Antibiotics and Duration

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Appreciation

- Brad Spellberg
- Phil Robinson

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

Disclosures

One Third of What you Learned in Medical School and Residency is Wrong .... The Trick is Learning Which Third!!

Objectives

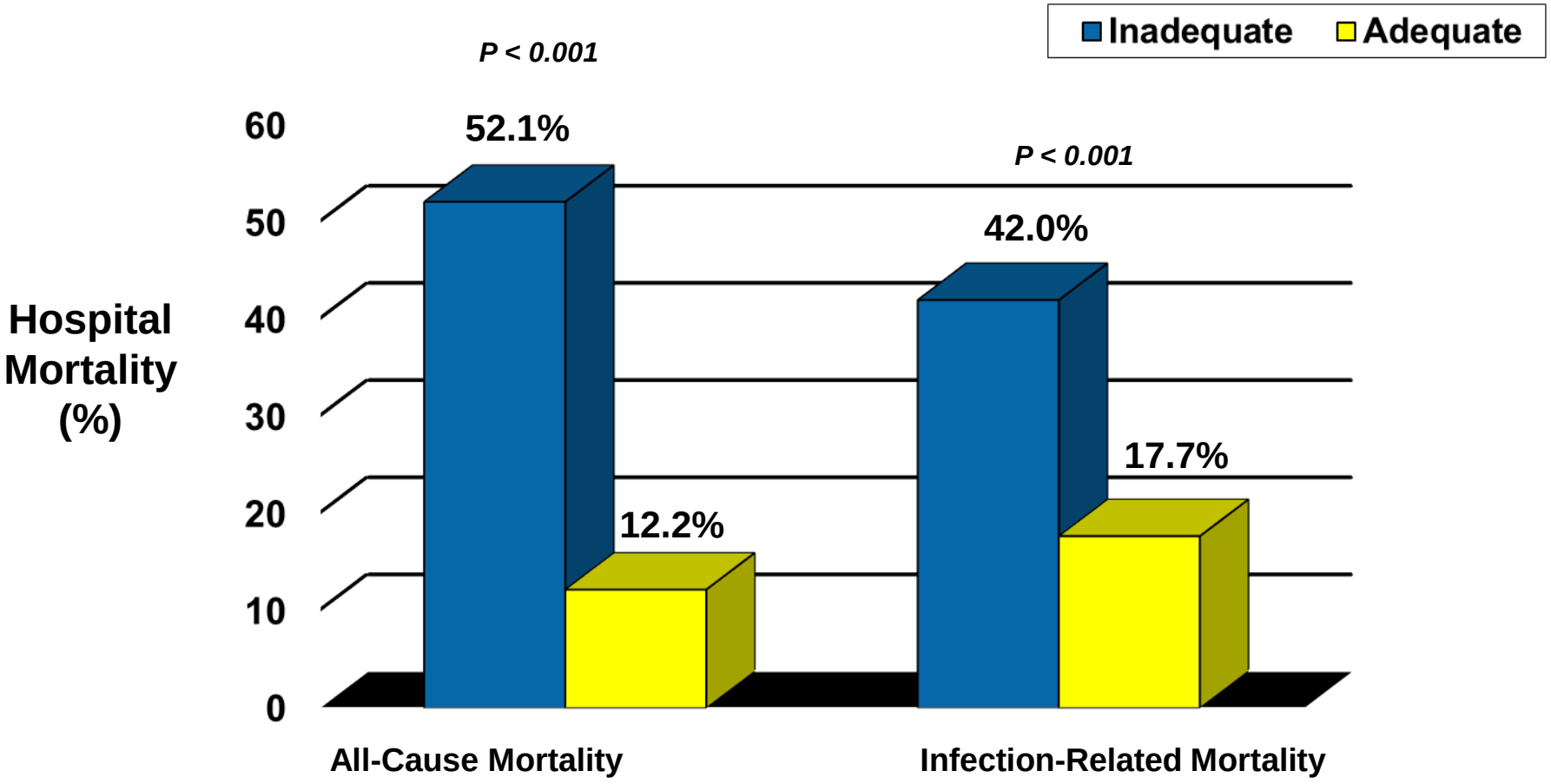
- Understand the Value of Antibiotics
- Understand Where Current Durations of Antibiotics were developed
- Review Current Indications of Antibiotic Duration

