treated with antibiotics in nursing homes and long-term acute care hospitals (LTACHs):
  - Respiratory tract infections (33%)
  - Urinary tract infections (32%)
  - Skin and soft tissue infections (12%)
- Nursing homes and LTACHs serve as reservoirs and amplifiers of MDRO spread
  - Patients transferred from LTACHs carry MDROs into other facilities



Chitnis et al. ICHE 2012;33:993 • Source: cdc.gov

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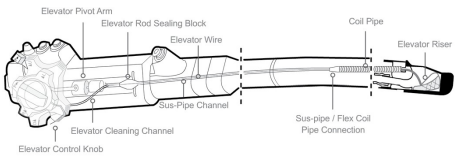
ENVIRONMENT: Endoscope-Related Outbreaks (2013)

EDITORIAL

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

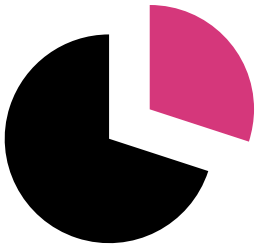
Gastrointestinal Endoscopes
A Need to Shift From Disinfection to Sterilization?

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



- Several outbreaks of carbapenemase-producing Enterobacteriaceae (CPE)
  - NDM and KPC carbapenemase genes identified
- Linked to elevator channel unique to side-viewing duodenoscopes (used for ERCP)
  - 9 patients infected over 5-month period at one center
  - NDM-producing E. coli cultured from scope elevator channel
- No reprocessing lapses identified — hospital was following all guidelines
  - Resolved when hospital switched to ethylene oxide gas sterilization
- Lessons:
  - Likely "tip of the iceberg" — endoscopes are an underrecognized MDRO vector
  - Reprocessing standards may be insufficient for complex-channel scopes

BUGS: Rising Threat from MDR Gram-Negative Bacteria (MDR-GNR) in the Hospital



% of all HAI caused by GNRs

% of ICU HAI caused by GNRs

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

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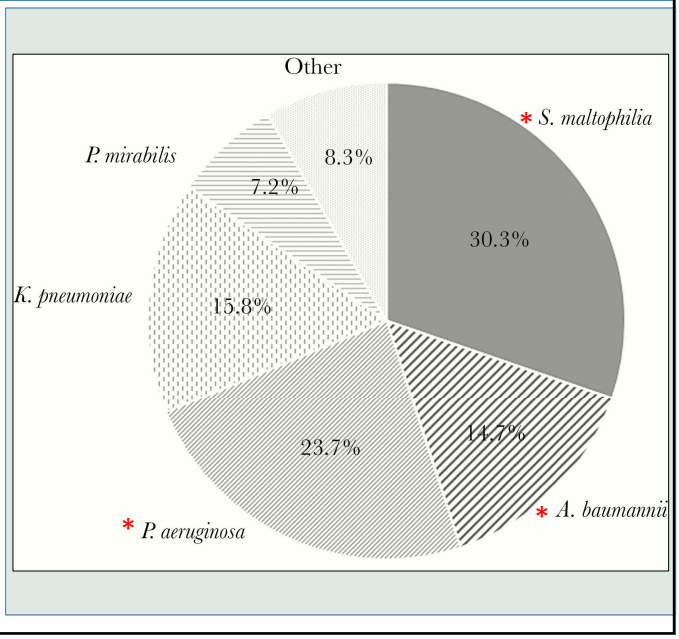
BUGS: Carbapenem-Resistant GNR Causing Bacteremia in the United States

- Most common CR pathogens in bacteremia (n=1,602 patients):
  - Primarily non-fermenting GNRs
  - *K. pneumoniae* most common among fermenting GNRs



Open Forum Infect Dis 2020;7(5):ofaa141

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Risk Factors & At-Risk Population Differs by BUG

	Enterobacterales	Non-fermenting GNRs
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 **Travel to areas of high prevalence** **Potential for community spread**	High-risk patients **ICU and burn units** Rarely community-acquired infection

ECDC CPE Risk Assessment 2011 • Peleg et al. Clin Microbiol Rev 2008;21:538–582

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ESBL-Producing Enterobacterales / Enterobacteriaceae

