Antimicrobial Resistance and Antimicrobial Stewardship: An Update

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Disclosures

- None

Objectives

- Review current and emerging trends in healthcare associated infections (HAI) and antimicrobial resistance
- Discuss the evidence supporting antimicrobial stewardship
- Describe elements of effective antimicrobial stewardship programs

CEDARS-SINAI

Impact of Healthcare Associated Infections

1.7 million patients impacted annually

5-10% of hospitalized patients

99,000 Deaths annually

$28.4 - 45 Billion

estimated annual direct medical costs to US hospitals

Increasing Antimicrobial resistance

Decreasing pipeline of new antibiotics

Mandatory Reporting of HAI in California

CDC

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

Healthcare Associated Infections: Key Issues 2015

- Increasing antimicrobial resistance
- Decreasing pipeline of new antibiotics
- Public reporting now legislated in US
- Mandatory MRSA screening
- HAI Reimbursement penalties
- Health care reform

Healthcare Associated Infections
Most Common Types of Healthcare Associated Infections

Estimates of Selected* Healthcare-Associated Infections Occurring in Acute Care Hospitals, 2011± or 2012†

Type of Healthcare-Associated Infection	Estimated No.
Catheter-associated urinary tract infections (wards and critical care units)	54,500†
Central line-associated bloodstream infections (wards and critical care units)	30,100†
Surgical Site Infections associated with 10 surgical procedures	53,700†
Hospital-onset Clostridium difficile infections (all hospital locations)	107,700±

* Infections closely tied to performance measures reported as part of the CMS Hospital Quality Reporting Program

Source: CDC – Estimates of Healthcare Associated Infections

HAI Attributable Costs and Excess Length of Stay

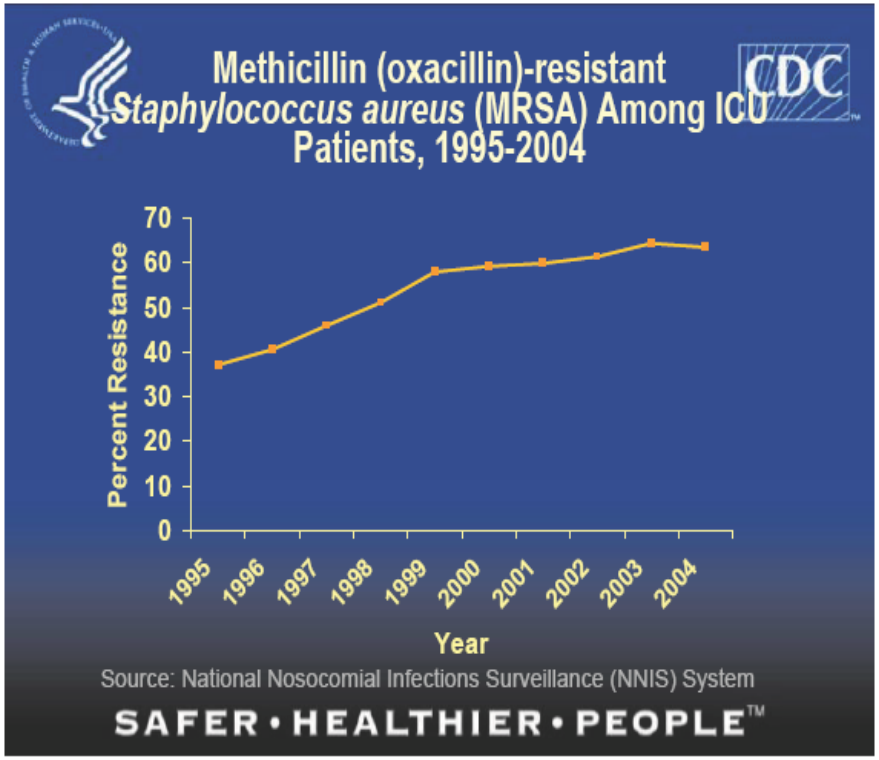
TABLE 1. Representative Reports of Attributable Costs and Excess Length of Stay (LOS) Associated With Various Hospital-Acquired Infections

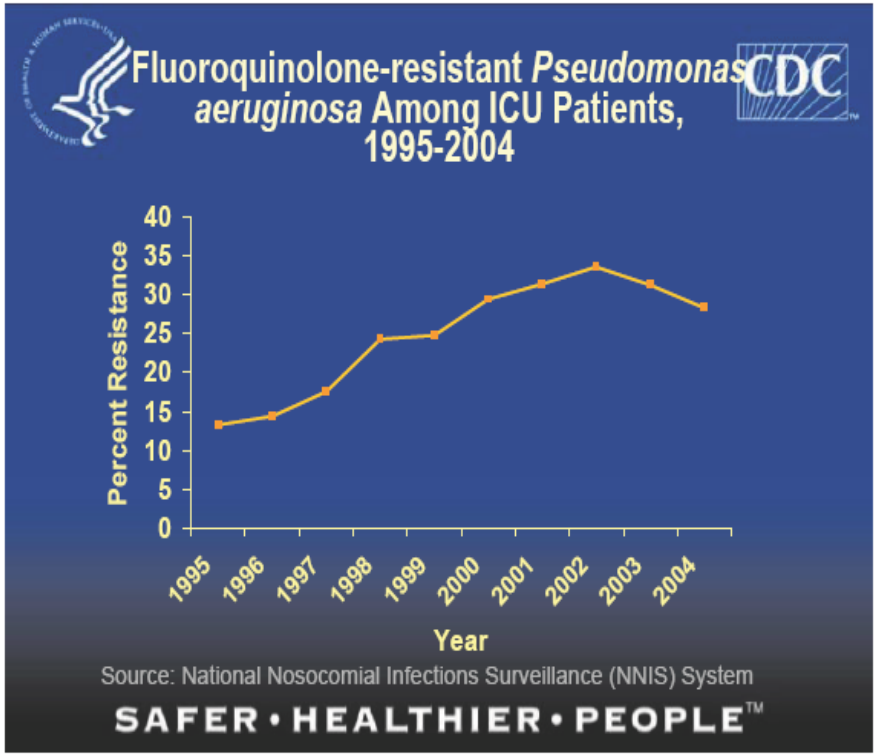
Infection type	Attributable costs, mean (range), 2005 US$	Excess LOS, mean (range), days	Reports
VAP	22,875 (9,986-54,503)	9.6 (7.4-11.5)	[19-23]
Catheter-related BSI	18,432 (3,592-34,410)	12 (4.5-19.6)	[24-26]
CABG-associated SSI	17,944 (7,874-26,668)	25.7 (20-35)	[27-30]
Catheter-associated UTI	1,257 (804-1,710)	...	[31, 32]

NOTE. BSI, bloodstream infection; CABG, coronary artery bypass graft surgery; SSI, surgical site infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

Perencevich et al *Infect Control Hosp Epidemiol* 2007; 28:1121-1133

Resistance Rates in the ICU





http://www.cdc.gov/ncidod/dhqp/pdf/ar/ICU_RESTrend1995-2004.pdf

NHSN Antimicrobial Resistance Trends 2009-2010

- MRSA trends stabilized
- *Acinetobacter* spp
  - >60% reported multidrug resistance and carbapenem resistance (CR)
  - 70%–80% of facilities reporting an HAI with *Acinetobacter* spp. reported at least one multidrug-resistant strain
- *Klebsiella* spp.
  - 13% carbapenem resistance (CR)
  - 1 in 5 hospitals reporting CLABSIs or CAUTIs with *Klebsiella* spp. reported CR

- Conclusion:
  - highly resistant GNB causing HAIs not limited to a small subset of hospitals
  - reinforces need for prevention efforts designed to prevent further emergence and spread

TABLE 8. Percentage of Pathogenic Isolates Resistant to Selected Antimicrobial Agents, by Location of Patient Reported to the National Healthcare Safety Network, 2009–2010

	CLABSI		CAUTI	
Pathogen, antimicrobial agents[a]	ICU	Non-ICU	ICU	Non-ICU
Staphylococcus aureus, oxacillins	51.5	59.3	52.0	63.3
Enterococcus species				
E. faecium, vancomycin	83.6	80.7	81.8	83.1
E. faecalis, vancomycin	9.4	9.5	5.5	11.8
Klebsiella (*pneumoniae/oxytoca*)				
ES cephalosporins 4	29.7	27.7	24.6	29.0
Carbapenems	14.2	10.9	12.4	12.6
Multidrug resistant 1	19.1	13.7	15.2	17.0
Escherichia coli				
ES cephalosporins 4	18.6	19.5	11.5	13.2
Fluoroquinolones 3	36.5	47.1	29.1	33.5
Carbapenems	1.9	2.0	1.7	2.9
Multidrug resistant 1	3.4	4.0	1.6	2.3
Enterobacter species				
ES cephalosporins 4	38.0	36.2	38.8	38.2
Carbapenems	4.9	2.2	5.5	3.5
Multidrug resistant 1	4.0	3.1	4.6	5.0
Pseudomonas aeruginosa				
Aminoglycosides	11.6	7.5	11.8	9.9
ES cephalosporins 2	28.3	22.6	22.5	28.3
Fluoroquinolones 2	30.3	30.8	31.8	35.5
Carbapenems	26.8	24.9	20.6	22.3
Piperacillin/tazobactam	19.6	13.8	16.1	17.1
Multidrug resistant 2	16.8	13.3	12.6	15.6
Acinetobacter baumannii				
Carbapenems	64.5	56.1	73.8	75.0
Multidrug resistant 3	69.7	60.4	78.6	76.1

