Antibiotic Stewardship: Everyone's Responsibility

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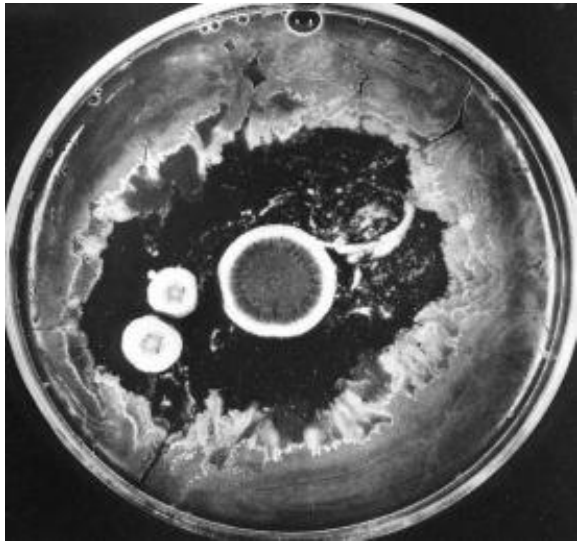
DISCLOSURES

- Grant support from Pfizer for the Sharing Antimicrobial Reports for Pediatric Stewardship (SHARPS) collaborative
- Consultant for Cubist and RPSdiagnostics

Objectives

- Discuss the history of antibiotics
- List the impact of antibiotic resistance
- List effective stewardship strategies to improve the use of antibiotics.
- Discuss the impact of antimicrobial stewardship on clinical outcomes




PHARMACY
PENICILLIN
250 MG TABLETS
TAKE ONE TABLET BY MOUTH
EVERY 6 HOURS UNTIL GONE
NO 16534200-03072

Which of the following antibiotics was the first used to treat a child?

- Erythromycin
- Methicillin
- Penicillin
- Sulfanilamide
- Vancomycin

Sulfa Antibiotic

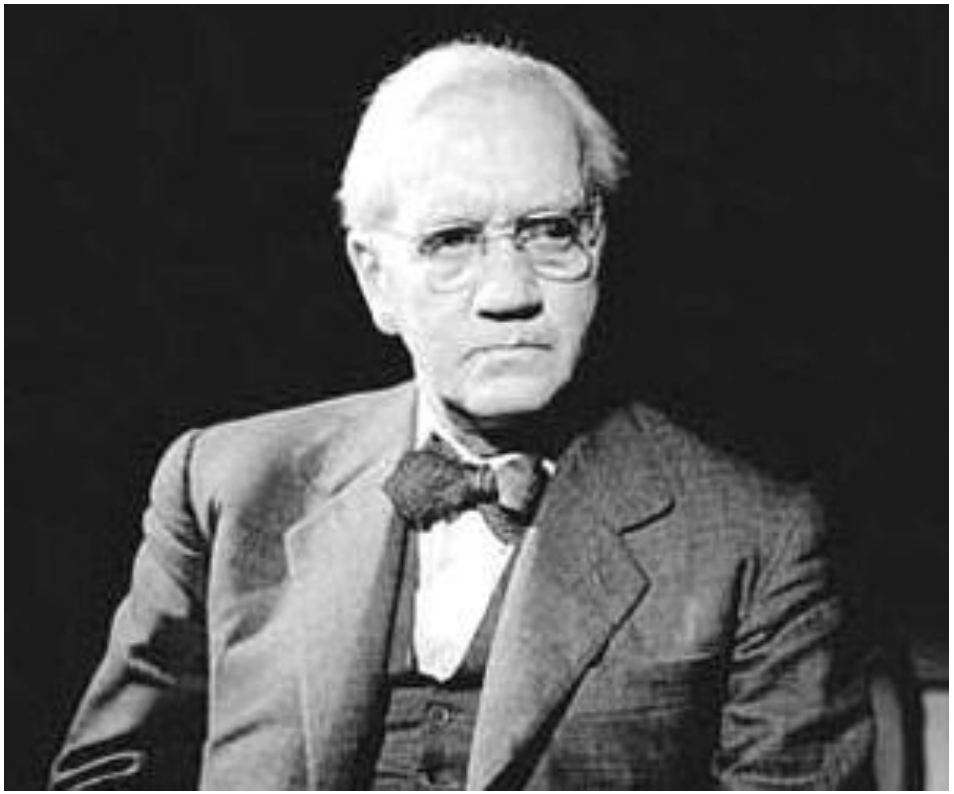
- Discovered by Dr. Gerhard Domagk
- Originated from research performed on red dyes
- Used in 1933 on 10 month old boy with *S. aureus* bloodstream infection
- Prontosil Rubrum used on Dr. Domagk's own 6yo daughter with an invasive cellulitis

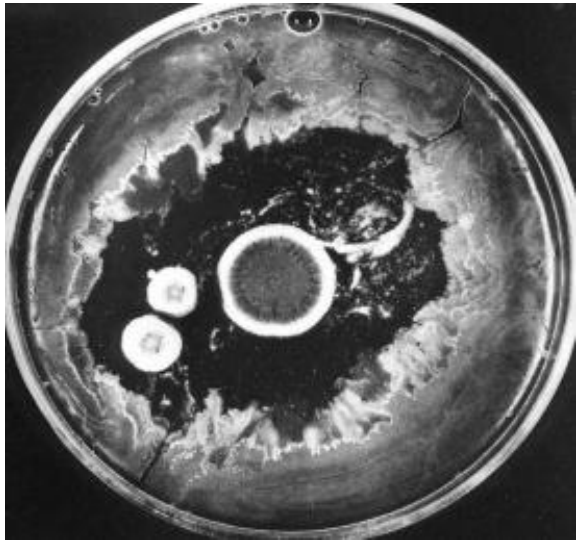
Spellberg B Rising Plague 2009

Impact of Sulfa Antibiotics

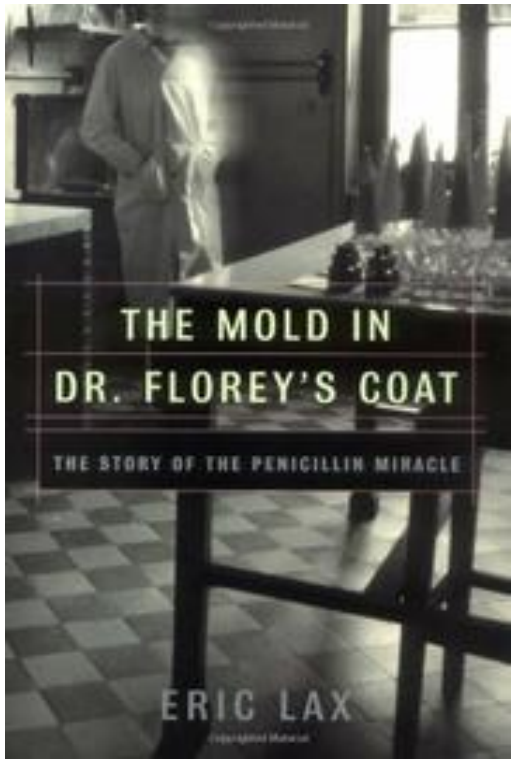
Lewis Thomas. Notes of a Medicine Watcher. '83. Viking Press

"For most of the infectious diseases on the wards of Boston City Hospital in 1937, there was nothing that could be done beyond bed rest and good nursing care. Then came the explosive news of sulfanilamide, and the start of the real revolution in medicine."





Dr. Howard Florey



www.chemheritage.org/discover/online-resources/chemistry-in-history/themes/pharmaceuticals/preventing-and-treating-infectious-diseases/florey-and-chain.aspx

February 12th, 1941

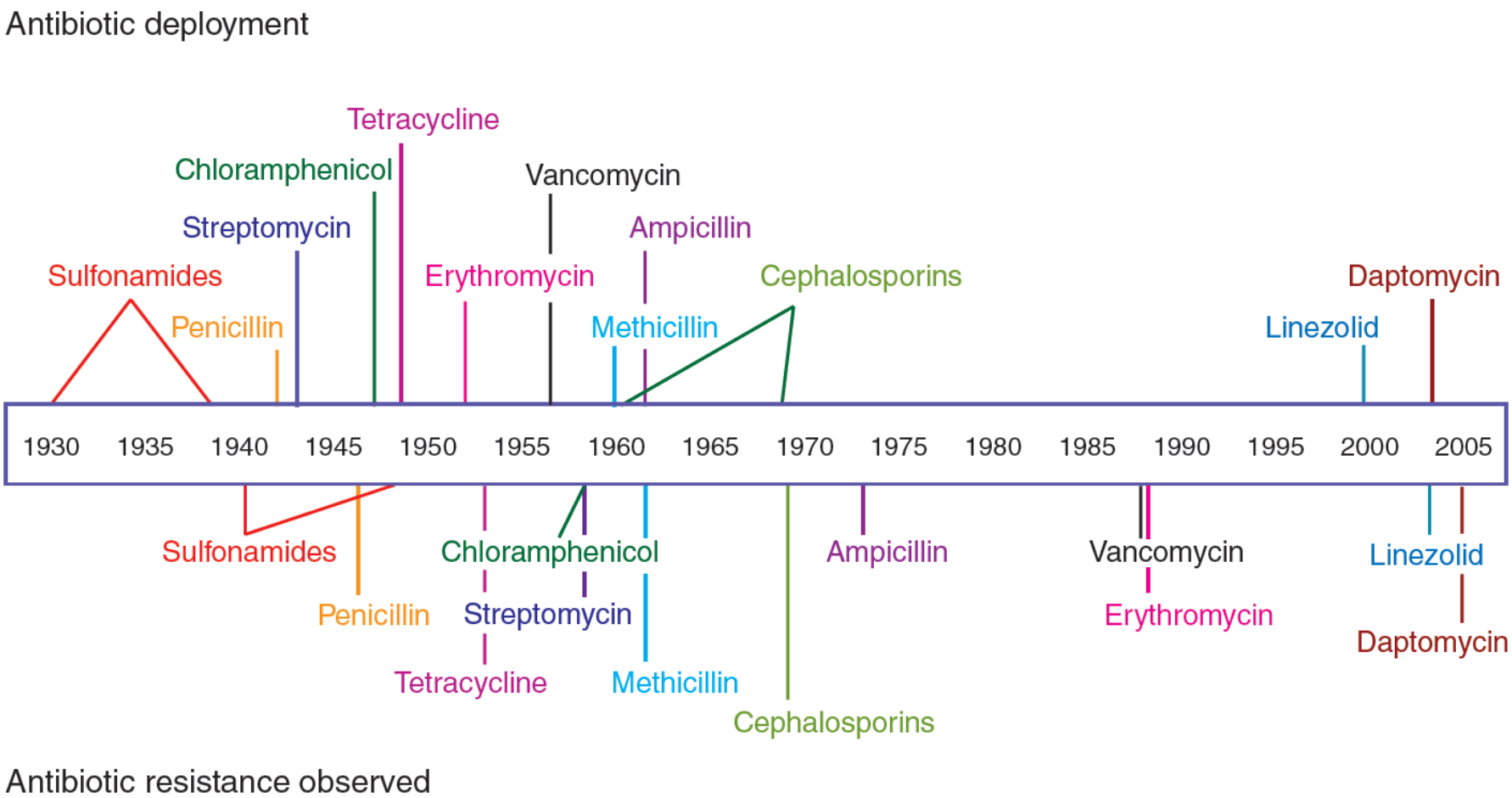
- Police Officer Albert Alexander
- Horrible infection of the face and eye
- Threat of losing eye and develops pneumonia
- Penicillin given- Dose/frequency unknown
- Limited Supply

Spellberg B Rising Plague 2009

- “The greatest possibility of evil in self-medication is the use of too small doses so that instead of clearing up infection the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who gets a septicaemia or pneumonia which penicillin cannot save.”

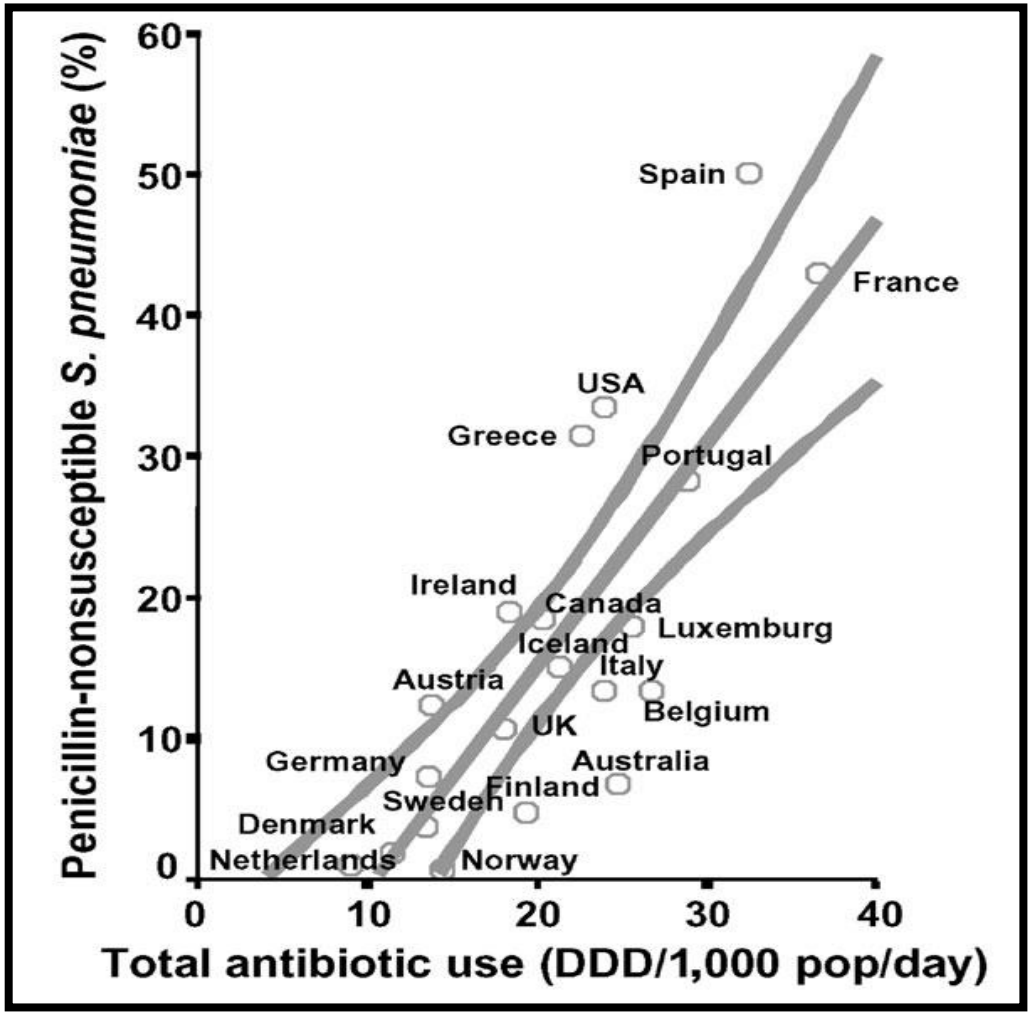
Alexander Fleming,
New York Times 1945

Antibiotic Timeline



Clatworthy 2007

Utilization and Resistance



Albrich WC et al EID 2004:10

Microbes

- 5×10^{31} on Earth (Humans $6\text{-}7 \times 10^{9}$)
  - 5-10 times more microbes living on and in a human than human cells in the body
  - Comprise 60% of biomass of the planet
- Living on earth for 3.5 billion years to live and adapt (Humans not near that long)
- Replicate every 20-30 minutes (Humans 20-30 years)

