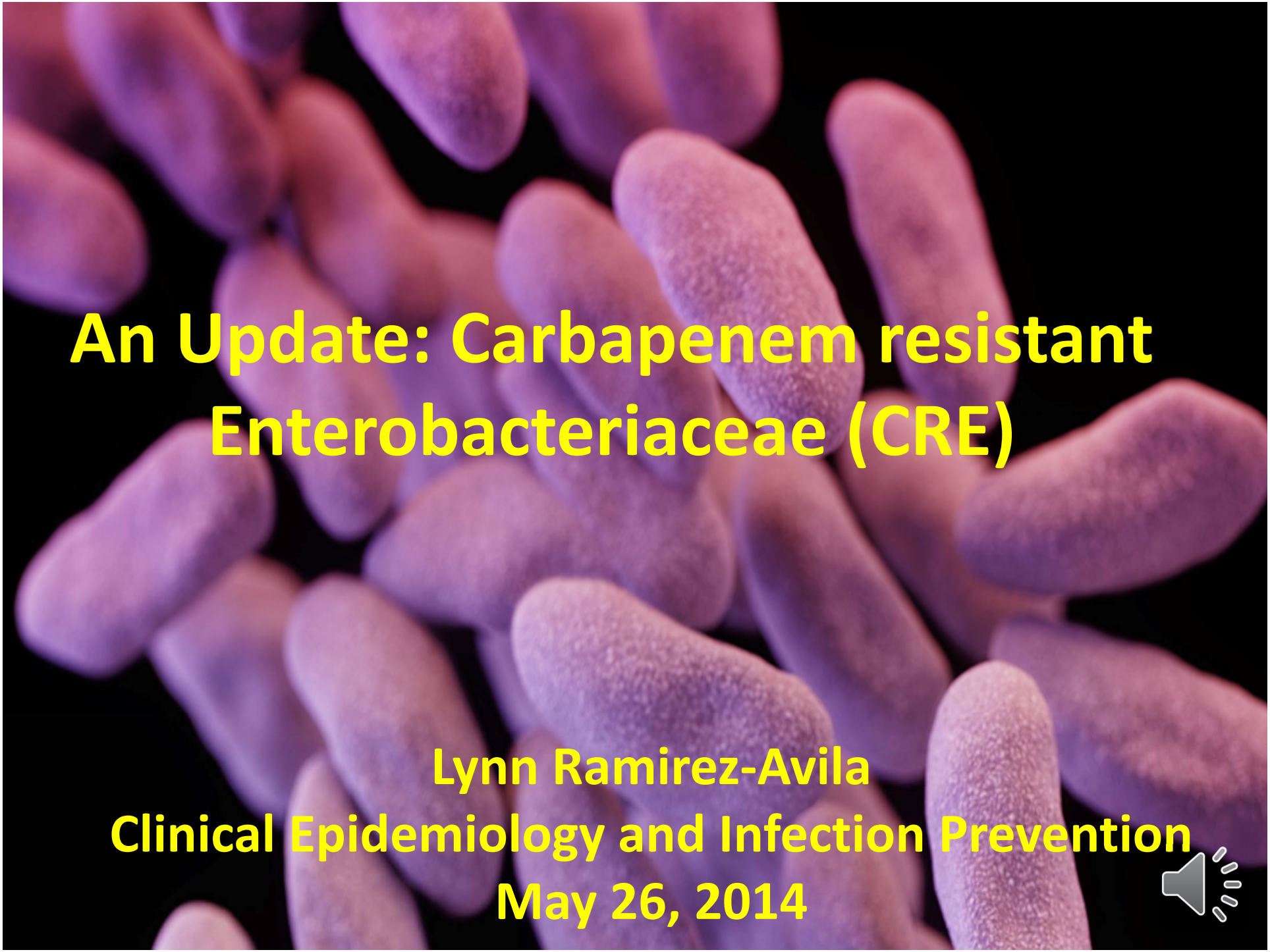

An Update: Carbapenem resistant Enterobacteriaceae (CRE)

Lynn Ramirez-Avila
Clinical Epidemiology and Infection Prevention
May 26, 2014

Outline

- Definitions
- Epidemiology
- Outcomes
- Treatment
- Prevention
- CRE in the UCLA HealthSystem

What are Enterobacteriaceae?

- Enterobacteriaceae
  - Normal flora that inhabit the GI tract
  - Gram negative rods
  - Can cause infections in the community & healthcare setting
  - More than 70 species
    - *Klebsiella pneumoniae*
    - *Escherichia coli*
    - *Enterobacter sp.*
    - Does not include Acinetobacter or Pseudomonas

Enterobacteriaceae

- Account for >21% of device-related infections
- Beta-lactam antibiotics have been the primary treatment of these organisms
  - Penicillin derivatives such as cephalosporins, penicillin/beta-lactamase combinations, carbapenems
- Resistance to the Beta-lactam antibiotics emerged several years ago

Logan CID 2012

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

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]*

- Carbapenem resistant Enterobacteriaceae (CRE) uncommon prior to 1992
- First described in 1996 in North Carolina as part of an outbreak investigation

Carbapenem resistant Enterobacteriaceae (CRE)

The Washington Post | Politics | Opinions | Local | Sports | National | World | Business | Tech | Lifes

Health & Science

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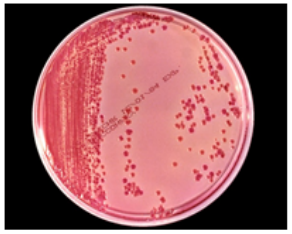
‘Superbug’ stalked NIH hospital last year, killing six

By Brian Vastag, August 22, 2012



As a deadly infection, untreatable by nearly every antibiotic, spread through the National Institutes of Health’s Clinical Center last year, the staff resorted to extreme measures. They built a wall to isolate patients, gassed rooms with vaporized disinfectant and even ripped out plumbing. They eventua
swabs to test every patient ir
hospital.

The Washington Times | NEWS | OPINION | VIDEO | SPORTS | LIFE | MEDIA

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CDC says ‘nightmare bacteria’ CRE superbug killing half of those who are infected

COMMENTS (28) SIZE: + / - PRINT | REPRINTS

By Cheryl K. Chumley - The Washington Times Wednesday, March 6, 2013

Morbidity and Mortality Weekly Report

Vital Signs: Carbapenem-Resistant Enterobacteriaceae

On March 5, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

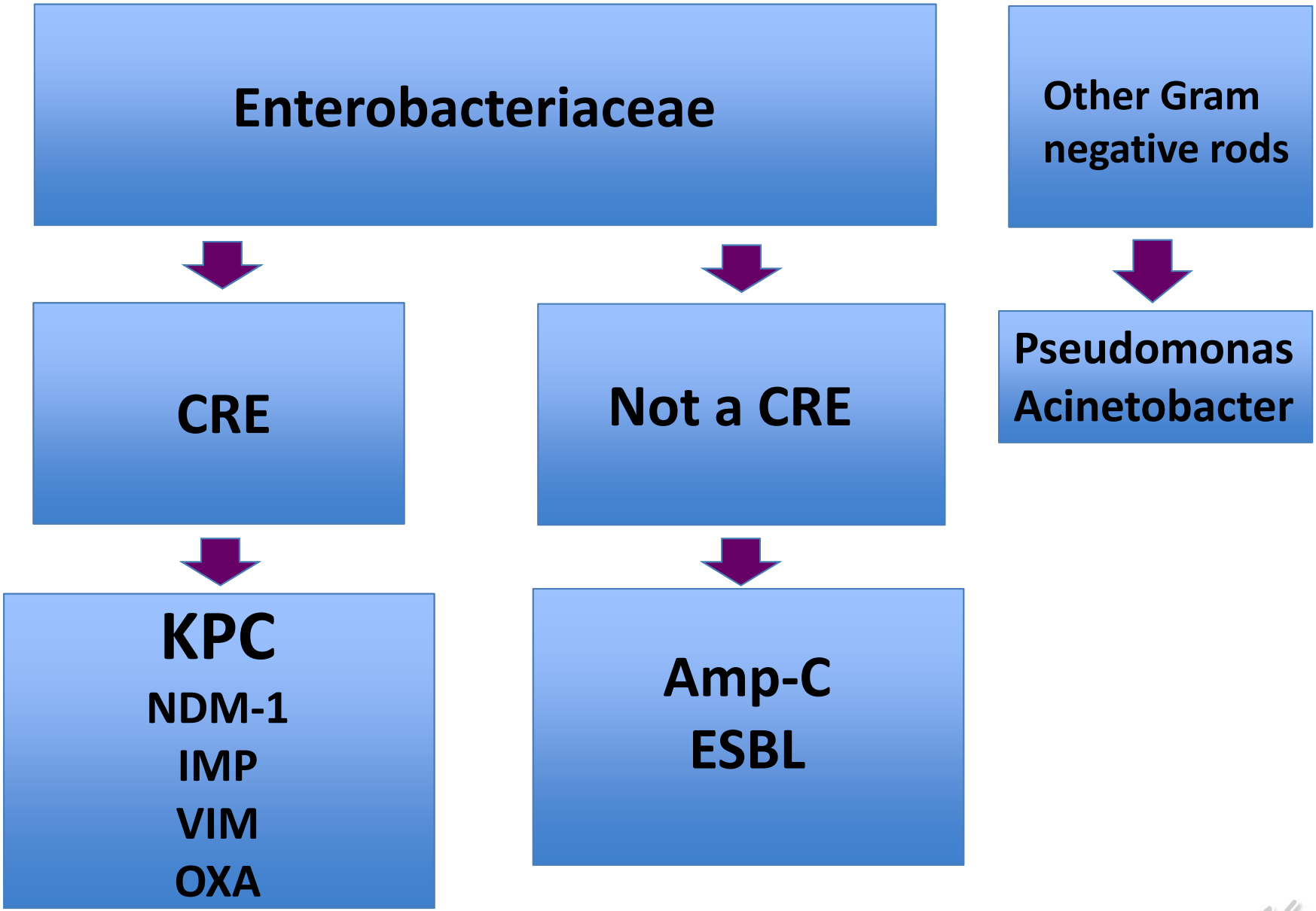
Abstract

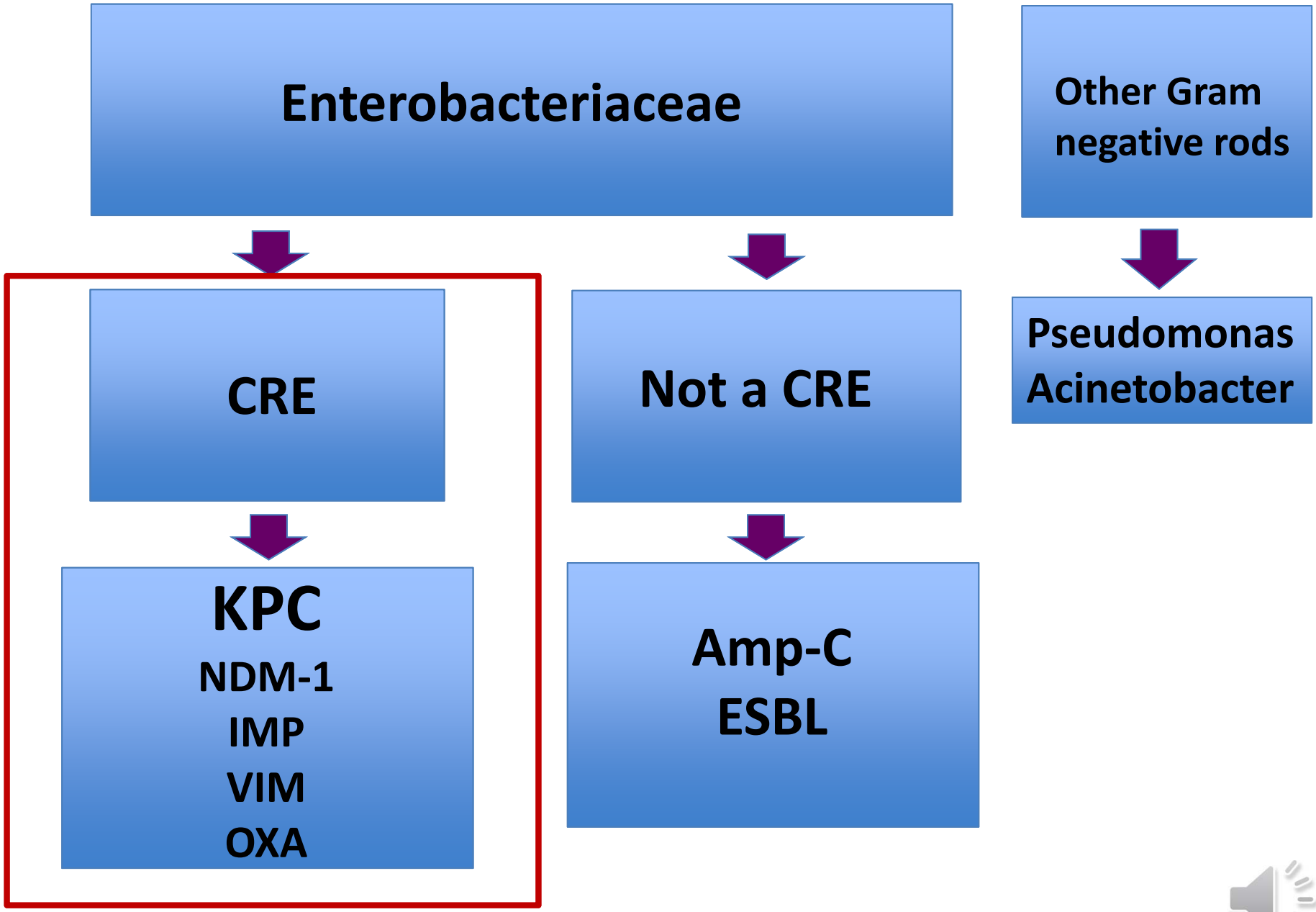
Background: Enterobacteriaceae are a family of bacteria that commonly cause infections in health-care settings as well as in the community. Among Enterobacteriaceae, resistance to broad-spectrum carbapenem antimicrobials has been

http://articles.washingtonpost.com/2012-08-22/national/35493591_1_superbug-arresistant-hospital-borne-infections; http://www.cdc.gov/mmwr/pdf/wk/mm6209.p
http://www.washingtontimes.com/news/2013/mar/6/cdc-says-nightmare-bacteria-cre-superbug-killing-h/

CRE

- CDC Definition
  - Nonsusceptible meropenem, imipenem, doripenem
  - Resistant to 3rd generation cephalosporins
    - Ceftriaxone, cefotaxime, ceftazadime
- Most common CRE in the United States
  - *Carbapenem resistant Klebsiella pneumonia* (CRKP)
    - CRKP produce Klebsiella pneumonia carbapenemase (KPC)