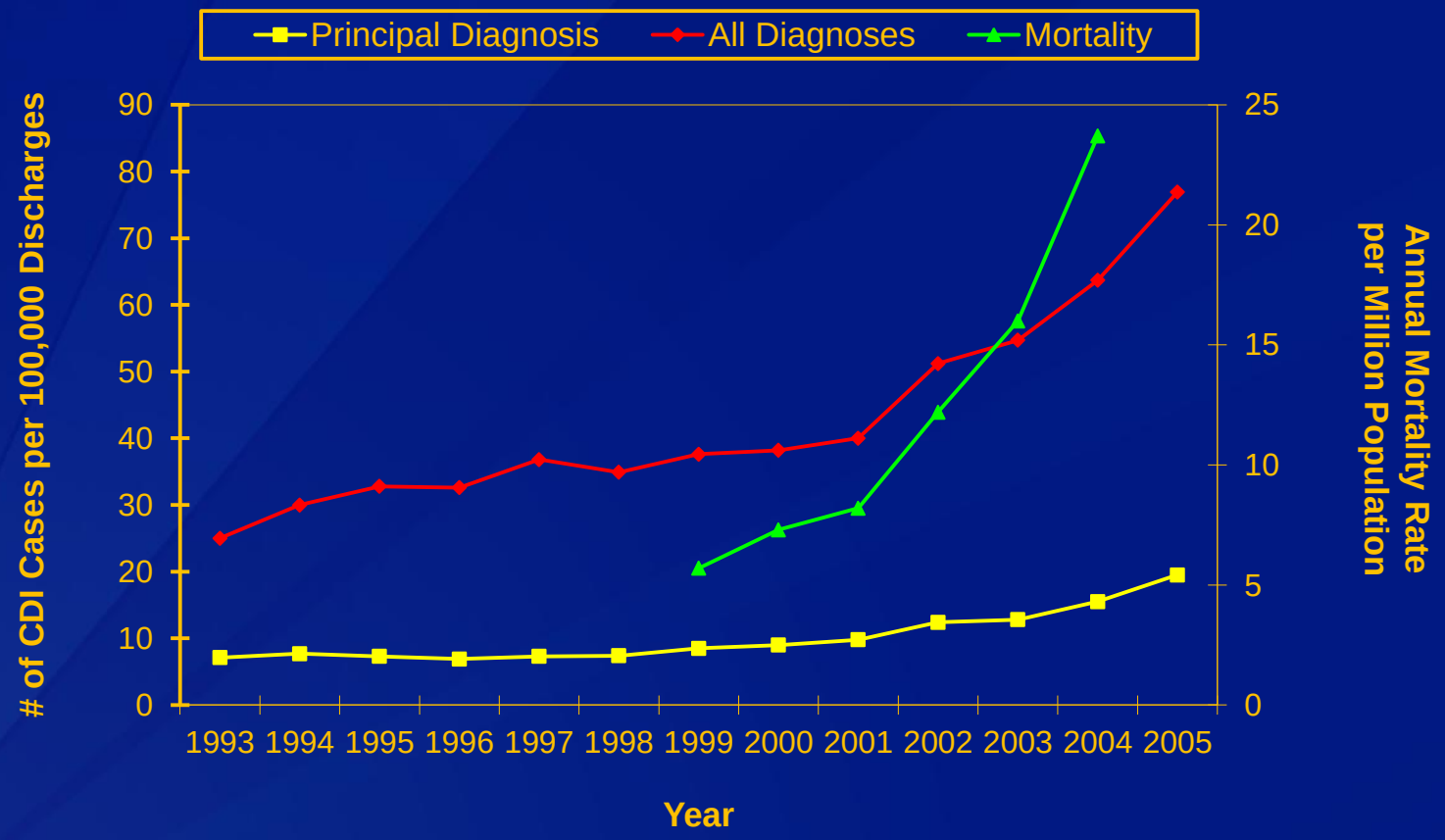
Dawn et al ICHE Vol. 34, No. 1 (January 2013), pp. 1-14

CDC Report 2013

Susceptibility Profile of KPC-Producing *K. pneumoniae*

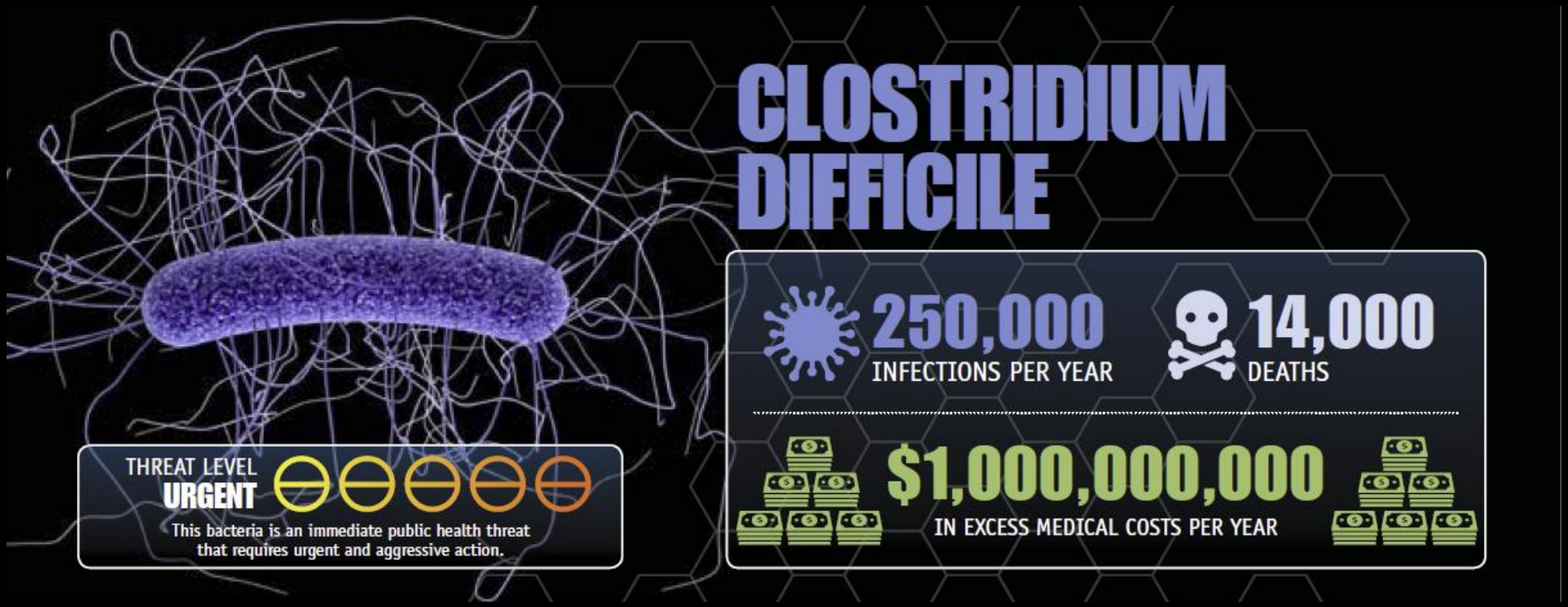
Antimicrobial	Interpretation	Antimicrobial	Interpretation
Amikacin	I	Chloramphenicol	R
Amox/clav	R	Ciprofloxacin	R
Ampicillin	R	Ertapenem	R
Aztreonam	R	Gentamicin	R
Cefazolin	R	Imipenem	R
Cefpodoxime	R	Meropenem	R
Cefotaxime	R	Pipercillin/Tazo	R
Cetotetan	R	Tobramycin	R
Cefoxitin	R	Trimeth/Sulfa	R
Ceftazidime	R	Polymyxin B	MIC >4mg/ml
Ceftriaxone	R	Colistin	MIC >4mg/ml
Cefepime	R	Tigecycline	R

C. difficile Incidence and mortality are increasing in US



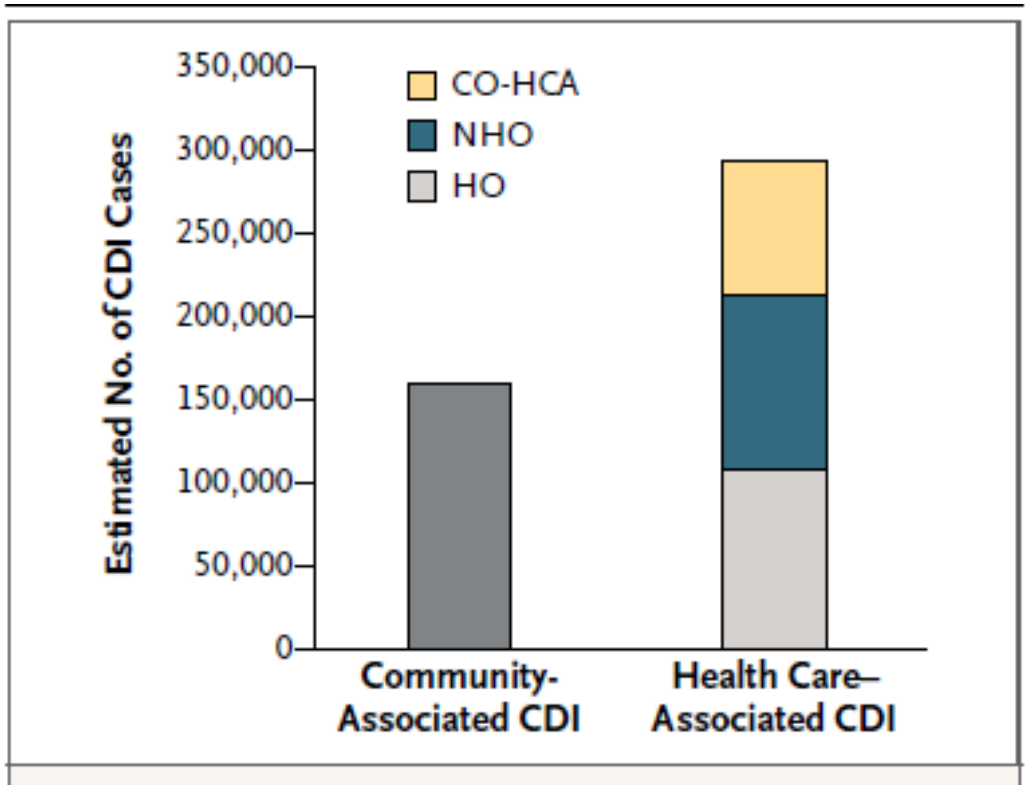
Elixhauser A, et al. Healthcare Cost and Utilization Project: Statistical Brief #50. April 2008. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf. Accessed March 10, 2010.
Redelings MD, et al. Emerg Infect Dis. 2007;13:1417-1419.

