

# Carbapenem-Resistant Enterobacteriaceae Management and Treatment Options

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# Overview

- Increase in ESBLs
- Epidemiology of CRE
- Infection control approaches
- Antimicrobial stewardship
- Treatment options

# Extended-spectrum $\beta$ -lactamases (ESBLs): The Forgotten (and Underrated) MDR GNB

- Most commonly identified in enterobacteriaceae
- Plasmid-mediated
- Impart decreased susceptibility to  $\beta$ -lactam antimicrobials
  - Often co-resistance to aminoglycosides, fluoroquinolones
- Carbapenems are drugs of choice for invasive infections due to ESBL-producers

# CTX-M: ESBL Epidemic

- Common ESBL worldwide, often produced by *Escherichia coli*
- Often causes UTI
- Now reported in US
  - Healthcare associated
  - Some community
- Community-based ESBL infection raise concern for continued increases in carbapenem use

# Trends in Human Fecal Carriage of Extended-Spectrum $\beta$ -Lactamases in the Community: Toward the Globalization of CTX-M

Paul-Louis Woerther, Charles Burdet, Elisabeth Chachaty and Antoine Andremont  
*Clin. Microbiol. Rev.* 2013, 26(4):744. DOI: 10.1128/CMR.00023-13.

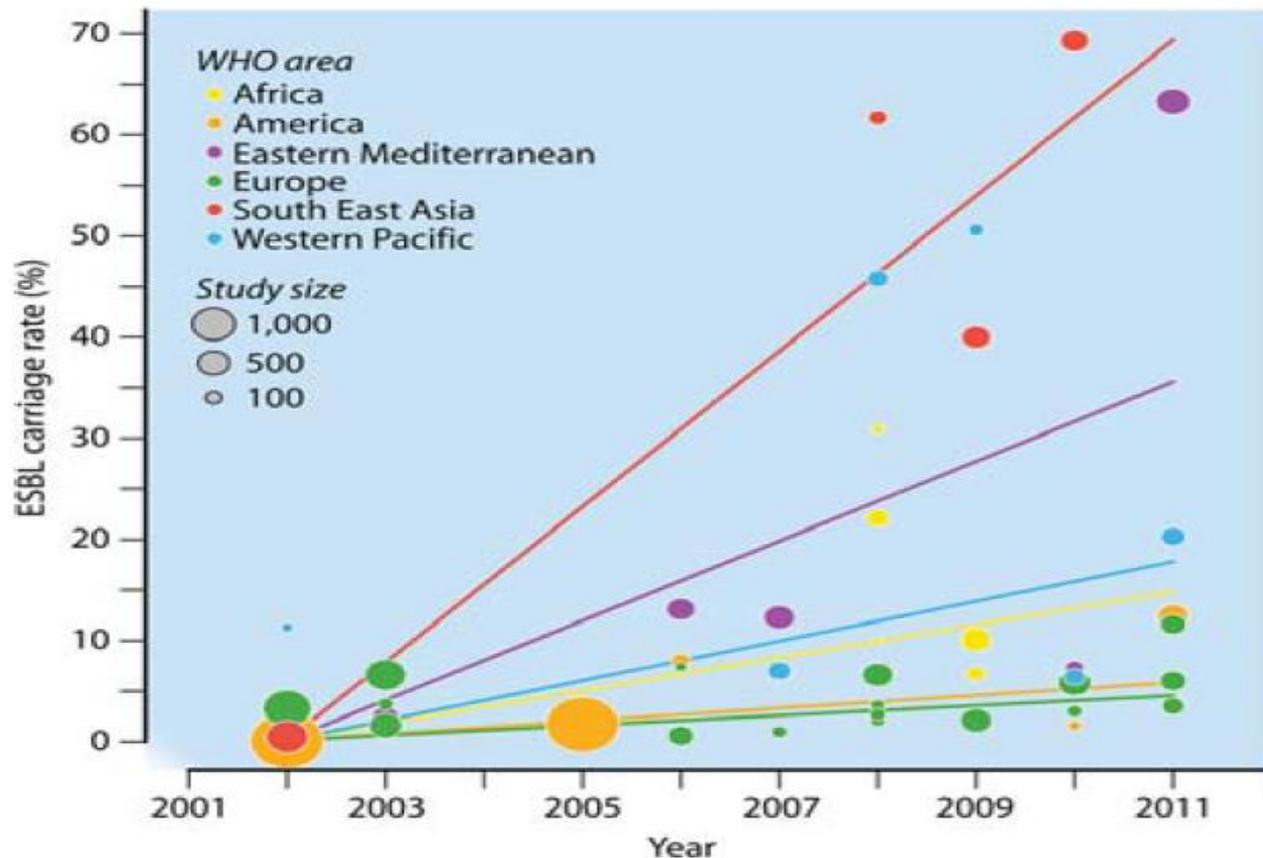


FIG 1 ESBL carriage rates in the community, according to their geographical and temporal distribution. Each bubble area is proportional to the size of the study.

# The CTX-M Detroit Experience

- From 2006-2011, total number of ESBL-producing *E. coli* increased from
  - 1.9% of all *E. coli* tested to 13.8% of all *E. coli* tested
- From 2/11-7/11 at Detroit Medical Center, 575 cases of ESBL-producing *E. coli* were identified
  - 82% urine
  - 8% wound
  - 5% blood
- 491 (85%) were CTX-M producers (predominantly CTX-M 15)
- CTX-M production was associated with increased resistance to other antibiotic classes
- Notable characteristics of ESBL-producing *E. coli*
  - > 75% POA
  - ~ 15% community-acquired
  - Prior B-lactam, TMP-SMX exposure common

# Unintended Consequences of Carbapenem Use

In attempt to reduce ESBL rate, imipenem became preferred empiric antimicrobial instead of 3<sup>rd</sup> generation cephalosporins

	1995	1996	Change (%)
Cephalosporin use*	5508 g	1106 g	-80
Imipenem use*	197 g	474 g	+140
Imipenem-resistant <i>Pseudomonas aeruginosa</i> (number)	67	113	+68.7