Enterobacteriaceae
Other Gram negative rods
CRE
Not a CRE
Pseudomonas
Acinetobacter
KPC
NDM-1
IMP
VIM
OXA
Amp-C
ESBL


Enterobacteriaceae
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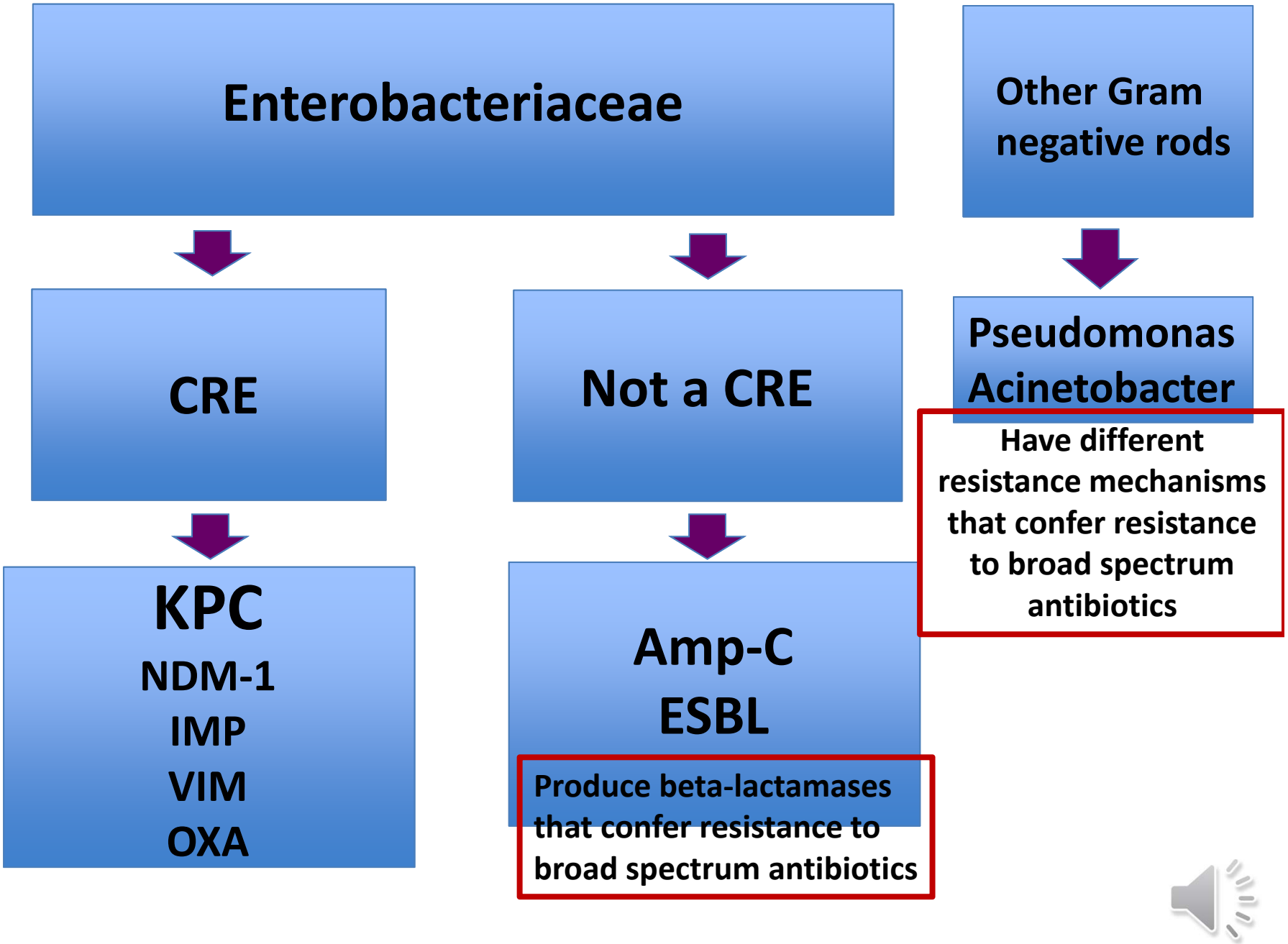
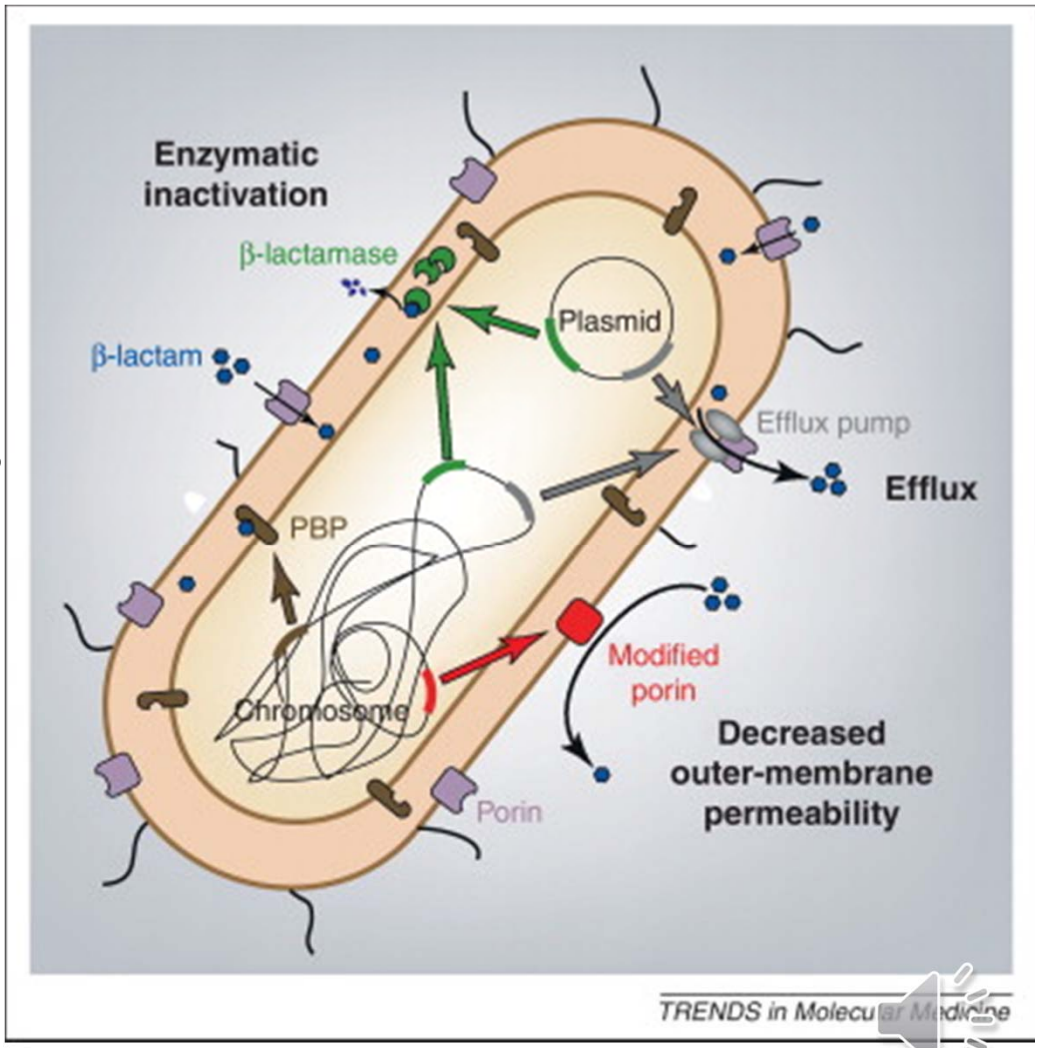

Enterobacteriaceae
Other Gram negative rods
CRE
Not a CRE
Pseudomonas
Acinetobacter
Have different resistance mechanisms that confer resistance to broad spectrum antibiotics
KPC
NDM-1
IMP
VIM
OXA
Amp-C
ESBL
Produce beta-lactamases that confer resistance to broad spectrum antibiotics

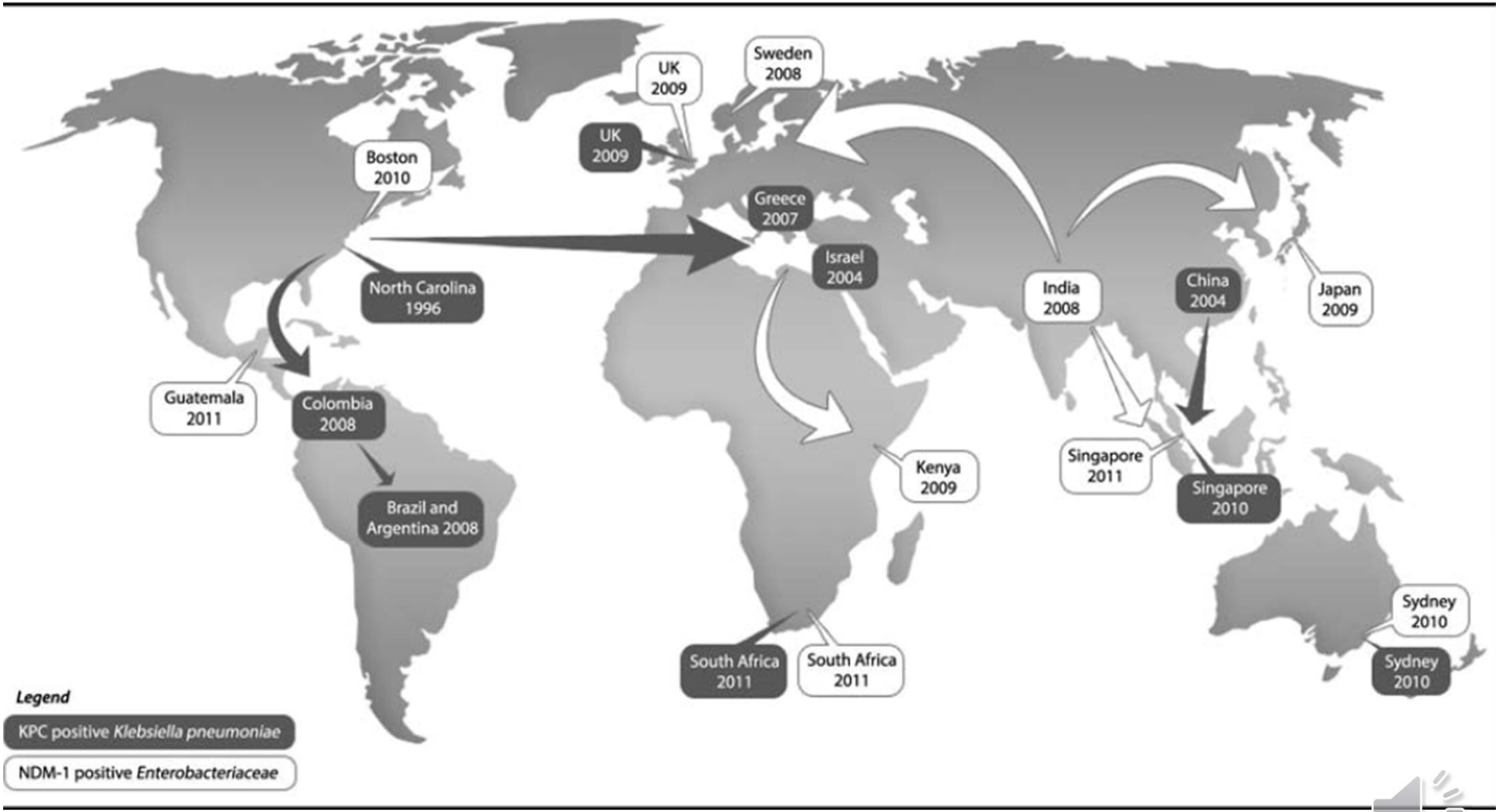
Carbapenamases

- Are enzymes that breakdown the antibiotic
- Different types
  - Class A, B, D, MBL
- Most common is a Class A enzyme →
  - **KPC** plasmid based enzyme
    - Most common clone ST258



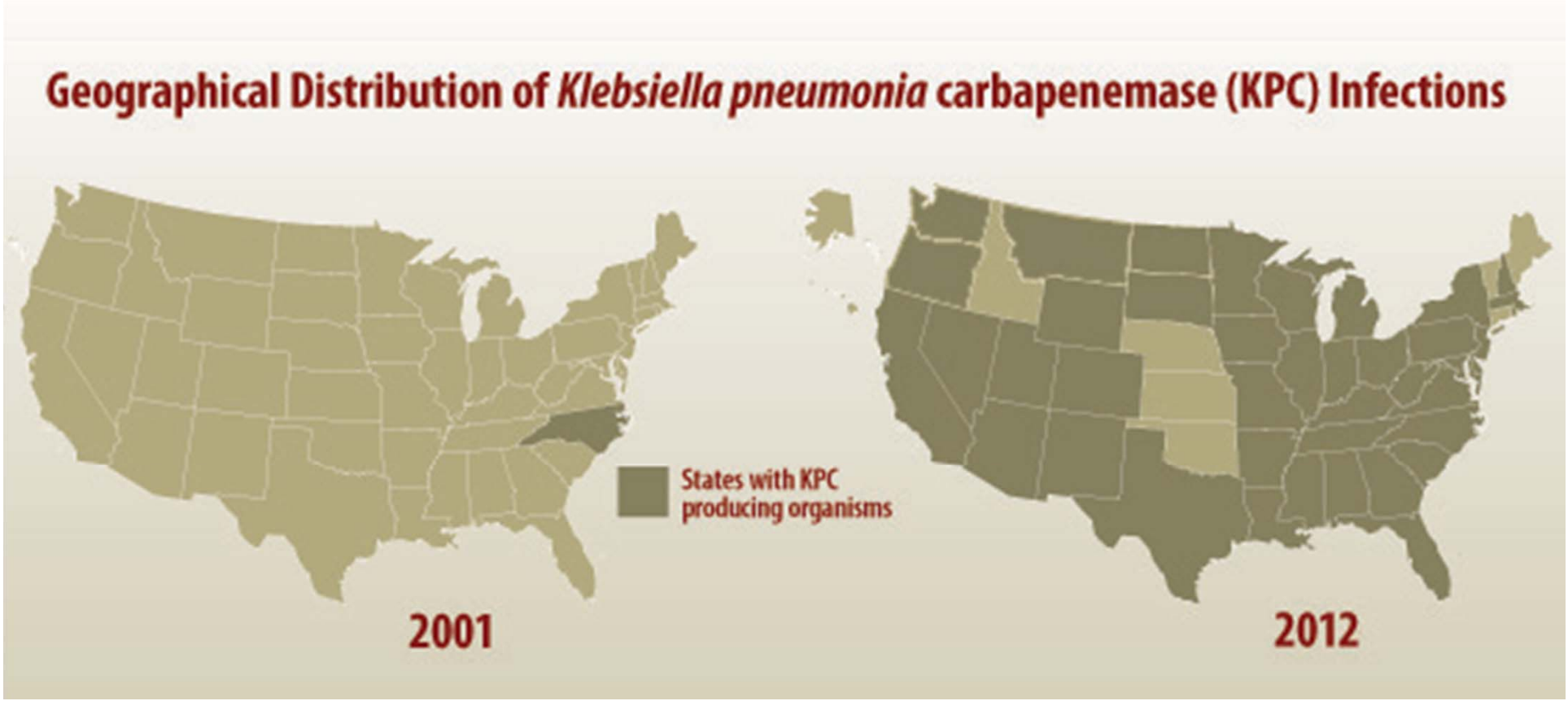
http://www.cell.com/cms/attachment/2002995576/2011441548/gr1.jpg