Spellberg B Clin Infect Dis 2008:46

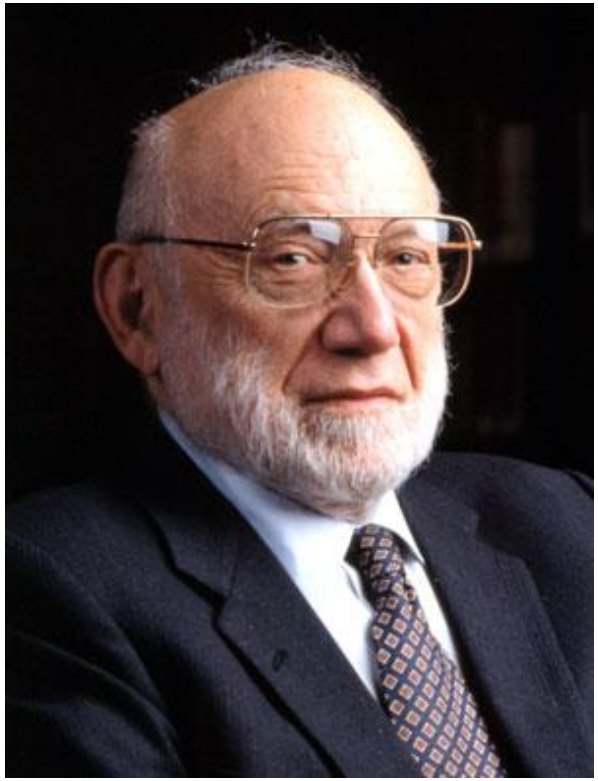
Microbes have been creating and defeating antibiotics for 20 million times longer than humans have even known antibiotics existed.

Brad Spellberg MD 5th Annual ASP conference June 2014

There are already, wide-spread in nature, resistance mechanisms to antibacterial agents we have not yet invented

Brad Spellberg MD 5th Annual ASP conference June 2014

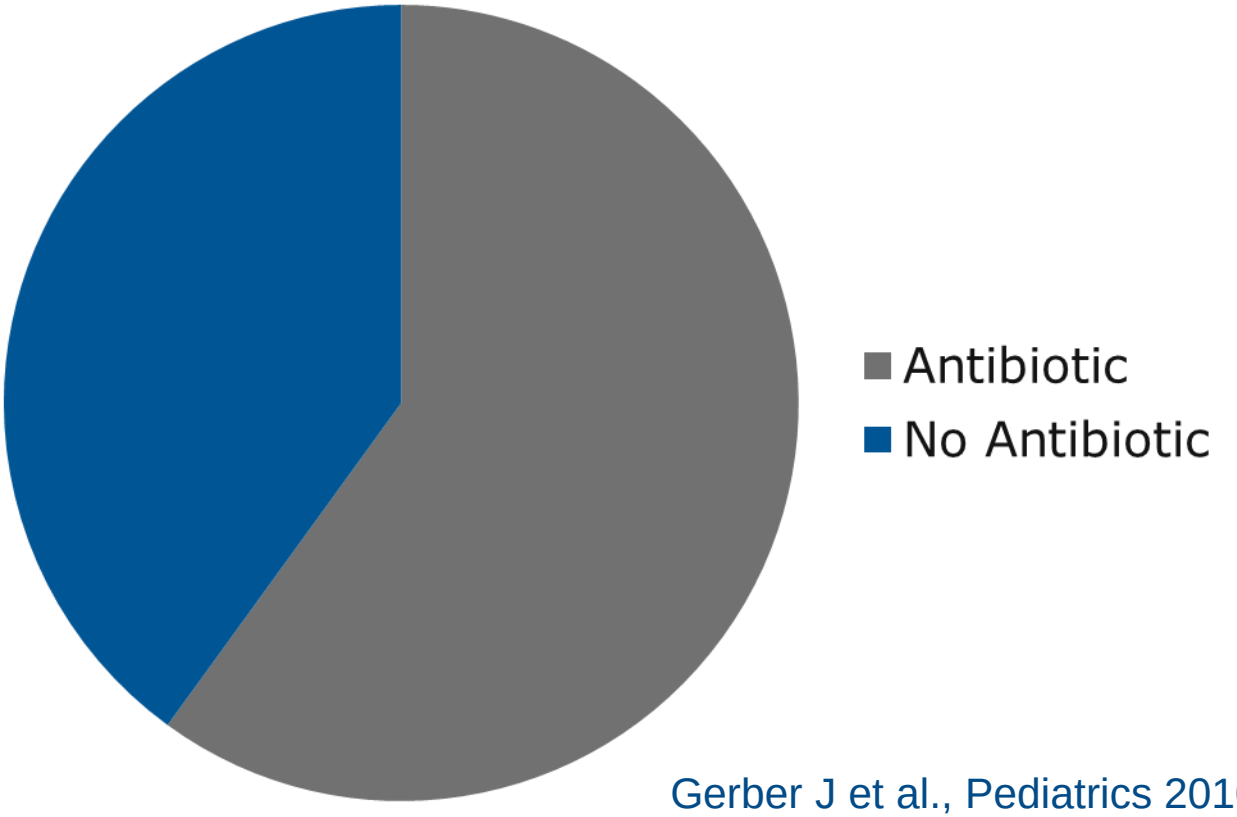
“The future of humanity and microbes will likely evolve as…episodes of our wits versus their genes.”



Nobel Laureate
Joshua Lederberg
Science 2000 288:287-93

Antibiotic Use in Freestanding Children's Hospitals

- 37 hospitals: 556,692 discharges in 2008



Gerber J et al., Pediatrics 2010; 126:1067

Antibiotic Use in Freestanding Children's Hospitals

- 37 hospitals: 556,692 discharges in 2008
- Among the hospitals large variability
  - 38-72% receive an antibiotic
  - 368-601 days per 1000 patient days
- Positive correlation with percent receiving an antibiotic and days of therapy
  - All antibiotics
  - Broad spectrum antibiotics

Gerber J et al., Pediatrics 2010; 126:1067

Appropriateness of Antibiotics

- 50% of antimicrobial use is either unnecessary or inappropriate
  - 30% of anti-anaerobic agents inappropriate
  - 50% of vancomycin use in adult populations is inappropriate
- 35% of initial vancomycin courses inappropriate in a pediatric institution

Donskey C et al. Arch Intern Med 2003
Bolon MK et al. ICHE 2005

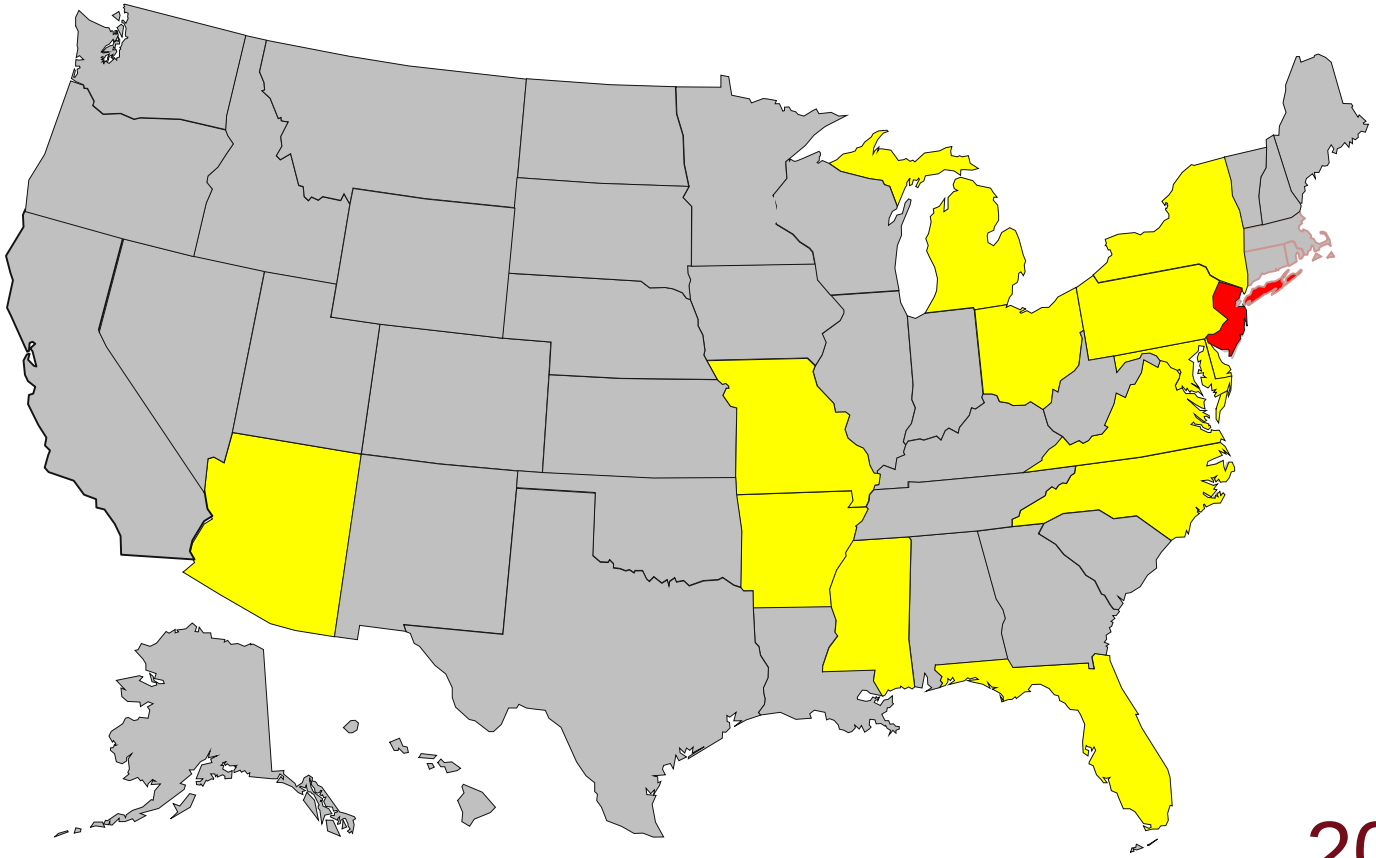
Inappropriate Antibiotic Use in the NICU

Inappropriate antibiotic-days: 806 (24%) of 3,334 days

CDC 12-Step	Days	%
Target the pathogen	309	38
Practice antimicrobial control	167	21
Treating colonization/ contamination	130	16
Say 'no' to antibiotics	140	17
Stop treatment	60	8

Patel SJ, PIDJ 2009

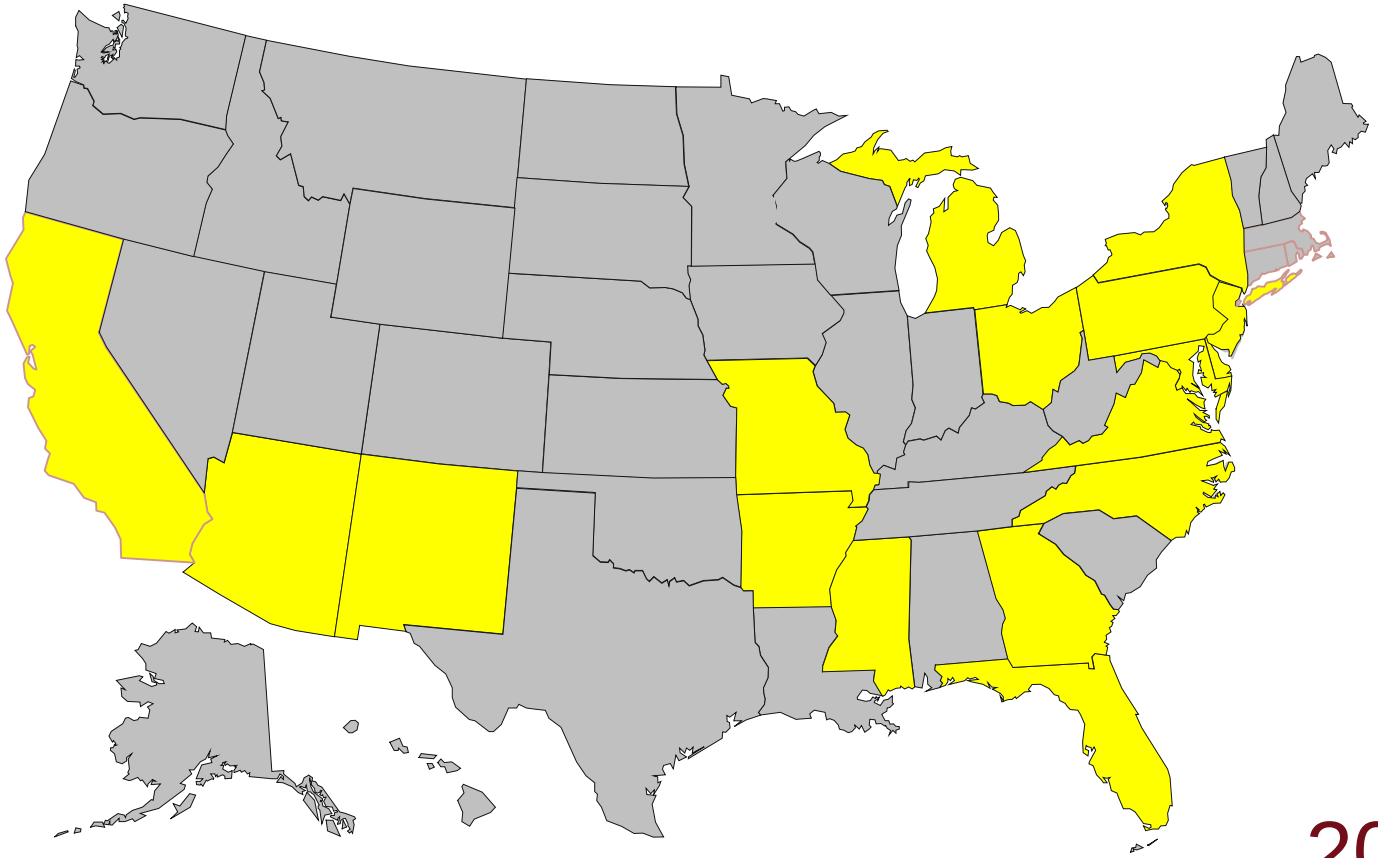
Carbapenem-Resistant Enterobacteriaceae (CRE)



