

The Epidemiology of Carbapenem-Resistant Enterobacteriaceae (CRE): Tackling the Problem across Healthcare Settings

Jennifer Han, MD, MSCE

Assistant Professor of Medicine and Epidemiology

Associate Healthcare Epidemiologist

Hospital of the University of Pennsylvania

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Disclosures

None to report



Deadly 'superbugs' invade U.S. health care facilities

DEADLY BACTERIA THAT DEFY DRUGS OF LAST RESORT

Drug-resistant superbug may be more widespread than previously known



Are we headed for an antibiotic apocalypse? Deadly superbugs

'Nightmare' bacteria on warpath

Objectives



- ◆ **Overview of carbapenem-resistant Enterobacteriaceae (CRE)**
- ◆ **The threat of CRE across healthcare settings**
 - Long-term acute care hospitals (LTACHs)
 - Regional amplifiers of CRE
- ◆ **How can we further reduce the emergence of CRE?**
 - The role of patient sharing
 - Collaboration across healthcare settings

Emerging Antibiotic Resistance in Gram-Negative Bacteria

- ♦ Carbapenems → “last line of defense”

Carbapenem	FDA Approval
Imipenem	1987
Meropenem	1996
Ertapenem	2001
Doripenem	2007

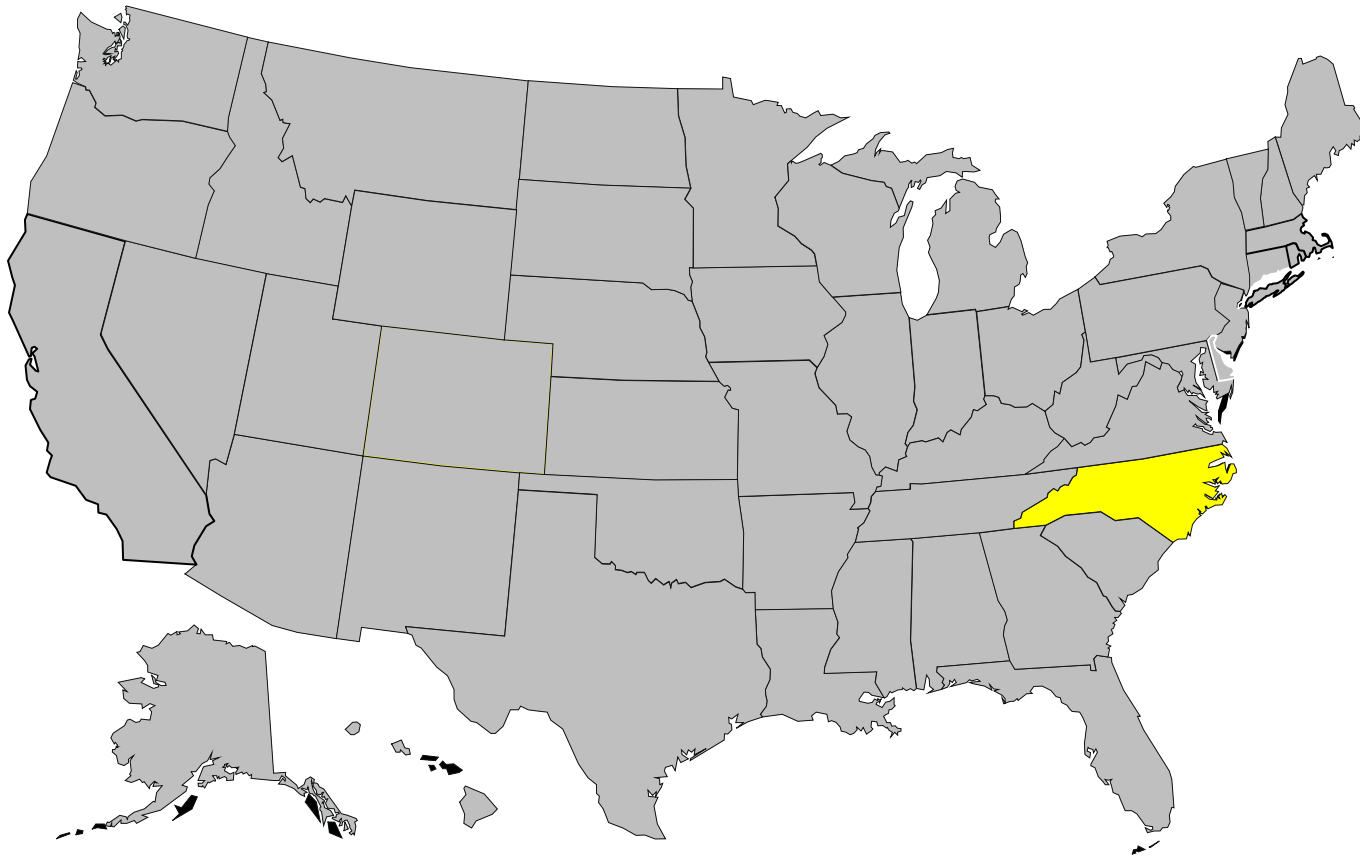
CRE: definitions

- ◆ **Enterobacteriaceae** → gram-negative bacteria causing both healthcare and community-acquired infections
 - *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species
- ◆ **Carbapenem-resistant Enterobacteriaceae (CRE)**
 - Enterobacteriaceae resistant to carbapenem antibiotics and/or
 - Carbapenemase production → hydrolyze beta-lactams
- ◆ **Carbapenemases** → highly transmissible plasmids
 - KPC most common in United States
 - Metallo-beta-lactamases with foreign medical care
 - NDM, VIM, IMP



Novel Carbapenem-Hydrolyzing β -Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

HESNA YIGIT,¹ ANNE MARIE QUEENAN,² GREGORY J. ANDERSON,¹
ANTONIO DOMENECH-SANCHEZ,³ JAMES W. BIDDLE,¹ CHRISTINE D. STEWARD,¹
SEBASTIAN ALBERTI,⁴ KAREN BUSH,² AND FRED C. TENOVER^{1*}



