


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

Tessa Andermann, MD MPH\*  
Immunocompromised Infectious Diseases  
UNC-Chapel Hill



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## Disclosures

- None

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## Overview

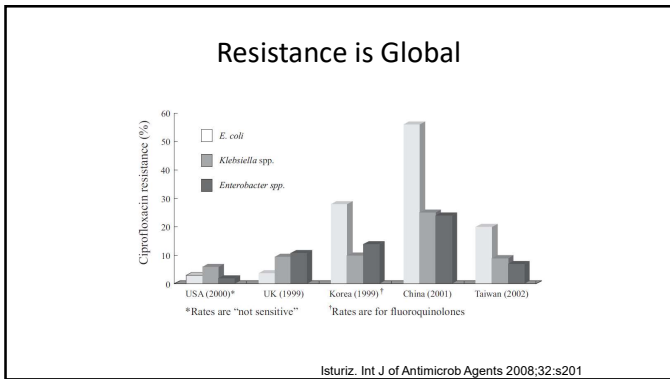
- Antimicrobial resistance (AMR)
- Drivers of AMR
- Risk factors for infection with MDROs
- Superbugs and super-resistance
  - ESBL-E, CRE/CPE, CRAB, DTR
- Consequences/costs of AMR

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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
- Impact on all aspects of modern medicine
  - Surgery
  - Oncology
  - Transplantation

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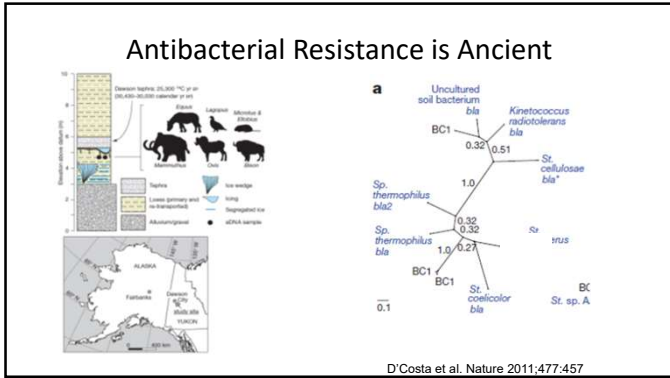


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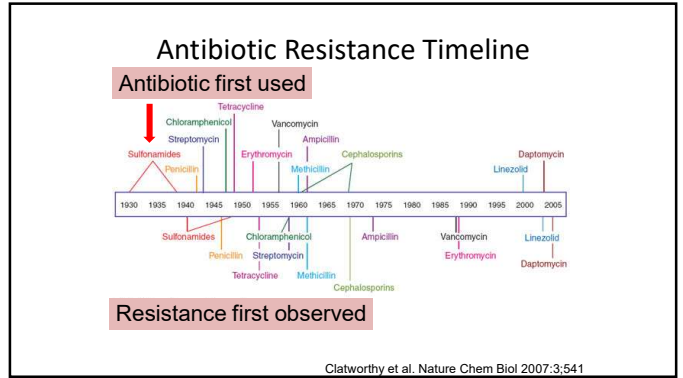
## Where did antimicrobial resistance originate from?

