Antimicrobial Stewardship: Doing our part to help solve the problems in healthcare

James A. McKinnell, M. D.

Consulting Specialist, M.D.

Los Angeles County Department of Public Health

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 lead antimicrobial stewardship initiatives in Skilled Nursing Facilities, Expert Stewardship, INC.
- I have no commercial/financial relationships related to decolonization, CHG, mupirocin, or iodophor products

Objectives

- Define Two Major Contributors to HAI Deaths
- Explain how Antibiotic Duration and Antibiotic Choice Affect *Clostridium difficile* infection
- Explain one benefit of Antibiotic Stewardship on Patient Quality

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.

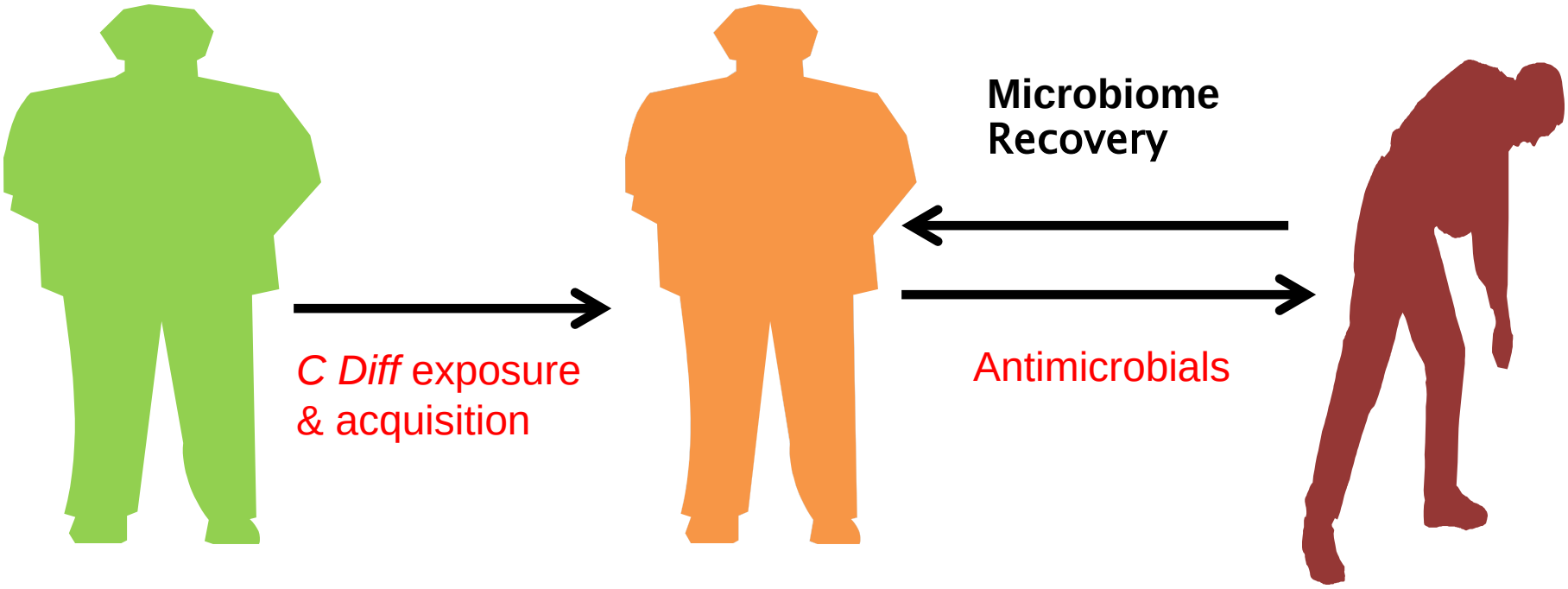
Major Contributors to HAI Deaths

- Unacceptable CDI rates
- Alarming Rates of Antibiotic Resistance

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

CDI Pathogenesis



Antimicrobials Predisposing to CDI

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

- 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

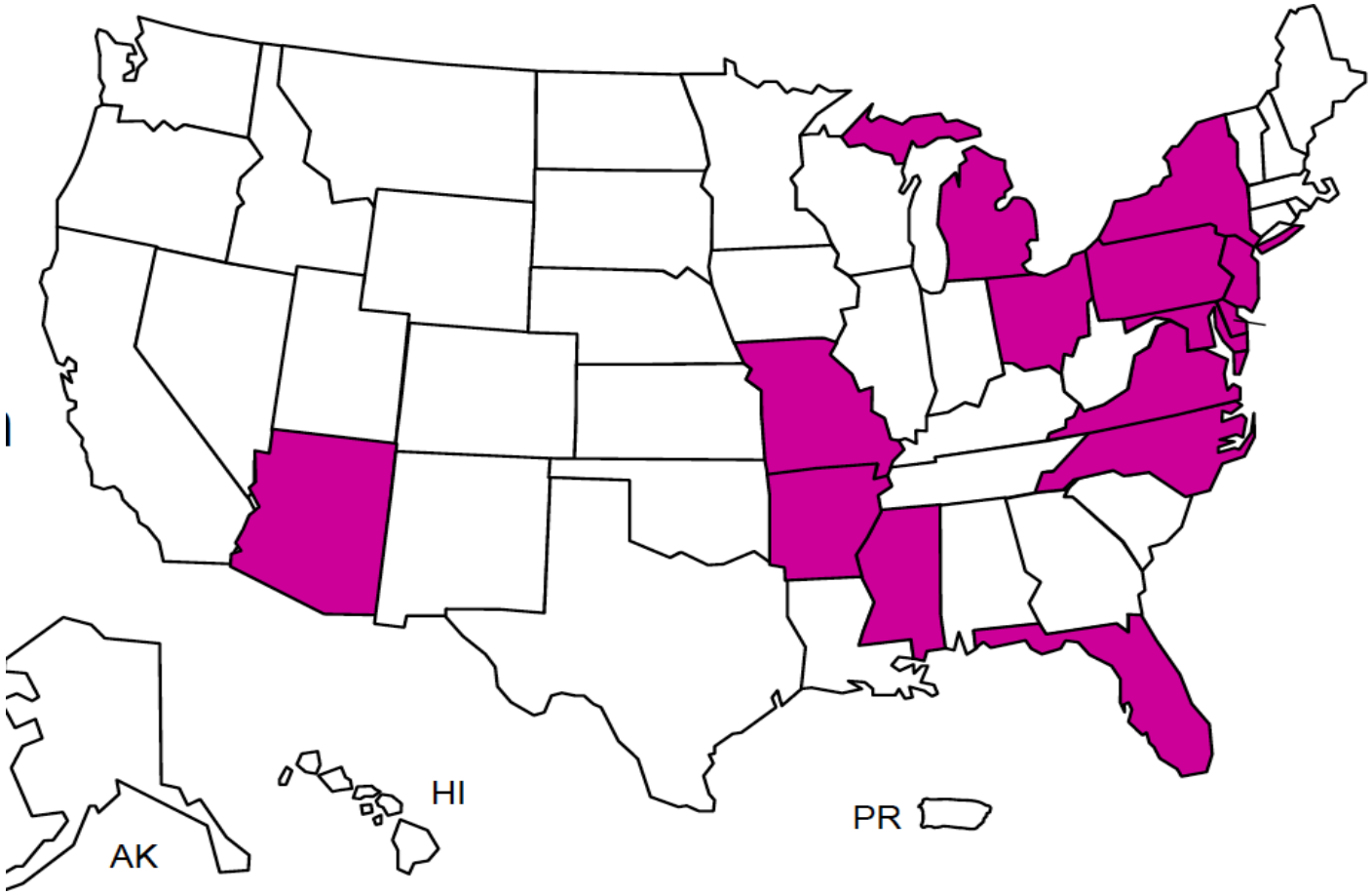
	Days of Antibiotic	
4-7 days	**8-18 days**	**>18 days**
1.4 times higher	3 times higher	7.8 times higher

15. Epson,E. Orange County CDI Prevention Collaborative: Antimicrobial Stewardship. CDPH. November 5, 2015. Permission granted for use of this slide by Dr. Erin Epson.
Original slide reference: Stevens,et al. Clin Infect Dis. 2011;53(1):42-48

- CDC Report, Antibiotic Resistance Threats in the US 2013

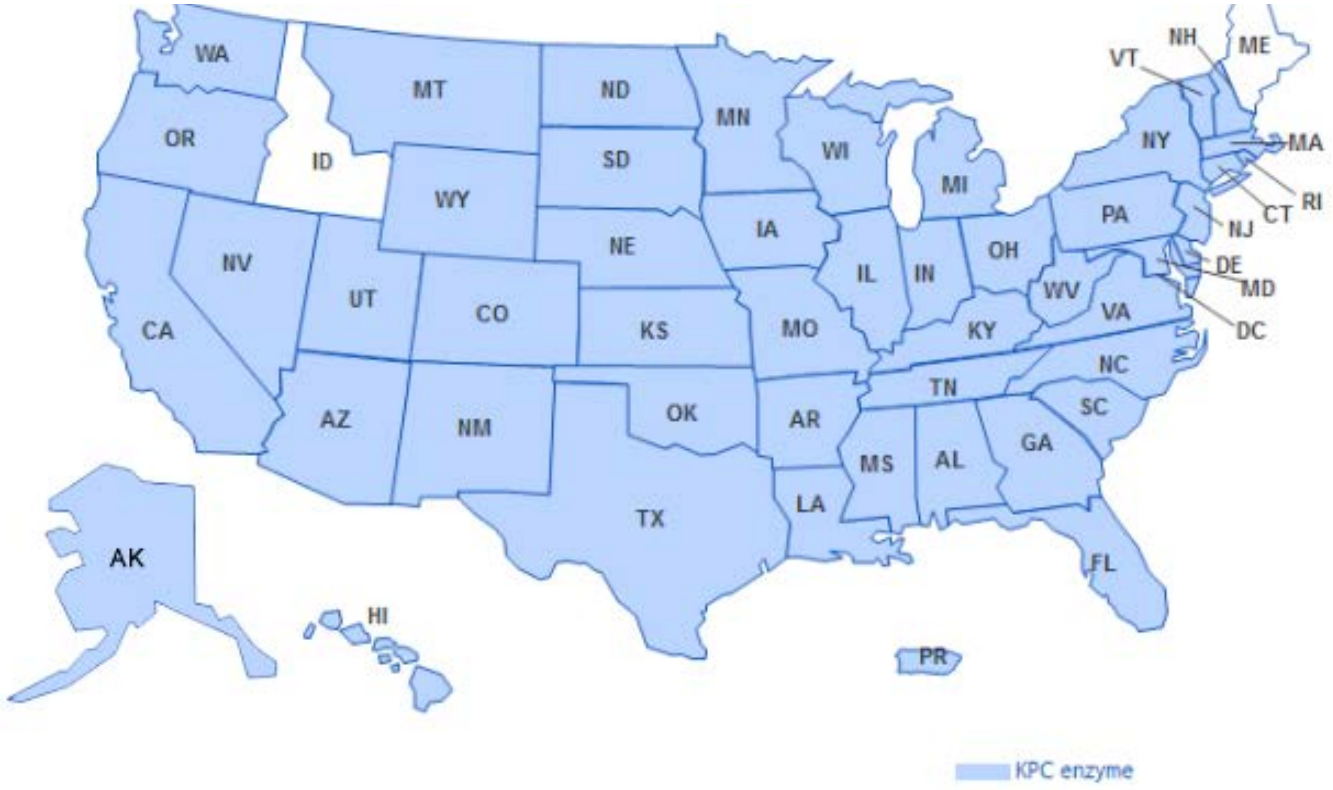
- One of only three pathogens with an URGENT Threat Level