Global Spread of CRE



Molton et al CID 2013

CRE: A National Problem

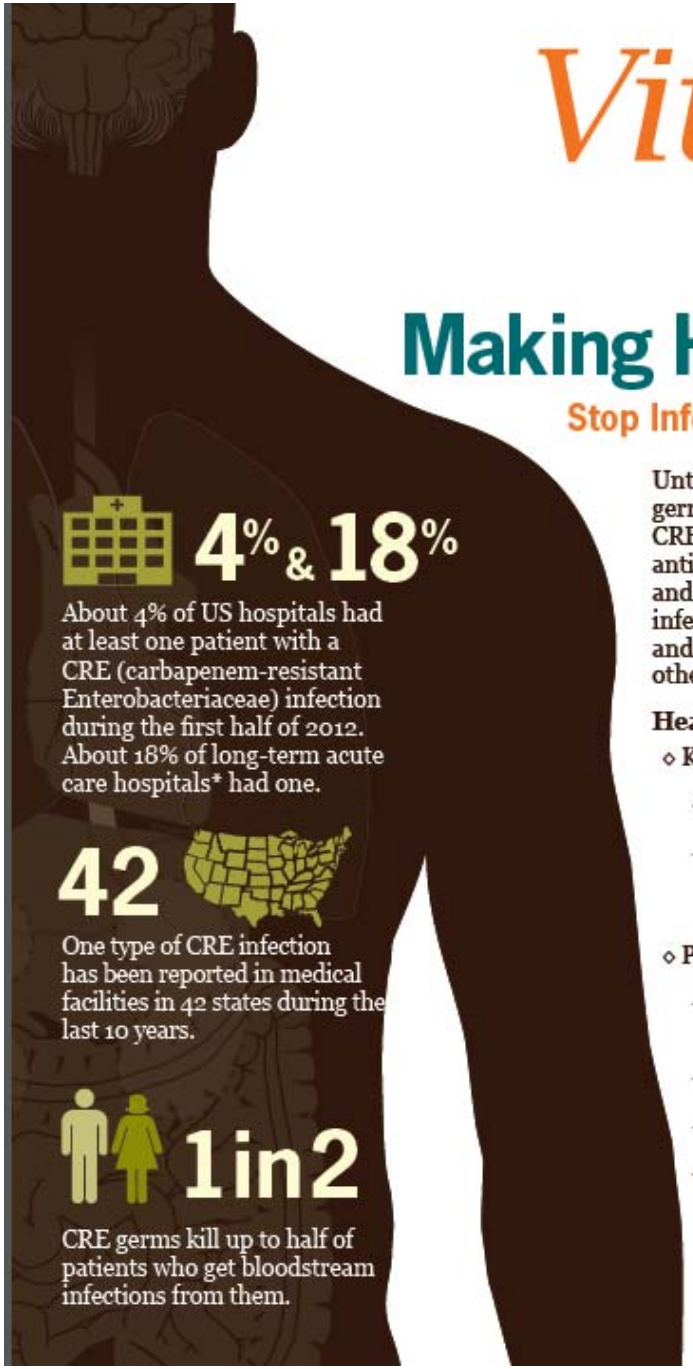


CDC, Get Smart Campaign http://www.cdc.gov/getsmart/campaign-materials/week/images/kpc-states.png

CRE Incidence

Organism	2001	2011
Klebsiella pneumoniae	1.6%	11%
E coli	1%	1-2%
Enterobacter spp.	1.4%	3.6%

http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=53



CDC Vitalsigns™

March 2013

Making Health Care Safer

Stop Infections from Lethal CRE Germs Now

4% & 18%

About 4% of US hospitals had at least one patient with a CRE (carbapenem-resistant Enterobacteriaceae) infection during the first half of 2012. About 18% of long-term acute care hospitals* had one.

42

One type of CRE infection has been reported in medical facilities in 42 states during the last 10 years.

1 in 2

CRE germs kill up to half of patients who get bloodstream infections from them.

Untreatable and hard-to-treat infections from CRE germs are on the rise among patients in medical facilities. CRE germs have become resistant to all or nearly all the antibiotics we have today. Types of CRE include KPC and NDM. By following CDC guidelines, we can halt CRE infections before they become widespread in hospitals and other medical facilities and potentially spread to otherwise healthy people outside of medical facilities.

Health Care Providers can

◇ Know if patients in your facility have CRE.

- Request immediate alerts when the lab identifies CRE.
- Alert the receiving facility when a patient with CRE transfers, and find out when a patient with CRE transfers into your facility.

◇ Protect your patients from CRE.

- Follow contact precautions and hand hygiene recommendations when treating patients with CRE.
- Dedicate rooms, staff, and equipment to patients with CRE.
- Prescribe antibiotics wisely.
- Remove temporary medical devices such as catheters and ventilators from patients as soon as possible.

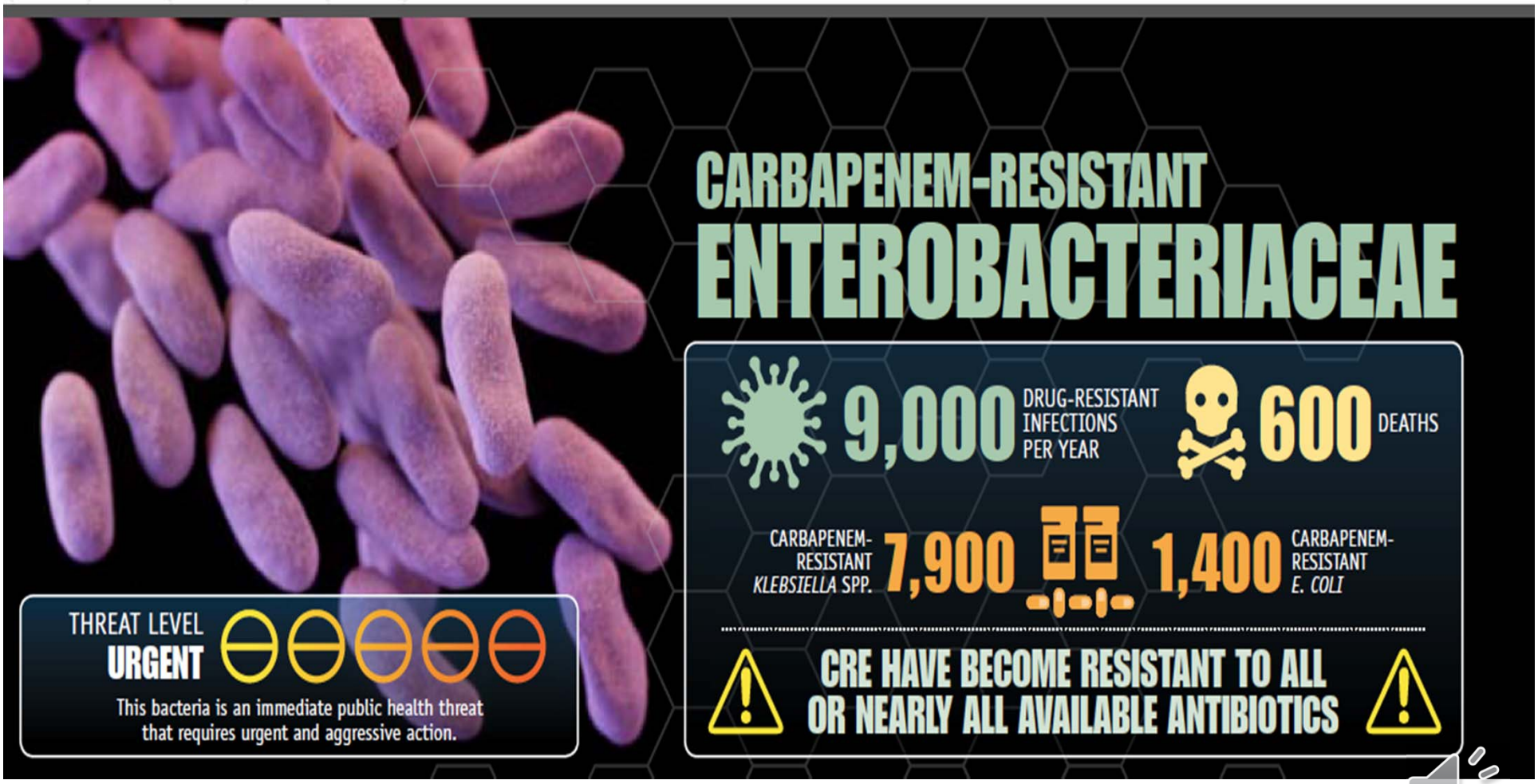
*Long-term acute care hospitals provide complex medical care, such as ventilation or wound care, for long periods of time.

➔ See page 4

Want to learn more? Visit

http://www.cdc.gov/vitalsigns/pdf/2013-03-vitalsigns.pdf

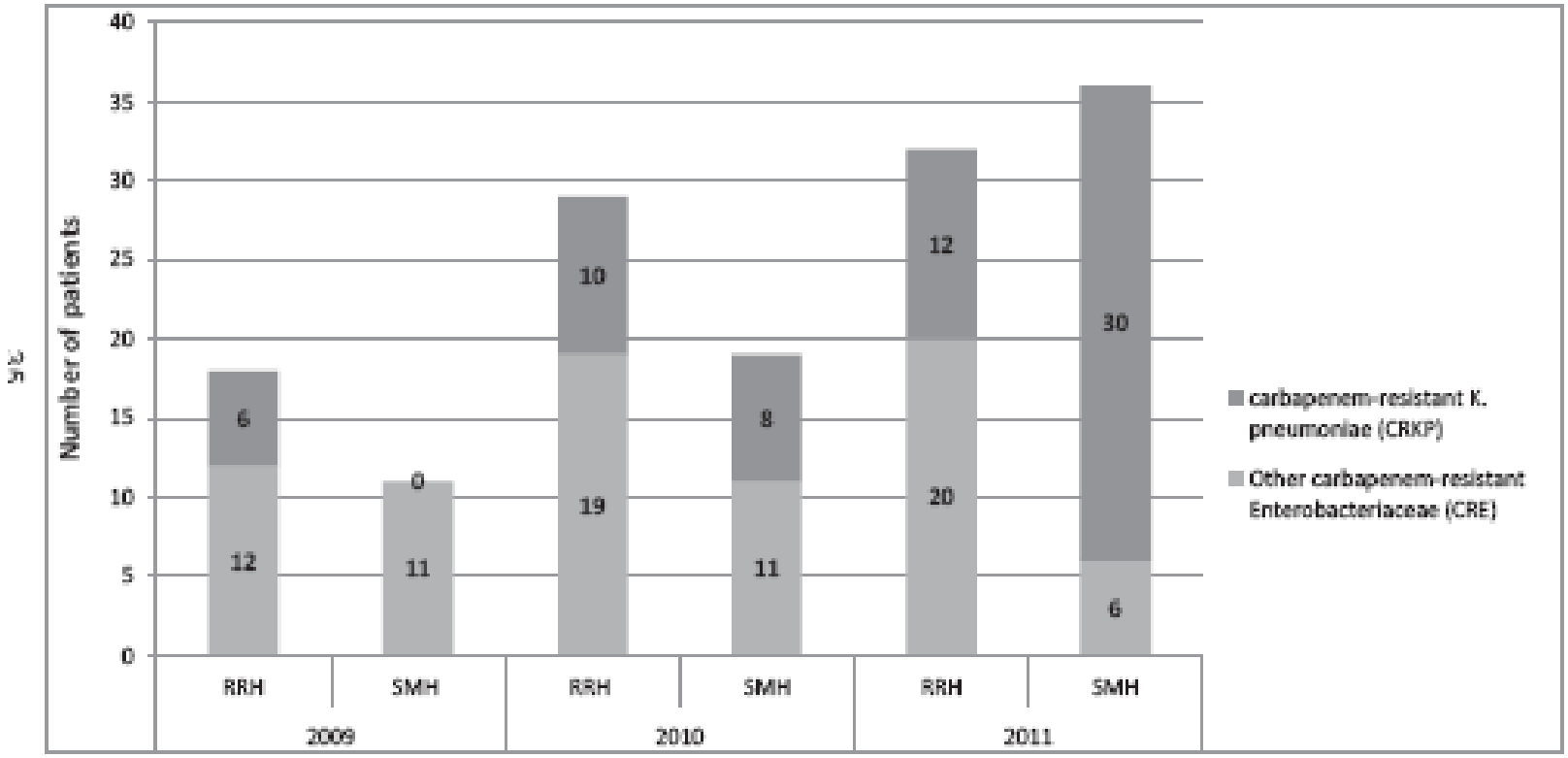
CDC Antibiotic Resistance Threat Report 2013



http://www.cdc.gov/drugresistance/threat-report-2013/pdf/

CRE at UCLA

Table 21B. Carbapenem-resistant *Enterobacteriaceae*: RRUMC and SMH-UCLA, 2009–2011



How are CRE identified?