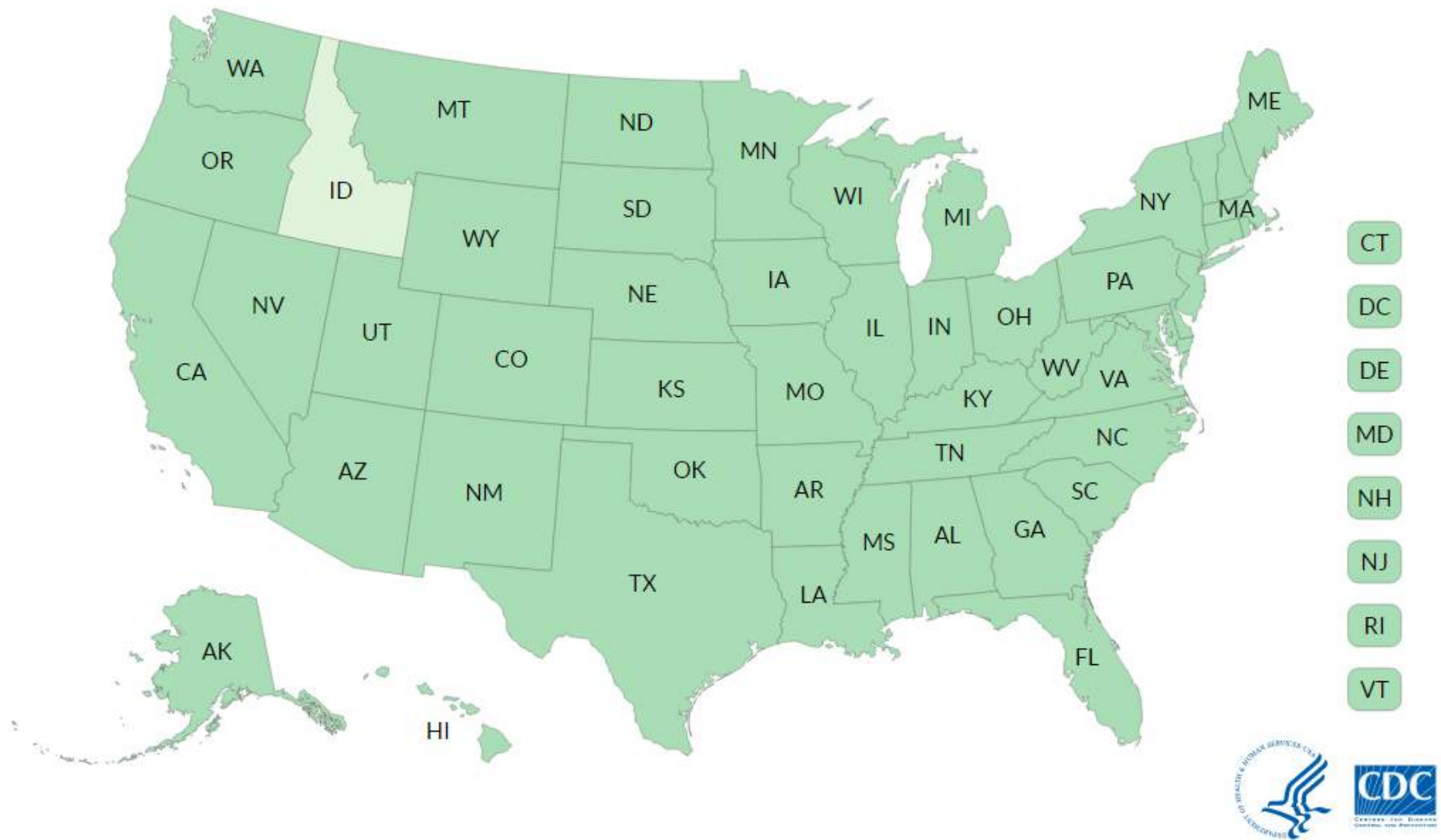
As of August 2017, how many U.S. states has CRE NOT yet been reported in?

- ◆ A. 23
- ◆ B. 12
- ◆ C. 6
- ◆ D. 3
- ◆ E. 1



 **Vitalsigns**[™]
www.cdc.gov/vitalsigns

Patients with KPC-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of August 2017, by state





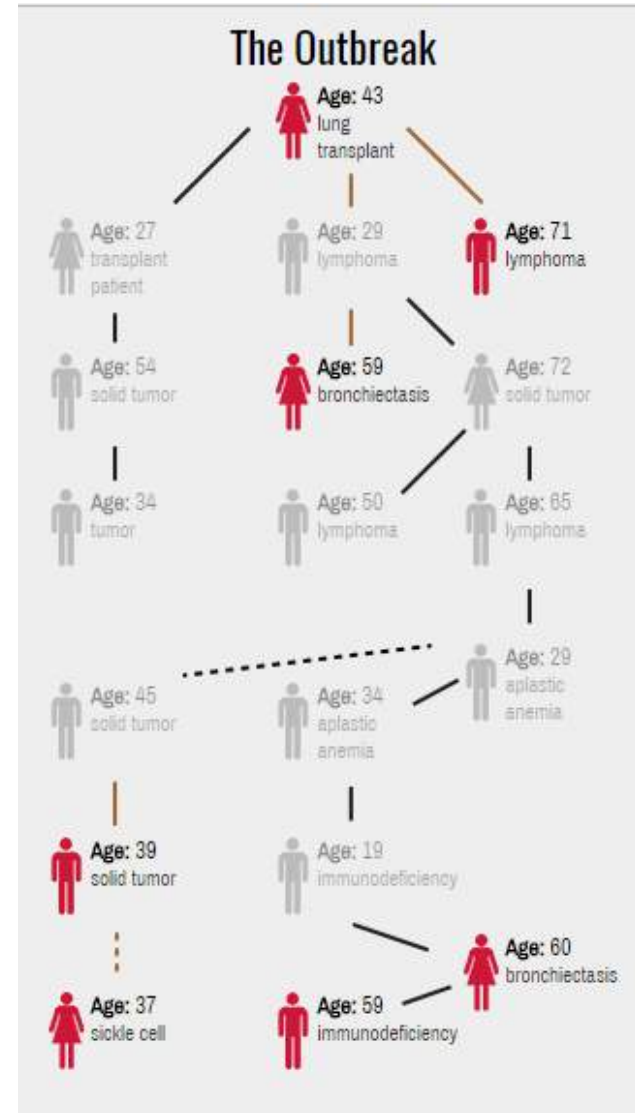
WASHINGTONIAN
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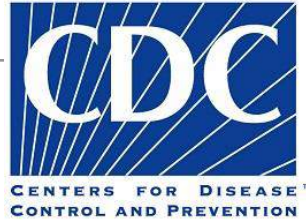
book 668

Outbreak at NIH

They tore out pipes, walled off a hallway, and sent in a robot. But staff at the National Institutes of Health seemed powerless to stop the spread of a drug-resistant superbug.

By John Buntin | June 4, 2013





HAZARD LEVEL URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (*C. difficile*), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

HAZARD LEVEL SERIOUS

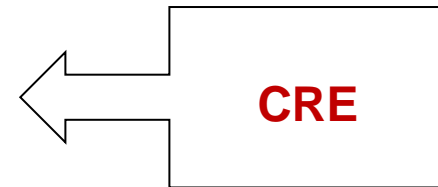
These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum β -lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumoniae*, Drug-resistant tuberculosis (MDR and XDR)