Cases of CRE in 2006



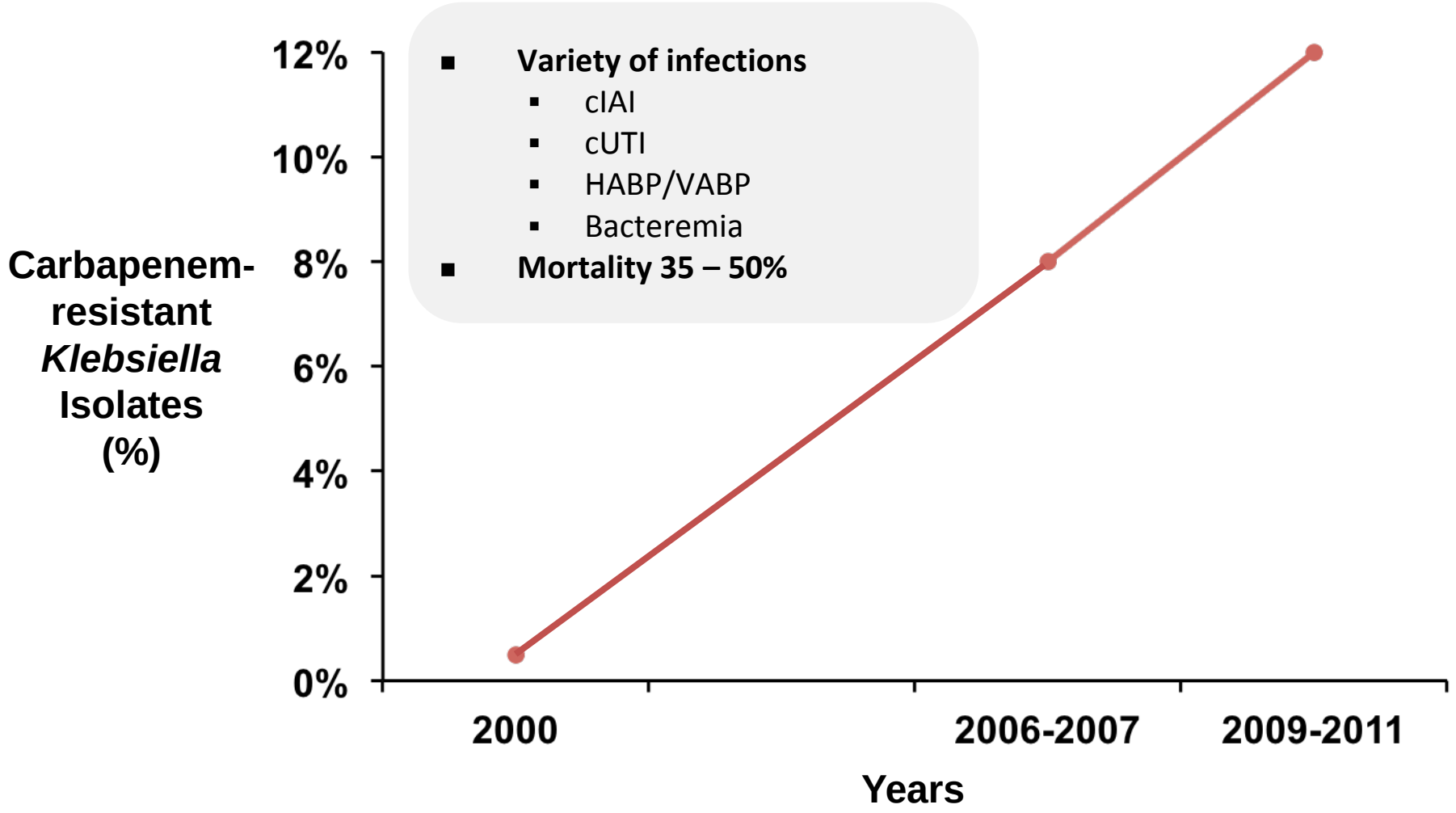
http://www.cdph.ca.gov/programs/hai/Documents/CREpresentationForLocalPublicHealth073114.pdf
Accessed 4/22/2015.

February 2015



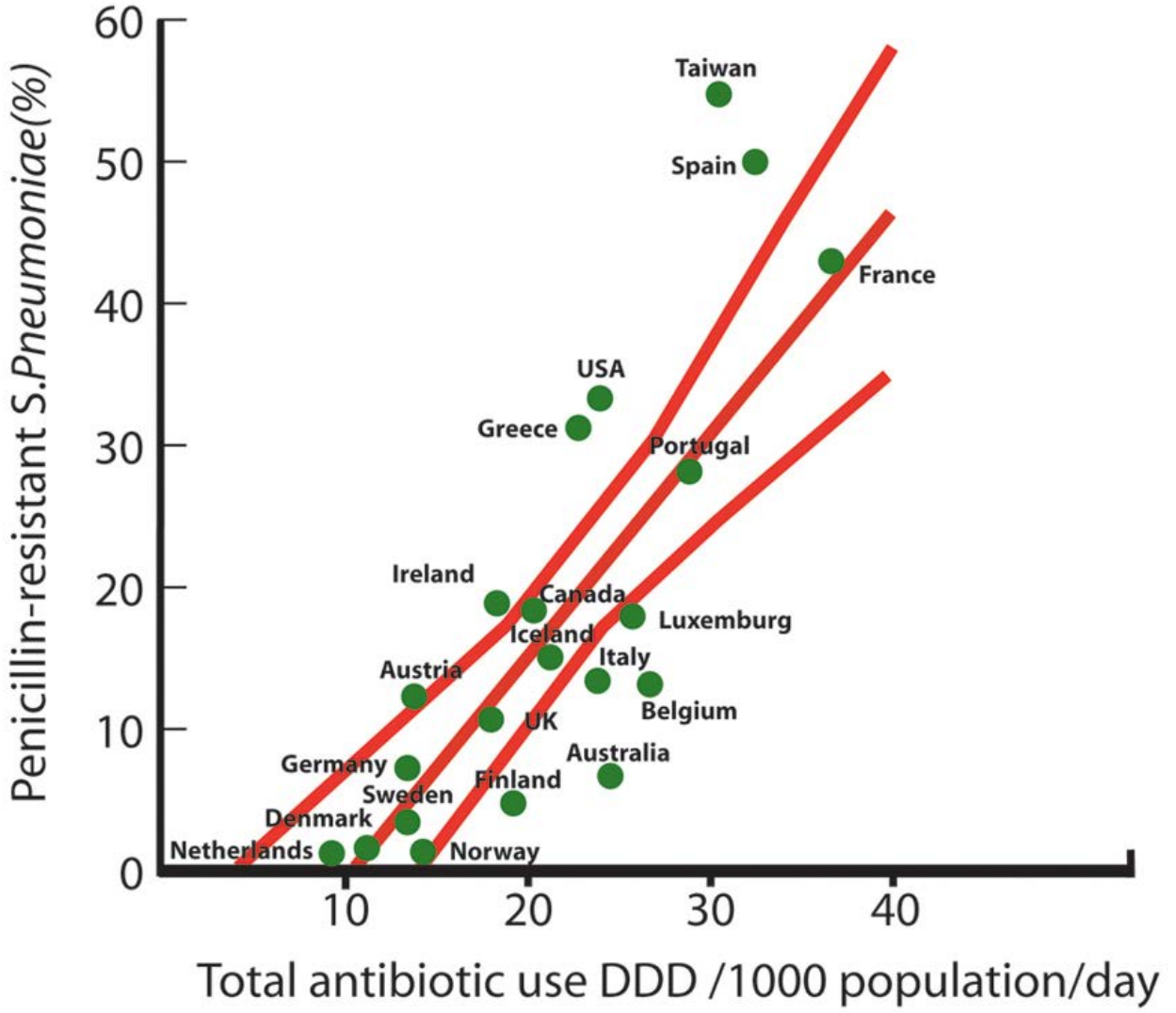
http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html Accessed 4/22/2015.

Steady Increase in CRE Incidence - US Hospital Reports to CDC



Satlin et al, 2014

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



By courtesy of Dr. Liselotte Diaz Högberg

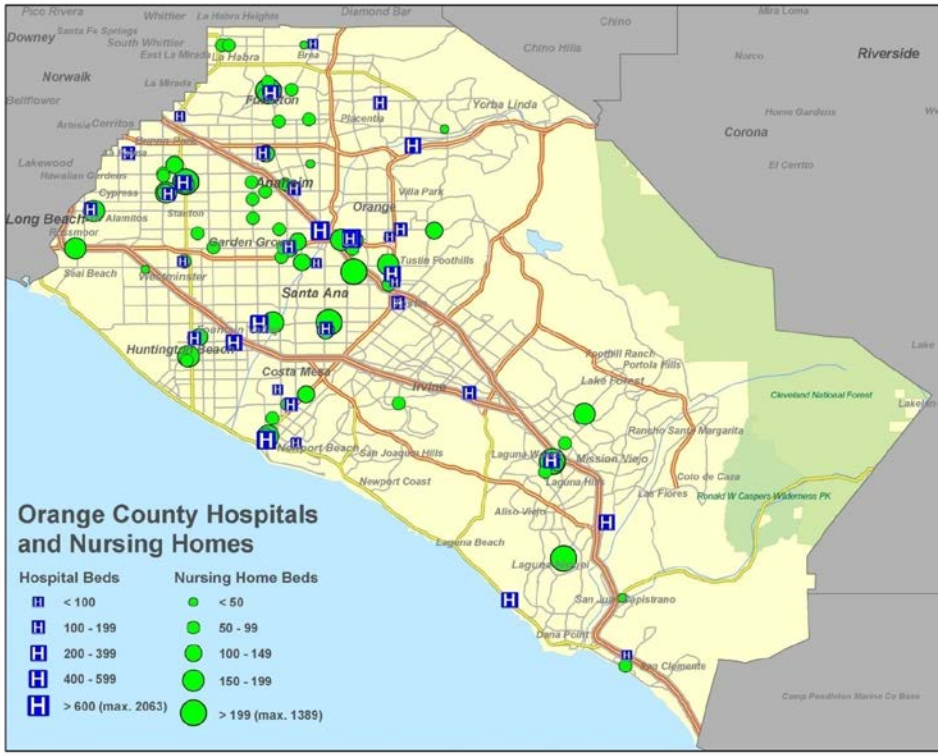
“How are CRE and Other MDROs spreading so effectively?”

