Past, Present, and Future of Antimicrobial Stewardship

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Disclaimer

- The information disseminated in this lecture is given in my personal capacity and not in my capacity as a VA employee nor does it necessarily reflect the views of the United States Department of Veterans Affairs

OBJECTIVES

PAST

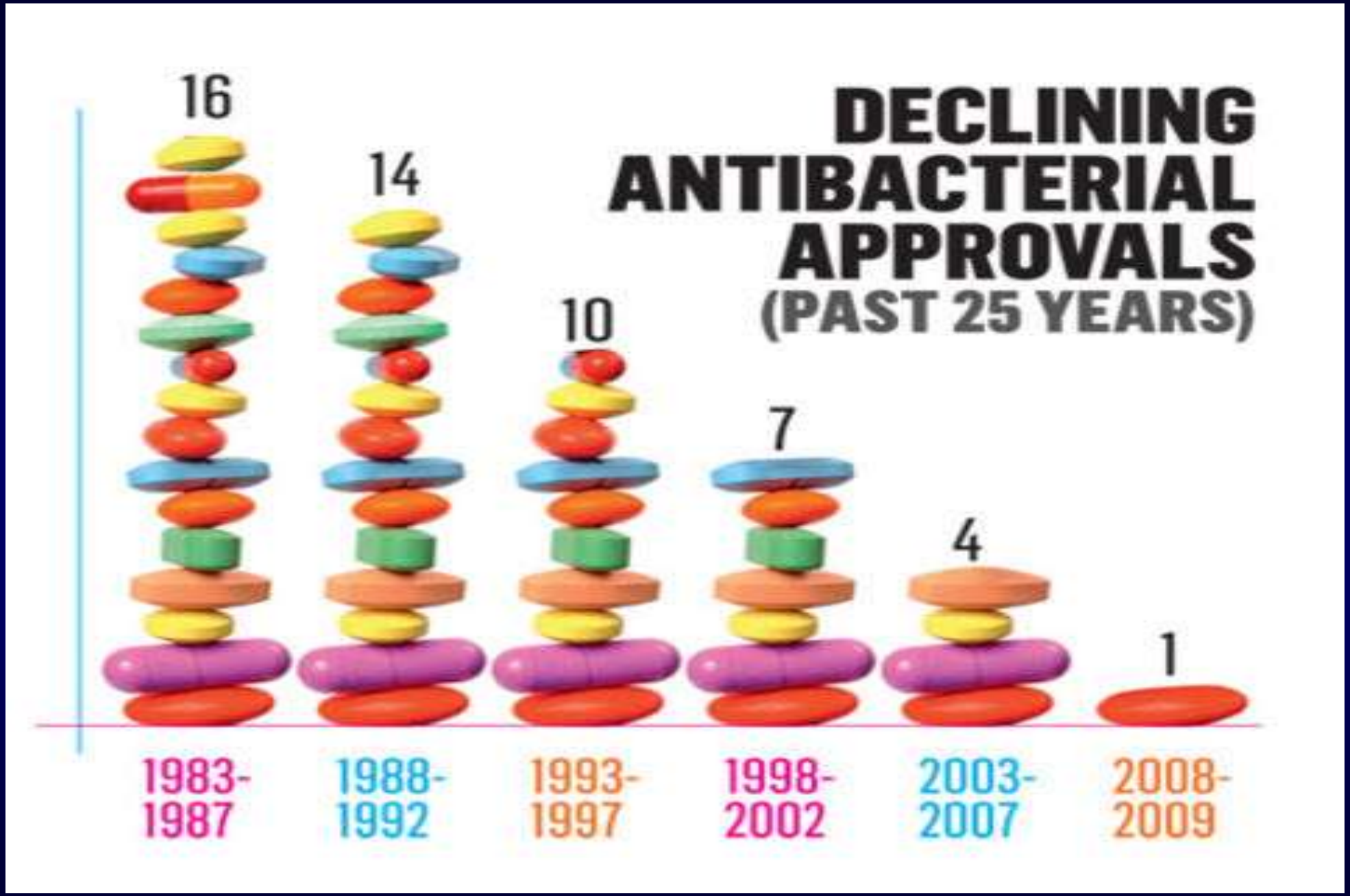
1. Demonstrate the need for antimicrobial stewardship to preserve current antimicrobial treatment

PRESENT

2. Identify the goals of antimicrobial stewardship
3. Discuss and apply antimicrobial stewardship interventions
4. Discuss commonly used metrics for evaluating an antimicrobial stewardship program