Susceptibility Profile

Antimicrobial	Interpretation	Antimicrobial	Interpretation
Amikacin	I	Chloramphenicol	R
Amox/clav	R	Ciprofloxacin	R
Ampicillin	R	Ertapenem	R
Aztreonam	R	Gentamicin	R
Cefazolin	R	Imipenem	R
Cefpodoxime	R	Meropenem	R
Cefotaxime	R	Pipercillin/Tazo	R
Cetotetan	R	Tobramycin	R
Cefoxitin	R	Trimeth/Sulfa	R
Ceftazidime	R	Polymyxin B	MIC >4µg/ml
Ceftriaxone	R	Colistin	MIC >4µg/ml
Cefepime	R	Tigecycline	S

http://www.floridahealth.gov/diseases-and-conditions/carbapenem-resistant-enterobacteriaceae/_documents/cdclinicianoutreach.pdf

CLSI 2012 Breakpoints

Appendix A: Previous and Current Clinical and Laboratory Standards Institute Interpretive Criteria for Carbapenems and Enterobacteriaceae

Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE) - 2012 CRE Toolkit [PDF - 2.98 MB]

Agent	Previous Breakpoints (M100-S19) MIC (µg/mL)			Current Breakpoints (M100-S22) MIC (µg/mL)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Doripenem	-	-	-	≤1	2	≥4
Ertapenem	≤2	4	≥8	≤0.5	1	≥2
Imipenem	≤4	8	≥16	≤1	2	≥4
Meropenem	≤4	8	≥16	≤1	2	≥4

Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty Second Informational Supplement (January 2012). CLSI document M100-S22. Wayne, Pennsylvania, 2012.

Phenotypic Testing

- Modified Hodge Test (MHT)
  - Not used anymore

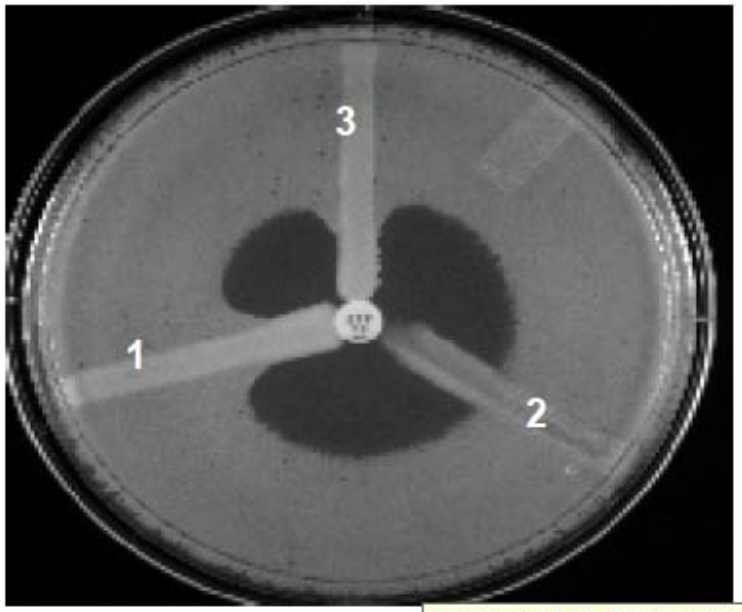


Figure 1. the MHT preforming on a 1

Figure 1. The MHT performed on a 100 mm MHA plate. (1) *K. pneumoniae* ATCC BAA 1705, positive result (2) *K. pneumoniae* ATCC BAA 1706, negative result; and (3) a clinical isolate, positive result

Who gets CRE?

Demographics

TABLE 1. Carbapenem-Resistant *Klebsiella pneumoniae* Case Characteristics

	Value
Total no. confirmed	675
Female sex	379 (56)
Age, mean (range), years	73 (1–103)
Reported from	
Acute care hospital	387 (57)
Long-term acute care hospital	231 (34)
Skilled nursing facility	57 (8)
Specimens with admit date	598 (89)
Hospital onset	363 (61)
Community onset	235 (39)
From skilled nursing facility	154 (66)
Collected on admission	141 (60)

NOTE. Data are no. (%), unless otherwise indicated.

Marquez et al ICHE 2013

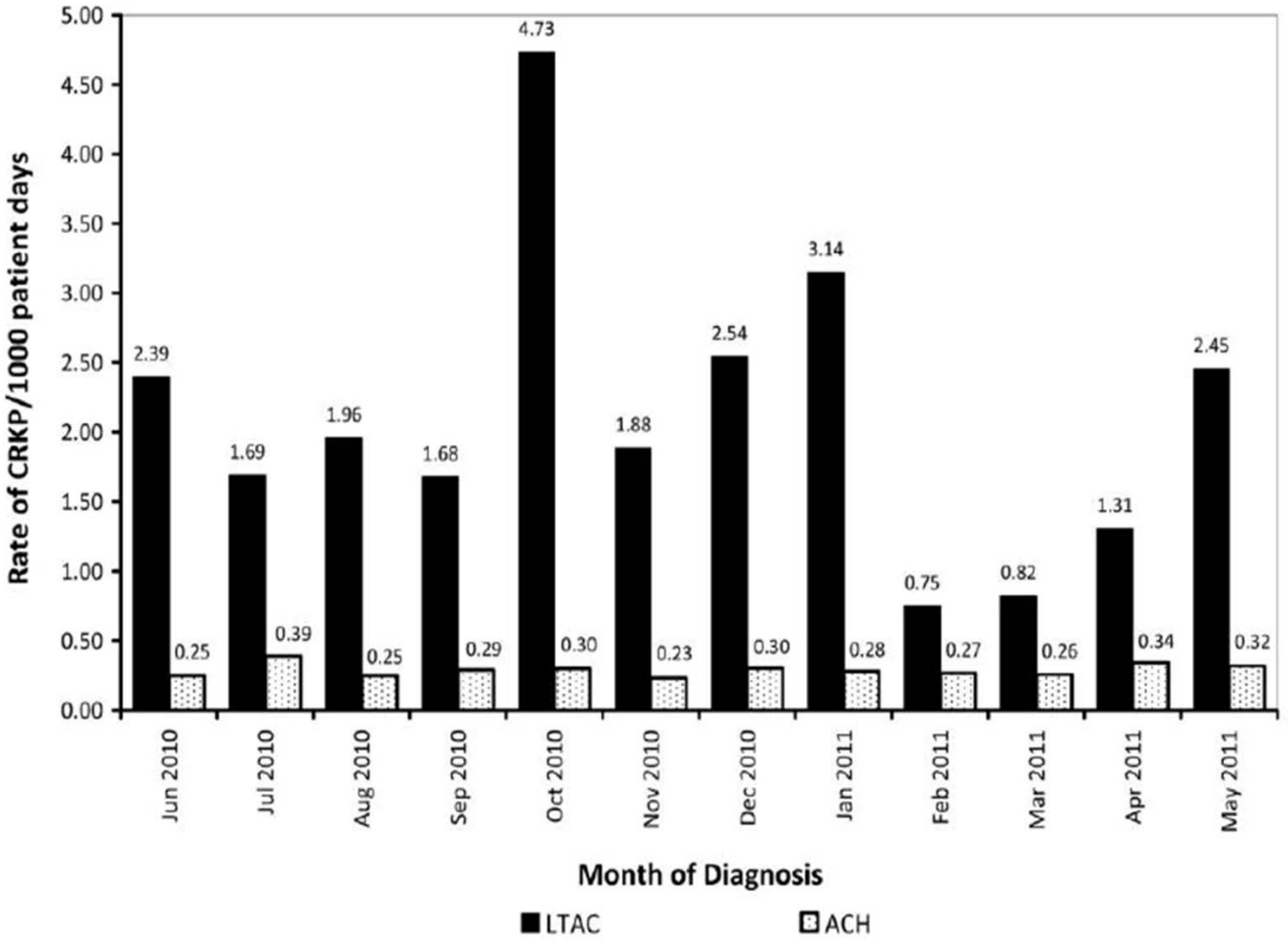


FIGURE 1. Monthly carbapenem-resistant *Klebsiella pneumoniae* (CRKP) pooled mean rate of infection by facility type for long-term acute care hospitals (LTACs; $n = 8$) and acute care hospitals (ACHs; $n = 57$) in Los Angeles County (excluding skilled nursing facilities and out-of-county reporting facilities).

Marquez et al ICHE 2013

Risk Factors for CRE

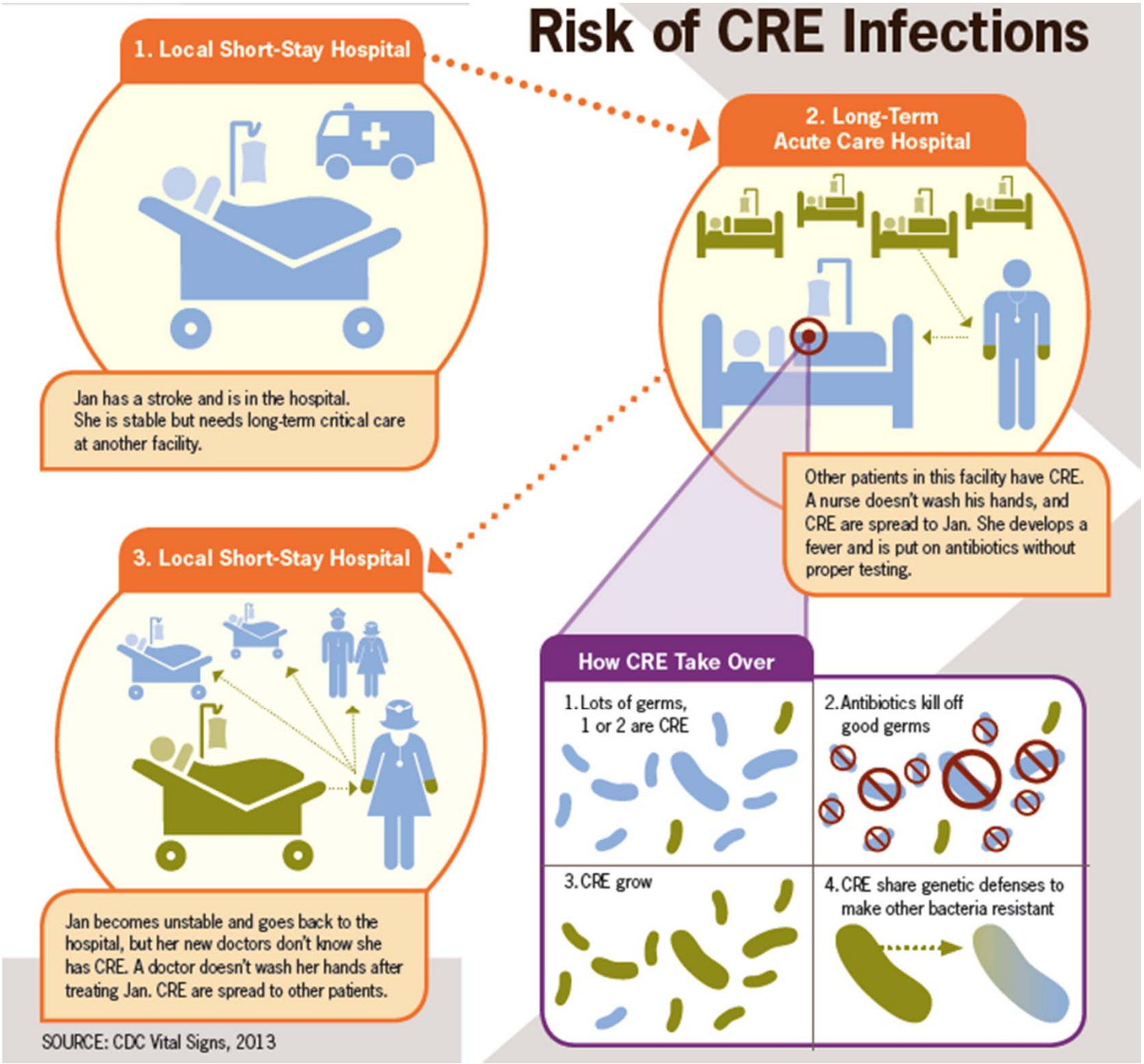
- Increased hospitalizations
- Prior extended-spectrum cephalosporin and fluoroquinolone use
  - Other studies have associated vancomycin
- Invasive procedures
- ICU stay
- Poor functional status

Patel et al ICHE 2008

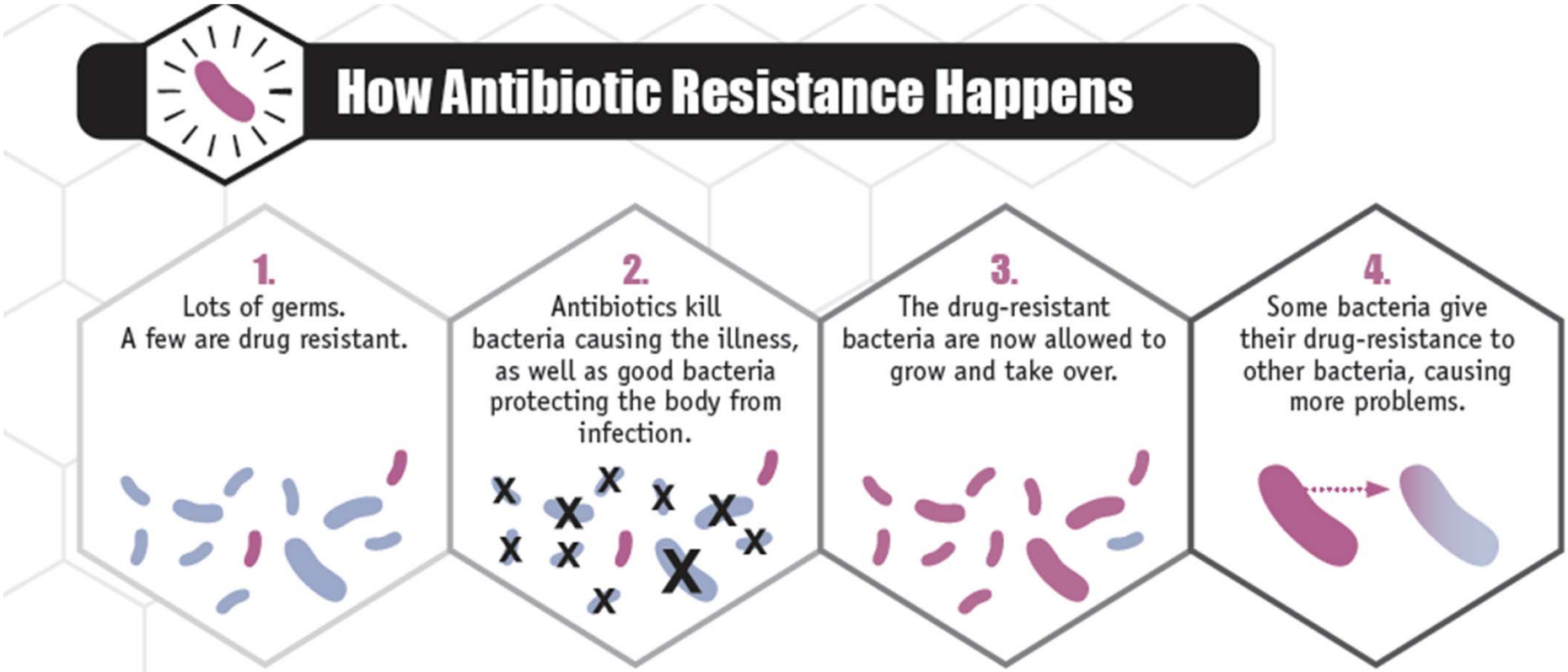
TABLE 2. Clinical Risk Factors Associated With Carbapenem-Resistant and Carbapenem-Susceptible *Klebsiella pneumoniae* Infections, From July 1, 2004, to June 30, 2006