The Pig Pen Principle

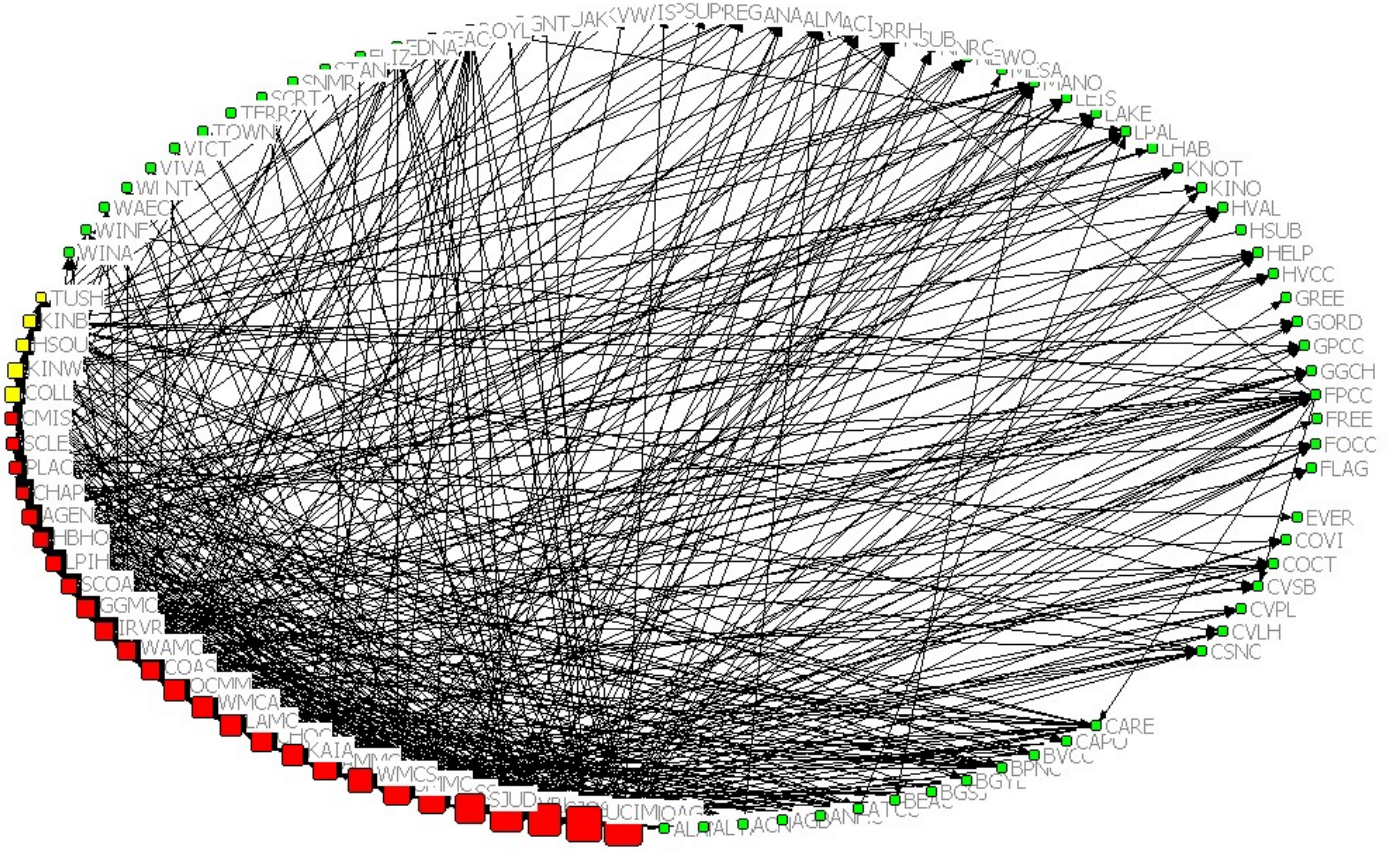
The Pig Pen Principle

Orange County, California
Ideal Virtual Laboratory

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



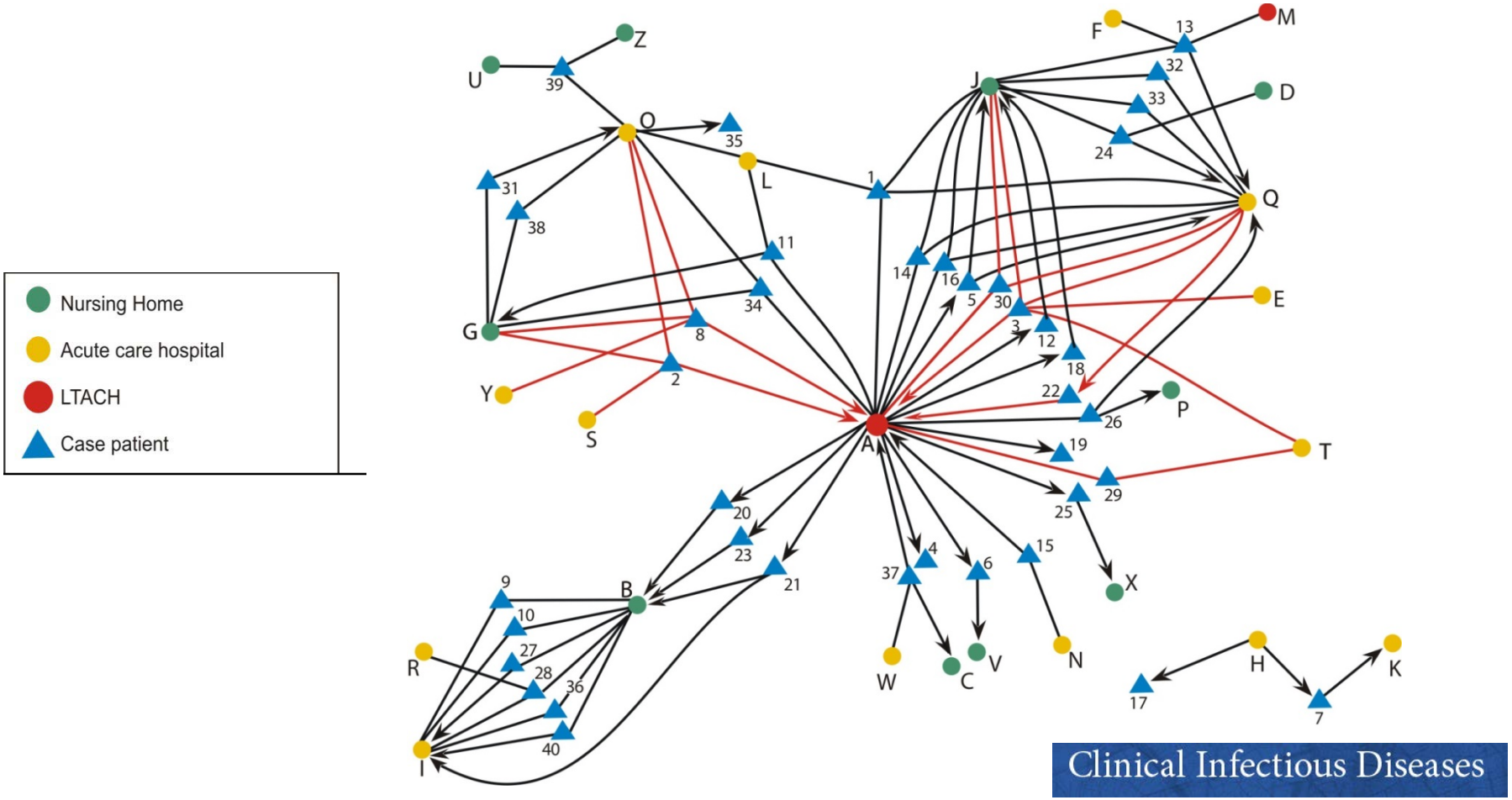
Sharing Patients – 10 Patients



Lee BY et al. Plos ONE. 2011;6(12):e29342

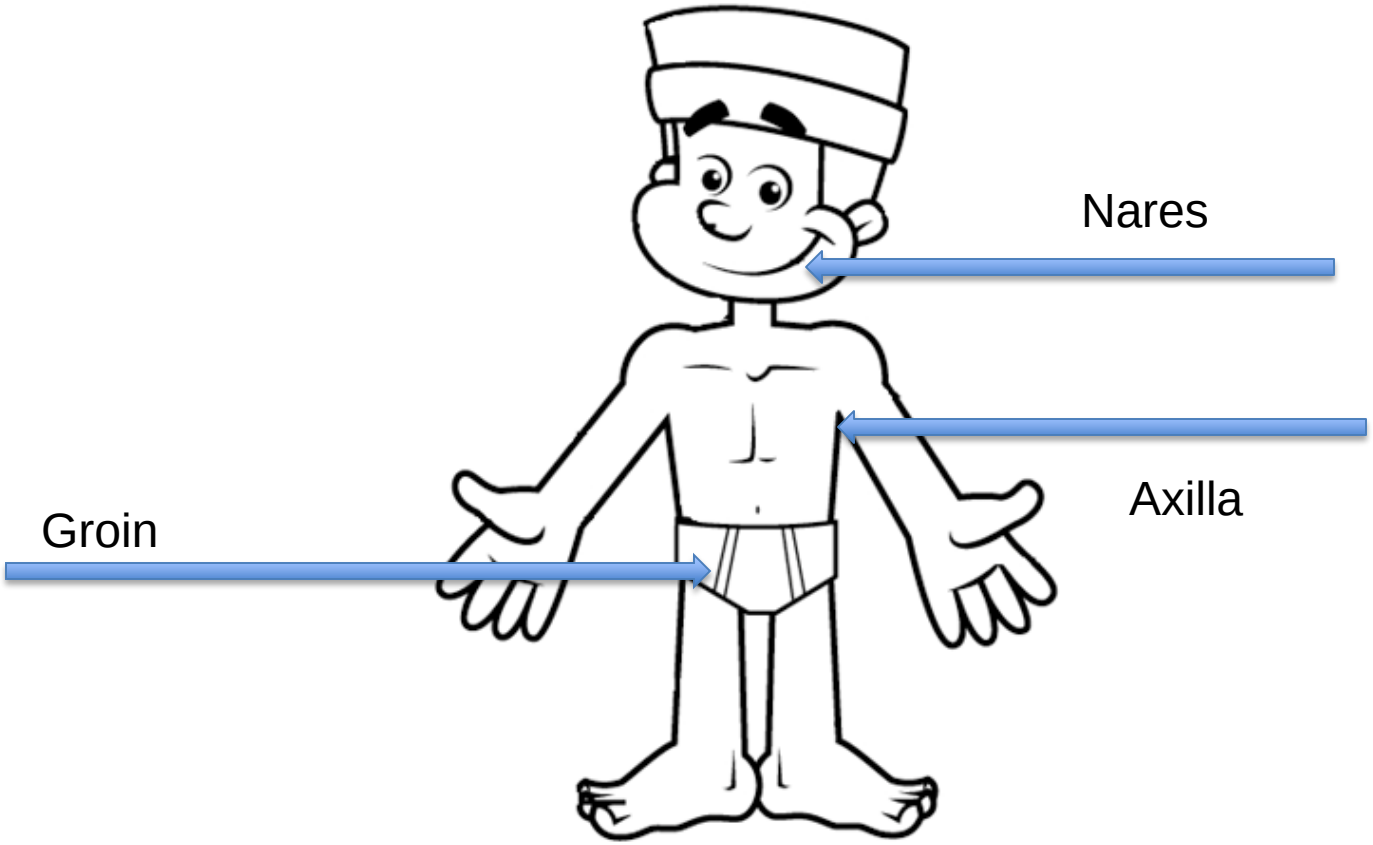
Emergence and Rapid Regional Spread of *Klebsiella pneumoniae* Carbapenemase–Producing *Enterobacteriaceae*