\*Unpaired median monthly gram use

Rahal, JAMA, 1998, 1233-37

# Carbapenem Resistance

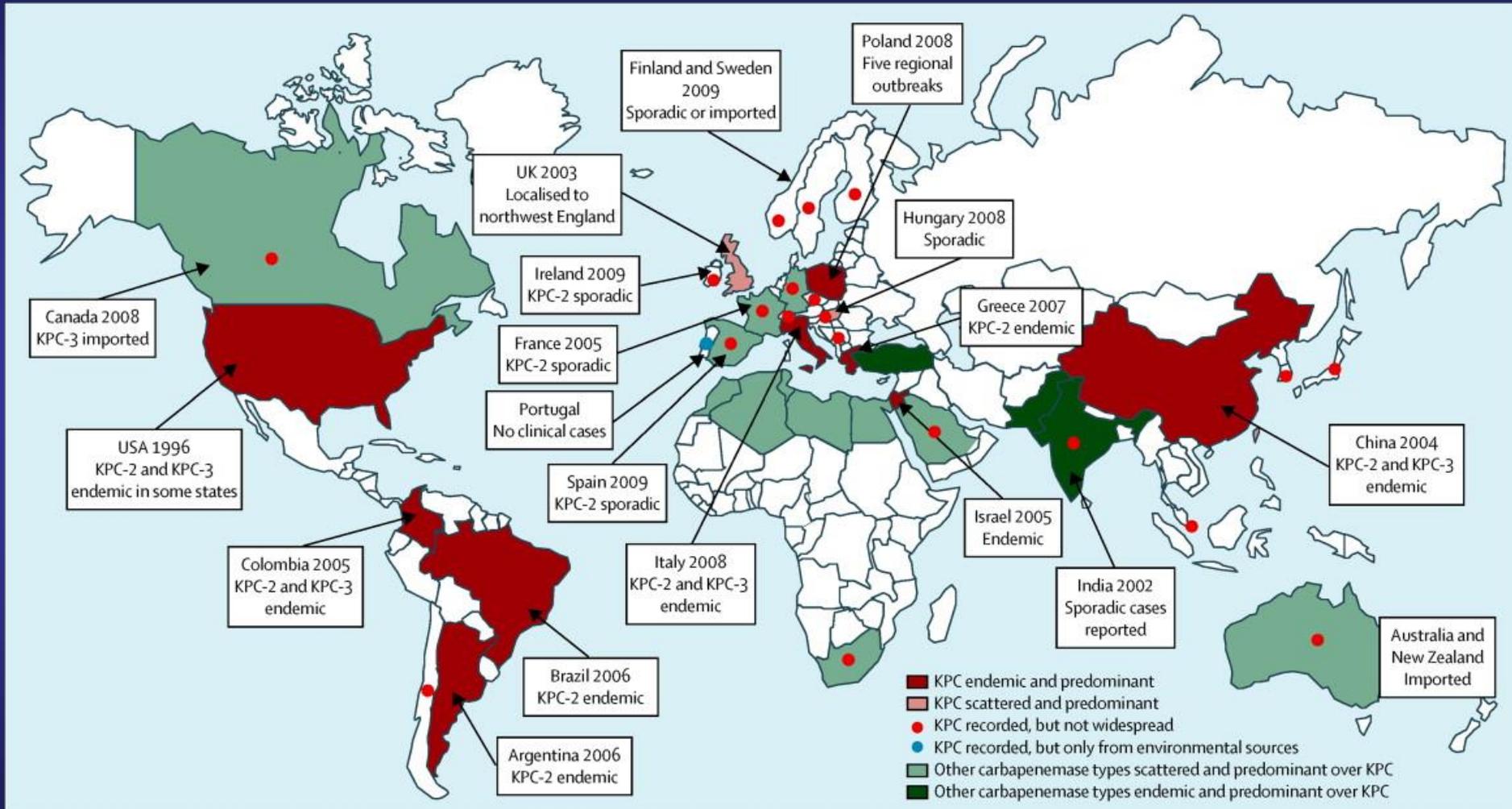
- Emerging problem in *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Enterobacteriaceae (CRE)
- Risk factors include ICU stay, prolonged exposures to healthcare, indwelling devices, antibiotic exposures
  - Long-term acute care centers (LTACs)
- Severely limits treatment options
  - Increased use of older, toxic agents such as colistin