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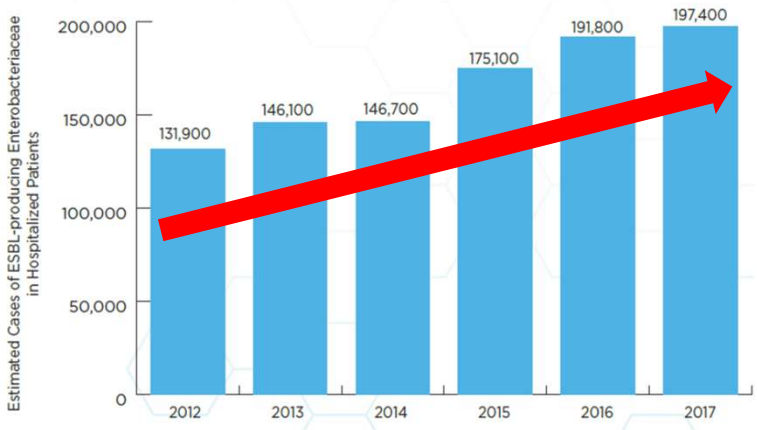
CDC Estimates of ESBL-Producing Enterobacterales

ESBL-producing Enterobacterales are a serious and increasing threat in both healthcare and community settings



CDC Antibiotic Resistance Threats in the United States,

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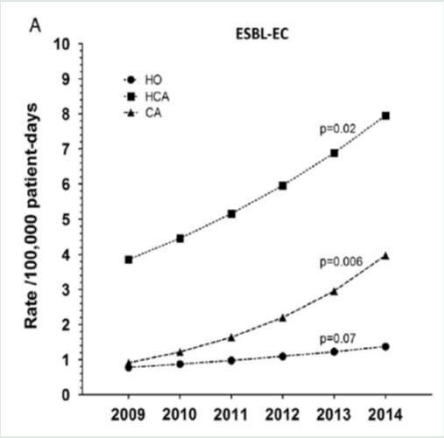
Community Spread of ESBL E. coli

- ESBL E. coli: highly community-associated
  - Patients admitted from home with ESBL E. coli infections
  - Incidence increasing in the community over time
- ESBL E. coli spread is patient-to-patient via community contact, food, environment

- 26 community hospitals
- Southeastern US



Healthcare associated

Community associated

Hospital onset

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

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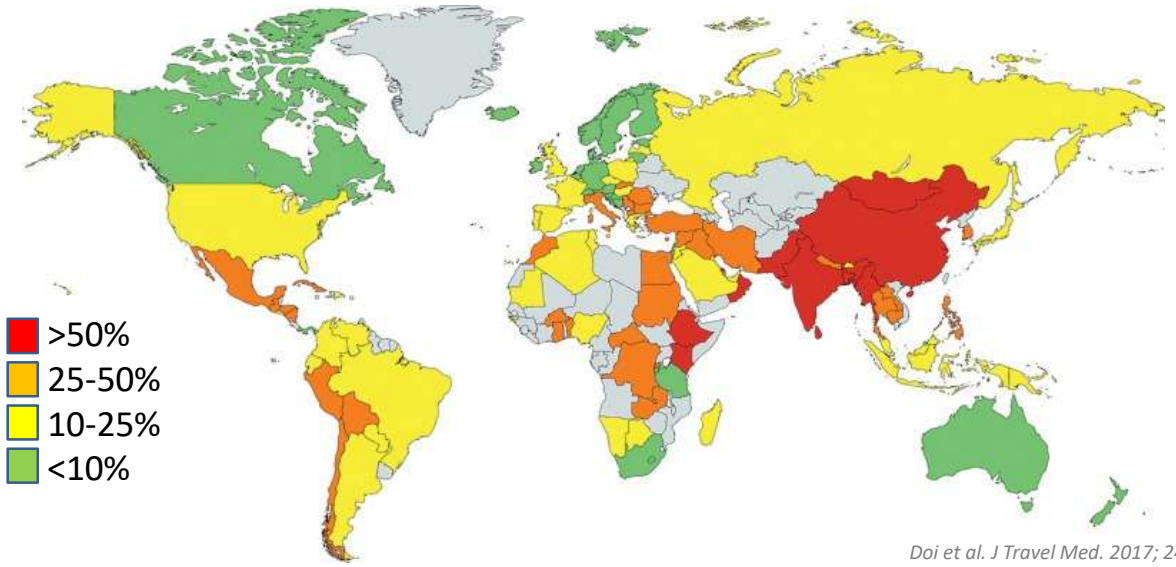
ESBL Producers Increasing Among Global *E. coli I*solates