HAZARD LEVEL CONCERNING

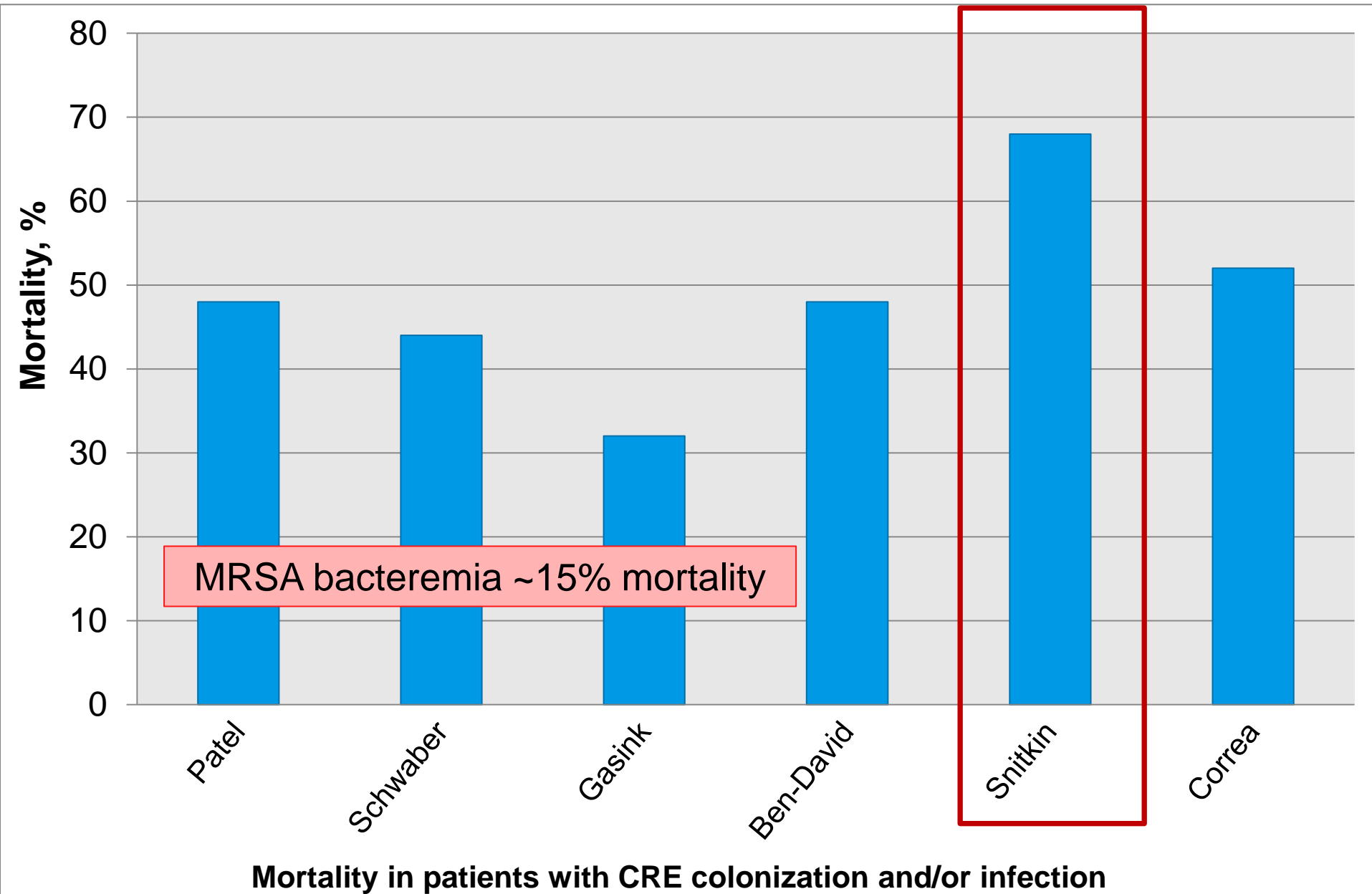
These are bacteria for which the threat of antibiotic resistance is low, and/ or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B



“...require urgent public health attention to identify infections and to limit transmission.”

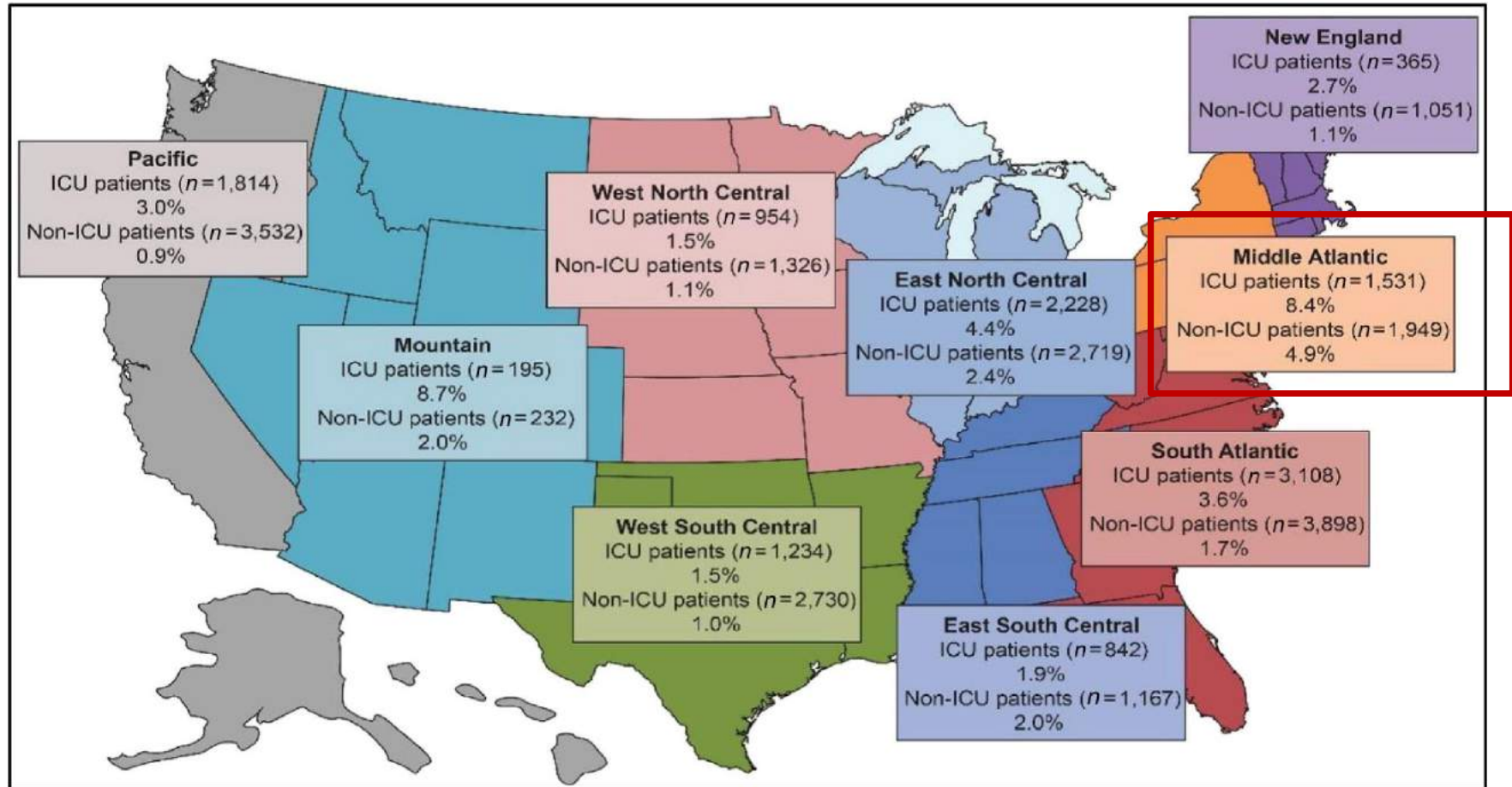
CRE: clinical outcomes in acute care hospitals



Carbapenem-Resistant Enterobacteriaceae (CRE) a major therapeutic challenge

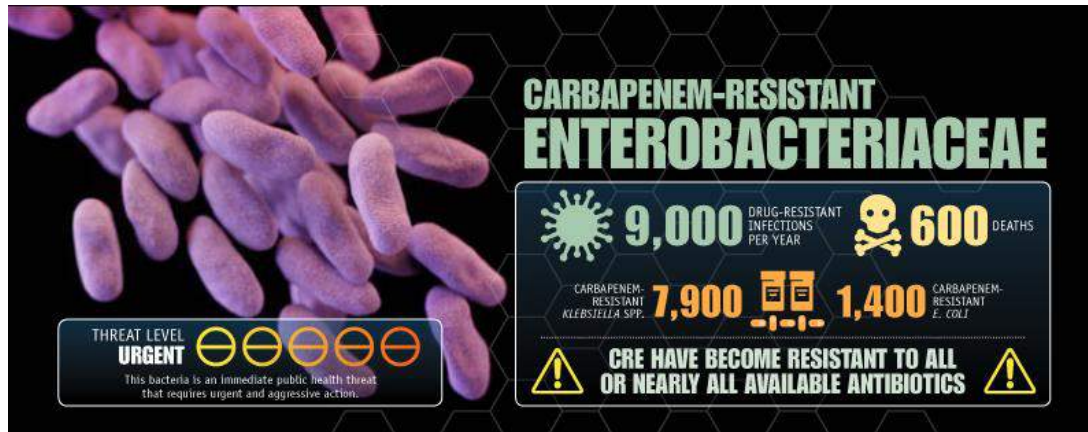
<u>Antimicrobial agent</u>	<u>Interpretation</u>	<u>Antimicrobial agent</u>	<u>Interpretation</u>
Amikacin	I	Ertapenem	R
Amox/clav	R	Gentamicin	R
Ampicillin	R	Imipenem	R
Aztreonam	R	Meropenem	R
Cefazolin	R	Gentamicin	R
Cefpodoxime	R	Tobramycin	R
Cefotaxime	R	TMP-SMX	R
Cetotetan	R		
Ceftriaxone	R		
Ceftazidime	R	Polymyxin B	≤ 2 µg/mL
Cefepime	R	Colistin	≤ 2 µg/mL
Ciprofloxacin	R	Tigecycline	≤ 2 µg/mL