# *Klebsiella pneumoniae* Carbapenemases (KPCs)

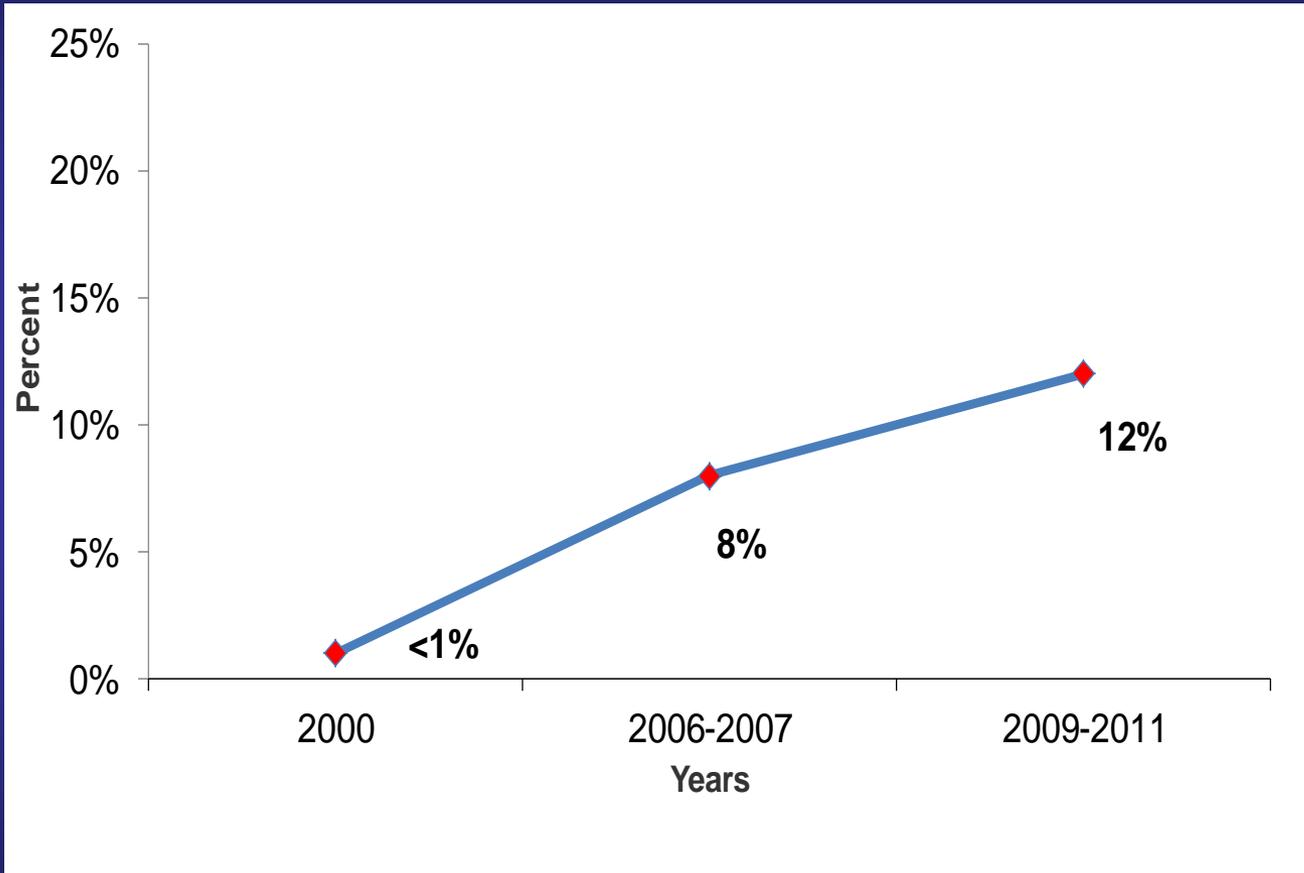
- Plasmid-mediated carbapenemase
- KPC-producing strains of *Klebsiella pneumoniae* and other enterobacteriaceae
  - KPC-2, KPC-3
- Endemicity in many locales in the US
  - Hyperendemicity in NYC
- Country-wide outbreak ongoing in Israel, Greece, Columbia and others

\*Bratu, AAC, 2005; Quale, CID, 2004; Leavitt, AAC, 2007; Carmeli, Clin Micro Infect, 2010

# Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases



# Dramatic Rise in CRE Incidence - US Hospital Reports to CDC



**CRE may cause variety of nosocomial infections**

- cIAI
- cUTI
- HABP/VABP
- Bacteremia

**Mortality up to 35 – 50%**

**Percentage of carbapenem-resistant *Klebsiella* isolates reported to CDC has steadily increased since 2000**

Satlin MJ, et al. Clin Infect Dis. 2014;58:1274-1283.

## Carbapenemase-producing CRE in the United States

Below is a map showing states with carbapenemase-producing CRE confirmed by CDC.



This map was last updated on February 2014

<http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html>

# CRE

- Risk Factors
  - Prolonged length of stay
  - Long term acute care (LTAC) facility exposure\*
  - Mechanical ventilation
  - Intensive Care Unit stay
  - Antimicrobial exposures
  - Poor functional status
- Outcomes
  - Carbapenem-resistance independently increases mortality
  - Overall mortality has ranged from 22-59%

# Long-term Care Facilities (LTCFs) and CRE

- Not all LTCFs are created equally
- Long-term acute care centers (LTACs) are associated with CRE to much a greater degree than other types of LTCFs
  - In one study from the midwest, more than 30% of LTAC residents were colonized with CRE
    - ~ 1% of residents in skilled nursing facilities

# Transfer from High-Acuity Long-Term Care Facilities Is Associated with Carriage of *Klebsiella pneumoniae* Carbapenemase–Producing *Enterobacteriaceae*: A Multihospital Study

Kavitha Prabaker, MD;<sup>1,2</sup> Michael Y. Lin, MD, MPH;<sup>1</sup> Margaret McNally, RN, BSN, PCCN;<sup>3</sup> Kartikeya Cherabuddi, MD;<sup>4</sup> Sana Ahmed, MD;<sup>5</sup> Andrea Norris, DO;<sup>5</sup> Karen Lolans, BS;<sup>1</sup> Ruba Odeh, DO;<sup>5</sup> Vishnu Chundi, MD;<sup>6</sup> Robert A. Weinstein, MD;<sup>1,2</sup> Mary K. Hayden, MD<sup>1</sup>  
for the Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program