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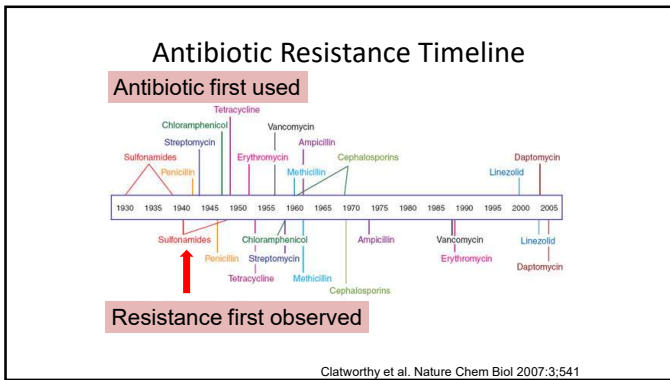
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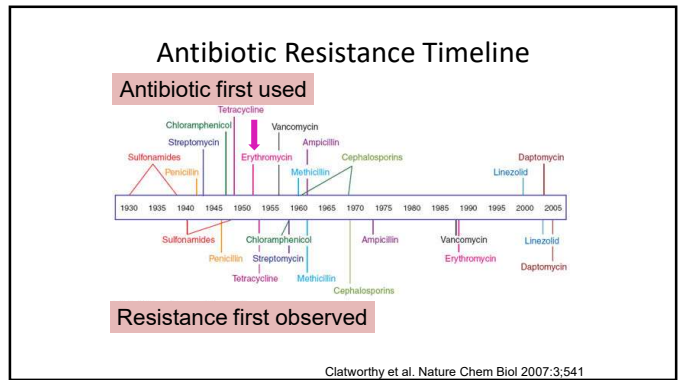
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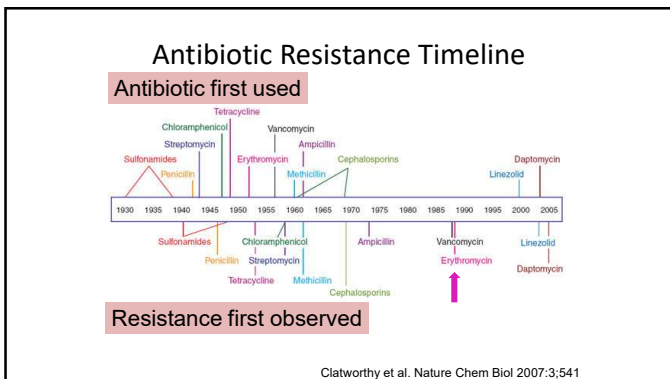
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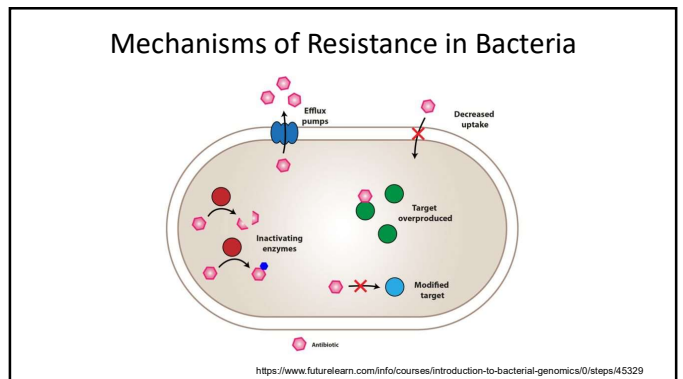
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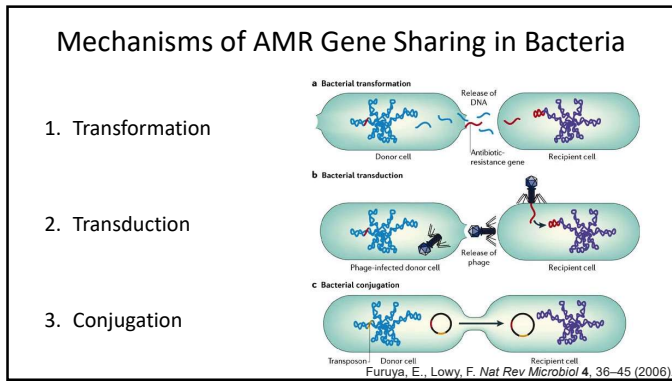
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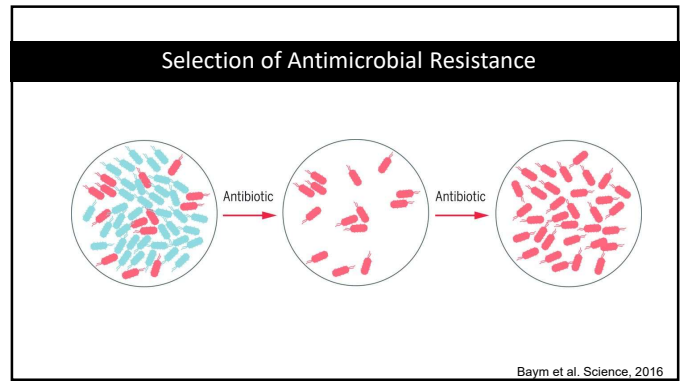
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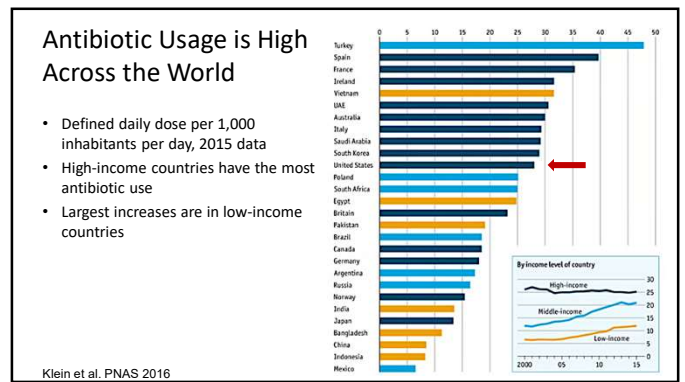
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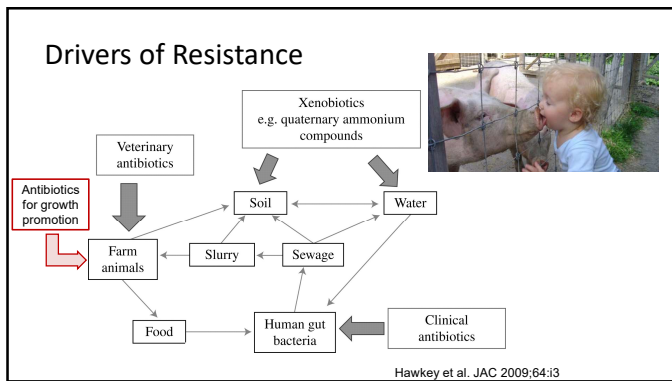
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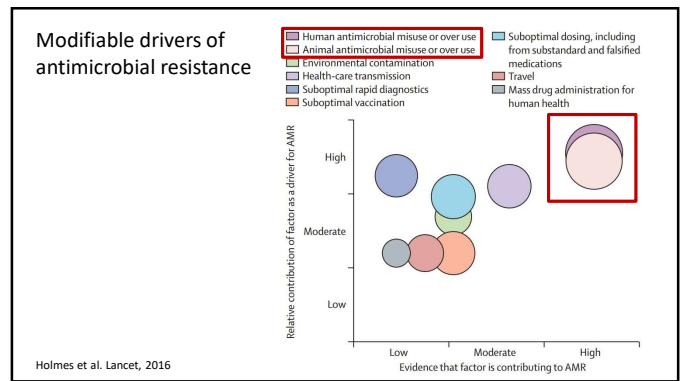
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# Risk Factors for Infections with Multidrug-Resistant Organisms (MDROs)