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

Inadequate antimicrobial therapy associated with higher mortality



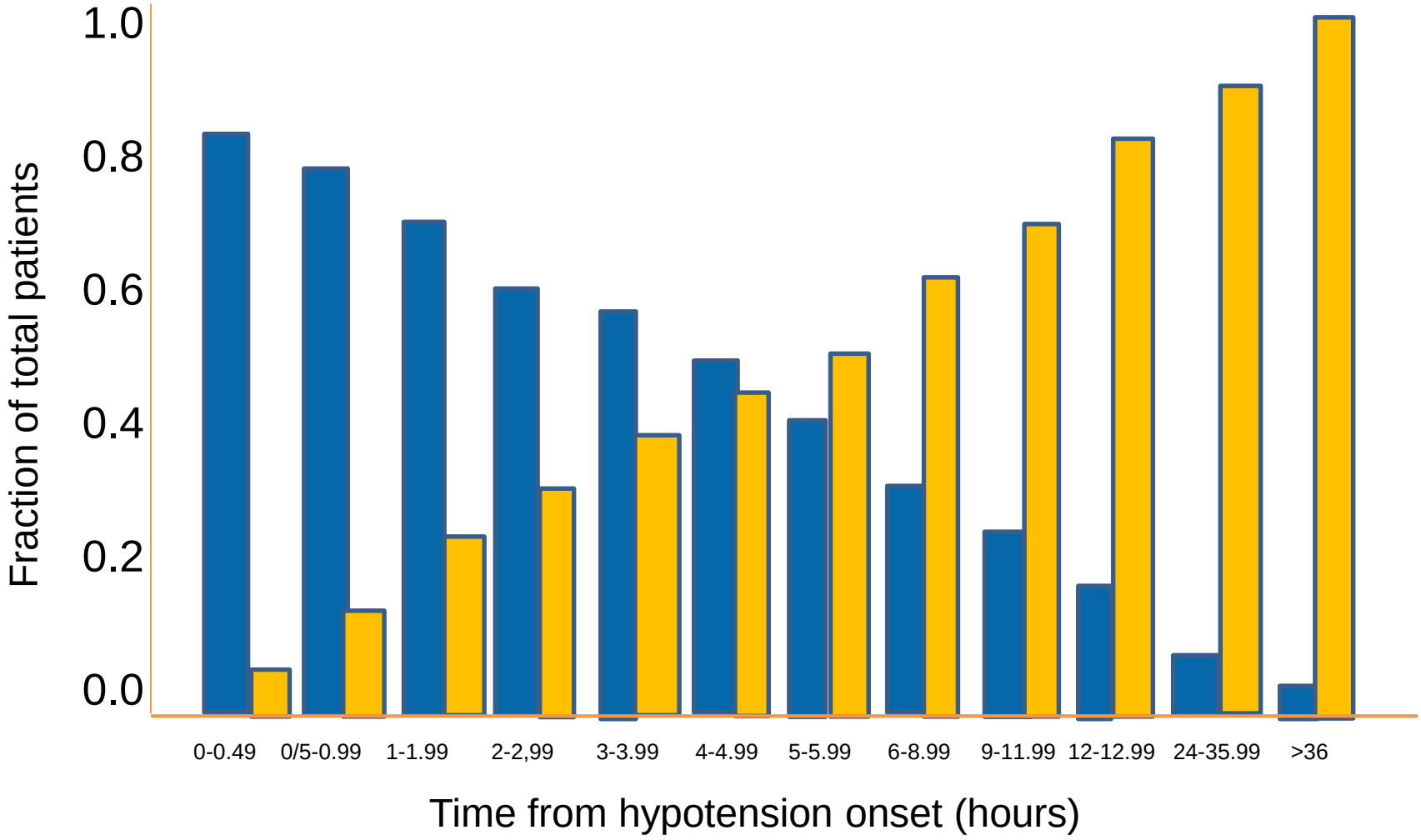
Prospective study (n=2000: 655 with infections)

25% of patients received inadequate treatment

Kollef MH., et al. *Chest.* 1999;115:462-474.

