

Why Antibiotic Stewardship?

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Disclosures

- I have received Government Research Funding from NIH, AHRQ, CDC, and CTSI
- I have served as a consultant for Achaogen, Allergan, Cempra, Science 37, Theravance, and ThermoFisher
- I have no commercial/financial relationships related to decolonization, CHG, mupirocin, or iodophor products

Objectives

- Understand the rising burden of *C. difficile* and how Antimicrobial Stewardship may help
- Understand how sharing patient can impact the spread of multi drug resistant organisms (MDRO)
- Understand the importance of rising resistance among fluroquinolones and treatment of Urinary Tract Infections

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

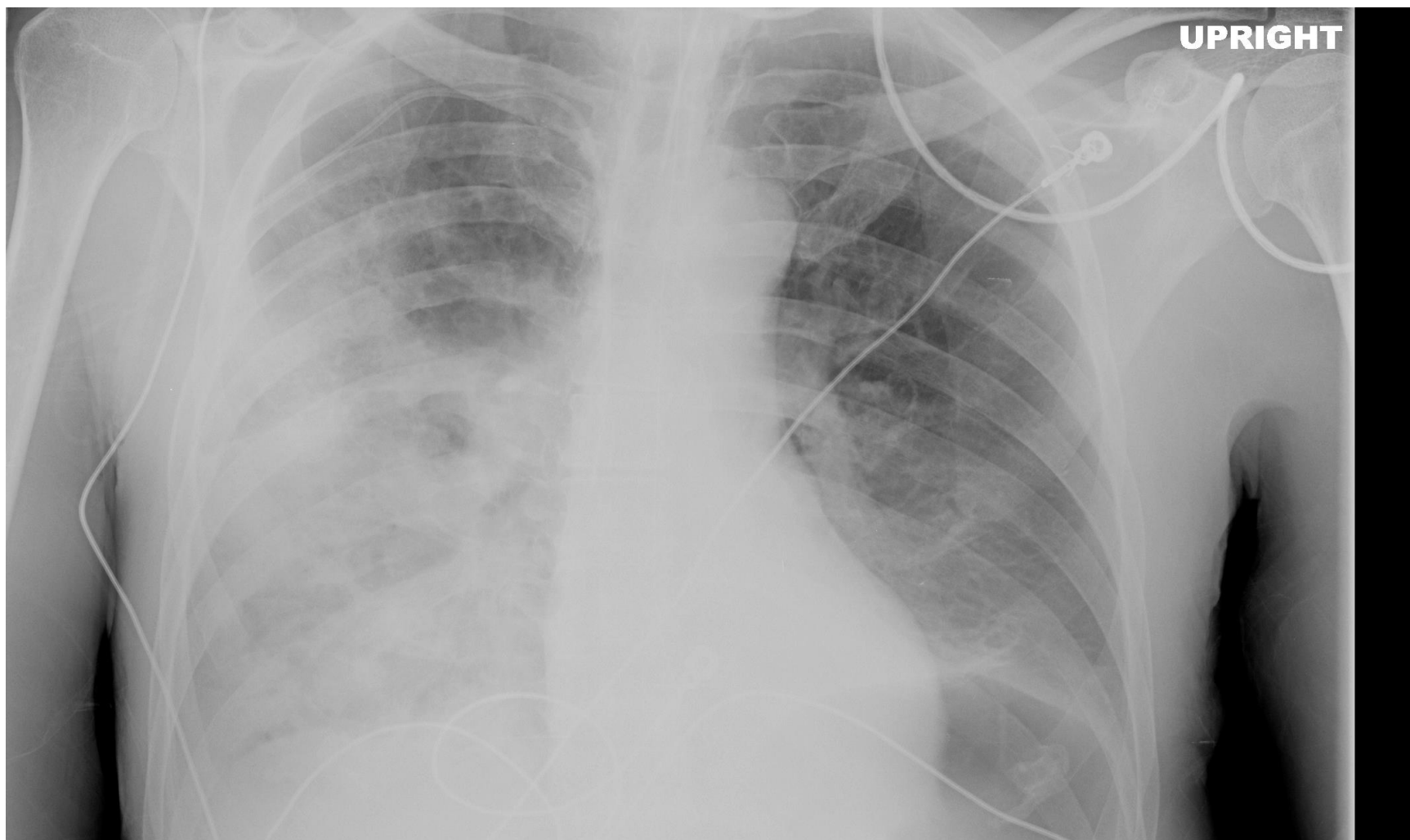
<http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm> Accessed 4/22/2015, rounded to the nearest thousand deaths.

http://www.cdc.gov/HAI/pdfs/hai/infections_deaths.pdf Accessed 4/22/2015.

Case

- L.O.P. is 72 yo female with pmh notable for moderate dementia and recurrent aspiration. She is a nursing home resident. Presents with SOB, fever and Cough.
- Febrile: 101.2 RR: 22 92% Fio2
- Rousable, but sleepy
- Frail with slight temporal wasting
- RLL Rhonchi

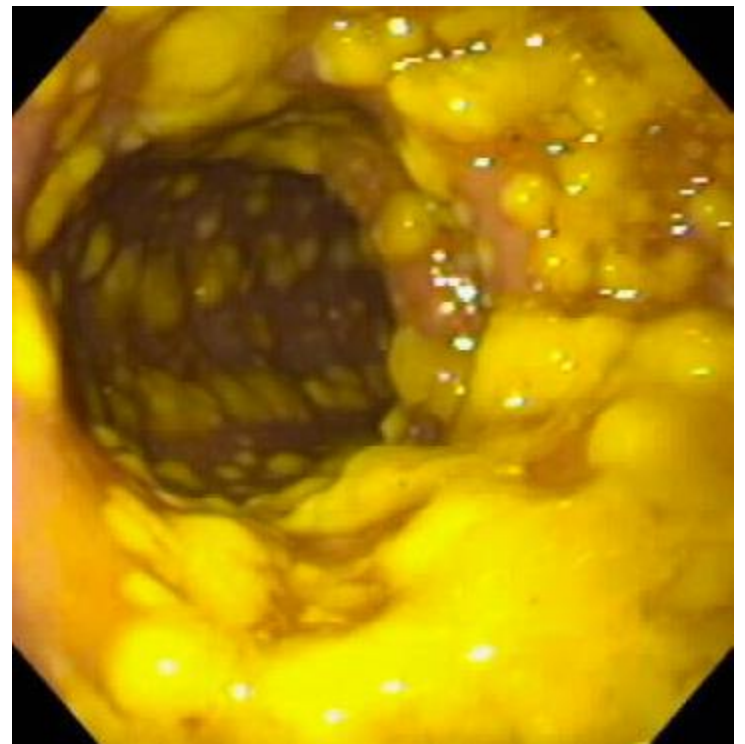
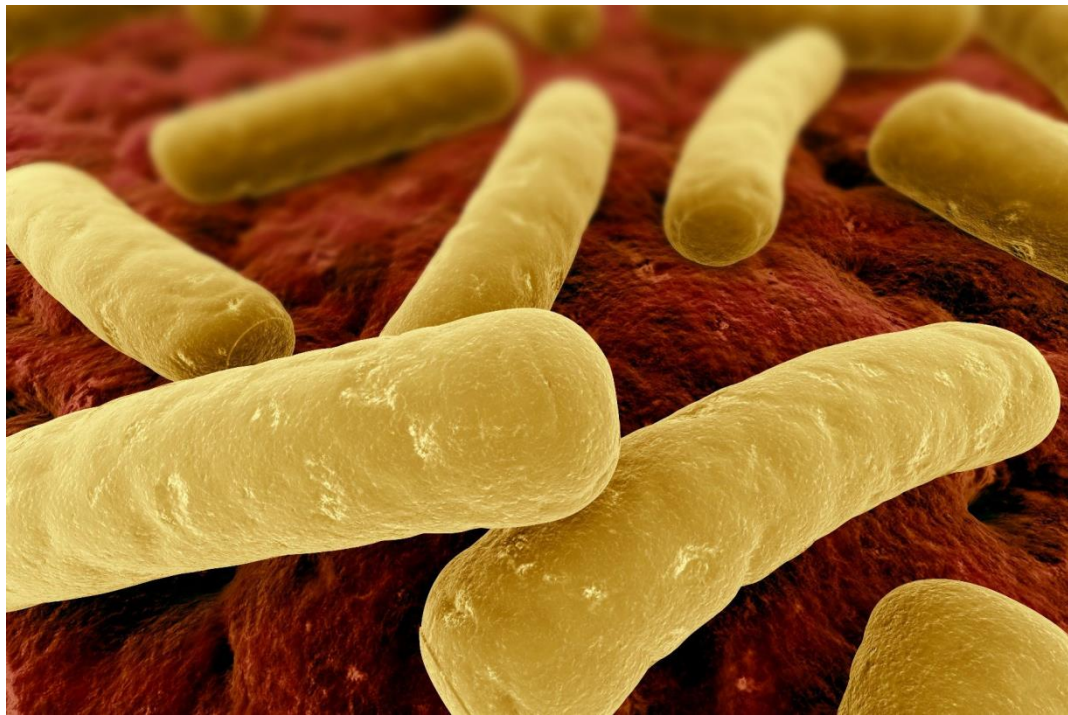
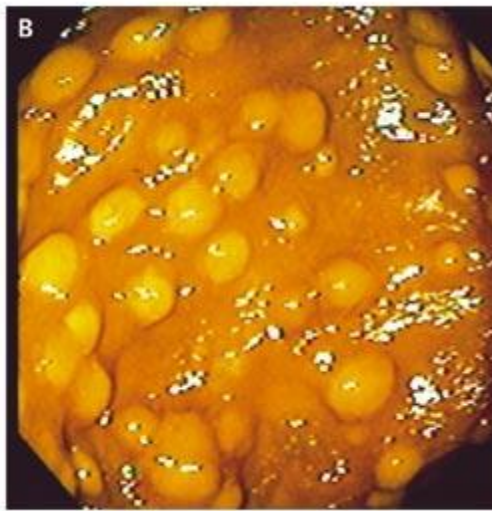
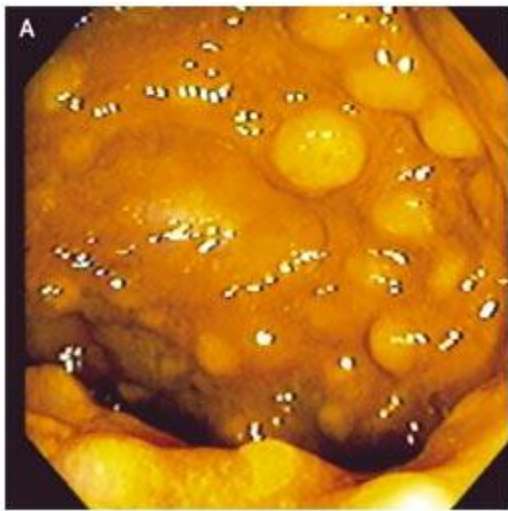
RLL Pneumonia



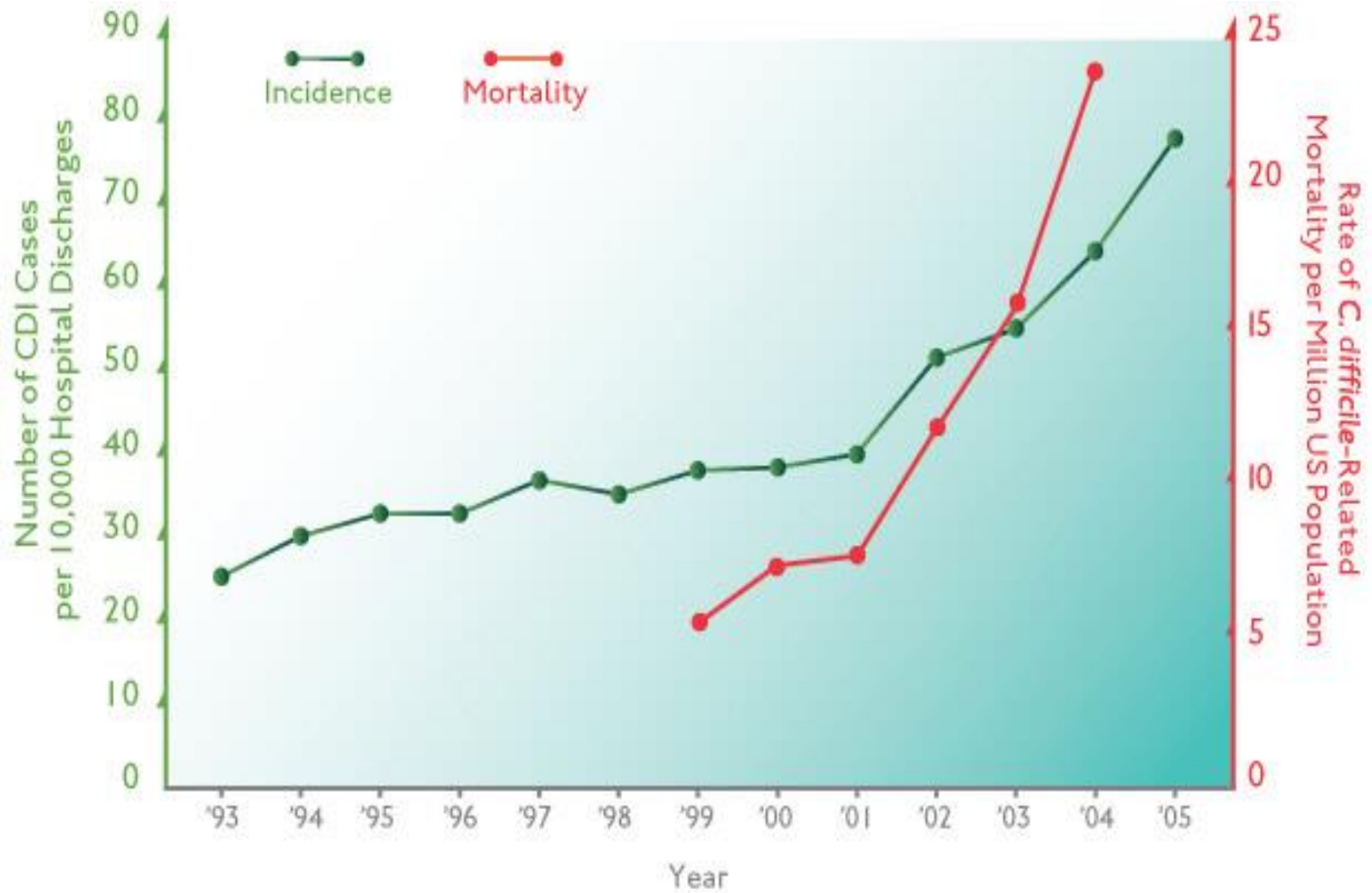
What are you going to prescribe
for this patient?

Resolution of the case

- L.O.P. is started on levofloxacin 750 mg IV qday.
- She responds well by day three.
- She is sent back to her facility to complete a 10 day course of oral levofloxacin 750 mg PO qDay.



Increasing US Mortality due to C difficile



* Daneman et al. JAC 66:2856, Dec 2011

CDI: Impact

	Number of annual cases	Cost	Number of annual deaths
Hospital-onset, hospital acquired (HO-HA)	165,000	\$ 1.3 B	9000
Community-onset hospital acquired (CO-HA) [4 weeks of hospitalization]	50,000	\$ 0.3 B	3000
Nursing home-onset	263,000	\$ 2.2 B	16,500

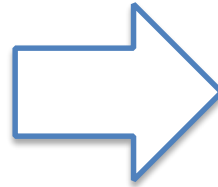
Antimicrobials Predisposing to CDI

Very commonly related	Less commonly related	Uncommonly related
Clindamycin Ampicillin Amoxicillin Cephalosporins Fluoroquinolons	Sulfa Macrolides Carbapenems Other penicillins	Aminoglycosides Rifampin Tetracycline Chloramphenicol

- Among symptomatic patients with CDI:
 - 96% received antimicrobials within the 14 days before onset
 - 100% received an antimicrobial within the previous 3 months
- 20% of hospitalized patients are colonized with *C. diff*

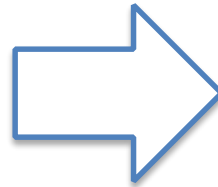
Antibiotics and CDI

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

Resolution of the case: Revisited

- L.O.P. is started on levofloxacin 750 mg IV qday.
- She responds well by day three.
- She is sent back to her facility to complete a 10 day course of oral levofloxacin 750 mg PO qDay.