CDC Report

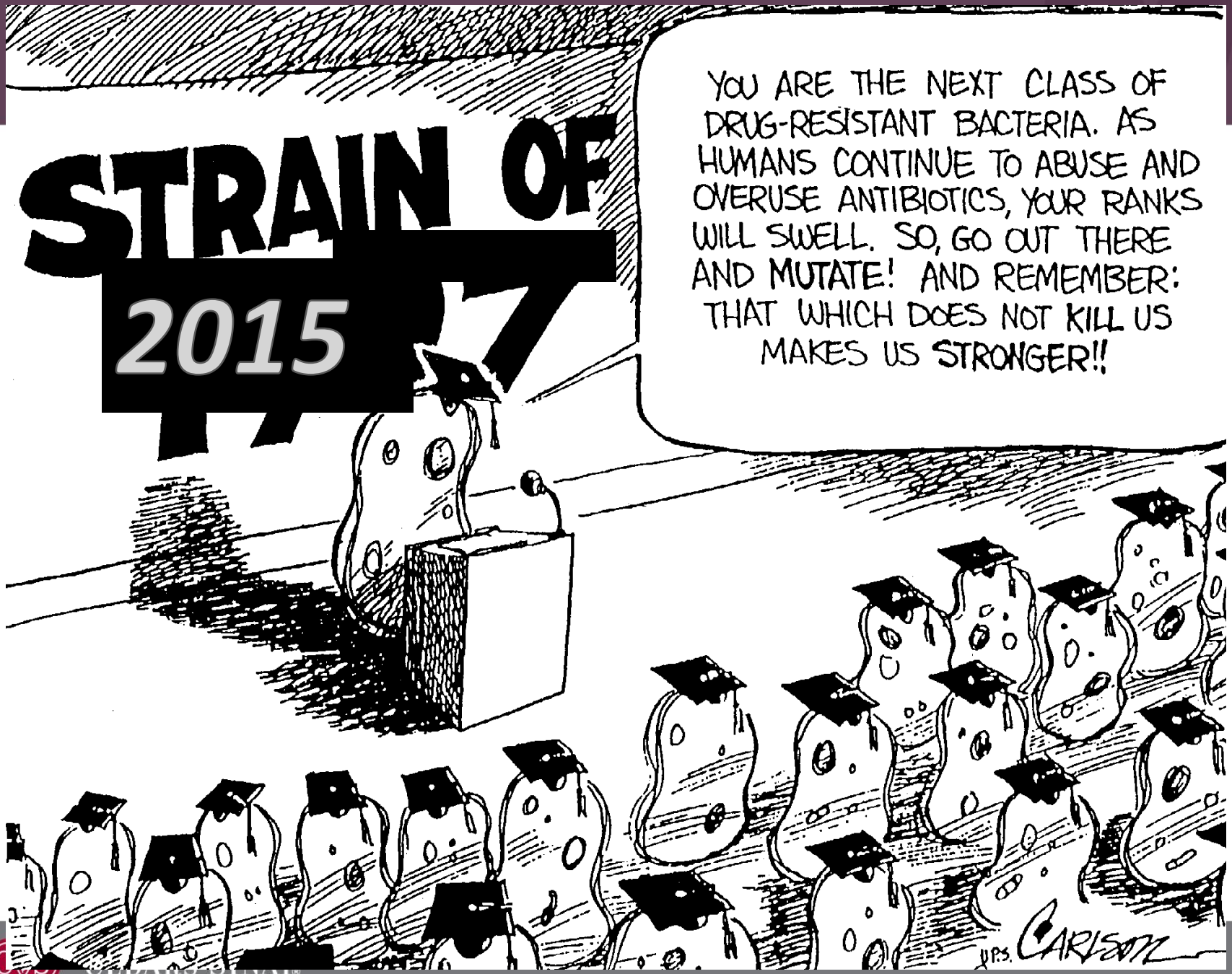

CLOSTRIDIUM DIFFICILE
250,000
INFECTIONS PER YEAR
14,000
DEATHS
$1,000,000,000
IN EXCESS MEDICAL COSTS PER YEAR
THREAT LEVEL
URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.

Estimated Burden of *C. difficile* Infection in the US

- Almost 500,000 cases and 29,000 deaths
- 82% of CA-CDI estimated to be associated with outpatient health care exposure



Lessa et al N Engl J Med 2015;372:825-34.


STRAIN OF
2015
YOU ARE THE NEXT CLASS OF DRUG-RESISTANT BACTERIA. AS HUMANS CONTINUE TO ABUSE AND OVERUSE ANTIBIOTICS, YOUR RANKS WILL SWELL. SO, GO OUT THERE AND MUTATE! AND REMEMBER: THAT WHICH DOES NOT KILL US MAKES US STRONGER!!
J.P.S. CARLSON

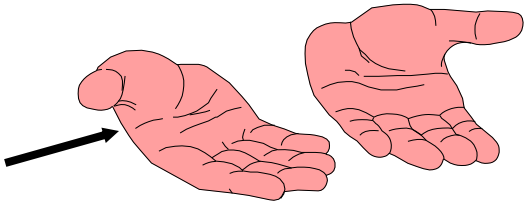
Factors Increasing Antibiotic Resistance

Patient

- Increased severity of illness
- More severely immunocompromised patients
- Newer devices and procedures
- Resistance in the community
- International travel, migration, distribution of fresh produce and prepared food items

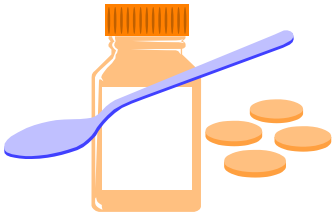
Healthcare worker

- Ineffective infection control and compliance
- Increased prophylactic, empiric antibiotics
  - Inappropriate and prolonged use of antibiotics



Others

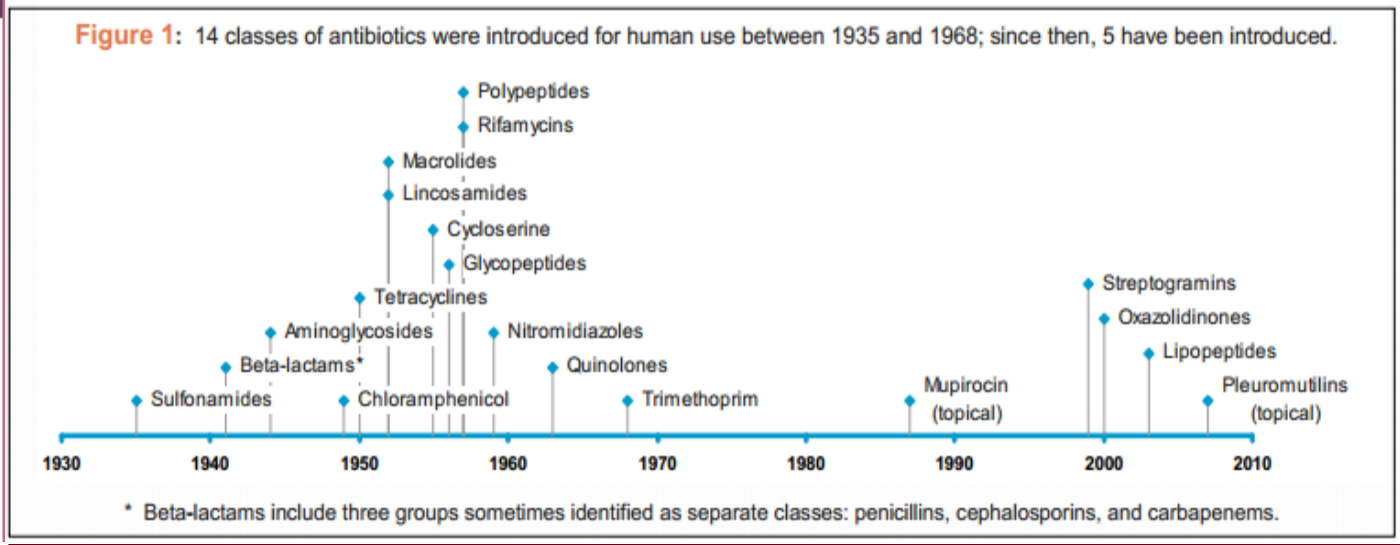
- Higher antibiotic use per area per unit time
  - Over-the-counter availability of antibiotics
  - Antibiotics used in animal feeds