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**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, 3<sup>rd</sup> generation cephalosporin-resistant

**ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 2019**

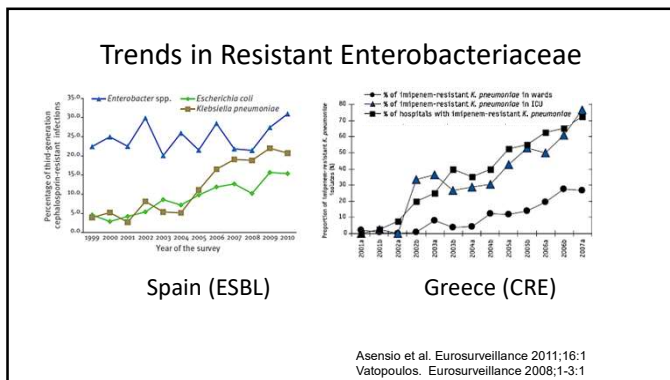
**Urgent Threats**

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

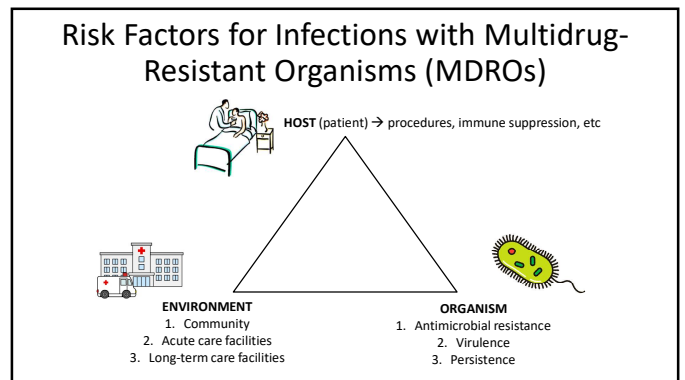
**Serious Threats**

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

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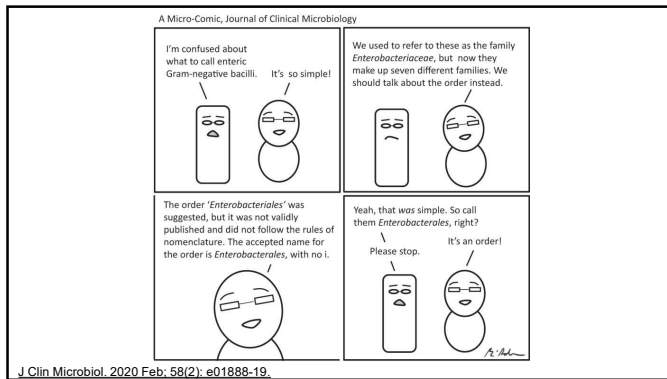
# But first some definitions...

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### Focus of AMR Lecture: GNRs

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

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## 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 3<sup>rd</sup>-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

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## 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*)

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## 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 IRT	Sulhydryl reagent variable Inhibitor-resistant TEM	Point mutation variants of SHV-1 TEM variants that are resistant to inhibition by clavulanate and sulbactam, but do not have ESBL phenotype
CHT	Complex mutant derived from TEM-1	TEM variants that are resistant to inhibition by clavulanate and sulbactam and also have ESBL phenotype
<b>CTX-M</b>	Cefotaxime-hydrolyzing $\beta$ -lactamase isolated in Munich	Derived from the chromosomal $\beta$ -lactamase from <i>Klebsiella</i> spp. Preferentially hydrolyses cefotaxime
GES	Guano-extended spectrum	More prevalent in <i>P. aeruginosa</i> than Enterobacterales
PER	<i>Pseudomonas</i> extended resistant	Some variants also hydrolyse carbapenems More prevalent in <i>P. aeruginosa</i> and <i>A. baumannii</i> than Enterobacterales
VEB	Vietnam extended-spectrum $\beta$ -lactamase	Inhibition by newer $\beta$ -lactamase inhibitors is variable Preferentially hydrolyses ceftazidime and aztreonam compared with cefotaxime
BEL	Belgium extended $\beta$ -lactamase	Inhibition by newer $\beta$ -lactamase inhibitors is variable
TLA	Named after the Tlghuica Indians (Mexico), from whom the first isolate was obtained	Preferentially hydrolyses ceftazidime and aztreonam compared with cefotaxime
SFO	From <i>Serratia fonticola</i>	Inducible
OXY	From <i>Klebsiella oxytoca</i>	Chromosomally encoded