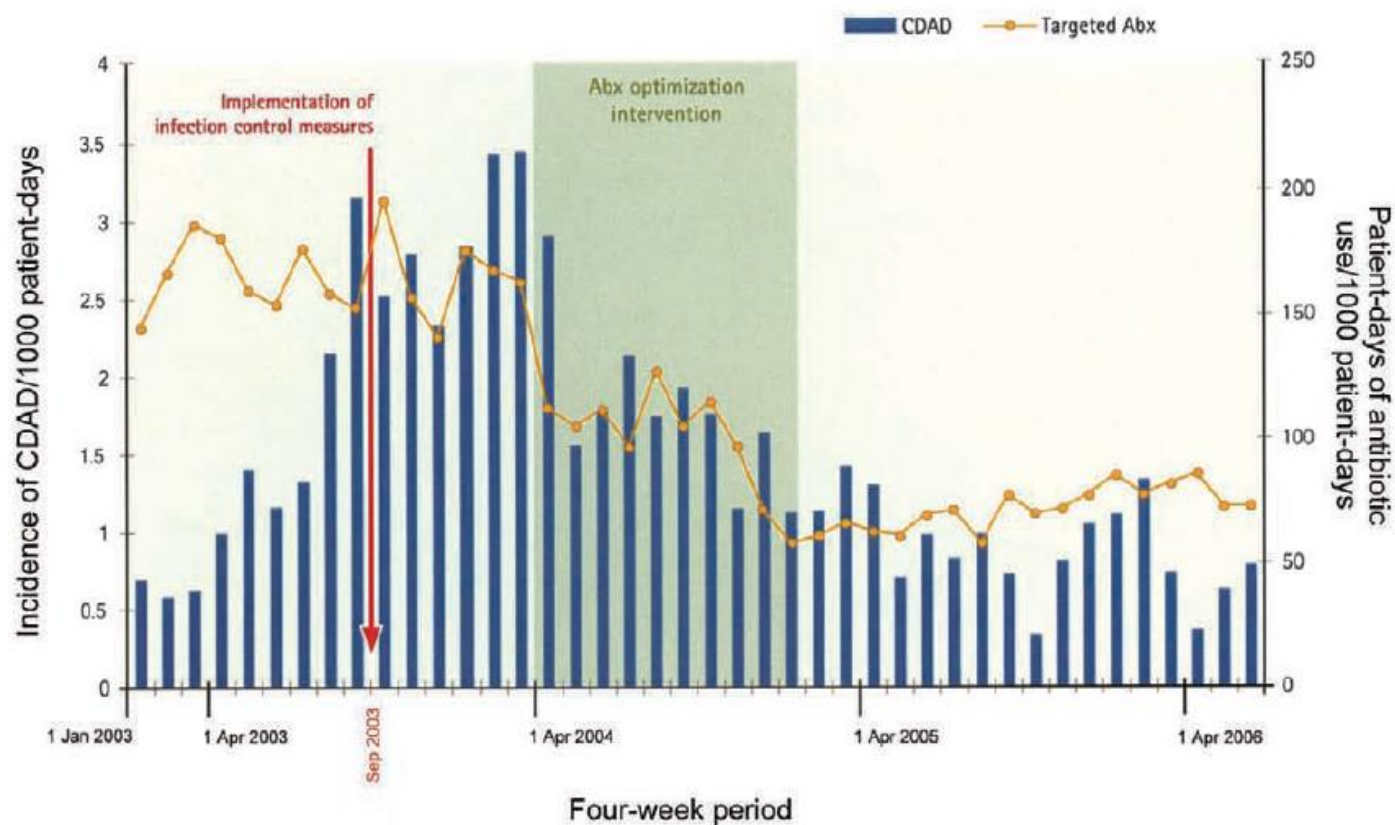
Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,¹ Sara E. Cosgrove,² Lilian M. Abbo,³ Conan MacDougall,⁴ Audrey N. Schuetz,⁵ Edward J. Septimus,⁶ Arjun Srinivasan,⁷ Timothy H. Dellit,⁸ Yngve T. Falck-Ytter,⁹ Neil O. Fishman,¹⁰ Cindy W. Hamilton,¹¹ Timothy C. Jenkins,¹² Pamela A. Lipsett,¹³ Preeti N. Malani,¹⁴ Larissa S. May,¹⁵ Gregory J. Moran,¹⁶ Melinda M. Neuhauser,¹⁷ Jason G. Newland,¹⁸ Christopher A. Ohl,¹⁹ Matthew H. Samore,²⁰ Susan K. Seo,²¹ and Kavita K. Trivedi²²

Strategies with **strong recommendations** include:

- Preauthorization and/or prospective audit with feedback
- Limit therapy to shortest effective duration
- Reduce use of antibiotics associated with a high risk of CDI
- Pharmacy-based interventions – Pharmacokinetic monitoring; IV to PO conversion

Formulary Restriction and/or Prospective Audit with Feedback Targeting High-Risk Antibiotics Can Reduce CDI Incidence



CDI: Risk Factors

- Exposure to antimicrobials (prior 2-3 months)
- Exposure to healthcare (prior 2-3 months)
- Infection with toxogenic strains of *C. difficile*
- Old age > 64 years
- Underlying illness
- Immunosuppression & HIV
- Chemotherapy (immunosuppression & antibiotic-like activities)
- Tube feeds and GI surgery
- Exposure to gastric acid suppression meds



Antibiotic Stewardship in Nursing Homes

4.1 MILLION

Americans are admitted to or reside in nursing homes during a year¹



UP TO **70%**
of nursing home residents
received antibiotics during a year²



UP TO **75%**
of antibiotics are
prescribed incorrectly^{3,4}

LTC Antibiotic
cost estimates:

\$38-\$137
million per year
in US

¹Incorrectly = prescribing the wrong drug, dose, duration or reason

²ANCA Quality Report 2013.

³Lim CJ, Kong DCM, Stuart RL. Reducing inappropriate antibiotic prescribing in the residential care setting: current perspectives. Clin Interv Aging. 2014; 9: 165-177.

⁴Nicolle LE, Bentley D, Garibaldi R, et al. Antimicrobial use in long-term care facilities. Infect Control Hosp Epidemiol 2000; 21:537-45.

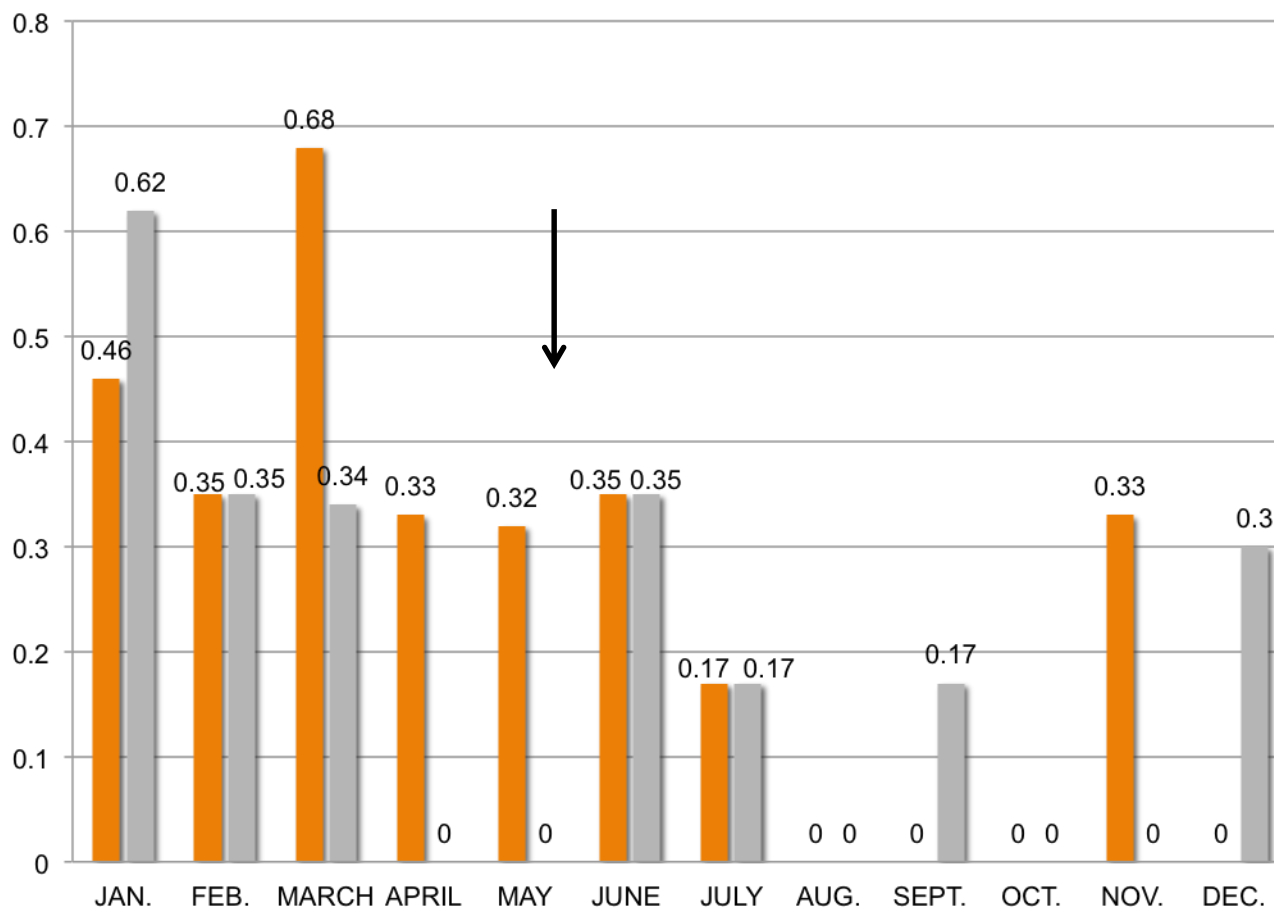


Centers for Disease
Control and Prevention
National Center for Emerging and
Zoonotic Infectious Diseases

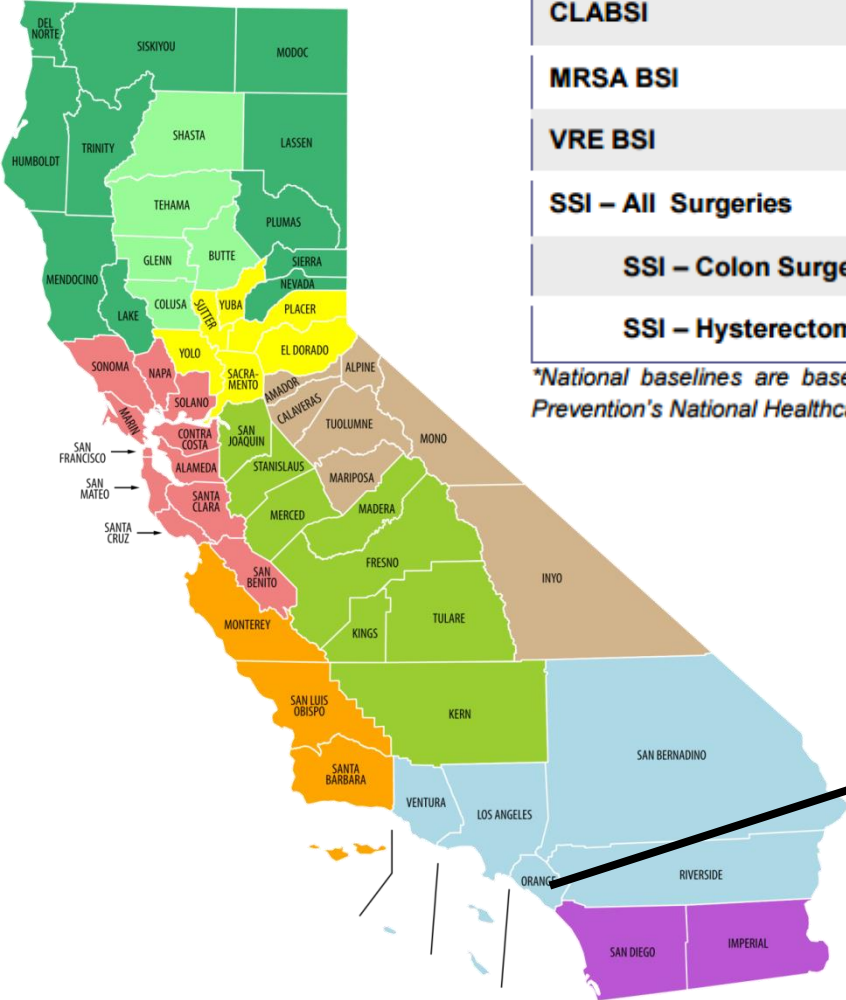
CDC. Get smart for healthcare: Antibiotic use in nursing homes. <http://www.cdc.gov/getsmart/healthcare/learn-from-others/factsheets/nursing-homes.html>. Last accessed 8/15/2016.

C-DIFF RATES 2016

■ CAI'S RATES ■ HAI'S RATES



National Epidemic with worsening rates in California



	No. of HAI Reported by California Hospitals in 2014	2014 California HAI Data Compared with National Baselines*
CDI	10,588	↑ 9% since 2011
CLABSI	2809	↓ 49% since 2008
MRSA BSI	705	↓ 24% since 2011
VRE BSI	782	No national baseline
SSI – All Surgeries	4,316	↓ 40% since 2008
SSI – Colon Surgery	911	No difference from 2008
SSI – Hysterectomy	168	↓ 20% since 2008

*National baselines are based on surveillance data reported by U.S. hospitals to the Centers for Disease Control and Prevention's National Healthcare Safety Network.

Orange County CDI rate is 15% higher compared to the rest of



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

The Era of Pan-Resistant Pathogens



The New York Times



Los Angeles Times

San Francisco Chronicle

The Washington Post

The French Grammar Lesson

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

Enterobacteriaceae?

?

Citrobacter?

freundii,[?] *koseri*,[?] *amalonaticus*?

Enterobacter?

cloacae,[?] *aerogenes*,[?] *sakasakii*?

Esherichia?

coli,[?] *albertii*?

Klebsiella?

pneumoniae,[?] *oxytoca*,[?] *granulomati*.

Morganella?

marganii?

Proteus?

mirabilis,[?] *vulgaris*?