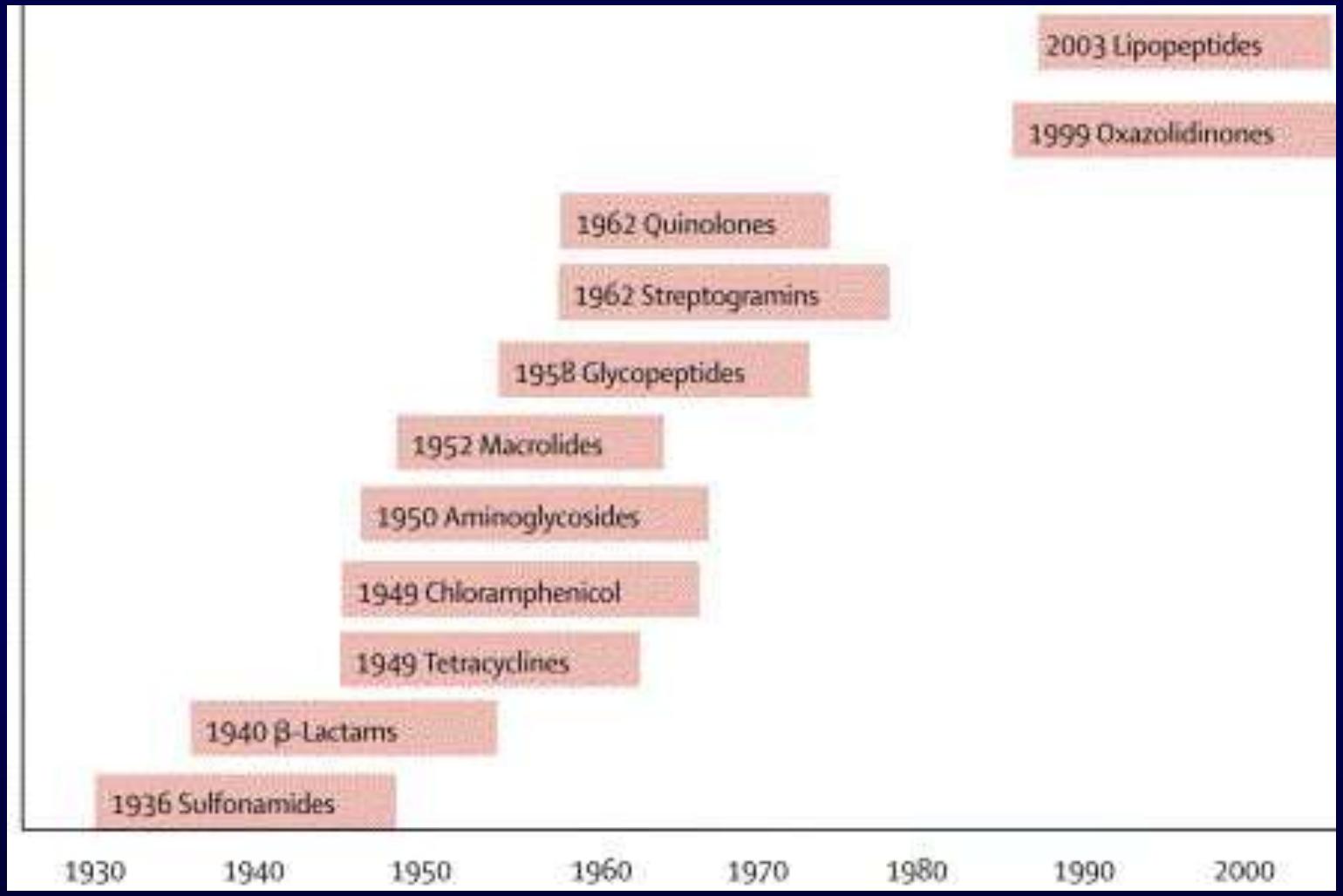
FUTURE

5. Describe the future needs for antimicrobial stewardship



Adapted from Spellberg B et al. Clin Infect Dis. 2008;46:155-164

Limited New Antibacterial Classes



Norrby SR et al. Lancet Infect Dis. 2005;5:115-119.