Castanheira et al. JAC-Antimicrobial Resistance 2021;3(3) <https://doi.org/10.1093/iacamrd>

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## CDC-Defined CRE

**US Centers for Disease Control and Prevention (CDC)**

- 2012 CRE definition:
  - Non-susceptible* to imipenem, meropenem, doripenem (MIC > 1 mcg/ml), AND
  - resistant to all 3<sup>rd</sup> gen. cephalosporins tested
- 2015 (current) CRE definition:
  - Resistant* to imipenem, meropenem, doripenem (MIC  $\geq$  4 mcg/ml), AND/OR *ertapenem* (MIC  $\geq$  2 mcg/ml) AND/OR
  - Documented to produce carbapenemase

**"CRE"  $\neq$  Carbapenemase Production (CPE)**

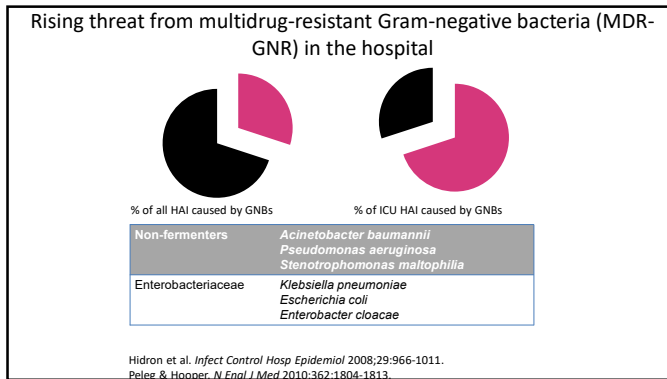
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## Carbapenemases

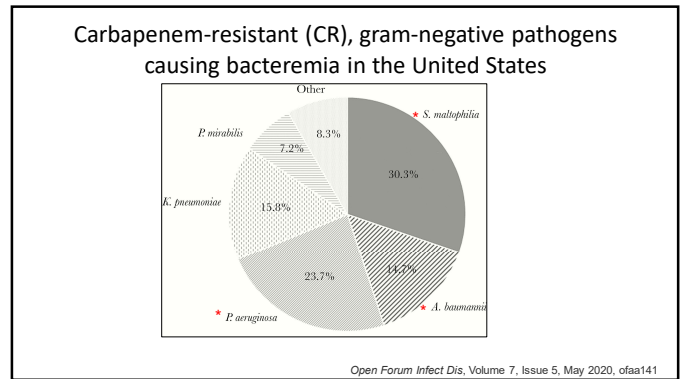
- KPC: Most common carbapenemase encountered in Enterobacterales in US
  - 13 variants; KPC-2 and KPC-3 most common
  - Class A serine-carbapenemase
  - Hydrolyzes carbapenems, cephalosporins, penicillins, aztreonam
- Other carbapenemases much less common in US
  - NDM, OXA, VIM, etc
  - Serine- and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

Ke et al. Biochem 2007;46:5732

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### Risk factors & at-risk population

Risk factors	Enterobacteriaceae	Non-fermenters
LOS	LOS	LOS
ICU stay	ICU stay	ICU stay
Catheters / devices	Catheters / devices	Catheters / devices
Ventilation	Ventilation	Ventilation
Prior antibiotics	Prior antibiotics	Prior antibiotics
Travel	Travel	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.

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### Risk factors are common across many MDR-pathogens

Risk Factors	Odds Ratio or Relative Risk (References)			
	Methicillin-Resistant <i>Staphylococcus aureus</i> (11, 12, 16-26)	Vancomycin-Resistant <i>Enterococcus</i> (27-48)	Extended-Spectrum $\beta$ -Lactamase-Producing Gram-Negative Bacilli (49-57)	<i>Clostridium difficile</i> (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	† (12, 17, 18, 22, 23, 26)	4.4 to 6.98 (35, 42)	† (51), NS (49, 56, 57)	1.71 to 6.7 (66, 76)
Renal failure	† (12, 17, 23, 26), NS (22)	8.4 (33)		
Hematologic cancer	† (12, 17, 23, 26)	8.4 (33)		
Hepatic failure	† (12, 17, 23, 26)	2.3 to 6.1 (29, 30, 32, 47)	11.6 (53)	2.0 (63)
Severity of illness	1.9 (24)	4.1 to 2.9 (32, 45)	3.6 (52)	3.1 (66)
Interhospital transfer of a patient: patient from a nursing home	6.9 (24)	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)
Extended length of stay	1.7 to 17.5 (16-19, 21-23, 25, 26)			

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

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### Endoscope-related outbreaks