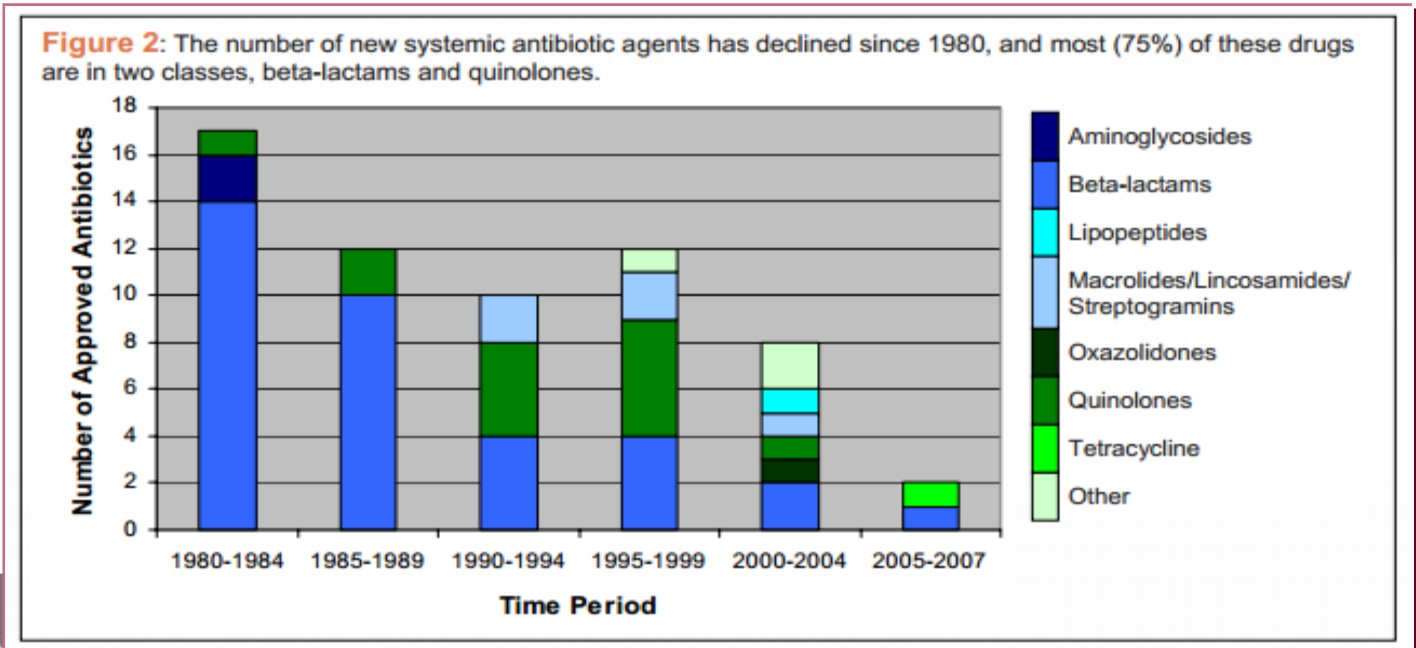


CID 1997;25:584-99

Declining Number of Antimicrobial Agents Approved

Number of new systemic antibiotic agents has declined since 1980

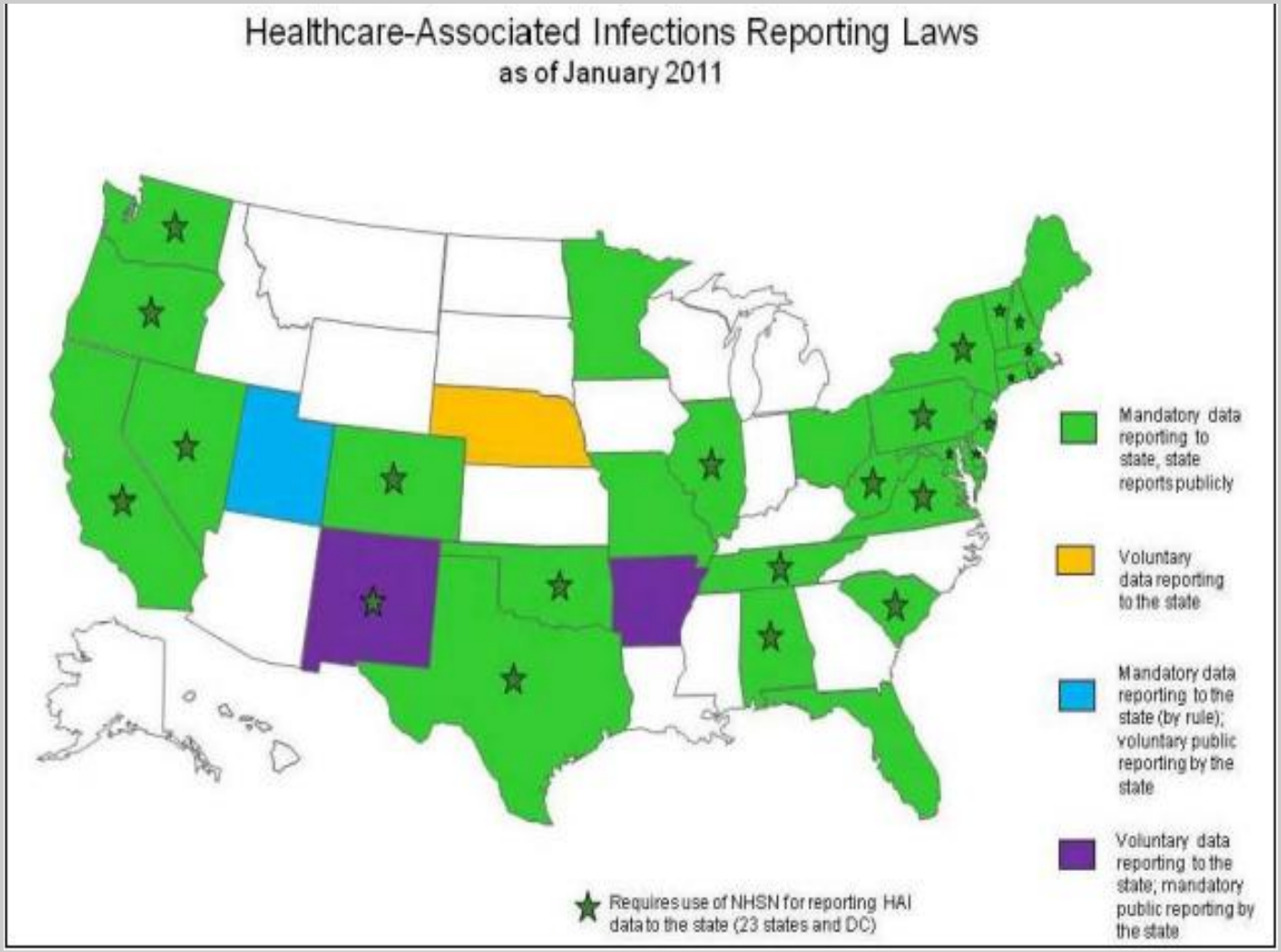




Source: http://www.cddep.org/sites/default/files/policy_brief6_may08_newdrugs1_6.pdf


CHANGE
AHEAD

Regulatory Requirements: State & Local



California Senate Bill 1311 : Antimicrobial Stewardship Program (ASP) Requirements

Each general acute care hospital, as defined in subdivision (a) of Section 1250, shall do all of the following by July 1, 2015:

(a) Adopt and implement an antimicrobial stewardship policy in accordance with guidelines established by the federal government and professional organizations. This policy shall include a process to evaluate the judicious use of antibiotics in accordance with paragraph (3) of subdivision (a) of Section 1288.8.

(b) Develop a physician supervised multidisciplinary antimicrobial stewardship committee, subcommittee, or workgroup.

(c) Appoint to the physician supervised multidisciplinary antimicrobial stewardship committee, subcommittee, or workgroup, at least one physician or pharmacist who is knowledgeable about the subject of antimicrobial stewardship through prior training or attendance at continuing education programs, including programs offered by the federal Centers for Disease Control and Prevention, the Society for Healthcare Epidemiology of America, or similar recognized professional organizations.

(d) Report antimicrobial stewardship program activities to each appropriate hospital committee undertaking clinical quality improvement activities.

Antibiotic Misuse

Five Truths About In-patient Antibiotic Use

- Antibiotics are misused in hospitals
- Antibiotic misuse is bad
- Improving antibiotic use can improve medical care
- There are many ways to improve antibiotic use
- Every facility can improve antibiotic use

Antibiotics are misused in hospitals

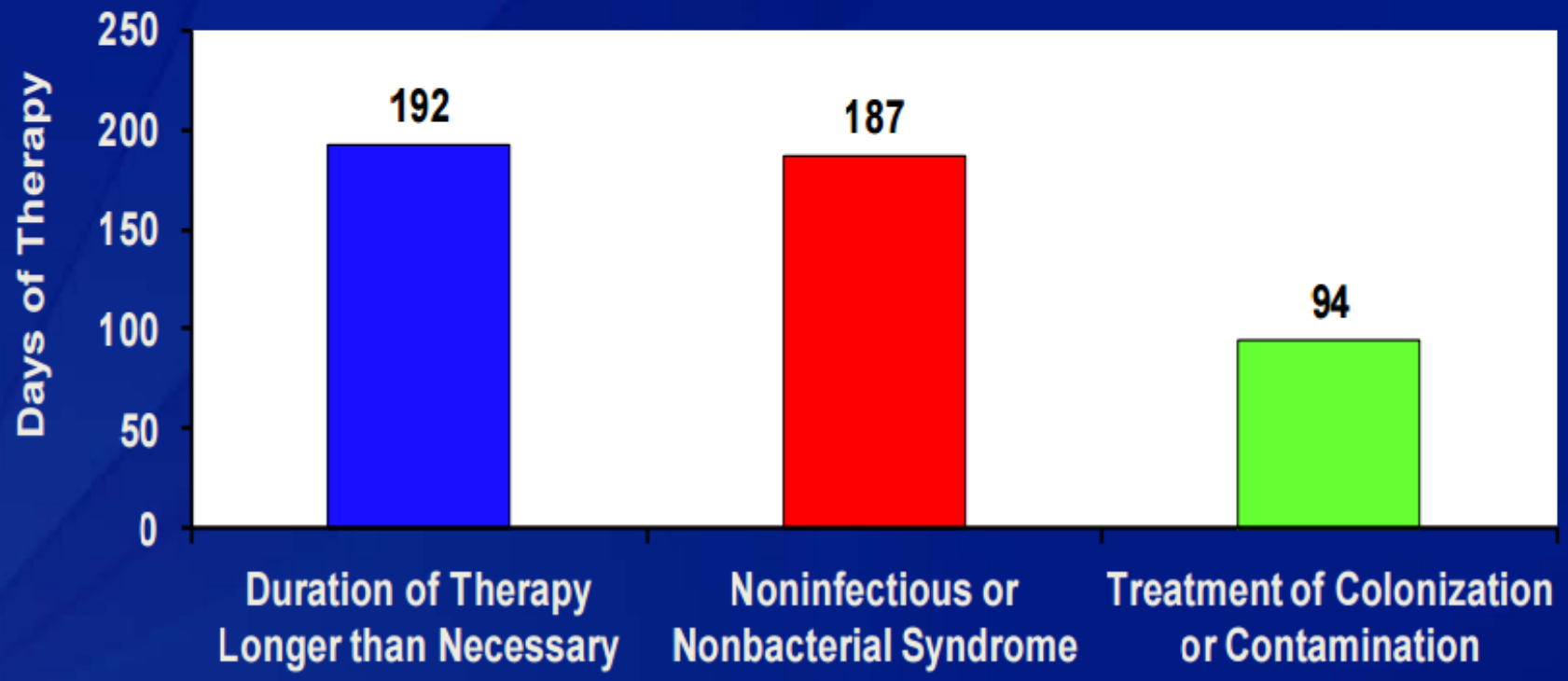
- "It has been recognized for several decades that up to 50% of antimicrobial use is inappropriate"
- IDSA/SHEA Guidelines for Antimicrobial Stewardship Programs
- http://www.journals.uchicago.edu/doi/pdf/10.1086/510393

Antibiotic are misuse in a variety of ways

- Given when they are not needed
- Continued when they are no longer necessary
- Given at the wrong dose
- Broad spectrum agents are used to treat very susceptible bacteria
- The wrong antibiotic is given to treat an infection

Most Common Reasons for Unnecessary Days of Therapy

576 (30%) of 1941 days of antimicrobial therapy deemed unnecessary



Hecker MT et al. *Arch Intern Med.* 2003;163:972-978.