Recent Approvals (Last 10 years)

GRAM POSITIVES

- **Daptomycin** (MRSA)
  - 2003
  - Lipopeptide
- **Tigecycline** (MRSA)
  - 2005
  - Glycylcycline
- **Telavancin** (MRSA)
  - 2009
  - Lipoglycopeptide
- **Ceftaroline** (MRSA)
  - 2010
  - 5th generation CS
- **Fidaxomycin** (C. diff)
  - 2011
  - Macrocycles
- **Fusidic acid?** (MRSA)

GRAM NEGATIVES

- **Tigecycline** (no P. aug, *Proteus* spp or Providencia, some *A. baumannii*
- **Ceftaroline** (no P. aug, or *A. baumannii*)

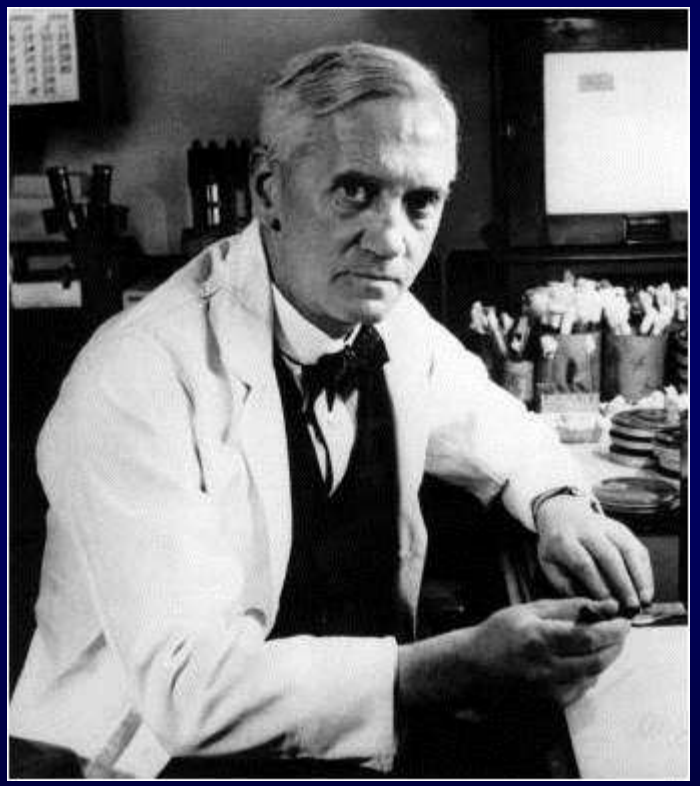
History of Resistance

- Antimicrobial resistance is not a new phenomenon
- Sulfonamides, penicillin, and streptomycin available for use in the 1930s-1940s
  - Recognized early that bacteria exposed to antimicrobial agents evolved strategies to survive them

SHEA/IDSA/PIDS. Infect Control Hosp Epidemiol 2012;33(4): 322-327.

Sir Alexander Fleming on June 26, 1945:

"The microbes are **educated to resist penicillin** and a host of penicillin-fast organisms is bred out….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.**"



Penicillin finder assays its future. New York Times 26 June 1945: 21.

Cause of Antibiotic Resistance

- Humans did NOT invent antibiotics
  - Bacteria "invented" antibiotics billions of years ago and "invented" antibiotic resistance at the same time
  - Bacteria have learned to target virtually every targetable biochemical pathway with antibiotics, and have learned to create defense mechanisms to defeat virtually all such antibiotics
- Resistance already exists to drugs we have not yet invented
  - Bacteria found in caves that have been isolated from the surface of the planet for 4 million years.
  - Resistance found to synthetic antibiotics that did not exist until the 20th century
- Bacteria cause resistance, not humans
  - Humans apply natural selection – select for pre-existing resistance
  - We don't create resistance, but do increase its rate of spread!

Spellberg B et al. NEJM 2013; 368:299-302.