- Ongoing global increase since 1990s with spread of CTX-M genes



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

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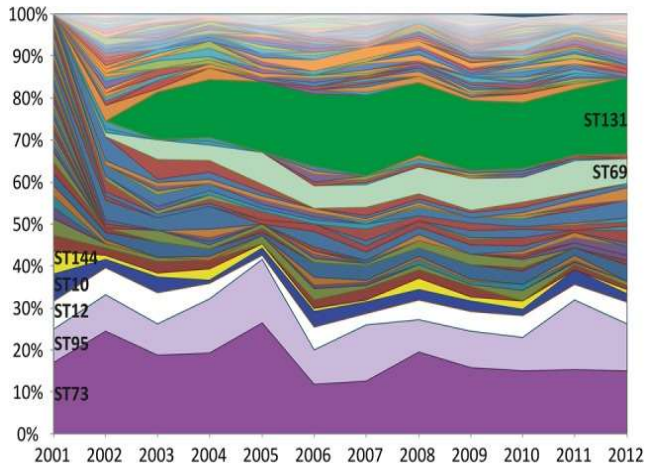
Sequence Type (ST) 131 E. coli — Triple Threat



- **Resistance:**
  - Fluoroquinolones + ESBL (CTX-M-15)
  - Co-resistance to multiple non-beta-lactam agents
- **Virulence:**
  - 10 commonly shared virulence genes
  - Associated with more severe infections including bacteremia
- **Transmissibility:**
  - Many documented community transmission cases
  - Animal and food sources identified

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

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Carbapenem-Resistant Enterobacterales (CRE)

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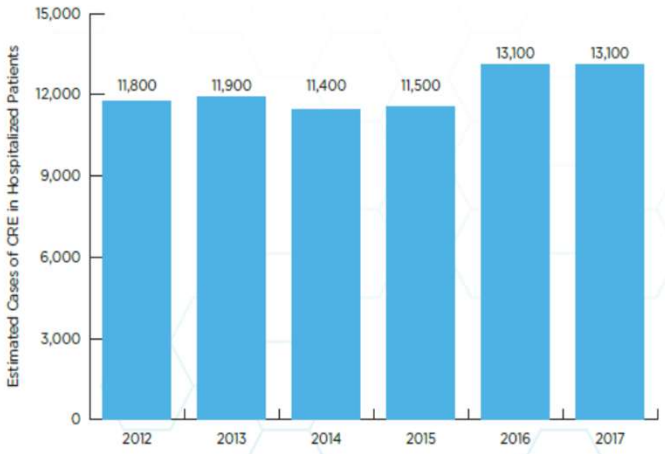
CDC Estimates of CRE in the US

CRE is a rapidly emerging urgent threat in US healthcare settings



CDC Antibiotic Resistance Threats in the United States, 2019

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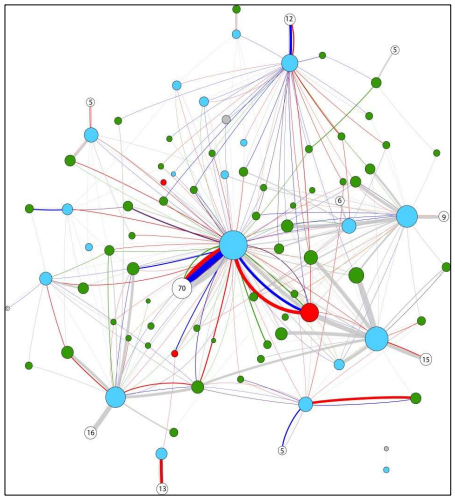
CRACKLE-1: High-connectivity Within the Network of Facilities

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

- Hospitalized patients with culture-positive carbapenem-resistant K. pneumoniae (CRKP)
- PCR for molecular strain typing on all available isolates
- Network analyses at the facility and individual patient level

Key finding: outbreaks were facility-driven, not community-driven
- High degree of facility connectivity
- CRE spread along patient transfer networks
- intervention requires regional coordination

