

# MDROs of Public Health Importance

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# Disclosures

- None relevant to this presentation

The opinions expressed here are my own and do not reflect the Los Angeles County Department of Public Health

# US Causes of Death

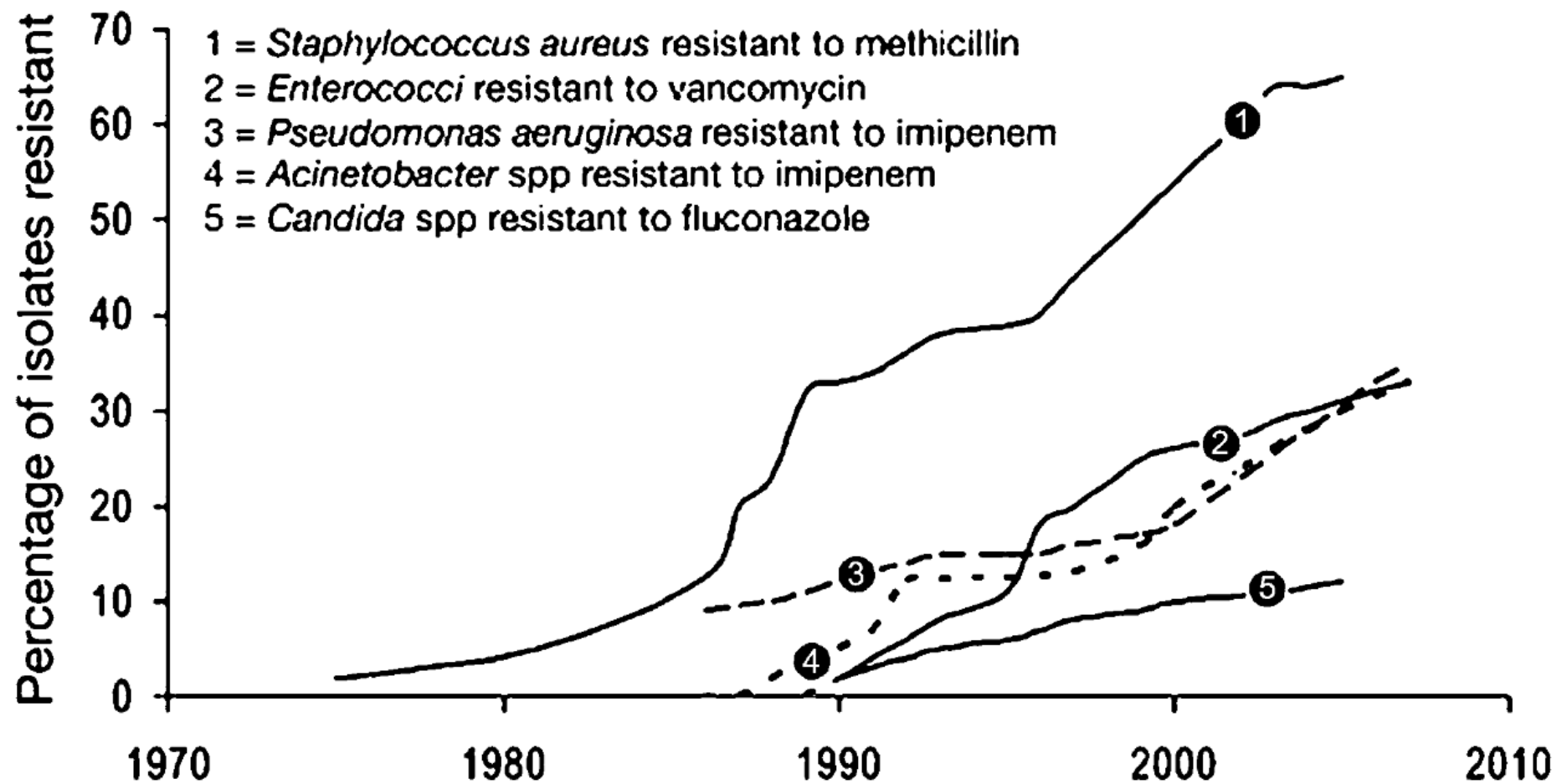
	2013	Deaths
1	Heart Disease	611,000
2	Cancer	584,000
3	Accidents	130,000
4	Stroke	129,000
5	Healthcare Associated Infections	100,000
6	Alzheimer's Disease	83,000

<http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm> Accessed 4/22/2015, rounded to the nearest thousand deaths.

[http://www.cdc.gov/HAI/pdfs/hai/infections\\_deaths.pdf](http://www.cdc.gov/HAI/pdfs/hai/infections_deaths.pdf) Accessed 4/22/2015.

# Infection Prevention Nosocomial Infections

- Hand Hygiene
- Isolation Precautions
  - Contact
  - Airborne
  - Biohazard
- Personal Protective Equipment
- Cleaning of the Environment



Insanity is  
repeating the same mistakes  
and  
expecting different results.  
-Narcotics Anonymous 1981

# CDI: Impact

	Number of annual cases	Cost	Number of annual deaths
Hospital-onset, hospital acquired (HO-HA)	165,000	\$ 1.3 B	9,000
Community-onset hospital acquired (CO-HA) [4 weeks of hospitalization]	50,000	\$ 0.3 B	3,000
Nursing home-onset	263,000	\$ 2.2 B	16,500

**25,000 HCA Deaths**

# US Causes of Death

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# CONTACT ISOLATION PRECAUTIONS

Visitors ~ See Nurse before entering

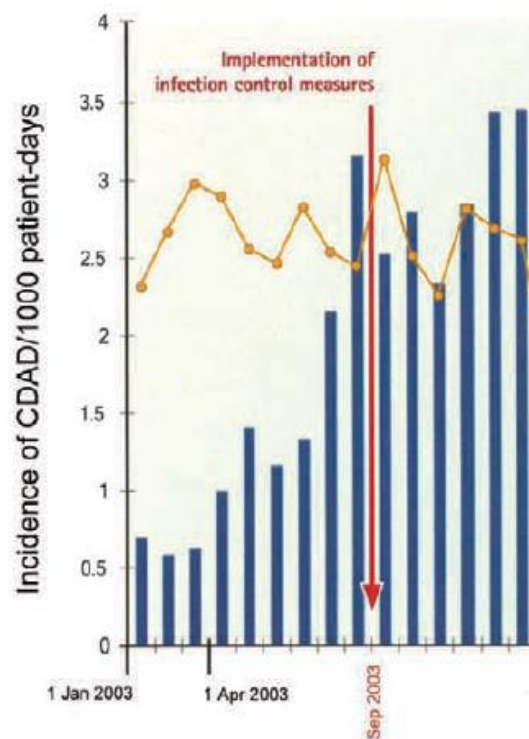


Clean Hands ~ Gown ~ Gloves

N-95 for High-Hazard Procedures (See other side)