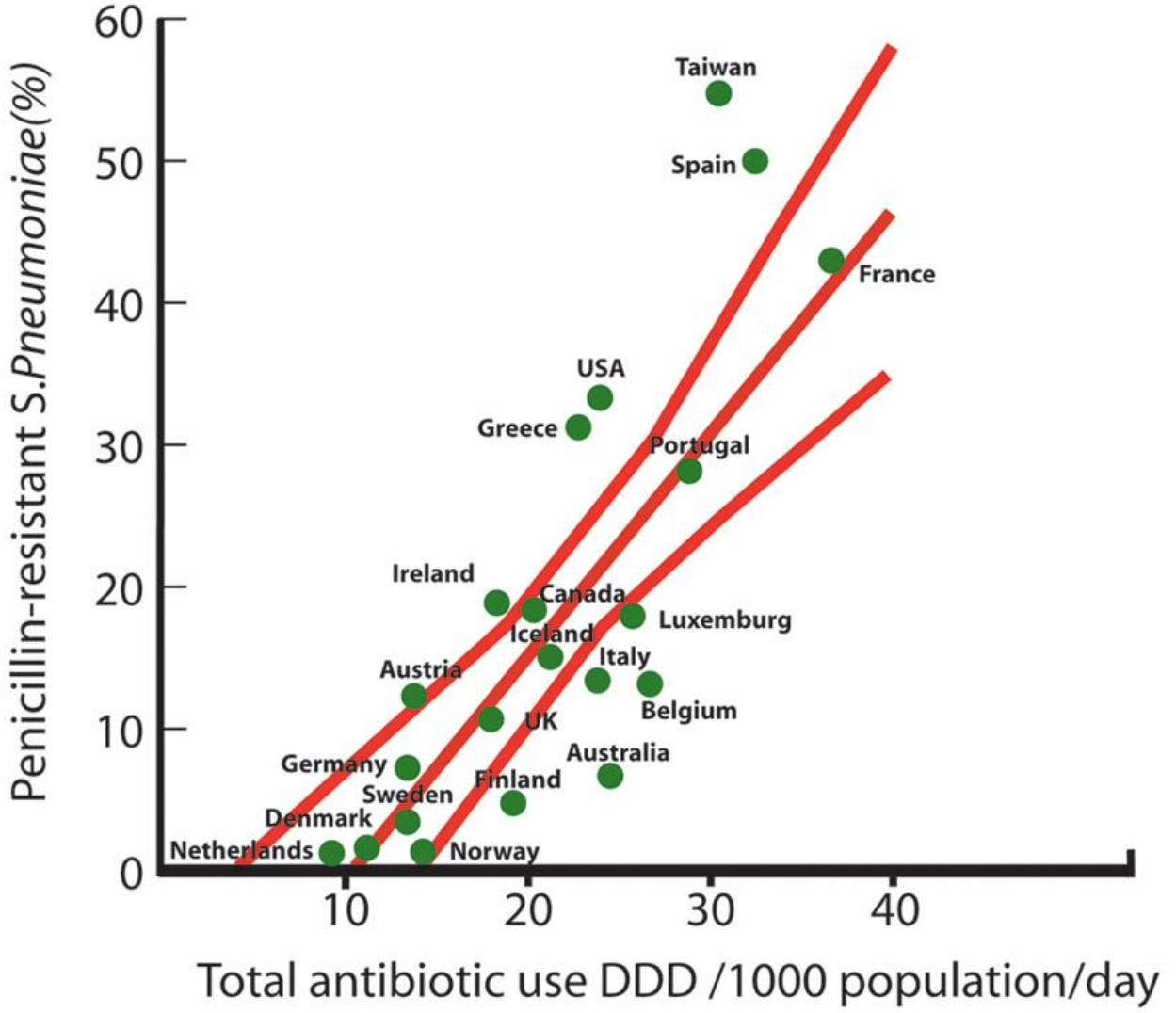
Relationship between survival and time to effective antimicrobial treatment among patients with septic shock

Retrospective multi-center study (n=2731)



Kumar A, et al. *Crit Care Med* 2006; 1589-1596 (June)

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



By courtesy of Dr. Liselotte Diaz Högberg

“Make sure you take every dose of your prescribed antibiotic, even after you feel better.”

Antibiotic Duration as Football Scores

- Community Associated Pneumonia 7-10
- HAP/VAP 10-14
- Pyelonephritis 10-14
- Cellulitis 7-10
- Bacteremia 14-42

Standard Abx durations: 1-2 Constantine units—based on 1695 year old decree

In AD 321, Roman Emperor Constantine the Great codified that there would be 7 days in a week. Even in the modern era of evidence-based-medicine, this 1695-year-old decree remains a primary reference for duration of antibiotic therapy: it leads physicians to treat infections in intervals of 7 days. Thus, it is gratifying when clinical trials challenge the standard antibiotic duration of 7 to 14 days.

The New Antibiotic Mantra—"Shorter Is Better"

Brad Spellberg, MD

JAMA Internal Medicine

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	≤5	≥7	Equal
Cellulitis	5-6	10	Equal
Osteo	42	84	Equal

Community Associated Pneumonia

3-5 Days

- **Multiple RCT showing 3-5 days NI to 7 - 10 days**
- **Includes pts with PORT IV and V**

(Uranga et al. JAMA IM)

- **Reduced emergence of resistance**

Singh et al. Am J Respir Crit Care Med 2000;162:505-11; Dunbar et al. Clin Infect Dis 2003;37:752-60; Zhao X et al. Diagn Microbiol Infect Dis 2014;80:141-7; Pakistan Multicentre Amoxycillin Short Course Therapy pneumonia study group. Lancet 2002;360:835-41; Greenberg et al. The Pediatric infectious disease journal 2014;33:136-42; Dunbar et al. Current medical research and opinion 2004;20:555-63; el Moussaoui et al. Bmj 2006;332:1355; Uranga et al. JAMA IM 2016 176:1257-65.

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.

INTRA-ABDOMINAL INFECTION **4-5 DAYS**

- **Recent Trial 4 Days Equal to 10 days**
- **Assuming Adequate Source Control**

Sawyer et al. 2015 NEJM 372:1996-2005.