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. Hayden[4] for the Centers for Disease Control and Prevention Epicenter Program



Clinical Infectious Diseases

SNF Surveillance Sites for MDRO



Pilot Project

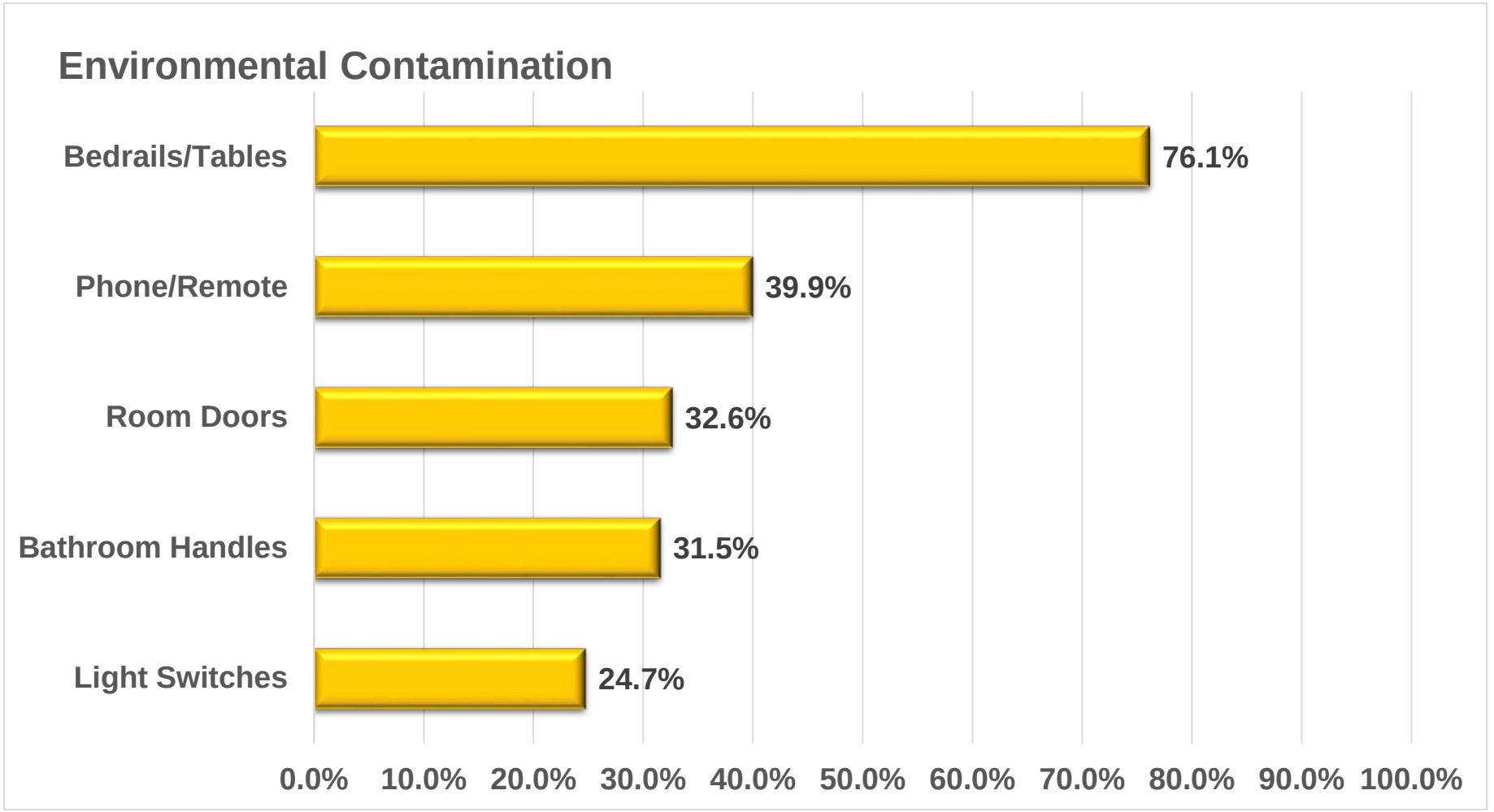
- Methicillin Resistant *Staphylococcus aureus* (MRSA)
- Vancomycin Resistant Enterococcus (VRE)
- Extended Spectrum Beta Lactamase Producers (ESBLs)
- Carbapenem Resistant Enterobacteriaceae (CRE)

45% of nursing home residents harbor an MDRO*

Data from over 40 nursing homes suggest these observations are generalizable

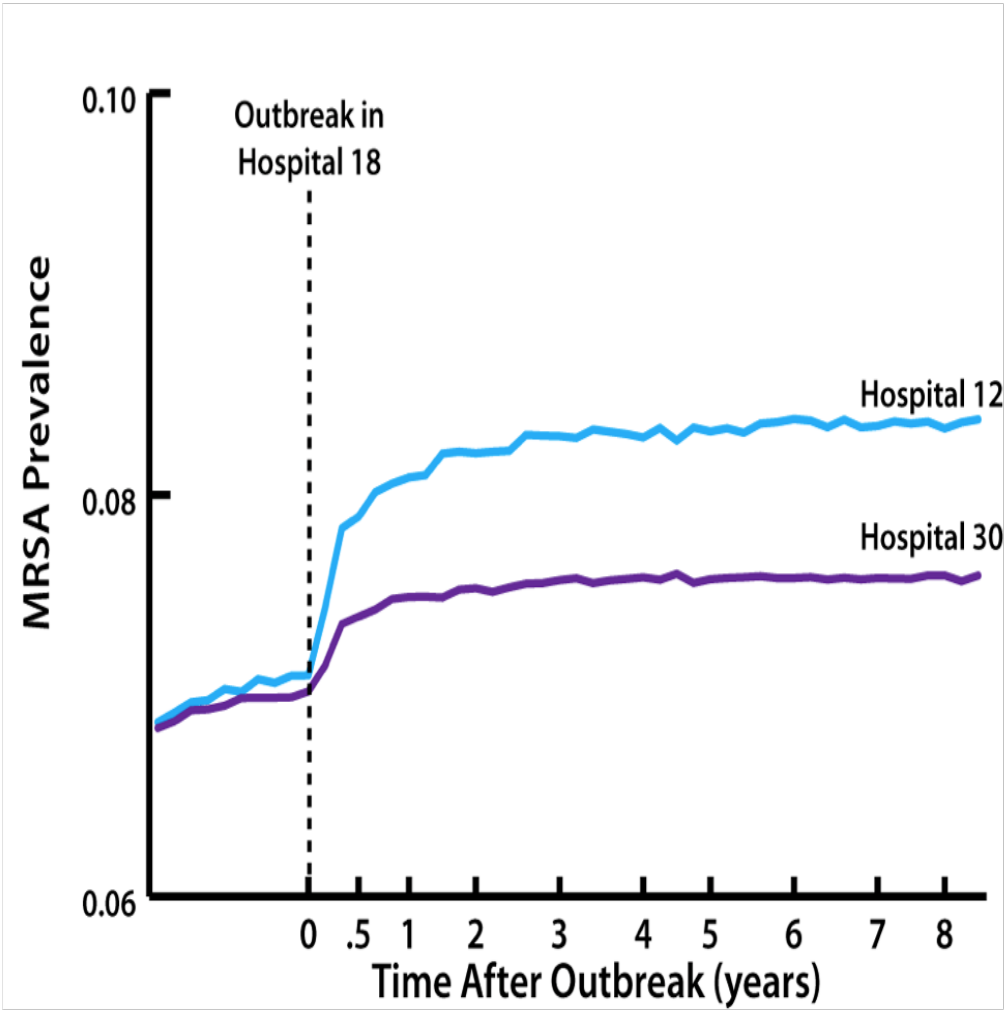
McKinnell et al, Protect Pilot, SHEA Spring 2016