2006

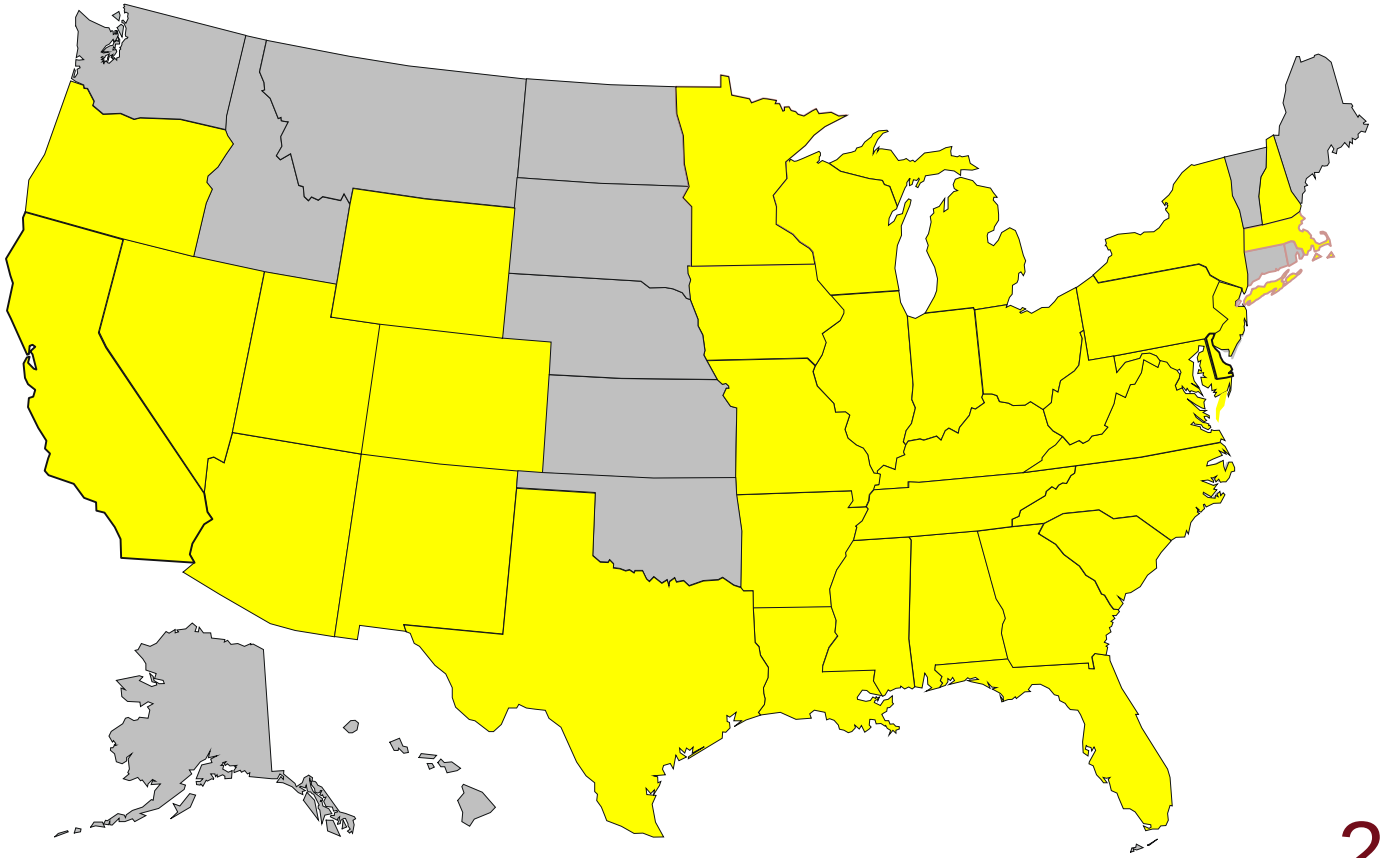
Nov. 2006

Carbapenem-Resistant Enterobacteriaceae (CRE)



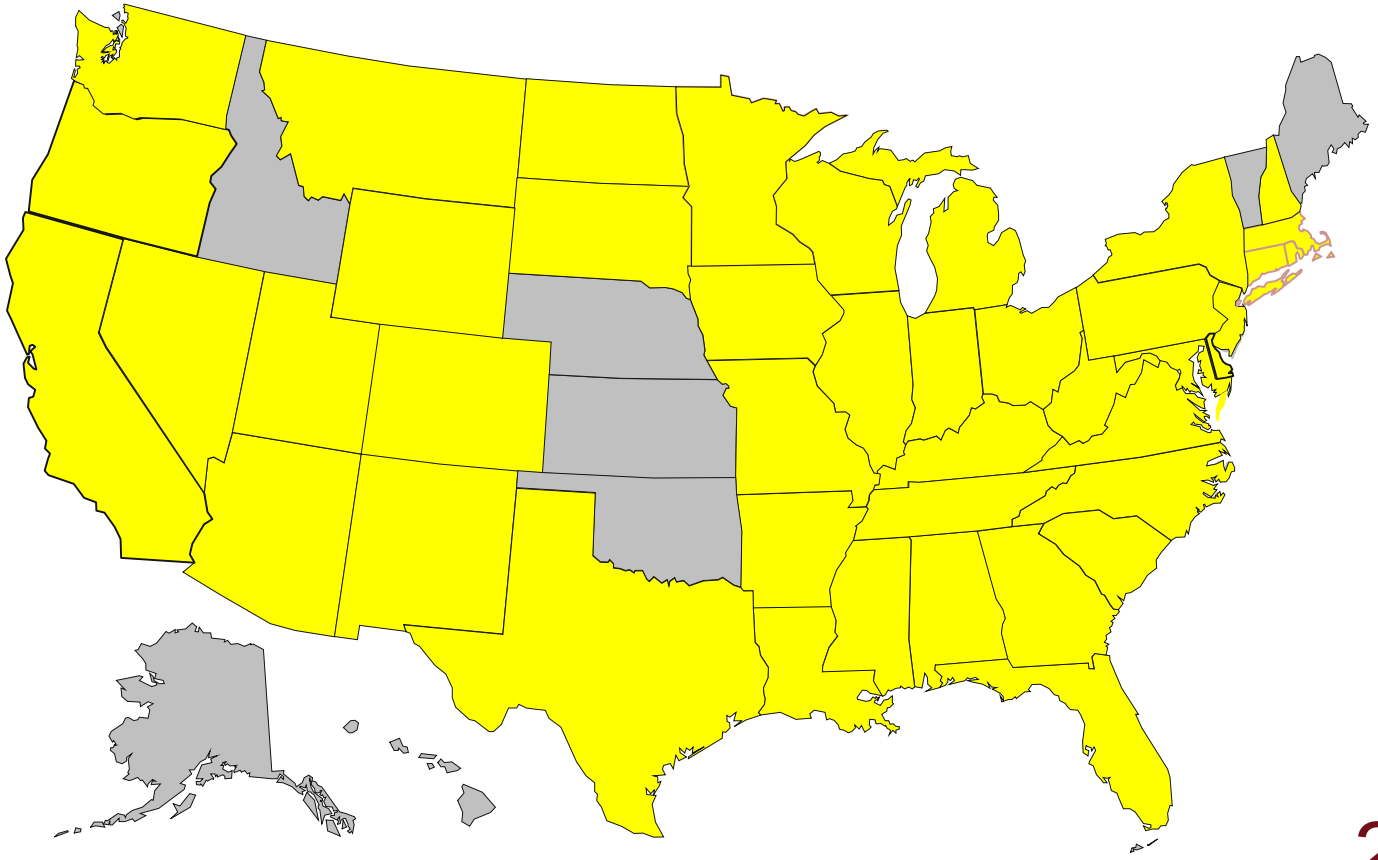
2007

Carbapenem-Resistant Enterobacteriaceae (CRE)



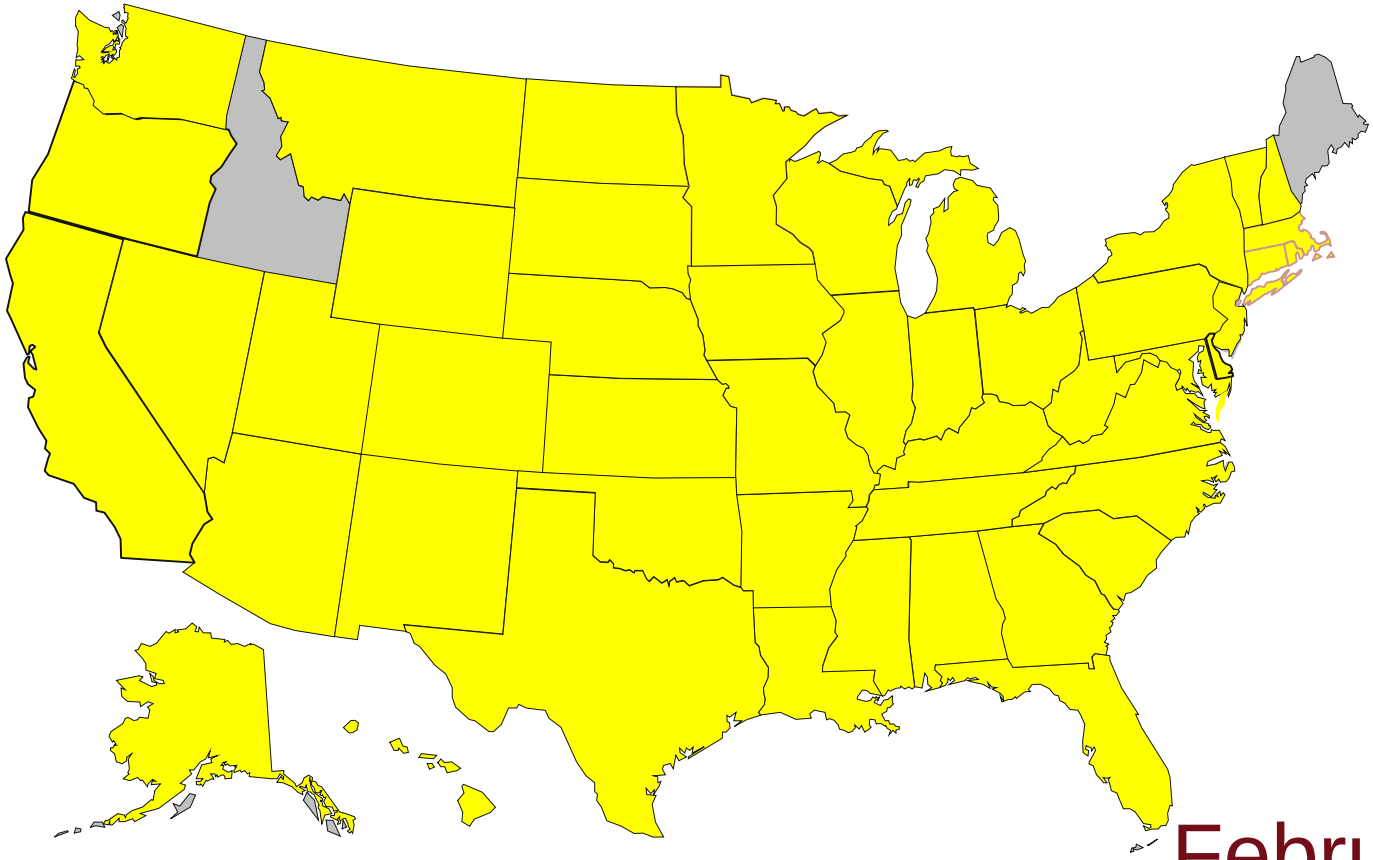
2011

Carbapenem-Resistant Enterobacteriaceae (CRE)



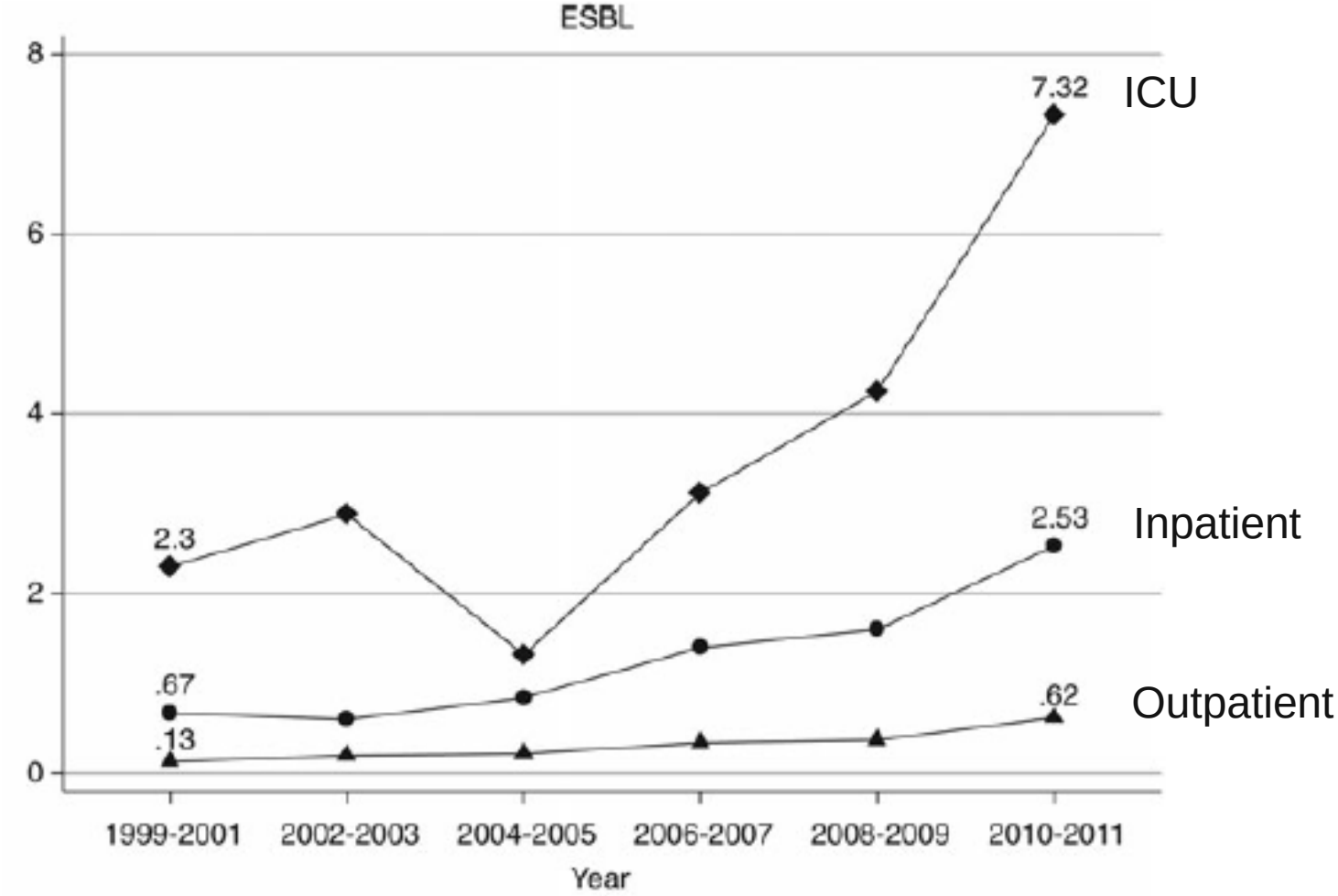
2012

Carbapenem-Resistant Enterobacteriaceae (CRE)