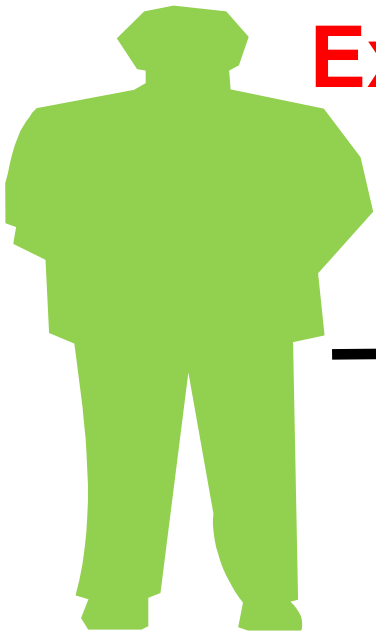


# Draconian Infection Control Measures



# CDI Pathogenesis

***C. difficile***  
**Exposure**



**Admitted to  
healthcare facility**

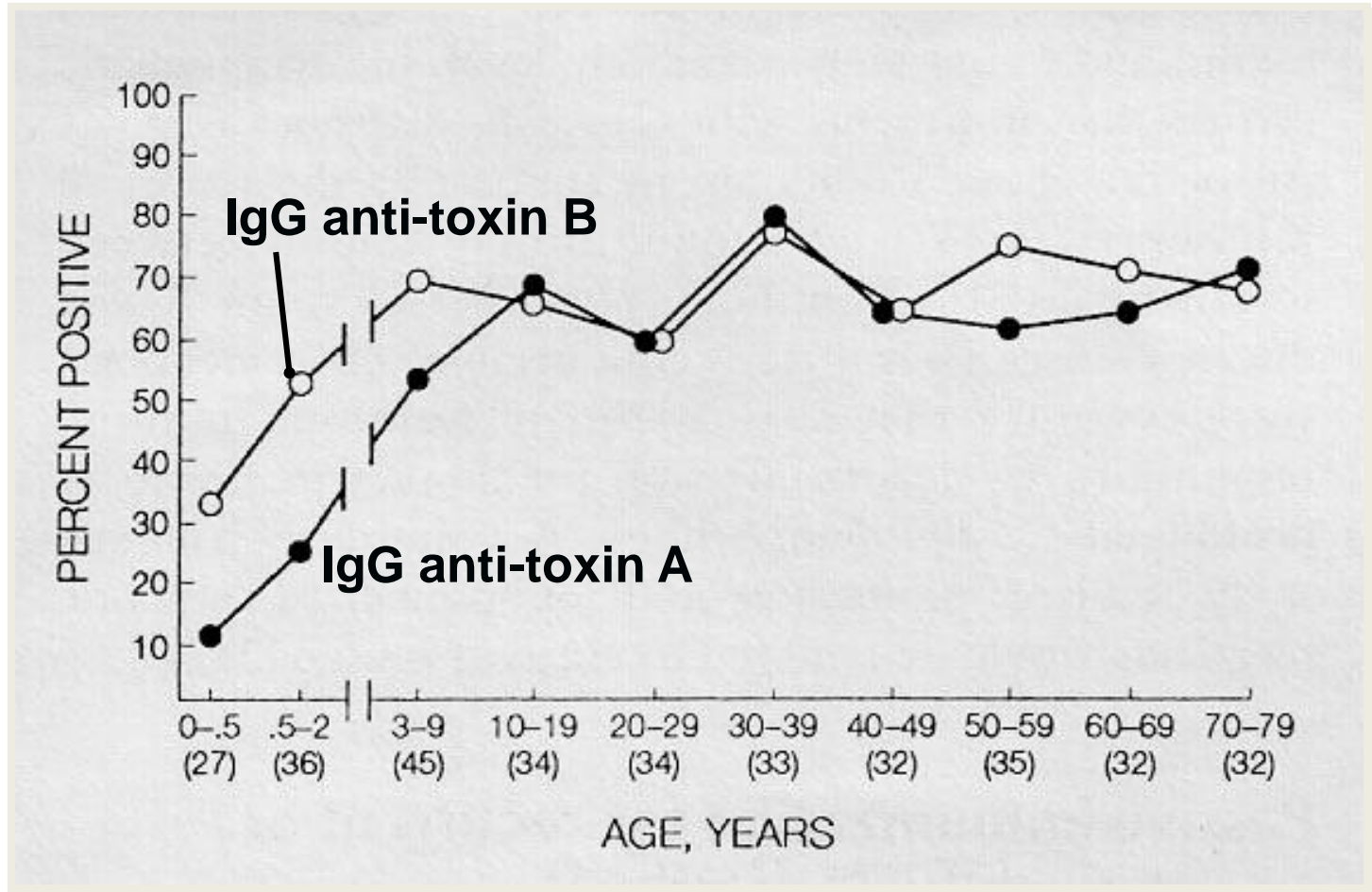


**Colonized  
no symptoms**

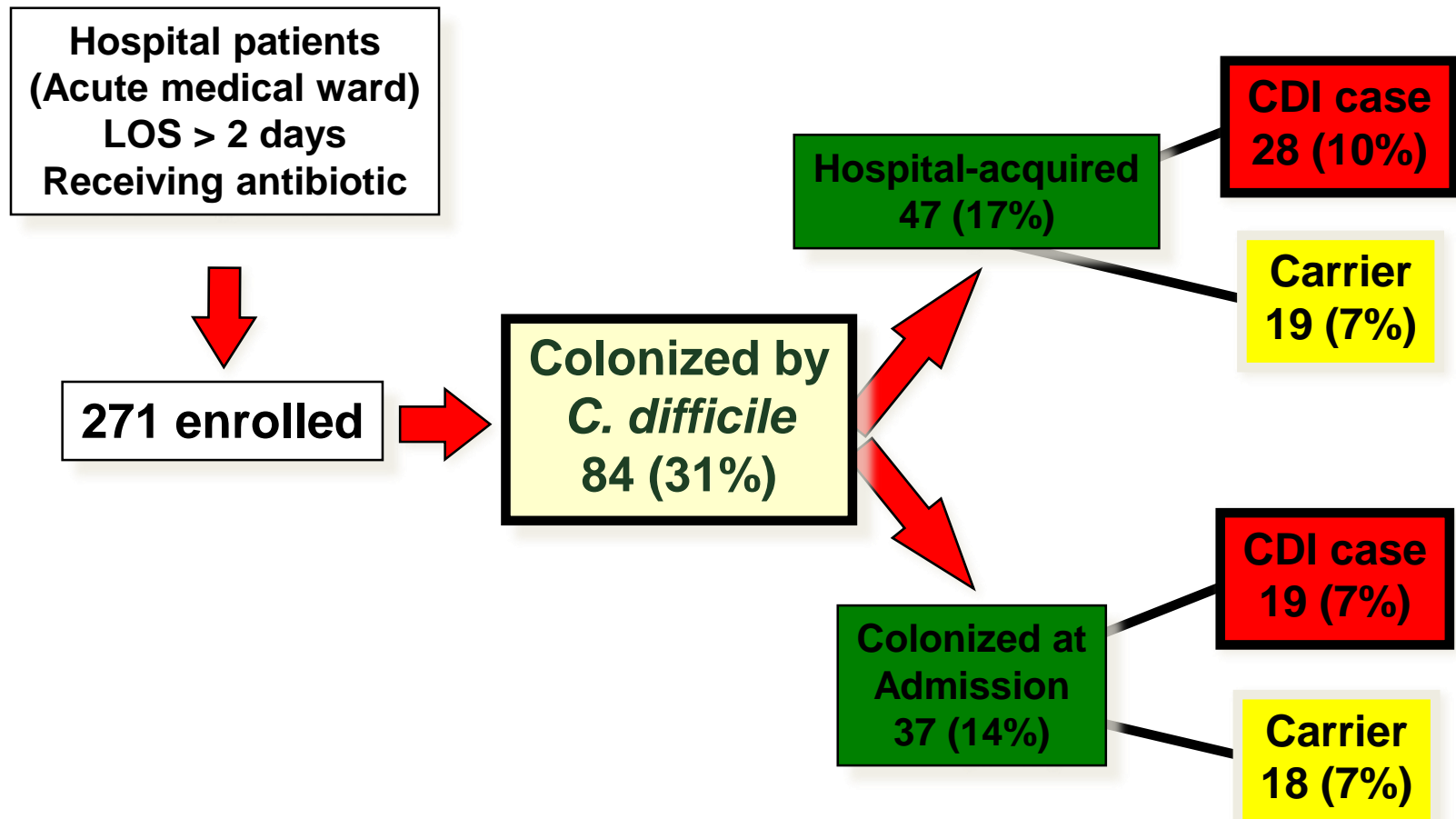


**Infected  
Symptomatic**

# Serum IgG Antibodies Against *C. difficile* Toxins Are Prevalent in the General Population



# Nosocomial *C. difficile* infection & asymptomatic carriage are common



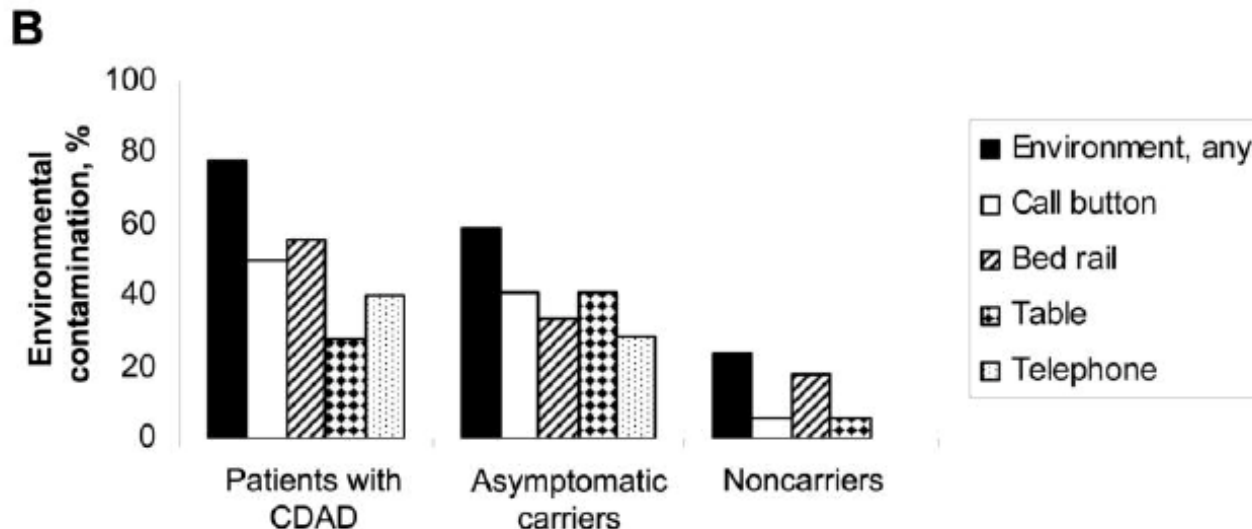
# Asymptomatic carriers are a potential source for transmission of *Clostridium difficile*

3-month study in LTCF with 73 residents

Five (7%) patients had CDI

35 (51%) were asymptomatic carriers (nine had a prior history of CDI)

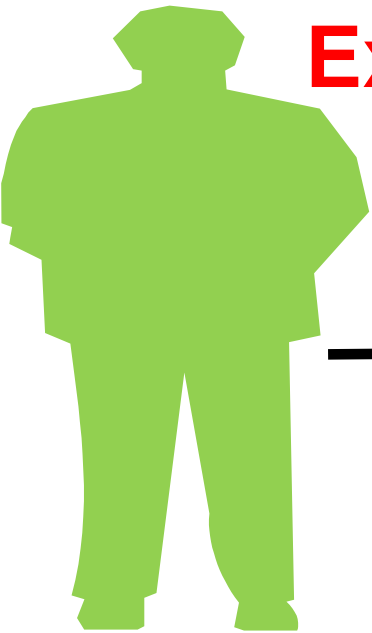
Asymptomatic carriers associated with significantly higher rates of skin (61% vs. 19%) and environmental contamination (59% vs. 24%) than non-carriers



# CDI Pathogenesis

***C. difficile***  
**Exposure**

**Antimicrobial  
Treatment**

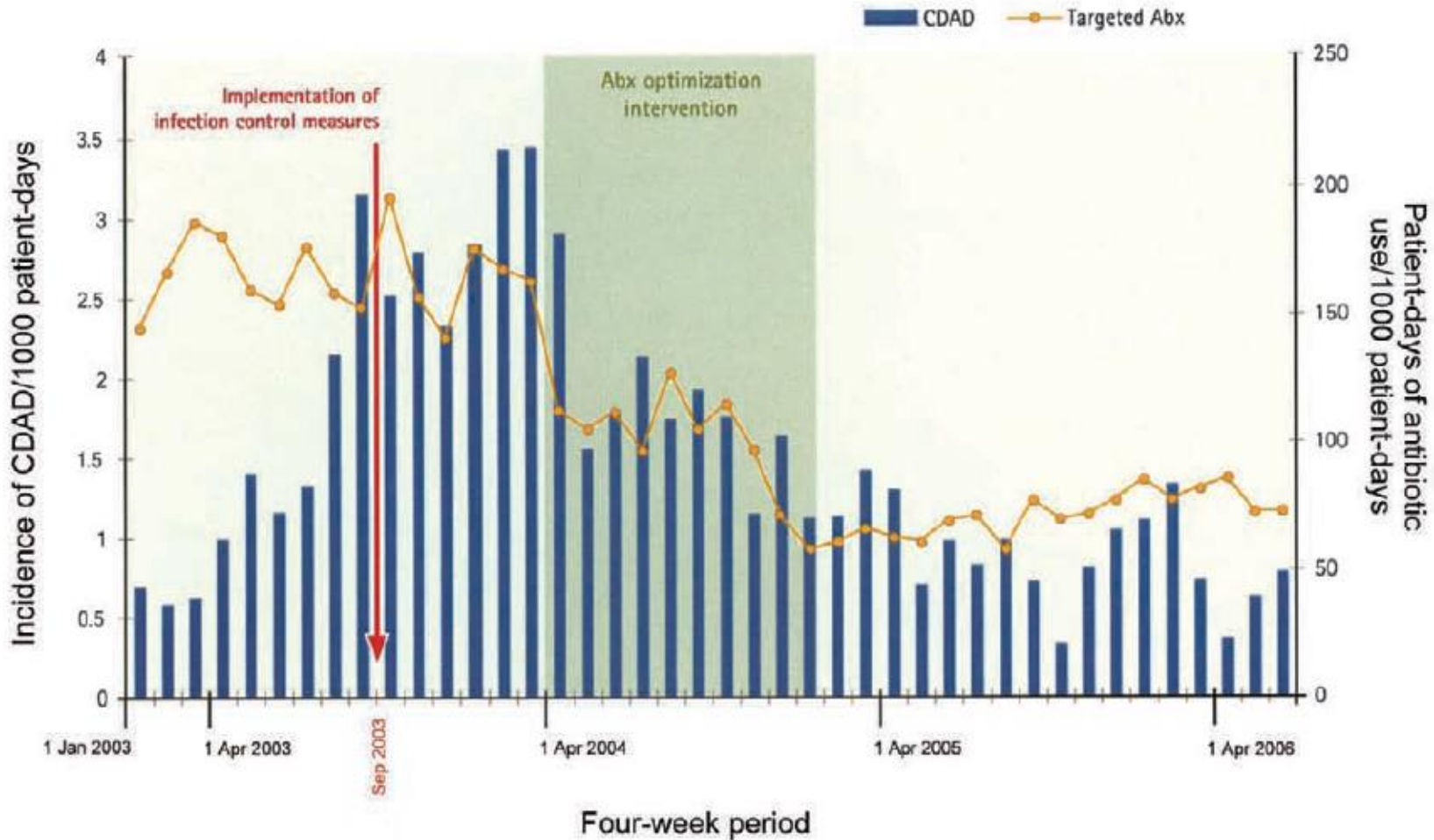


**Admitted to  
healthcare facility**

**Colonized  
no symptoms**

**Infected  
Symptomatic**

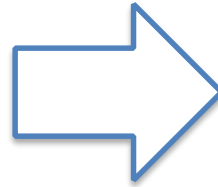
# Targeting High-Risk Antibiotics Reduces CDI





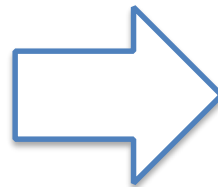
# Antibiotics and CDI

**Risk of CDI compared to resident on 1 antibiotic**



	Number of ATBs		
	2 ATBs	3-4 ATBs	5+ ATBs
	2.5 times higher	3.3 times higher	9.6 times higher

**Risk of CDI compared to resident on ATBs for <4 days**



	Days of Antibiotic		
	4-7 days	8-18 days	>18 days
	1.4 times higher	3 times higher	7.8 times higher

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# Effects of control interventions on *Clostridium difficile* infection in England: an observational study



Kate E Dingle, Xavier Didelot, T Phuong Quan, David W Eyre, Nicole Stoesser, Tanya Golubchik, Rosalind M Harding, Daniel J Wilson, David Griffiths, Alison Vaughan, John M Finney, David H Wyllie, Sarah J Oakley, Warren N Fawley, Jane Freeman, Kirsti Morris, Jessica Martin, Philip Howard, Sherwood Gorbach, Ellie J C Goldstein, Diane M Citron, Susan Hopkins, Russell Hope, Alan P Johnson, Mark H Wilcox, Timothy E A Peto, A Sarah Walker, Derrick W Crook, the Modernising Medical Microbiology Informatics Group\*



- Incidence of *C. difficile* in UK dropped by 80% after 2006
- Decline was due to multiple interventions
- However, Fluoroquinolone reduction is thought to be the primary driver for change

One Third of What You Learned in Medical School is  
Wrong.

**The Trick is Figuring Out Which Third**

## Dr. McKinnell's Notes on Antibiotic Duration

- CAP 7-10
- HAP/VAP 10-14
- Pyelonephritis 10-14
- Cellulitis 7-10
- Bacteremia 14-42

# HCAP/VAP 7 DAYS

- **Several RCTs 7-8 days equal to 10-15 days**
- **Reduced emergence of resistance**
  
- **MRSA and Pseudomonas infections may require longer therapy**

Capellier et al. PLoS One 2012;7:e41290; Chastre et al. JAMA 2003;290:2588-98; Kalil et al. CID 2016;63:e61-e111

# Short Course Therapy!!!!

Diagnosis	Short (d)	Long (d)	Result
CAP	3 or 5	7, 8, or 10	Equal
HAP	7	10-15	Equal
VAP	8	15	Equal
Pyelo	7 or 5	14 or 10	Equal
Intra-abd	4	10	Equal
AECB	$\leq 5$	$\geq 7$	Equal
Cellulitis	5-6	10	Equal
Osteo	42	84	Equal

# MDRO of Public Health Importance

- *Clostridium difficile*

Pay Attention to Duration of Treatment

Avoid Ciprofloxacin and Levofloxacin



- CDC Report, Antibiotic Resistance Threats in the US 2013
- One of only three pathogens with an URGENT Threat Level



# The French Grammar Lesson

Family? ? ? ? Genus? ? ? ? Species?