Risk factor	Case patients ($n = 99$)	Control patients ($n = 99$)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Patient-specific risk factor						
Diabetes	27 (27)	20 (20)	1.45 (0.75–2.82)	.27		
HIV infection	2 (2)	5 (5)	0.40 (0.08–2.14)	.29		
Heart disease	23 (23)	16 (16)	1.52 (0.72–3.20)	.27		
Liver disease	39 (39)	29 (29)	1.67 (0.90–3.08)	.10	1.64 (0.57–4.74)	.36
Renal insufficiency	34 (34)	23 (23)	1.75 (0.94–3.27)	.08	1.46 (0.56–3.81)	.44
Transplant recipient	41 (41)	14 (14)	5.70 (2.65–12.16)	<.001	3.71 (1.41–9.73)	.008
Healthcare-associated factors						
Use of CVC	90 (91)	55 (56)	8.32 (3.74–18.53)	<.001	1.96 (0.58–6.70)	.28
Receipt of mechanical ventilation	65 (66)	22 (22)	6.62 (3.53–12.43)	<.001	2.44 (1.06–5.61)	.04
ICU stay	68 (69)	33 (33)	4.45 (2.45–8.11)	<.001	0.51 (0.12–2.10)	.35
Length of stay before infection, days						
Mean ± SD	25.19 ± 24.9	6.44 ± 10.1				
Median	21	1	1.09 (1.06–1.12)	<.001	1.05 (1.01–1.08)	.01
Prior antibiotic therapy with anti–gram negative activity	98 (99)	55 (56)	78.17 (10.48–583.10)	<.001		
Class of antibiotic used						
Cephalosporin	63 (64)	31 (31)	3.82 (2.11–6.91)	<.001	2.65 (1.45–6.12)	.02
β-lactam and/or β-lactamase inhibitor	54 (55)	33 (33)	2.30 (1.30–4.10)	<.005	1.07 (0.44–2.60)	.88
Fluoroquinolone	36 (36)	23 (23)	1.87 (1.00–3.48)	.05	0.78 (0.3–2.02)	.60
Carbapenem	54 (55)	6 (6)	19.25 (7.61–48.70)	<.001	14.97 (5.29–42.35)	<.001
Monobactam	6 (6)	1 (1)	7.04 (0.82–60.68)	.08	1.64 (0.03–85.17)	.81
Aminoglycoside	14 (14)	3 (3)	5.44 (1.49–19.85)	.01	2.95 (0.57–15.28)	.19

Patel et al ICHE 2008



http://www.cdc.gov/vitalsigns/pdf/2013-03-vitalsigns.pdf



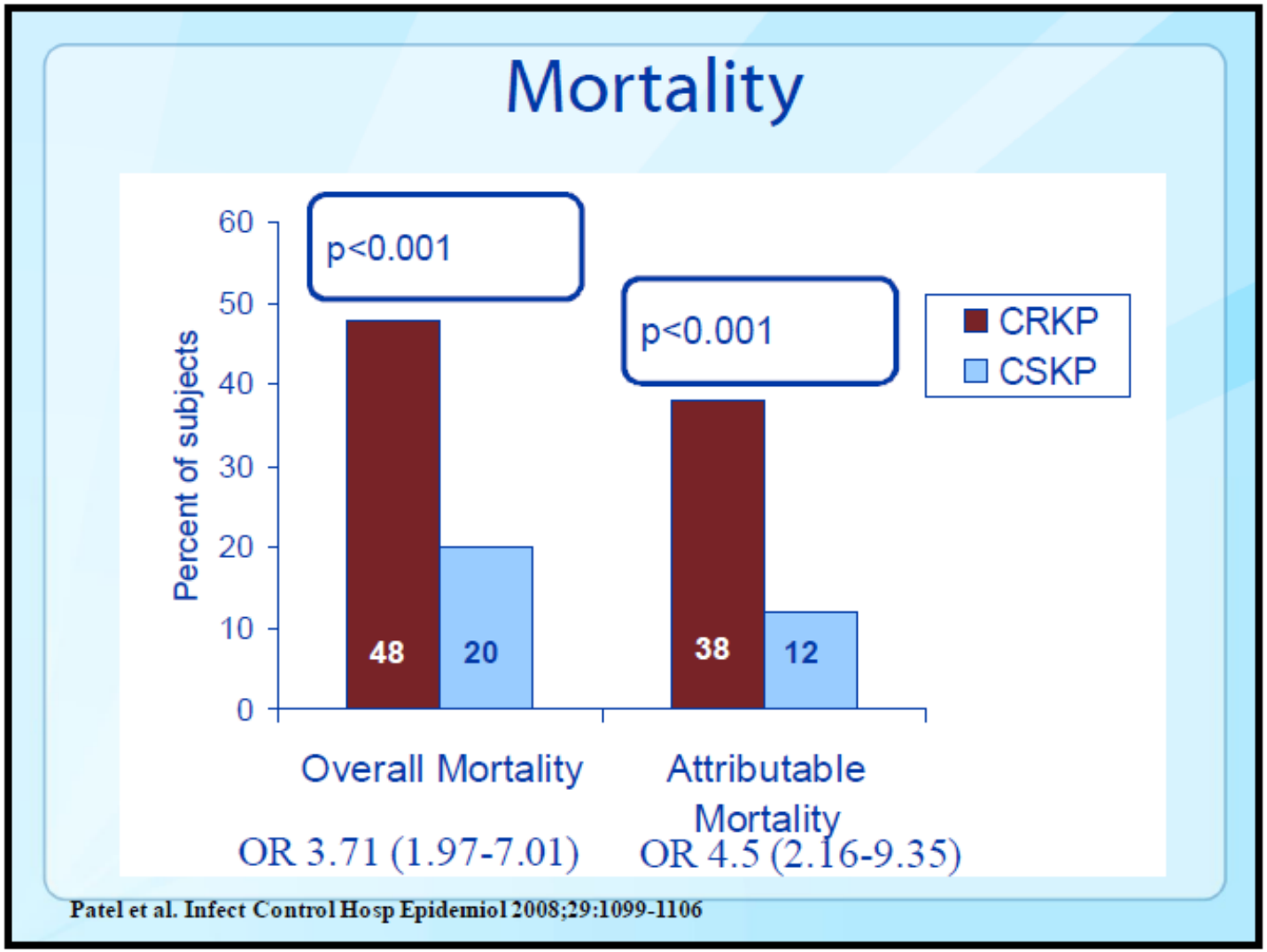
http://www.cdc.gov/drugresistance/threat-report-2013/pdf/

Why are CRE Clinically Important?

Why are CRE Clinically Important?

- High mortality rates associated with CRE and CRKP infection

CRE and Outcomes



Why are CRE Clinically Important?

- Mortality
  - 50% mortality associated with CRE blood stream infections
  - Pan-resistant CRE strains cause 75% mortality
- Mortality
  - Risk factors age, mechanical ventilation, malignancy, heart disease, and ICU stay
  - Removal of the focus of infection (device, debridement, or drainage) associated with survival

Gupta et al CID 2011

Why are CRE Clinically Important?

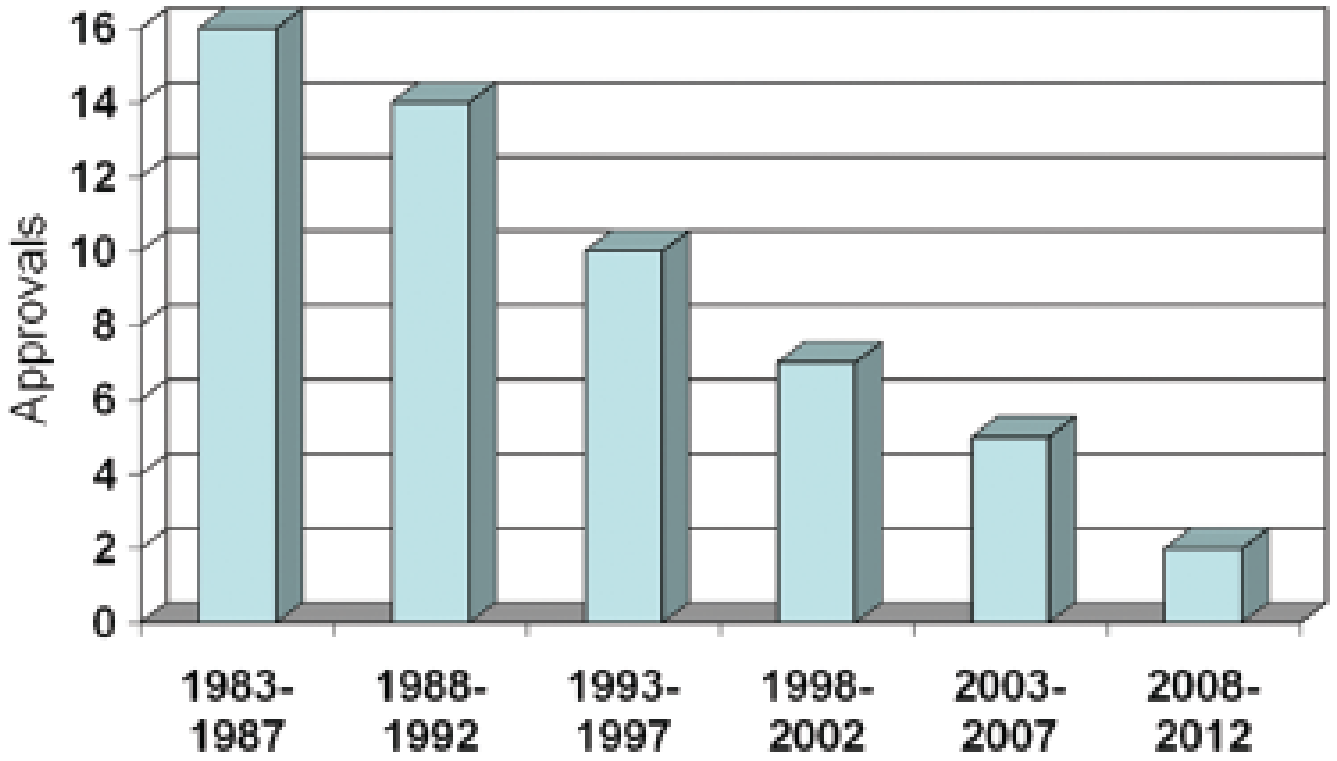
- Limited treatment options

Bad Bugs, No Drugs: Current Resistance Trends

CRE Treatment Options

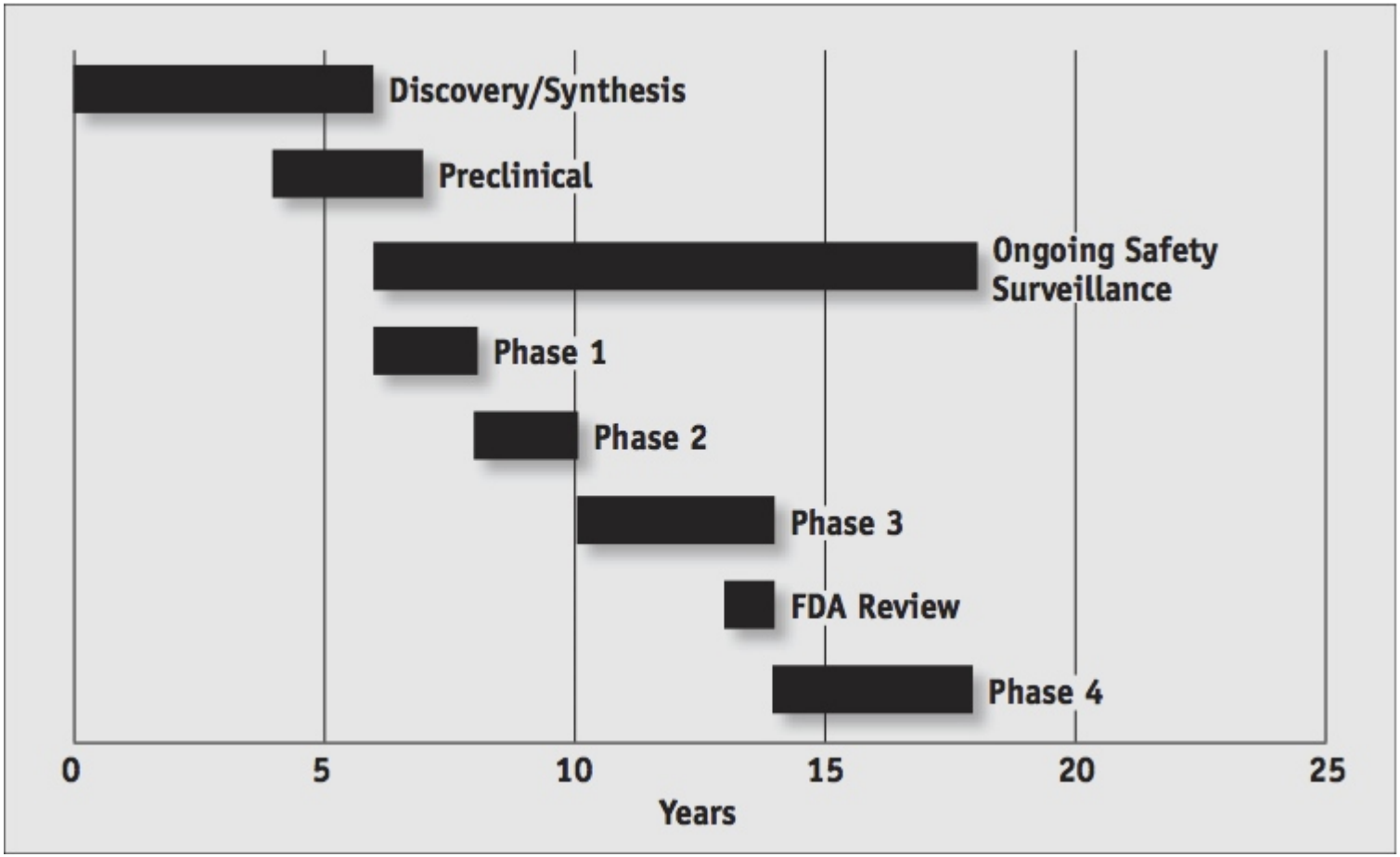
- Limited treatment options
  - Colistin
  - Polymixin B
  - Tigecycline
- Many KPC are ‘pan-resistant’
  - Aminoglycosides
  - Fluoroquinolones

New Antibacterial Agents Approved 1983-2012



Boucher et al. *Clin Infect Dis*. 2013; 56: 1685

Timeline for Development of a New Medication



Stone, Scientific American, http://blogs.scientificamerican.com/guest-blog/2011/10/06/molecules-to-medicine-clinical-trials-for-beginners/

Challenges for Antibiotic Research and Development

- Smaller market:
  - Antibiotics work well and fast
  - Compared with chronic, long-term conditions
- Limited long-term potential
  - Bacteria become resistant!