Antibiotic misuse adversely impacts patients- *C. difficile*

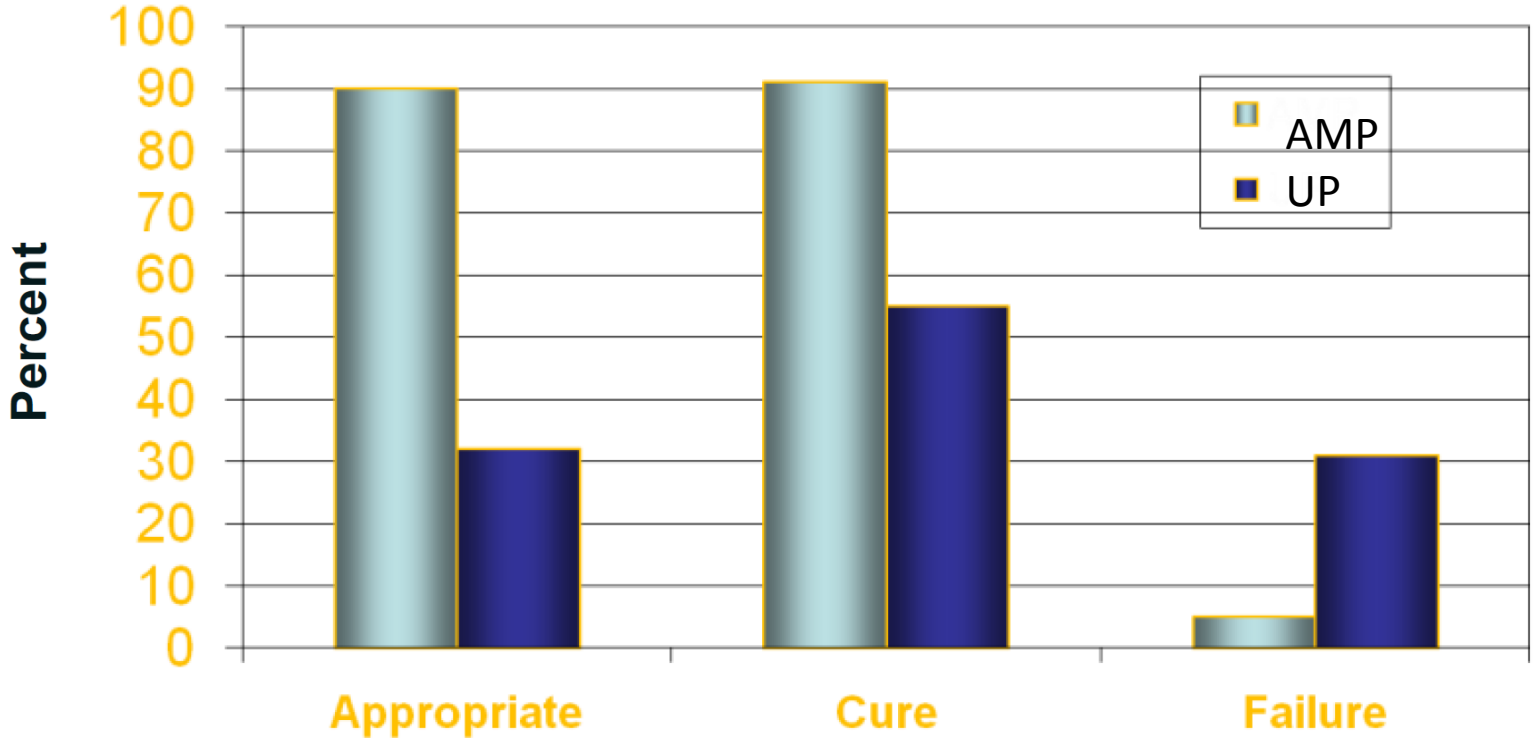
- **Antibiotic exposure is the single most important risk factor for the development of *Clostridium difficile* associated disease (CDAD).**
  - Up to 85% of patients with CDAD have antibiotic exposure in the 28 days before infection[1]

1. Chang HT et al. *Infect Control Hosp Epidemiol 2007;* 28:926–931.

Does Antimicrobial Stewardship work?

"The first step toward change is awareness"

Clinical outcomes better with antimicrobial management program



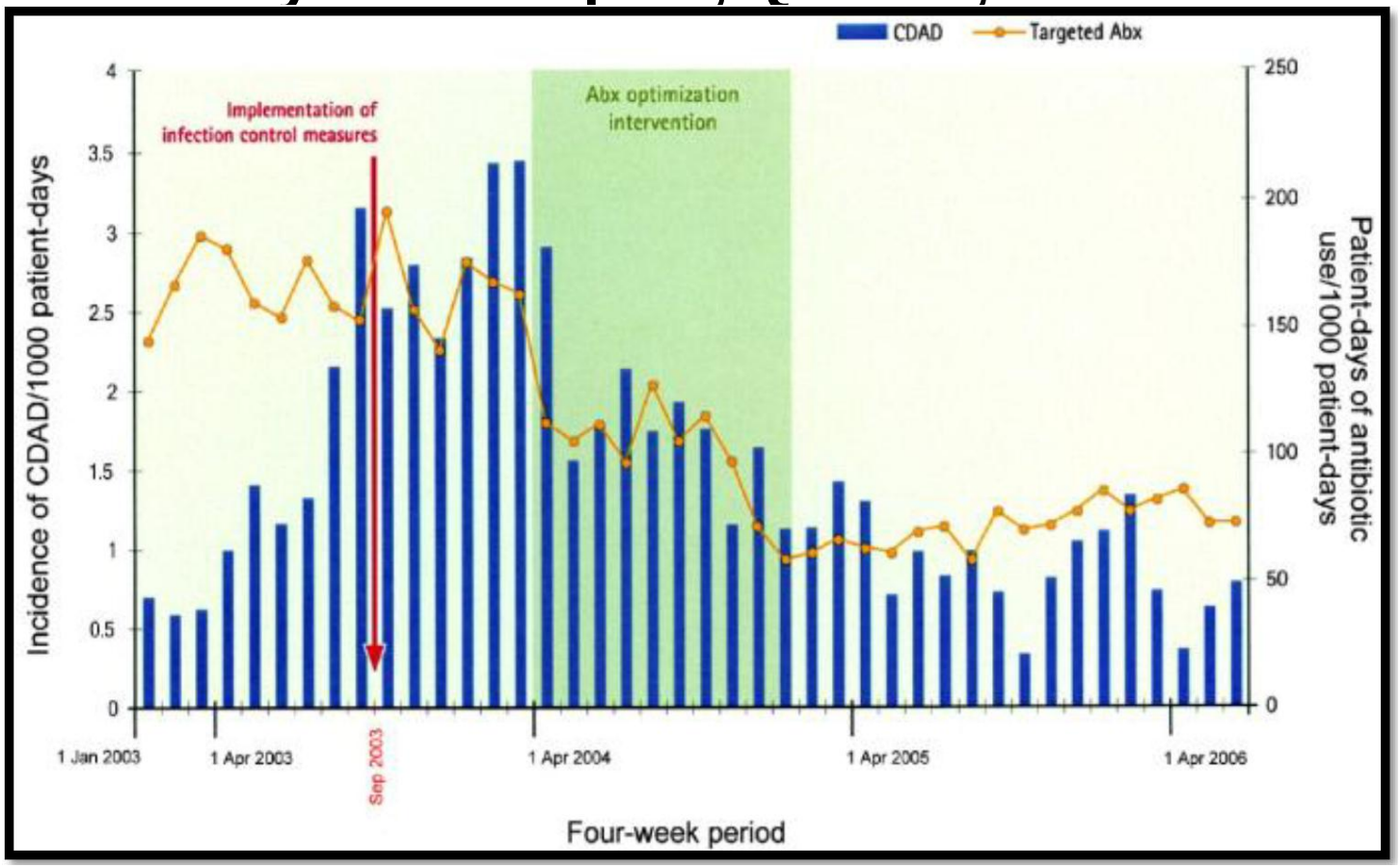
RR 2.8 (2.1-3.8) RR 1.7 (1.3-2.1) RR 0.2 (0.1-0.4)

AMP = Antibiotic Management Program UP = Usual Practice

Fishman N. *Am J Med.* 2006;119:S53.

Targeted antibiotic consumption and nosocomial *C. difficile* disease

Tertiary care hospital; Quebec, 2003-2006



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

What is Antimicrobial Stewardship?

- ***Antimicrobial stewardship*** is a rational, systematic approach to the use of antimicrobial agents to achieve optimal outcomes[1,2]
- The primary goal should be to improve patient care and public health[1,2]
  - Financial goals are *secondary*

Correct agent	→	Cure or prevent infection
Correct dose		Minimize toxicity
Appropriate duration		Prevent resistance

- Dellit TH et al. *Clin Infect Dis.* 2007;44:159-177.
- IDSA/SHEA/PIDS. *Infect Control Hosp Epidemiol.* 2012;33:322-327.

Antimicrobial Stewardship

Goals

- Prevent or slow the emergence of antimicrobial resistance
- Optimize selection, dose and duration of Rx
- Reduce adverse drug events including secondary infection (e.g. *C. difficile* AAD)
- Reduce morbidity and mortality
- Reduce length of stay
- Reduce health care expenditures

MacDougall CM and Polk RE. Clin Micro Rev 2005;18(4):638-56.