Enterobacteriaceae?

?

*Citrobacter*?

*freundii*,<sup>?</sup> *koseri*,<sup>?</sup> *amalonaticus*?

***Enterobacter***?

*cloacae*,<sup>?</sup> *aerogenes*,<sup>?</sup> *sakasakii*?

***Esherichia***?

*coli*,<sup>?</sup> *albertii*?

***Klebsiella***?

*pneumoniae*,<sup>?</sup> *oxytoca*,<sup>?</sup> *granulomati*.

*Morganella*?

*marganii*?

*Proteus*?

*mirabilis*,<sup>?</sup> *vulgaris*?

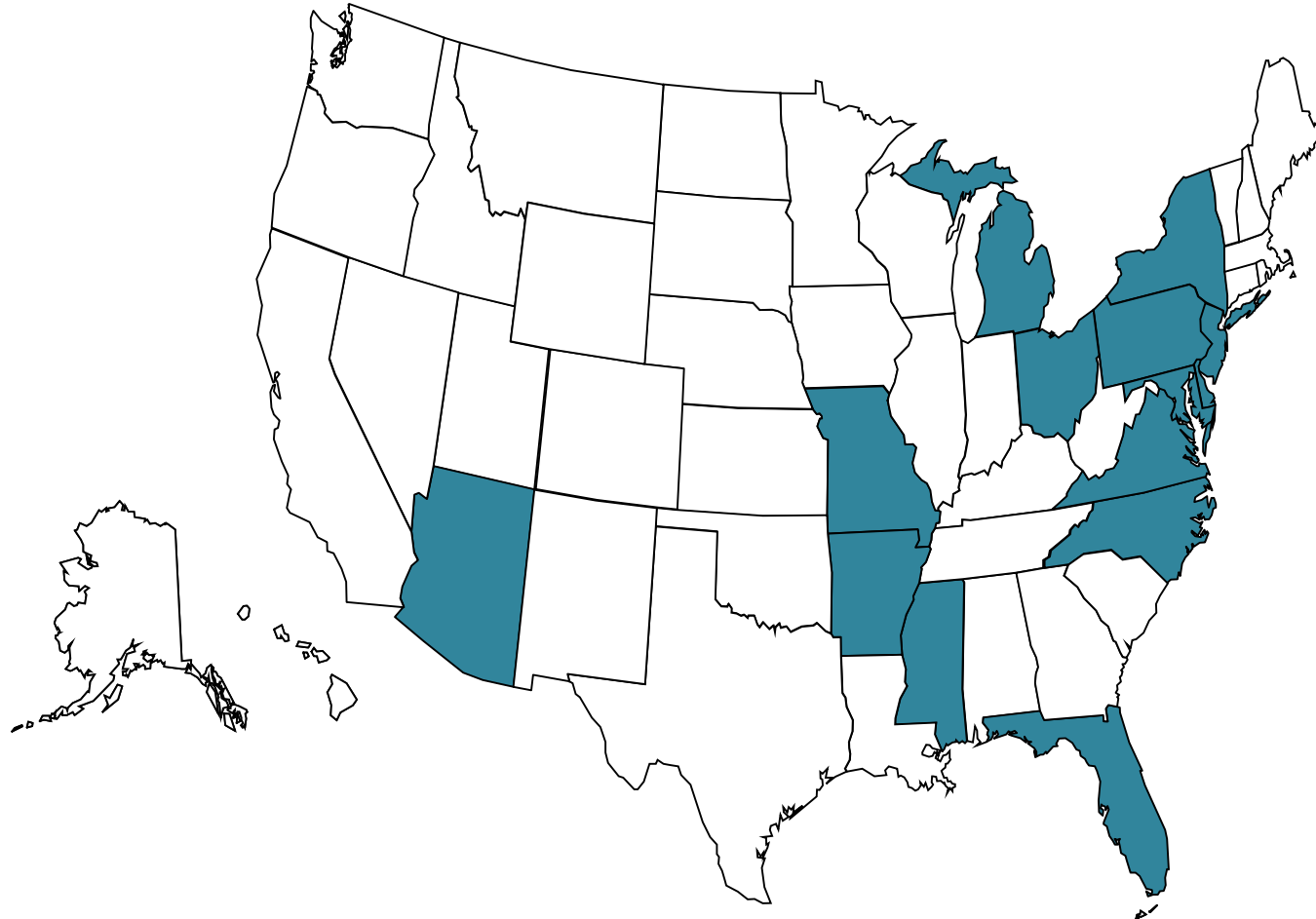
*Providencia*?

*stuartii*,<sup>?</sup> *rettgeri*?

*Serratia*?

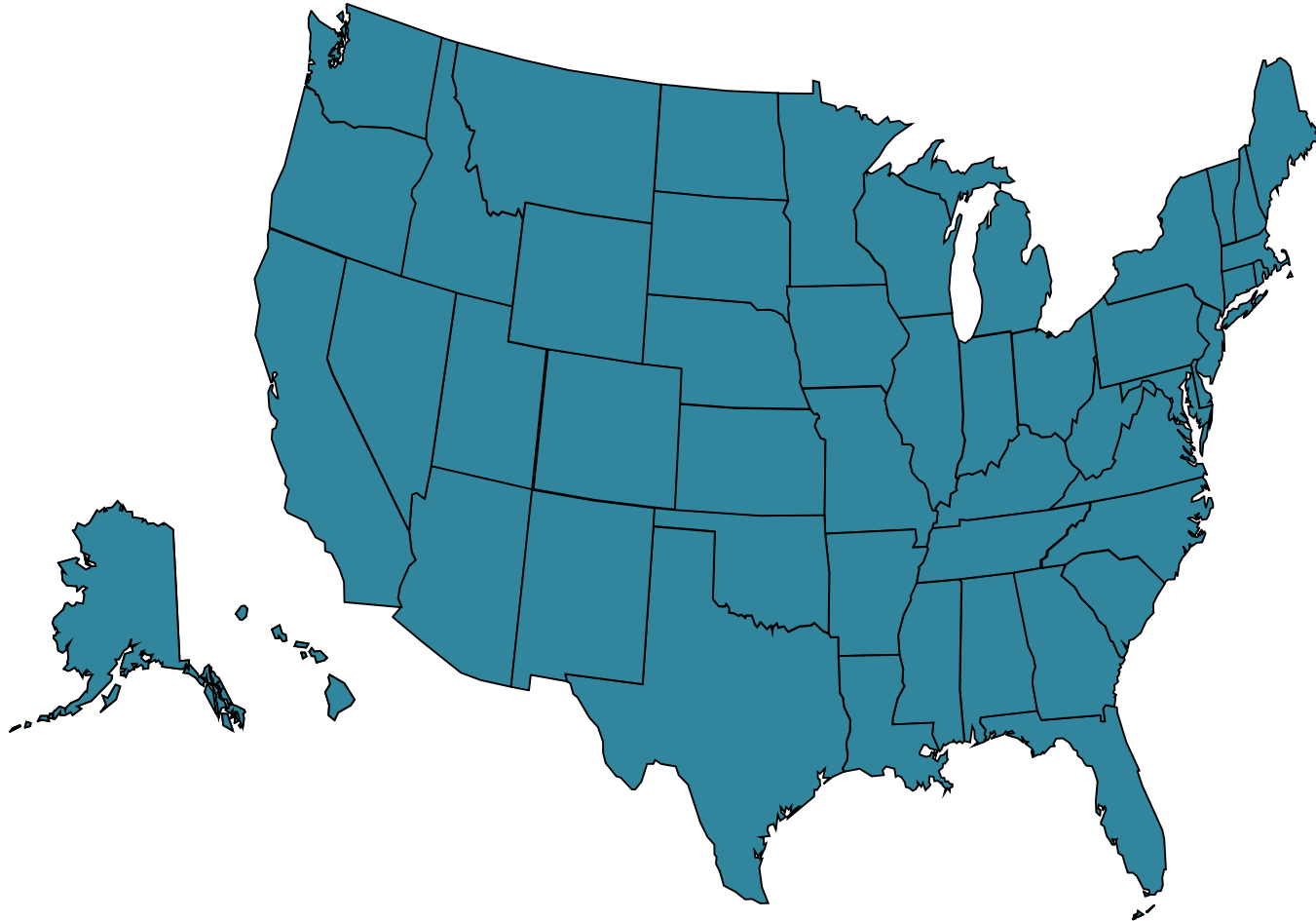
*marcescens*?

# Spread of CRE in US Reported to CDC in 2006



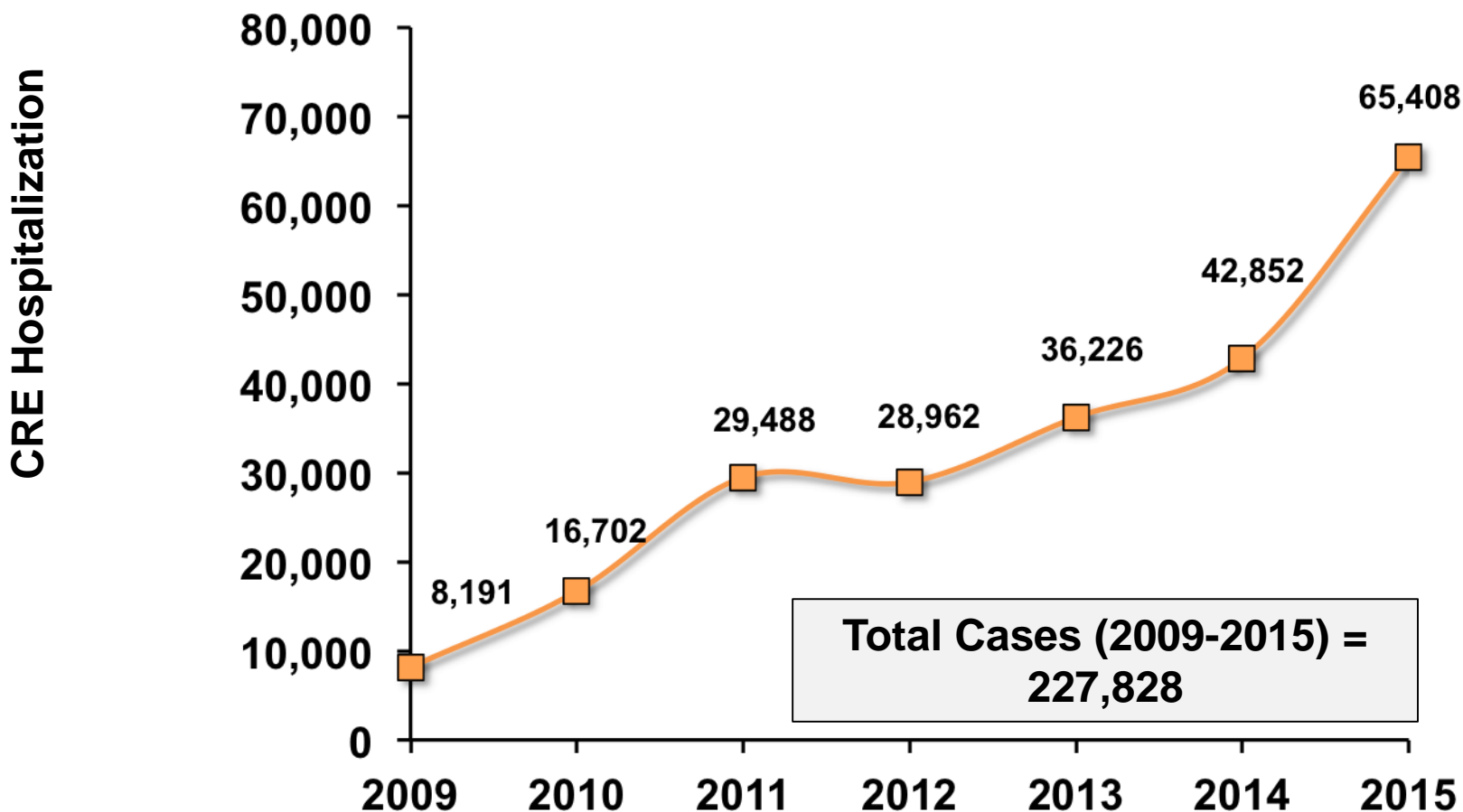
<http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html>