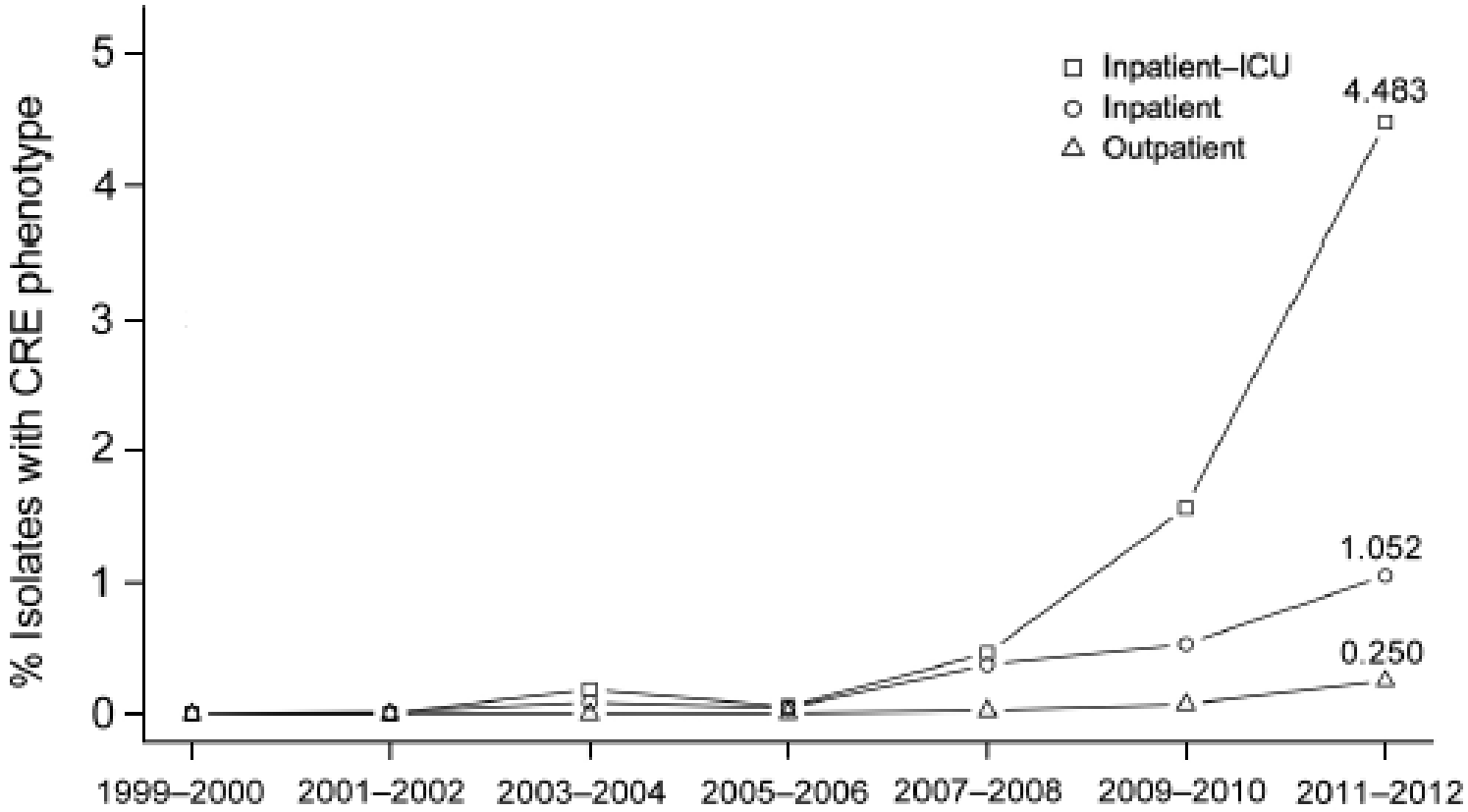
February 2015

Gram Negative Resistance in Children



Logan LK, JPIDS 2014; 3:320-8.

Carbapenem-Resistant *Enterobacteraceae* in Children



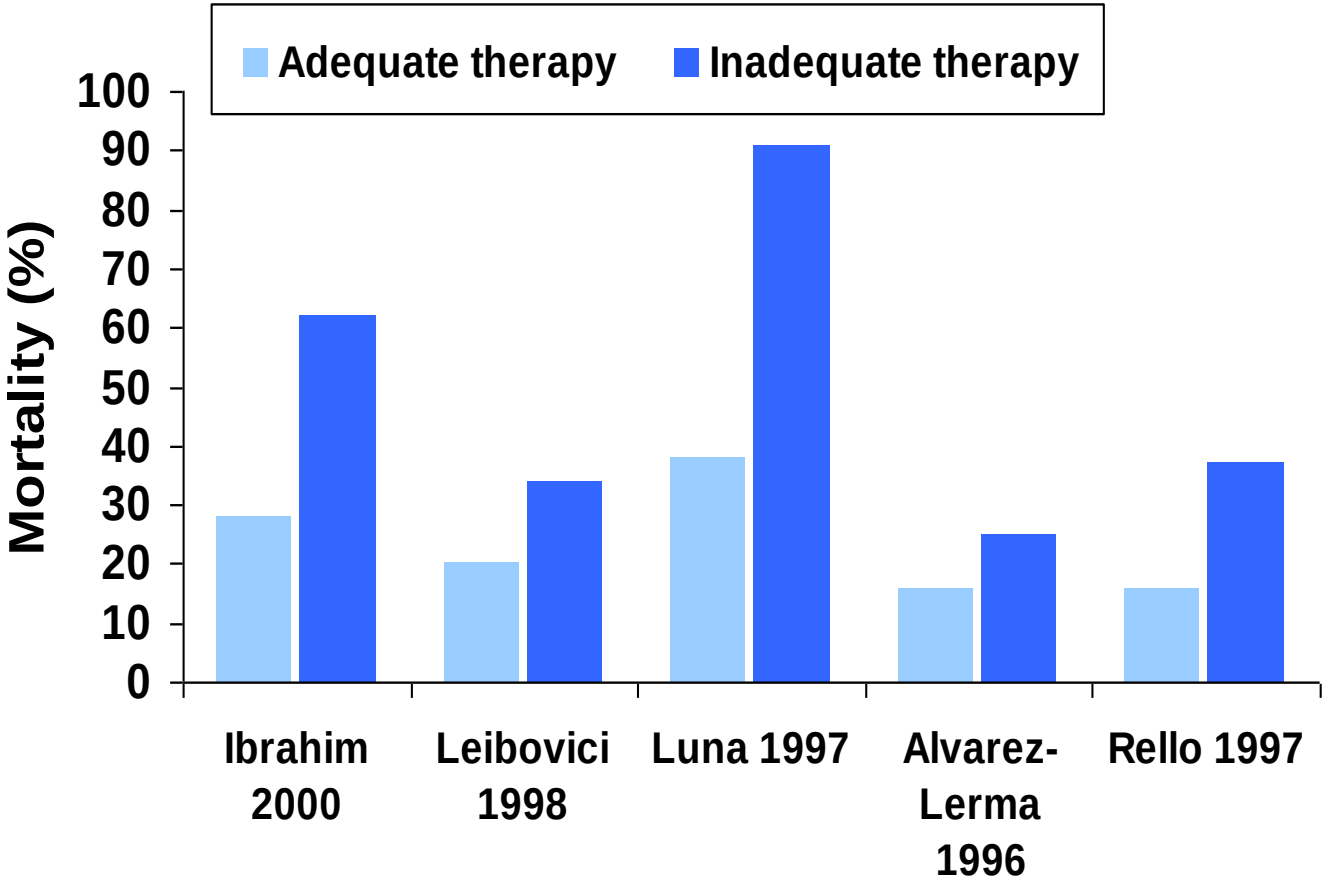
Logan LK, EID 2015; 21:2014

Antimicrobial Resistance and Patient Outcomes

- Increase in mortality, morbidity, length of hospitalization, and cost of care
  - *Staphylococcus aureus*
  - *Enterococci*
  - Gram-negative bacilli
- Delays in therapy or severity of illness likely contribute to worse outcomes

Cosgrove S, Clin Infect Dis 2006; 42 (suppl 2):S82-89.

Inadequate Antibiotic Therapy Increases Mortality



Bloodstream Infections **Nosocomial Pneumonia/VAP**

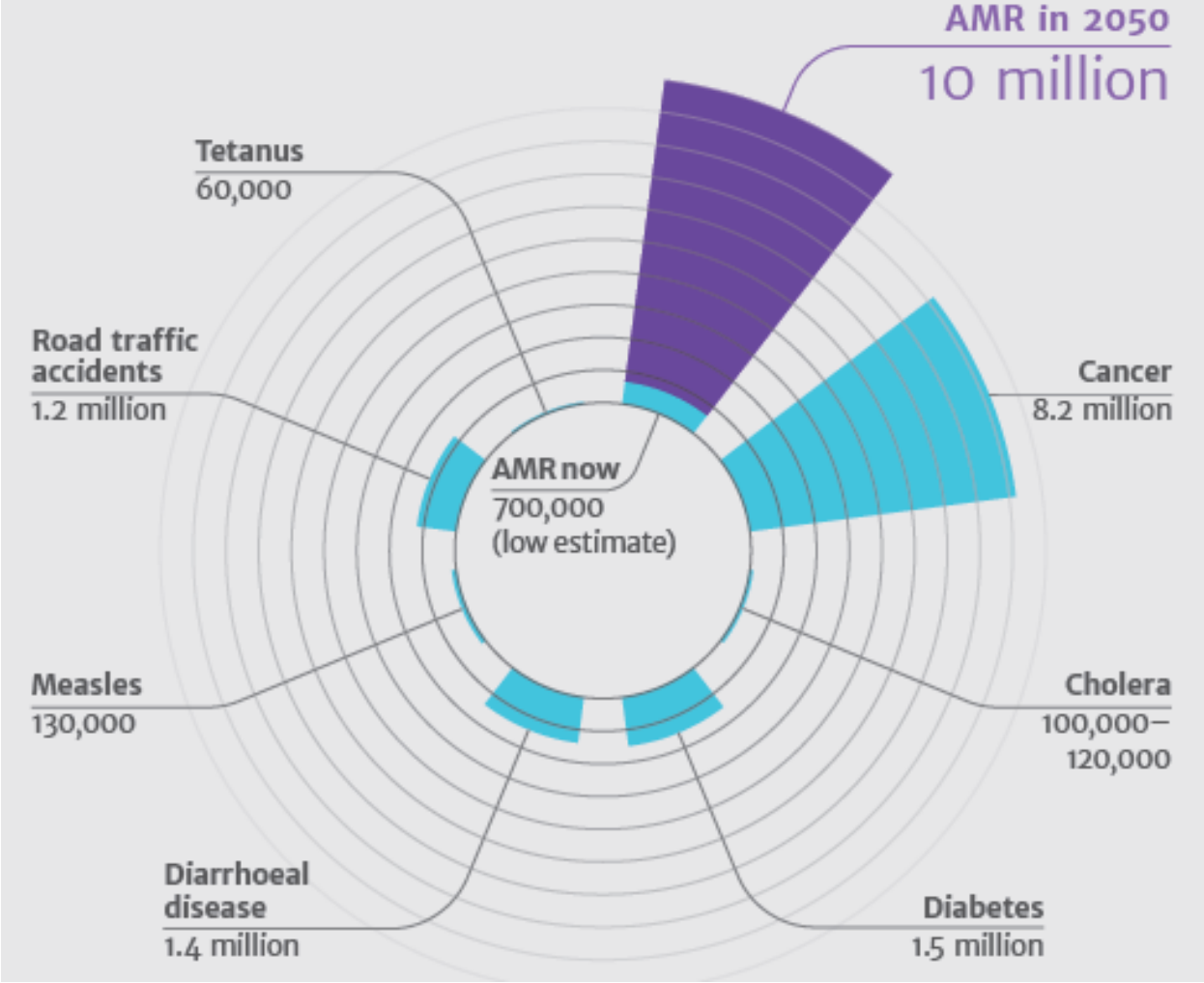
[1]Ibrahim et al. *Chest.* 2000;118:146.
[2]Leibovici et al. *J Intern Med.* 1998;244:379.
[3]Luna et al. *Chest.* 1997;111:676.
[4]Alvarez-Lerma et al. *Intensive Care Med.* 1996;22:387–394.
[5]Rello et al. *AJRCCM.* 1997;156:196–200.