CRE prevalence in acute care hospitals



Abbreviations: CRE = carbapenem-resistant Enterobacteriaceae; ICU = intensive care unit. Indications include cUTI, cIAI, hospital-associated pneumonia, and BSIs.

But is this the entire picture???



Acute care hospitals

Other healthcare settings??

Objectives



- ◆ **Overview of carbapenem-resistant Enterobacteriaceae (CRE)**

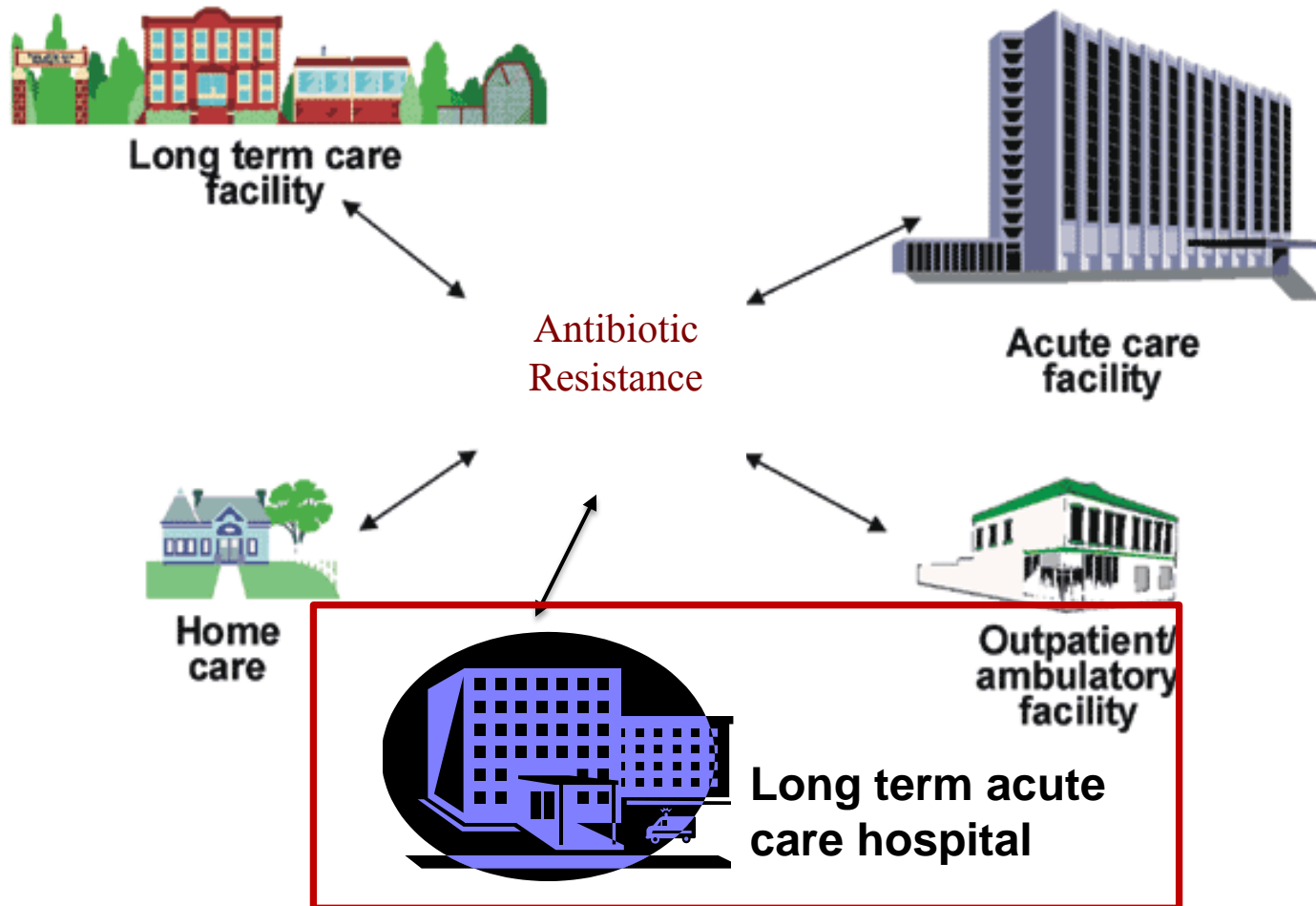
- ◆ **The threat of CRE across healthcare settings**

- Long-term acute care hospitals (LTACHs)
- Regional amplifiers of CRE

- ◆ **How can we further reduce the emergence of CRE?**

- The role of patient sharing
- Collaboration across healthcare settings

Antibiotic resistance in the 21st century: “no institution is an island”



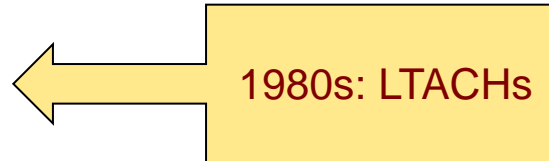
What is an LTACH?

- ◆ Hospital Length of Stay

- 1975 = 11.4 days

- 2004 = 6.5 days

- 2006 - 2011 = 4.8 days



- ◆ Require hospitalization for ≥ 25 days (CMS)