Ohl CA. J. *Hosp Med*. In press.

Dellit TH, et. al. Clin Infect Dis. 2007;44:159-177

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

[1]Harborview Medical Center and the University of Washington, Seattle; [2]Maine Medical Center, Portland; [3]Emory University, Atlanta, Georgia; [4]Hines Veterans Affairs Hospital and Loyola University Stritch School of Medicine, Hines, and [5]Stroger (Cook County) Hospital and Rush University Medical Center, Chicago, Illinois; [6]University of Utah, Salt Lake City; [7]Mayo Clinic College of Medicine, Rochester, Minnesota; [8]University of Pittsburgh Medical Center, Pittsburgh, and [9]University of Pennsylvania, Philadelphia, Pennsylvania; [10]William Beaumont Hospital, Royal Oak, Michigan; [11]Ochsner Health System, New Orleans, Louisiana; and [12]University of Miami, Miami, Florida

CDC Vitalsigns™

March 2014

Making Health Care Safer

Antibiotic Rx in Hospitals: Proceed with Caution

1 in 2

More than half of all hospital patients receive an antibiotic.

3x

Doctors in some hospitals prescribed 3 times as many antibiotics as doctors in other hospitals.

30%

Reducing the use of high-risk antibiotics by 30% can lower deadly diarrhea infections by 26%.

Antibiotics save lives, but poor prescribing practices are putting patients at unnecessary risk for preventable allergic reactions, super-resistant infections, and deadly diarrhea. Errors in prescribing decisions also contribute to antibiotic resistance, making these drugs less likely to work in the future.

To protect patients and preserve the power of antibiotics, hospital CEOs/medical officers can:

- Adopt an antibiotic stewardship program that includes, at a minimum, this checklist:
  1. **Leadership commitment:** Dedicate necessary human, financial, and IT resources.
  2. **Accountability:** Appoint a single leader responsible for program outcomes. Physicians have proven successful in this role.
  3. **Drug expertise:** Appoint a single pharmacist leader to support improved prescribing.
  4. **Act:** Take at least one prescribing improvement action, such as requiring reassessment within 48 hours, to check drug choice, dose, and duration.
  5. **Track:** Monitor prescribing and antibiotic resistance patterns.
  6. **Report:** Regularly report to staff prescribing and resistance patterns, and steps to improve.
  7. **Educate:** Offer education about antibiotic resistance and improving prescribing practices.
- Work with other health care facilities to prevent infections, transmission, and resistance.

→ See page 4

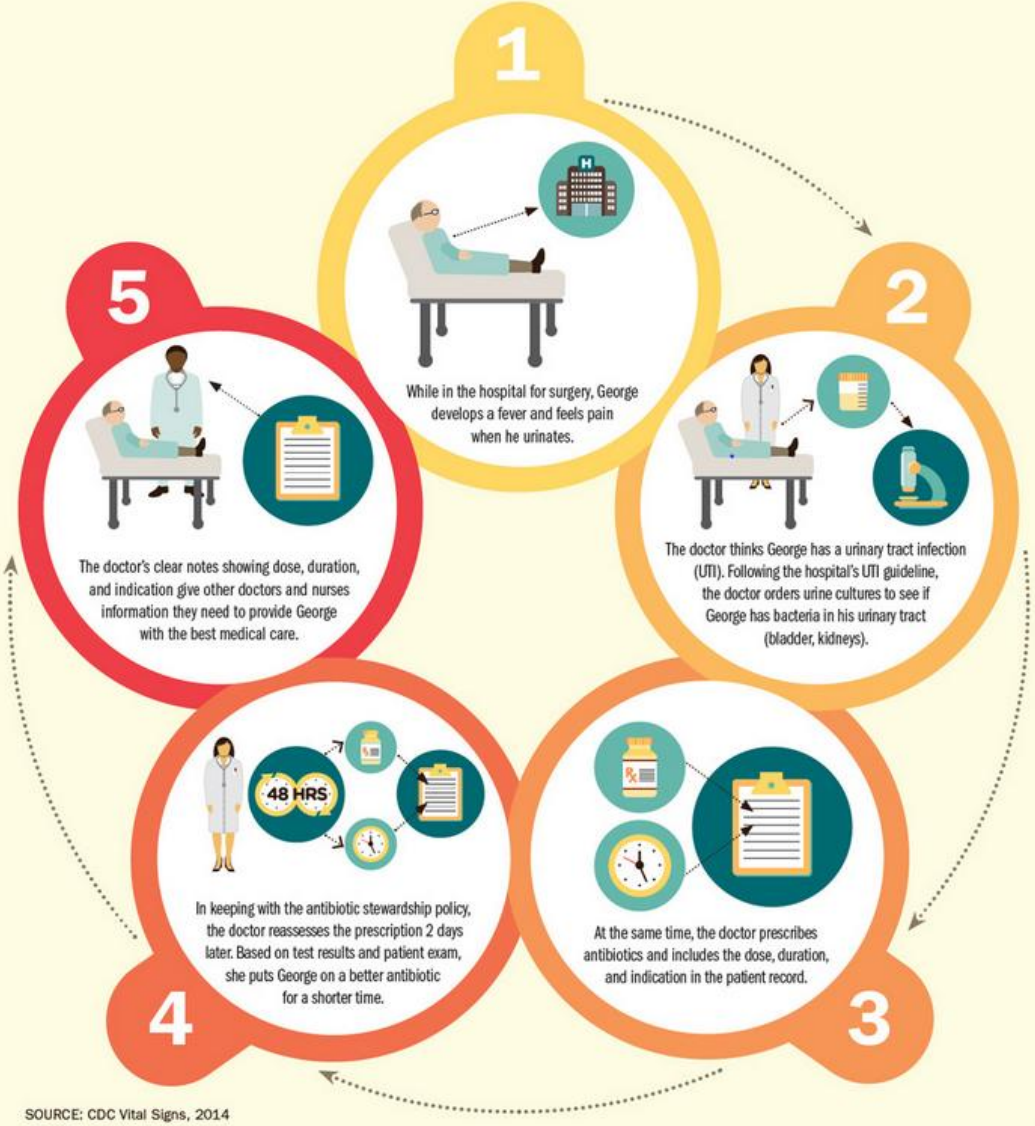
Want to learn more? Visit www.cdc.gov/vitalsigns

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion

CDC

Improving antibiotic prescribing in hospitals

Key moments for improving the cycle of antibiotic prescribing practices



SOURCE: CDC Vital Signs, 2014

CDC: 12 Steps to Prevent Antimicrobial Resistance: Hospitalized Adults

Prevent Infection

1. Vaccinate
2. Get the catheters out

Diagnose and Treat Infection Effectively

3. Target the pathogen
4. Access the experts

Use Antimicrobials Wisely

5. Practice antimicrobial control
6. ***Use local data***
7. Treat infection, not contamination
8. Treat infection, not colonization
9. Know when to say “no” to vanco
10. Stop treatment when infection is cured or unlikely

Prevent Transmission

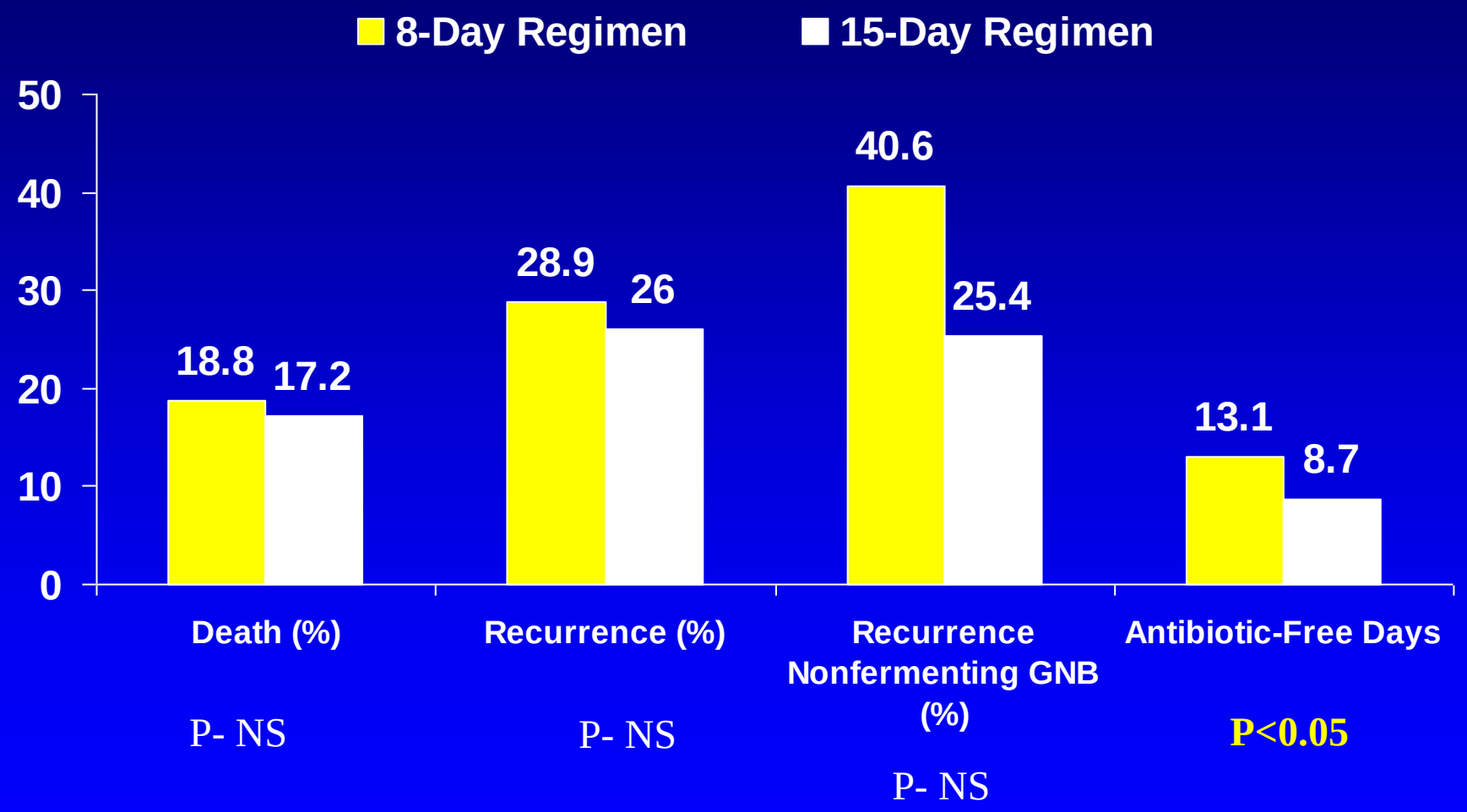
11. Isolate the pathogen
12. Break the chain of contagion

Ventilator-Associated Pneumonia
8 vs. 15 Days of Antibiotic Therapy

- Prospective, randomized, double-blind (until day 8) clinical trial
  - 51 French ICUs
- Patients received mechanical ventilation for at least 48 hours
- Drug selection based on discretion of treating physician
  - Protocol specified adherence to ATS guidelines
- Primary outcome measure
  - Death
  - Microbiologically confirmed recurrence
  - Antibiotic-free days assessed 28 days after first bronchoscopy for suspected onset of VAP

Chastre J, et al. *JAMA*. 2003;290:2588-2598.