AECB/COPD
3-5 DAYS

- **Dozens of Studies**
- **Meta-analysis show that 3-5 days of therapy equal to 7 or more days.**

El Moussaoui 2008 Thorax 68:415-22

CELLULITIS/ABSCESS
3-5 DAYS

- **Numerous trials show that 5-7 equal to 10-14 days**
- **Drainage of abscess is key**
- **When you drain and abscess, treat especially if surrounding cellulitis.**

Hepburn 2004 Arch Int Med 164:1669-74; Prokocimer 2013 JAMA 309:559-69; Moran 2014 Lancet ID 14:696-705.

EXCEPTIONS

- **Short Course TB trials underway**
- **Chronic infections still require prolonged therapy – e.g. prosthetic hip infections**
- **Data on Endocarditis is evolving**
- **Rheumatic fever may require 5 days of cephalosporins but 10 days of penicillin – data not clear**

Short Course Therapy!!!!

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"The most viable strategy for reducing antimicrobial selective pressure is to treat infections only for as long as is necessary."

Dr. Lou Rice, Executive Chair of Medicine, Warren Alpert School of Medicine of Brown University. 2008 Maxwell Finland Lecture at IDSA Annual Meeting

Longer Therapy Actually Hurts the Patient

- Longer therapy causes more selective pressure—off-target in microbiome and in the environment
- Even at the site of infection, studies of short vs. long-course therapy have found greater emergence of resistance with longer therapy (Chastre '03 JAMA 290:2588-9; Singh '00 Am J Resp Crit Care Med 162:505-11)

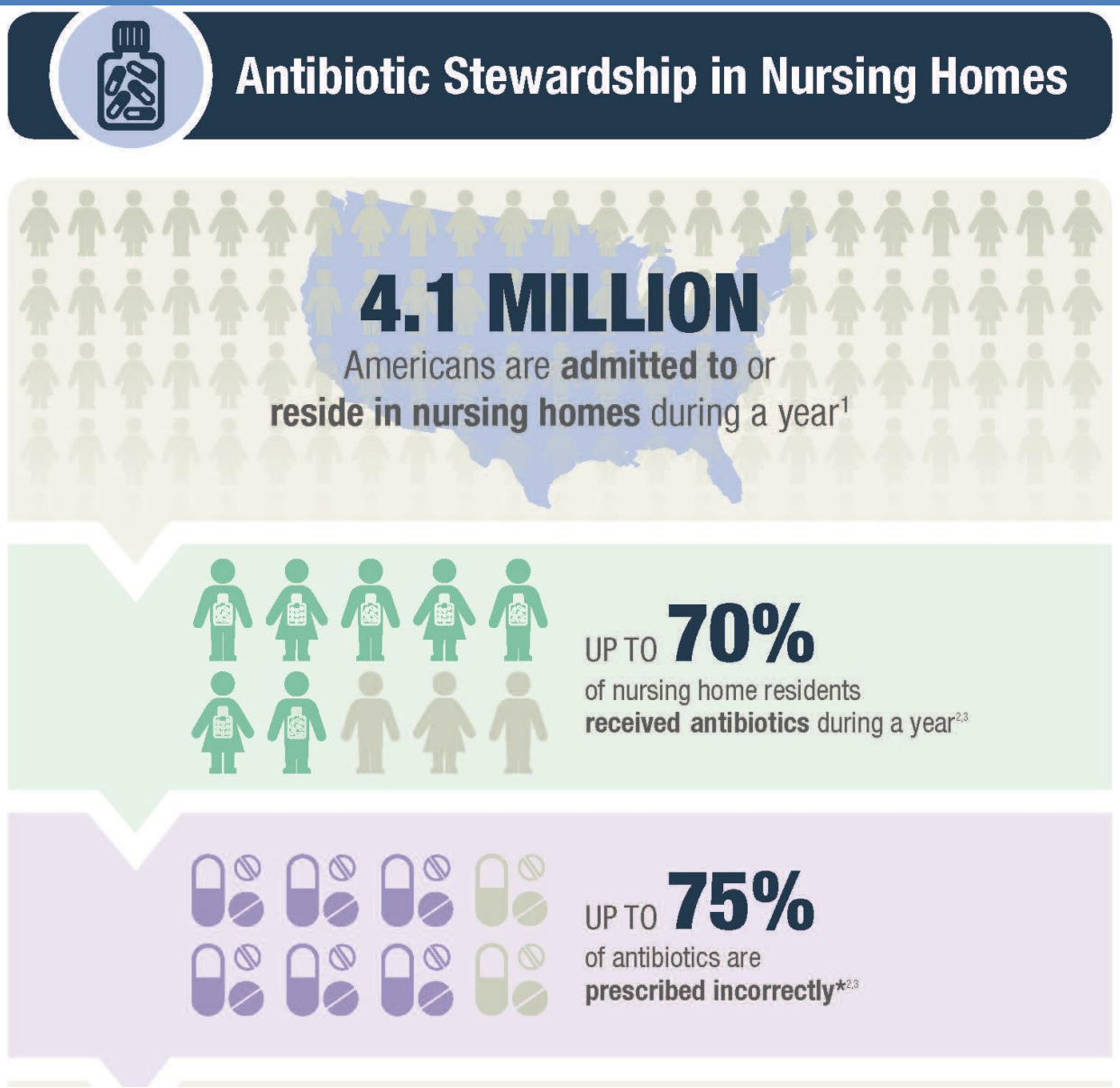
Fight the Errors of our Forebarers

- Stop telling patients to complete course of Abx even if their symptoms are gone
- Taking antibiotics after symptom resolution provides no efficacy but selects for resistant among microbiome
- If patients feel better, they should call their doctor to ask to stop early