Bad Bugs, No Drugs

Infectious Diseases Society of America (IDSA) 2010

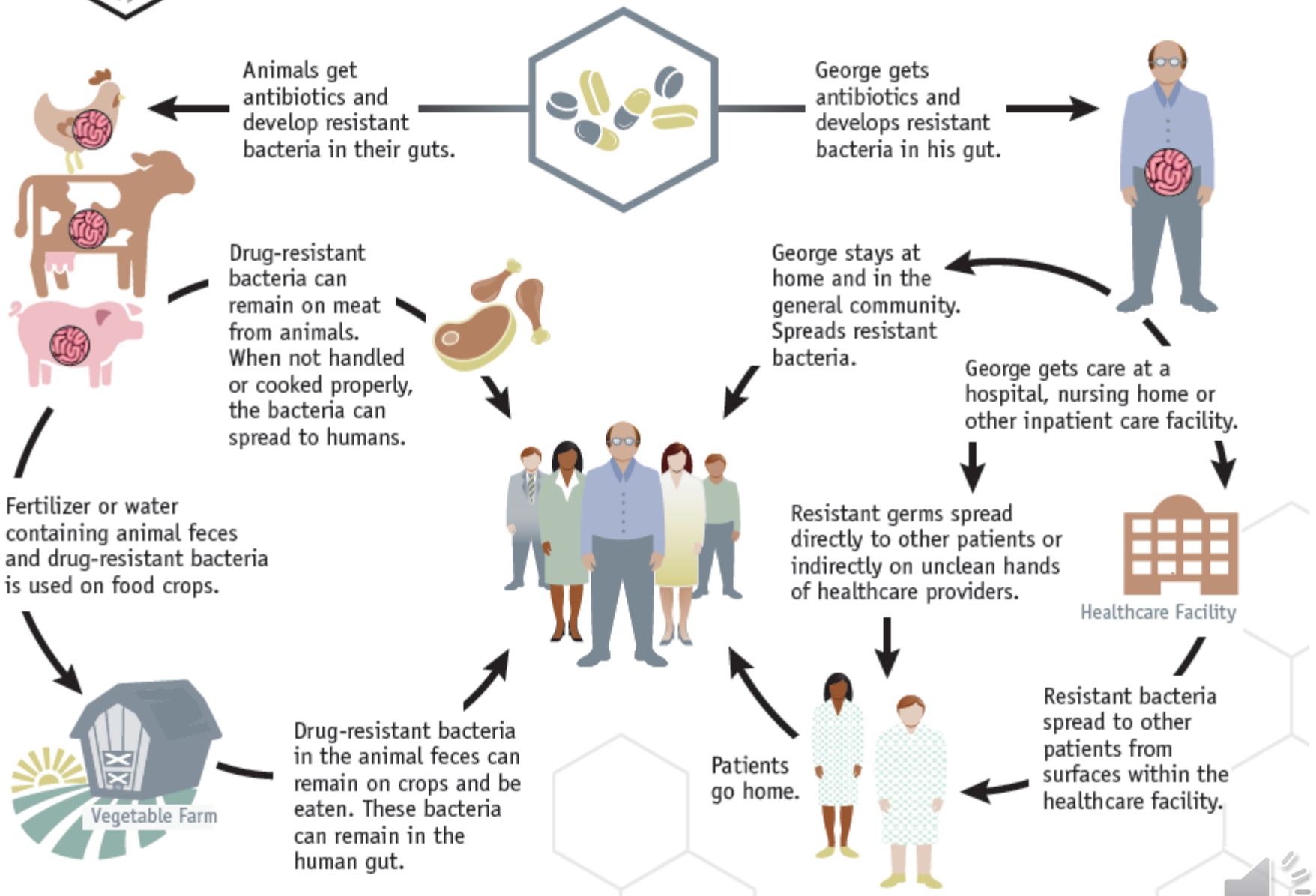
10 × ’20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America

Why are CRE Epidemiologically Important?

Why are CRE Epidemiologically Important

- Resistance is highly transmissible
  - Between organisms: plasmids and transposons
  - Between patients: HANDS!
- These organisms are common causes of infection
  - *E. coli* and urinary tract infections
  - Acuity of patient population has increased dramatically in recent decade
    - Increase number of transplant and oncology patients
- CRE have been documented in the community setting

Examples of How Antibiotic Resistance Spreads

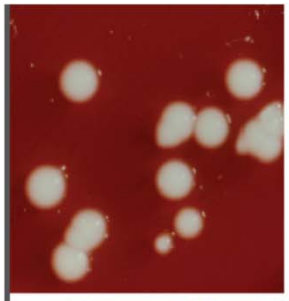


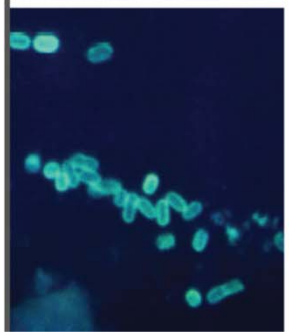
Simply using antibiotics creates resistance. These drugs should only be used to treat infections.

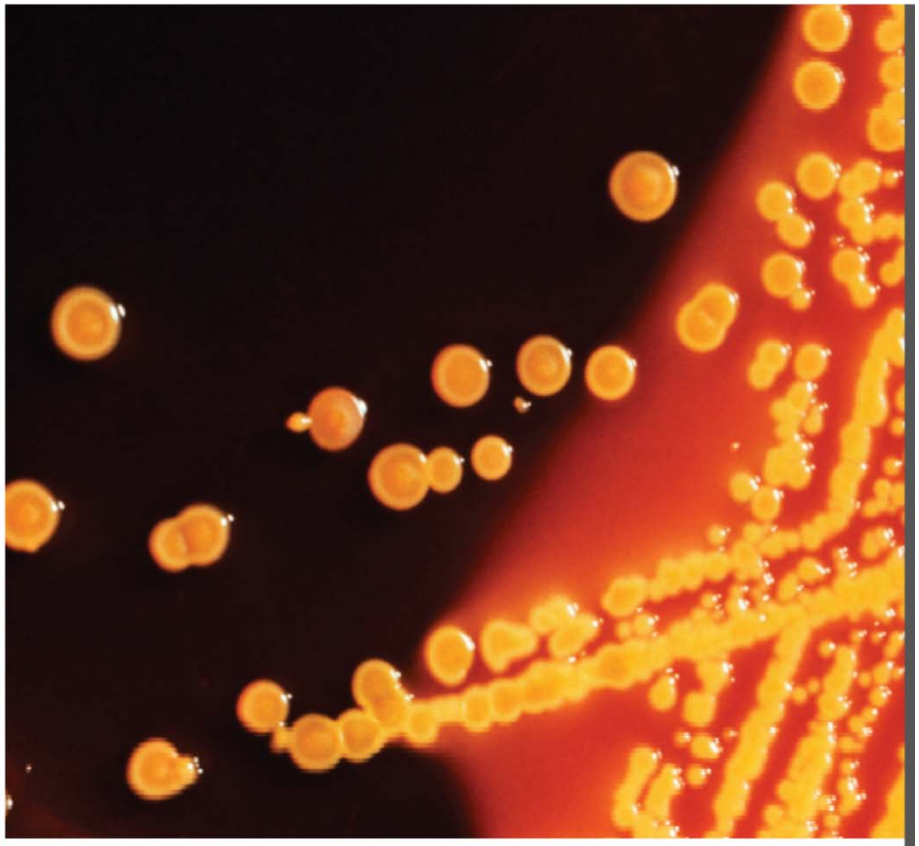
Prevention

What do we do now?

- CRE are not endemic in most of the United States
  - How do we keep it that way…







Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE)

2012 CRE Toolkit

Prevention

- Need to practice comprehensive infection control measures. Per CDC:
  - Hand hygiene
  - Contact precautions
  - Education of healthcare workers
  - Cohort staff/patients
  - Notify laboratory
  - Antimicrobial Stewardship
  - CRE contact screening
  - Consider
    - Active surveillance cultures
    - Chlorhexidine bathing

CDC Guidance for Control of CRE 2012 CRE Toolkit

Transmission Pathways

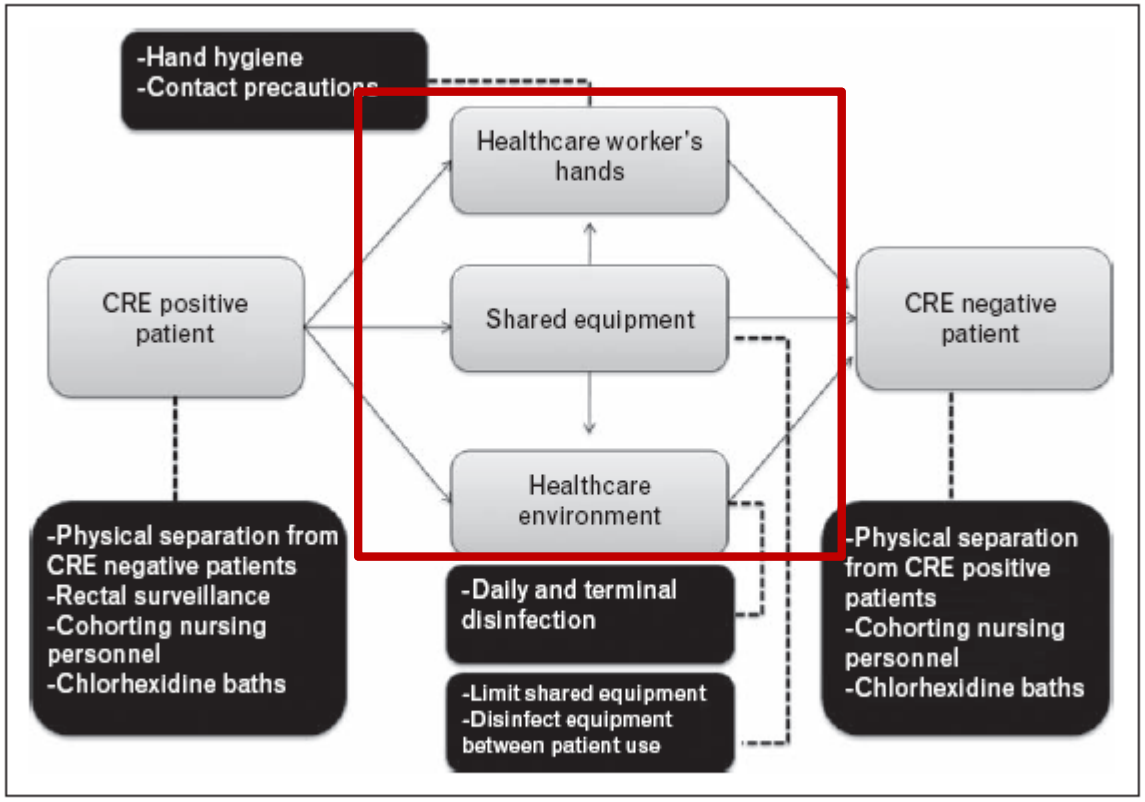


FIGURE 1. Horizontal transmission pathways of carbapenem-resistant *Enterobacteriaceae*. CRE, carbapenem-resistant *Enterobacteriaceae*. Light boxes: components of transmission pathways. Dark boxes: interventions aimed at mitigating horizontal transmission.

Munoz-Price et al, Curr Opin 2013

Most important source of transmission of pathogens in the hospital setting

Healthcare worker hands

Hand Hygiene Adherence in Hospitals

Year of Study	Adherence Rate	Hospital Area
1994 (1)	29%	General and ICU
1995 (2)	41%	General
1996 (3)	41%	ICU
1998 (4)	30%	General
2000 (5)	48%	General

1. Gould D, *J Hosp Infect* 1994;28:15-30. 2. Larson E, *J Hosp Infect* 1995;30:88-106. 3. Slaughter S, *Ann Intern Med* 1996;3:360-365. 4. Watanakunakorn C, *Infect Control Hosp Epidemiol* 1998;19:858-860. 5. Pittet D, *Lancet* 2000:356;1307-1312.

Efficacy of Hand Hygiene Preparations in Killing Bacteria

Contact Precautions

- CDC
  - Any person colonized or infected with CRE should be placed on Contact Precautions
  - CRE colonization duration unknown though some studies report prolonged period (>6 mo)
    - Risk factors: exposure to antibiotics, admission from another healthcare facility, and <3mos since first CRE test
- UCLA HealthSystem
  - Any carbapenem resistant Enterobacteriaceae
    - *Klebsiella pneumoniae*
    - *E coli*
    - *Enterobacter sp.*
    - Contact isolation for the hospitalization and subsequent hospitalizations
    - No clearance protocol available

CDC Guidance for Control of CRE 2012 CRE Toolkit

Other Prevention Measures

- Healthcare personnel education
  - Focus on hand hygiene and Contact precautions
- Minimize the use of devices
- Patient and staff cohorting
  - Single patient room
  - Dedicated staff to care for them
- Laboratory Notification
  - Laboratory to notify infection prevention of any CRE
- CRE Screening
  - Of any epidemiologically linked patient of CRE infected/colonized patient

CDC Guidance for Control of CRE 2012 CRE Toolkit

Antibiotic Stewardship programs (ASP)

- Limited studies for CRE prevention
  - Two studies include ASP as part of CRE bundle
  - One study evaluated ASP as the sole intervention
    - Reduction in the use of beta-lactams ineffective in reducing CRE acquisition
    - Use of fluoroquinolones associated with higher acquisition of fluorquinolone resistant CREs
- More studies needed to evaluate ASP
  - Current goal to decrease total volume of antibiotics prescribed

Munoz-Price et al, Curr Opin 2013

John et al CID 1997; 24: 471

UCLA ASP

‘Back end’ ASP program

- Adult: Started July 2010
- Pediatric: Started March 2013

– Targeted prospective audit with feedback
– Education/marketing
– Availability of expertise at the point of care
  – Antibiotic handbook
  – Antibiotic hotline
– Data monitoring
  – Streamlining/de-escalation
  – IV to PO
  – Redundant coverage