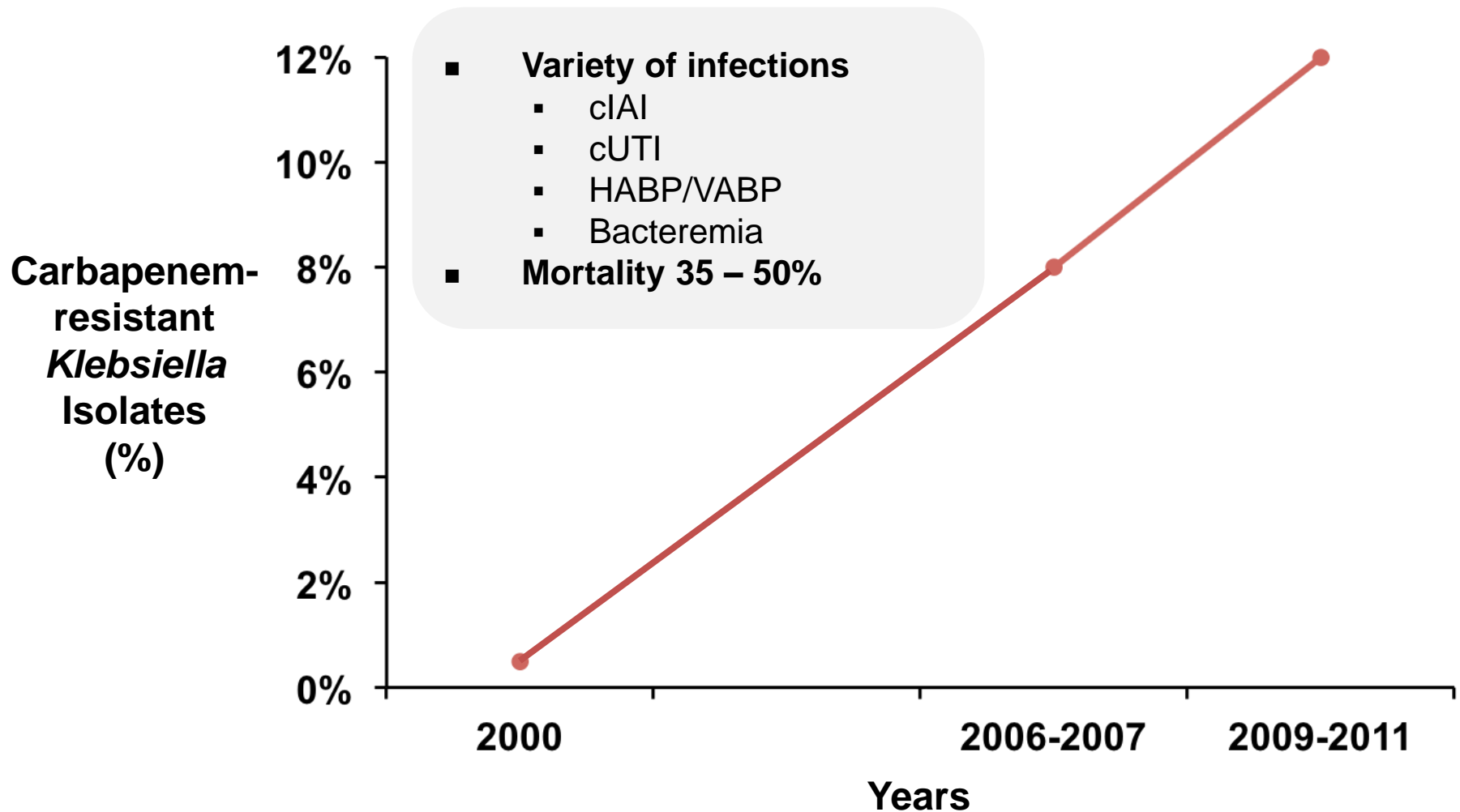
Providencia?

stuartii,[?] *rettgeri*?

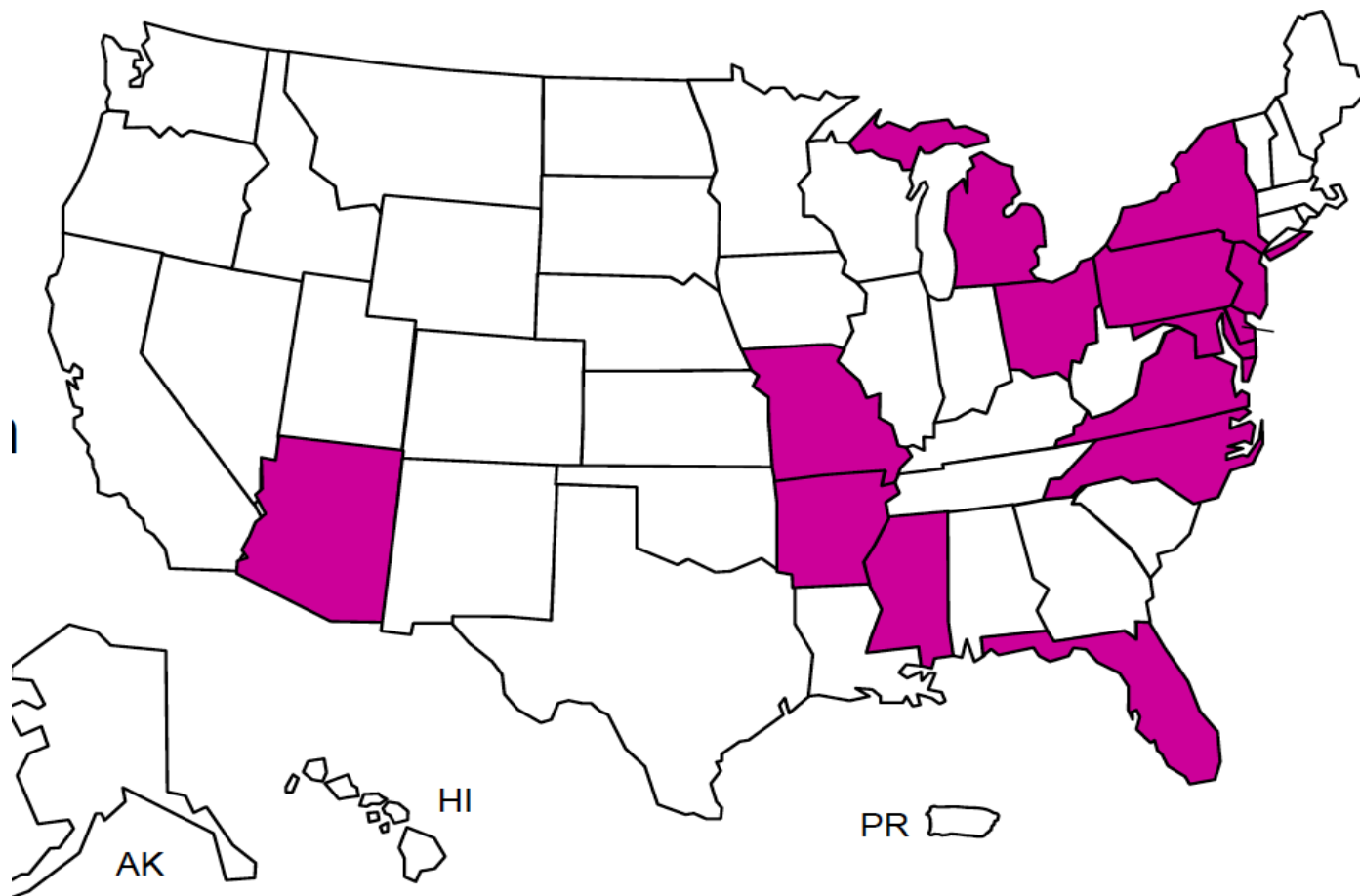
Serratia?

marcescens?

Steady Increase in CRE Incidence - US Hospital Reports to CDC

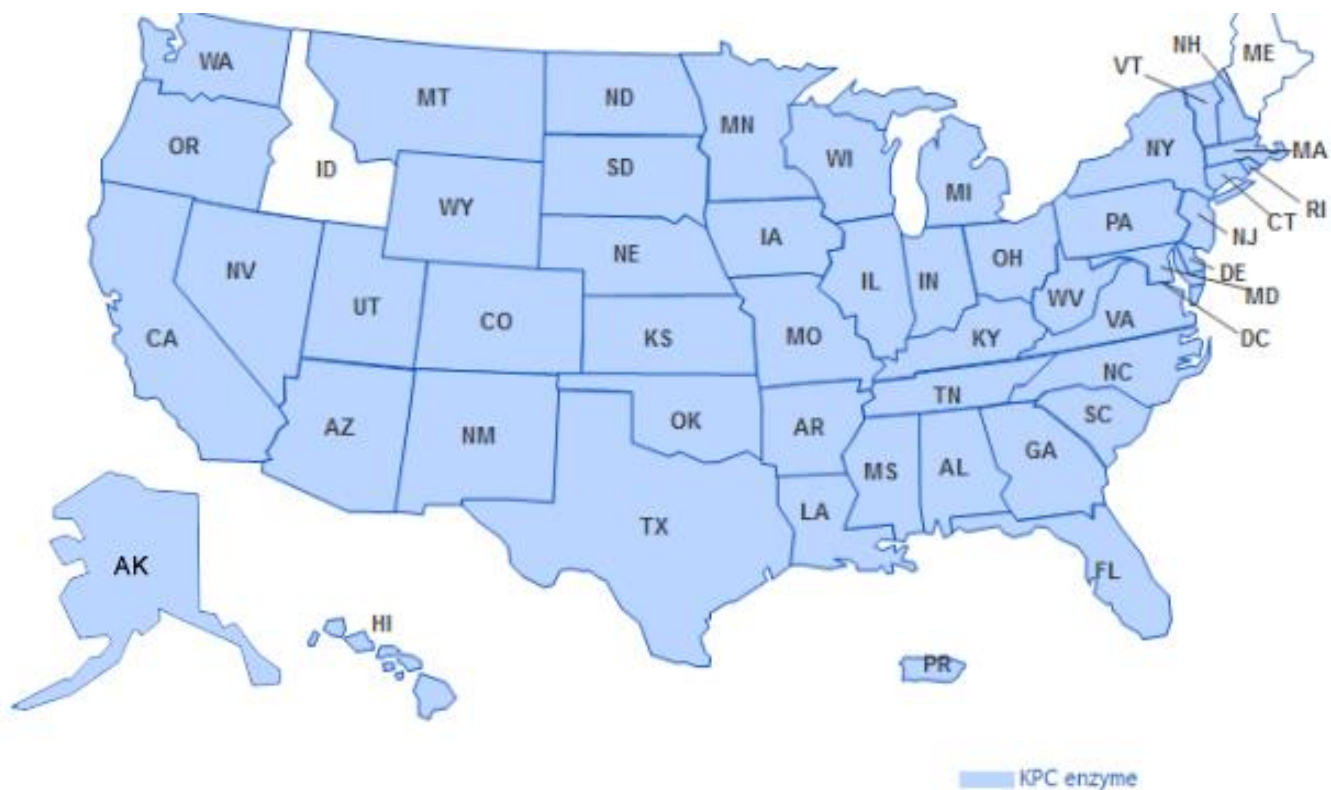


Cases of CRE in 2006



<http://www.cdph.ca.gov/programs/hai/Documents/CREpresentationForLocalPublicHealth073114.pdf>
Accessed 4/22/2015.

February 2015

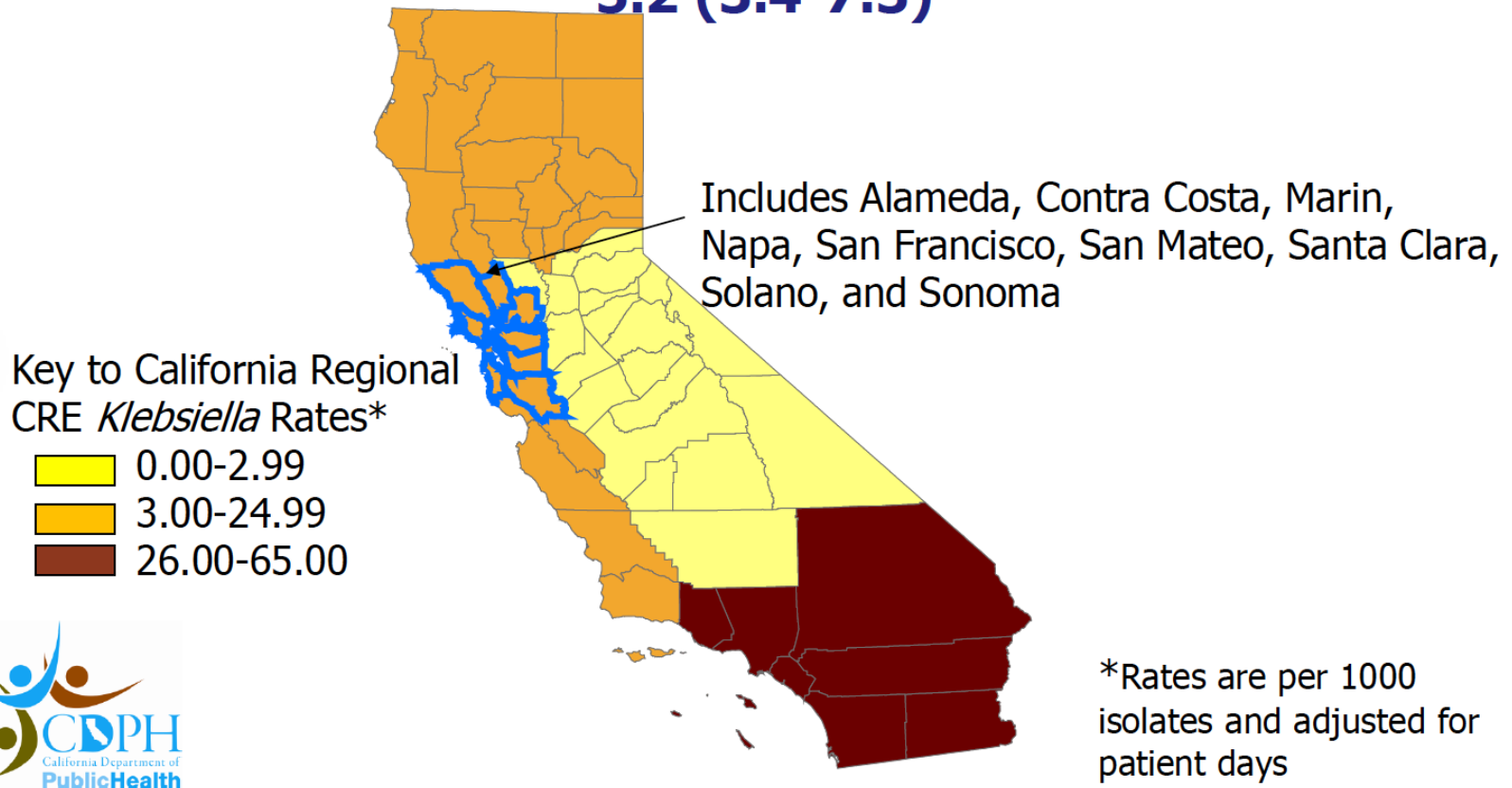


<http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html> Accessed 4/22/2015.

Bay Area

Regional Prevalence of CRE *Klebsiella* Species
per 1000 Isolates (95% Confidence Interval)

5.2 (3.4-7.3)



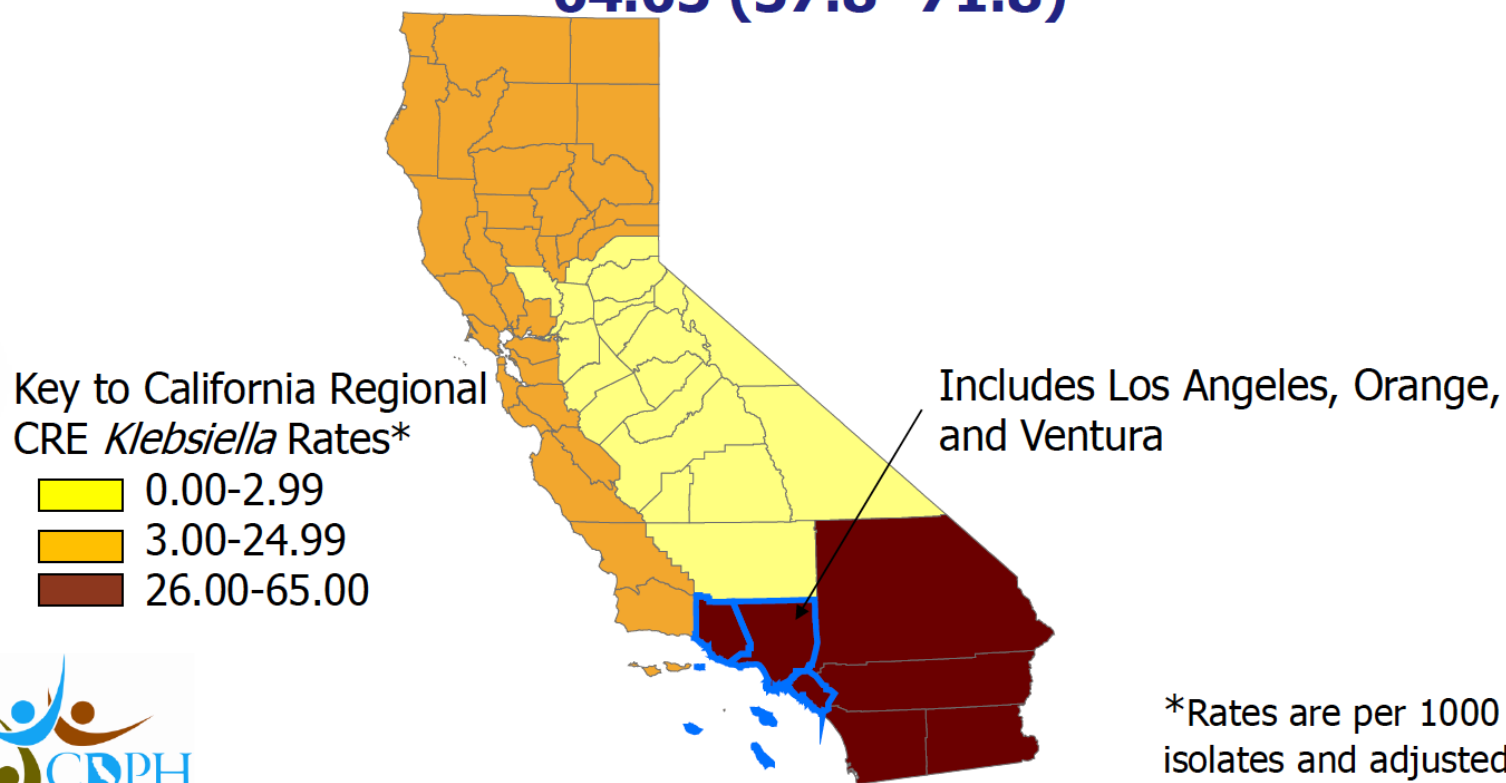
<http://www.cdph.ca.gov/programs/hai/Documents/CREpresentationForLocalPublicHealth073114.pdf>

Accessed 4/22/2015.