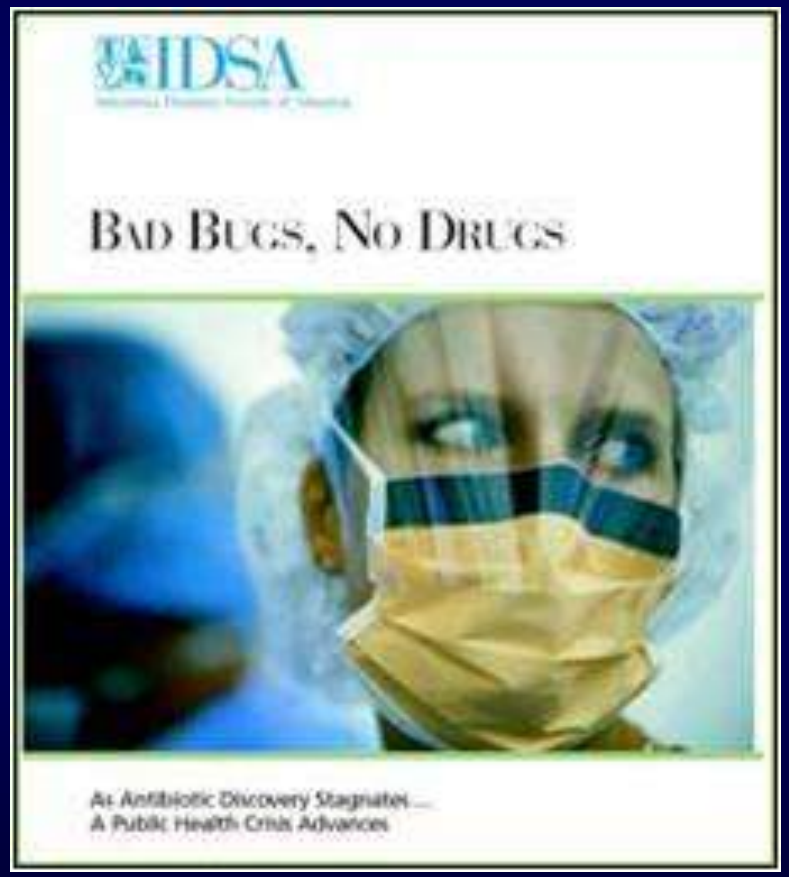
Widespread Resistance

- National surveillance data and independent studies show that drug resistant, disease-causing bacteria have multiplied and spread at alarming rates in recent decades

SHEA/IDSA/PIDS. Infect Control Hosp Epidemiol 2012;33(4): 322-327.

IDSA Report

“ BAD BUGS, NO DRUGS: As Antibiotic Discovery Stagnates ...A Public Health Crisis Brews”



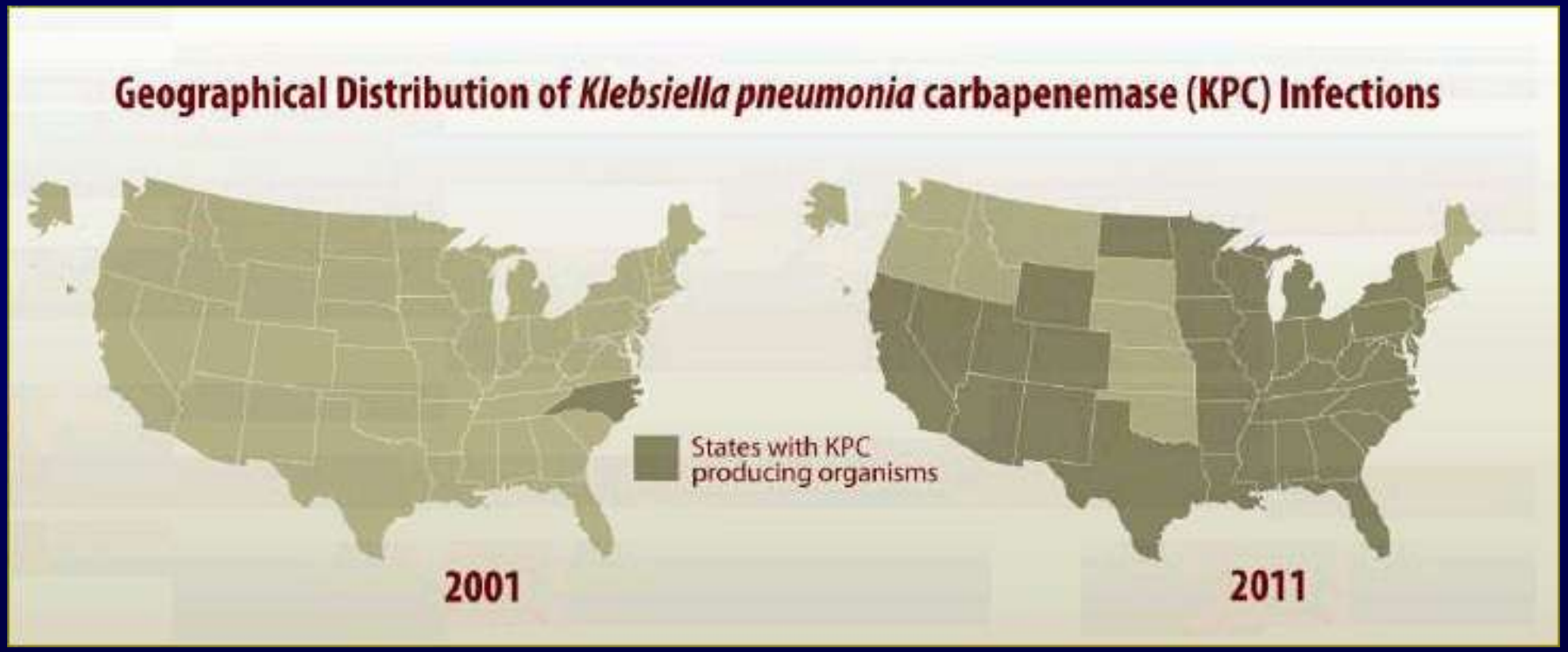
IDSA. Bad Bugs, No Drugs. July 2004.