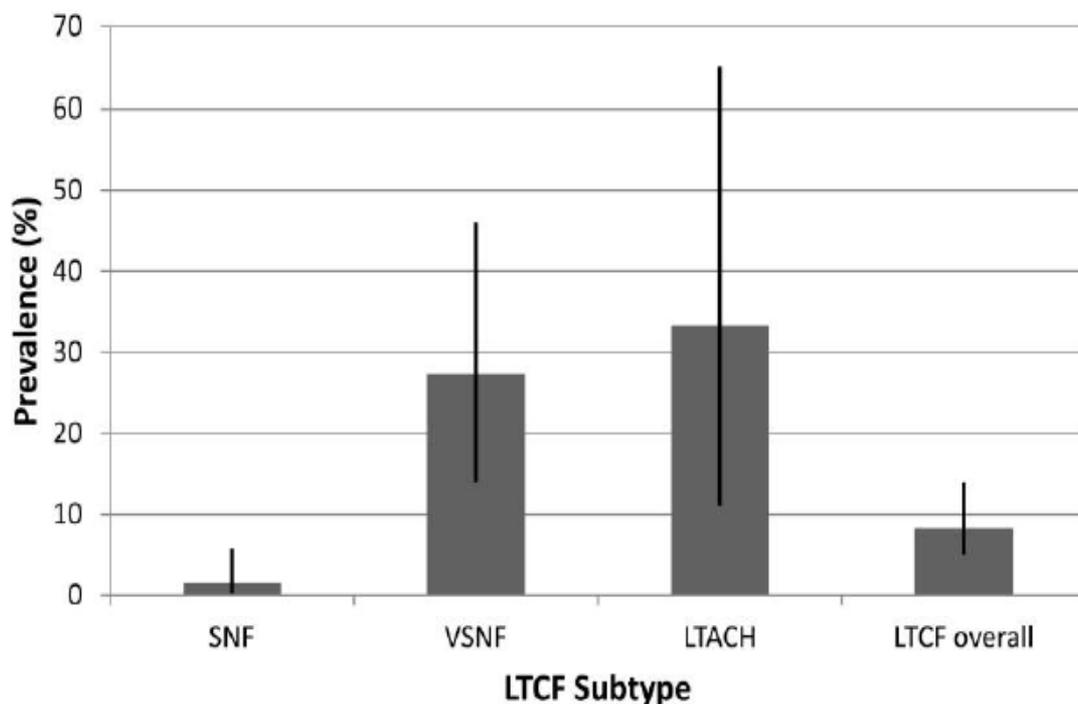


FIGURE 1. Average prevalence and 95% confidence limits of carriage of *Klebsiella pneumoniae* carbapenemase–producing *Enterobacteriaceae* among patients from specific long-term care facility (LTCF) subtypes, at the time of acute care hospital admission. SNF, skilled nursing facility without a ventilator unit; VSNF, skilled nursing facility with a ventilator unit; LTACH, long-term acute care hospital.

# Prevention of CRE

- Infection control
  - Contact precautions
  - Source control
  - Environmental hygiene
  - Screening high risk patients
- Antimicrobial stewardship
- Bundle approaches

# Active Surveillance

- Use of “screening” cultures to identify patients colonized with pathogens (usually MDR) of interest
- Goal is to prevent spread in the hospital by identifying patients who are colonized and intervening to prevent spread
- Universal vs targeted strategies
- Rectal swabs or stool specimens
  - Selective media
  - Rapid diagnostics such as PCR
- Screening alone does nothing
  - Need process in place to act upon screening results

# Chlorhexidine: Mechanism of Action

- Broad spectrum (Gram-positive, Gram-negative bacteria, fungi)
- Bactericidal and/or bacteristatic depending on concentration
- Works rapidly (can kill 100% of bacteria within 30 seconds)
- Can kill all categories of microbes
  - Little risk for development of resistance

# Role of CHG Bathing With Regards to Hospital Infection and MDRO

- Protect the patient
  - Decrease the degree of colonization/burden of pathogens on skin of individual patient
  - By doing so, decrease risk for device-related infection (ie CLABSI)
- Protect other patients
  - By decreasing the burden of pathogens on an individual patient, the likelihood of spread to other patients (via contaminated healthcare workers and/or environment) is decreased
- Success in preventing infections CLABSI and infections due to MRSA, VRE, Acinetobacter

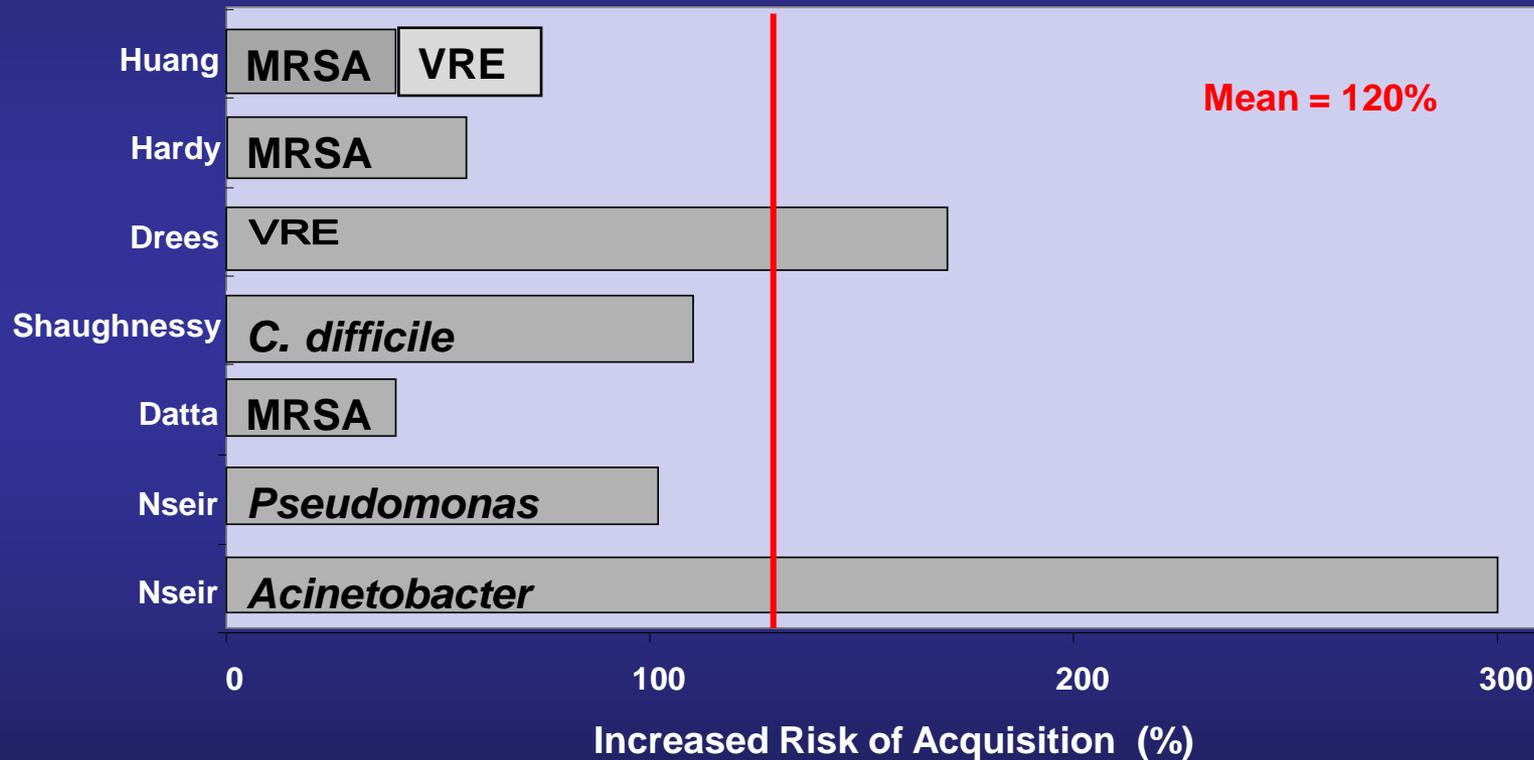
Huang et al, NEJM, 2013; Journal of Hospital Infection (2007) 67, 149-155;  
Arch Surg. 2010;145(3):240-246