CDC Threat Report

- 23,000 Americans die annually from an antibiotic resistant infection
- 2 million Americans are infected annually with an antibiotic resistant infection
- 250,000 Americans suffer from *C. difficile* infection
  - 19,000 die from *C. difficile* infection

http://www.cdc.gov/drugresistance/threat-report-2013/

Deaths Attributable to AMR



Amr-review.org accessed 10-20-2015

Antibiotic-Associated Adverse Events

Clostridium difficile

- Increasing in hospitalized children
- 10 fold increase in community-onset
- Hospital-Onset C. difficile infections associated
  - Increased risk of mortality OR 6.73 (3.77-12.02)
  - Increased length of stay- 5.5 days (4.5-6.5 days)
  - Increased hospital costs- $93K (80-107,200)

Kim J et al. Pediatrics 2008 122:1266
Sammons J et al Clin Infec Dis 2013: 57:1-8

Antibiotic-Associated Adverse Events

- Trimethoprim-Sulfamethoxazole ADRs requiring hospitalization have significantly increased at CMH
  - 2000-2004- 5
  - 2005-2009- 104
- Nationally they have almost tripled
  - 5 cases per 100,000 admissions in 2000
  - 13 cases per 100,000 admissions in 2009

Goldman JL et al. Pediatrics 2013

Potential Solutions

- New Antimicrobial Development
- Antimicrobial Stewardship Programs
- Better Diagnostics
- Know best lengths of therapy
- Reduction of Hospital Acquired Infections
- Vaccines
- Decrease Antimicrobial Use in Agriculture

Children's Mercy ASP

Children's Mercy Hospital-Kansas City

- 354 bed tertiary care free-standing hospital
- 40 bed PICU, 70 bed NICU
- 2 campuses
- All Pediatric Subspecialties
- Average daily census of 250

Children's Mercy ASP

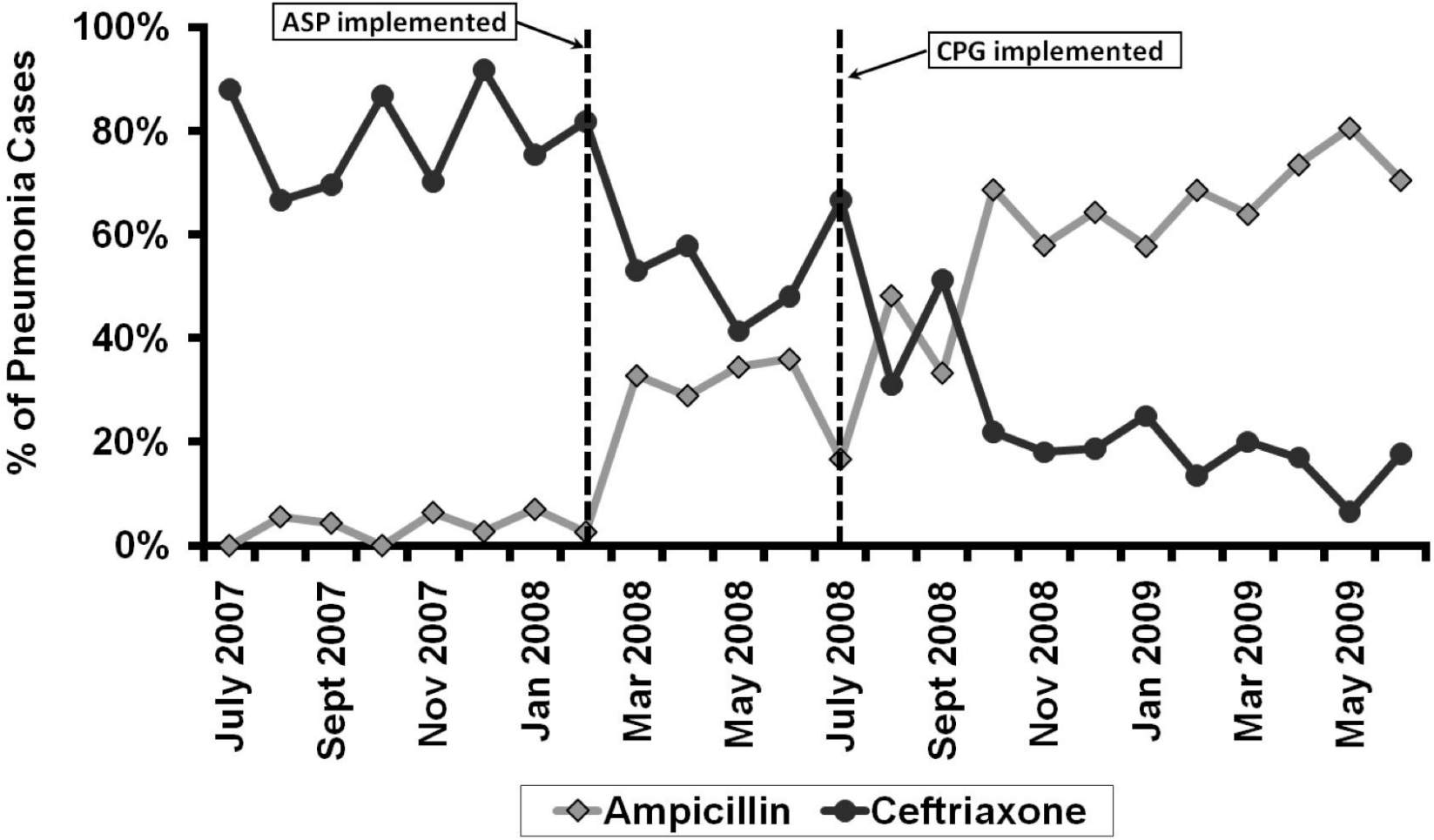
ASP strategies

- Prospective-audit with feedback
- Prior-approval
- Clinical practice guideline(s)
  - Community-acquired pneumonia
  - Febrile infant < 60 days of age
- Empiric antibiotic guideline

Impact of CAP Guideline

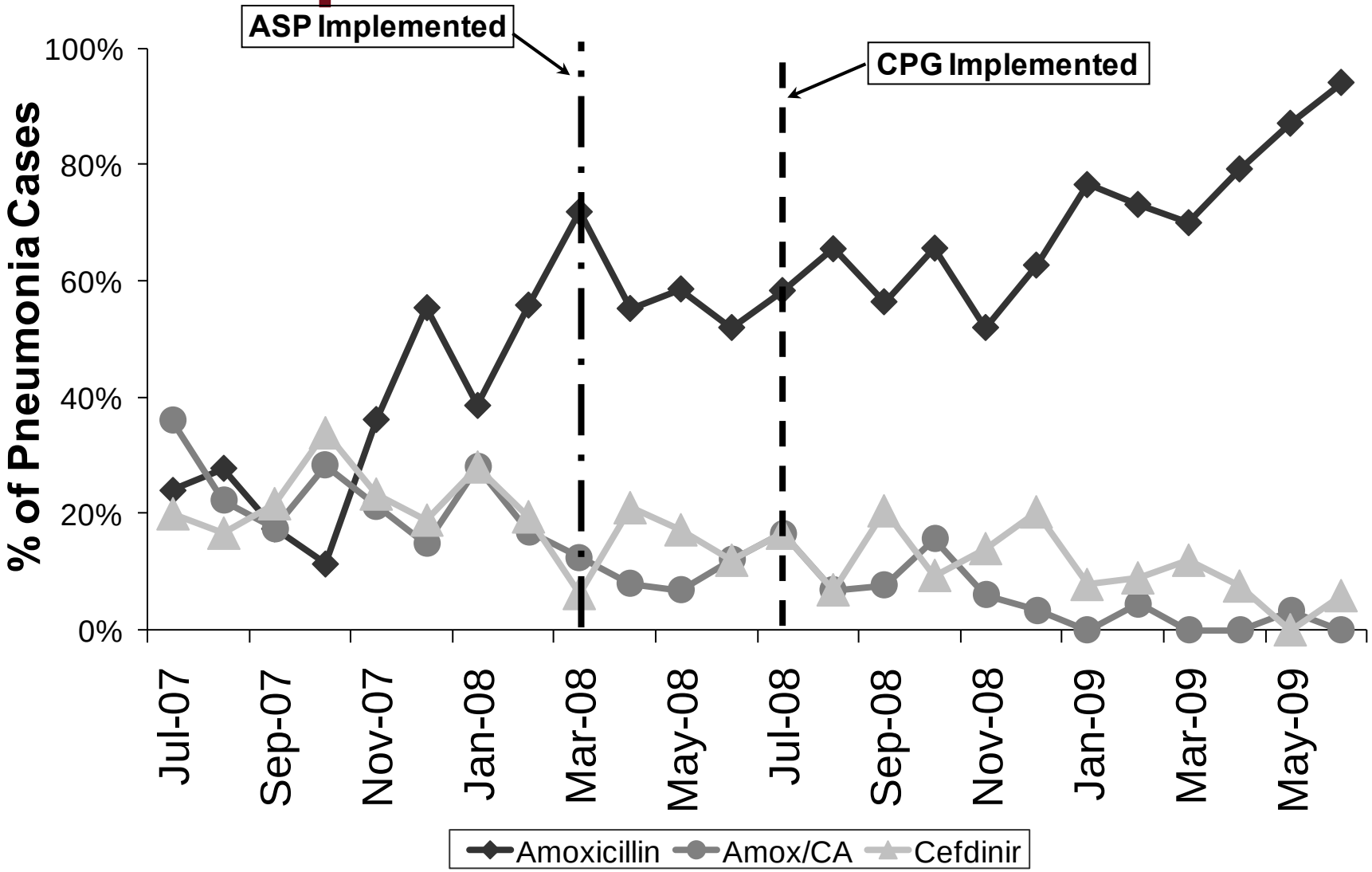
- Implemented in July of 2008
- Guideline recommendations were
  - Ampicillin for hospitalized uncomplicated CAP
  - Blood cultures on all hospitalized children
  - Duration of therapy of 7 days
- National Guideline published 2011
  - Similar recs except duration of therapy 10 days

Impact of CAP Guideline



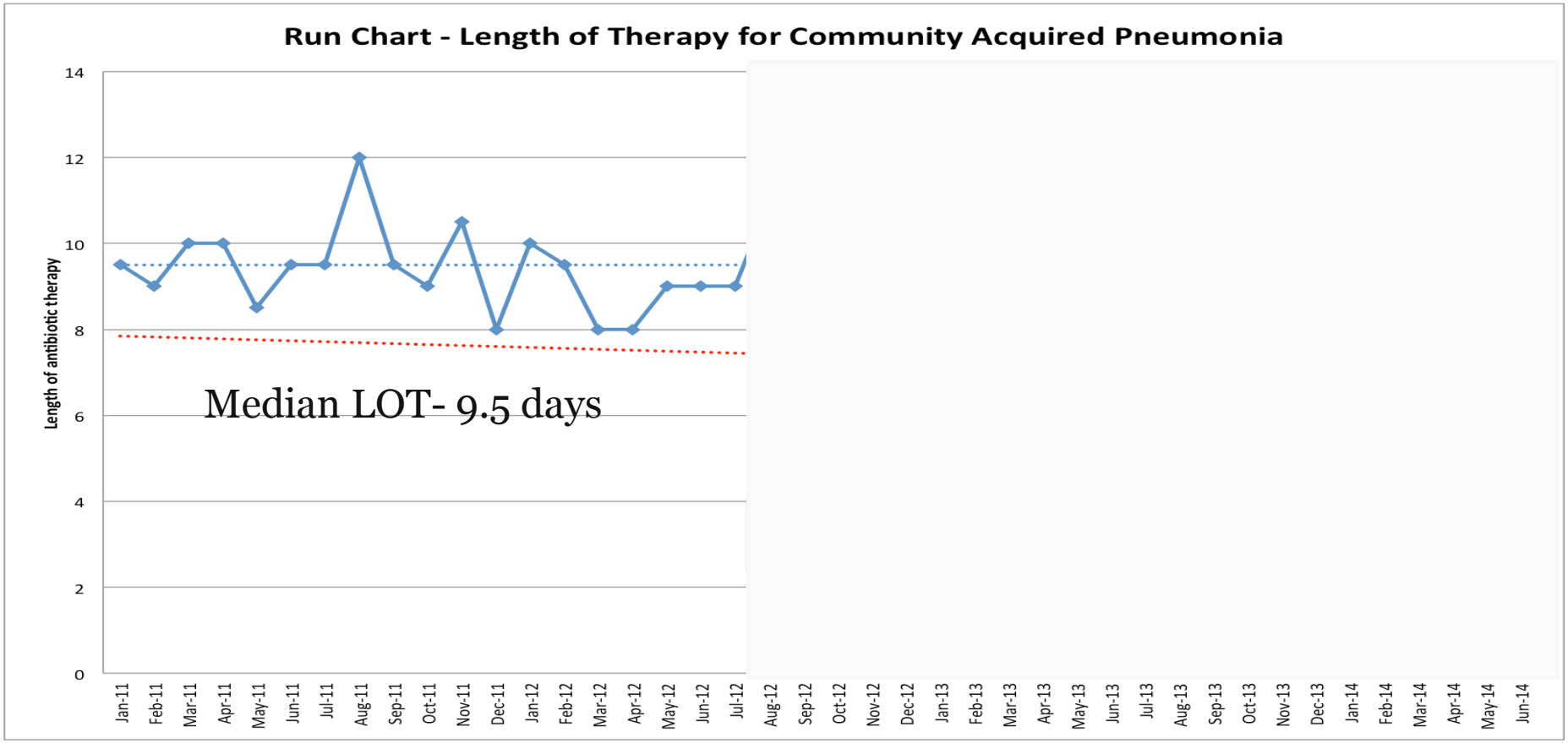
Newman R et al. Pediatrics 2012 129:e597-04

Impact of CAP Guideline



Newman R et al. Pediatrics 2012 129:e597-04

Impact of CAP Guideline



Johnson M et al PAS 2015

Children's Mercy ASP

Prospective-Audit with Feedback

- All inpatients 6 days a week
- Review patients on monitored antibiotic two calendar days after initiation
- Appropriateness and duration determined
- Discuss with teams and physicians about recommendations of ASP
- Recommendations agreed upon provided in patient chart

Monitored Antibiotics

- Ceftazidime
- Cefepime
- Ceftriaxone
- Cefotaxime
- Meropenem
- Aztreonam
- Vancomycin
- Linezolid*
- Daptomycin*
- Amoxicillin/Clavulanate
- Ampicillin/Sulbactam
- Piperacillin/Tazobactam
- Ticarcillin/Clavulanate
- Ciprofloxacin
- Moxifloxacin
- Levofloxacin*
- Amikacin
- Tobramycin

*Require Prior Approval

CMH ASP

Data from 3/3/08- 3/2/13

- 14,402 Patient Reviews performed
- Recommendations- 2317
  - Stop therapy- 45%
  - Modify therapy- 26%
  - Optimize therapy- 19%
  - Consult Infectious Diseases- 10%
- 22% Disagreement with recommendations