Los Angeles Area

Regional Prevalence of CRE *Klebsiella* Species
per 1000 Isolates (95% Confidence Interval)

64.65 (57.8- 71.8)



*Rates are per 1000
isolates and adjusted for
patient days



<http://www.cdph.ca.gov/programs/hai/Documents/CREpresentationForLocalPublicHealth073114.pdf>

Accessed 4/22/2015.

LA-DPH County Antibioqram 2013

Seventy Acute Care Facilities (70%)

Acute Care Hospitals 67% (61/91)

75% ACH patient days (n=3,770,438)

74% beds (n=18,316)

LTACH 100% (10/10)

All LTAC patient days (n=199,795)

All beds (n=772).

GN Resistance

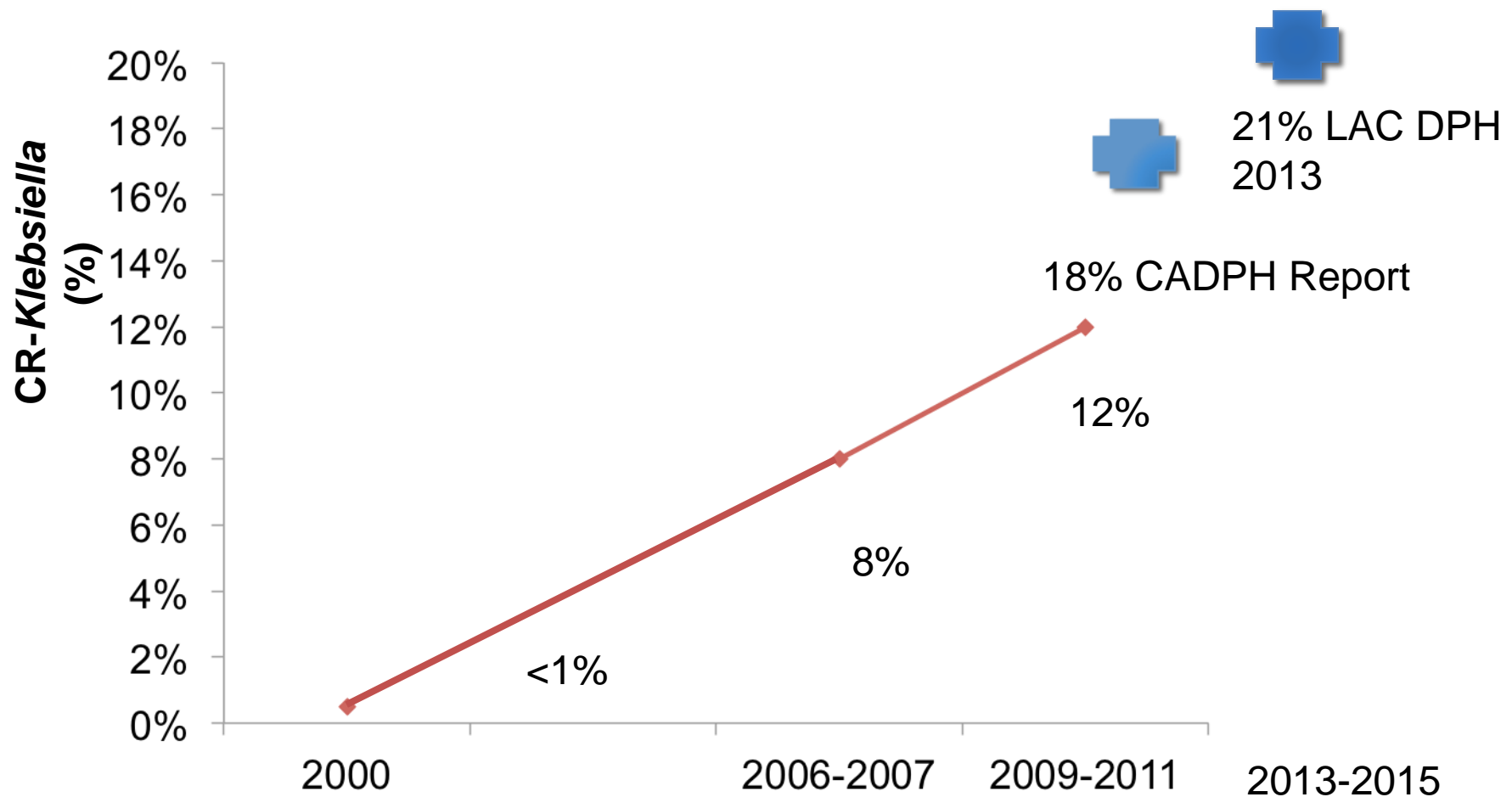
- **Carbapenem Resistance was High**

Klebsiella spp. were 21% (range: 0-77%, n=3,531 isolates) for ACH and 71% (57-88%, n=1,009) for LTAC

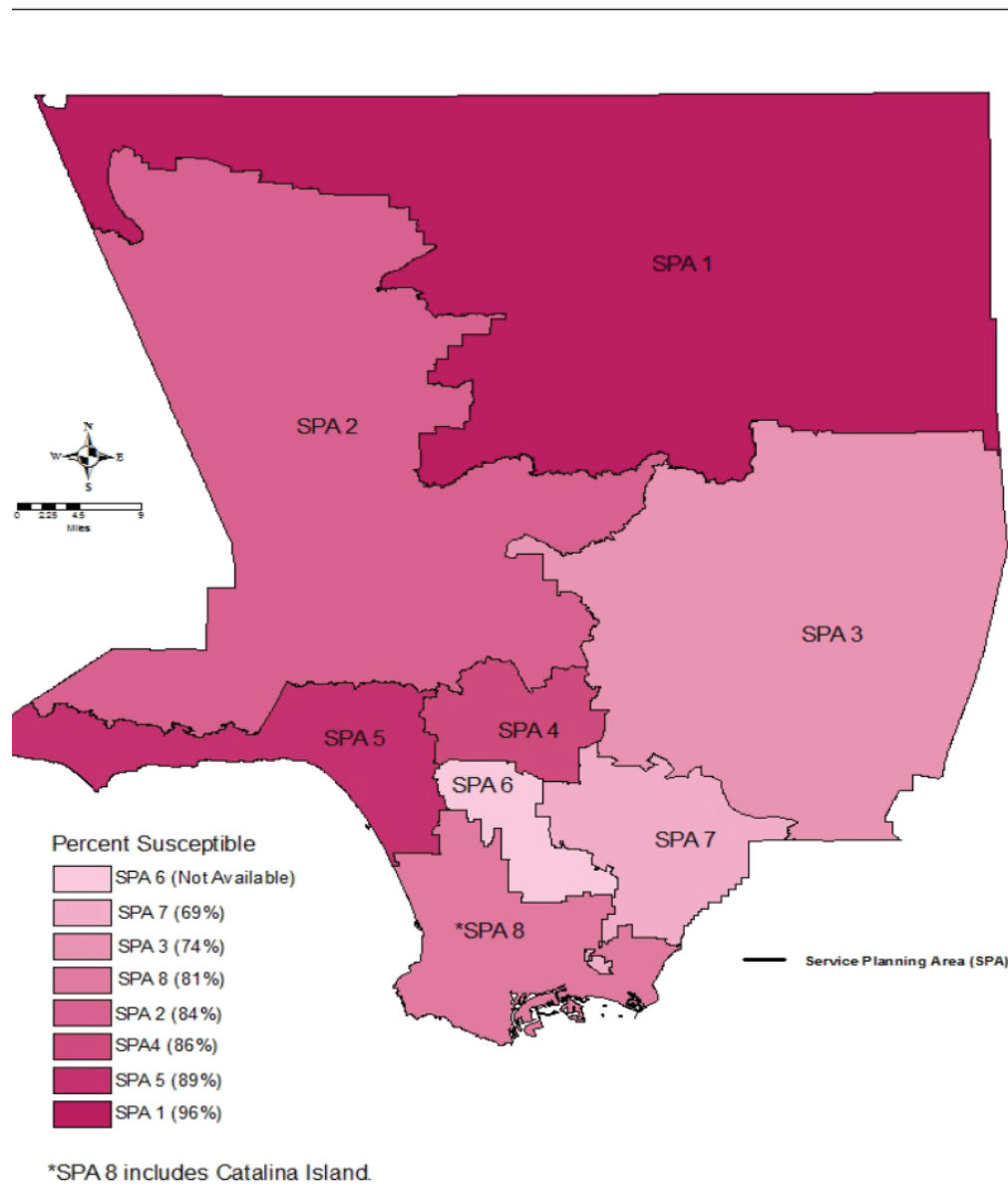
Pseudomonas spp. was 30% (0-46%, n=4,859) for ACH and 59% (39-64%, n=971) for LTAC

Acinetobacter spp. was 67% (0-100%, n=1,851) and 87% (82-99%, n=1180).

Steady Increase in CRE Incidence - US Hospital Reports to CDC



Distribution of Carbapenem Susceptibilities among *Klebsiella* spp. by Service Planning Areas, Los Angeles County, 2013

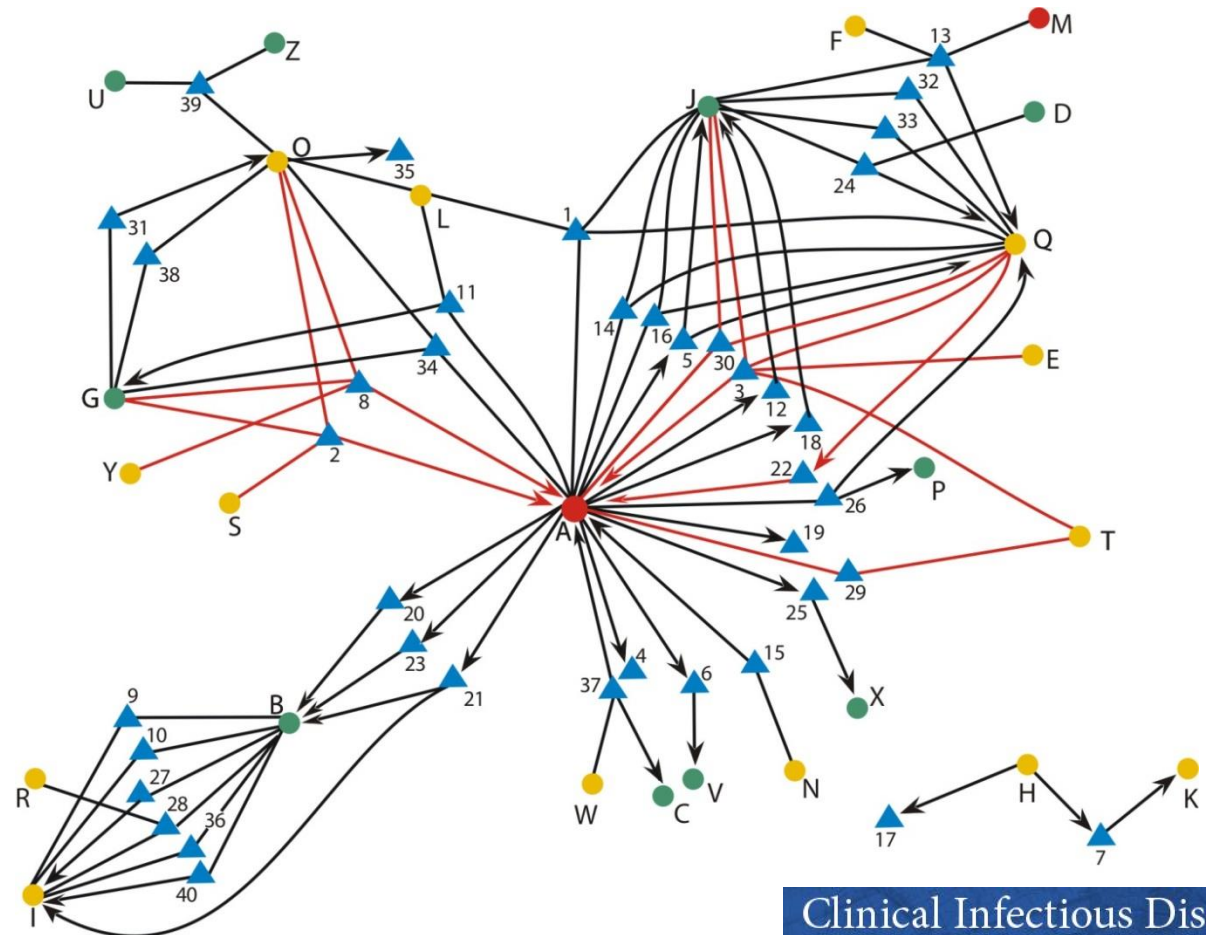
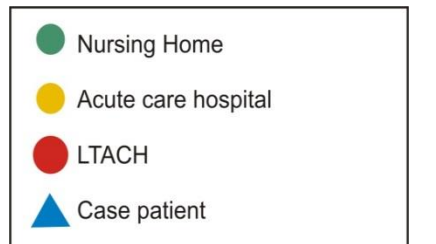


“How are CRE and Other MDROs spreading so effectively?”