SNF Patient with Known Colonization



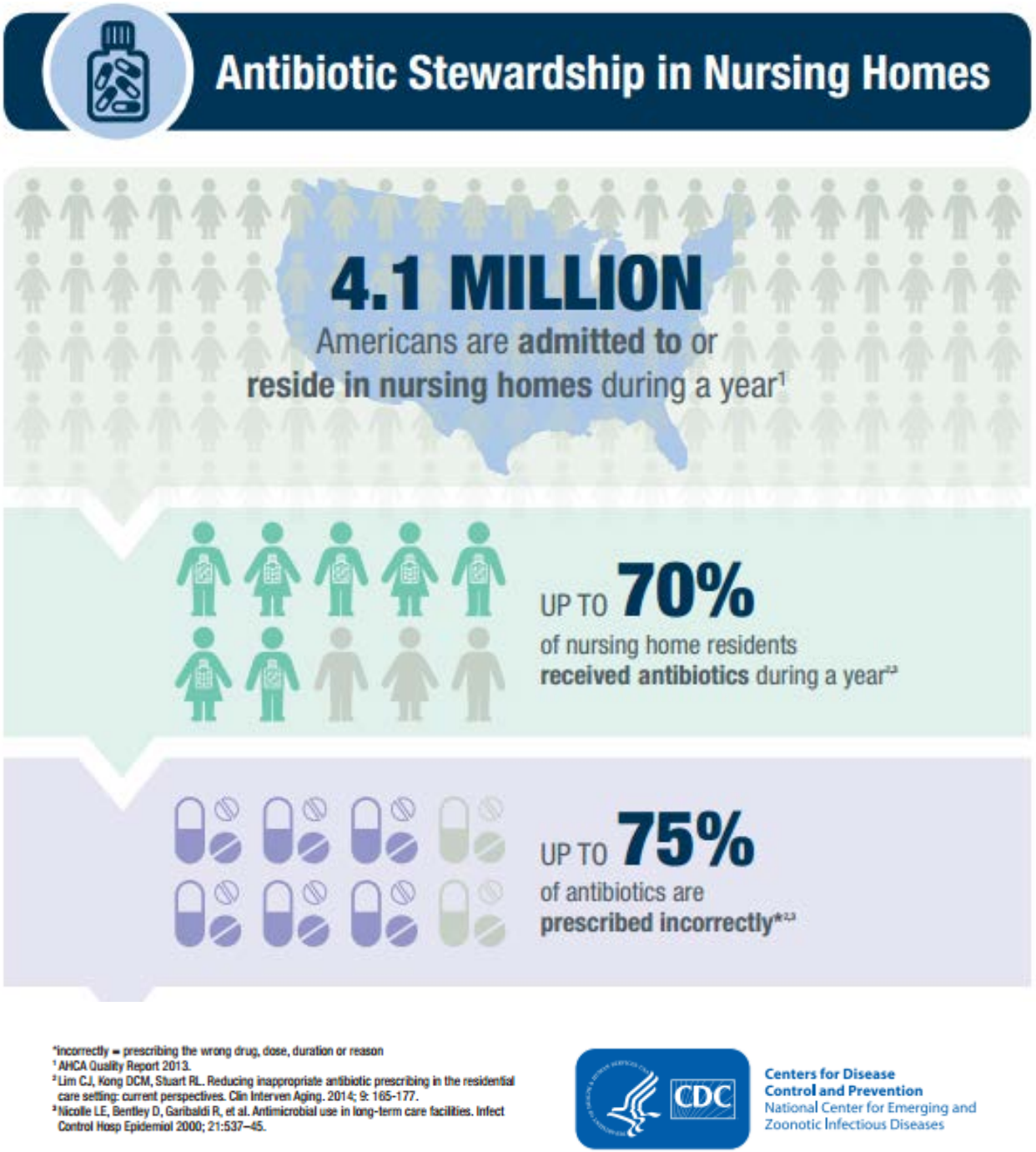
Bolaris et al, Protect Pilot, SHEA 2016 Spring Meeting.

Sustained Single Hospital Outbreak



Regulatory Pressure

- California State
- Centers for Medicare and Medicaid Services



LTC Antibiotic cost estimates:

$38-$137 million per year in US

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.

Regulatory Requirements

- “By the end of 2017, CMS and CA require long-term care and nursing home facilities to develop and implement robust ASPs that adhere to best practices”

“National Action Plan for Combating Antibiotic Resistance”

March 2015

Basic ASP Tier Elements for SNFs: Less Challenging Components

1. Antimicrobial stewardship (AS) policy/procedure
2. Written statement in support of ASP with evidence for necessary budget/staffing
3. AS activities reported to facility's Quality Assurance-Performance Improvement (QAPI) program.
4. Establish physician-supervised, multidisciplinary antimicrobial stewardship committee

DEADLINE: January 1, 2017

Basic ASP Tier Elements for SNF: More Challenging Components

5. Program support from a physician or pharmacist with specific training on antimicrobial stewardship
6. AS education provided to nursing staff, medical staff, residents, and visitors

DEADLINE: January 1, 2017

New COP Requirements

Steps to Stewardship

1) Get Leadership Support
2) Form a Multi-Disciplinary Team with Expertise
3) Define the Stewardship Opportunities for Improvement(Tracking)
4) Develop an Action Plan and Educate(Action and Educate)
5) Report on Results (Reporting)

- Repeat Steps 3-5

CMS COP

- We would **require that the Governing Body** ensure that systems are in place and operational for infection surveillance, prevention, and control, and antibiotic use activities, in order to demonstrate the implementation, success, and sustainability of such activities

CMS COP – ASP Leader

1) Development and Implementation of hospital-wide antibiotic stewardship program

2) All Documentation, written or electronic, of antibiotic stewardship program activities

3) Communication and collaboration with medical staff, nursing, and pharmacy leadership

4) Communication and collaboration with hospital IP and QAPI

5) Competency-based training and education of hospital personnel and staff, including medical staff, and contracted services in the hospital

Key Components For Success

- Regulatory Compliance
- Analysis of Antibiotic Utilization
- Education
  - MD
  - Nursing Staff
  - Residents and Families
- Improved Quality and Care for Patient

“One Third of What You Learned in Medical School is Wrong…

The Trick is Determining Which Third.”

Dr. Mc Kinnells' Duration Notes

Disease State	Duration (days)
Community Associated Pneumonia	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

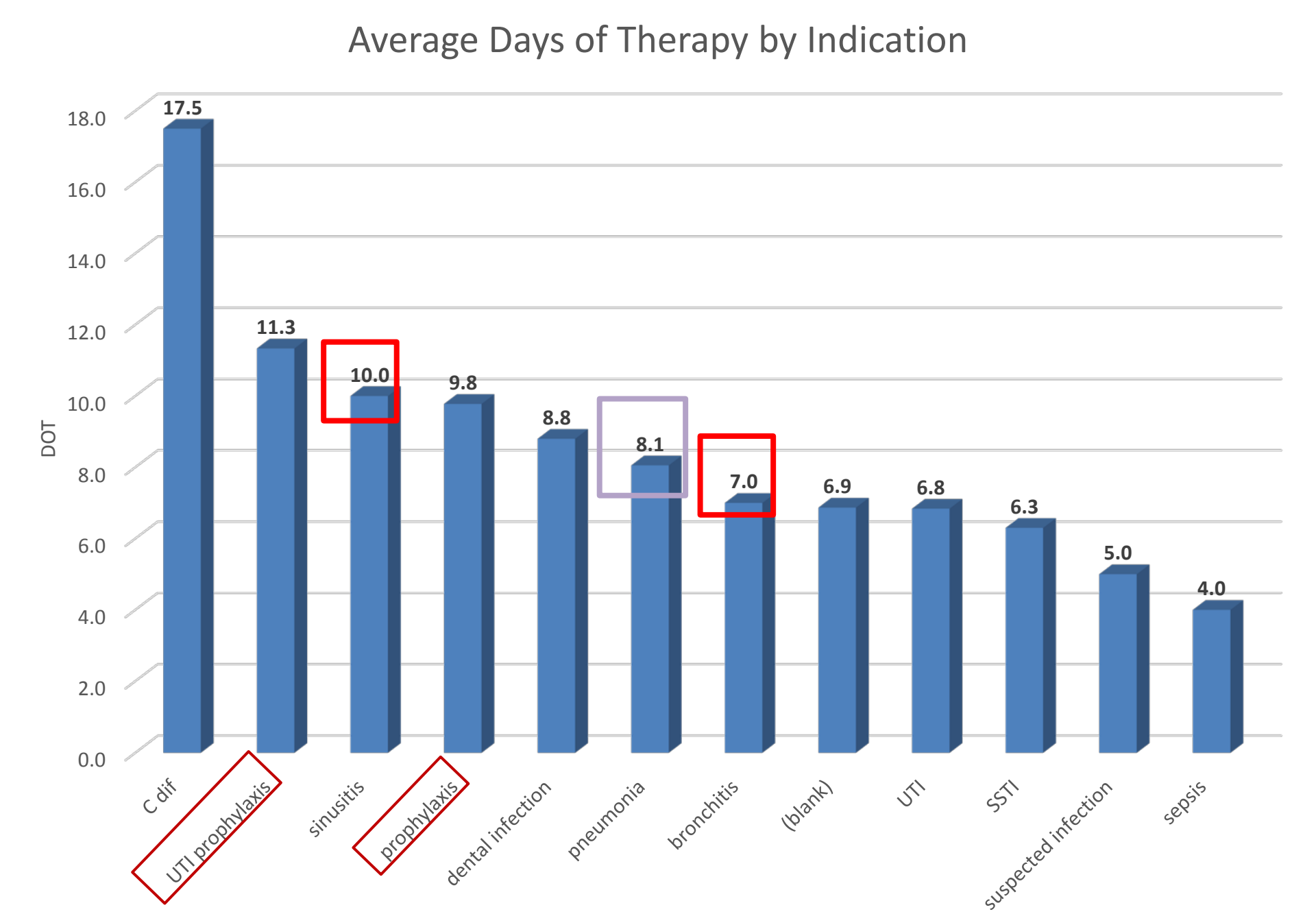
PYELONEPHRITIS
5-7 DAYS

- **Several RCTs 5-7 days equal to 10-14 days**
- **Short course effective despite diabetes and GNB bacteremia**

Jernelius et al. Acta Med Scand 1988;223:469-77; de Gier R, Karperien A, Bouter K, et al. 1995. Int J Antimicrob Agents 6:27-30; Talan DA, Stamm WE, Hooton TM, et al. 2000 JAMA 283:1583-90; Sandberg et al. 2012 Lancet 380:484-90; Peterson et al. 2008 Urology 71:17-22; Klausner et al. 2007. Current medical research and opinion 23:2637-45.

No Benefit, More Resistance!!!