Goldman J et al. ICHE 2015 36:673-80

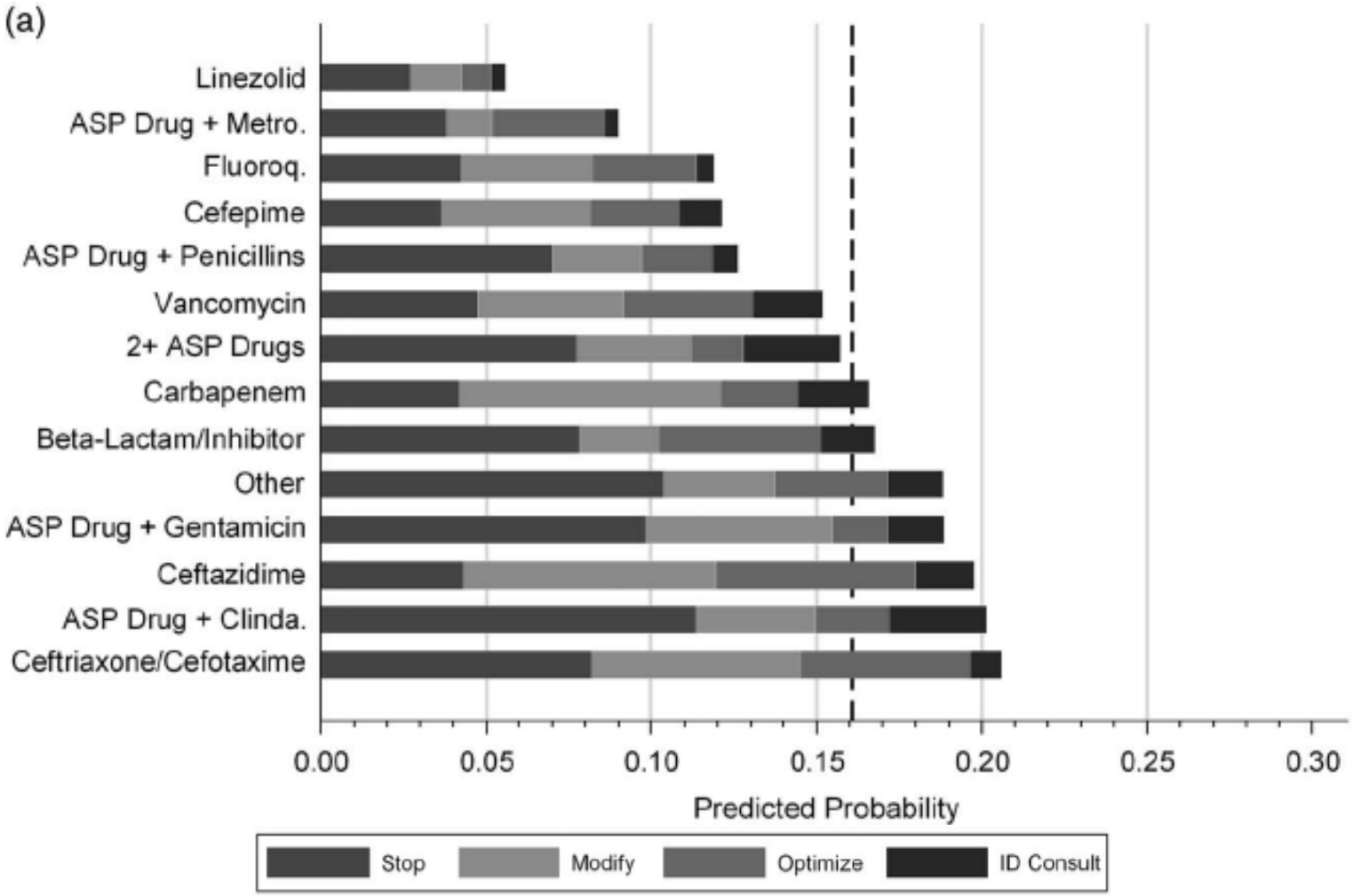
CMH ASP

TABLE 2. Diagnostic Categories for Commonly Reviewed Antimicrobial Indications

ENT (%)	Respiratory (%)	Surgery(%)	Genitourinary (%)
Tracheitis (40)	CF exacerbation (62)	Intra-abdominal process (72)	UTI (94)
Otitis media (19)	Aspiration pneumonia (17)	Appendectomy (9)	Perirectal abscess (2)
Pharyngitis (12)	HAP/VAP (14)	Postoperative management (9)	Fistula (1)
Orbital cellulitis (9)	Sinusitis (5)	VPSI (5)	Renal abscess (1)
Adenitis (9)		Surgical site infection (2)	
Mastoiditis (6)		Hardware infection (2)	
Tonsillitis (3)			

Goldman J et al. ICHE 2015 36:673-80

CMH ASP



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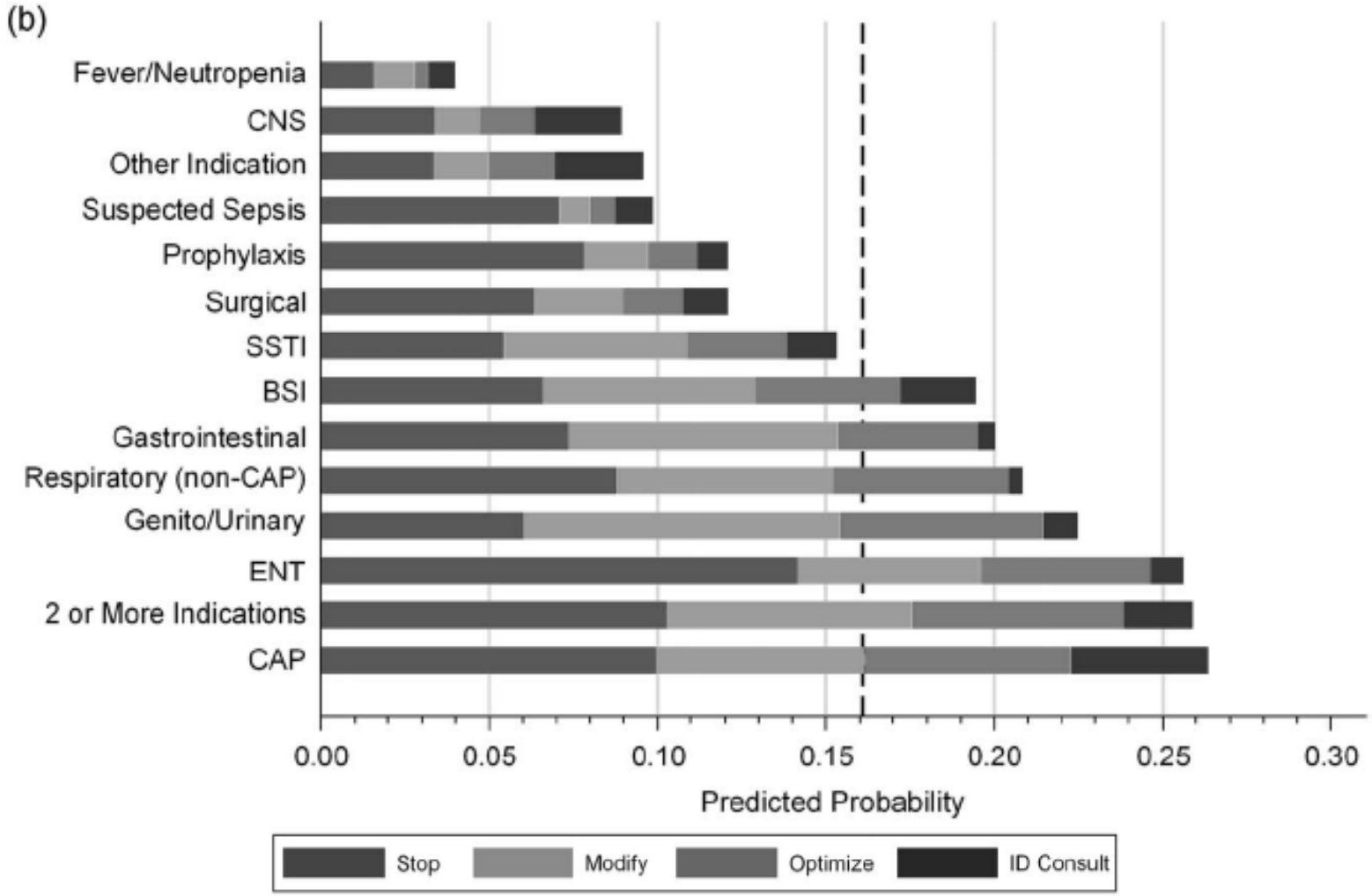
CMH ASP



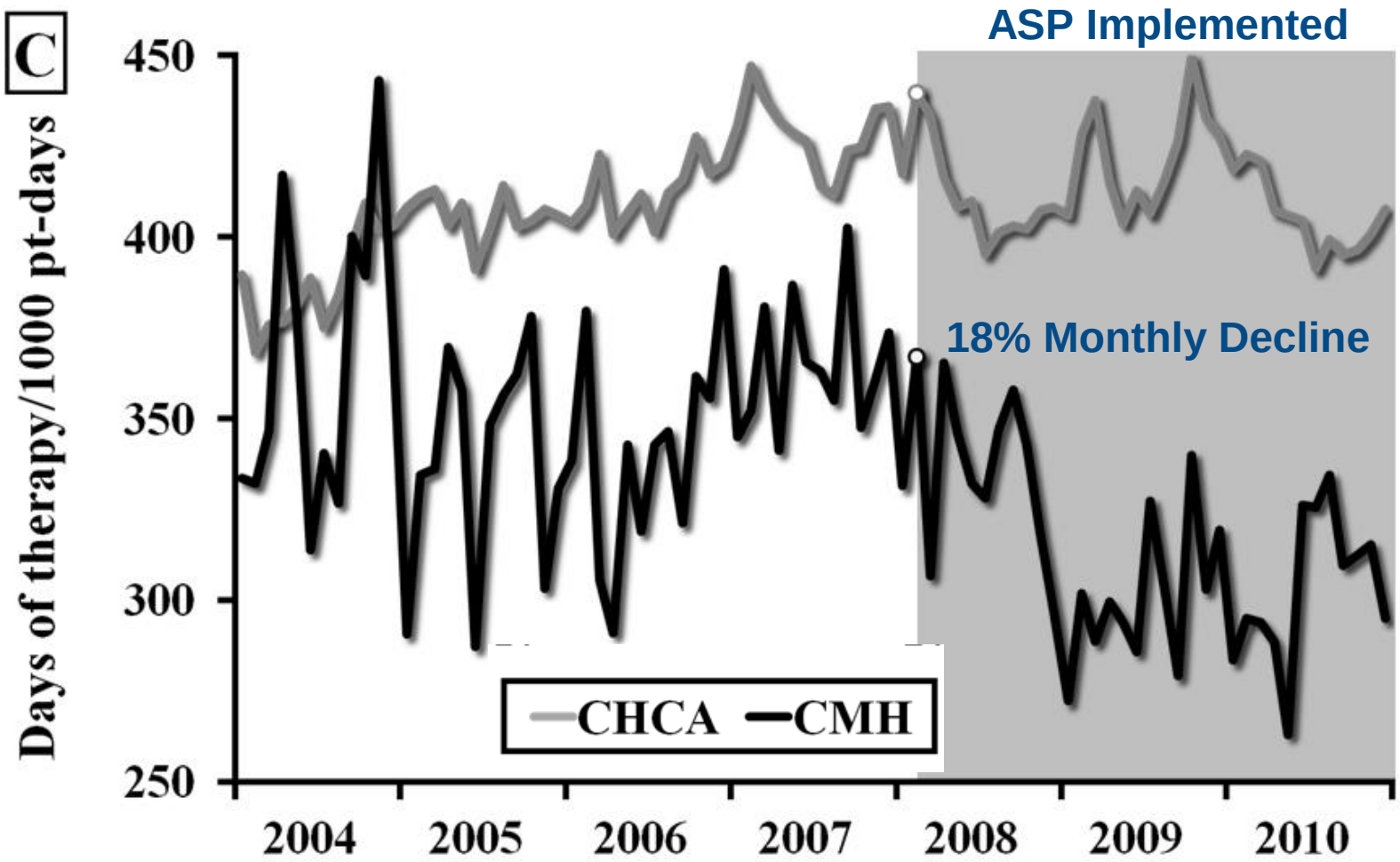
Goldman J et al. ICHE 2015 36:673-80

CMH ASP

- 22% Disagreement with recommendations
- Most common antibiotics
  - Linezolid: OR 7.2 (95% CI 2.1-24.6)
  - Carbapenem: OR 2.8 (95% CI 1.4-5.3)
- Most common indications
  - ENT: OR 4.2 (95% CI 2.4-7.2)
  - CAP: OR 4.1 (95% CI 2.4-7.0)