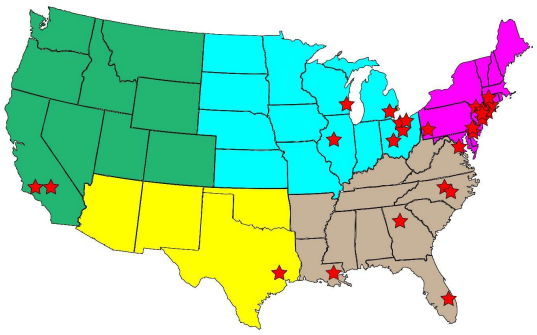


van Duin et al. Lancet Infect Dis 2020;20(6):731–741

CRE in the US: CRACKLE-2 Data

MDRO Network
Antibacterial Resistance Leadership Group

- Prospective, observational, multi-center, cohort study (2016-2017)
  - Period: 2016–2017
  - Consecutive hospitalized patients with CDC-defined CRE
  - 1,040 patients from 49 US medical centers analyzed
- Comprehensive characterization of CRE subtypes, species, and outcomes
- Analysis of first unique 1,040 patients from 49 US medical centers



van Duin et al. Lancet Infect Dis 2020;20(6):731–741

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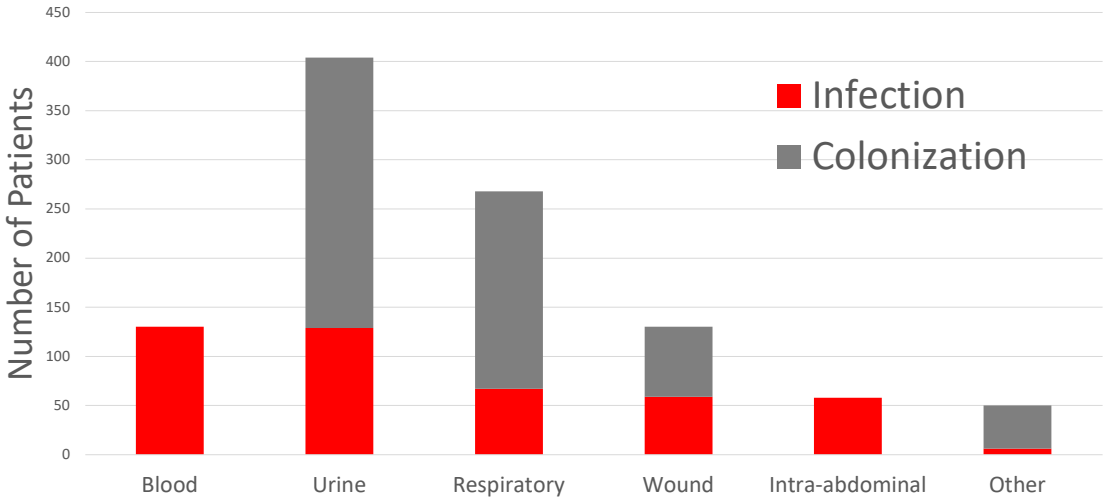
Distribution of CRE Culture Sources (CRACKLE-2)



van Duin et al. Lancet Infect Dis 2020;20(6):731–741 • n=1,040 patients

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CRE: 3 Subsets (CRACKLE-2)

- All isolates met CDC criteria for CRE at local microbiology laboratory
- 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 only by local testing)