# Environmental Cleaning

- Environmental sources of contamination/infection
  - Increasingly recognized as sources of infection
- Adequacy of cleaning of patients' rooms suboptimal
- Improve monitoring and feedback of efficacy of cleaning
  - Direct observation and culturing not efficient, time-consuming and expensive
- Other options: ATP bioluminescence and fluorescent dyes
  - Monitor process, efficacy of cleaning

# Previously Contaminated Rooms Increase Transmission Risk

Seven studies as of February 2011



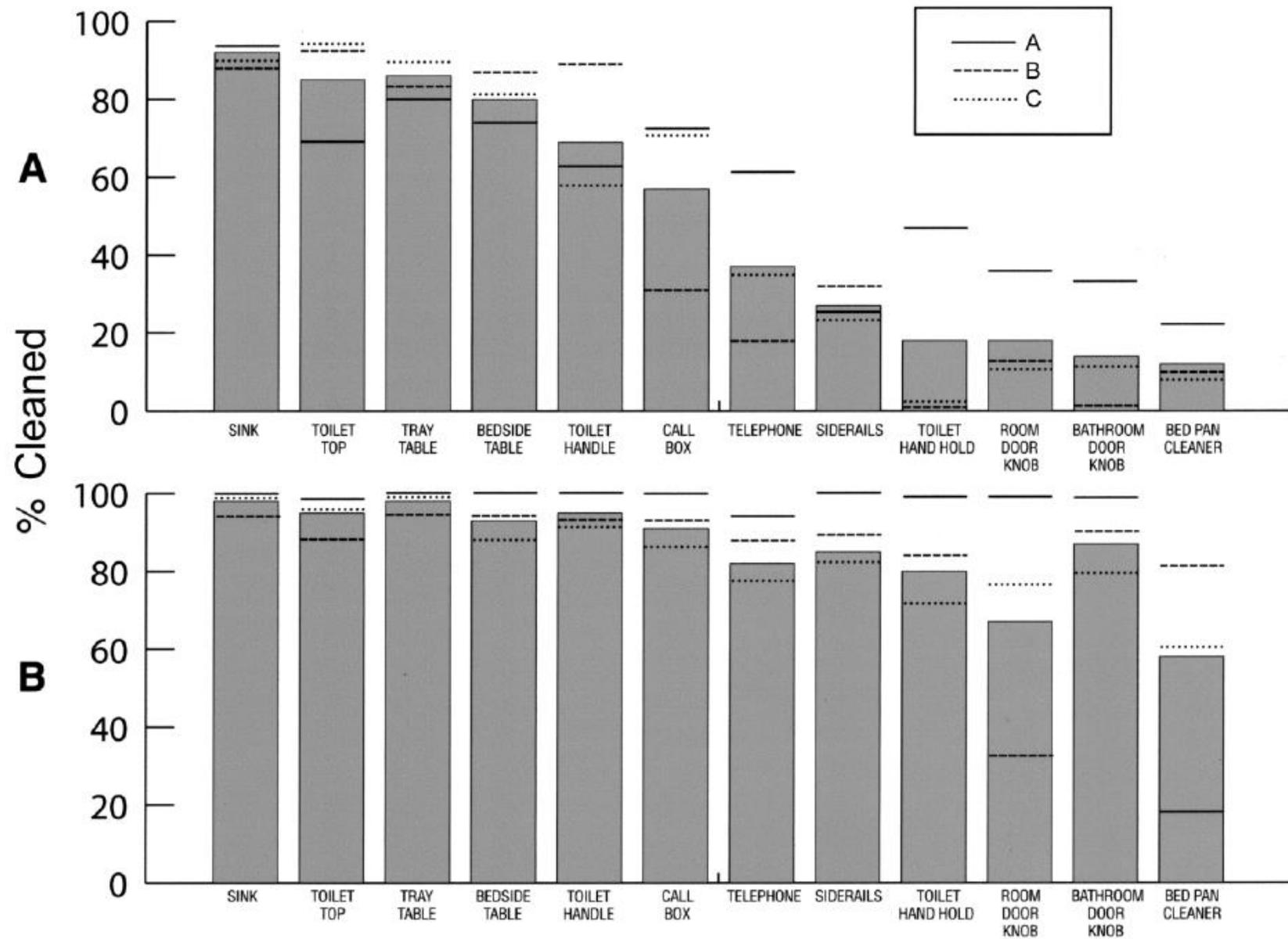
# Improved Cleaning of Patient Rooms Using a New Targeting Method

**Philip C. Carling,<sup>1,2,3,4</sup> Janet L. Briggs,<sup>1</sup> Jeanette Perkins,<sup>3</sup>  
and Deborah Highlander<sup>4</sup>**

<sup>1</sup>Department of Hospital Epidemiology, Carney Hospital, and <sup>2</sup>Boston University School of Medicine, Boston, <sup>3</sup>Department of Hospital Epidemiology Rehabilitation Hospital of the Cape and Islands, Sandwich, and <sup>4</sup>Department of Hospital Epidemiology, Quincy Medical Center, Quincy, Massachusetts

**Clinical Infectious Diseases 2006;42:385–8**

Used fluorescent dyes as part of quality improvement process for environmental cleaning