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



Some prophylaxis orders did not specify for what indication

Antimicrobials Predisposing to CDI

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

- 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*

2016 Antibiogram

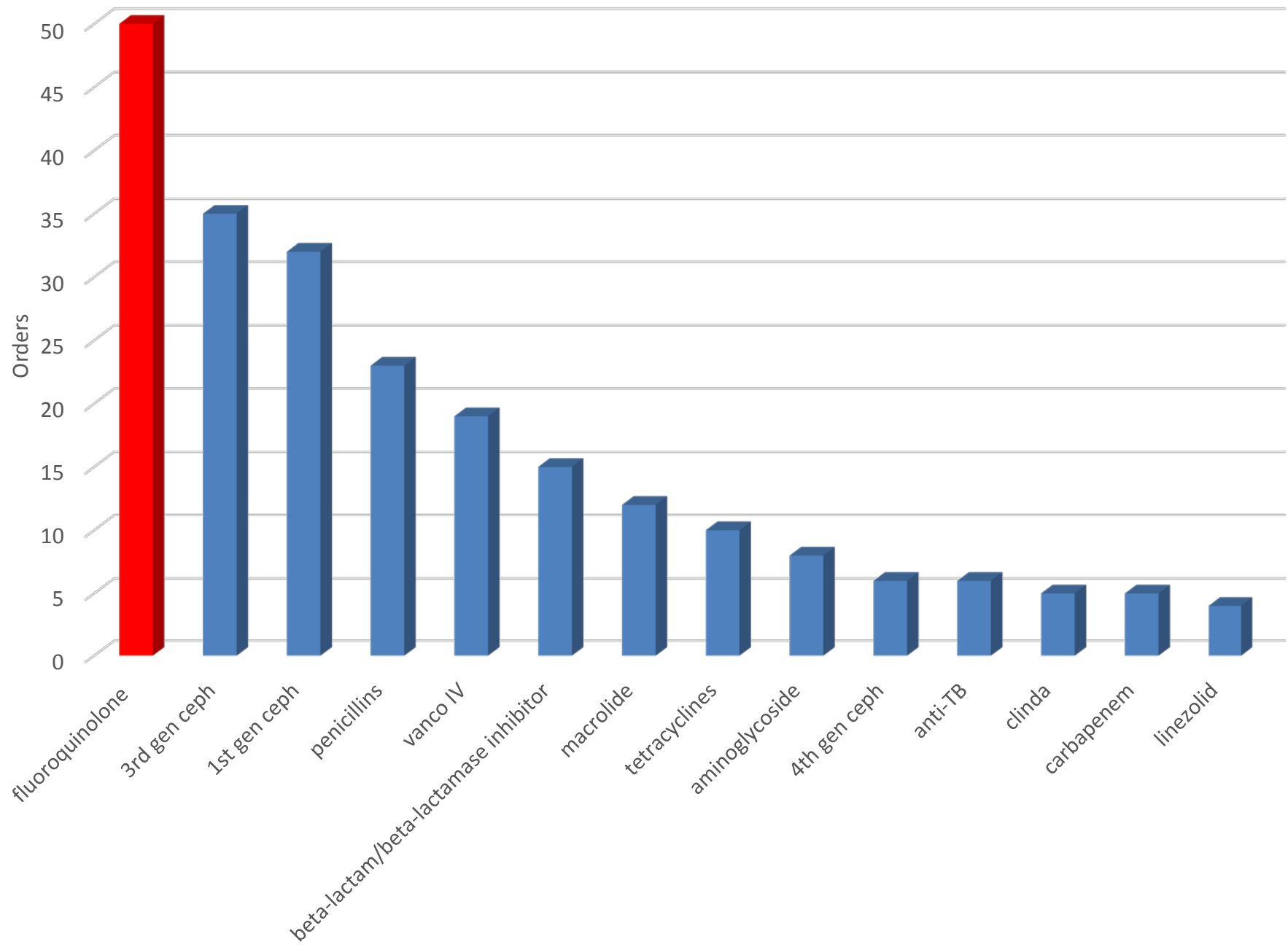
	Ent. faecalis	Ent. faecalis	Kleb pneu	Kleb pneu	E. coli	E. coli	Staph. aureus	Pseu. aeruginosa	Prot. Mir.	Mor morganii
# OF SPECIMENS	4	2	9	1	31	12	5	5	18	1
ESBL,MRSA,VRE,MDRO		VRE+		ESBL		ESBL+	MRSA+			
AMIKACIN			100	100	100	100		100	100	100
AMPICILLIN	100	50	0	0	32	0		0	50	0
CEFTAZIDINE			100	0	94	0		40	83	0
CEFTRIAXONE			100	0	97	0		0	83	0
CIPROFLOXACIN	50	0	67	100	35	8	0	0	17	0
GENTAMICIN			89	100	81	75	60	20	50	0
IMPINEM			100	100	100	92		100		
LEVOFLOXACIN	50	0	78	100	35	8	0	0	44	0
NITROFURANTOIN	100	100	56	0	90	83	100	0	6	0
PIP/TAZO			100	100	97	92		80	83	100
TRIMETH/SULFA			78	100	48	25	80	0	44	0
CEFAZOLIN			78	0	77	0		0	67	0
CEFTOXITIN			78	100	81	33		0	67	0
CEFEPIME			100	0	94	0		80	78	100
ERTAPENEM			100	100	100	100			100	100
TIGECYCLINE	75	100	78	100	100	100	100	0	11	0
CLINDAMYCIN							60			

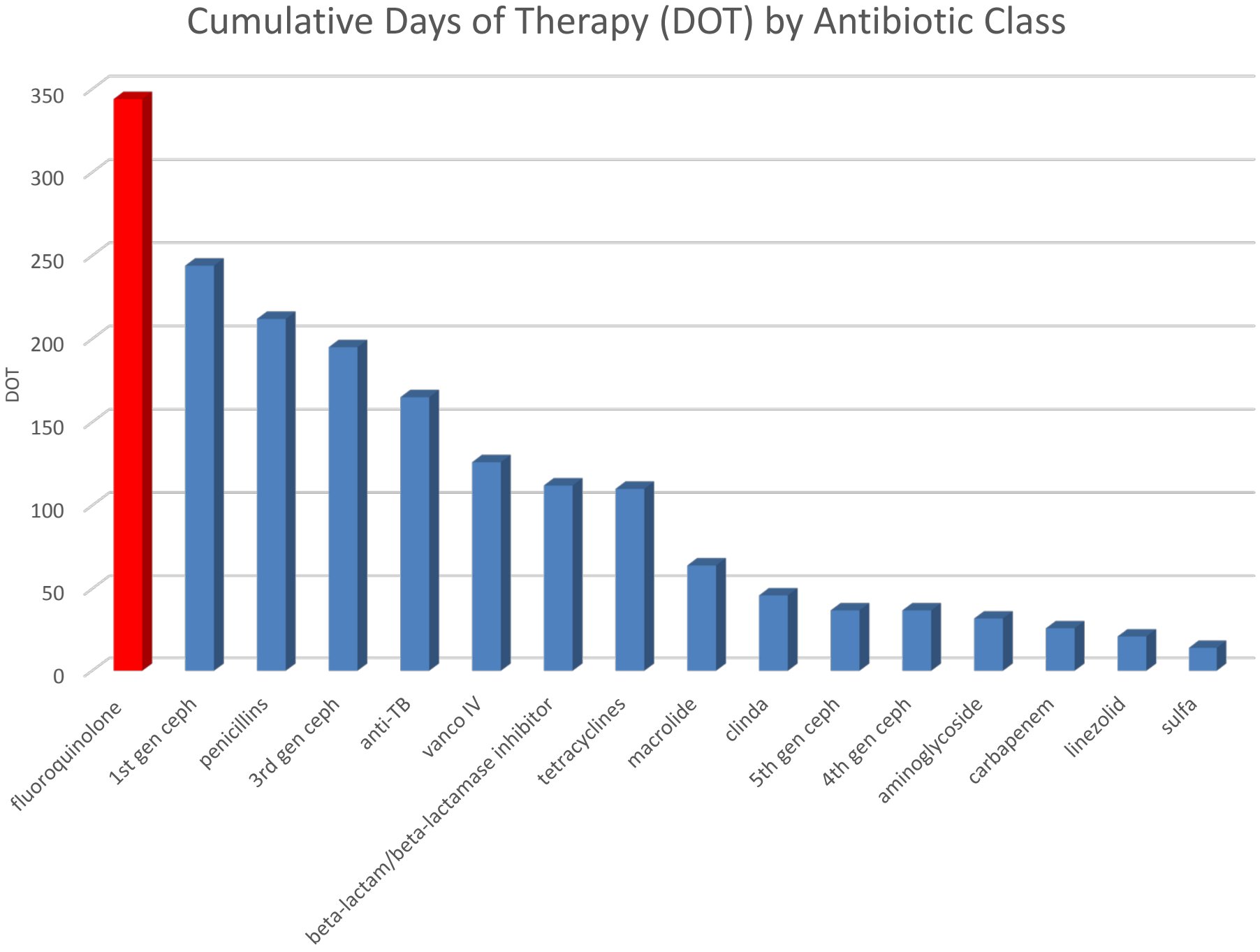
FDA Black Box Warning

The FDA first added a Boxed Warning to fluoroquinolones in July 2008 for the increased risk of tendinitis and tendon rupture. In February 2011, the risk of worsening symptoms for those with myasthenia gravis was added to the Boxed Warning. In August 2013, the agency required updates to the labels to describe the potential for irreversible peripheral neuropathy (serious nerve damage).

In November 2015, an FDA Advisory Committee discussed the risks and benefits of fluoroquinolones for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections based on new safety information. The new information focused on two or more side effects occurring at the same time and causing the potential for irreversible impairment. The advisory committee concluded that the serious risks associated with the use of fluoroquinolones for these types of uncomplicated infections generally outweighed the benefits for patients with other treatment options.

Today's action also follows a May 12, 2016, drug safety communication advising that fluoroquinolones should be reserved for these conditions only when there are no other options available due to potentially permanent, disabling side effects occurring together. The drug safety communication also announced the required labeling updates to reflect this new safety information.


Number of Unique Antibiotic Orders by Class
Orders
50
45
40
35
30
25
20
15
10
5
0
fluoroquinolone
3rd gen ceph
1st gen ceph
penicillins
vanco IV
beta-lactam/beta-lactamase inhibitor
macrolide
tetracyclines
aminoglycoside
4th gen ceph
anti-TB
clinda
carbapenem
linezolid


Cumulative Days of Therapy (DOT) by Antibiotic Class
DOT
350
300
250
200
150
100
50
0
fluoroquinolone
1st gen ceph
penicillins
3rd gen ceph
anti-TB
vanco IV
beta-lactam/beta-lactamase inhibitor
tetracyclines
macrolide
clinda
5th gen ceph
4th gen ceph
aminoglycoside
carbapenem
linezolid
sulfa

Prescribing Patterns of the Highest Antibiotic Prescribers

Prescriber	Antibiotic Orders (n)	Ave DOT	FQ Orders	non-FQ Orders	FQ ave DOT
Doctor	48	7.6	12.5%	87.5%	6.7
Doctor	21	7	33.3%	66.7%	6.6
Doctor	21	6.3	9.5%	90.5%	8.5
Doctor	20	6.2	40.0%	60.0%	7.3
Doctor	20	6.3	35.0%	65.0%	4.6
Doctor	15	8.4	20.0%	80.0%	10.3

Duration of Antibiotic

Antibiotic use drives antibiotic resistance and *Clostridium difficile*:

- Antibiotics that last more than 7 days increased risk of CDI more than 3-fold[1].
- Three or more antibiotics increased risk of CDI more than 3-fold[1].
- Fluoroquinolones increased risk of CDI by 4-fold[1].