EDITORIAL

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#### Gastrointestinal Endoscopes

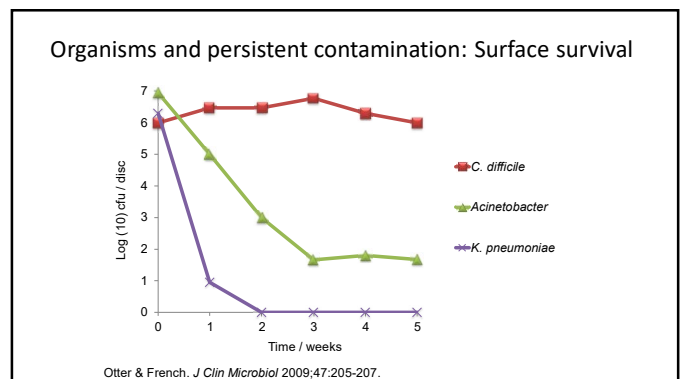
#### A Need to Shift From Disinfection to Sterilization?

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

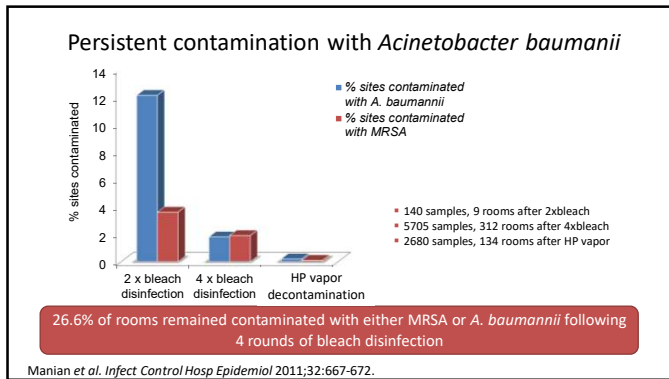
Several outbreaks featuring carbapenemase-producing Enterobacteriaceae -NDM and KPC carbapenemase genes

- possibly related to elevator channel in scopes
- likely "tip of the iceberg"

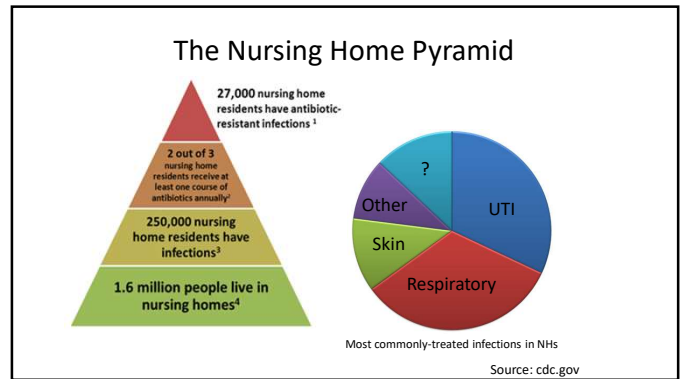
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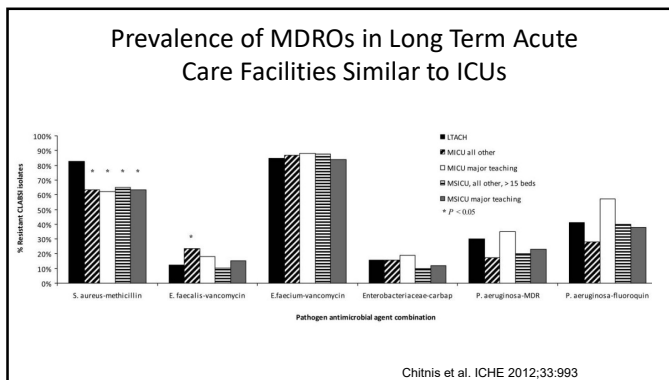
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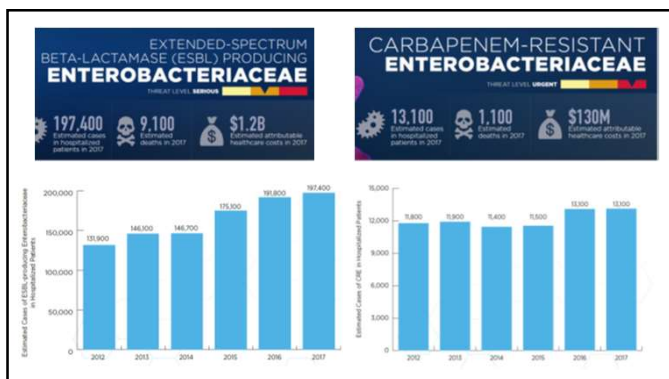
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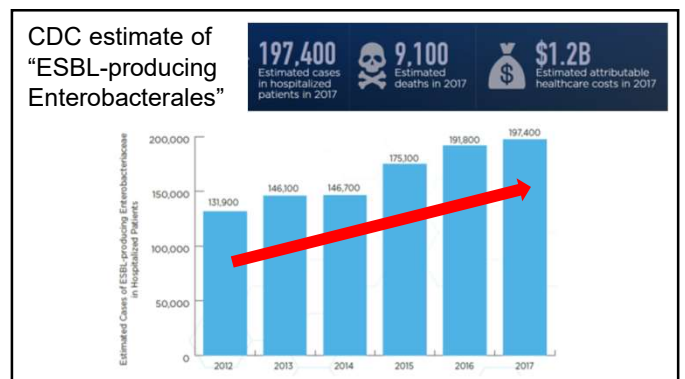
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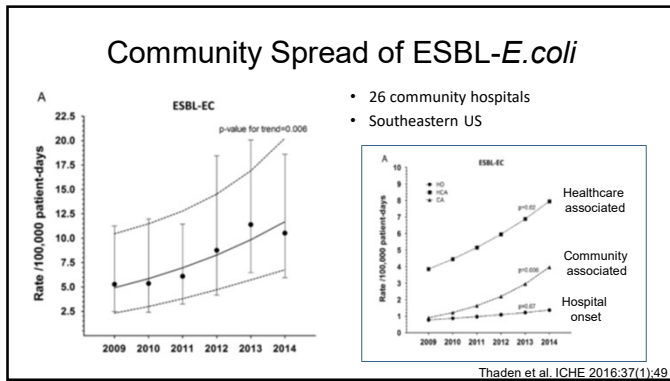