The Pig Pen Principle

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

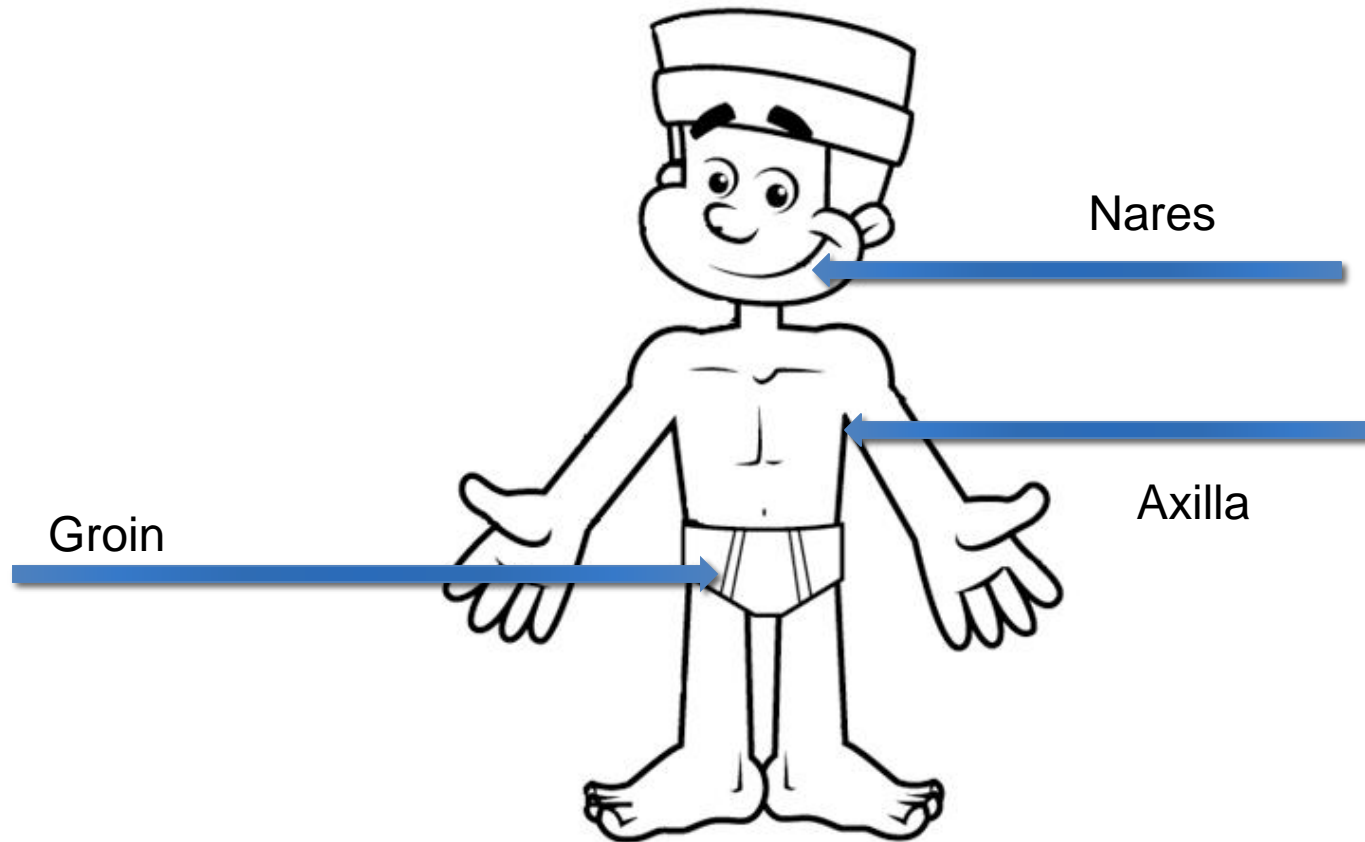
Sarah Y. Won,^{1,2} L. Silvia Munoz-Price,³ Karen Lolans,⁴ Bala Hota,^{4,5} Robert A. Weinstein,^{4,5} and Mary K. Hayden⁴ for the Centers for Disease Control and Prevention Epicenter Program



The Pig Pen Principle



SNF Surveillance Sites for MDRO



Pilot Project

- Methicillin Resistant *Staphylococcus aureus* (MRSA)
- Vancomycin Resistant Enterococcus (VRE)
- Extended Spectrum Beta Lactamase Producers (ESBLs)
- Carbapenem Resistant Enterobacteriaceae (CRE)

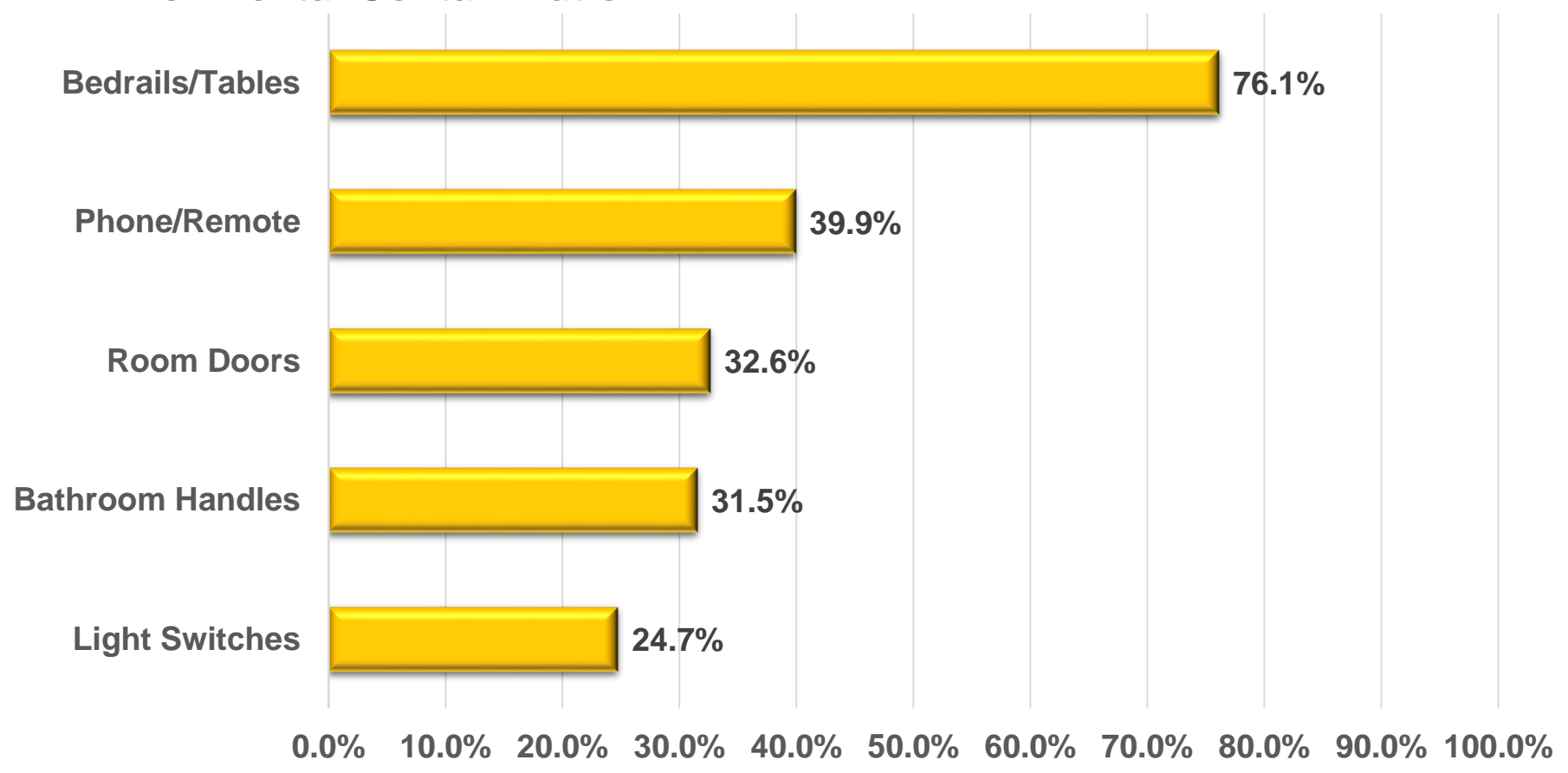
45% of nursing home residents harbor an MDRO*

Data from over 40 nursing homes suggest these observations are generalizable

McKinnell et al, Protect Pilot, SHEA Spring 2016

SNF Patient with Known Colonization

Environmental Contamination

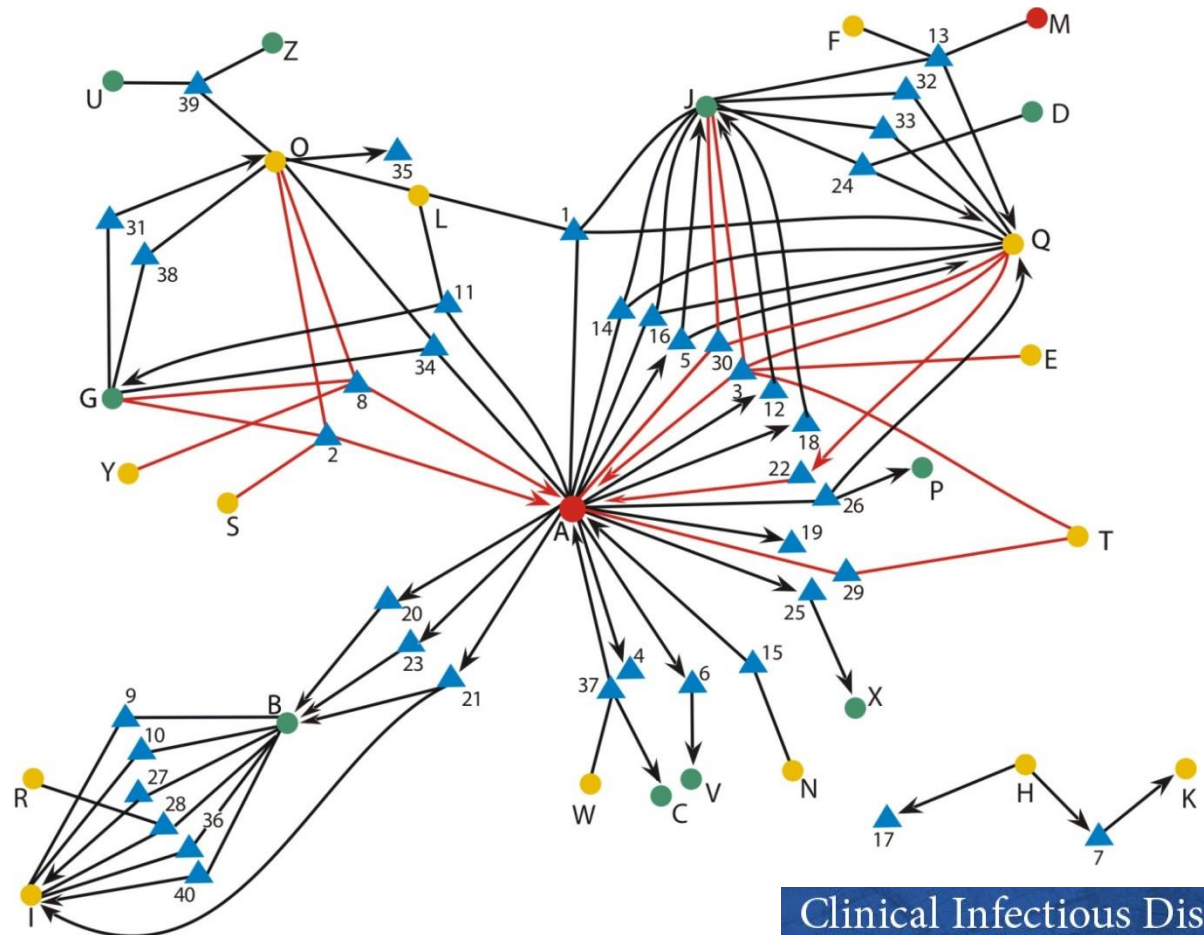
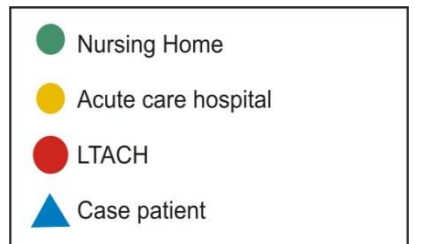


SNF Patient with Known Colonization

Residents		Environment		Environmental Discordant MDRO			
Resident MDRO	Patients with MDRO	Concordant MDRO	Discordant MDRO	MRSA	VRE	ESBL	CRE
MRSA+	223	58%	65%	--	55%	23%	3%
VRE+	93	86%	68%	32%	--	29%	9%
ESBL+	119	32%	91%	41%	71%	--	4%
CRE+	6	50%	83%	17%	83%	67%	--

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

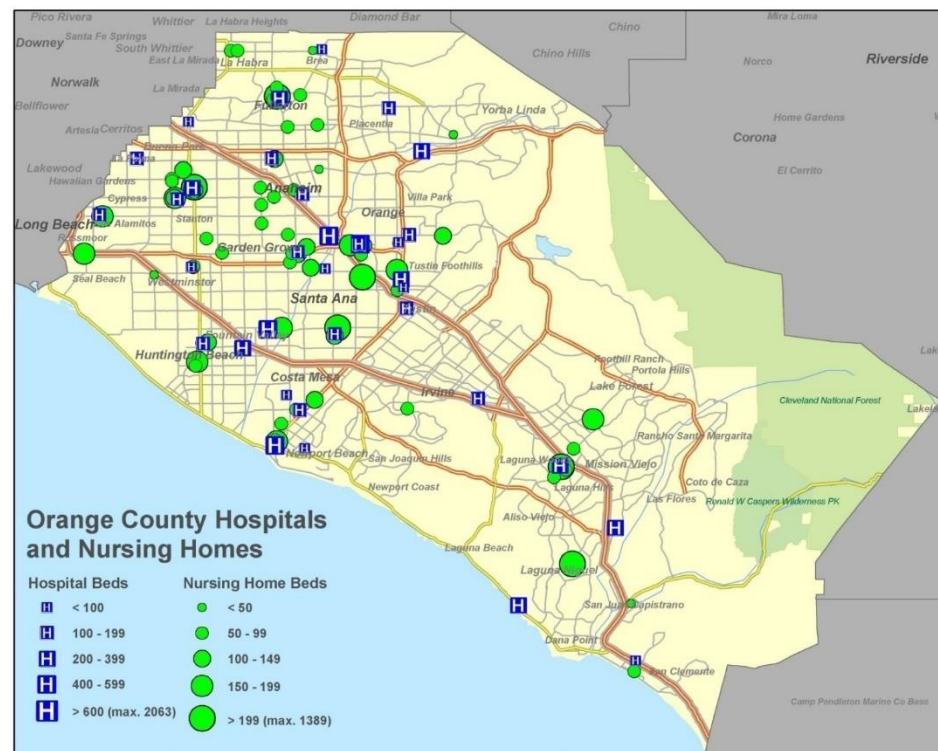
Sarah Y. Won,^{1,2} L. Silvia Munoz-Price,³ Karen Lolans,⁴ Bala Hota,^{4,5} Robert A. Weinstein,^{4,5} and Mary K. Hayden⁴ for the Centers for Disease Control and Prevention Epicenter Program



Orange County, California

Ideal Virtual Laboratory

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



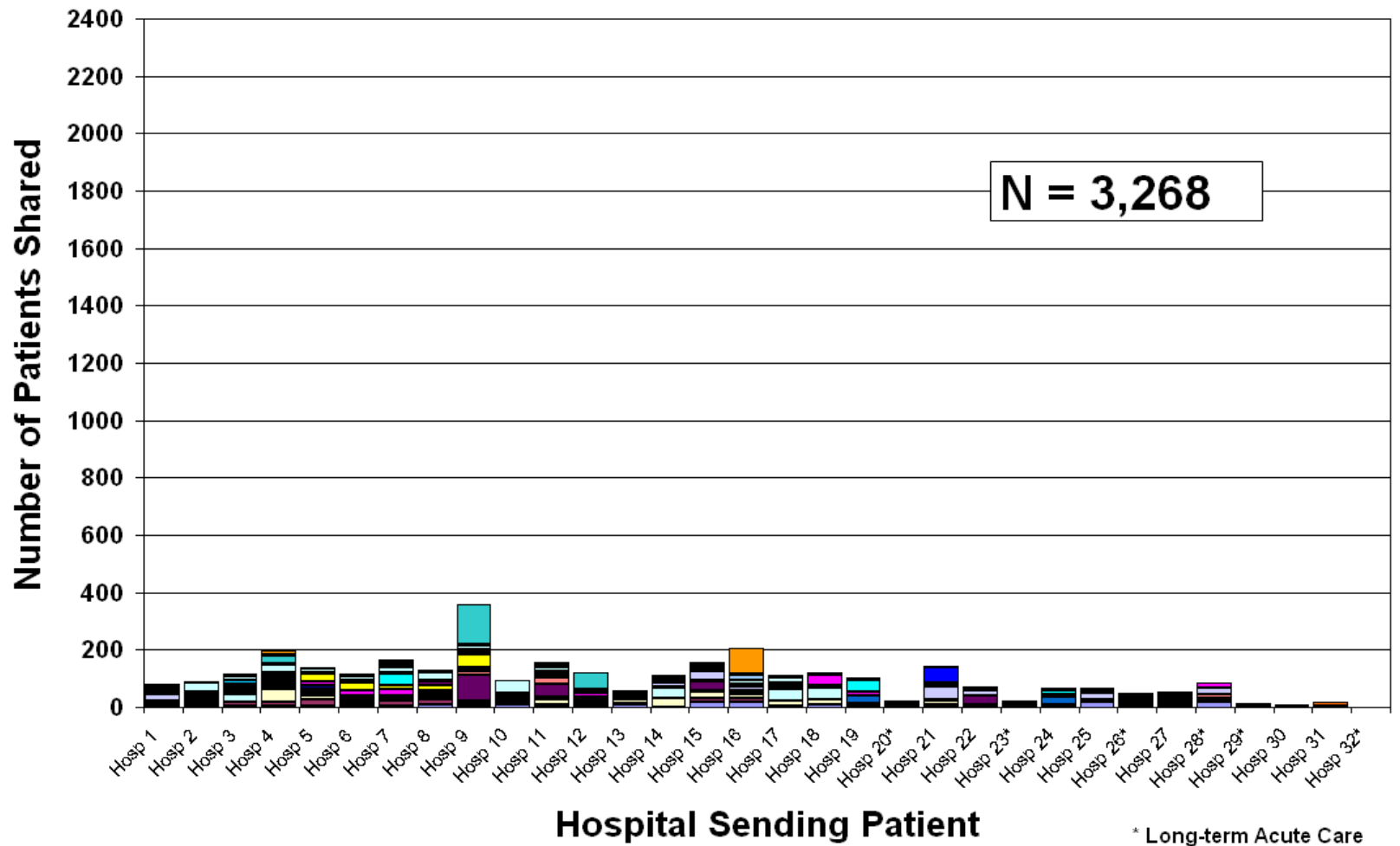
Orange County

- 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 (6th largest US county)
- >320,000 admissions annually