LAC – DPH to the Rescue

Healthcare Associated Infection Antibiotic Resistance Control Task Force

Epidemiology, Infectious Disease Physicians, Infectious Disease Pharmacists, Microbiologists, Infection Prevention Specialists, and Others



CDC (http://www.cdc.gov/media/releases/2015/p0915-nursing-home-antibiotics.html)

New 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"

Basic ASP Tier Elements for SNFs: Less Challenging Components

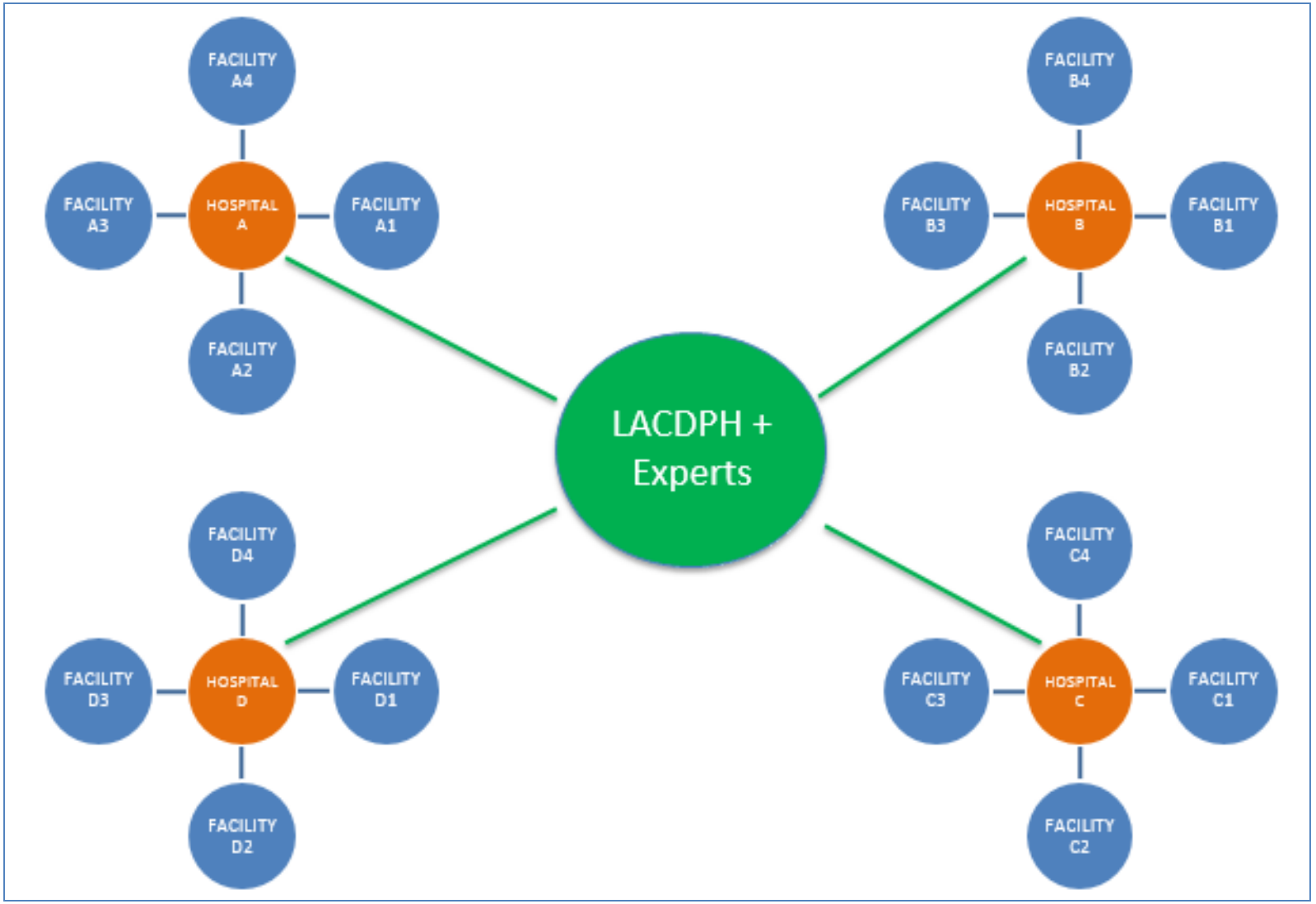
1. Antimicrobial stewardship (AS) policy/procedure
2. Written statement in support of ASP with evidence for necessary budget/staffing
3. AS activities reported to facility's Quality Assurance-Performance Improvement (QAPI) program.
4. Establish physician-supervised, multidisciplinary antimicrobial stewardship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