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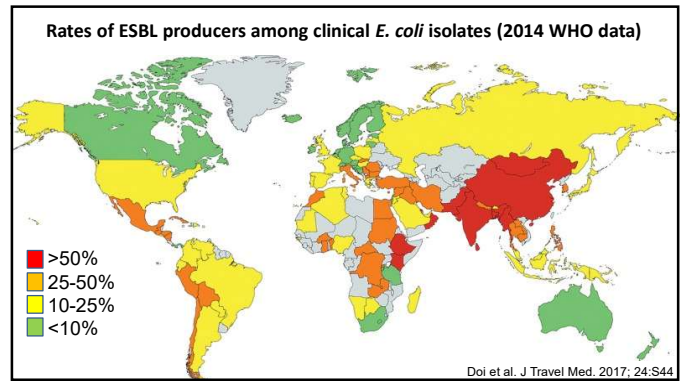


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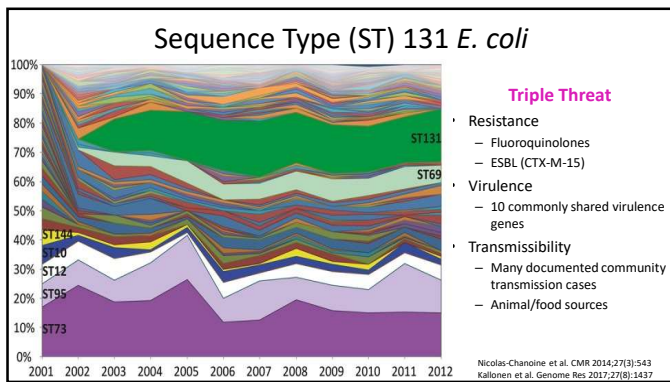




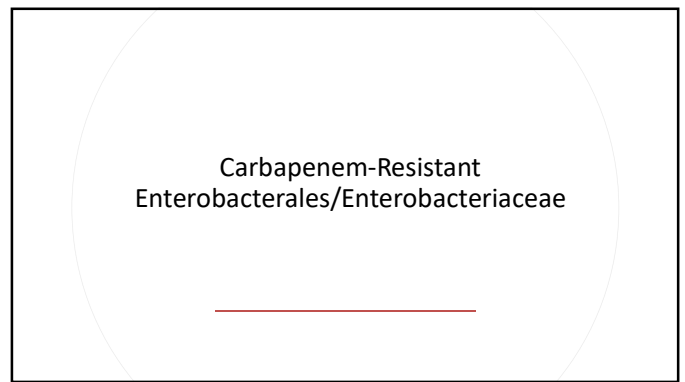
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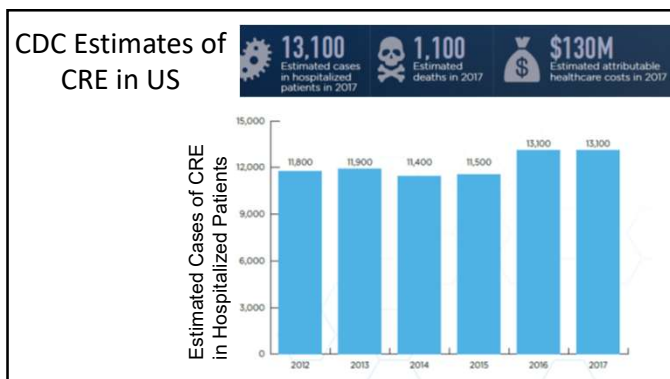
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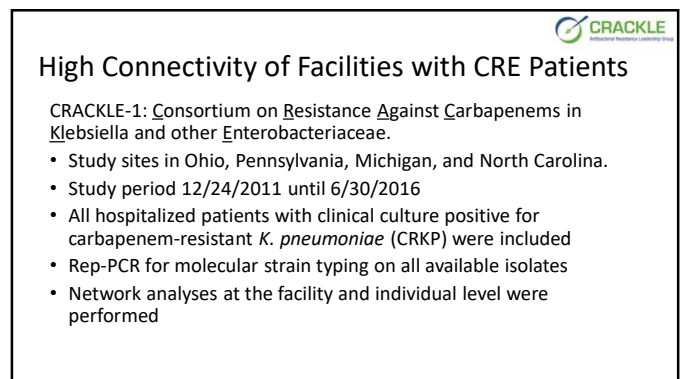
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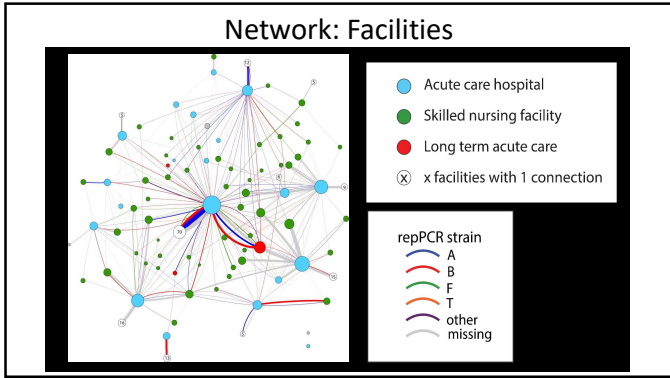