# Growing Spread of CRE Reported to CDC in 2018



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

# Steady Increase in CRE Cases in US





- Novel Antibiotics (Ceftazidime-Avibactam, Imipenem-Relebactam, Meropenem-Vaborbactam and Plazomicin) have reduced mortality from 50% to <20% in most studies

# Two Forms of Carbapenem-Resistant Enterobacteriaceae

Carbapenemase  
producing  
(CP-CRE)

Sub-type

**KPC**

NDM, IMP, VIM

OXA 23, 48

Non-carbapenemase  
producing  
(Non-CP-CRE)

Additional mechanism

Porin mutation

Efflux pump

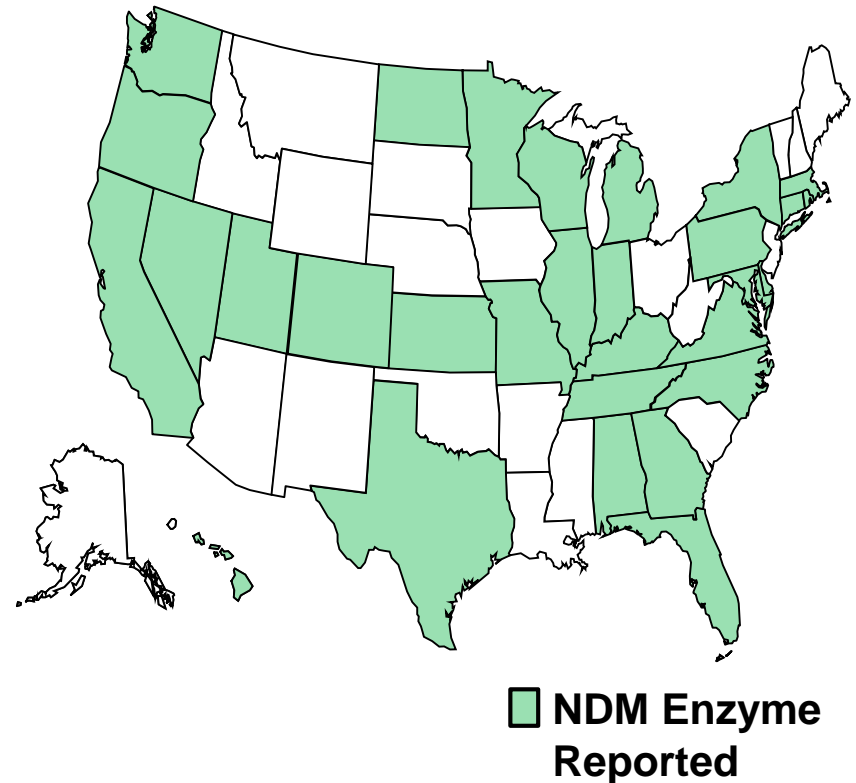
**+**

Sub-type

AMP-C, ESBL

# Non-KPC CRE on the Rise

- Los Angeles 2015-2017
  - 1,000 CRE isolates
  - 20% non-KPC
- Vancouver 2008–2017
  - >3,500 CRE isolates
  - 703 CP organisms
  - 90% non-KPC



# Ongoing CRE Surveillance in LA

- 31 clinical labs since 2015
- 1,263 isolates collected
- 77% of CRE in LA County are CP
- 34 Non-KPC CP Producers
  - 16 OXA (first detected 2015)
  - 11 NDM (first detected 2015)
  - 6 VIM (first detected 2016)
  - 1 IMP (first detected 2017)



“How are CRE and Other MDROs spreading so effectively?”

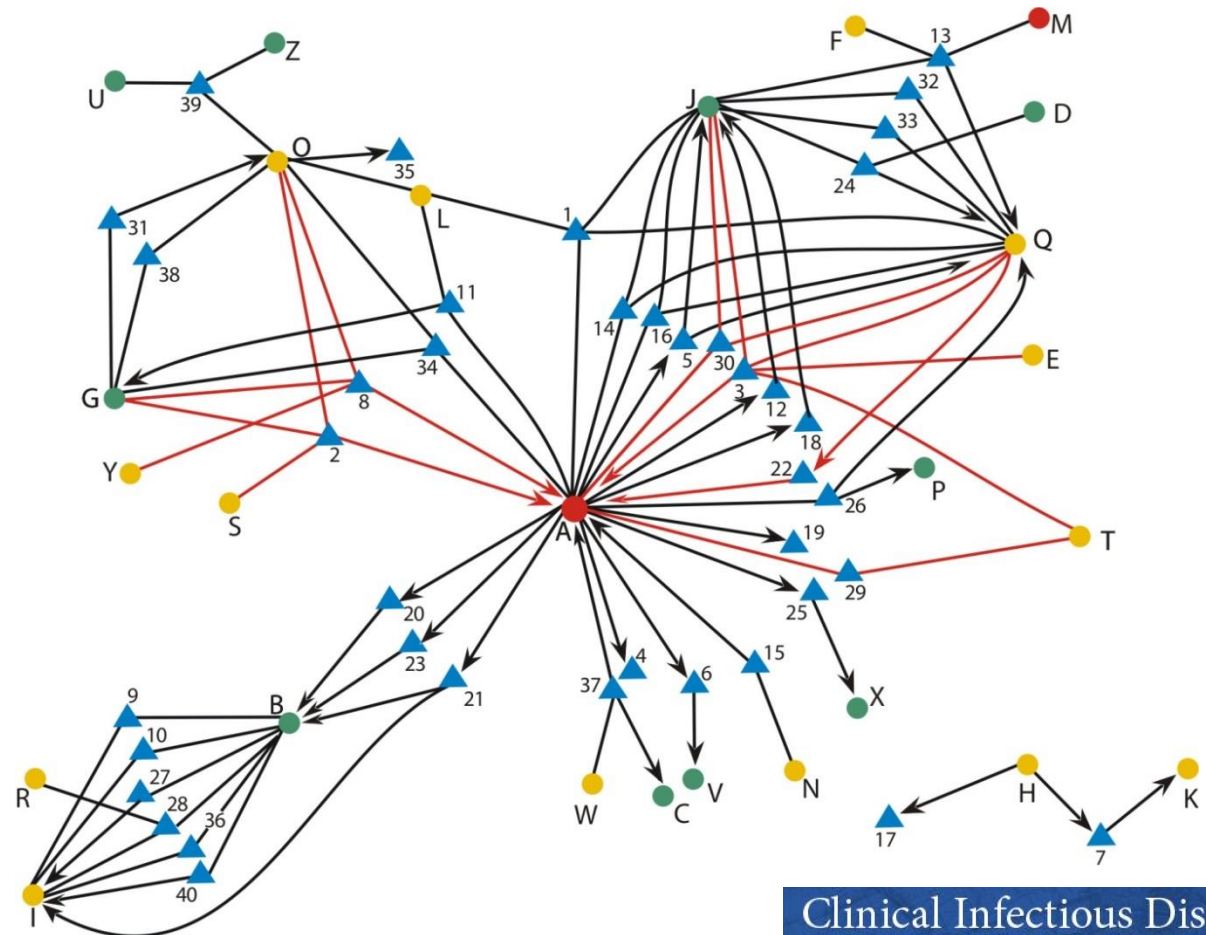
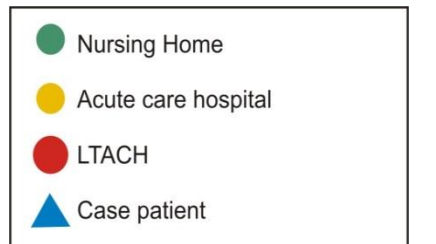
The Pig Pen Principle

# The Pig Pen Principle



# Emergence and Rapid Regional Spread of *Klebsiella pneumoniae* Carbapenemase-Producing *Enterobacteriaceae*

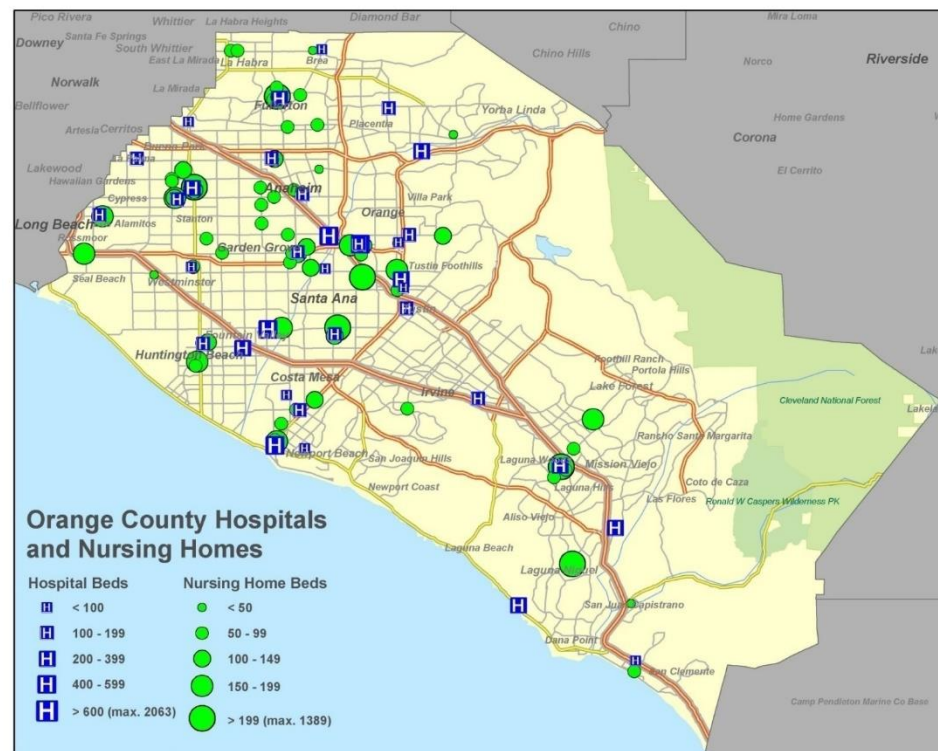
Sarah Y. Won,<sup>1,2</sup> L. Silvia Munoz-Price,<sup>3</sup> Karen Lolans,<sup>4</sup> Bala Hota,<sup>4,5</sup> Robert A. Weinstein,<sup>4,5</sup> and Mary K. Hayden<sup>4</sup> for the Centers for Disease Control and Prevention Epicenter Program



# Orange County, California

## Ideal Virtual Laboratory

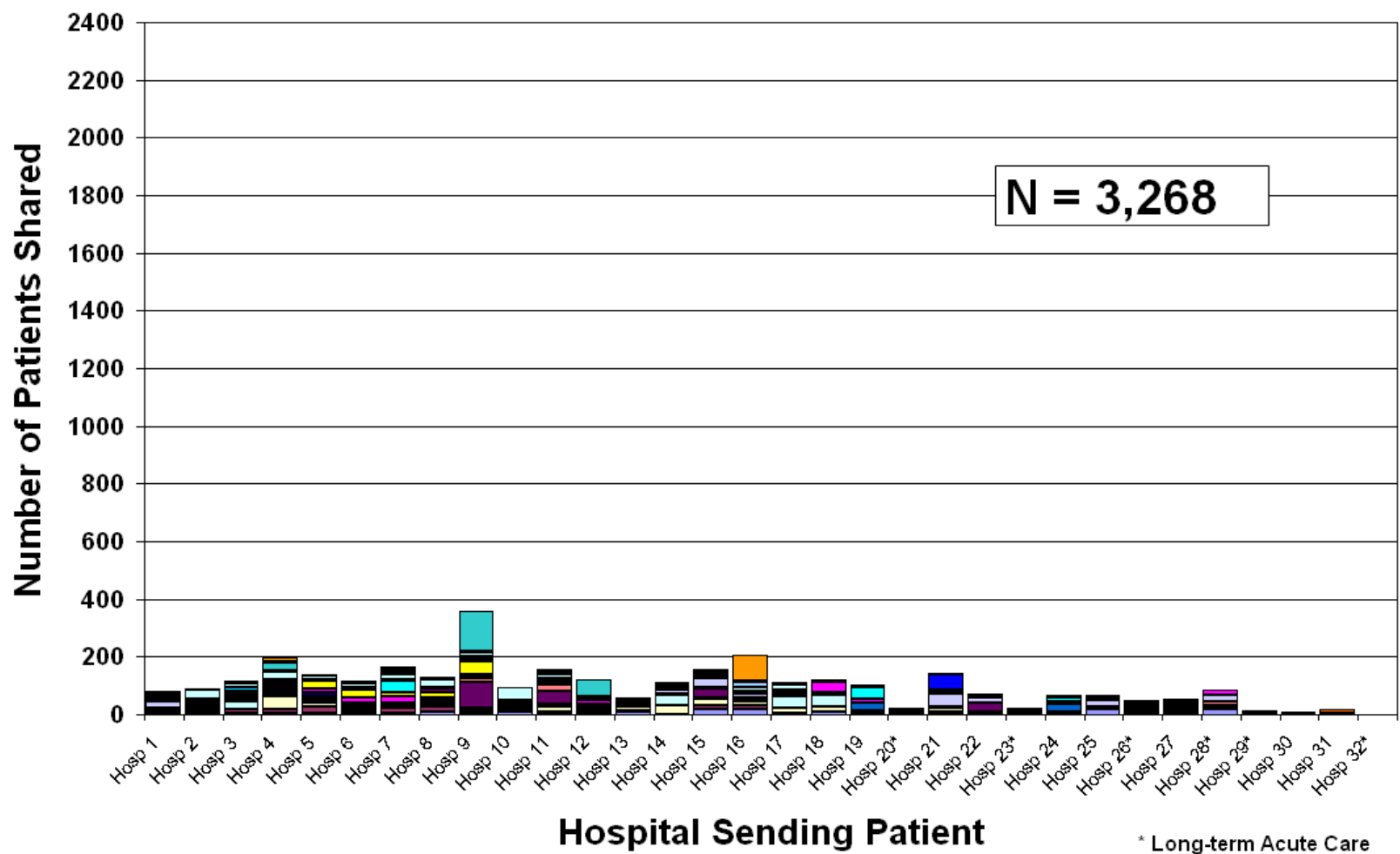
- Relatively enclosed
  - Ocean to West
  - Forest to East
  - Undeveloped land to South
  - Traffic to North