van Duin et al. Lancet Infect Dis 2020;20(6):731–741

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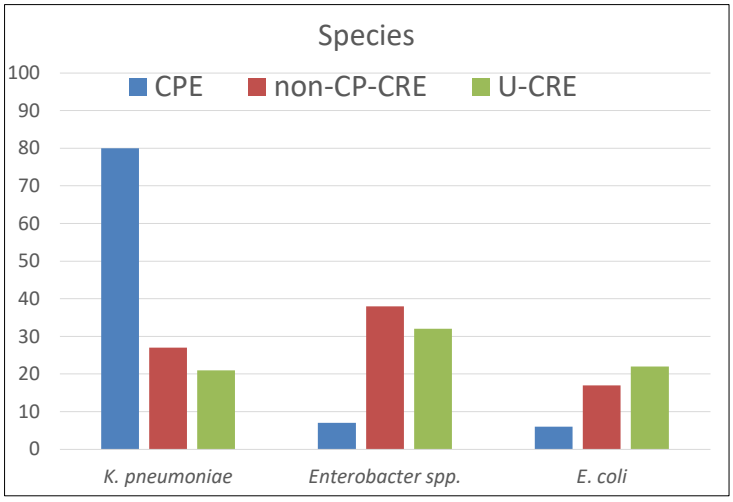
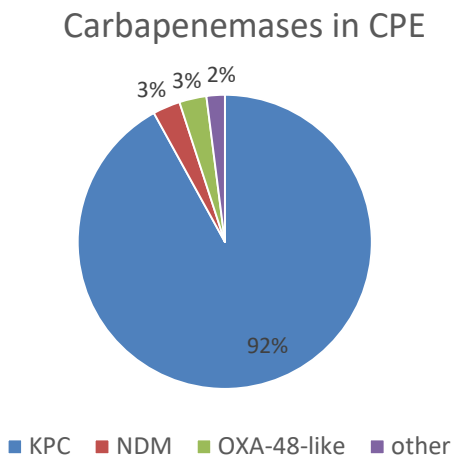
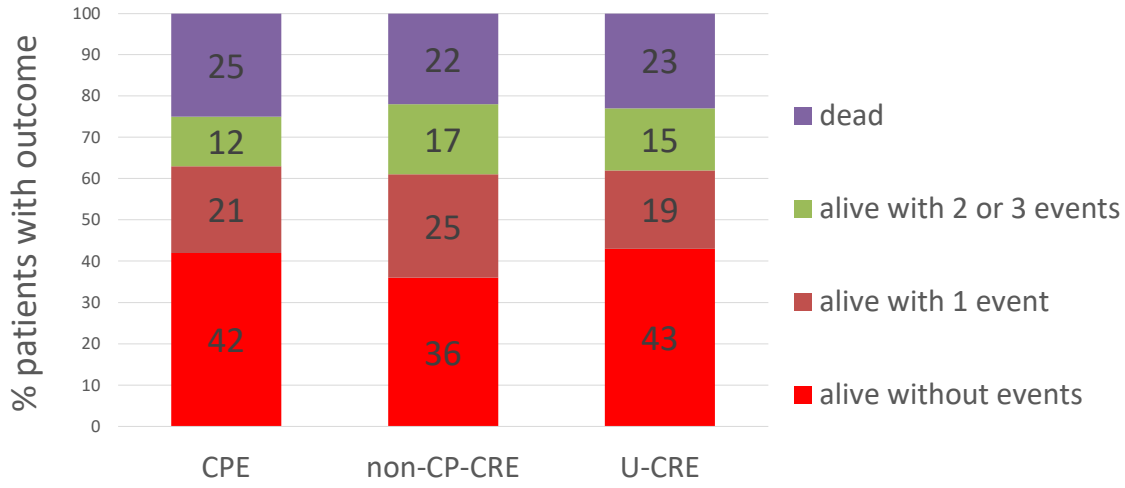
Species with Carbapenemases (CRACKLE-2)





van Duin et al. Lancet Infect Dis 2020;20(6):731–741

DOOR Outcomes Are Similar Across All Three CRE Patient Groups



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

van Duin et al. Lancet Infect Dis 2020;20(6):731–741

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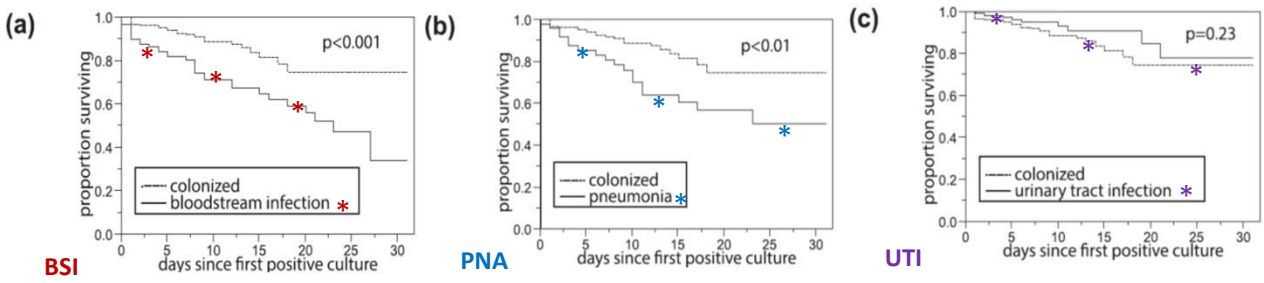
Evaluating Outcomes in CRE Infections