UCLA Adult Antibiotic Use

The Environment

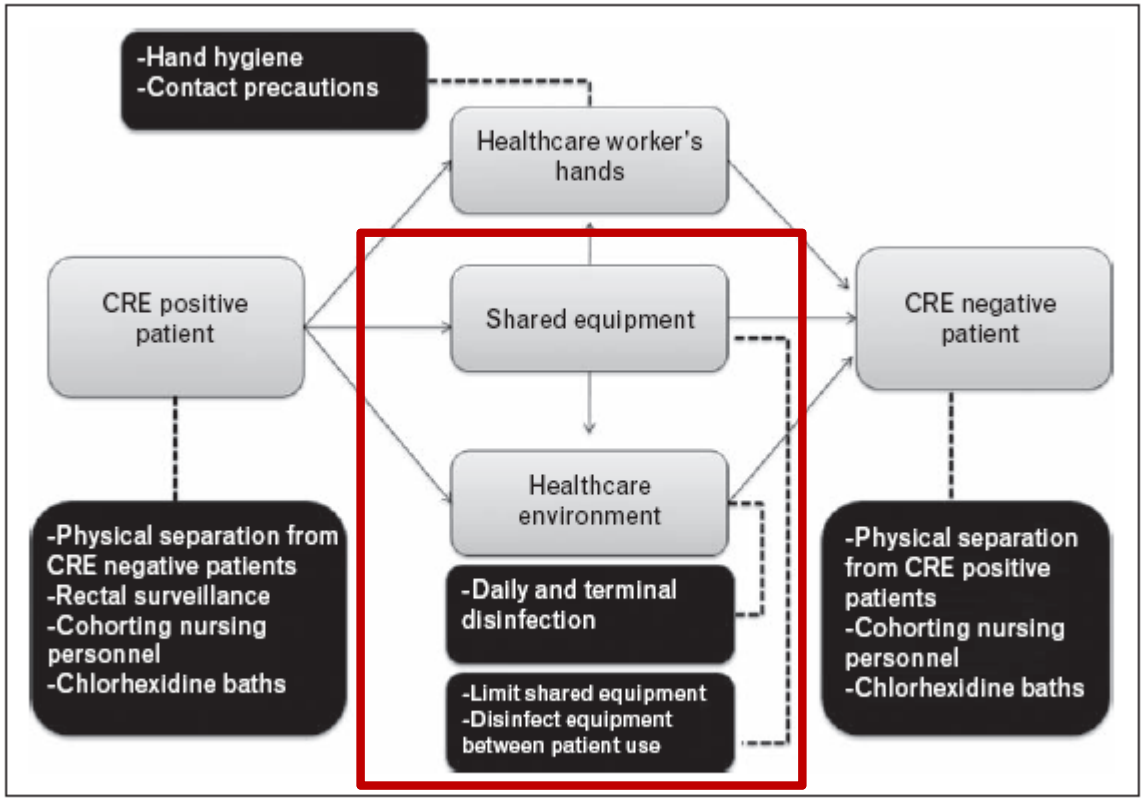


FIGURE 1. Horizontal transmission pathways of carbapenem-resistant *Enterobacteriaceae*. CRE, carbapenem-resistant *Enterobacteriaceae*. Light boxes: components of transmission pathways. Dark boxes: interventions aimed at mitigating horizontal transmission.

Munoz-Price et al, Curr Opin 2013

Supplemental Strategies

- Active surveillance testing
  - Of any patient who may not be epidemiologically linked but who meet certain pre-specified criteria
    - Admission from a long-term care facility
    - Admission to a high risk setting
- Chlorhexidine (CHG)
  - Has been used in CRE outbreak situations
    - 3 studies have included CHG as part of their CRE bundle
    - Difficult to assess utility of CHG in these studies as it was part of a package intervention
    - Consider in certain settings

CDC Guidance for Control of CRE 2012 CRE Toolkit; Munoz-Price et al, Curr Opin 2013

Case Study:
CRE in the UCLA HealthSystem

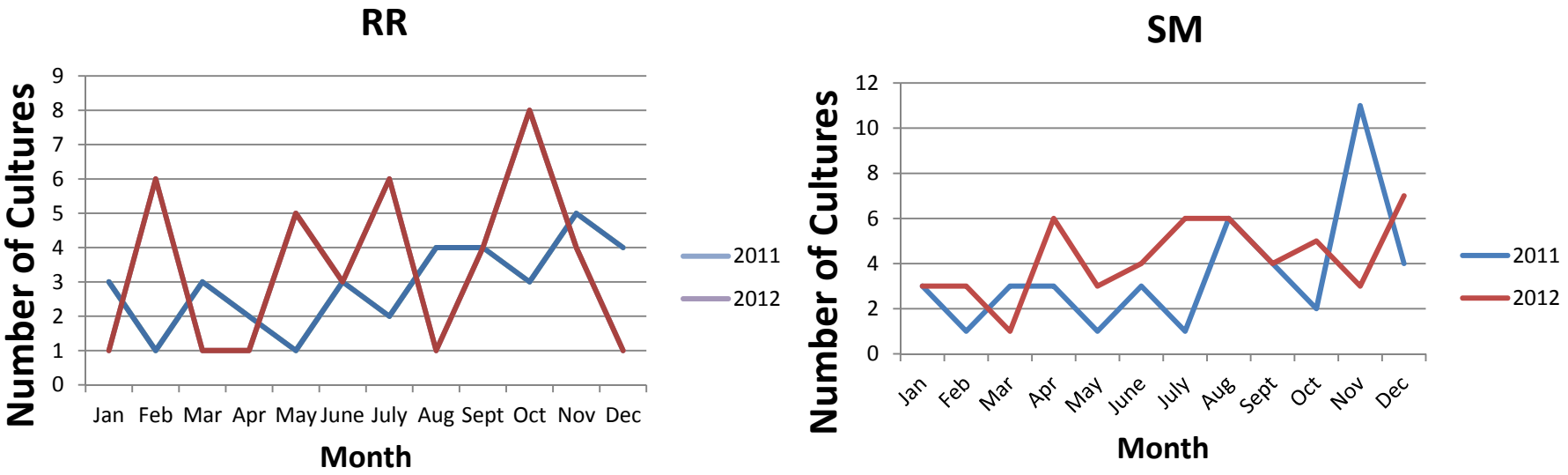
General Methods

- CRE defined as any of the Enterobacteriaceae that are resistant to meropenem
- For analysis, used cultures Jan 1, 2011-Dec 31, 2012
  - Reviewed patient charts to obtain additional data
  - Each organism per patient was considered to be a separate event; all others were excluded from analysis

Overview of CDC LabID Method

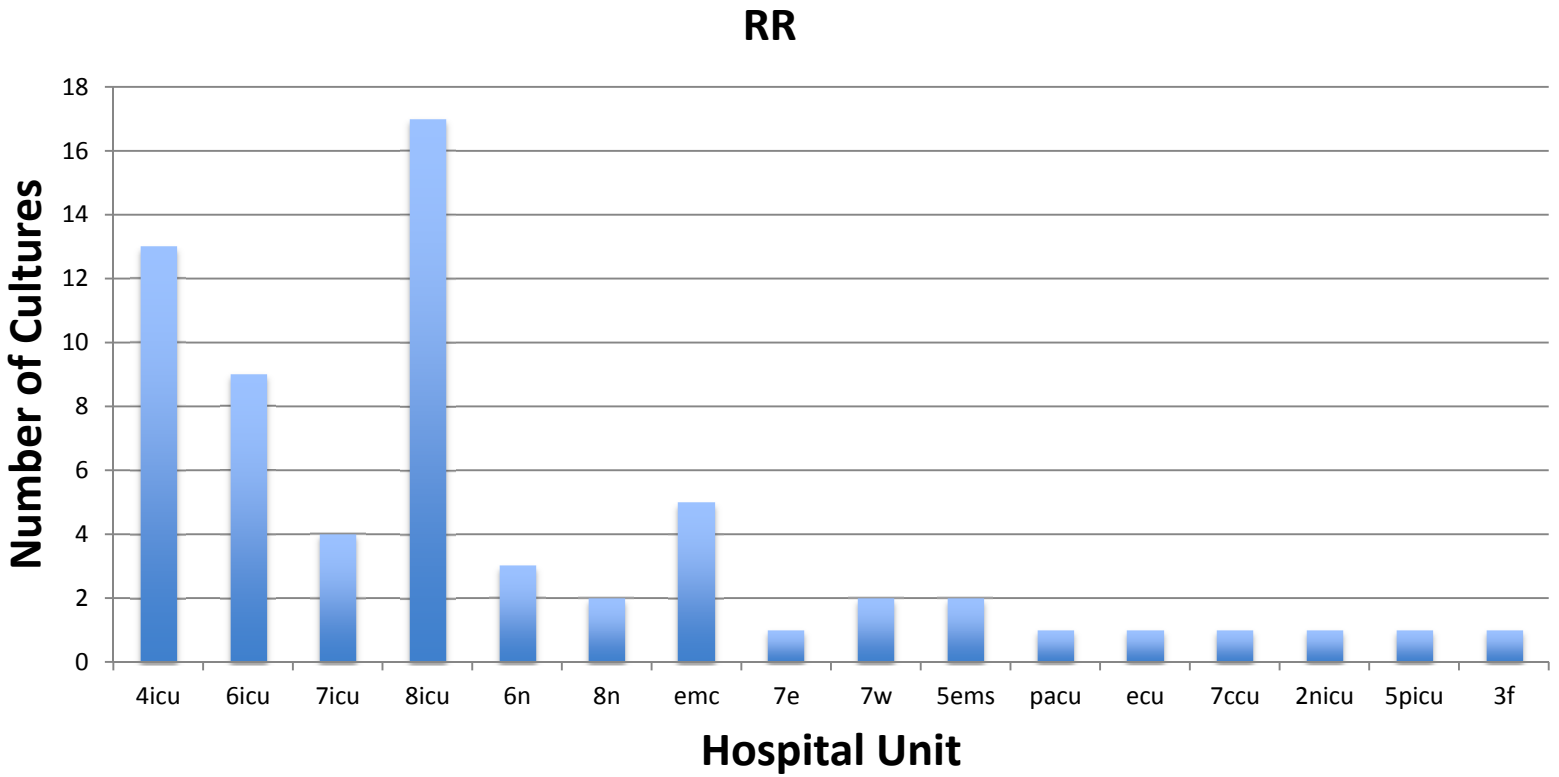
- Method for collecting and tracking positive lab results
  - Does not take into consideration whether a culture represents colonization or true infection
- Used to assess burden of disease
- Separate events are considered to be organisms per patient per calendar month per hospital unit per specimen source
- Used different method for analysis to adapt data to be more relevant for RR/SM patient population

Monthly number of cultures by facility by year



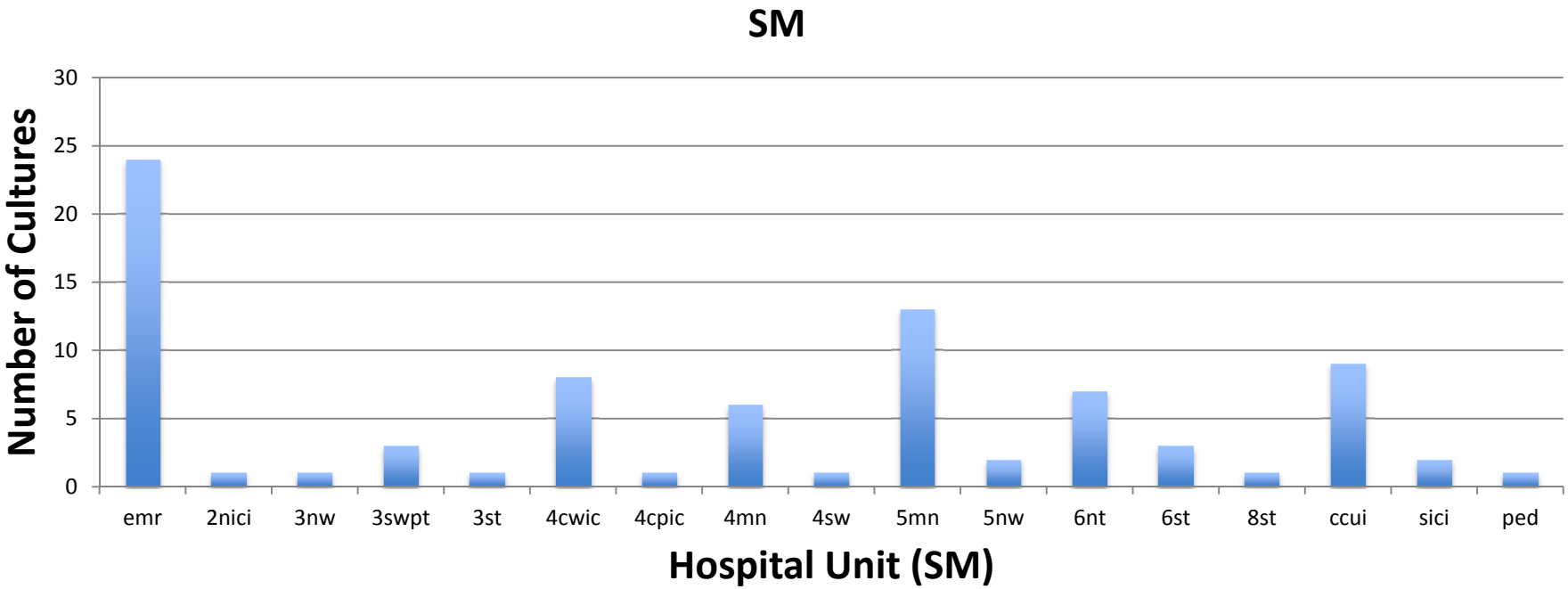
- RR: 76 cultures (35 from 2011; 41 from 2012)
- SM: 93 cultures (42 from 2011; 51 from 2012)

Cultures by hospital unit (inpatients only)