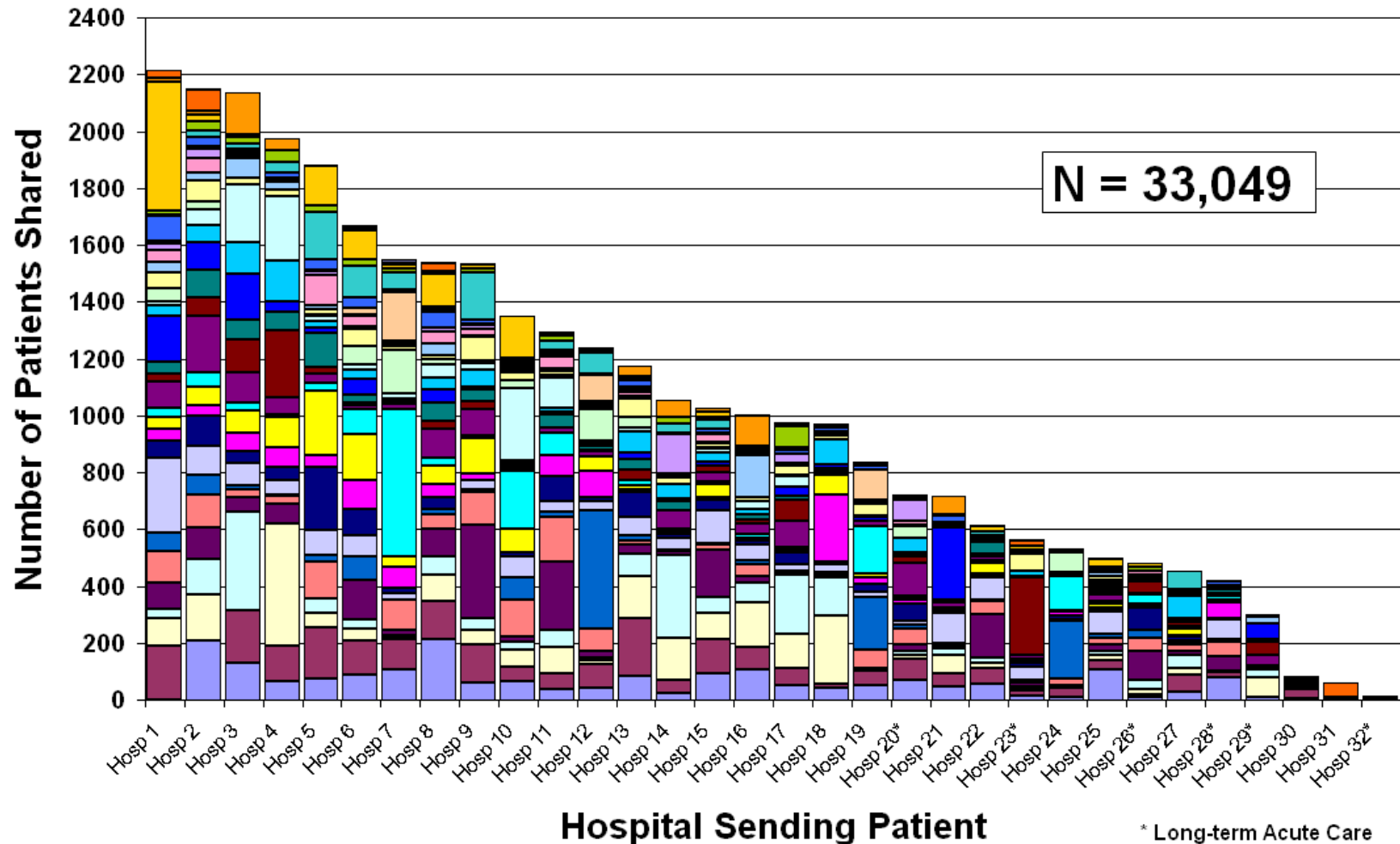
# Orange County

- 32 Acute Care Hospitals
  - 6 Long-Term Acute Care Hospitals (LTACs)
  - 2 Dedicated Children's Hospitals
- 71 nursing homes
- Serves population of 3.1 million  
(6<sup>th</sup> largest US county)
- >320,000 admissions annually

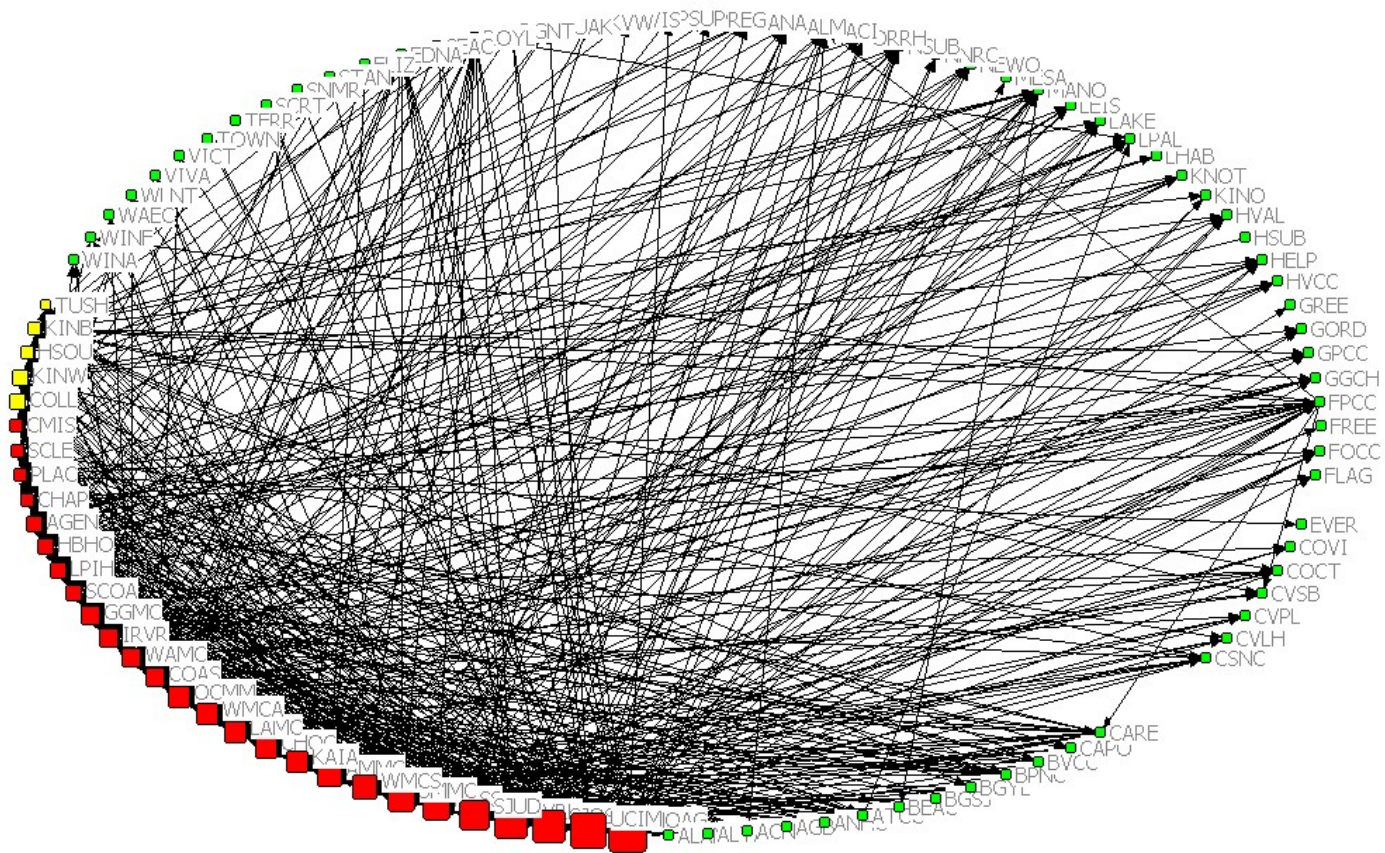
# Hospitals Share Patients – Direct



# Hospitals Share Patients-Indirect



# Sharing Patients – 10 Patients





# MDRO of Public Health Importance

- *Clostridioides difficile* (*Clostridium difficile*)
  - Pay Attention to Duration of Treatment
  - Avoid Ciprofloxacin and Levofloxacin
- *CRE*
  - Activity with last line agents not guaranteed

# LA County Antibiogram

- *Acinetobacter baumannii*  
61% Carbapenem Resistant  
Minocycline and Tigecycline are challenging
- *Pseudomonas aeruginosa*  
20% Carbapenem Resistant

Data presented as: Percent Susceptible (# of Isolates Tested)	# of all isolates tested (# of hospitals reporting)	Ampicillin	Ampicillin/ Sulbactam	Piperacillin/ Tazobactam	Ceftriaxone	Ceftazidime	Cefepime	Cefazolin	Ertapenem	Imipenem	Meropenem	Amikacin	Gentamicin	Tobramycin	Ciprofloxacin	Levofloxacin	Trimethoprim/ Sulfamethoxazole	Nitrofurantoin	Minocycline	Tigecycline
		Acinetobacter baumannii	2,723 75	R	43 2,084	27 1,776	10 1,320	27 1,894	40 1,139	R	R	27 1,120	39 1,436	36 1,925	37 2,661	40 2,084	27 2,030	26 1,985	48 2,287	-
Pseudomonas aeruginosa	23,921 83	R	R	85 23,524	R	81 20,258	85 21,045	R	R	80 12,142	84 17,770	96 22,185	85 23,575	93 21,464	73 19,554	65 16,206	R	R	-	R

# Ceftazidime-Avibactam & Ceftolozane-Tazobactam for *P. aeruginosa* Resistant to: Ceftazidime, Meropenem, & Pip-Tazobactam

Cumulative % inhibited at an MIC of:

	#	≤0.25	0.5	1	2	4	8	16	32	>32
Ceftazidim e- Avibactam	330		0.3	1.5	15.2	45.1	71.8	87.9	93	100
Ceftolozan e- Tazobacta m	175			12.6	39.4	68.6	85.1	89.7	92	100

Sader HS et al. *Antimicrob Agents Chemother* 2015;59:3656-3659. Table 1  
Farrell DJ et al. *Antimicrob Agents Chemother* 2013;57:6305-6310. Table 3

## Ceftazidime-Avibactam Versus Ceftolozane-Tazobactam for *P. aeruginosa* Resistant to: Ceftazidime, Meropenem, & Pip-Tazobactam\*

	Number of Isolates	Caz/Avi	C/T
<b>Humphries</b>	<b>105</b>	<b>29%</b>	<b>52.4%</b>
<b>Grupper</b>	<b>103</b>	<b>54%</b>	<b>79%</b>
<b>Sader</b>	<b>47</b>	<b>70.2%</b>	<b>72.3%</b>

\*Buehrle et al and Gonzalez et al excluded due to too few isolates for BLR resistance phenotype  
 Humphries et al. *Antimicrobial agents and chemotherapy*. 2017 Dec 1;61(12):e01858-17.

Grupper et al. *Antimicrob Agents Chemother*. 2017 Sep 22;61(10). pii: e00875-17. doi: 10.1128/AAC.00875-17. Print 2017 Oct.