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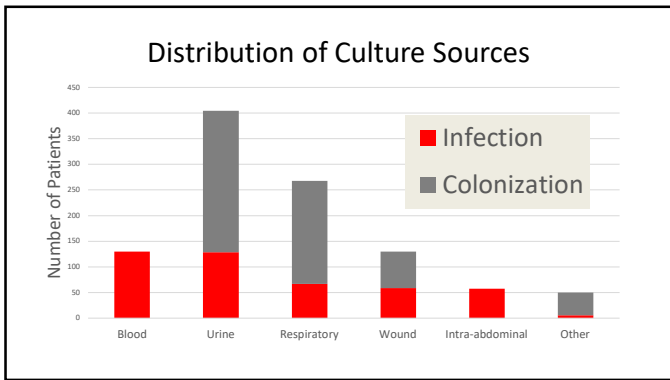
### CRE in US (CRACKLE-2 data)

MDRO Network  
Antibiotic Resistance Leadership Group

- 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.

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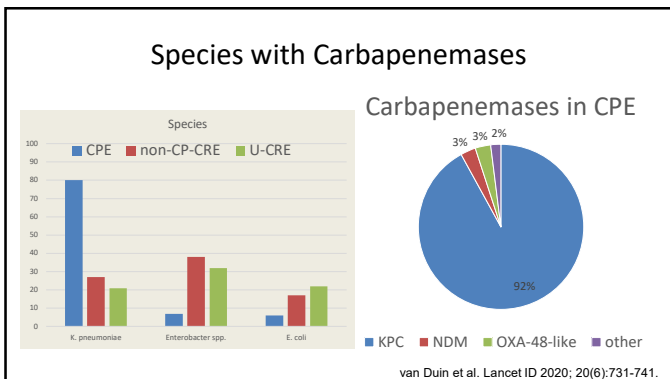
### CDC-CRE: 3 subsets

All isolates met CDC criteria for CRE at local micro lab

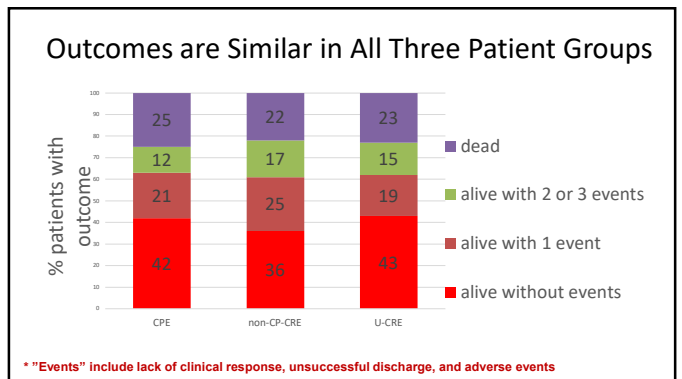
- CPE:** Carbapenemase-producing Enterobacterales
  - Carbapenemase gene present on whole genome sequencing and/or targeted PCR
- Non-CP-CRE:** Non-carbapenemase-producing CRE
  - No carbapenemase gene present
  - Carbapenem resistance confirmed in central laboratory
- U-CRE:** "Unconfirmed" CRE
  -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