Ventilator-Associated Pneumonia
8 vs. 15 Days of Antibiotic Therapy (cont'd)



Chastre J, et al. *JAMA*. 2003;290:2588-2598.

Survey of Intubated Patients at CSMC

- Chart review found 21 of 23 intubated patients (91%) are on abx:
  - 19/23 (83%) on anti-*Pseudomonas* agents
  - 12/23 (52%) on anti-MRSA agents
  - 10/23 (43%) on anti-fungal agents
- Of the 10 intubated patients currently on treatment for pneumonia:
  - 2 patients had Pseudomonas isolated from sputum, yet 9 were on anti-Pseudomonal treatment (pip-tazo, cefepime, carbapenems)
  - 0 patients had MRSA isolated from sputum, yet 4 were on vancomycin
- Conclusions: Broad antimicrobial use does not appear to match the spectrum of pathogens isolated from respiratory cultures

How to implement Antimicrobial Stewardship

Elements for constructing a comprehensive antimicrobial stewardship program

Multidisciplinary team

- Infectious diseases physician
- Clinical pharmacist (with ID training)

  Both compensated for their time
- Additional
  - Clinical microbiology
  - Information systems specialist
  - Infection control professional/ hospital epidemiologist

Medical Staff function

Clinical Infectious Diseases 2007;44:159-177

Elements for constructing a comprehensive antimicrobial stewardship program

- Support/collaboration
  - Hospital administration
  - Medical staff leadership
  - Local providers
  - Part of quality/ safety program

Clinical Infectious Diseases 2007;44:159-177

Key elements of an ASP

- Know your local antimicrobial resistance profile (antibiogram)
- Drive decisions of antimicrobial formulary based on antibiogram
- Develop local guidelines for empiric and prophylactic antimicrobial use based on evidence based guidelines AND local antimicrobial trends
- Obtain consensus from key stakeholders
- Use committee process to establish expectations
- Develop measures to track (drug utilization or interventions and outcomes)
- Give regular updates on progress on key metrics
- Keep messages simple “5 Rights”
- Educate! But it is not enough

Recommended Components of an Antimicrobial Stewardship Program

- Foundation = *2 core, proactive strategies*
  - Prospective audit with intervention and feedback
  - Formulary restriction and preauthorization

Getting Started

- Establish a core planning committee
  - Subcommittee of P&T?
  - Subcommittee of Infection Control?
  - Other interested and like minded people
- Establish goals and mission statement
- Draft an idea
  - Program structure
  - Program elements
- Identify existing and needed resources
- Market the need – use real case examples!
- Focus on process and clinical outcomes

Rethinking Our Relationships Across the Continuum

Hospitals Must Partner With Previously Siloed Stakeholders[1]

Continuum of Care

	Preacute Care	Inpatient Acute Care	Postacute Care
Stakeholders involved:	PCP, Patient	Specialists, Hospitalists, Nurses, Case Manager, Patient, Allied Health	Home Health, SNF, Medical Home, PCP, Patient, Specialists
Care coordination imperatives:	▪ Adequate preventive care ▪ Disease prevention	▪ Length of stay management ▪ Inpatient utilization management ▪ Reduce readmissions	▪ Partner with postacute providers ▪ Standardize care site transitions ▪ Reduce readmissions

▪ PCP = primary care physician. SNF = skilled nursing facility.

▪ 1. The Advisory Board Company. *Improving Provider Communication and Patient Transitions*. Washington, DC: The Advisory Board Company; 2011.

Facilities work together to protect patients.

Common Approach *(Not enough)*

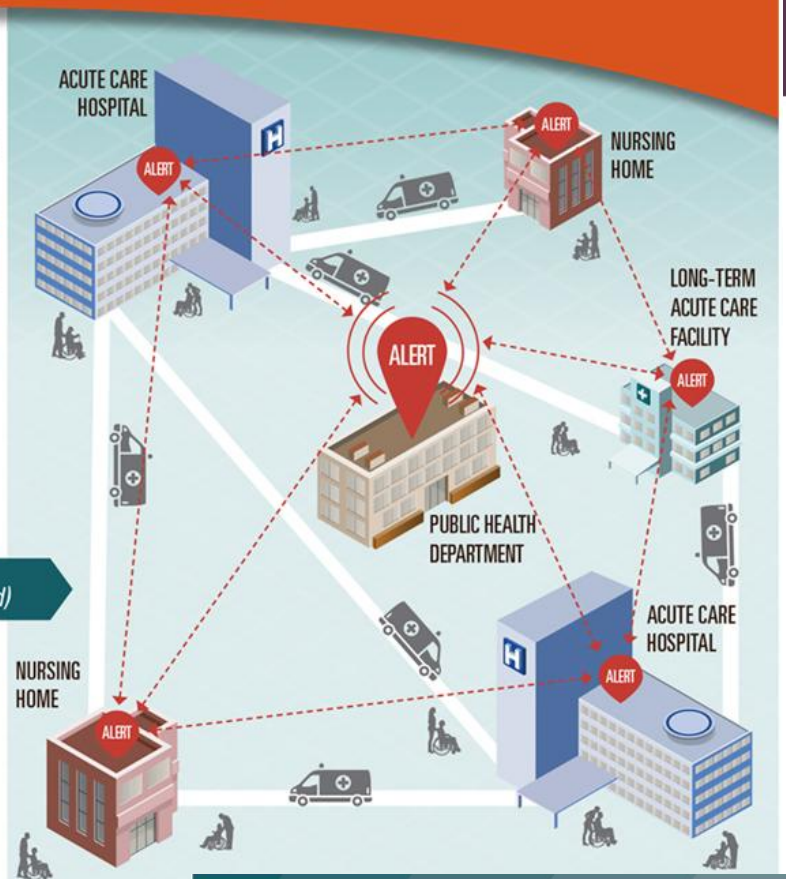
- Patients can be transferred back and forth from facilities for treatment without all the communication and necessary infection control actions in place.

Independent Efforts *(Still not enough)*

- Some facilities work independently to enhance infection control but are not often alerted to antibiotic-resistant or *C. difficile* germs coming from other facilities or outbreaks in the area.
- Lack of shared information from other facilities means that necessary infection control actions are not always taken and germs are spread to other patients.

Coordinated Approach *(Needed)*

- Public health departments track and **alert** health care facilities to antibiotic-resistant or *C. difficile* germs coming from other facilities and outbreaks in the area.
- Facilities and public health authorities share information and implement shared infection control actions to stop spread of germs from facility to facility.



More patients get infections when facilities do not work together.

(Example: 5 years after CRE enters 10 facilities in an area sharing patients)

Common Approach (status quo)

2,000 patients will get CRE.

CRE will impact 12% of patients.

Independent Efforts

1,500 patients will get CRE.

CRE will impact 8% of patients.

Coordinated Approach

400 patients will get CRE.

CRE will impact 2% of patients.