Bad Bugs, No Drugs: No ESKAPE!

	ESKAPE Pathogens	Class	"Superbugs"
E	*Enterococcus faecium*	Gm+	Vancomycin-resistant *E. faecium (*VRE)
S	*Staphylococcus aureus*	Gm+	Methicillin-resistant *S. aureus* (MRSA)
K*	*Klebsiella pneumoniae* **Or C = Clostridium difficile (C. Diff) – Gm+*	Gm-	Extended-spectrum beta-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemase (KPCs)
A	*Acinetobacter baumanii*	Gm-	ESBLs, carbapenemases
P	*Pseudomonas aeruginosa*	Gm-	ESBLs, carbapenemases
E	*Enterobacter* species (Ie *E. coli, proteus spp, serratia spp*..)	Gm-	ESBLs, Carbapenem-resistant *Enterobacteriaceae* (*CRE)*

Rice LB. J Infect Dis 2008; 197:1079–81.

Resistance is Everywhere



Centers for Disease Control and Prevention. Get Smart for Healthcare. Available at: http://www.cdc.gov/getsmart/healthcare/

Public Health Threat

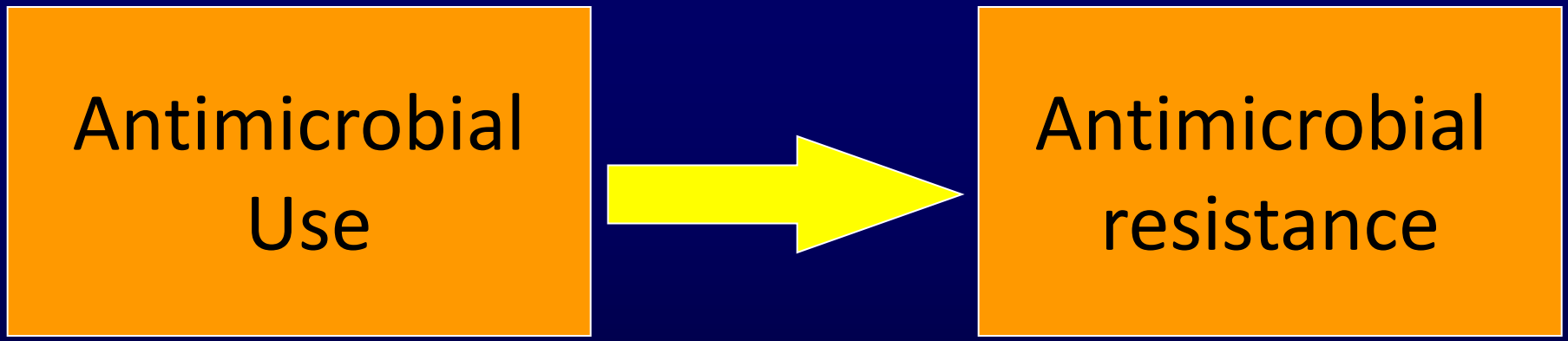
- Threat of infections without treatment is impending
  - Already have been reports of pan-resistant (resistant to all available antibiotics) pathogens
- If the current rate of resistance continues, some experts believe we may enter a postantibiotic era
- **Must** preserve the limited effective antibiotics that are currently available

Falagas ME, et al. Int J Antimicrob Agents 2008;32:450-454.
Tenover FC. JAMA 1996;275(4):300-304.