Pneumonia	**5-7 Days**
Cellulitis	**5 Days**
Simple Cystitis	**3-5 Days**
Pyelonephritis	**7 Days**
Foley UTI	**5-10 Days**
C. diff	**14 Days**
Bacteremia	**ID Consult**

These duration recommendations are guidelines only and do not replace clinical evaluation, judgement, and monitoring.

[1] Stevens et al, CID, 2011. Cumulative Antibiotics and Risk of CDI

Updated June 25, 2017

IV to PO Switches

Patients who can tolerate an oral diet should be switched to oral antibiotic therapy when clinically indicated. Possible IV to Oral Antibiotic switches:

Vancomycin IV → Bactrim or Doxycycline PO
Bactrim and Doxycycline still retain near 100% sensitivity against MRSA and MSSA. Clindamycin is not recommended.

Fluoroquinolone IV → Fluoroquinolone PO
Excellent oral bio-availability and therapeutic equivalency; Fluoroquinolones should never be used as first-line agents if possible.

Ceftriaxone [UTI] → Keflex
Cephalosporins retain excellent activity on our antibiogram.

Ceftriaxone [PNEUMONIA] → Azithromycin +/- Augmentin
As per the pneumonia recommendation.

IV to IV Switches

Brand Name to Generic
Unasyn IV → Ampicillin/sulbactam IV
Generic to Generic
Oxacillin IV → Cefazolin IV

EXPERT STEWARDSHIP

320 SUPERIOR AVENUE | SUITE 290
NEWPORT BEACH, CA | 92633
PHONE | (800) 480-3910

Blue Book

"The purpose of the antimicrobial stewardship program is to provide guidance on the appropriate selection, dosing, route, and duration of antimicrobial usage."

-Infectious Disease Society of America (IDSA)

These Antimicrobial Stewardship Guidelines do NOT replace good clinical judgment.

Based upon 2016 Antibiogram Results and Clinical Practice Patterns in 2016

Antibiotic Stewardship

- Improved Quality and Care for Patient

IDSA FEATURES

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

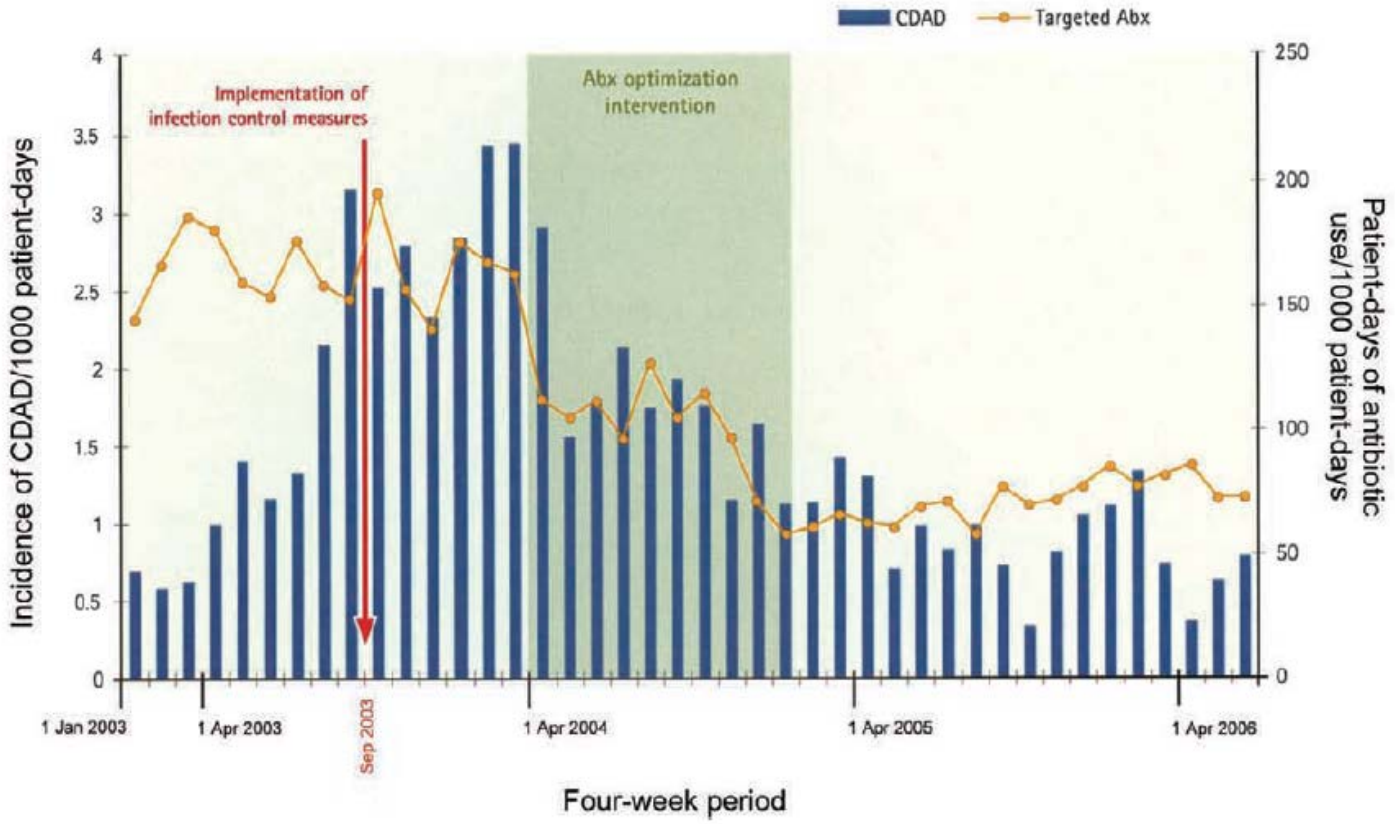
Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

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. Trivedi[22]

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



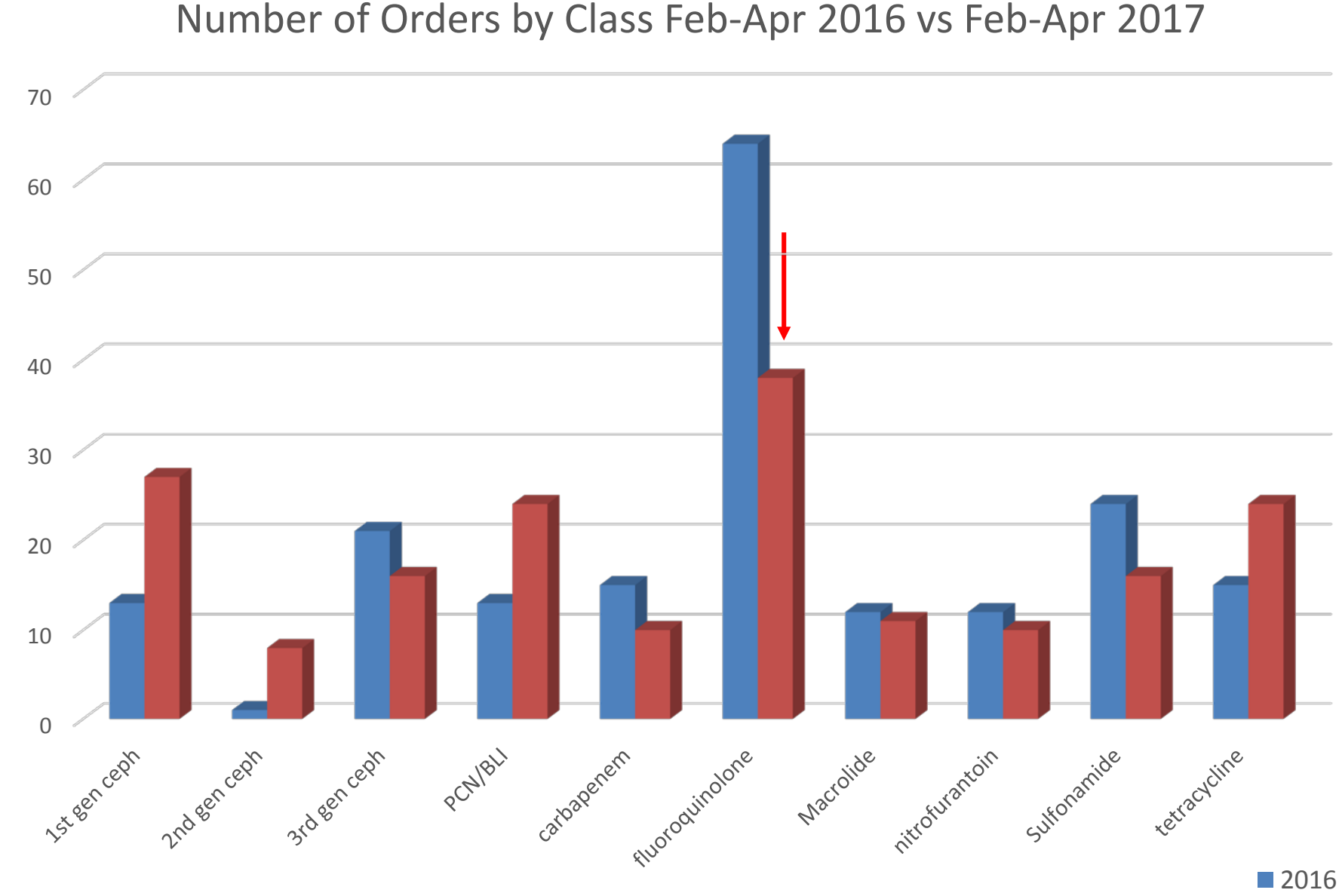
Valiquette, et al.
Clin Infect Dis. 2007;45:S112-21

Antimicrobial Stewardship Across Transitions of Care

- Ensure communication of **antibiotic indication and anticipated duration** when patients/residents transfer between facilities