Antimicrobial Use: Nursing Homes

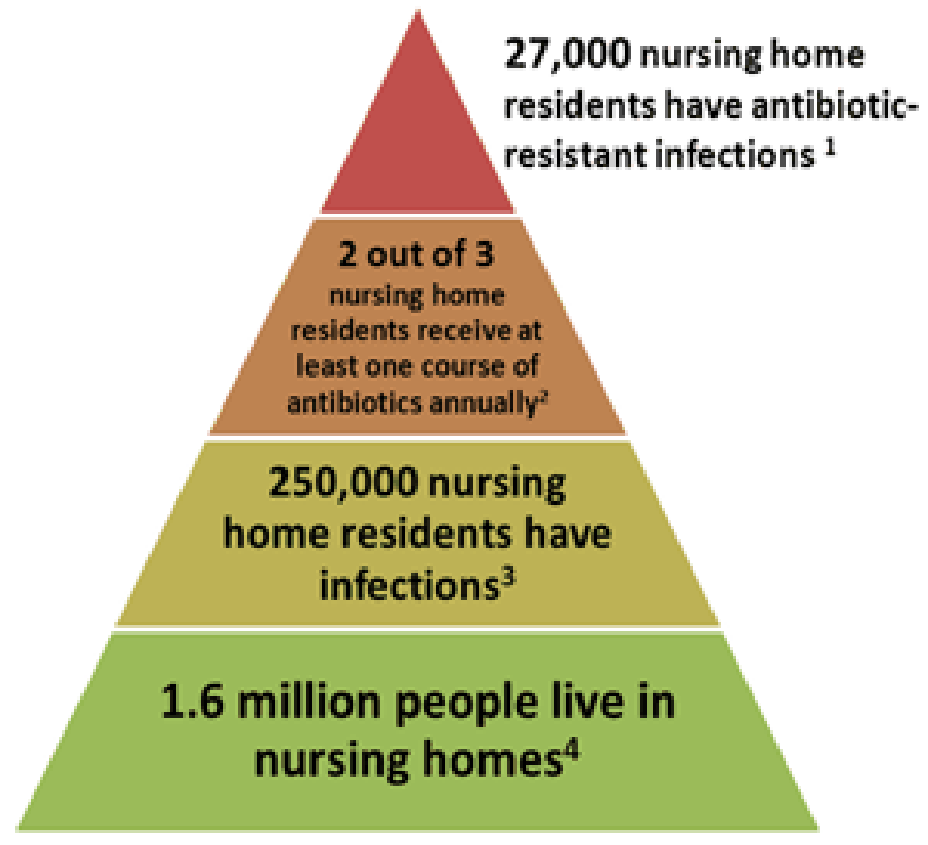
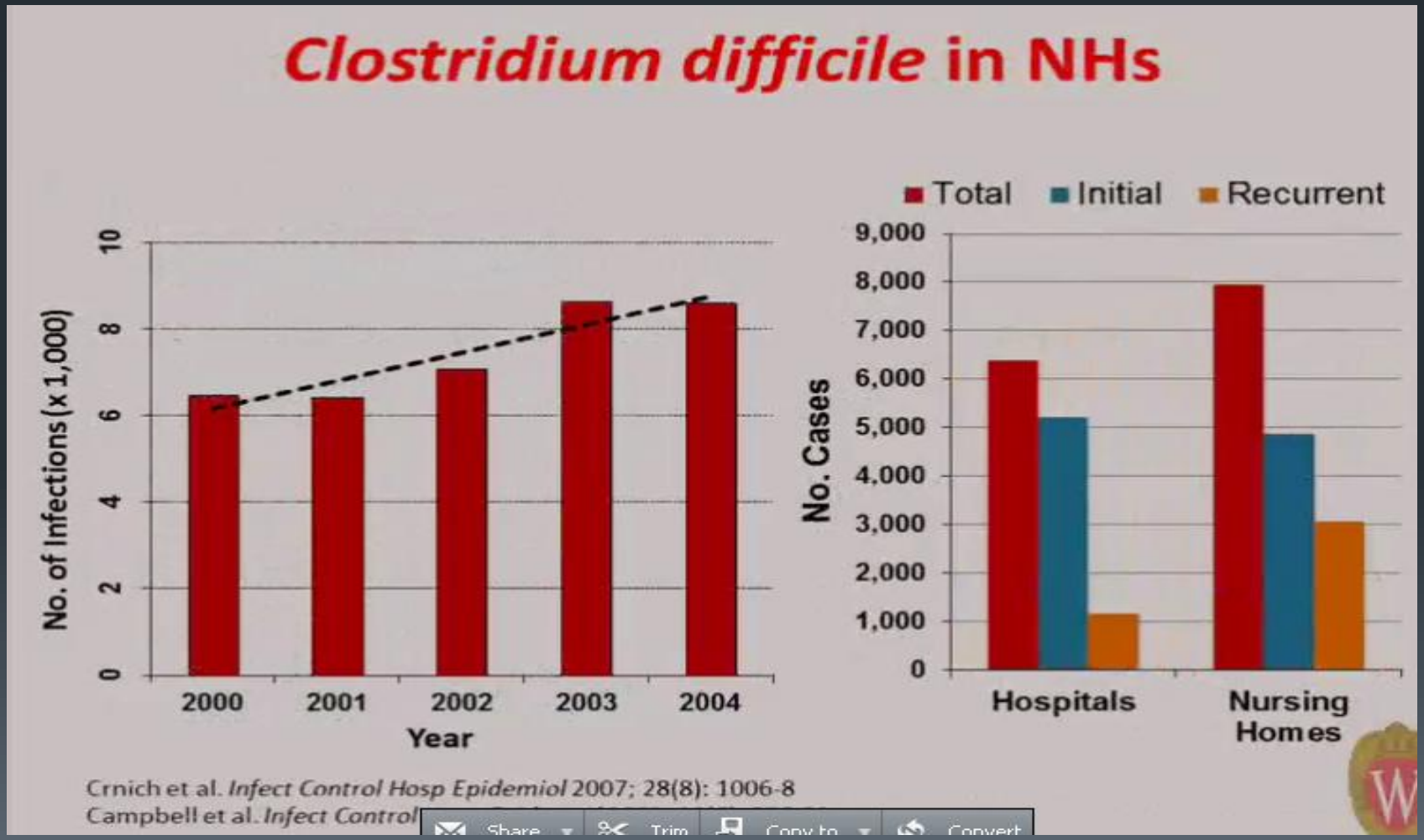


Image from: http://www.cdc.gov/getsmart/healthcare/learn-from-others/factsheets/nursing-homes.html

1. Centers for Medicare and Medicaid Services, Long Term Care Minimum Data Set, Resident profile table as of 05/02/2005. Baltimore. MD.
2. Loeb, M et.al. Antibiotic use in Ontario facilities that provide chronic care. J Gen Intern Med 2001; 16: 376-383.
3. Centers for Medicare and Medicaid Services, Long Term Care Minimum Data Set, Resident Profile Table as of 05/02/2005. Baltimore, MD.
4. Centers for Disease Control and Prevention, National Center for Health statistics, 1999 National Nursing Home Survey. Nursing Home Residents, number, percent distribution, and rate per 10,000, by age at interview, according to sex, race, and region: United States, 1999.

Clostridium difficile in NHs: Acquisition



New Regulations on AS in SNFs

- President's Council of Advisors on Science and Technology (PCAST) Report
  - Introduced September 2014
  - "*By the end of 2017, CMS should have Federal Regulations in place that require…long-term care and nursing home facilities to develop and implement robust AS programs that adhere to best practices.'*

- CA SB361: SNFs: Antimicrobial Stewardship Guidelines
  - Introduced by Senator Hill February 24, 2015
  - Requires "*all skilled nursing facilities* by no later than *January 1, 2017, to adopt and implement an AS policy."*
  - AND*…" require each SNF, within 3 months of the establishment of AS guidelines by the federal CDC or professional organizations, including SHEA, to amend its policy to be consistent with those antimicrobial stewardship guidelines."*

Antimicrobial Stewardship in Skilled Nursing Facilities (SNFs):

CS Collaboration with geographic network of SNFs

- Assist ECP SNFs in establishing Antibiotic Stewardship Program elements using checklist and tools
- Choose one QI activity for FY16 on AS
  - Propose focus on UTI

Why Focus on UTIs?

Treatment for suspected UTI estimated to account for 30-60% of antibiotic prescriptions in LTCFs[1]

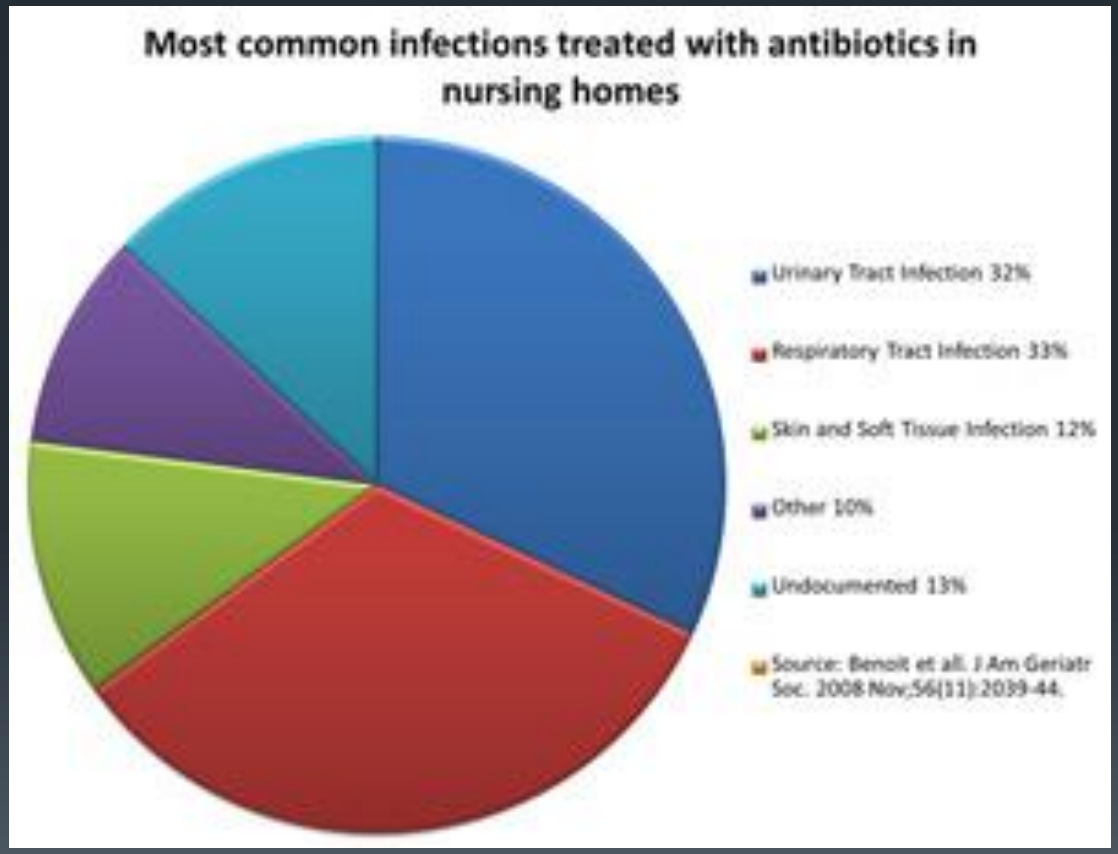


Image from: http://www.cdc.gov/getsmart/healthcare/learn-from-others/factsheets/nursing-homes.html

[1] *J Am Geriatr Soc*. 2008;56:2039-44. PMID 19016937.

Conclusions

- Combination of effective antimicrobial stewardship with a comprehensive infection control program has been shown to limit the emergence and transmission of antimicrobial resistance bacteria
- The time for stewardship is now.
- Every facility should be doing stewardship
  - Limited interventions as a place to start, more comprehensive programs as the goal
- Improving antibiotic use is a public health imperative
- Collaboration with health care partners across the continuum of care will be critical to overall success

THANK YOU!!