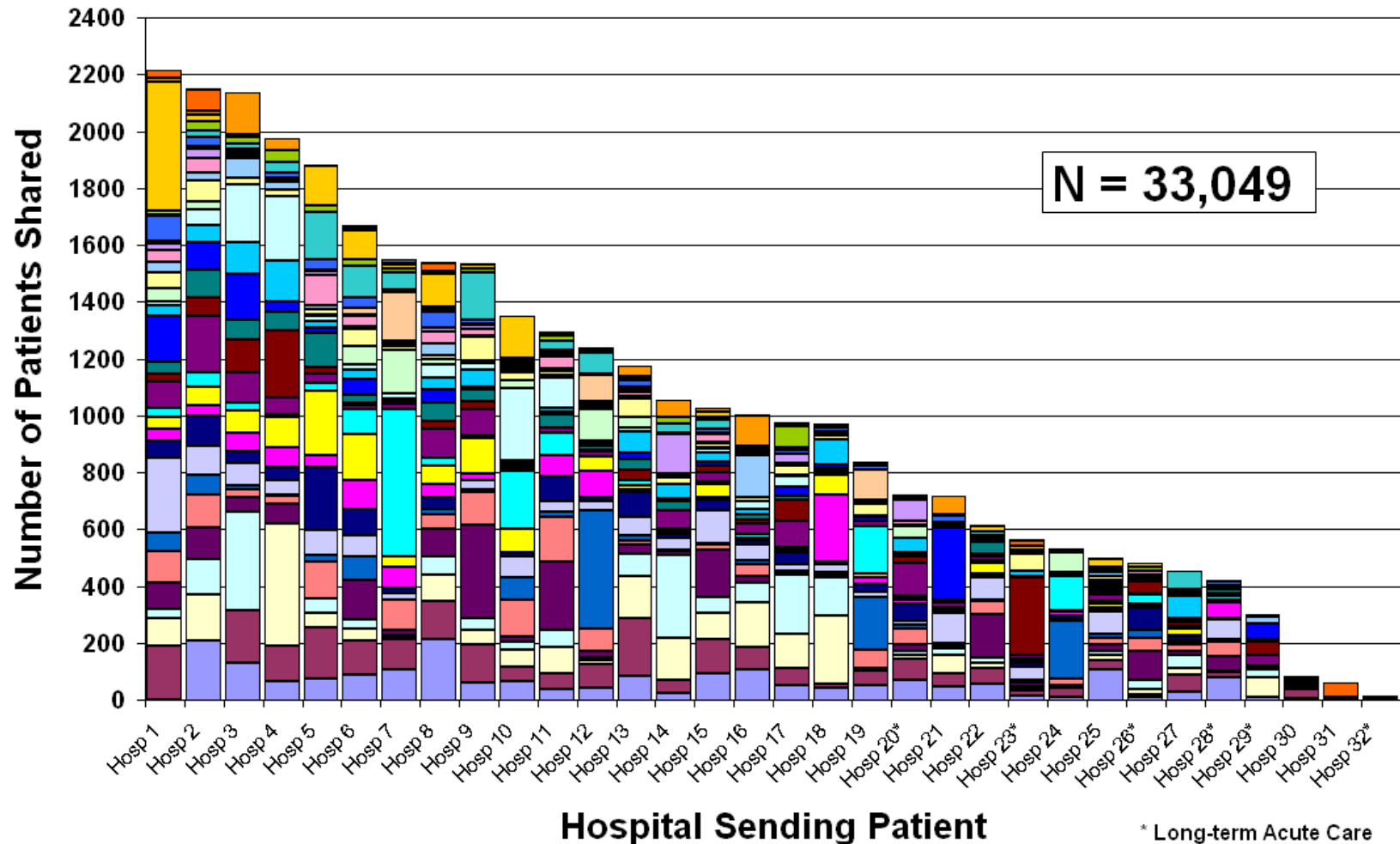
Data Sources

Parameter	Source
Hospital Characteristics (unit size, volume)	2013 Hospital IP Survey 2013 Mandatory CA Hospital Dataset
Hospital Length of Stay Distribution	2013 Mandatory CA Hospital Dataset
Hospital Clinical CRE Prevalence/Incidence	2008-2013 Hospital IP Survey
LTAC Clinical CRE Prevalence/Incidence	Literature
Hospital-Hospital Transfer Matrix	2013 Mandatory CA Hospital Dataset
Nursing Home Length of Stay	2013 CMS Minimum Data Set (MDS)
Nursing Home CRE Prevalence/Incidence	Literature, Regional nursing home lab
Hospital-Nursing Home Transfer Matrix	Linked Hospital Data/MDS data
Loss Rate	Literature

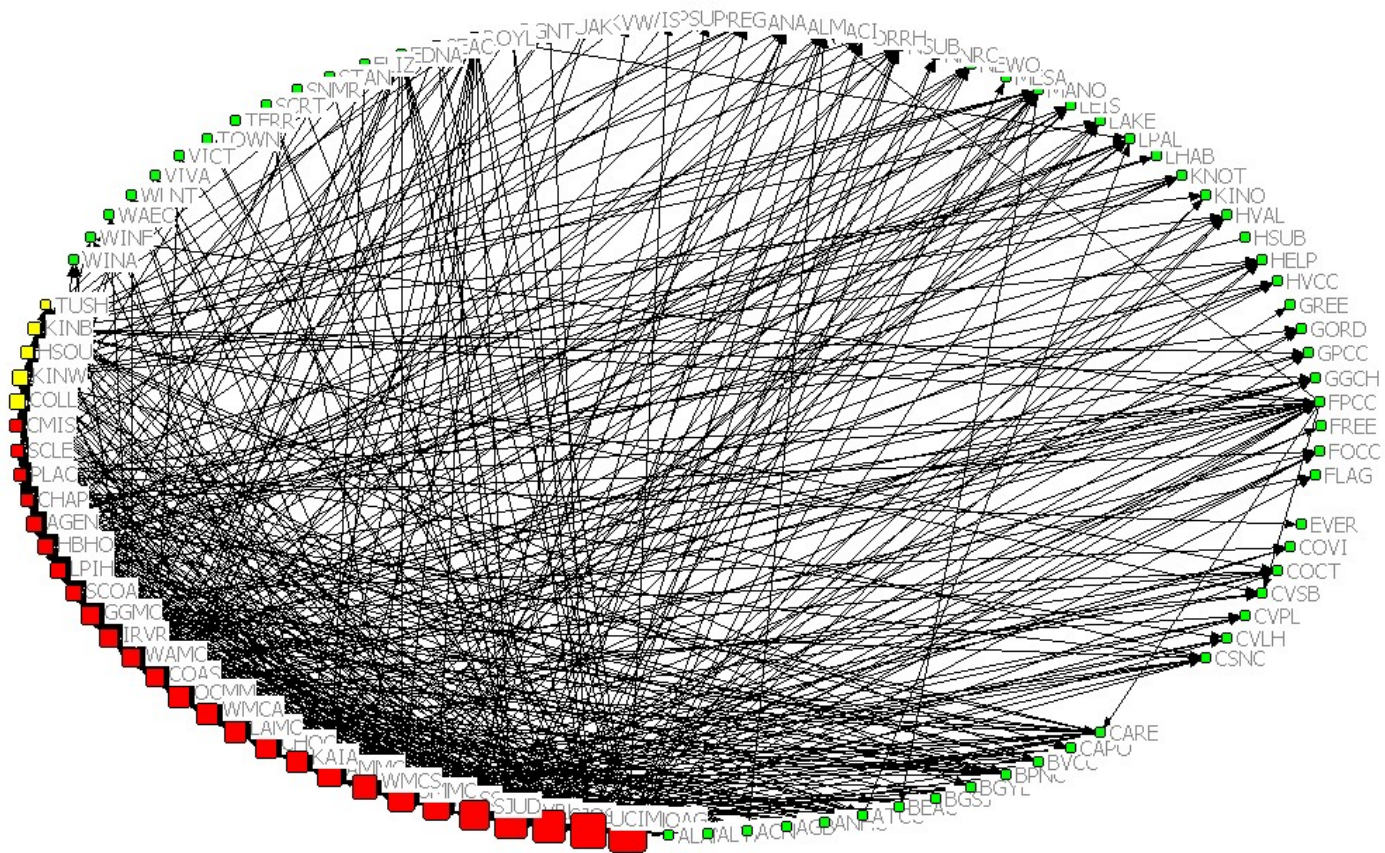
Hospitals Share Patients – Direct



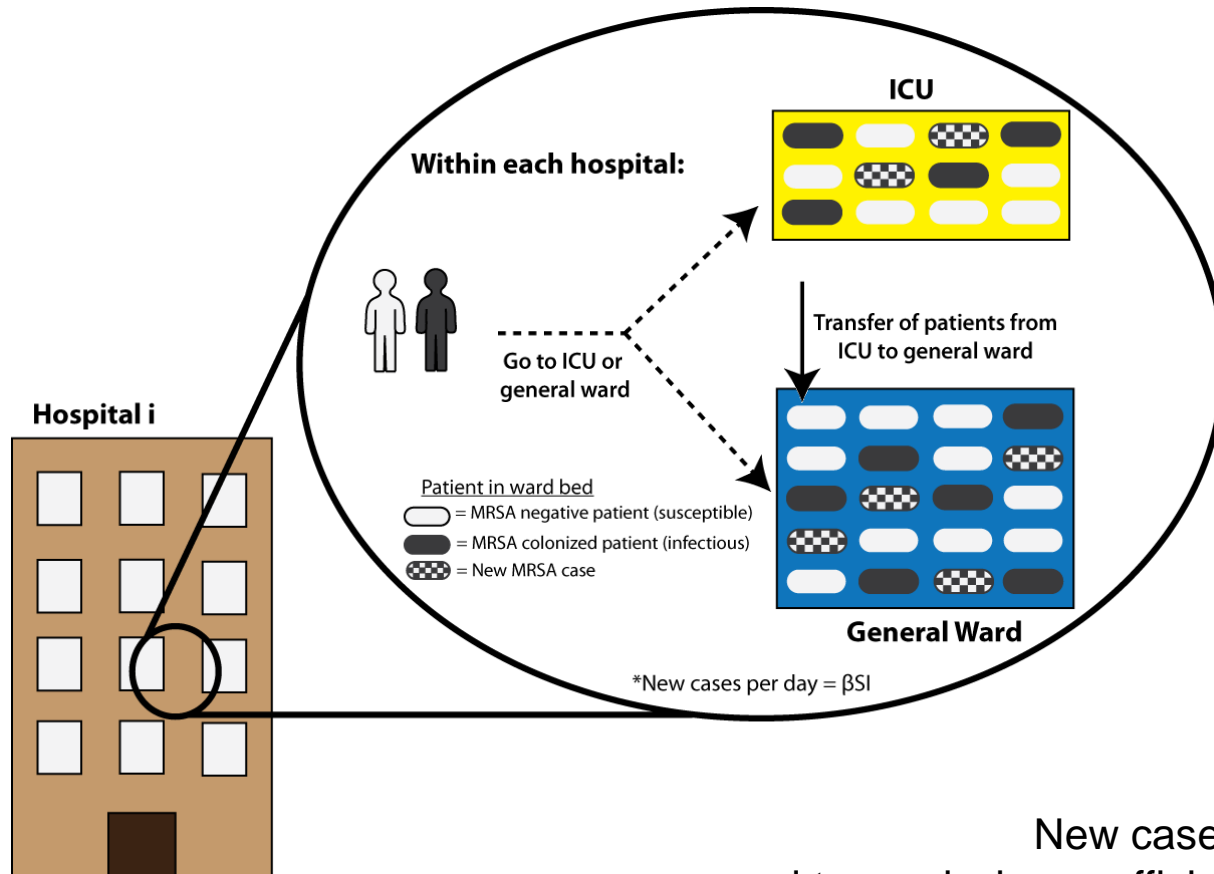
Hospitals Share Patients-Indirect



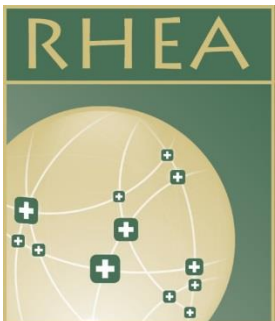
Sharing Patients – 10 Patients



CRE Transmission Model



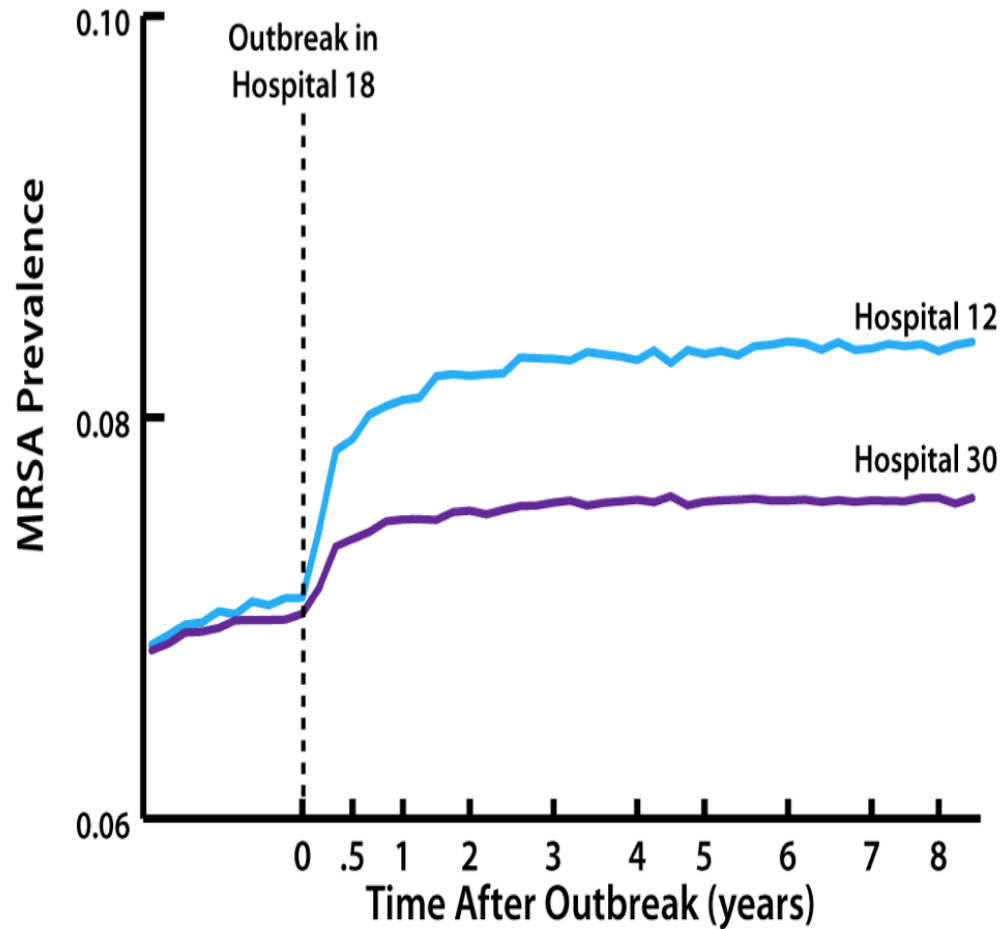
New cases per day =
ward transmission coefficient x number
of susceptible x number of infectious