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

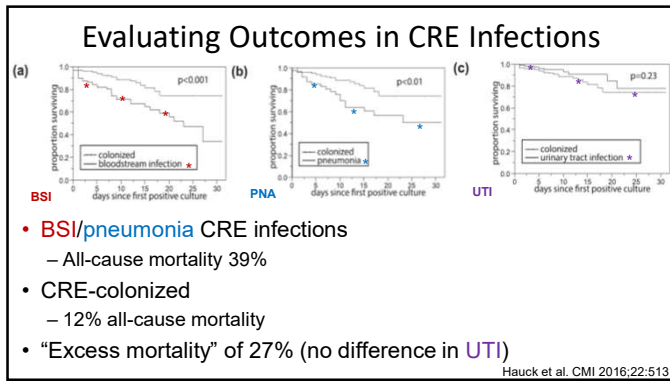
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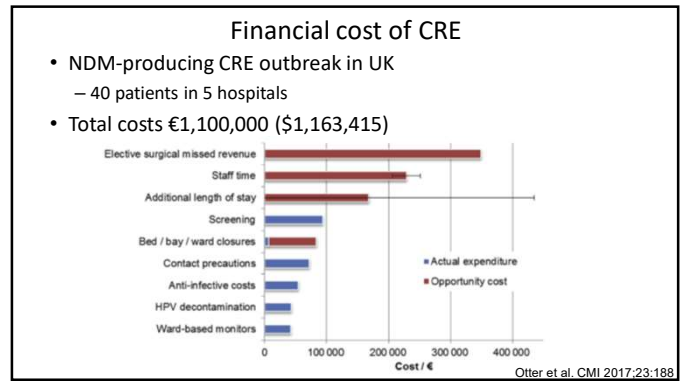
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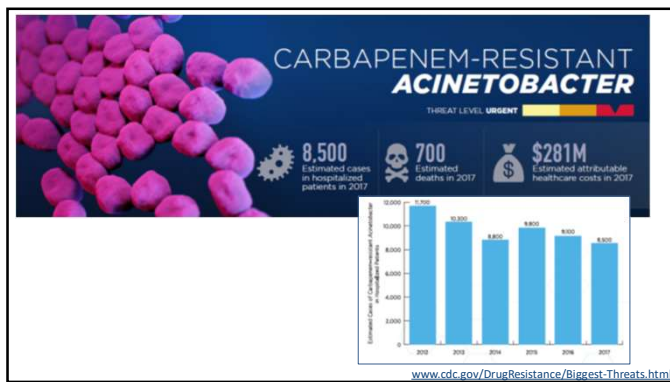
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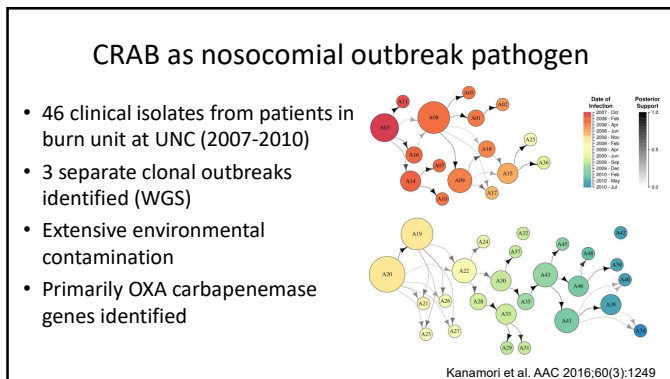


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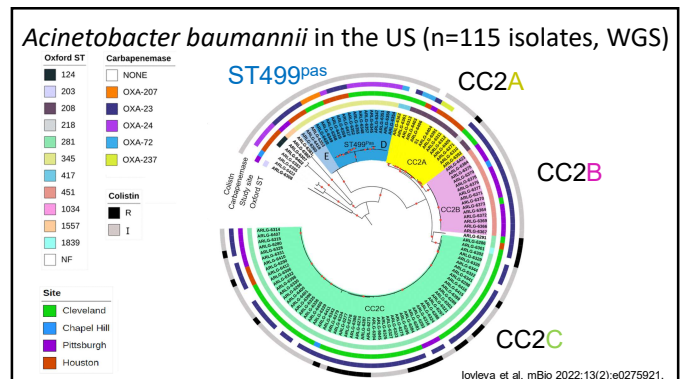
### Carbapenem-resistant *Acinetobacter baumannii* (CRAB) in the US

- 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%

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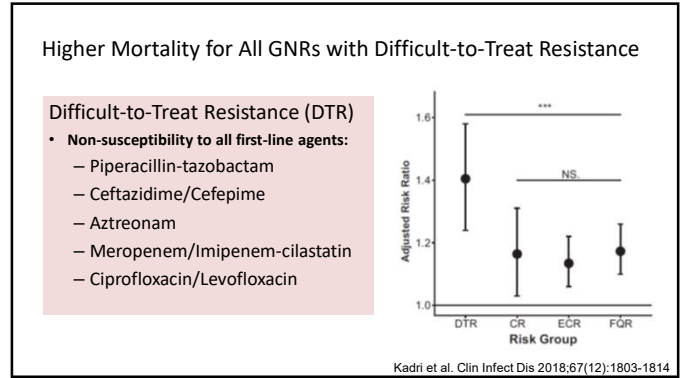
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**Summary**

- 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

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**Questions?**

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?

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?

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