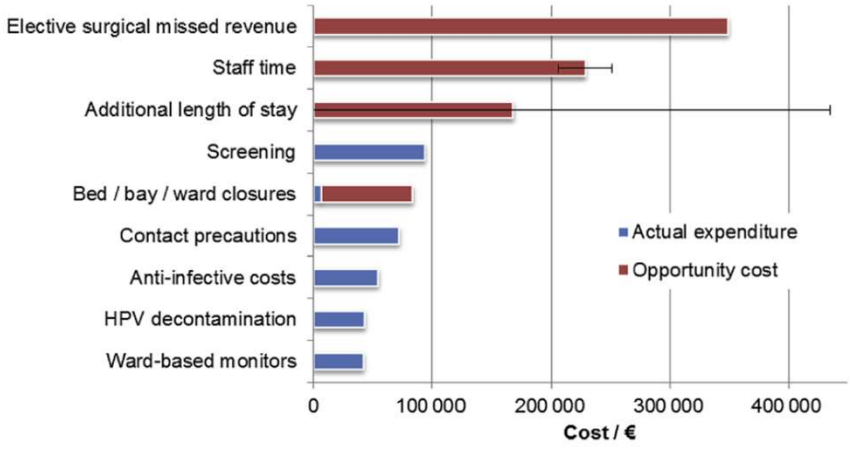


- **BSI**/**pneumonia** CRE infections
  - All-cause mortality 39%
- CRE-colonized
  - All-cause mortality 12%
- "Excess mortality" of 27% (but no difference in UTI)

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

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Carbapenem-Resistant Acinetobacter baumannii (CRAB)

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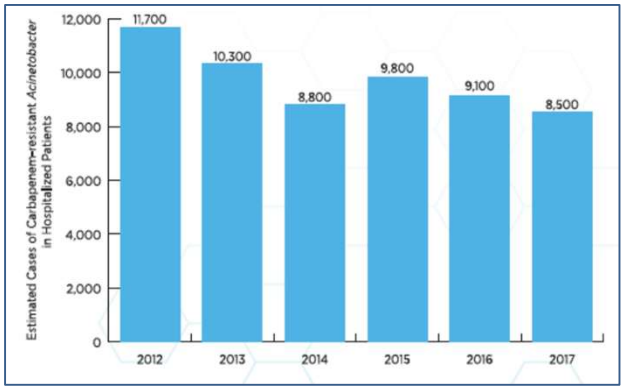
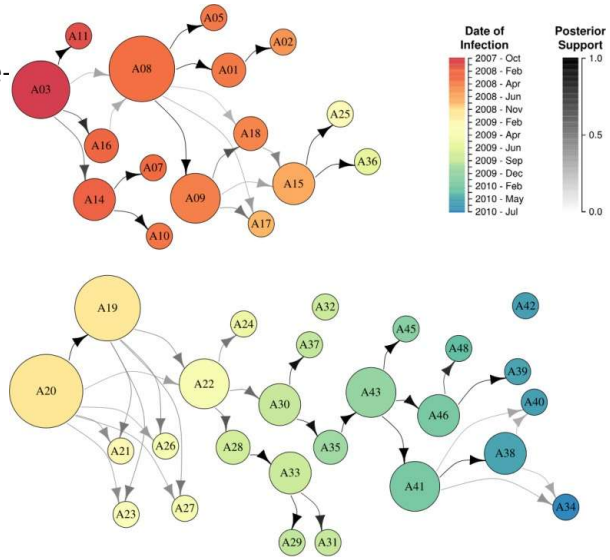
CRAB in the US

- Healthcare-associated; affects the most severely ill patients
  - ICU patients, ventilated patients, burn unit patients
- Capable of sustained nosocomial outbreaks
- Environmental persistence: survives weeks to months on dry surfaces
- Commonly multidrug-resistant
- Rapid acquisition of AMR genes through horizontal, plasmid-mediated transfer