Select CRE Parameter Estimates

Parameter	Estimate
Target prevalence by year 7 from 1 st known case	LTACs: 25%, NH: 8%, ICU: 3%
Known to unknown hospital carriers	1:8
Persistent carriage	30%
Spontaneous loss	Half-life = 1 year
Sensitivity of a single rectal swab	70%
Sensitivity/specificity of screening test	91% / 94%
Screening test turn around	1 day
Contact precautions compliance	50%
Length of stay	Mimicked by VRE in OC

Sustained Single Hospital Outbreak

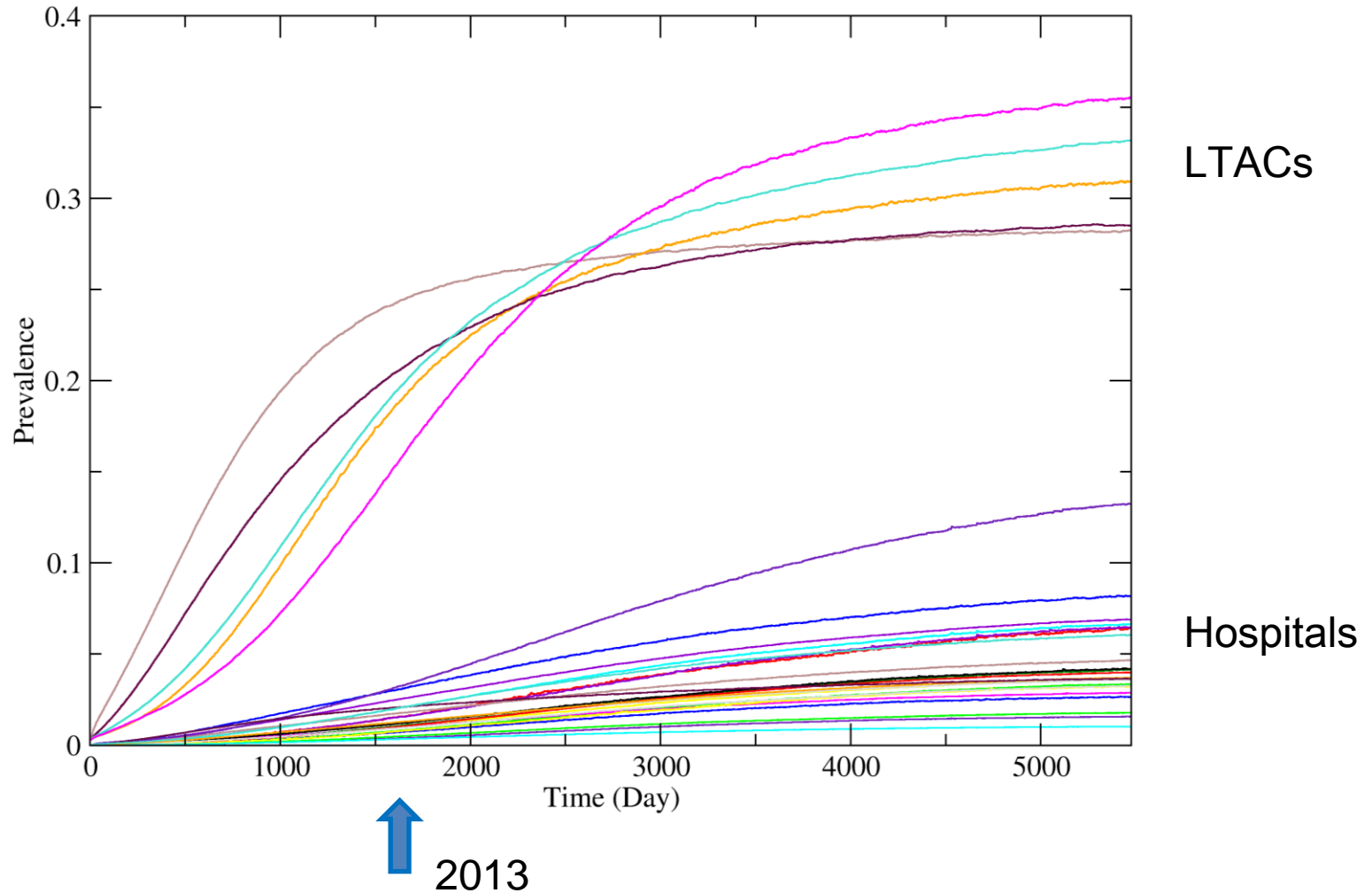


Modeling: Base Case

- Contact precautions for CRE
 - Known carriers to hospital
 - Upon readmission
 - Notify upon transfer
 - Nursing homes: if CRE infection
(assume 50% of known CRE is infected on admission)
- No screening, no decolonization

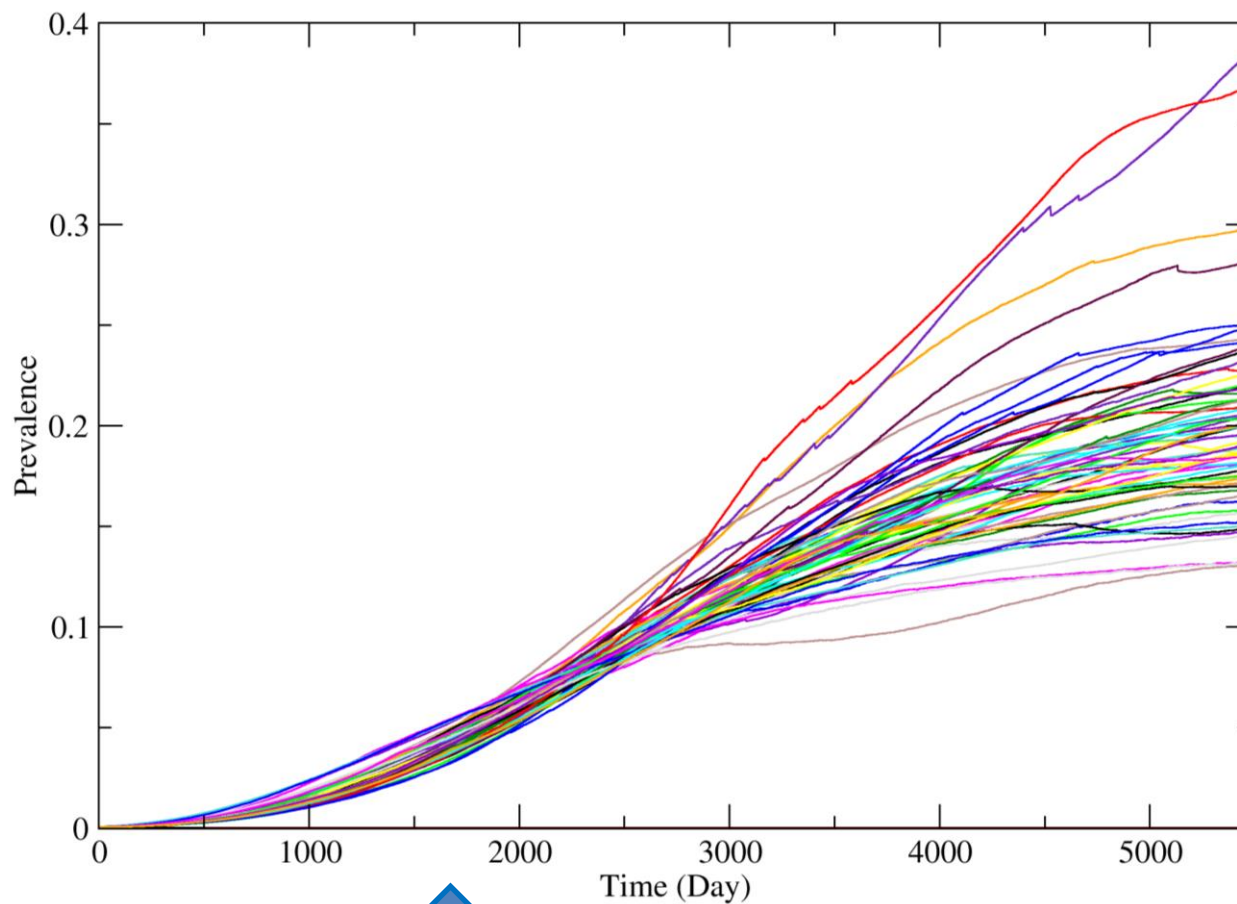
Base Model: OC Hospitals

CRE Prevalence



Base Model: OC Nursing Homes

CRE Prevalence



↑
2013

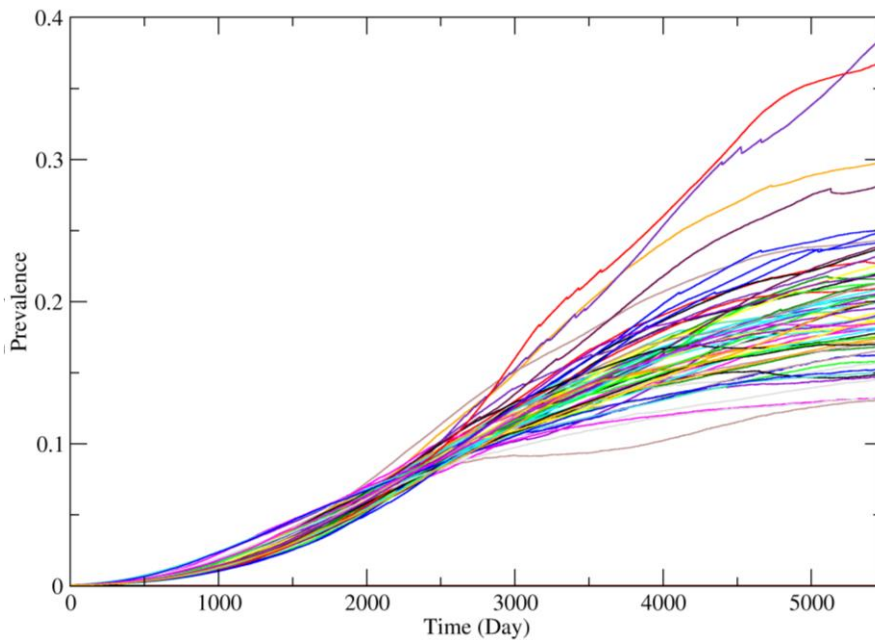
Modeling: Intervention

- Hospital and LTAC Intervention:
 - Screen all direct transfers for CRE → CP if positive
 - Enhanced notification on transfer