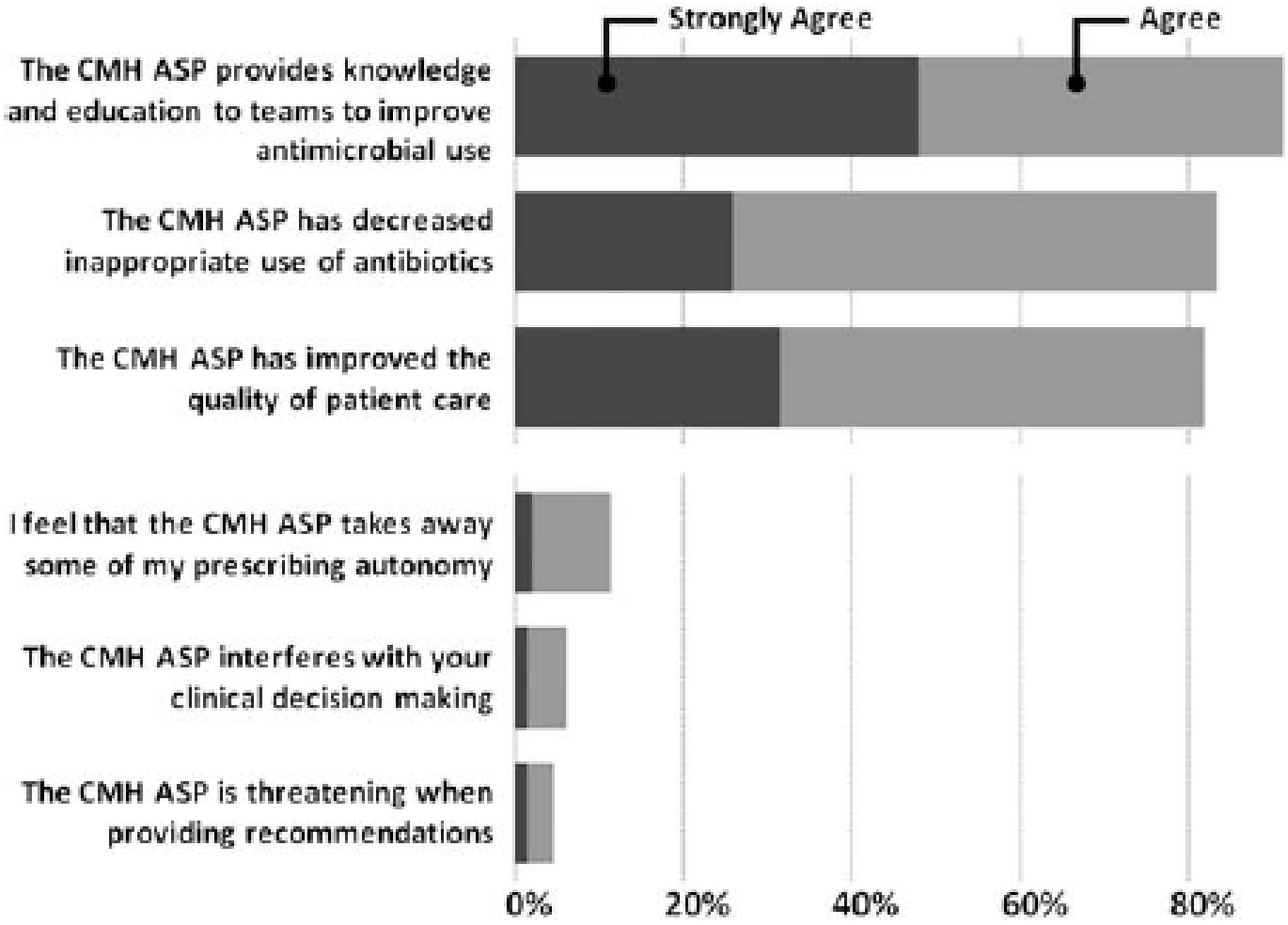
Goldman J et al. ICHE 2015 36:673-80

Results: Select Antibiotics



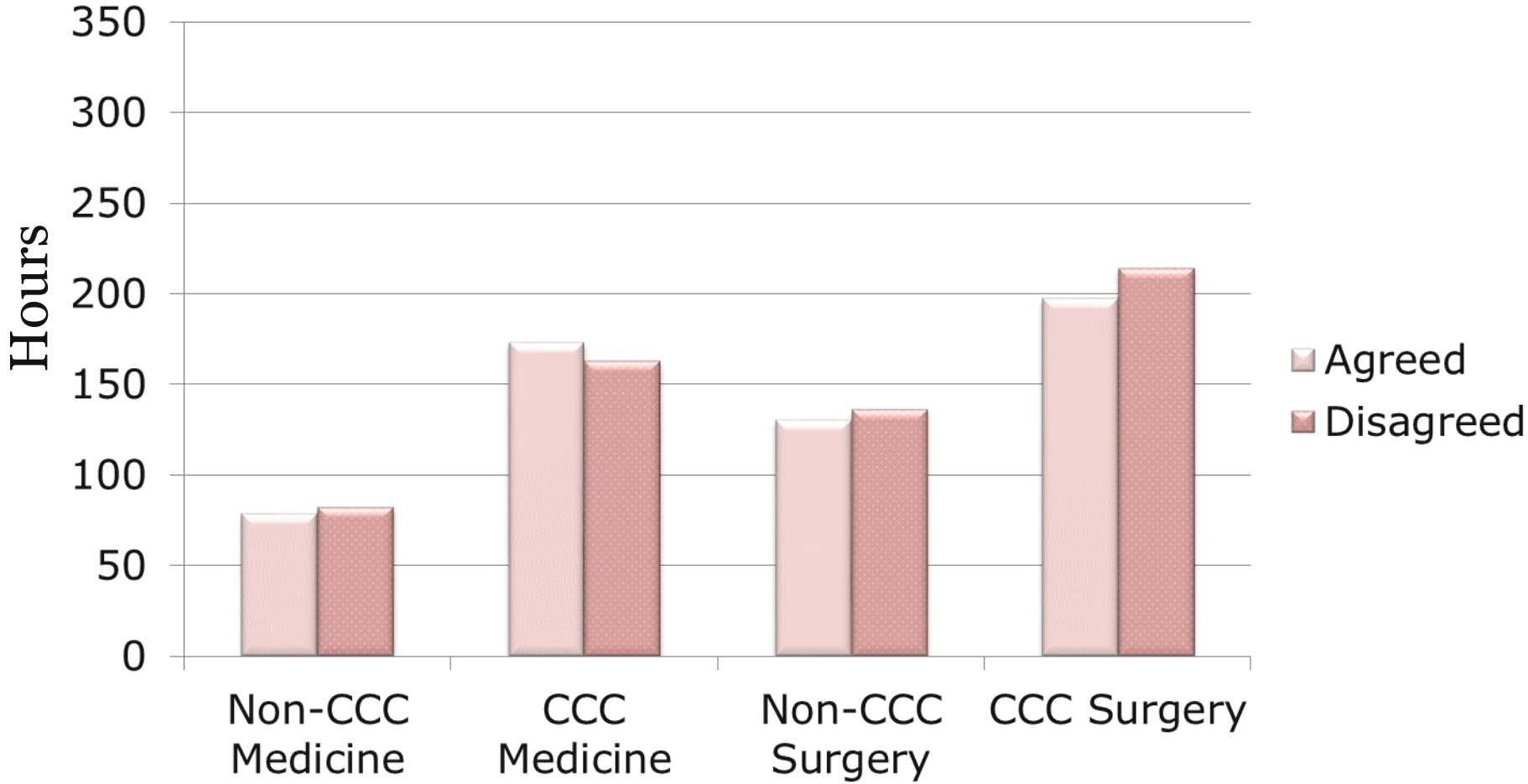
Newland JG et al. JPIDS 2012;1:179

Clinician Survey



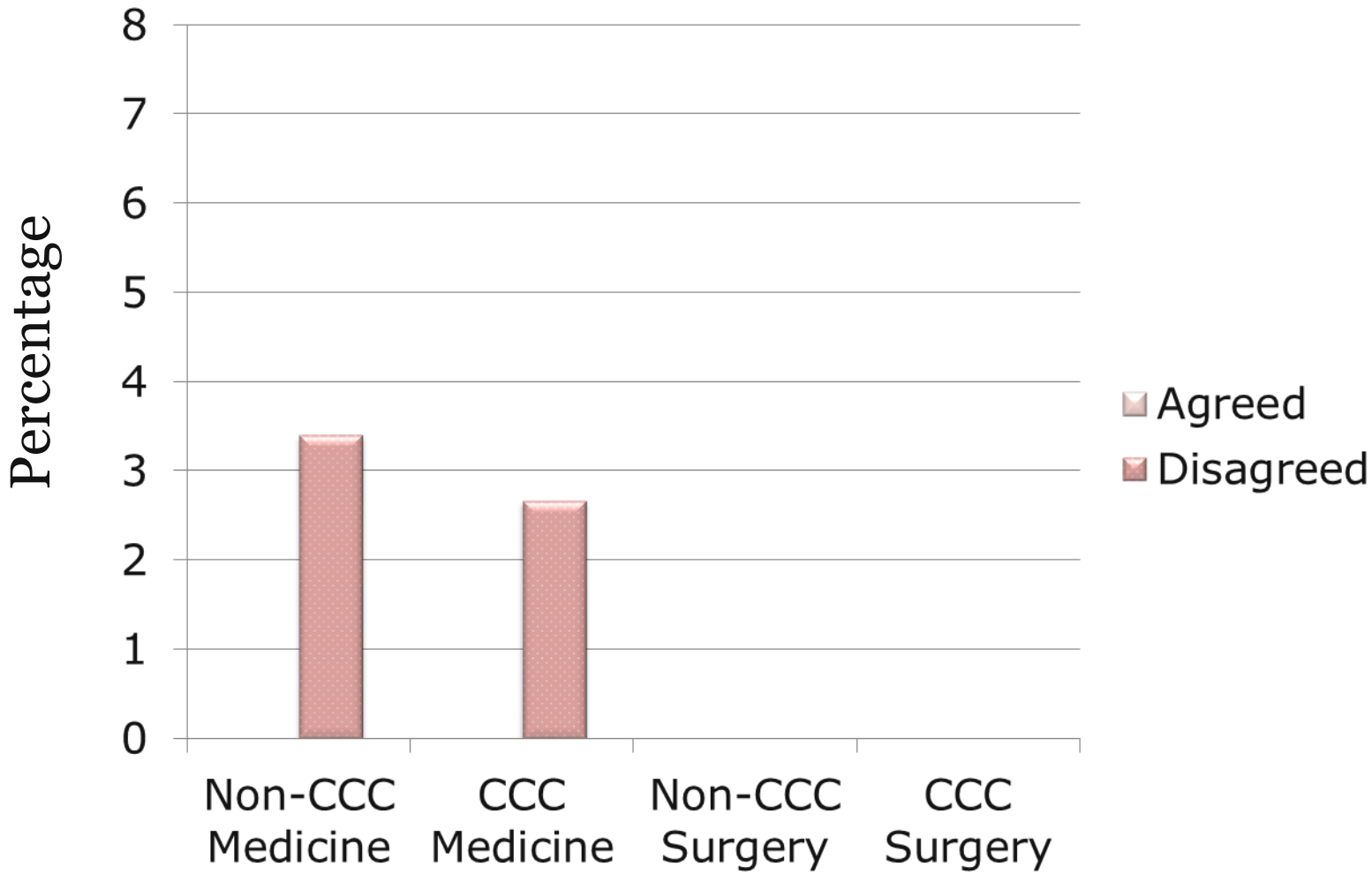
Stach LM et al. JPIDS 2012 ;1:190-197.

Agreed vs. Disagreed: LOS



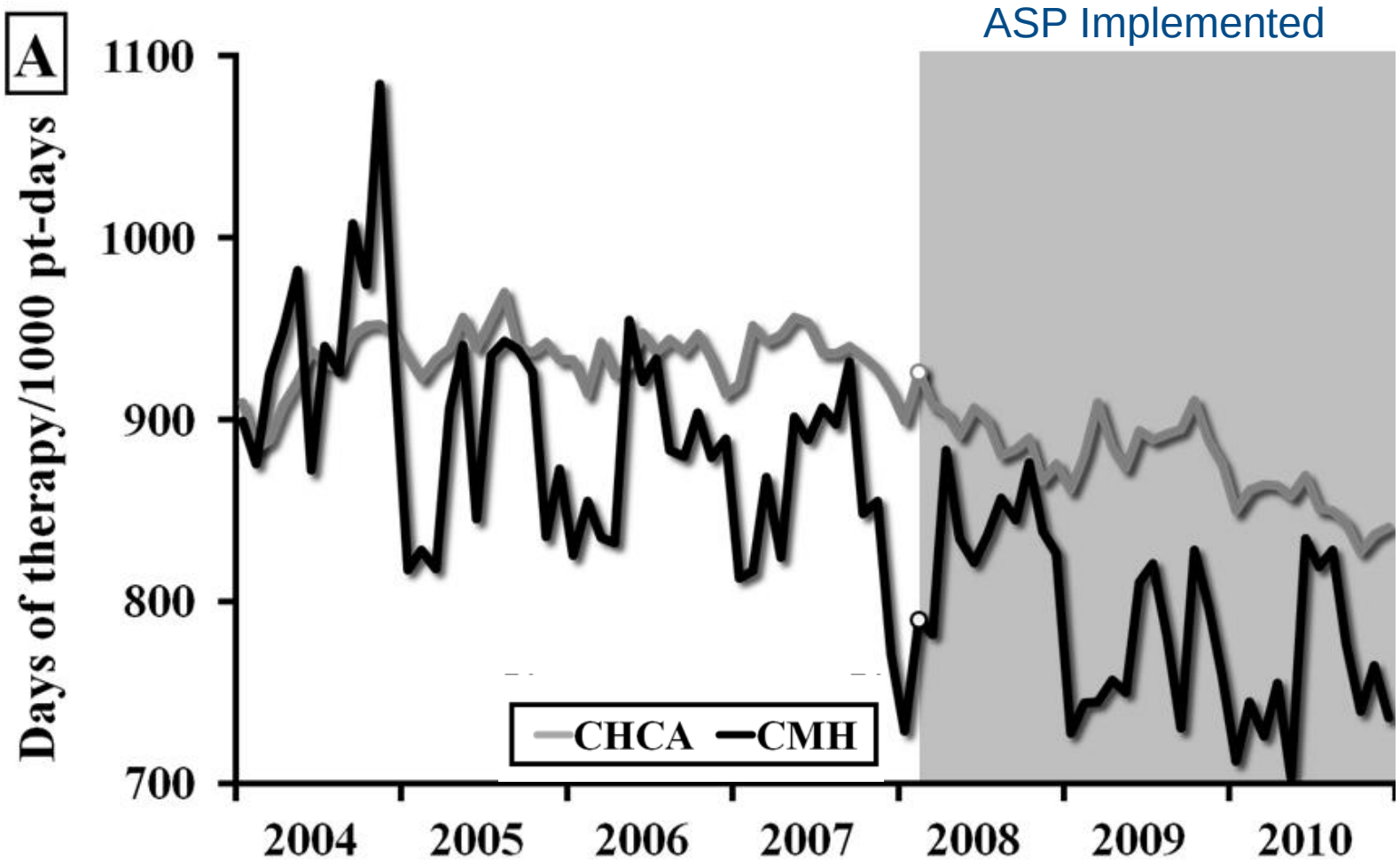
Newland JG et al. IDweek 2014

Agreed vs. Disagreed: Readmission



Newland JG et al. IDweek 2014

Results: All Antibiotics



Newland JG et al. JPIDS 2012;1:179

Children's Hospitals ASPs

TABLE 2. Comparison of Antimicrobial Management Strategies between Hospitals with and without Antimicrobial Stewardship Programs (ASPs)

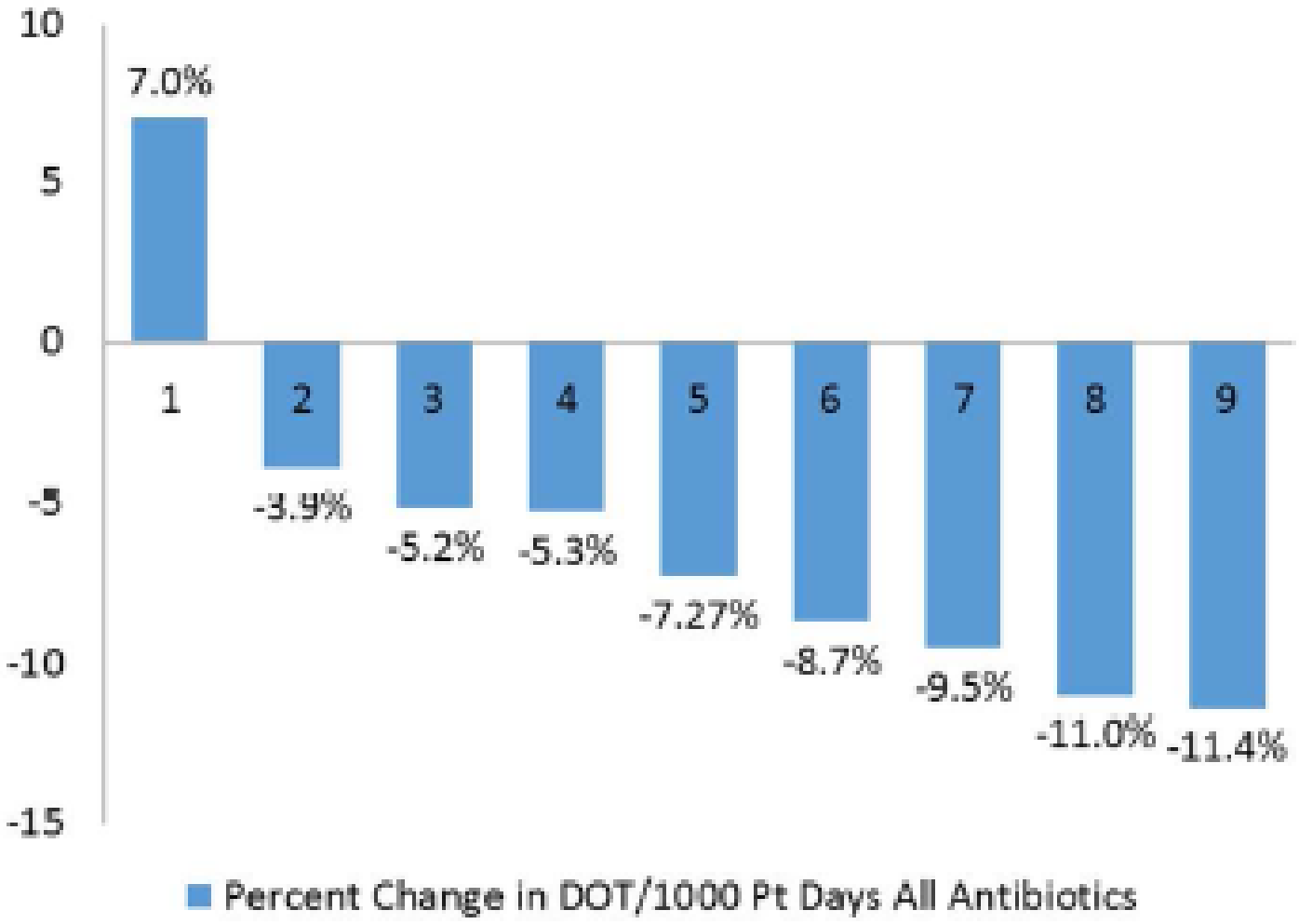
Variable	No. (%) of respondents		
	Without ASP (n = 22)	With ASP (n = 16)	P
Main approach			
Prospective audit and feedback alone	2 (9)	2 (13)	.524
Formulary restriction alone	9 (41)	3 (19)	>.99
Both	7 (32)	10 (63)	.311
Neither specified	4 (18)	1 (6)	Reference