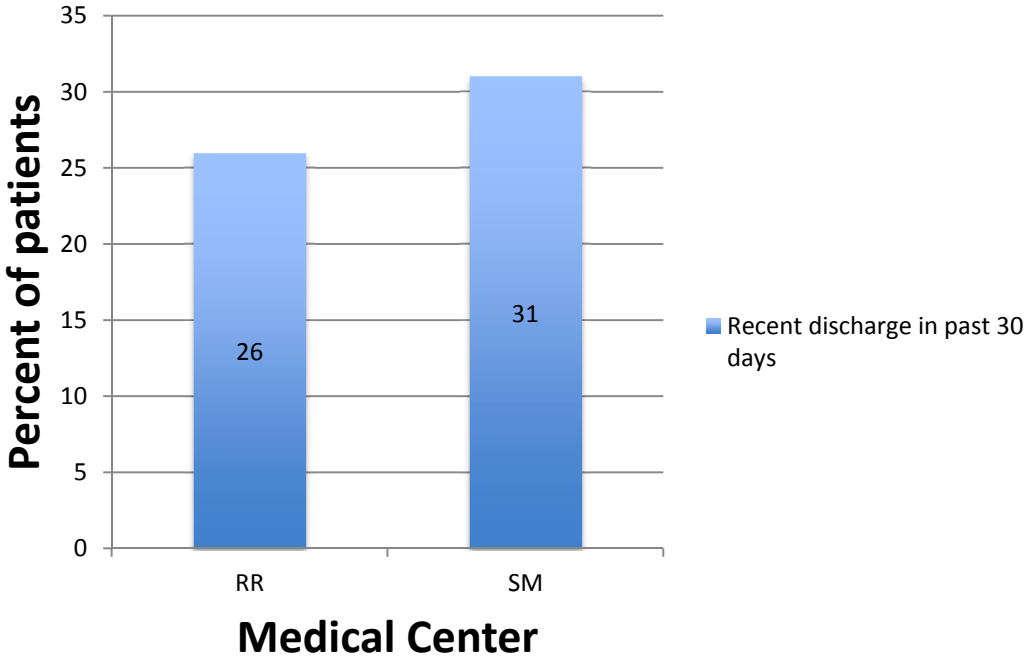
- RR: 64 inpatients
- Only takes into consideration discharge condition of admission encompassing positive culture (death during later admission not counted in this measure)

Cultures by hospital unit (inpatients only)



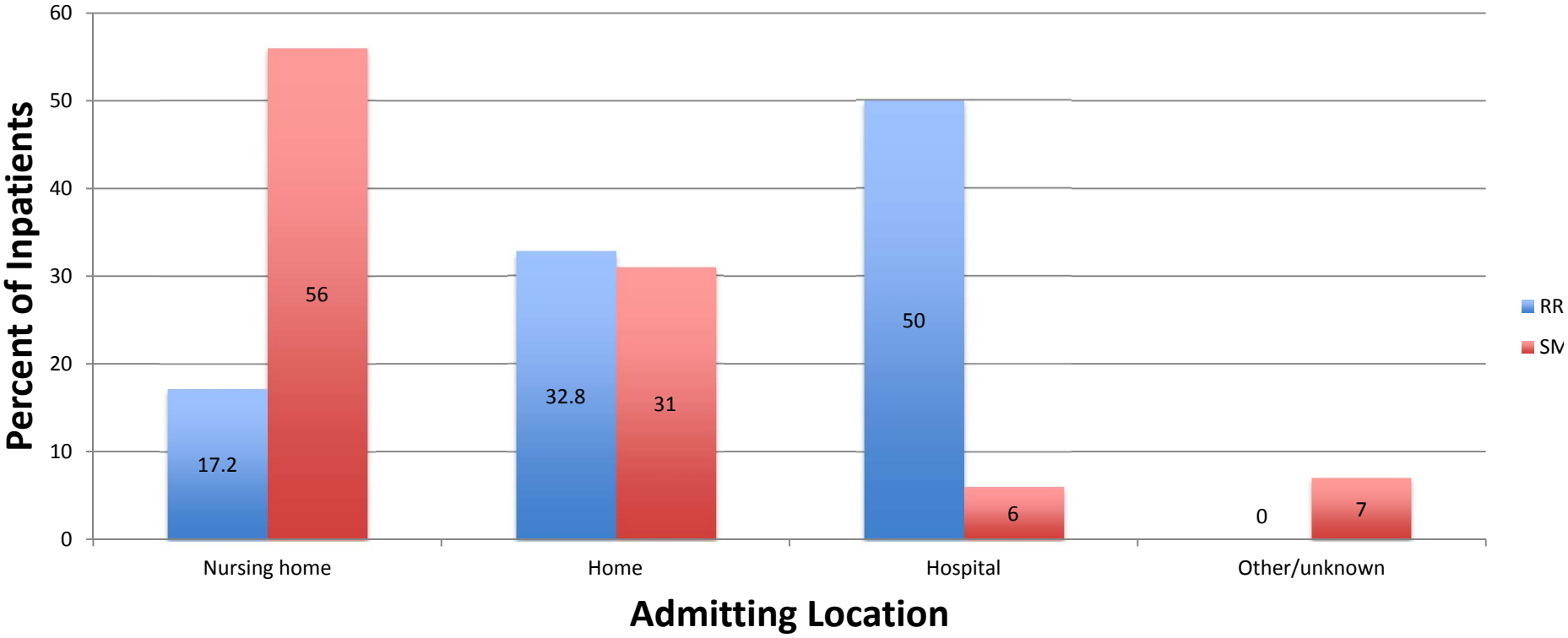
- SM: 84 inpatients
- Only takes into consideration discharge condition of admission encompassing positive culture (death during later admission not counted in this measure)

Patients with recent discharge from same facility in past 30 days



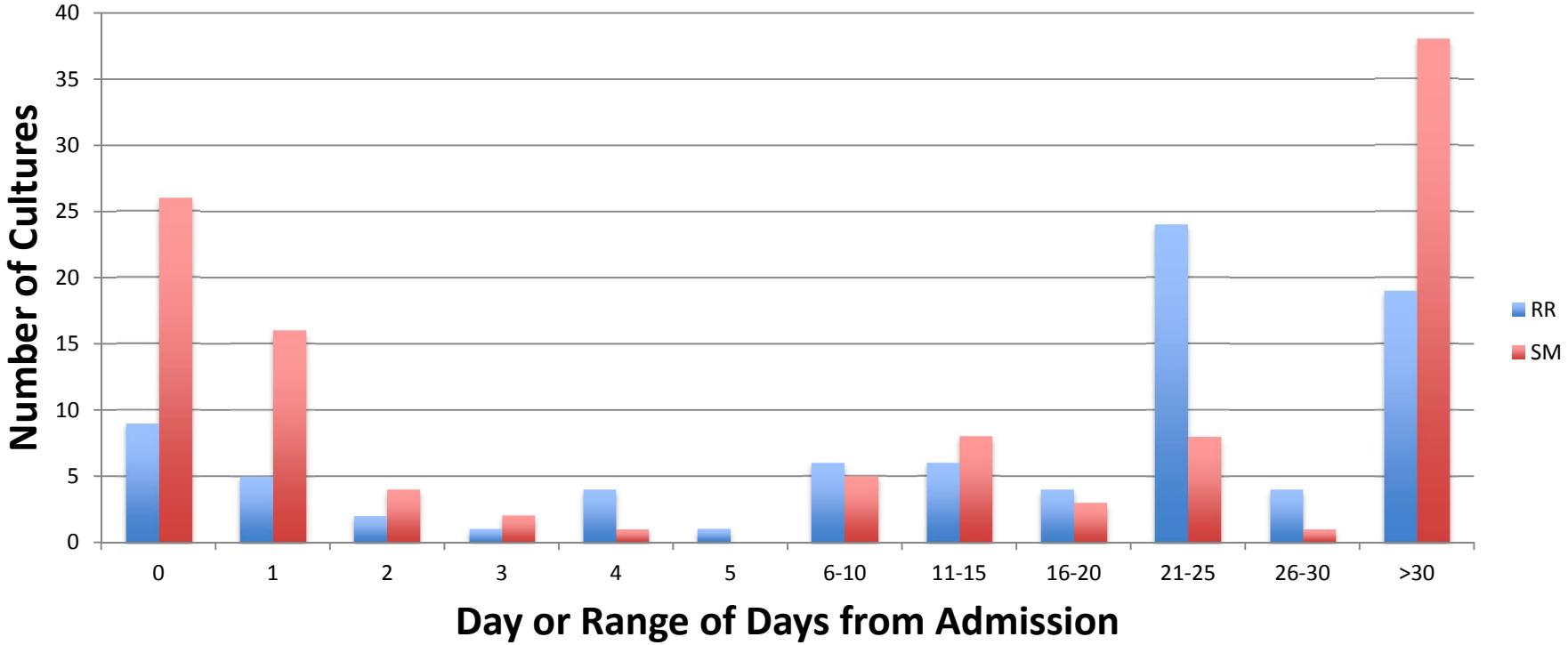
- RR: 76 cultures
- SM: 93 cultures
- Recent discharge from other facility or transfer from other hospital not included in this measure

Admitting location (for inpatients only)



- RR: 64 inpatient cultures, SM: 84 inpatient cultures
- Location obtained either from admission H&P or patient demographic information, when available
- Other/unknown include homeless patients (2 from SM) and various other types of homes

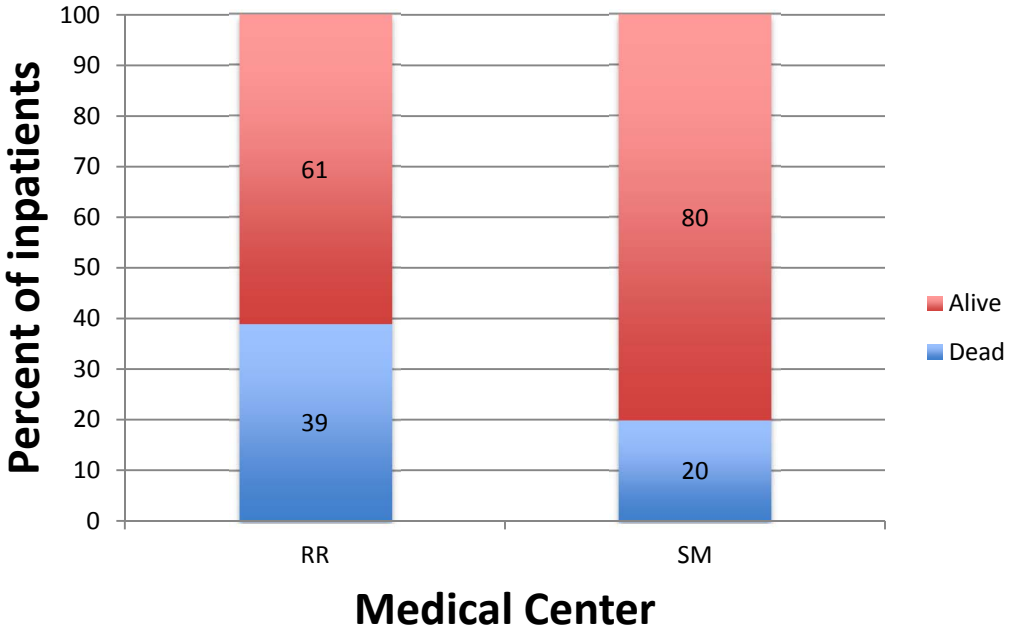
Distribution of days from admission to positive culture



- RR: 64 inpatient cultures
  - Mean time from admission to culture: 25 days
- SM: 84 inpatient cultures
  - Mean time from admission to culture: 11 days

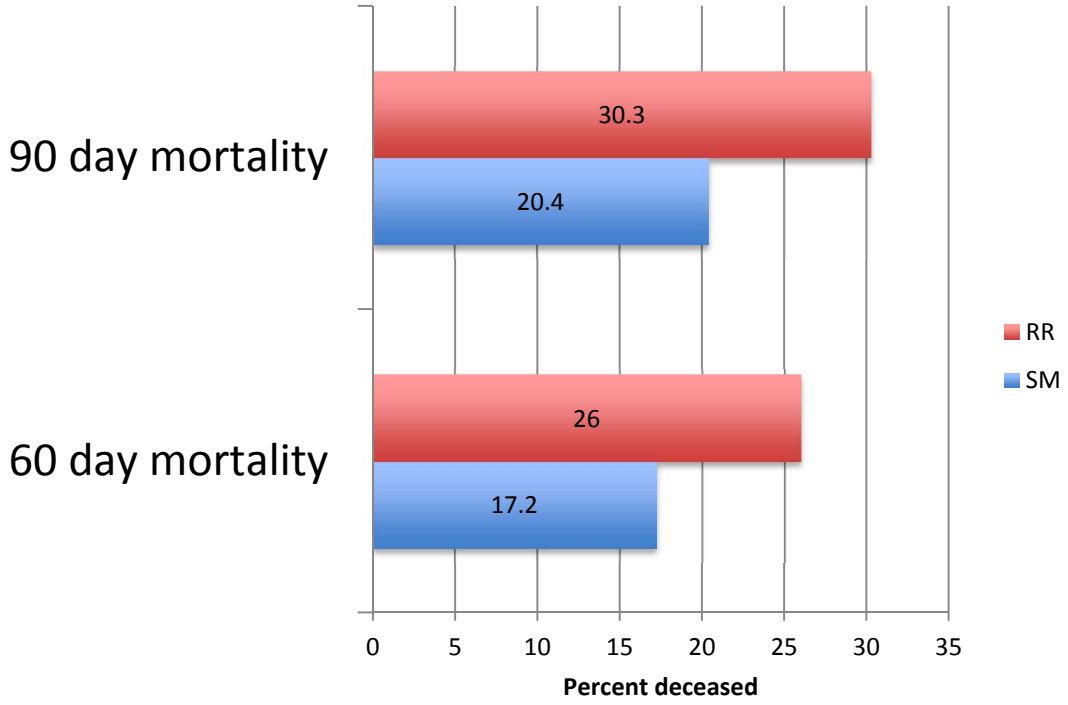
Serling-Boyd, UCLA, 2013

Discharge condition (in hospital mortality) for inpatients only



- RR: 64 inpatient cultures
- SM: 84 inpatient cultures
- Only takes into consideration discharge condition of admission encompassing positive culture (death during later admission not counted in this measure)

60 and 90 day mortality (all patients)



- RR: 76 cultures
- SM: 93 cultures
- Takes into consideration any date of death included in CareConnect
- Used date to calculate number of days from time of culture

UCLA Response

- Change in policy/practice
  - Santa Monica Hospital
    - Screen all geriatric patients via rectal swab
      - All patients admitted from certain longterm care facilities, such as GoldStar placed on empiric contact precautions pending results of rectal swabs
  - Ronald Reagan Medical Center
    - CRE infected population different
      - Long-term hospitalized patients
      - Importance of robust infection prevention practices and judicious antibiotic use KEY

In Summary

- Carbapenem resistant Enterobacteriaceae (CRE) is growing problem
- Most common CRE is the Carbapenem Resistant Klebsiella pneumoniae (CRKP) that produces a Klebsiella pneumonia carbapenemase (KPC)
- Clinically
    - Risk factors include hospitalization, antibiotic exposure, invasive devices, long-term acute care facility (LTAC), and increased acuity
    - CRE associated with increased mortality
    - Few treatment options exist
- Epidemiologically
    - CRE resistance mechanisms can spread amongst bacteria
    - CRE can spread amongst people
- Prevention via a bundled approach is key to halting the spread
    - Adequate hand washing
    - Contact precautions
    - Cohorting
    - Antibiotic Stewardship
    - Contact tracing versus active surveillance