**Figure 2.** The percentage of high-touch objects cleaned prior to (A) and after (B) educational interventions in 3 hospitals (A, B, and C)

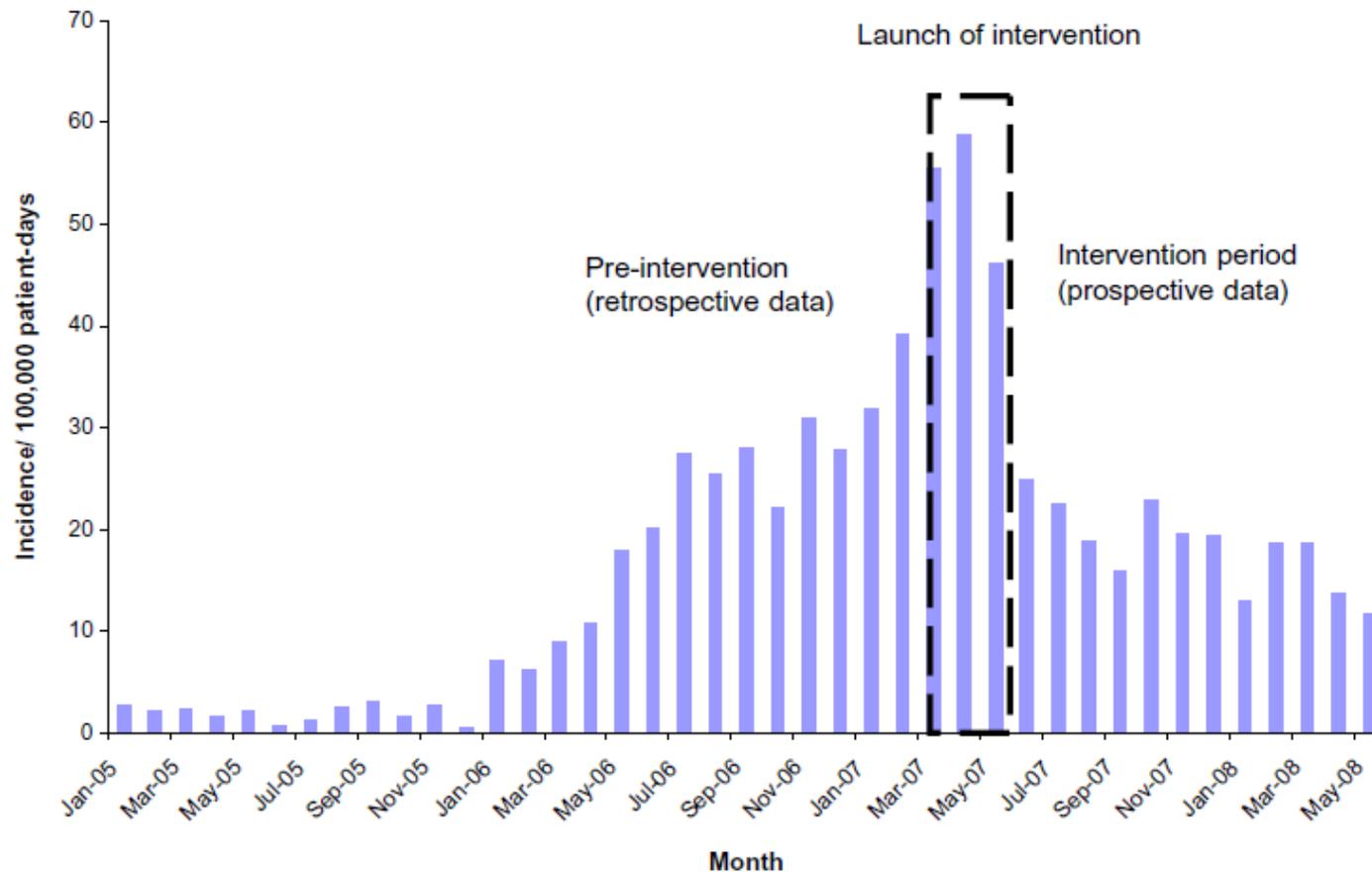
# Bundles

- A bundle is a structured way of improving the processes of care and patient outcomes: a small, straightforward set of evidence-based practices (e.g. 3-5) that, when performed collectively and reliably, have been proven to improve patient outcomes.