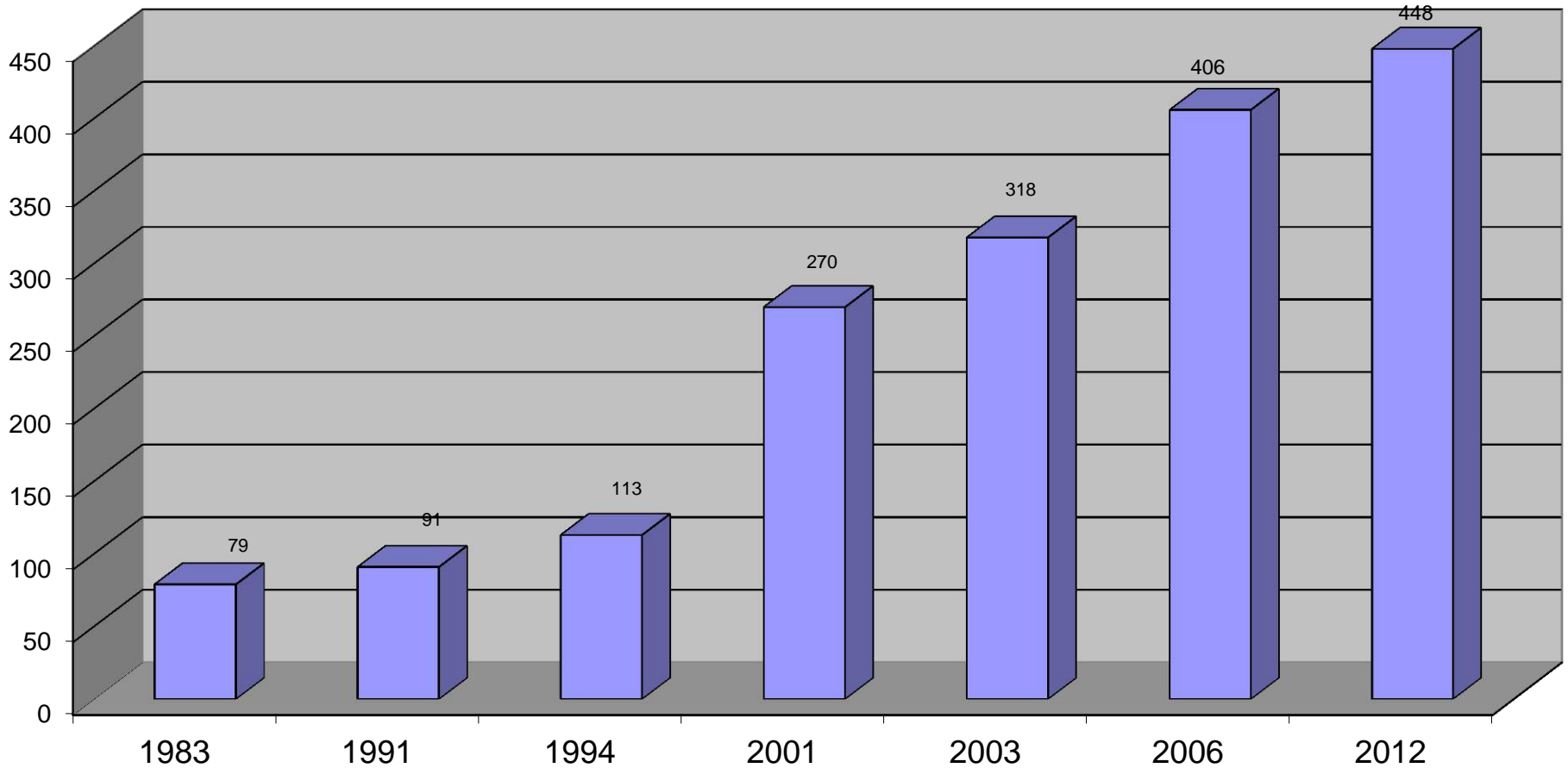
- ◆ Complex medical conditions → 90% transferred from ACHs with average LOS of 14 days

- ◆ Acuity of care meets acute care hospital requirements

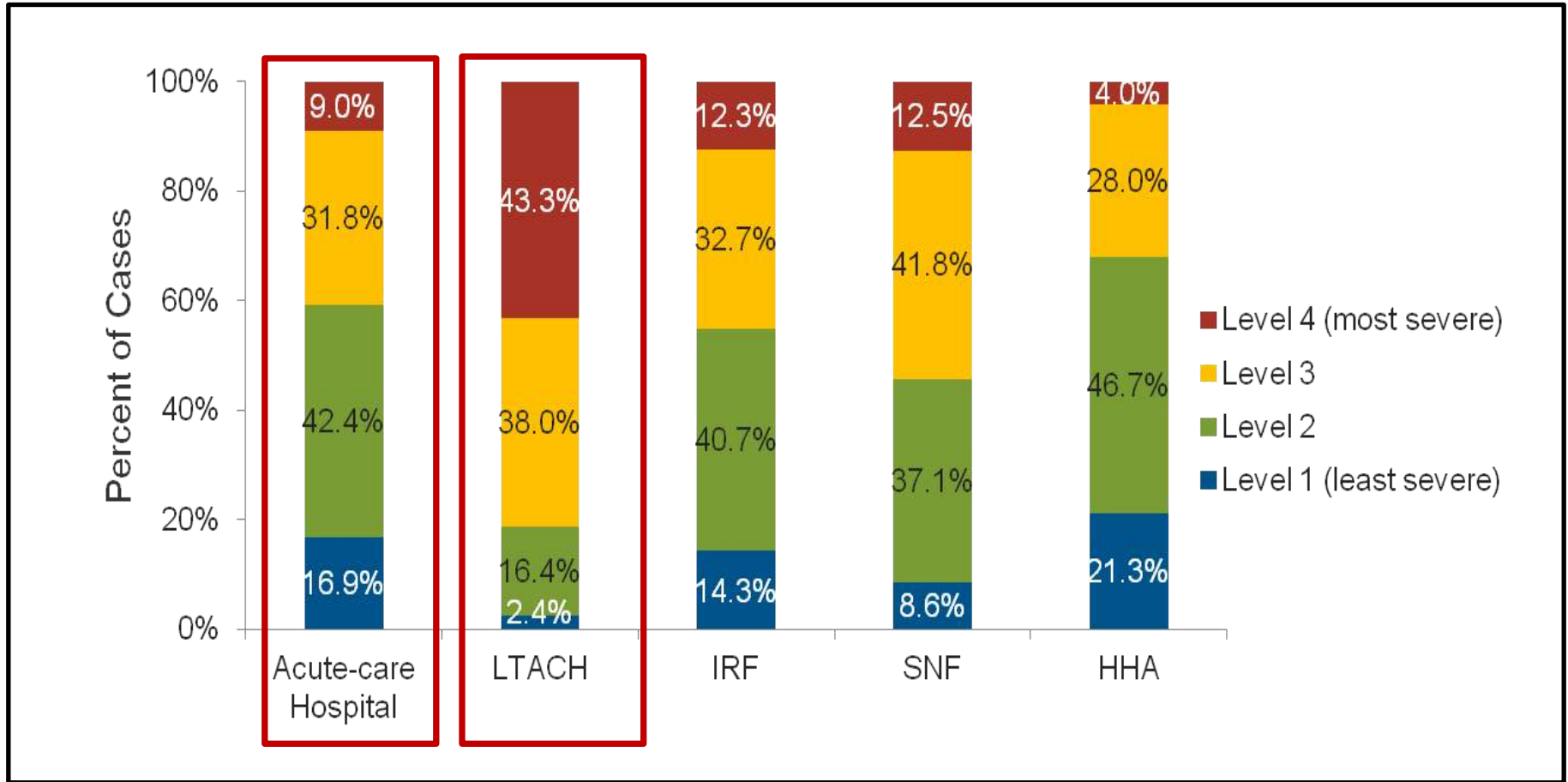
- Licensed and certified *under same criteria* as short-term acute care hospitals