Basic ASP Tier Elements for SNF: More Challenging Components

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

LA County Antimicrobial Resistance Network (ARN)

- Support acute care hospitals (ACHs) in engaging their network SNFs to meet upcoming ASP requirements
- Improve inter-facility communication to reduce spread of multidrug-resistant organisms (MDROs)



LA County Department of Public Health Antibiotic Resistance Network

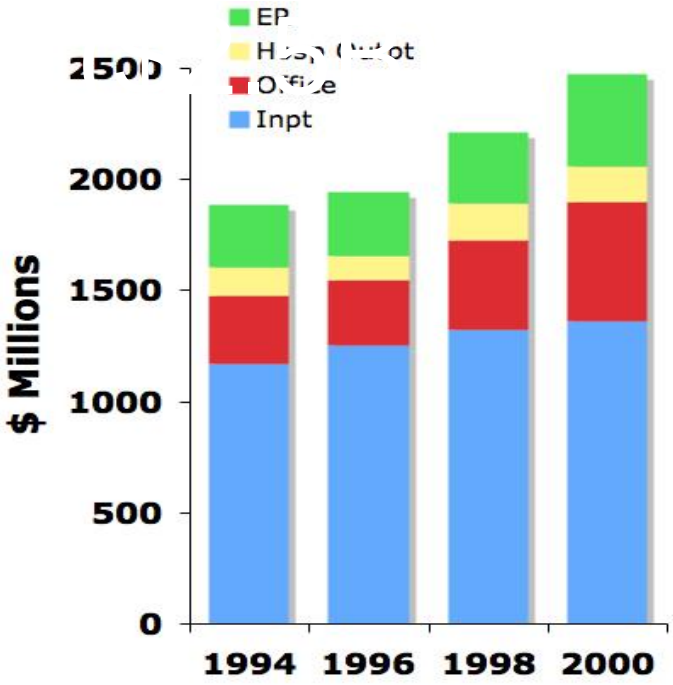
UTI

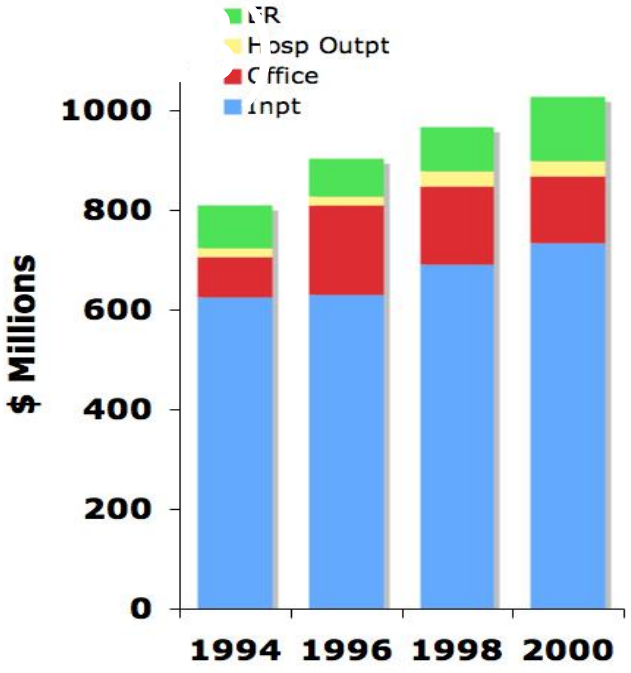
Estimates for Outpatient UTI in the US in 1995:

- 11.3 million Rx with $1.6 Billion in costs

Foxman B et al. *Ann Epidemiol* 2000;10:509-15

US Expenditures





Griebling, Journal of Urology 173:1281,8 (2005)

UTI

25-35% women 20-40 y/o have had a UTI

- 1.8 - 6.1 days of symptoms
- 0.6 - 1.2 days of missed work or classes
- 0.4 - 0.6 days in bed

Foxman B et al. *Ann Epidemiol* 2000;10:509-15
Foxman B et al. *Am J Public Health* 1985;75:1308-13
Schappert SM; *Vital Health Stat* 1994; 13:1-110.