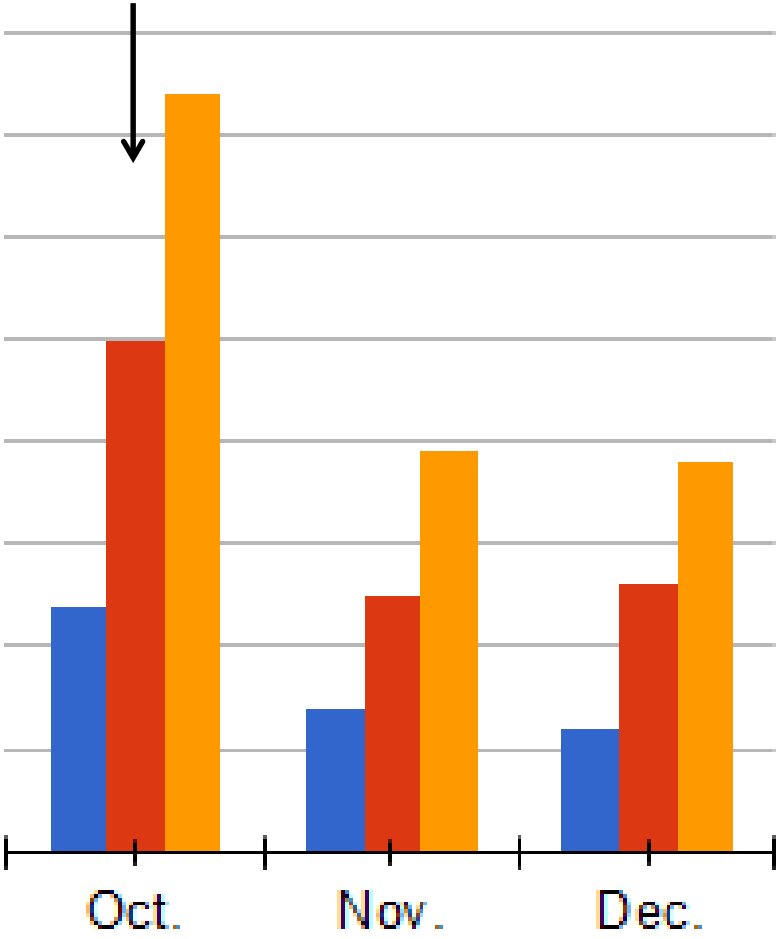
- Ensure communication and documentation of **patient/resident symptoms** upon transfer
  - Ensure appropriate diagnostic testing and infection control measures implemented promptly
  - Avoid unnecessary or inappropriate diagnostic testing

- Establish **consistency of practice and messaging** about antimicrobial use across diverse care settings



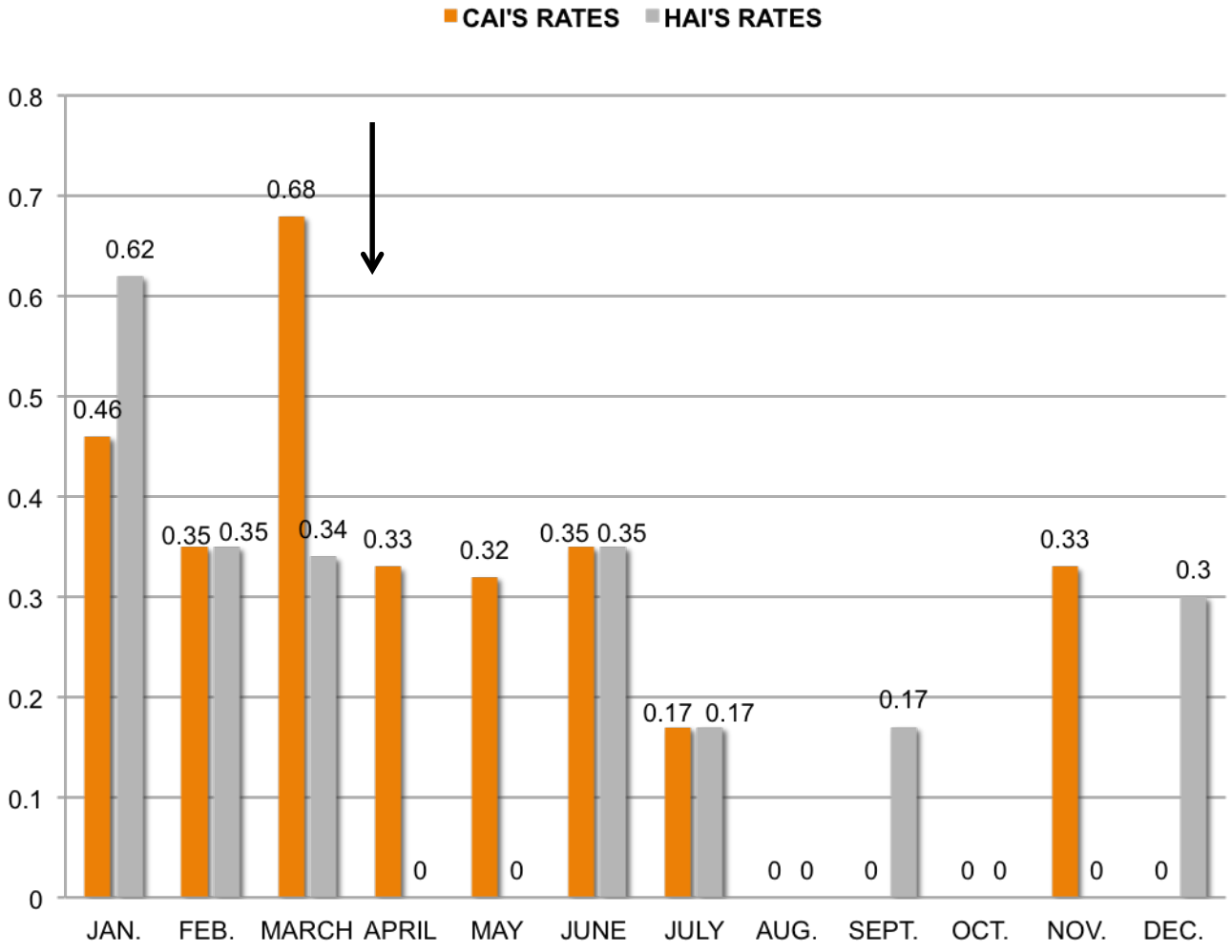
Total number antibiotic orders did not change in Feb-Apr 2016 vs Feb-Apr 2017, 151 and 155 orders, respectively. However there was an overall drop in FQ orders in 2017 period.

Guideline and Education Interventions



Guidelines and Education are facility specific and should not be applied to your facility

C-DIFF RATES 2016

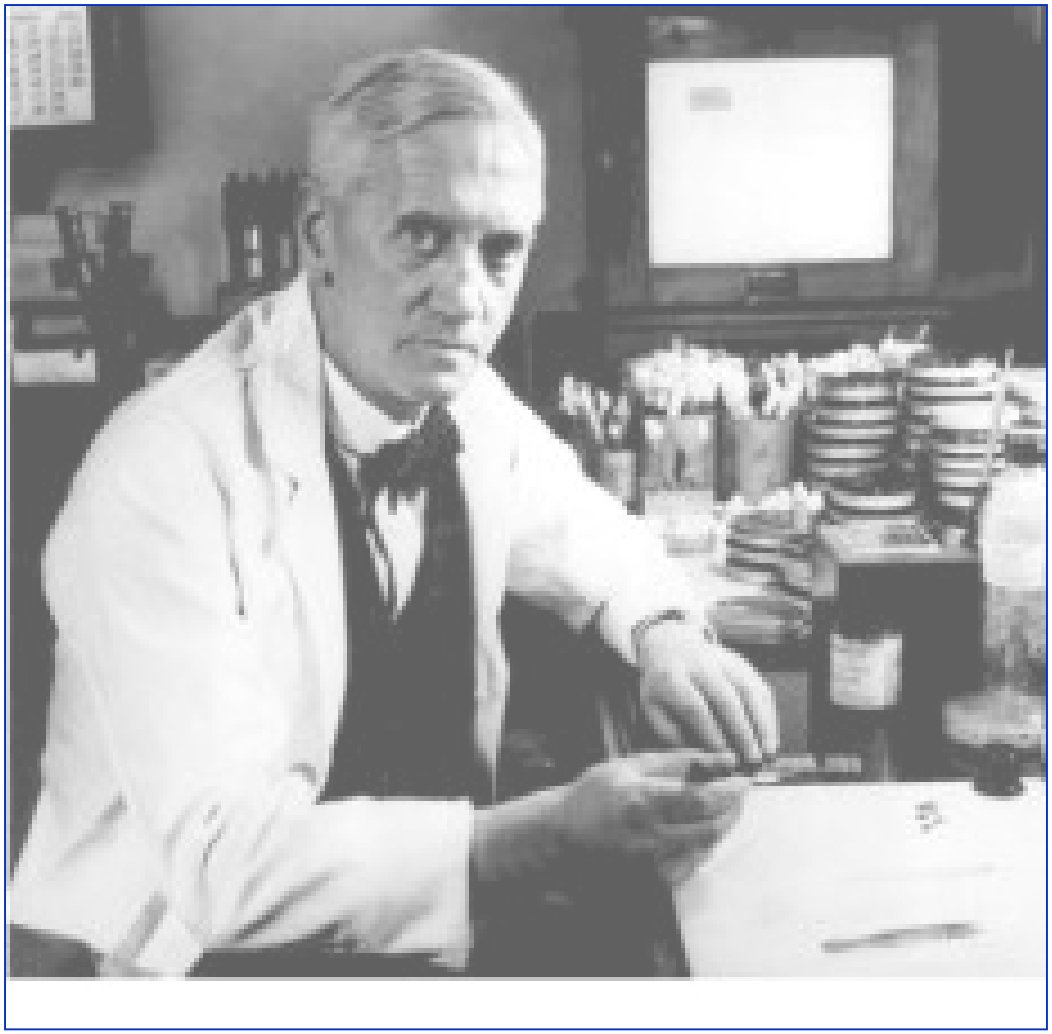


Value of Antibiotics

Disease	Pre-Antibiotic Death Rate	Death With Antibiotics	Change in Death
Community Pneumonia[1]	~35%	~10%	**-25%**
Hospital Pneumonia[2]	~60%	~30%	**-30%**
Heart Infection[3]	~100%	~25%	**-75%**
Brain Infection[4]	>80%	<20%	**-60%**
Skin Infection[5]	11%	<0.5%	**-10%**
By comparison…treatment of myocardial infarction with aspirin or fibrinolytic drugs[6]			***-3%***

[1]IDSA Position Paper '08 Clin Infect Dis 47(S3):S249-65; [2]IDSA/ACCP/ATS/SCCM Position Paper '10 Clin Infect Dis 51(S1):S150-70; [3]Kerr AJ. Subacute Bacterial Endocarditis. Springfield IL: Charles C. Thomas, 1955 & Lancet 1935 226:383-4; [4]Lancet '38 231:733-4 & Waring et al. '48 Am J Med 5:402-18; [5]Spellberg et al. '09 Clin Infect Dis 49:383-91 & Madsen '73 Infection 1:76-81; [6]'88 Lancet 2:349-60

…. 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

Thank you for your attention…