LTACH Growth

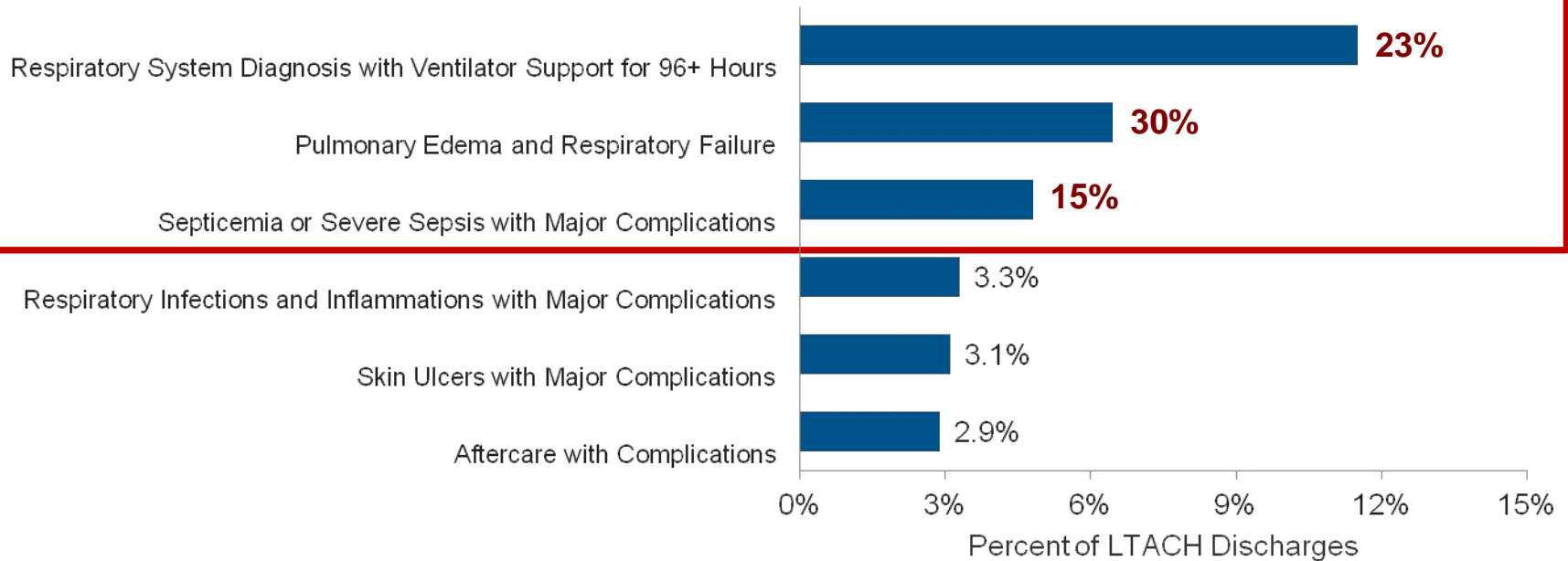
- Number of LTACHs increased ~65% from 2001 to 2012
- Free-standing versus hospital-based



Patient severity of illness varies by healthcare setting



Conditions among Medicare beneficiaries admitted to LTACHs 2012



Source: Medicare Payment Advisory Commission. (2010). *March Report to the Congress: Long-term Care Hospital Services*. Washington, DC.

LTACHs and antibiotic use

TABLE 2. Comparison of Antimicrobial Use at Long-Term Acute Care Hospitals (LTACHs) and at National Nosocomial Infections Surveillance system (NNIS) Medical Intensive Care Units (ICUs)

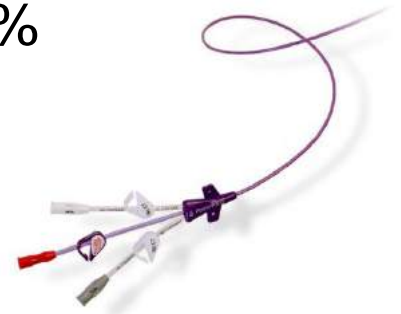
Antimicrobial	Antimicrobial use, DDDs/1,000 patient-days					
	In NNIS medical ICUs, by percentile distribution of values ^a					In LTACHs, mean value ^b
	10th	25th	50th	75th	90th	
Antipseudomonal penicillins	13.0	27.5	66.2	113	171	31.9
Third-generation cephalosporins	92.2	109	194	322	386	77.6
Carbapenems	0	7.9	23.9	37.2	98.3	31.8
Fluoroquinolones	29.5	56.8	86.5	146	257	241
Vancomycin (intravenous)	42.9	55.7	75.2	153	220	90.2

^a Reported by 35 NNIS medical ICUs from January 1998 through June 2003.³

^b Reported by 45 LTACHs during 2002 and/or 2003. Fourteen of the 45 LTACHs provided data from both study years; therefore, a maximum of 59 LTACH-years of data were available for analysis.

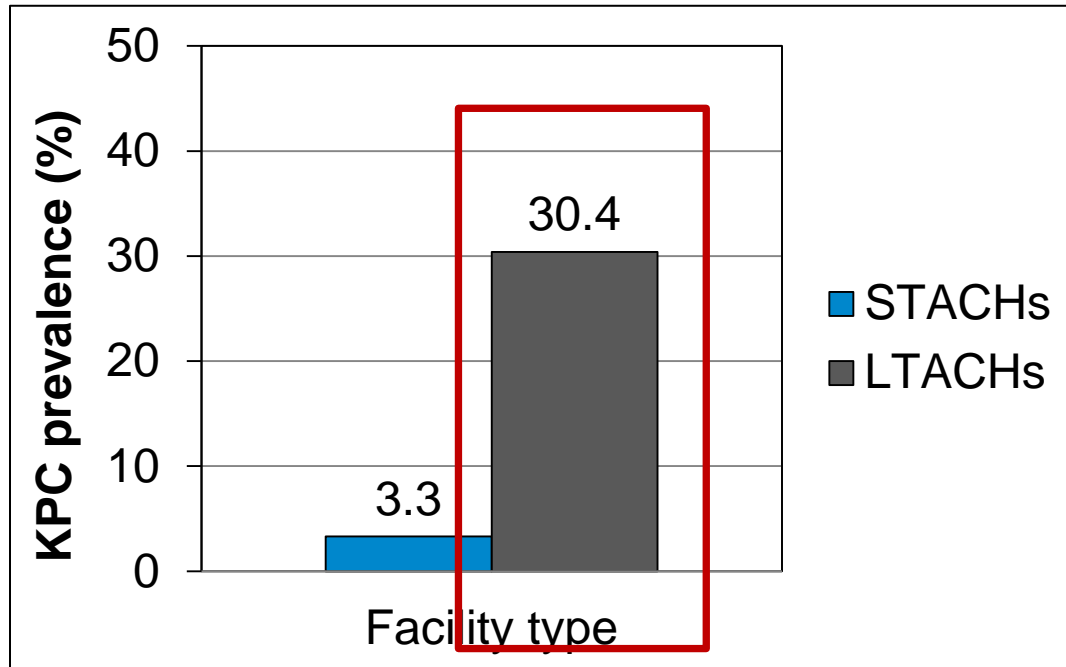
LTACHs: the “Perfect Storm” for emergence of antibiotic resistance

- ◆ **Complex patient population with average LOS >25 days**
 - “Chronically, critically-ill”
 - 1-year mortality after LTACH admission ~52%
- ◆ **Device utilization high**
 - Up to ~75% central venous catheter use
- ◆ **Rate of antibiotic use high**
 - Comparable or higher than ICU setting
- ◆ **Logistics of isolation and cohorting**



Epidemiology of CRE in LTACHs

- Cross-sectional point prevalence survey, 2011, n~400 patients
- Chicago-area: Hospital ICUs (n = 24) and LTACHs (n = 7)



- Large, most likely unrecognized CRE colonization pressure in LTACHs

CRE in LTACHs: what are the implications?