Children's Hospitals ASPs

TABLE 2. Comparison of Antimicrobial Management Strategies between Hospitals with and without Antimicrobial Stewardship Programs (ASPs)

Variable	No. (%) of respondents: Without ASP (n = 22)	No. (%) of respondents: With ASP (n = 16)	P
Any	15 (68)	16 (100)	.014
Antimicrobial use	7 (32)	12 (75)	.02
Antimicrobial costs	5 (23)	10 (63)	.02
Antimicrobial resistance	7 (32)	6 (38)	.742
Compliance with ASP recommendations	NA	12 (75)	NA
Rate of *Clostridium difficile* infection	16 (73)	6 (38)	.047

Impact of a Formal ASP

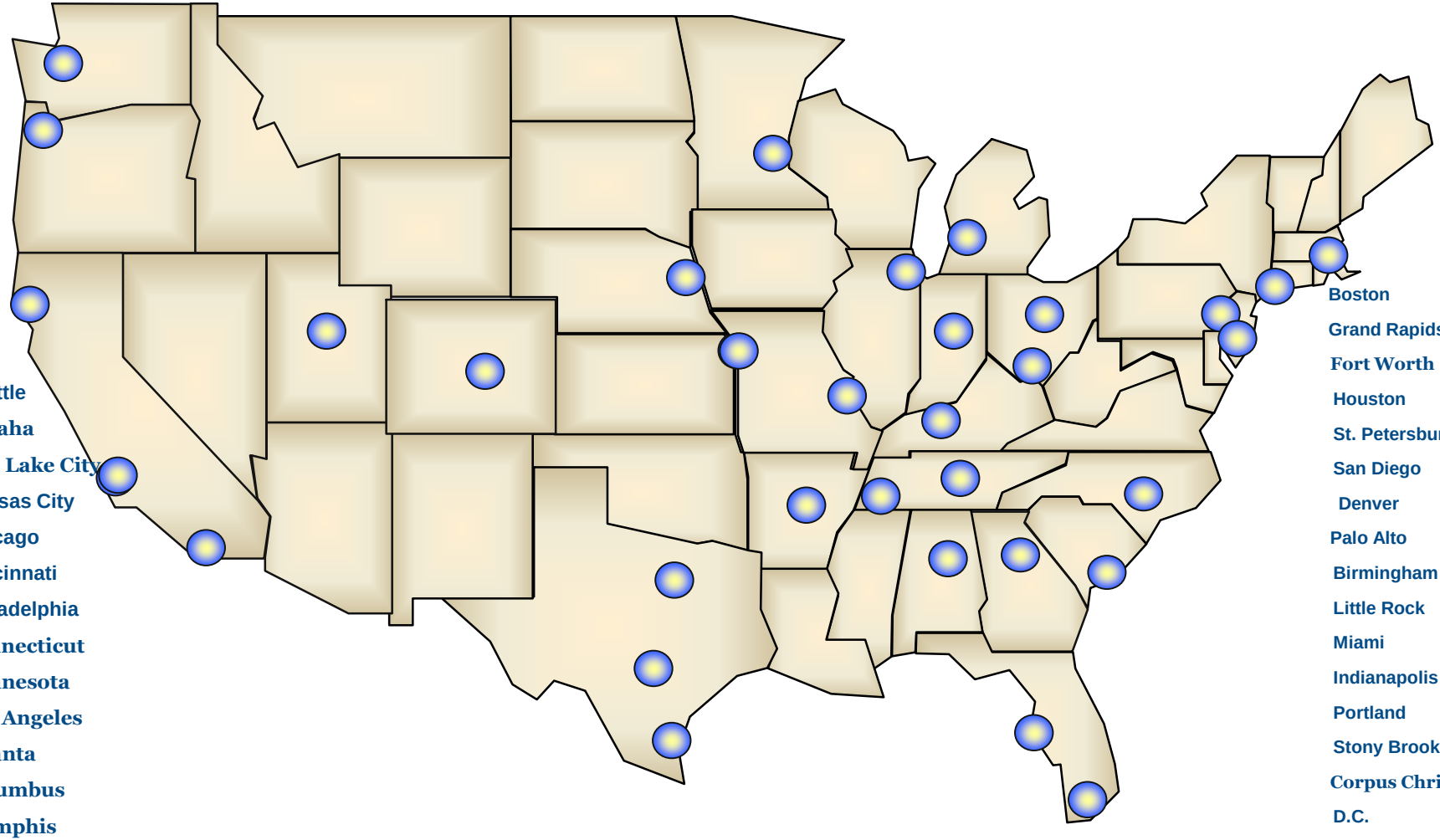


Hersh A, et al. Pediatrics 2015 135:33-9

SHARPS Collaborative

- SHaring Antimicrobial Reports for Pediatric Stewardship
- Quality improvement collaborative of 40 children's hospitals
- Utilizing PHIS reports on antibiotic use to help determine best interventions
- Social media presence: @Sharpsgroup and http://sharpsgroup.tumblr.com/

SHARPS Hospitals



Seattle
Omaha
Salt Lake City
Kansas City
Chicago
Cincinnati
Philadelphia
Connecticut
Minnesota
Los Angeles
Atlanta
Columbus
Memphis
Charleston
Louisville

Boston
Grand Rapids
Fort Worth
Houston
St. Petersburg
San Diego
Denver
Palo Alto
Birmingham
Little Rock
Miami
Indianapolis
Portland
Stony Brook
Corpus Christi
D.C.
St. Louis
Nashville

Summary

- Microbes have been developing ways to survive for billions of years
- Antimicrobial resistance will continue to impact clinical care and patient safety
- Antimicrobial Stewardship Programs are beneficial
- More work is needed to describe the clinical benefits of ASPs

Acknowledgements

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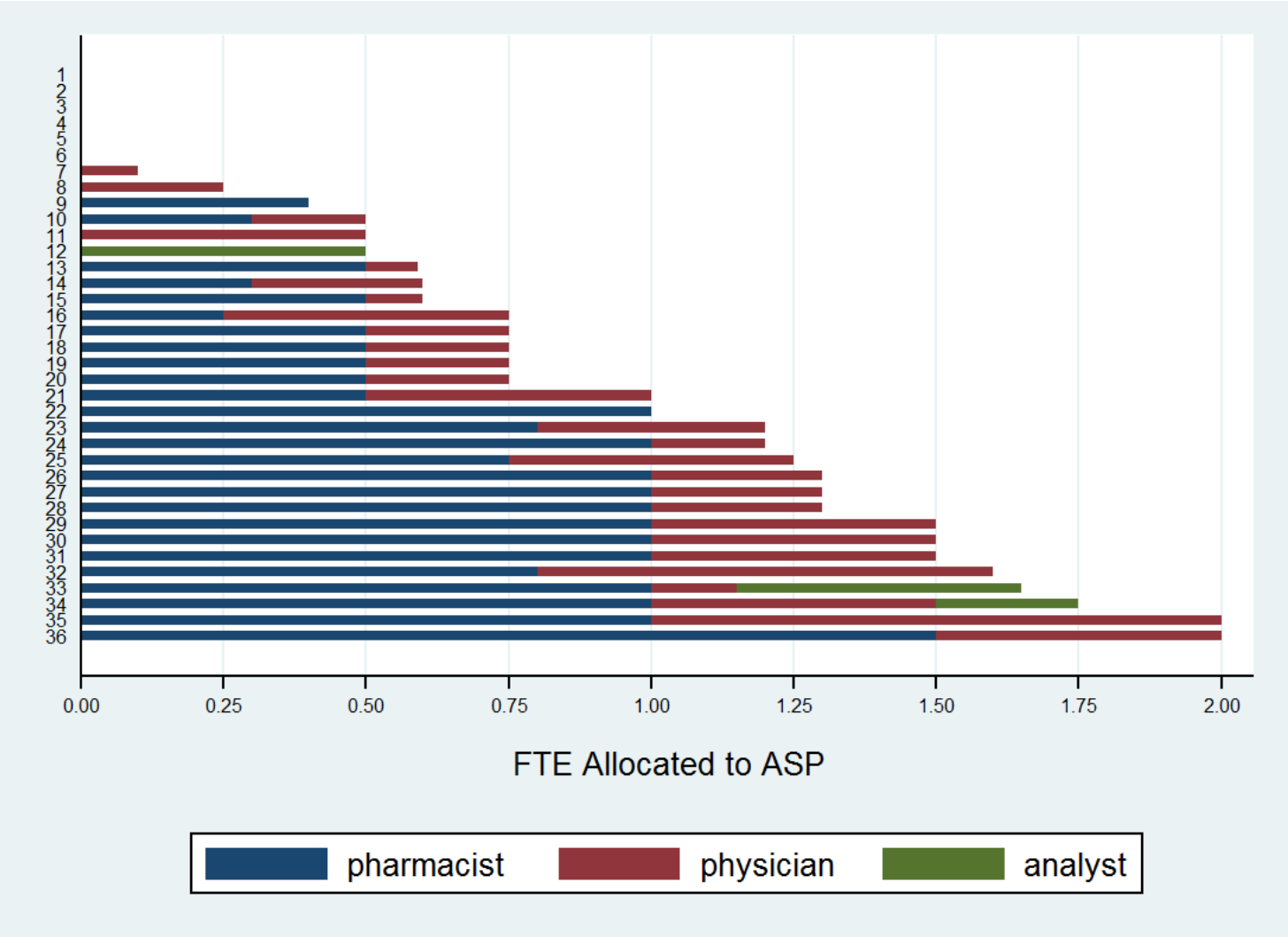
- Chris Day MD
- Jennifer Goldman MD
- Angie Myers, MD MPH
- Mary Anne Jackson MD

SHARPS Collaborative

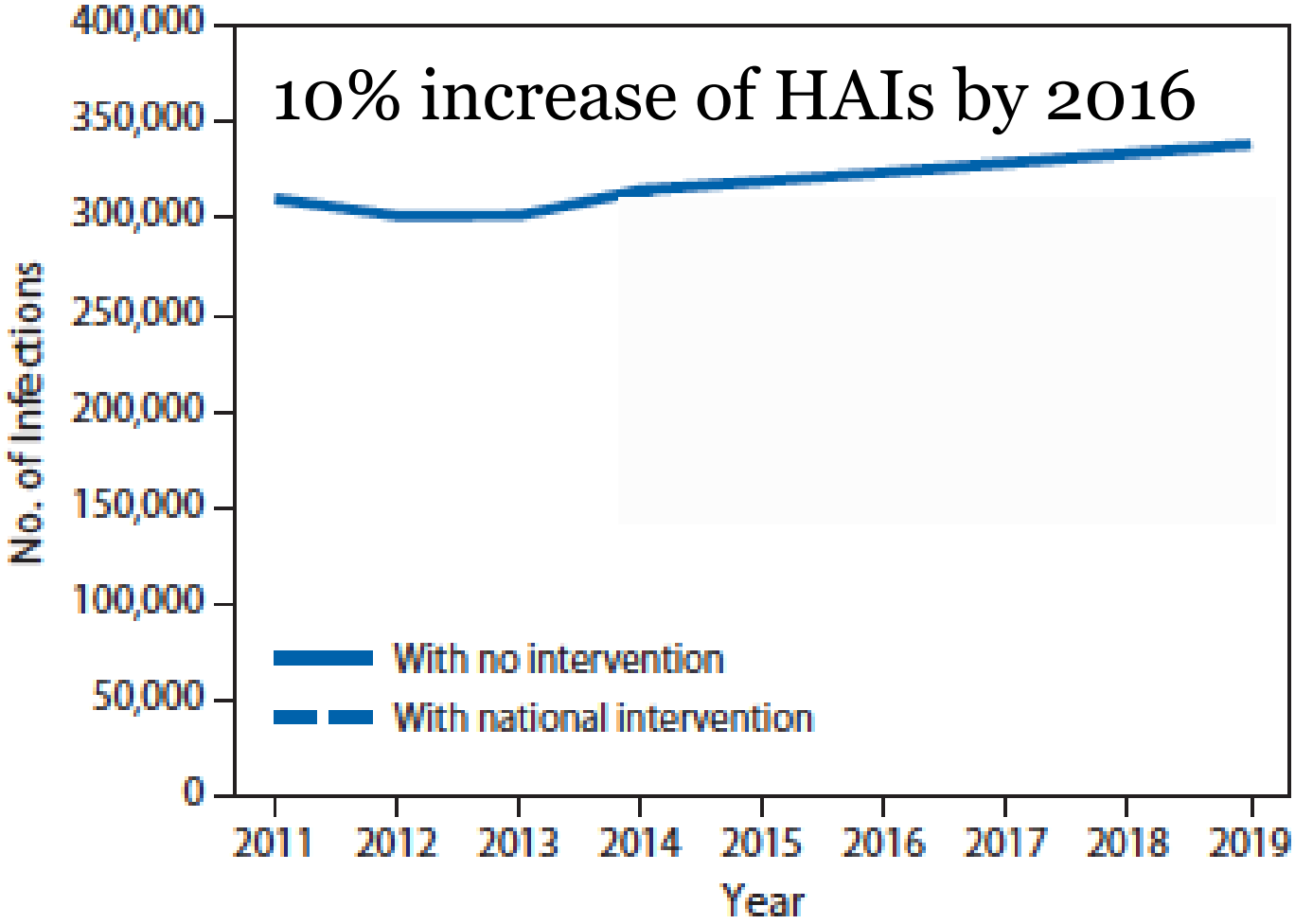


CDC Vital Signs

- Estimated the impact of a coordinated approach to reduce antibiotic resistant infections and *C. difficile* infections
- Modeled in 10 and 102 facility healthcare systems
- Impact modeled after UK and Israel which saw 30-50% reduction in infections

Slayton RB et al. MMWR 2015;64.

Impact of National Effort



Slayton RB et al. MMWR 2015;64.

Impact of National Effort

- Implementation of infection control and antibiotic stewardship will in 5 years:
  - Reduce MDR HAIs or CDI deaths by 37,000
  - Reduce MDR HAIs or CDI infections by 619,000