Sader et al. *J Antimicrob Chemother*. 2018 Jul 27. doi: 10.1093/jac/dky279. [Epub ahead of print]

# MDRO of Public Health Importance

- *Clostridioides difficile* (*Clostridium difficile* )

## **Antibiotic Stewardship**

- CRE

Activity with last line agents is not guaranteed

- CRO (CRAB, CRP)

Activity with last line agents is not guaranteed

“How can we control spread of CRO?”

The Pig Pen Principle

“Many Believe that Decolonization is the  
Answer”

# Prevention of Colonization and Infection by *Klebsiella pneumoniae* Carbapenemase- Producing Enterobacteriaceae in Long-term Acute-Care Hospitals

MAJOR ARTICLE





# Hygiene

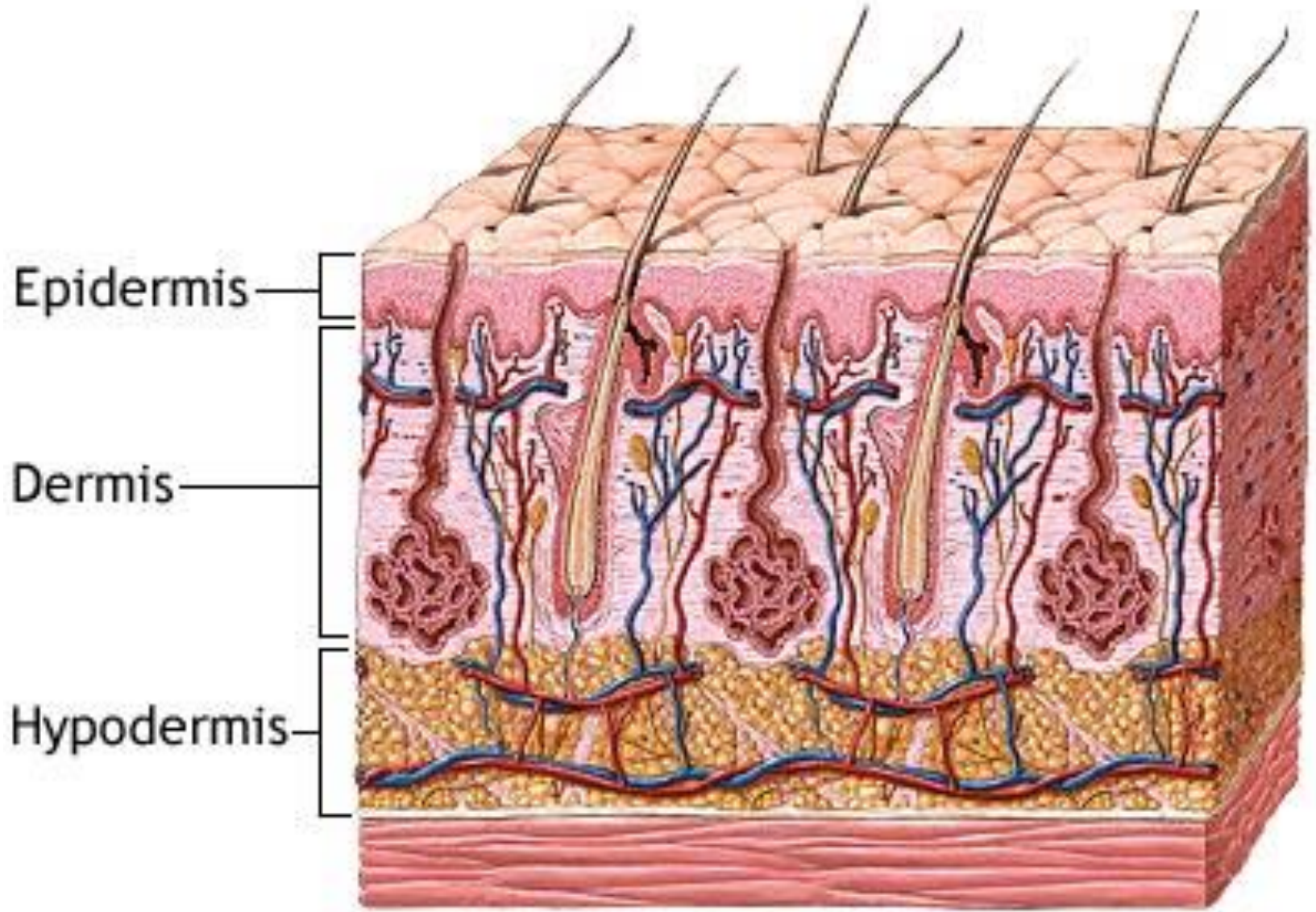
- Many Patient are Dependent on HCW for Personal Hygiene
- Bathing Frequency and Efficacy is Highly Variable
- Patient Hand Hygiene Programs are Uncommon

Mody JAMA Intern Med. 2013; 173(10):853-4.  
SHEA/APIC Guideline. ICHE 2008; 29(9):785-814.

# Skin Cleansing

- Use of topical antiseptics to clean patients
  - Chlorhexidine (CHG) for skin and wound bathing
  - Mupirocin or iodophor for nasal use
- CHG and iodophor used in healthcare for 60+ years with strong safety record

**Standard of Care when we want to prepare patients for Surgery.**



# SHIELD ORANGE COUNTY

## *IMPACT OF REGIONAL DECOLONIZATION*

JAMES A. MCKINNEL, MD

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ASSOCIATE PROFESSOR OF MEDICINE

DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA

LUNDQUIST INSTITUTE AT HARBOR-UCLA



**Shared  
Healthcare  
Intervention to  
Eliminate  
Life-threatening  
Dissemination of MDROs in  
Orange County**

# SHIELD OC Regional Collaborative

- Collaborative: CDC, California, and OC county public health
- Coordinated by UC Irvine and Harbor UCLA
- 38-facility decolonization intervention (NH, LTAC, Hospitals)
- **Recruitment based on patient sharing networks**
- Outcomes
  - Point prevalence MDROs
  - **Countywide MDRO burden (clinical cultures)**



# Characteristics of SHIELD OC Facilities

	<b>NH</b>	<b>LTACH</b>	<b>Hospital</b>
<b>N Facilities</b>	<b>18</b>	<b>3</b>	<b>17</b>
<b>Mean age</b>	<b>76</b>	<b>72</b>	<b>47</b>
<b>% Male</b>	<b>40%</b>	<b>53%</b>	<b>42%</b>
<b>Mean Licensed Beds</b>	<b>133</b>	<b>83</b>	<b>247</b>
<b>Average Daily Census</b>	<b>115</b>	<b>63</b>	<b>141</b>
<b>Mean LOS</b>	<b>69.3</b>	<b>30.6</b>	<b>4.1</b>
<b>Elixhauser Comorbidity Score</b>	<b>3.8</b>	<b>2.9</b>	<b>1.9</b>
<b>% Diabetes</b>	<b>36%</b>	<b>13%</b>	<b>12%</b>
<b>% Chronic Lung Disease</b>	<b>22%</b>	<b>21%</b>	<b>11%</b>
<b>% Renal Failure</b>	<b>21%</b>	<b>23%</b>	<b>8%</b>

# SHIELD OC Intervention

- **NH and LTAC – Decolonize all patients**
- **Hospitals – Decolonize patients in contact precautions**

<https://www.cdc.gov/hai/research/cdc-mdro-project.html>

# SHIELD OC Intervention

- **NH and LTAC – Decolonize all patients**
  - CHG on admission and for all routine bathing
  
- **Hospitals – Decolonize patients in contact precautions**
  - CHG Daily

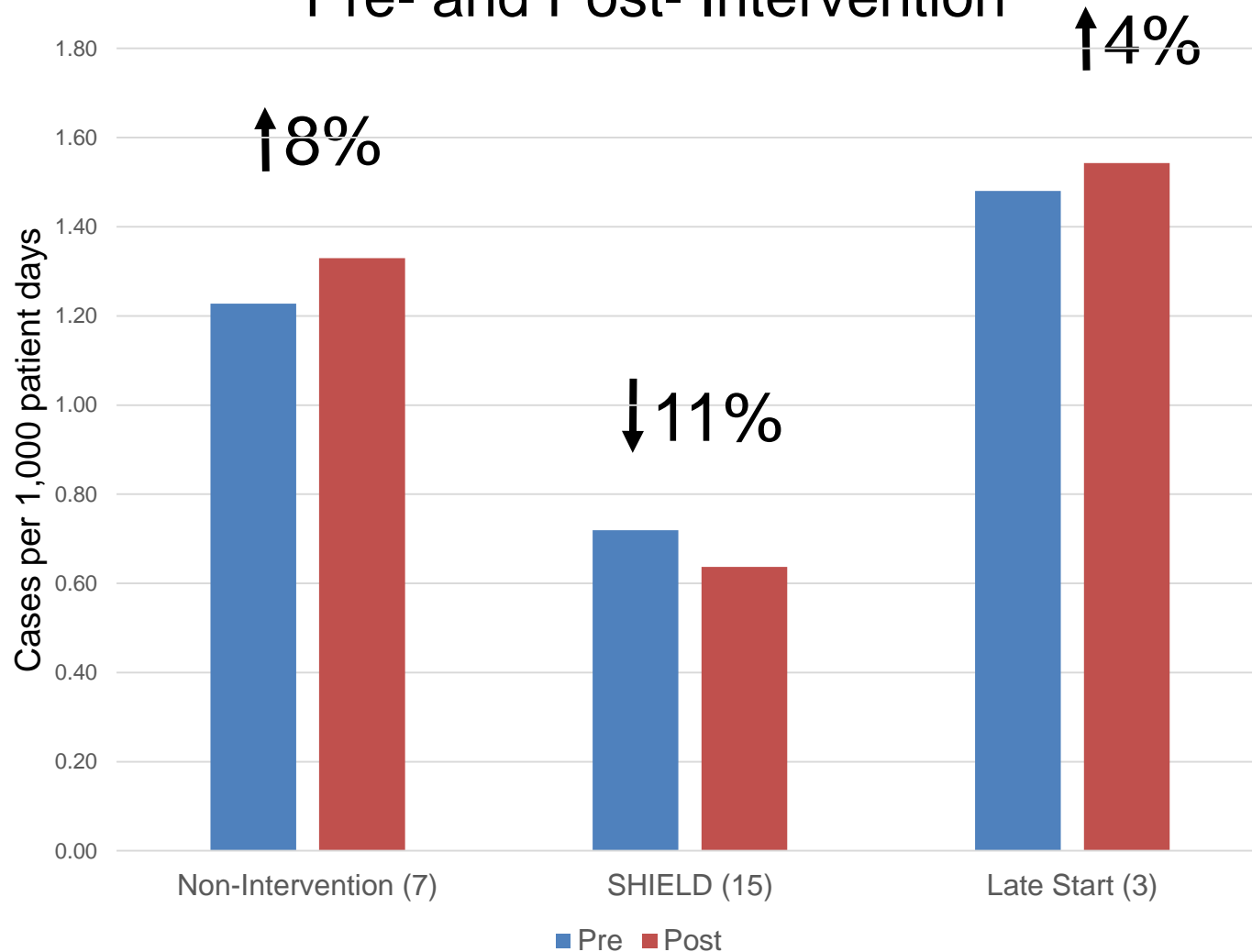
<https://www.cdc.gov/hai/research/cdc-mdro-project.html>