- ◆ **LTACHs are major reservoirs of CRE**
 - ◆ **Carbapenem resistance rate ~25%**
 - ◆ **Overall, very high resistance rates to broad-spectrum gram-negative agents (e.g., aminoglycosides, fluoroquinolones)**
 - ◆ **Notably high rate of resistance to colistin/polymyxin B of ~16%**
- **Regional approach to surveillance, infection prevention, and antimicrobial stewardship are key**

Objectives



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Regional burden of CRE: role of patient sharing

◆ Illinois acute care hospitals (n = 99) and LTACHs, 2014

Table 1. Characteristics of Short-Term Acute Care Hospitals That Reported at Least 1 Carbapenem-Resistant *Enterobacteriaceae* Case to the Illinois Extensively Drug-Resistant Organism Registry During, 2014

Hospital Characteristic	Mean	Median	Interquartile Range
Cases	3.5	1.0	0–4
Case rate (per 10 000 patient-days)	1.0	0.2	0–1.1
No. of beds	157	126	27–234
No. of admissions (per year)	7388	5301	1040–10 892
Patient-days	35 545	24 181	4618–48 072
No. of patients shared with an LTACH	2.6	0	0–3
No. of patients shared with an LTACH (Chicagoland region only)	7.9	5	2–11

Patient-Sharing Characteristics	Mean	Minimum	Maximum
No. of hospital connections (degree)	64	1	145
Degree (Chicagoland)	92	17	145
Degree (non-Chicago urban)	71	11	138
Degree (rural)	27	1	86

Regional burden of CRE: role of patient sharing

Table 3. Adjusted Associations Between Hospital Characteristics (Centrality and Long-Term Acute Care Hospital Sharing) and Carbapenem-Resistant *Enterobacteriaceae* Rates (per 10 000 Patient-days) Among Short-Term Acute Care Hospitals in Illinois

Hospital Characteristic	Rate Ratio	95% Confidence Interval	P Value
Degree centrality, by region ^a			
Chicagoland ^b	1.027	1.002–1.052	.03
Non-Chicago urban ^b	1.025	1.002–1.048	.03
Rural county ^b	1.056	1.030–1.082	<.0001
Long-term acute care hospital sharing ^a			
≥4 vs <4 patients	2.08	.85–5.08	.11

- ◆ **Higher CRE rates in facilities with greater patient sharing**
- ◆ **Each additional hospital connection**
 - 6% increase in CRE rate in rural facilities
 - 3% increase in CRE rate in urban facilities

“No institution is an island” – social networks

CONNECTEDNESS = INTERFACILITY SOLUTIONS

- ◆ Knowledge/education and sharing of CRE rates
- ◆ Standardized communication about CRE on patient transfers
- ◆ Regional coordinated surveillance, infection prevention, and antimicrobial stewardship interventions
- ◆ Not all “social networks” overlap
→ Departments of Health are key



Vital Signs: Estimated Effects of a Coordinated Approach for Action to Reduce Antibiotic-Resistant Infections in Health Care Facilities — United States

Rachel B. Slayton, PhD¹, Damon Toth, PhD², Bruce Y. Lee, MD³, Windy Tanner, PhD²,

- ◆ **Historically, infection control interventions designed to ↓ spread of MDROs have been implemented individually**
- ◆ **Modeling data from NHSN and Emerging Infections Program**
 - CRE, *C. difficile*, MRSA, MDR *P. aeruginosa*
- ◆ **Accounting for shared patient networks and inter-facility spread**
 - Small (n = 10) and large (n ~100) networks as examples

Vital Signs: Estimated Effects of a Coordinated Approach for Action to Reduce Antibiotic-Resistant Infections in Health Care Facilities — United States

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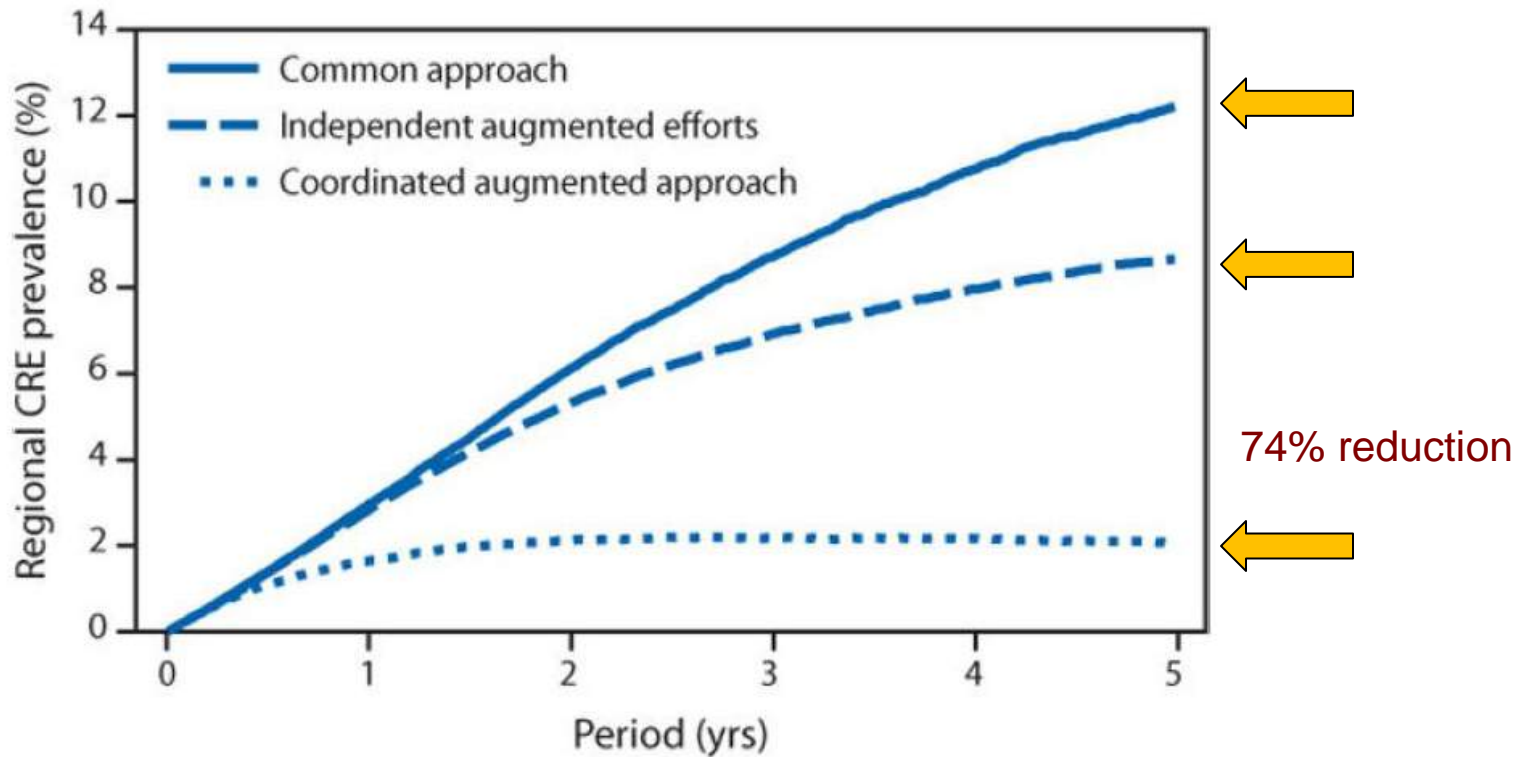
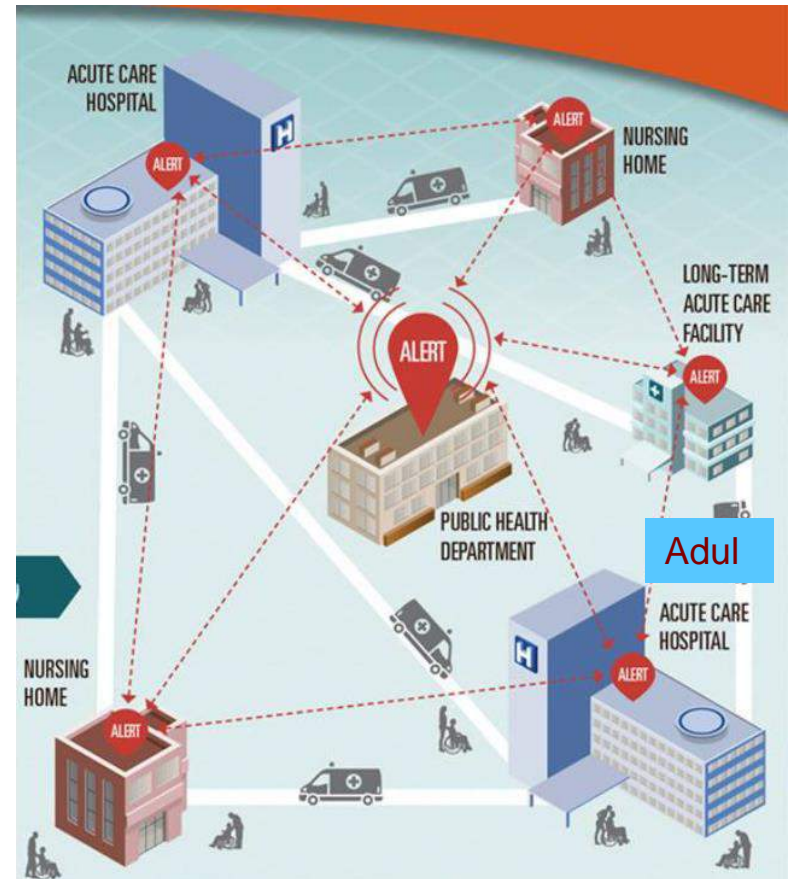