CRAB as a Nosocomial Outbreak Pathogen

- 46 isolates from burn unit at UNC (2007–2010)
- 3 separate clonal outbreaks identified by whole-genome sequencing (WGS)
- Extensive environmental contamination
- Primarily OXA carbapenemase genes identified
- **Key implications for infection control:**
  - WGS essential to distinguish outbreak from sporadic cases
  - Environmental sampling required to identify reservoirs
  - Enhanced cleaning and cohort isolation may be necessary



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

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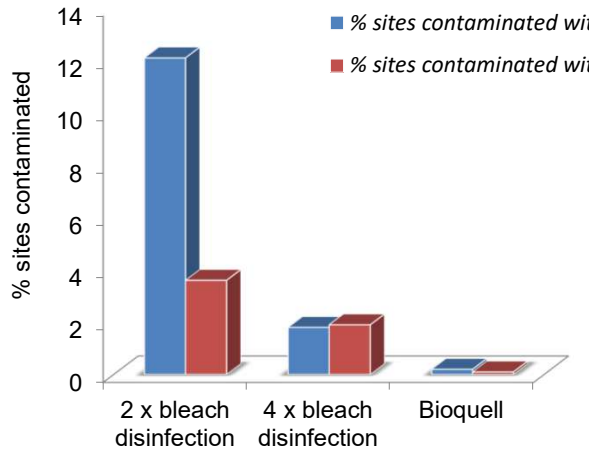
Persistent Contamination with Acinetobacter baumannii

- 26.6% of rooms remained contaminated with MRSA or A. baumannii after 4 rounds of bleach
- HP vapor decontamination outperformed bleach but did not eliminate contamination



- Implications for infection control:
  - Standard bleach protocols insufficient for *A. baumannii* in outbreak settings
  - Consider enhanced terminal cleaning protocols for CRAB patients

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

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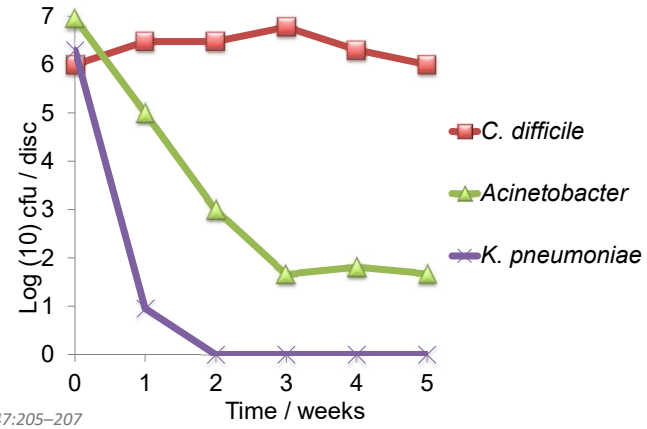
Persistent Contamination and Surface Survival

- Klebsiella eliminated by hydrogen peroxide vapor
- Acinetobacter survived hydrogen peroxide vapor decontamination
- C. difficile (spore-former) survived and persisted over weeks
- Organism-specific survival determines cleaning strategy



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

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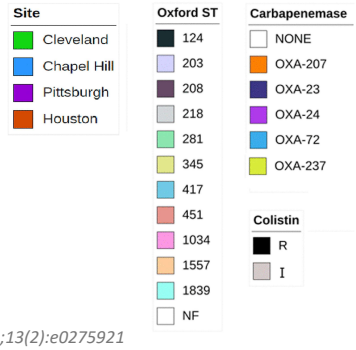
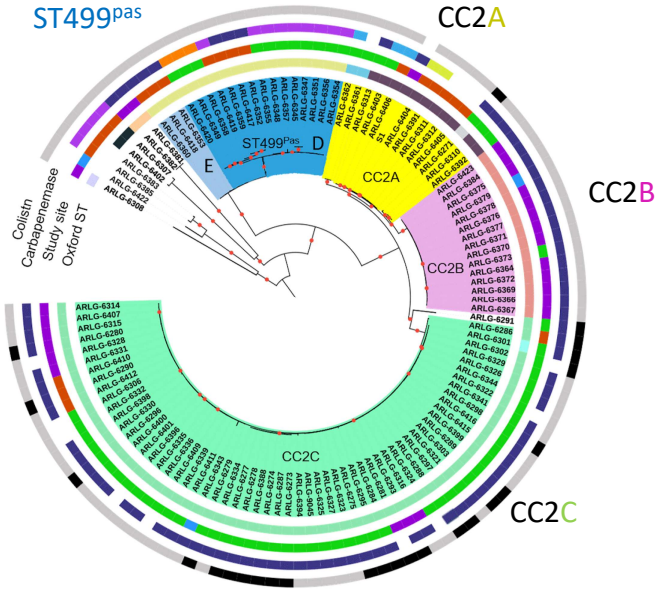
Acinetobacter baumannii in the US (n=115 Isolates, WGS)