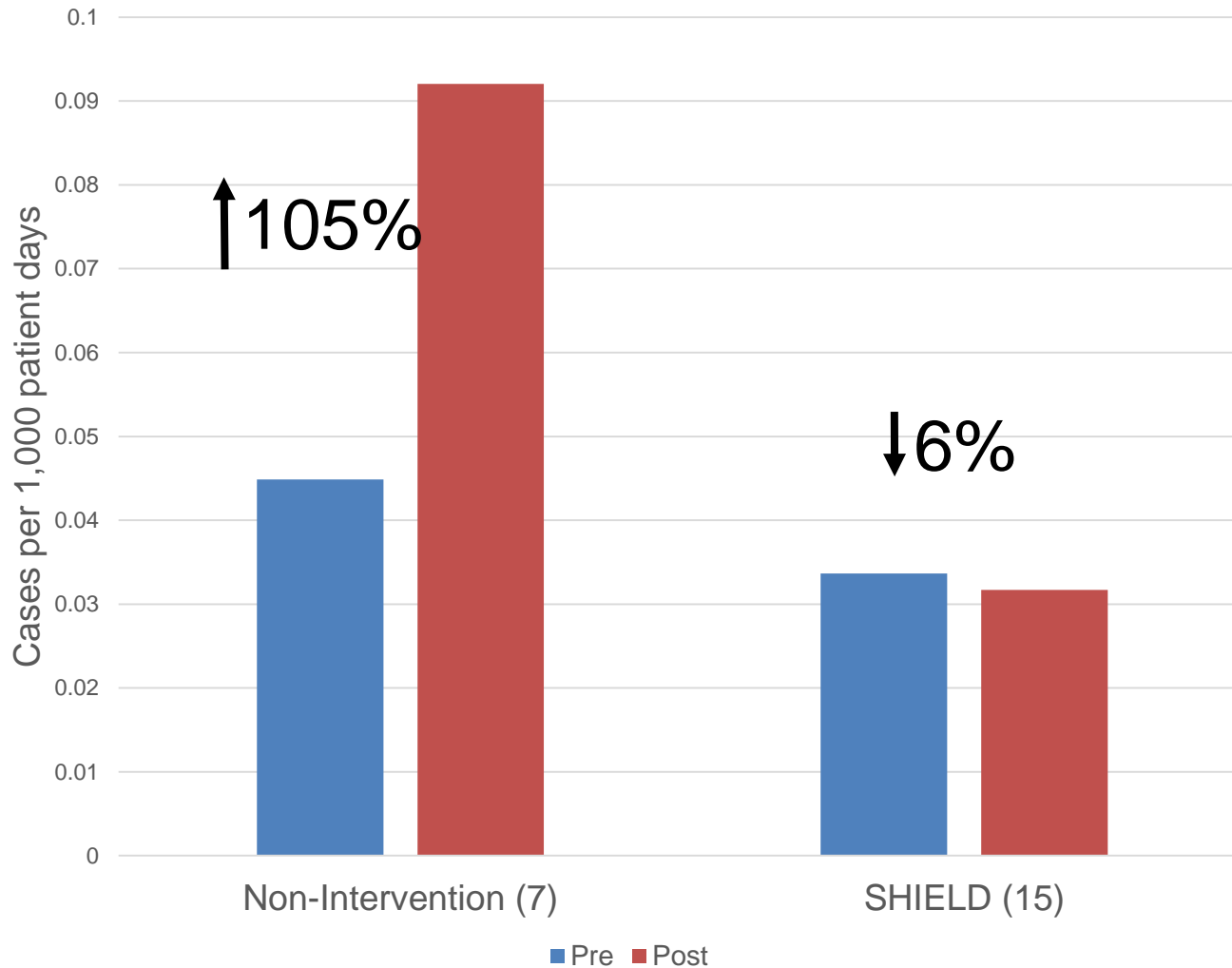
# SHIELD OC Intervention

- **NH and LTAC – Decolonize all patients**
  - CHG on admission and for all routine bathing
  - Nasal iodophor on admission **and every other week**
  
- **Hospitals – Decolonize patients in contact precautions**
  - CHG daily
  - **Nasal iodophor for 5 days on admission**

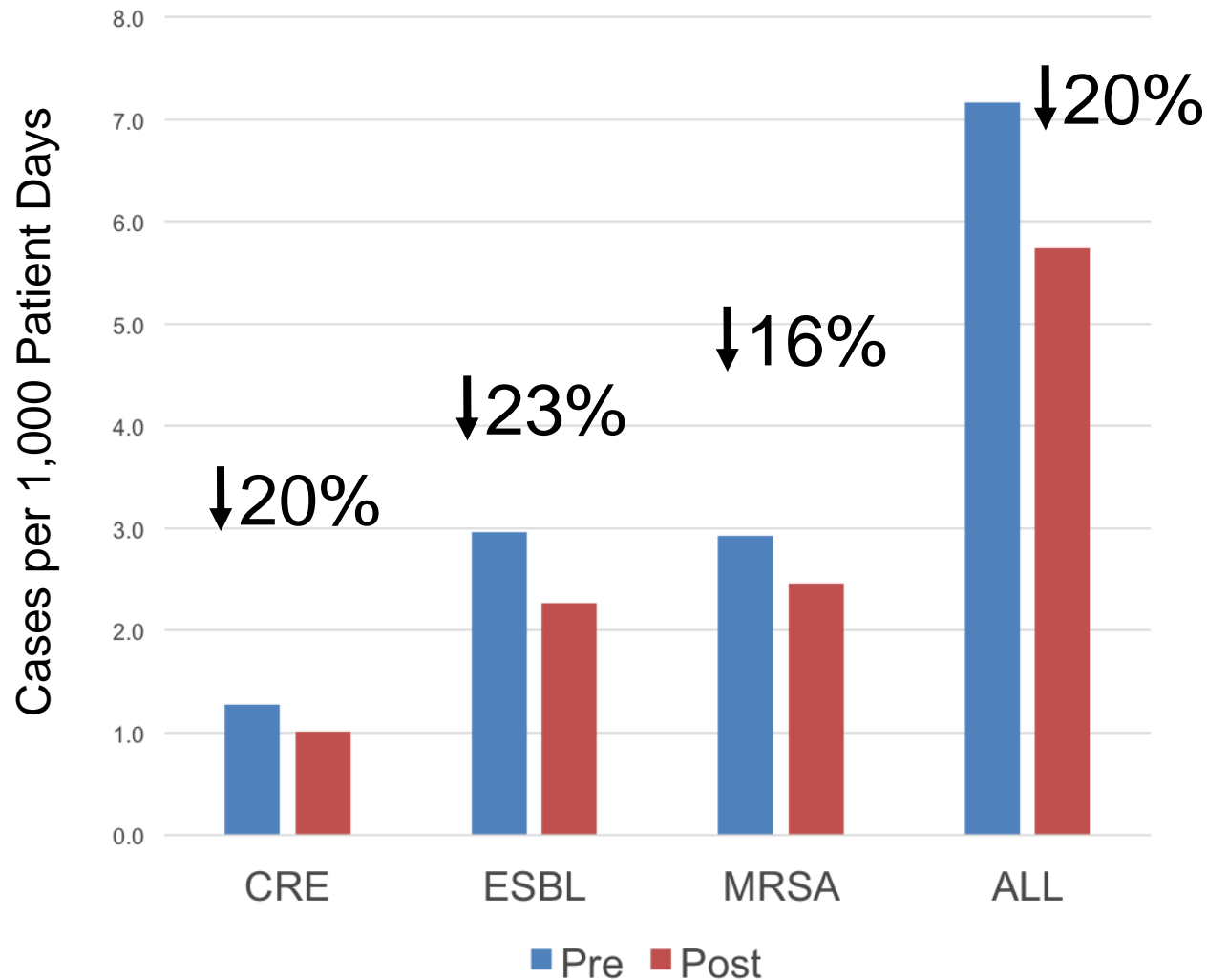
# Rates of Adults Acute Care Hospital Inpatient Healthcare Onset MDROs in Orange County: Pre- and Post- Intervention



# CRE Hospital Onset Rates in OC Hospitals, Pre- and Post- Intervention



# Long Term Acute Care Hospital MDRO Rates, Pre- and Post-Intervention



# MDRO of Public Health Importance

- *Clostridioides difficile* (*Clostridium difficile* )

## **Antibiotic Stewardship**

- CRE

## **Infection Control and Decolonization**

- CRO (CRAB, CRP)

## **Infection Control and Decolonization?**

# MRSA-the most important pathogen?

- 40% of all Healthcare Infections Worldwide
- High mortality, particularly for Bloodstream Infections
- Emerging resistance to last line agents-Daptomycin and Vancomycin

# CDC US Burden of MRSA and MSSA

## Take action against all staph.

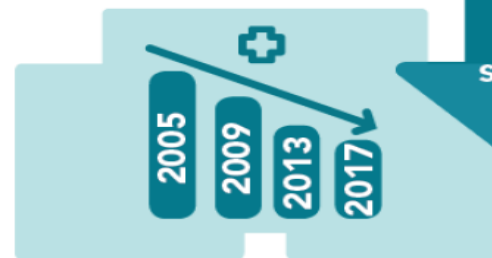
Progress is slowing but success is possible.

US rates of hospital-onset MRSA infections dropped 17% each year until 2013.



Progress has slowed recently and staph may be rising in communities.

US Veterans Affairs (VA) medical centers reduced high rates of staph infections by making it a priority in every facility.



By 2017, the VA reduced staph infections by 43% after adding prevention steps like screening new patients.

<https://www.cdc.gov/vitalsigns/staph/index.html>

Released March 5, 2019



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CHANGING LIVES BY ERADICATING ANTIBIOTIC RESISTANCE

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*AN INDIVIDUAL RANDOMIZED CLINICAL TRIAL  
OF EDUCATION VS DECOLONIZATION OF MRSA+  
PATIENTS DISCHARGED FROM HOSPITALS TO REDUCE  
POST-DISCHARGE INFECTION*

Funded by AHRQ; [clinicaltrials.gov](https://clinicaltrials.gov): NCT01209234



# What is CLEAR?

- Changing **L**ives by **E**radicating **A**ntibiotic **R**esistance
- CLEAR, which was recently published in the NEJM, was a post-discharge trial of MRSA carriers who were randomized to education alone vs education plus repeated decolonization for 6 months post-discharge and followed for infection outcomes for 1 year



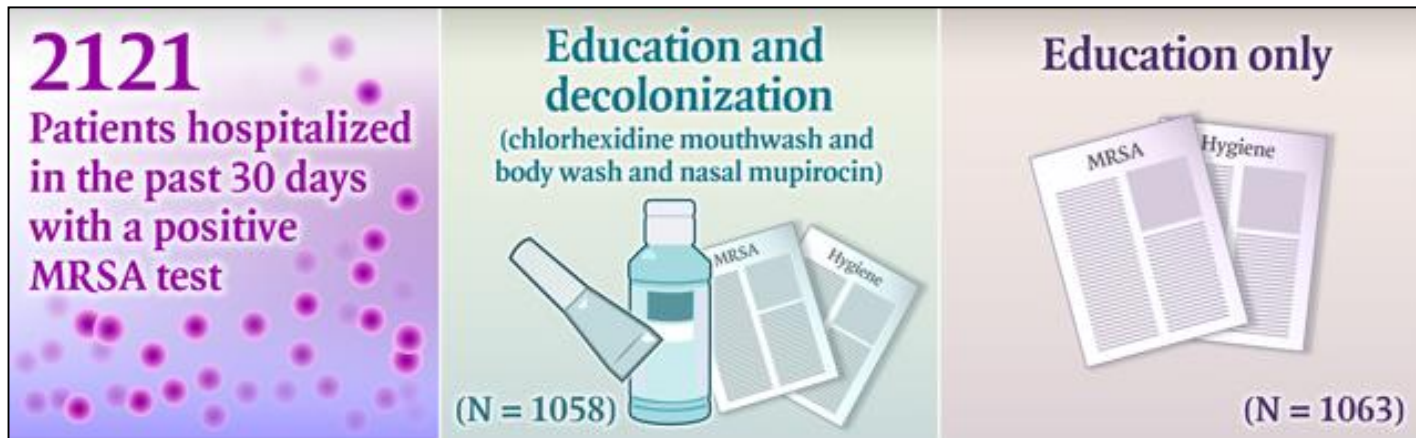
# The Project CLEAR Trial

- **2,121 inpatients, ~535,000 days of follow up**
- **Two Arms**
  - Arm 1: Education
  - Arm 2: Education + Serial Decolonization
- **Inclusion Criteria**
  - $\geq 18$  years old
  - Hospitalized within the past 30 days
  - MRSA+ culture within 30 days of hospitalization

# Serial Decolonization

- 5-day regimen twice monthly for 6 months
  - Twice daily 2% nasal mupirocin
  - Twice daily 0.12% chlorhexidine oral rinse
  - Daily 4% rinse-off chlorhexidine bath/shower
- 1-year follow up
  - Body swabs and surveys
  - Months 1, 3, 6, 9 post-recruitment
  - Phone exit survey at month 12

# Project CLEAR Evidence Summary



- In the year following discharge, decolonization:
  - ✓ reduced MRSA infection and hospitalization by 30%
  - ✓ reduced all-cause infection and hospitalization by 17%
- Number needed to treat to prevent an infection or a hospitalization is less than 35

“Chlorhexidine Bathing with Nasal Decolonization for six months post hospitalization should be considered for all MRSA carriers”

# What is CLEAR LA?

- LA DPH program for hospitals with high MRSA rates
- Program: Provide hospitalized MRSA carriers with a decolonization kit at discharge
- Why participate?
  - ✓ Be part of a collaborative
  - ✓ Collectively reduce MRSA prevalence
  - ✓ Reduce MRSA infections & readmissions

# MDRO of Public Health Importance

- *Clostridioides difficile* (*Clostridium difficile* )

## **Antibiotic Stewardship**

- CRE

## **Infection Control and Decolonization?**

- CRO (CRAB, CRP)