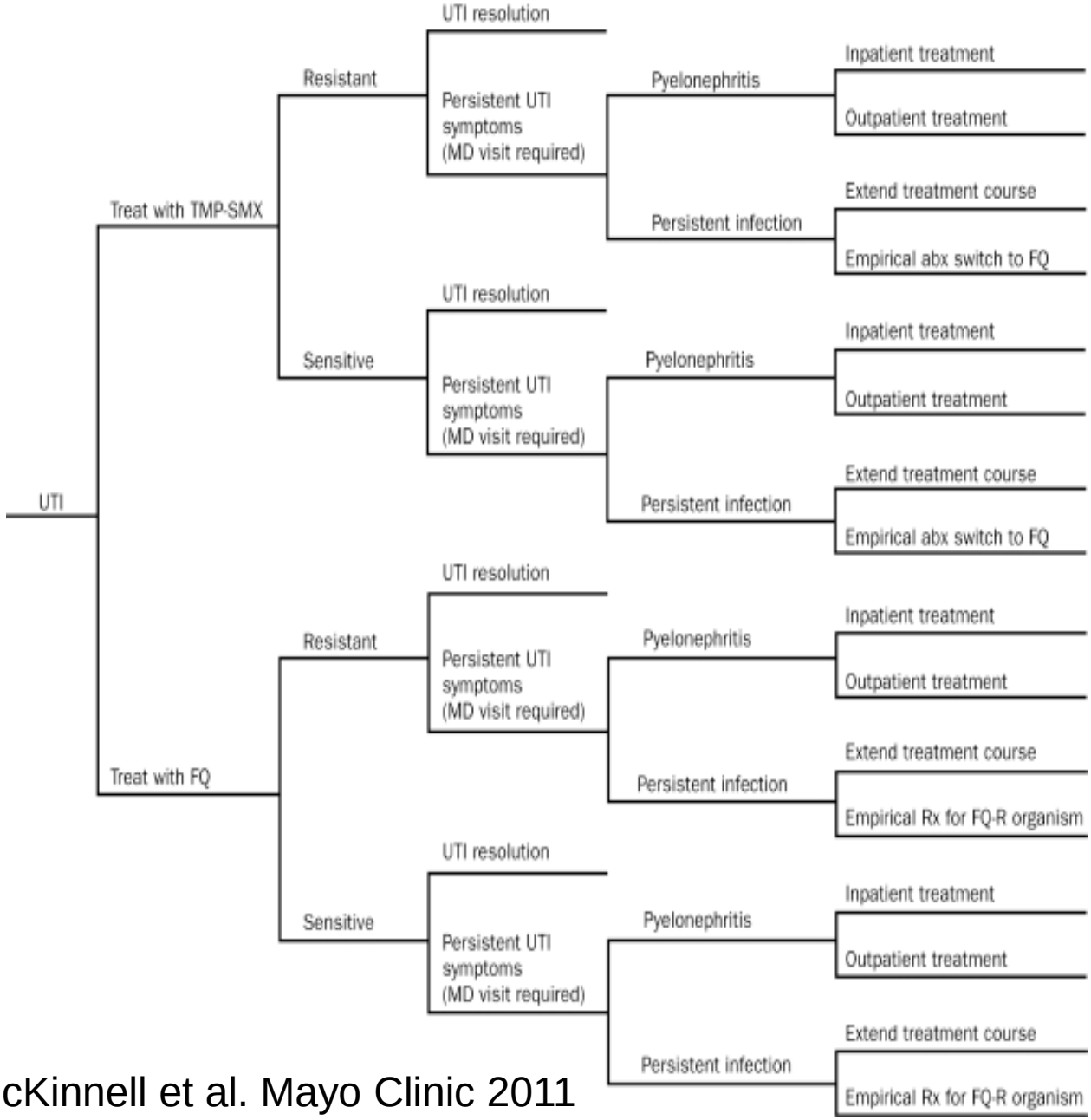
GN Resistance

- **Fluroquinolone Resistance was High**

  Among E. Coli it was 32%

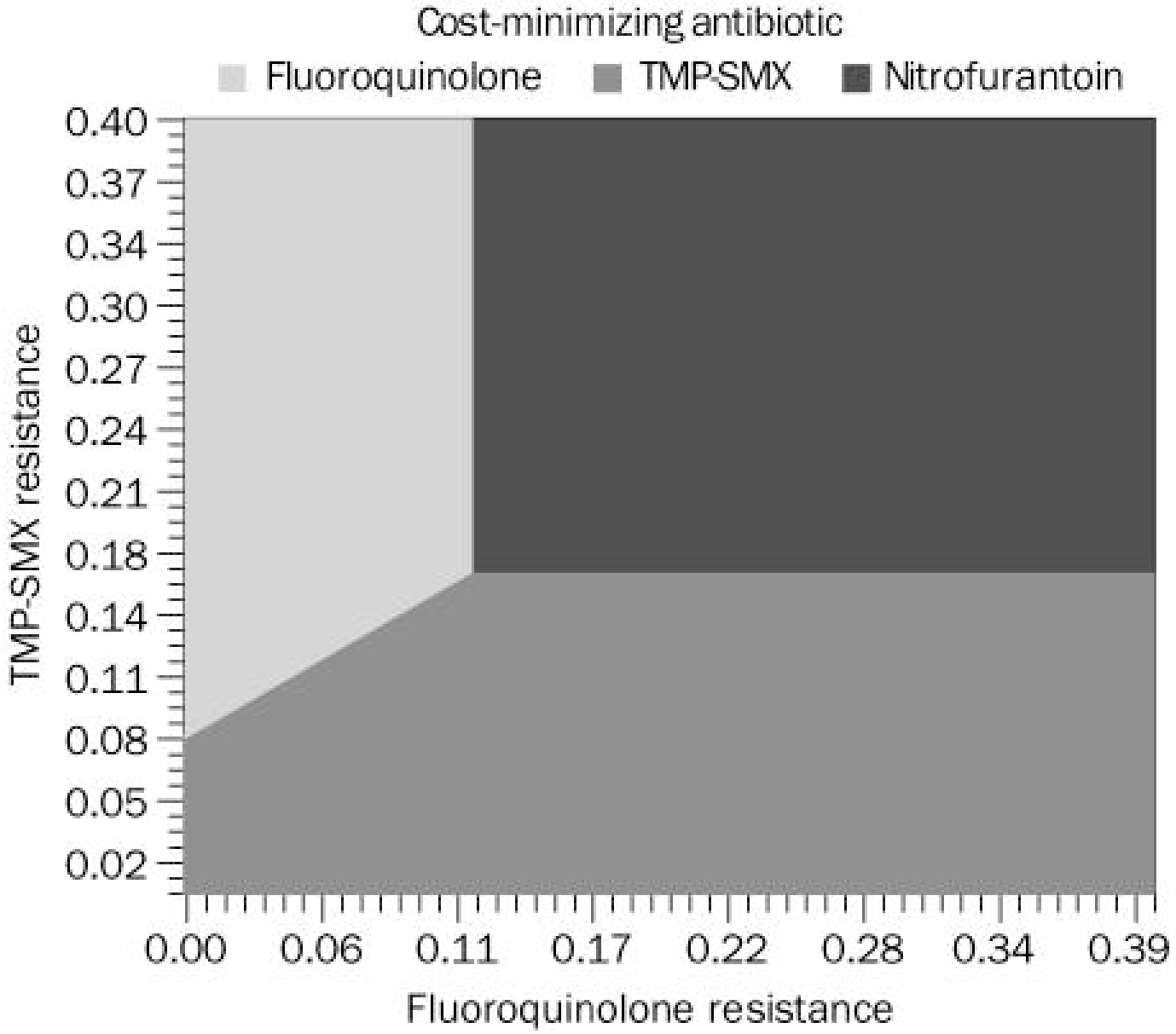
  TMP/SMX resistance not included

  Nitrofurantoin resistance not included



Description	Probability
TMP-SMX resistance	0.15
Fluoroquinolone resistance	0.025
Nitrofurantoin resistance	0.012
Clinical cure of TMP-SMX–resistant infection treated with TMP-SMX	0.55
Clinical cure of TMP-SMX–sensitive infection treated with TMP-SMX	0.91
Clinical cure of fluoroquinolone-resistant infection treated with fluoroquinolone	0.78
Clinical cure of fluoroquinolone-sensitive infection treated with fluoroquinolone	0.94
Clinical cure of nitrofurantoin-resistant infection treated with nitrofurantoin	0.67
Clinical cure of nitrofurantoin-sensitive infection treated with nitrofurantoin	0.89
Hospitalization for pyelonephritis	0.2
Pyelonephritis if initial empirical therapy unsuccessful	0.04
Vaginal yeast infection after ≤3 d of therapy	0.05
Vaginal yeast infection after >3 d of therapy	0.07
Medical visit for vaginal yeast infection	0.25
Change of therapy due to lack of clinical response to TMP-SMX (vs extending TMP-SMX treatment)	0.75
Change of therapy due to lack of clinical response to fluoroquinolone (vs extending fluoroquinolone treatment)	0.25
Change of therapy due to lack of clinical response to nitrofurantoin (vs extending nitrofurantoin treatment)	0.75

McKinnell et al. Mayo Clinic 2011



McKinnell et al. Mayo Clinic 2011

LAC DPH Outpatient Stewardship Project

- LAC DPH Healthcare Outreach Unit is planning a multi-faceted intervention to improve provider prescribing in outpatient settings
- Intervention includes a core package:
  - Poster commitment
  - Treatment guidelines
  - Communication skills training
  - Additional strategies tailored to facility's needs

LAC DPH Outpatient Stewardship Project, cont.

- Benefits to participation:
  - Tailored assistance in implementation of CDC Core Elements
  - Improved provider knowledge of resistance and appropriate prescribing for upper respiratory infections
  - Free resources to support providers in improving antibiotic prescribing
  - Increased coordination and exchange of antibiotic stewardship best practices

LAC DPH Outpatient Stewardship Project, cont.

- Seeking volunteer primary care clinics to participate
  - Ability to collect/ report prescribing data
  - Identify stewardship champion in facility

For more information, contact Kelsey OYong:
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(213) 240-7941