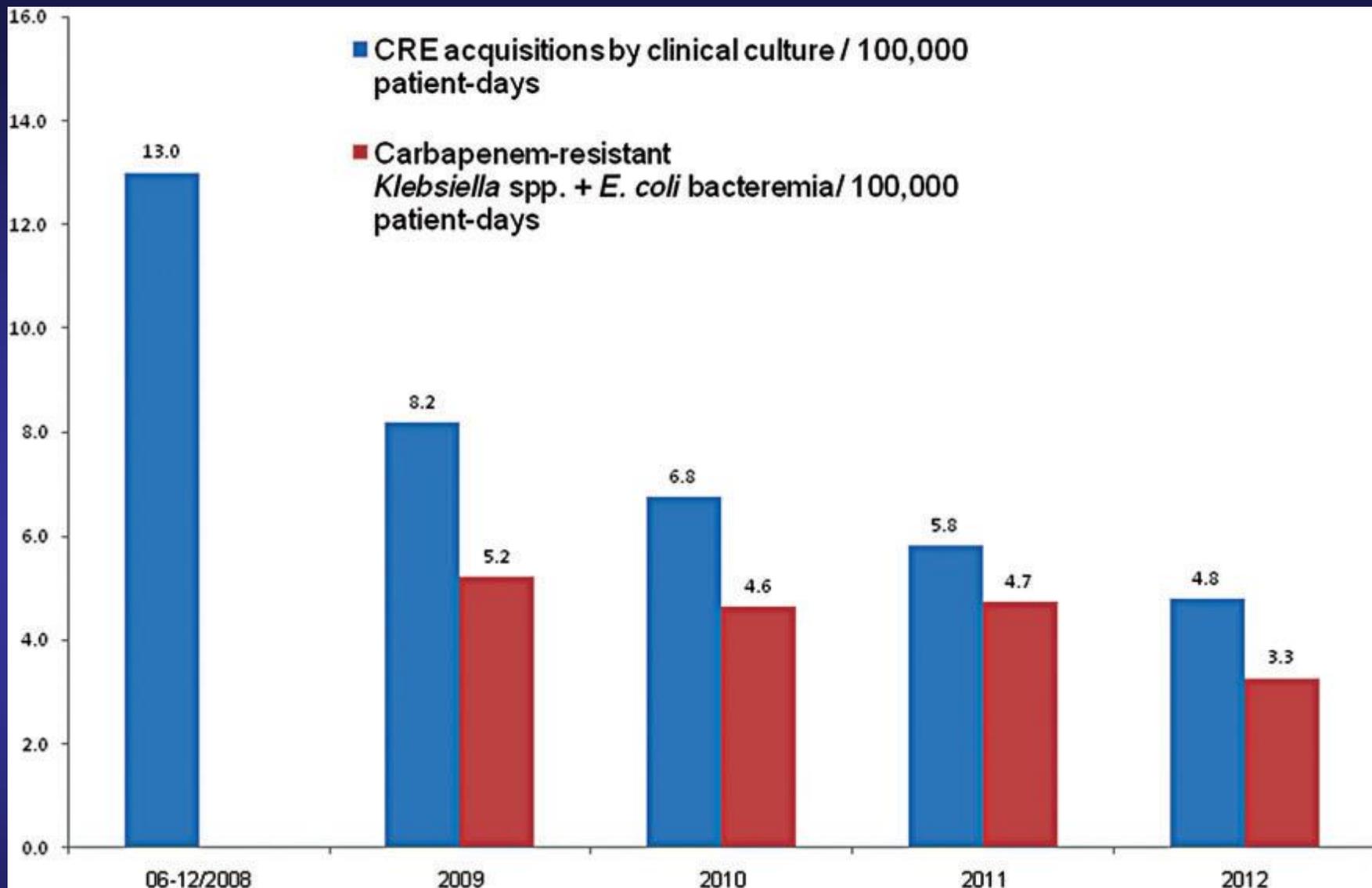
Resar R, Joint Commission Journal on Quality and Patient Safety. 2005; 243-248

# Infection control successes for CRE

- Montefiore Medical Center
  - ICU based initiative
  - Active surveillance for detection of CRE coupled with contact precautions for all colonized patients
  - Led to 53% reduction in prevalence of CRE colonization in the unit
- Israeli experience
  - Nationwide intervention
  - Ministry of Health mandated reporting of CRE, isolation of patients with CRE, and other contact measures to decrease transmission
  - Self-contained nursing units for patients



**Figure 1.** Monthly incidence of carbapenem-resistant Enterobacteriaceae detected by clinical culture per 100,000 patient-days, January 2005–May 2008. The intervention was gradually implemented nationwide from March through May 2007. Data through May 2007 were assembled retrospectively. Data from 1 June 2007 through 31 May 2008 were collected prospectively. The intervention led to a reduction in monthly incidence from a pre-intervention peak of 55.5 cases per 100,000 patient-days in March 2007 to 11.7 cases per 100,000 patient-days in May 2008 ( $P < .001$ ).



Schwaber et al., Clinical Infectious Diseases 2014; 697-703

# What About Antimicrobial Stewardship?

- Antimicrobial stewardship is relatively new discipline in the US
- Attempts to create processes to ensure good, routine antimicrobial care
  - Effective empiric therapy
  - Limiting unnecessary broad spectrum antibiotics
  - Minimize adverse events

# Antimicrobial Stewardship - Goals

- Optimize appropriate use of antimicrobials
  - The right agent, dose, timing, duration, route
- Optimize clinical outcomes
  - Reduce emergence of resistance
  - Limit drug-related adverse events
  - Minimize risk of unintentional consequences
- Help reduce antimicrobial resistance
  - The combination of effective antimicrobial stewardship and infection control has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria
- Strategies for controlling MDR GNB
  - De-escalation, shorter durations of therapy, limiting carbapenem use