## **Infection Control and Decolonization?**

- MRSA

## **Decolonization**

# Invasive *C. auris* Infections

- Half of clinical cases are bloodstream infections
- Half of patients with *C. auris* bloodstream infections die during that hospitalization





# Substantial Antifungal Resistance Among *C. auris*

1



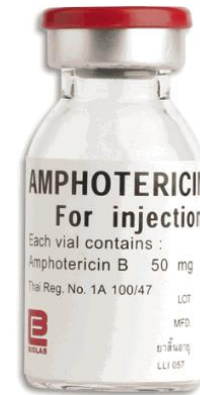
93% resistant to fluconazole  
54% resistant to voriconazole

2



7% resistant to  
echinocandins

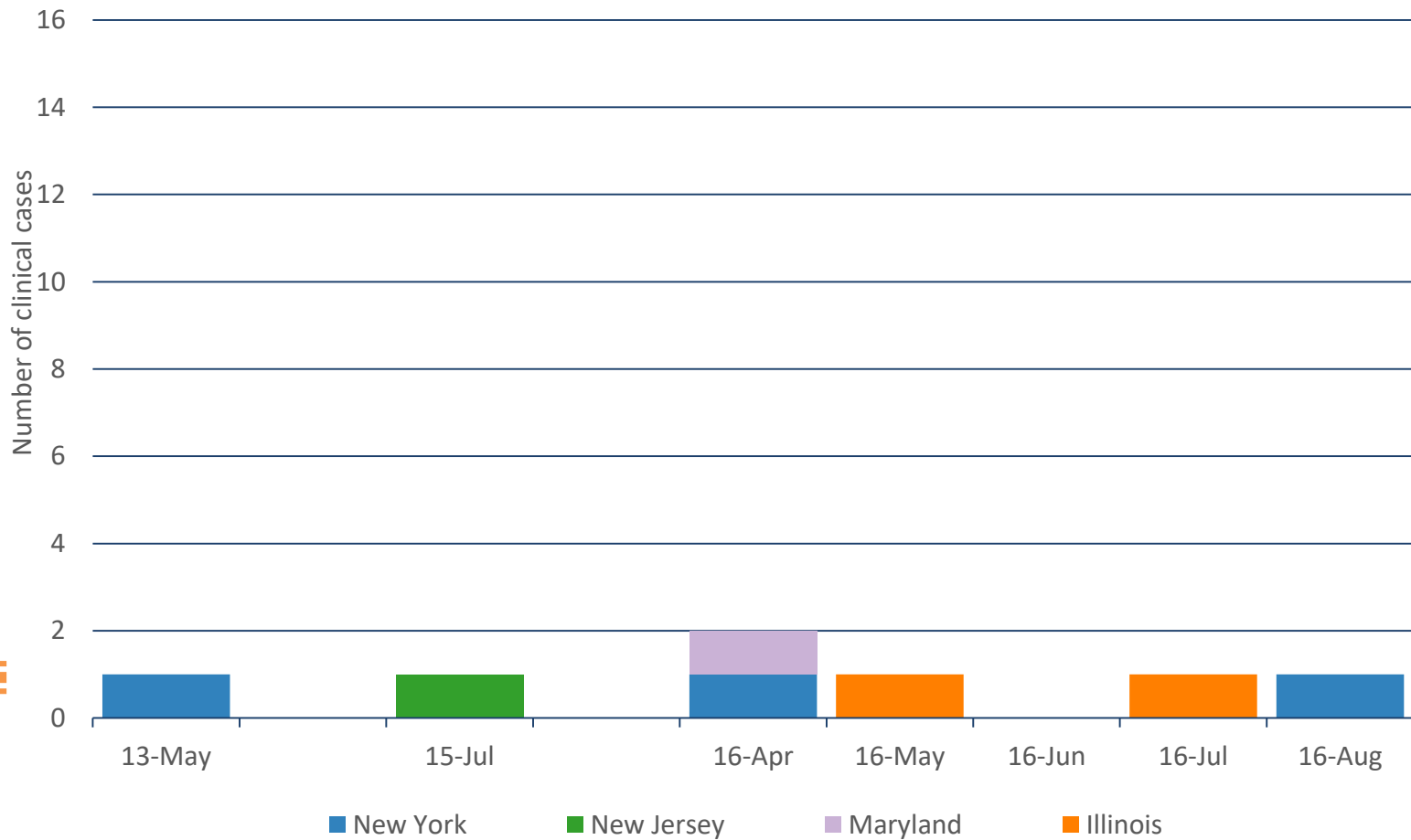
3



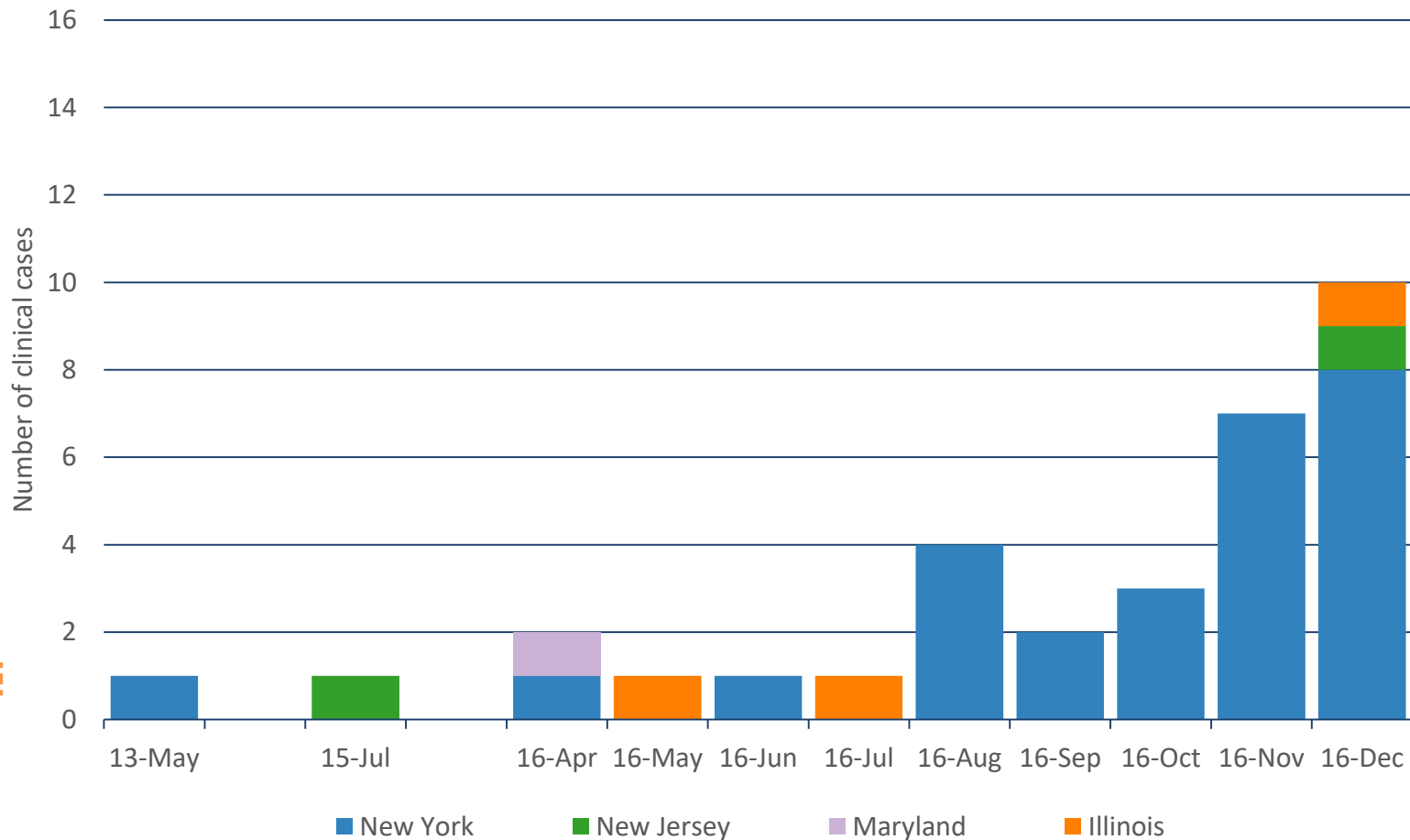
35% resistant to  
amphotericin B

- 41% isolates multidrug resistant
- 4% resistant to all three classes

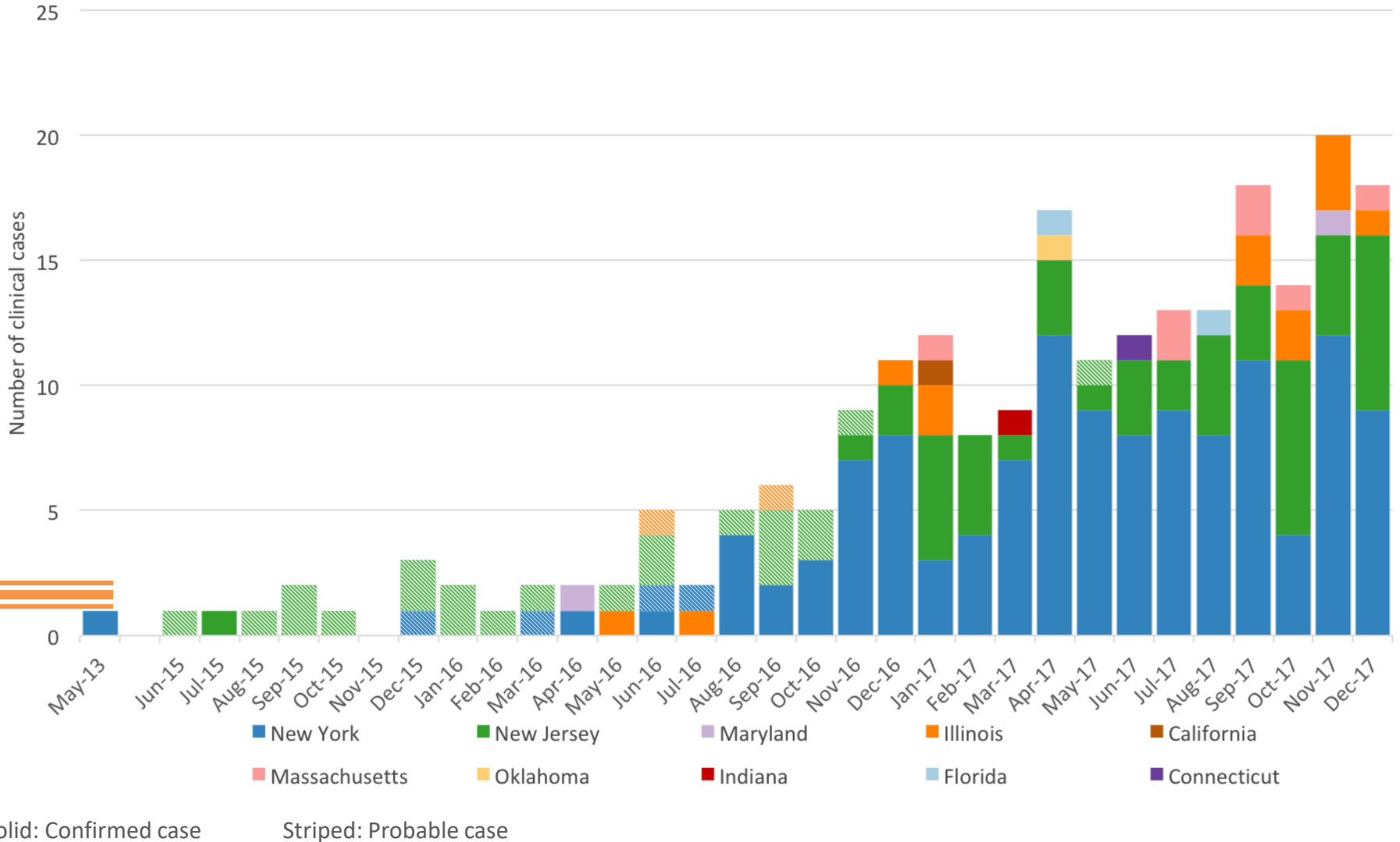
# *C. auris* Cases Reported by State — United States, 2013–August 2016



# *C. auris* Cases Reported by State — United States, 2013–December 2016



# C. auris Cases Reported by State United States, 2013–2017





Health care facilities, health departments, and CDC are **ON ALERT** for antibiotic resistance.



Public health teams nationwide can launch early, aggressive responses to contain spread and protect people—at the first sign of antibiotic resistance, every time.

Find guidance, lab protocols, and more resources:  
[www.cdc.gov/HAI/Outbreaks/MDRO](http://www.cdc.gov/HAI/Outbreaks/MDRO)

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- MRSA  
**Decolonization**
- *Candida auris*  
**Infection Control, Containment and Decolonization**