- Clonal complexes CC2A, CC2B, CC2C dominate in l clinical isolates
- ST499 also identified in recent years
- Genomic surveillance reveals clonal spread within and across facilities





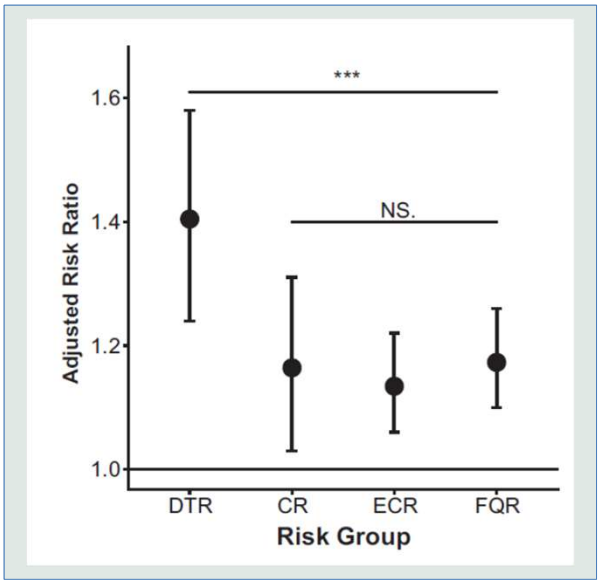
Iovleva et al. mBio 2022;13(2):e0275921

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

54

Higher Mortality for GNRs with Difficult-To-Treat Resistance (DTR)

- DTR = Non-susceptibility to ALL first-line agents:
  - Piperacillin-tazobactam
  - Ceftazidime / Cefepime
  - Aztreonam
  - Meropenem / Imipenem-cilastatin
  - Ciprofloxacin / Levofloxacin
- DTR associated with significantly higher mortality vs. non-DTR infections



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

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Novel Treatment Options and the Antibiotic Pipeline

- The pipeline is thin: IC prevention is essential because treatment options are limited
- Recently approved agents for MDR-GNRs within the past 10 years:
  - Ceftazidime-avibactam: active against KPC- and OXA-48-producing CRE
  - Ceftolozane-tazobactam: active against MDR Pseudomonas aeruginosa
  - Meropenem-vaborbactam: active against KPC-producing CRE
  - Imipenem-cilastatin-relebactam: active against KPC- and some OXA-producing CRE
  - Cefiderocol: siderophore cephalosporin; broad GNR coverage including NDM and CRAB
- Challenges:
  - Market failure: antibiotics are not profitable — multiple companies have gone bankrupt
  - Resistance emerges quickly even to novel agents
  - WHO 2022 pipeline analysis: most agents are derivatives of existing classes
- Conclusion: Prevention remains the most cost-effective strategy

WHO Antibacterial Pipeline Report 2022 • Theuretzbacher et al. Nat Rev Microbiol 2020;18:286–298

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Summary

- MDROs are a growing global threat: 1.27 million deaths directly attributable to AMR in 2019
  - Projected to reach 1.91 million annual attributable deaths by 2050
- Worse outcomes in patients with MDRO infections vs. susceptible organisms
- Carbapenem-resistant gram-negative bacteria are especially worrisome
  - Limited treatment options; poor outcomes; high financial costs
- ESBL producers more easily treated but spread quickly in the community
- Infection control interventions are essential and effective:
  - Novel antibiotics provide options but are not a substitute for prevention

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