FIGURE 2. Projected regional prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) over a 5-year period under three different intervention scenarios — 10-facility model, United States*

“No institution is an island” – social networks

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eXtensively
D rug
R esistant
O rganism
Registry



Mandatory reporting began November
1, 2013

https://www.xdro.org/img/MEMO_XDRO%20Registry_090413_Final.pdf

www.xdro.org

- ◆ **Mandatory reporting of CRE by:**
 - Acute care hospitals
 - LTACHs
 - LTCFs
 - Laboratories
- ◆ **First CRE positive culture per patient stay**

XDRO Report

XDRO culture information

* **Organism name (genus/species)**
Please Select Organism: ▼

* **Specimen source**
Please Select Specimen: ▼

*XDRO criteria (select all that apply)

[Reporting rule](#)

Molecular test (e.g. PCR) specific for carbapenemase

Phenotypic test (e.g. Modified Hodge) specific for carbapenemase production

For E. coli and Klebsiella spp. only: Resistant to ALL 3rd gen cephalosporins tested and non-susceptible (intermediate or resistant) to one carbapenem. Ignore ertapenem.

* **Date (culture acquisition)**

mm / dd / yyyy

* **Mechanism of resistance**

Please Select Mechanism: ▼
(molecular test required)

Facility information

* **Facility name**
Illinois Department Of Public Health

* **Patient MRN**

* **Date of admission/Encounter Date**
mm / dd / yyyy

Culture obtained as outpatient

Patient demographics

* **First name**

Middle name(if applicable)

* **Last name**

* **Gender**
 Male Female

* **Date of birth(mm/dd/yyyy)**
mm / dd / yyyy

Social Security Number(last4)

Race
Please Select One: ▼

Ethnicity
 Hispanic or Latino
 Not Hispanic or Latino

* **Street address**

* **City** * **County**

* **State** * **Zip code**
Illinois ▼

Comments

Include any information that may help infection preventionists who view your submission. Comments are not routinely monitored by IDPH. To communicate directly with IDPH, please email DPH.XDRORegistry@Illinois.gov

For laboratories and IDPH only

* **Select facility that sent specimen:**

Please Select Facility: ▼

[CANCEL](#) [SAVE DRAFT](#) [SUBMIT](#)

Search Patient

* Last name * Date of birth / / First name

Search Instruction

a. Available fields

Last name (required), first name (optional), DOB (required).

b. Search algorithm

- i. If you enter all 3 fields, then attempt to match (exact; case insensitive) on all 3 fields.
- ii. If no match returns on 3 fields, then attempt to match (exact; case insensitive) on last name and DOB (ignore first name completely).

c. Results display

- i. In general, You will see the search results for exactly how you entered the information. If there are no exact matches for last name and dob, you will see a NULL result.

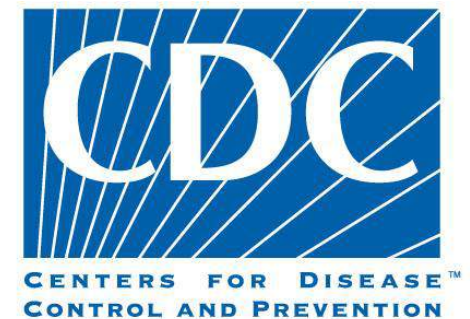
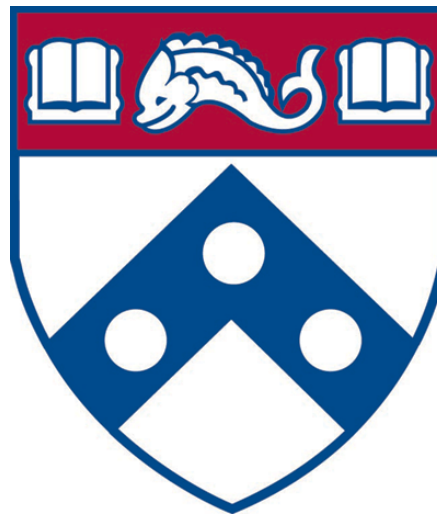
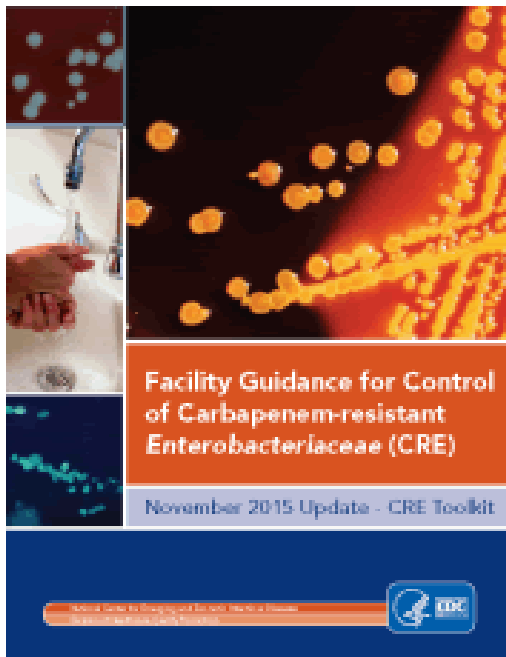
- ◆ **November 1, 2013 to October 31, 2014**
 - First report per patient
- ◆ **115 acute care hospitals, 5 LTACHs, 46 LTCFs**
- ◆ **1,557 CRE reports, ~4.3/day**

Conclusions

- ◆ **CRE is one of the most urgent antibiotic resistance threats**
- ◆ **Rates of CRE are increasing nationally, especially in long-term care settings**
 - Awareness and surveillance are critical
- ◆ **No institution is an island**
 - Knowledge of patient sharing networks and regional CRE rates is critical
- ◆ **Interventions to reduce the further spread of CRE need to focus on coordinated, collaborative efforts**
 - Standardized communication
 - Regional infection control and antibiotic stewardship strategies

Thank you!

jennifer.han@uphs.upenn.edu



<http://www.cdc.gov/HAI/organisms/cre/index.html>