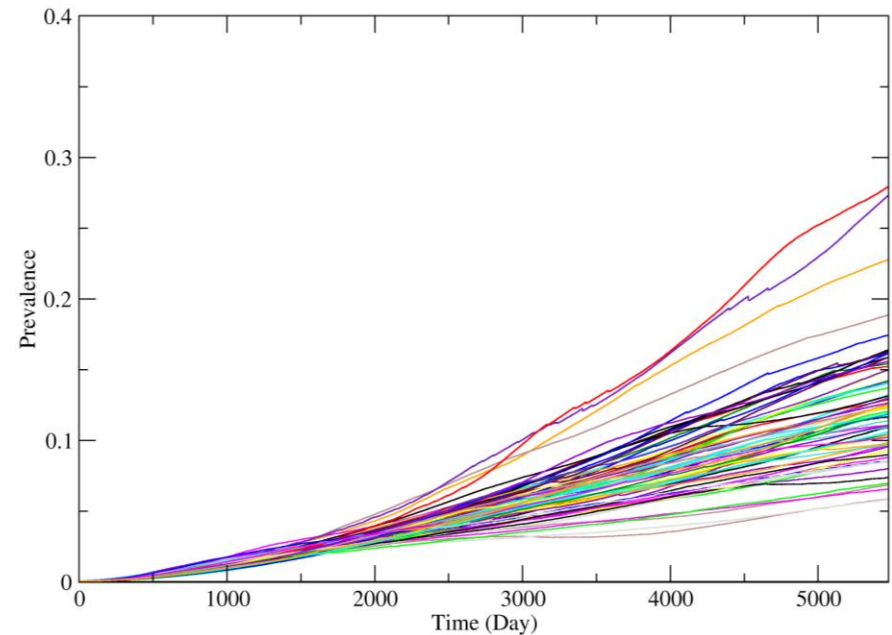
Intervention: Hospital Efforts

Nursing Home CRE Prevalence

Base Case



Trigger = 10 CRE

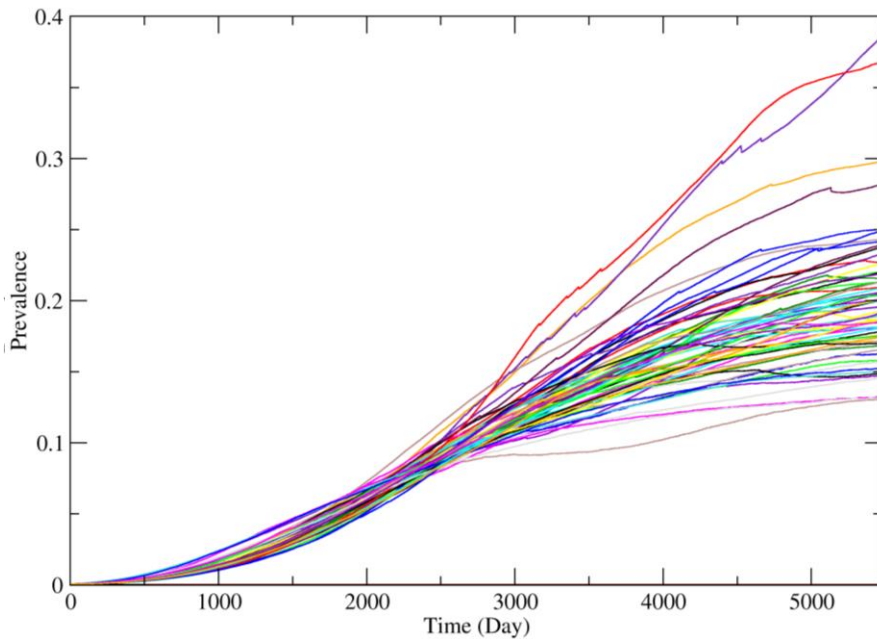


Hospitals and LTACs implement intervention when they have 10 known CRE cases

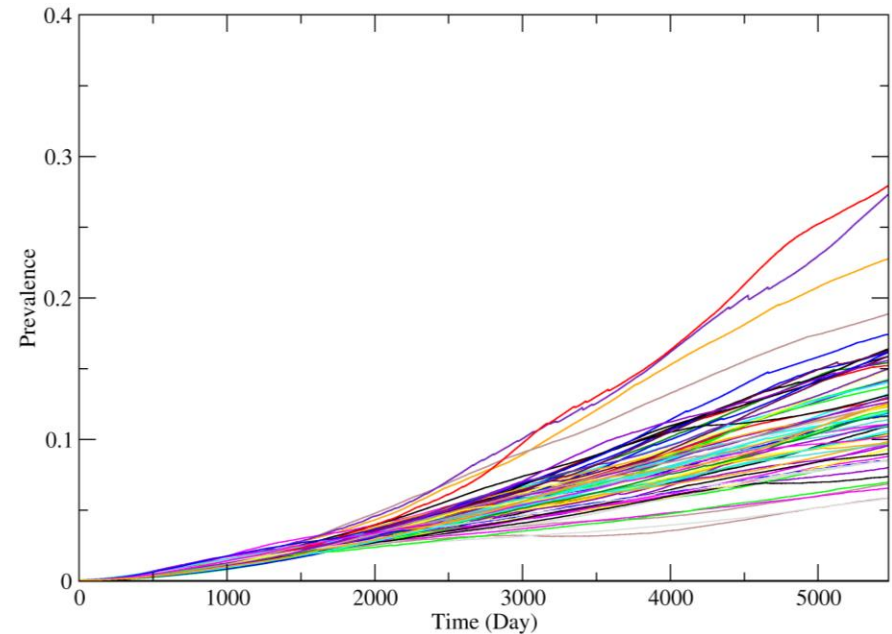
Intervention: Hospital Efforts

Nursing Home CRE Prevalence

Base Case



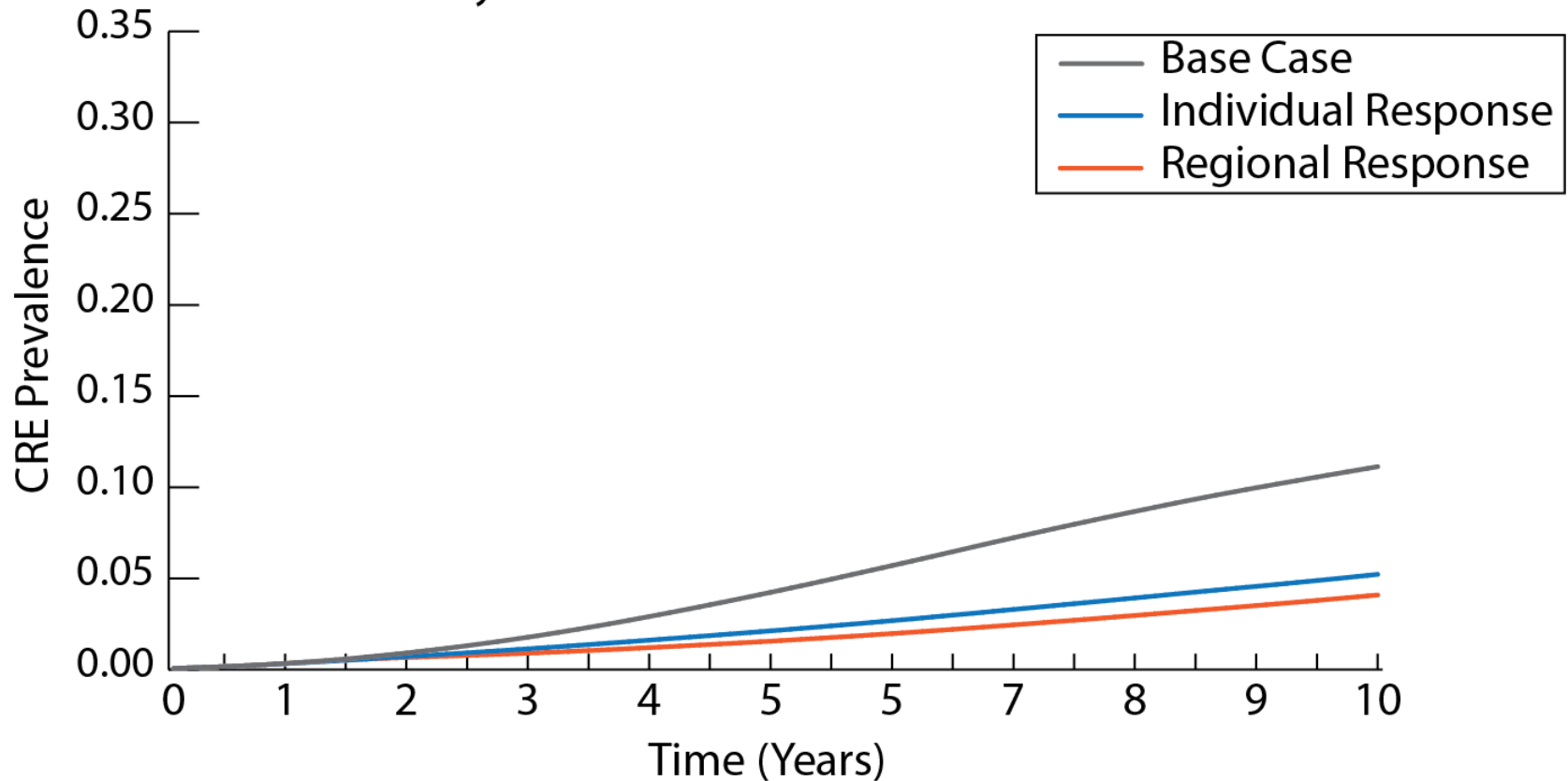
Trigger = 10 CRE



Hospitals and LTACs implement intervention when they have 10 known CRE cases

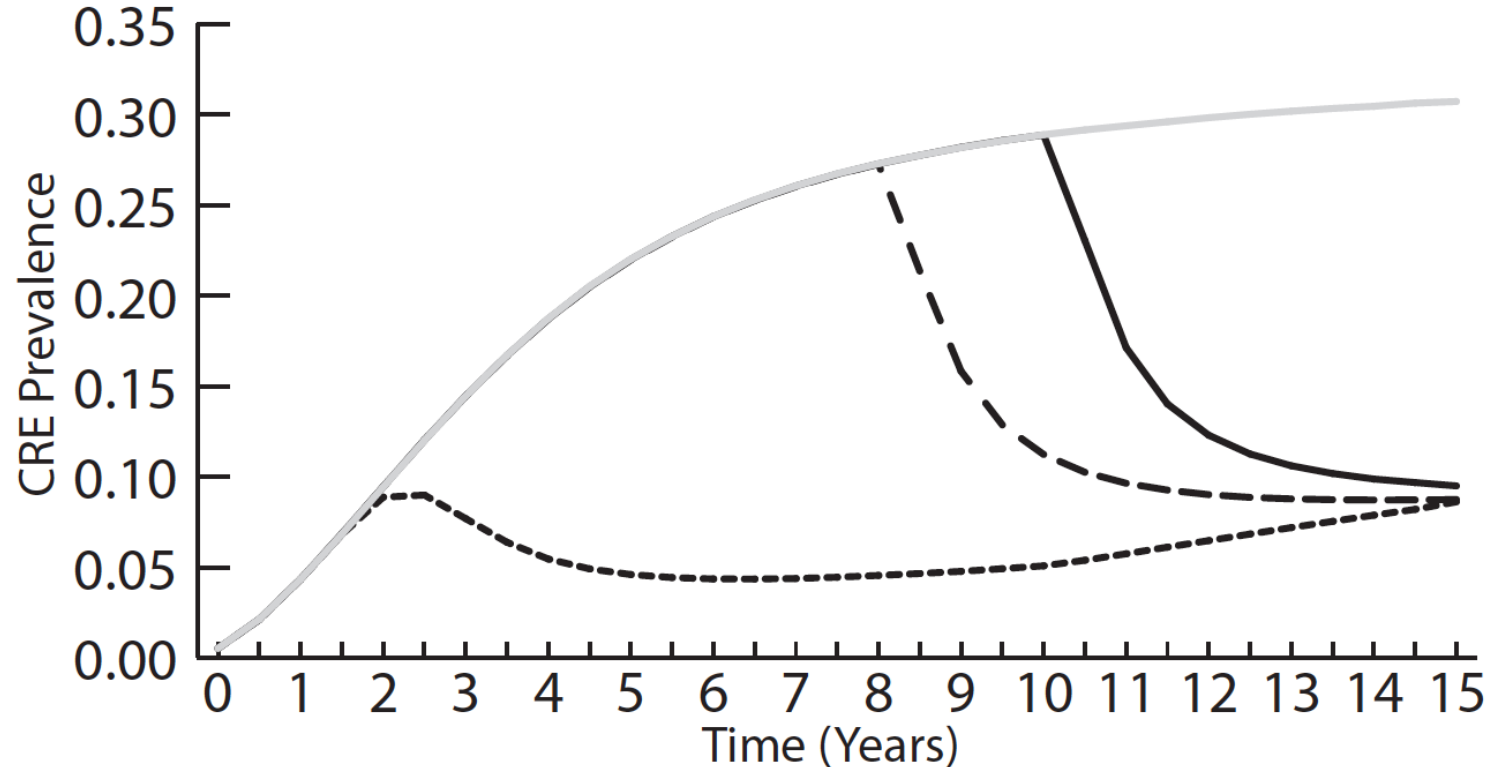
Individual vs Regional Impact: Trigger 10

Countywide CRE Prevalence: All Facilities

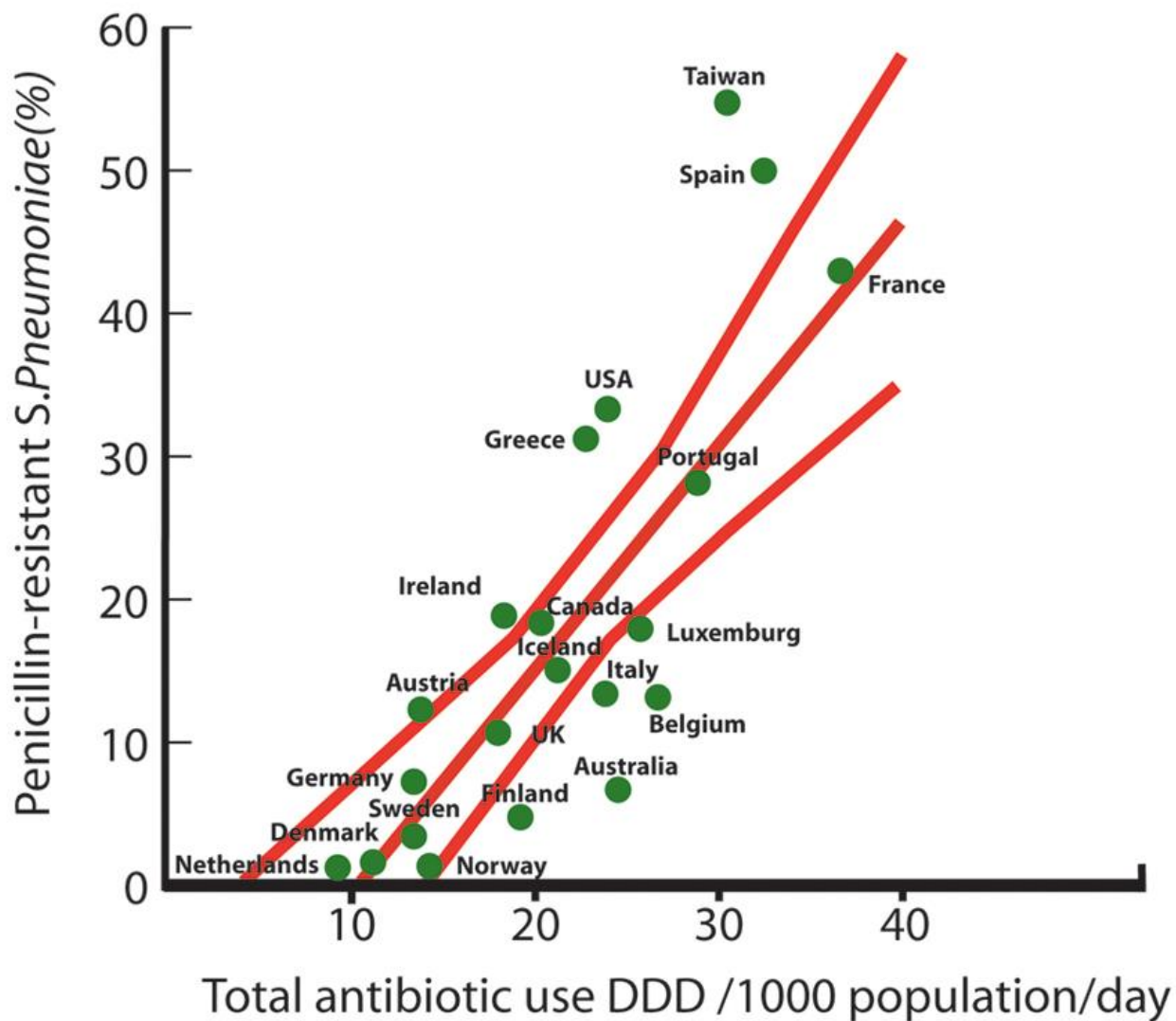


Are Contact Precautions Enough?

B. LTAC CRE Prevalence



“The more we use them, the more we lose them...”



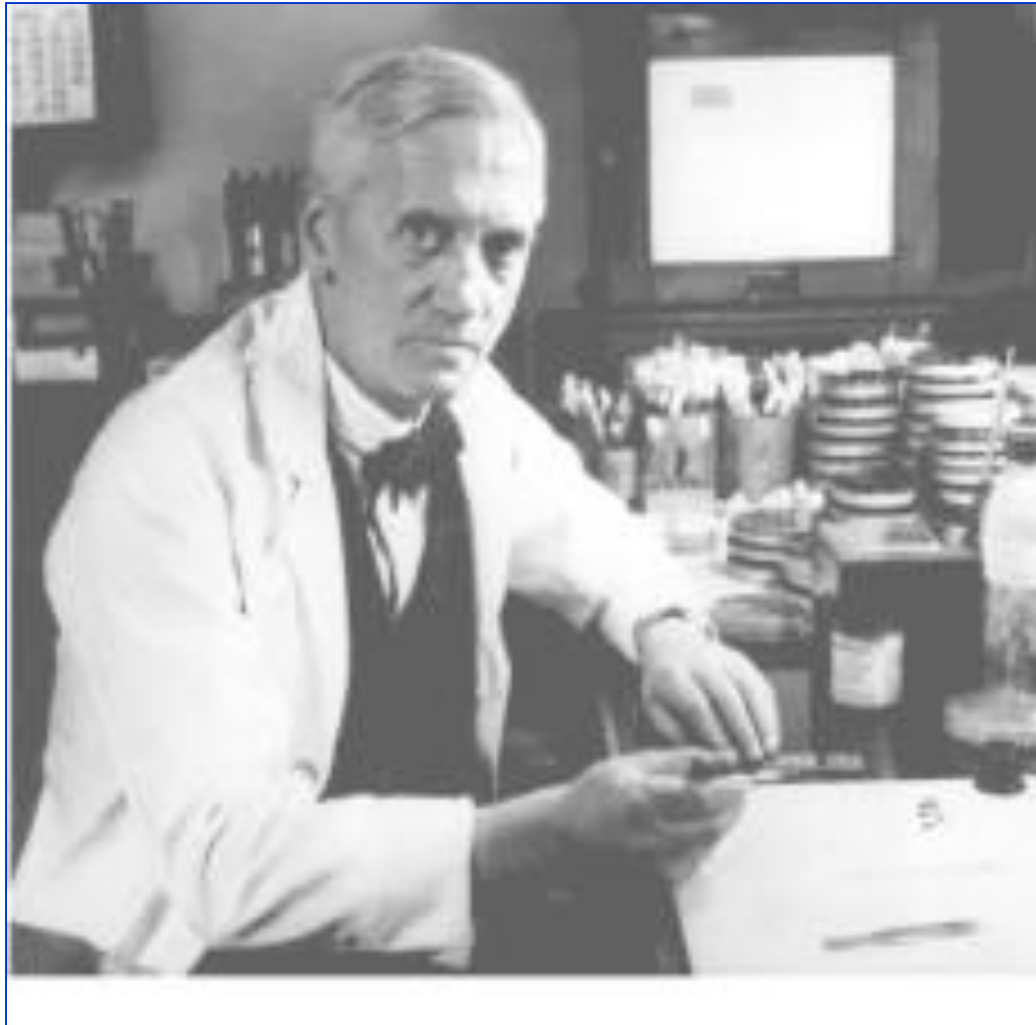
By courtesy of Dr. Liselotte Diaz Högborg

National Priority

- “Over-prescribing is a serious problem. Using antibiotics when they aren't needed is one of the main causes of antibiotic resistance. So we need to give doctors the information and guidance they need to make the right call in hard situations.” President Barak Obama



.... microbes are educated to resist penicillin ... In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.



- Sir Alexander Fleming, NY Times June
1945