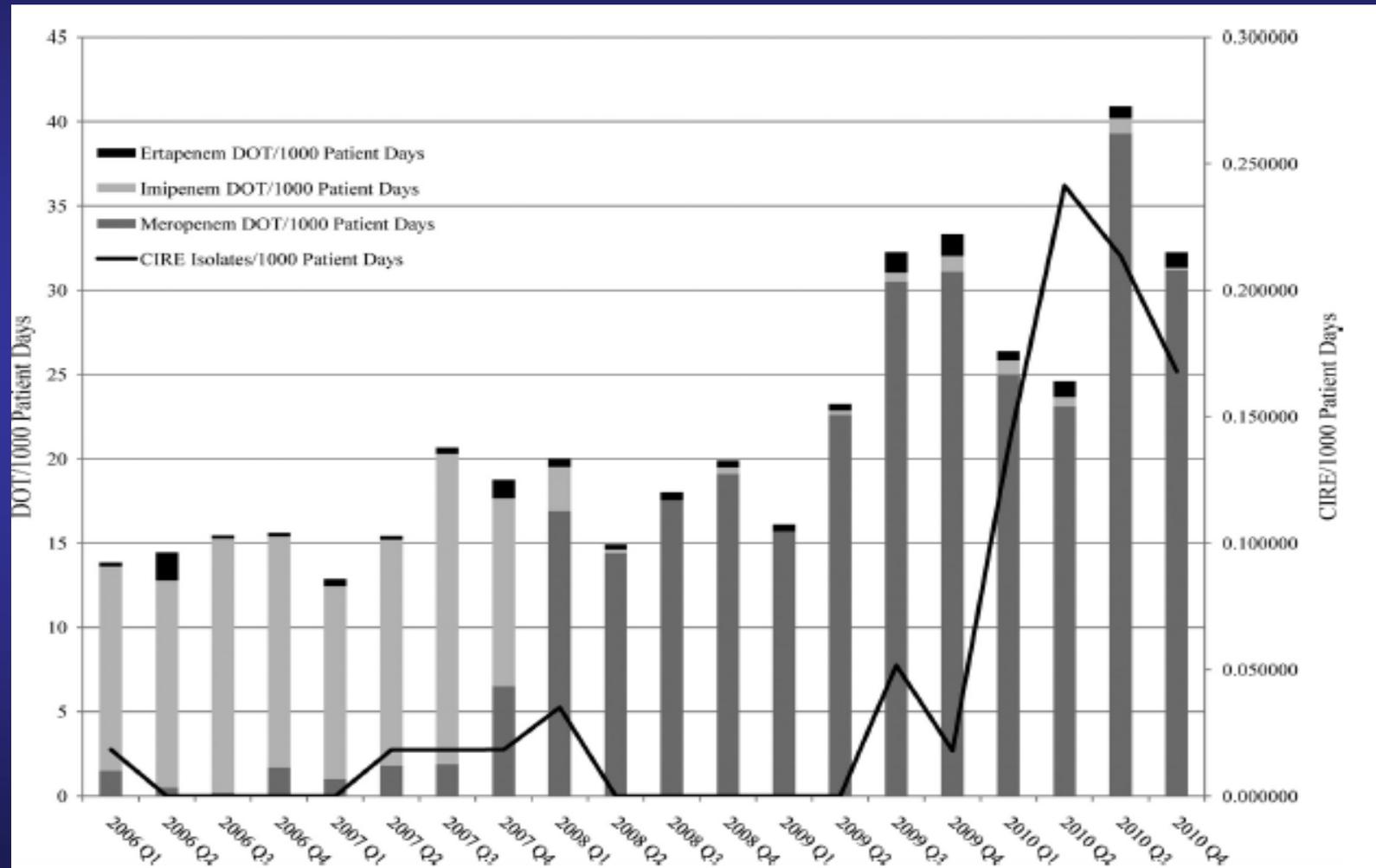
# A “Rational” Stewardship Strategy

- Broad spectrum therapy for empiric treatment of suspected invasive nosocomial infection
- Rapid de-escalation by day 3-4
- When possible, short durations of in-hospital antibiotics for selected populations
- Avoid anti-pseudomonal agents when possible
- “Hit hard, de-escalate, get out”

World Health Organization Report. Available at: <http://www.who.int/infectious-disease-report/2000/index.html>.

Perez-Gorricho B. *Int J Antimicrob Agents*. 2003;21:222-228.

# Correlation of CRE with carbapenem usage



# It's Not Just Carbapenems!

## Risk for Overall Antimicrobial Exposures and CRE

	<b>CRE vs <u>Uninfected</u> OR (95% CI)</b>	<b>CRE vs <u>ESBL</u> OR (95% CI)</b>	<b>CRE vs <u>Susceptible</u> OR (95% CI)</b>	<b>CRE vs all controls <u>combined</u> OR (95% CI)</b>
Antibiotic exposure in previous 3 months	11.4 (2-64.3)	5.2 (1.4 19.4)	12.3 (3.3-45)	7.1 (1.9-25.8)

91 unique patients with CRE were included. Exposure to antibiotics within 3 months was an independent predictor that characterized patients with CRE isolation in all analyses

Marchaim D, et.al. Infect Control Hosp Epidemiol. 2012;8: 817-30

# Proposed CRE Bundle

- Limit use of broad-spectrum antimicrobials via de-escalation and decreasing duration of therapy
  - Limit carbapenem use
  - Limit overall antimicrobial use (de-escalation, duration)
- Infection control
  - Contact precautions
  - Selective screening (CRE)
  - CHG Bathing

# Newer Treatment Options for CRE

- Tigecycline – good in vitro activity;
  - Concerns regarding emergence of resistance during treatment
  - Poor track record in critically ill patients
- Ceftazidime-avibactam – good in vitro activity vs KPCs
  - No clinical experience in treating CRE
  - ? Emergence of resistance concerns
  - Concern over avibactam's ability to inhibit ESBL + carbapenemase

## Older Agents for CRE

- Fosfomycin – most reports indicate good in vitro activity vs CRE
    - IV formulation not available in the US
    - Paucity of favorable clinical data
    - Rapid emergence of resistance during therapy has been reported
    - Some reports of declining activity
  - Aminoglycosides - amikacin and gentamicin both have activity against CRE; amikacin usually more potent
    - Aminoglycosides should not be used outside of urinary tract as monotherapy for invasive GNB infections, CRE
  - Polymyxins – excellent in vitro activity
    - Nephrotoxicity
    - PK/PD limitations (particularly for colistin) and unknowns
    - Majority of clinical data retrospective, not controlled, biased
- Satlin MJ Antimicrob Agents Chemother. 2011 Dec;55(12):5893-9.

# Strategies for Treating XDR-GNB

- Little if any controlled data
- Mortality rates are high
- For invasive infections, if no first line agent is active, then combination therapy is preferred
  - Agents with activity traditionally limited to polymyxins, aminoglycosides, tigecycline
  - Carbapenems often used in combination for synergy
    - Better effect when carbapenem MICs are lower
  - Clinical impact of combination therapy for XDR-GNB unknown
    - Some retrospective studies suggest mortality advantage when using 2 or more drugs with in vitro activity\*
    - Concerns re: unnecessary overuse of carbapenems
  - Efficacy of newer agents (ceftazidime-avibactam) unknown

# Agents in the Pipeline

Agent	Class	Status	Notable activity against CRE
Aztreonam-avibactam	Monobactam-BLI	Phase I	Aztreonam active against MBLs
Plazomicin	Aminoglycoside	Phase III	More potent against KPC
Eravacycline	Fluorocycline	Phase III	Not inhibited by carbapenemases
Carbavance	Carbapenem +borate inhibitor	Phase III	Some metallo activity?
Relebactam	Carbapenem-BLI	Phase II	Active against KPC
BAL30072	Monosulfactam	Phase I	KPC, MBL, OXA

# Conclusions

- CRE is a growing threat in many regions around the world
  - Frequency is increasing
- Major infection control challenge
  - Regional approaches, bundled approaches
  - Importance of antimicrobial stewardship
- Treatment options limited

Questions?