INAPPROPRIATE ANTIBIOTIC USE

The Bitter Truth

- Estimated that 50% of antimicrobial use in hospitals is inappropriate



Reinmann HA, et. al. Arch Environ Health 1966;13: 631-6.
Centers for Disease Control and Prevention. Get Smart for Healthcare. Availble at: http://www.cdc.gov/getsmart/healthcare/

Inappropriate Use

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

Inappropriate Antimicrobial Use

- Overuse and misuse leads to the emergence and spread of resistant bacteria
  - Getting an antibiotic increases a patient's chance of becoming colonized or infected with a resistant organism

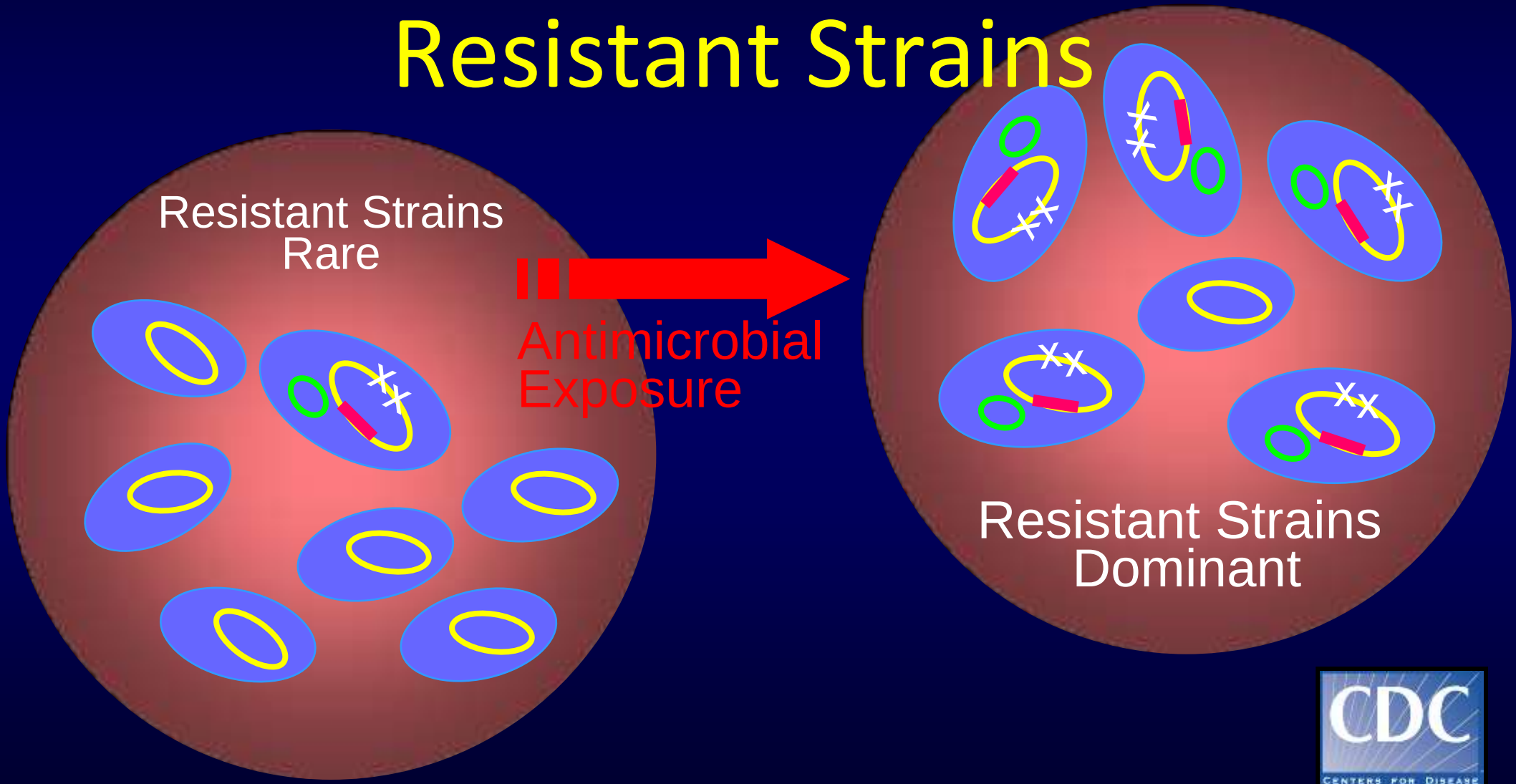
Reinmann HA, et. al. Arch Environ Health 1966;13: 631-6.
Centers for Disease Control and Prevention. Get Smart for Healthcare. Availble at: http://www.cdc.gov/getsmart/healthcare/

Antibiotics Are a Shared Resource

- How we use antibiotics in one patient today directly how effective the drug will be in another patient tomorrow
  - Resistant bacteria have the potential to spread to others, promoting resistant infections

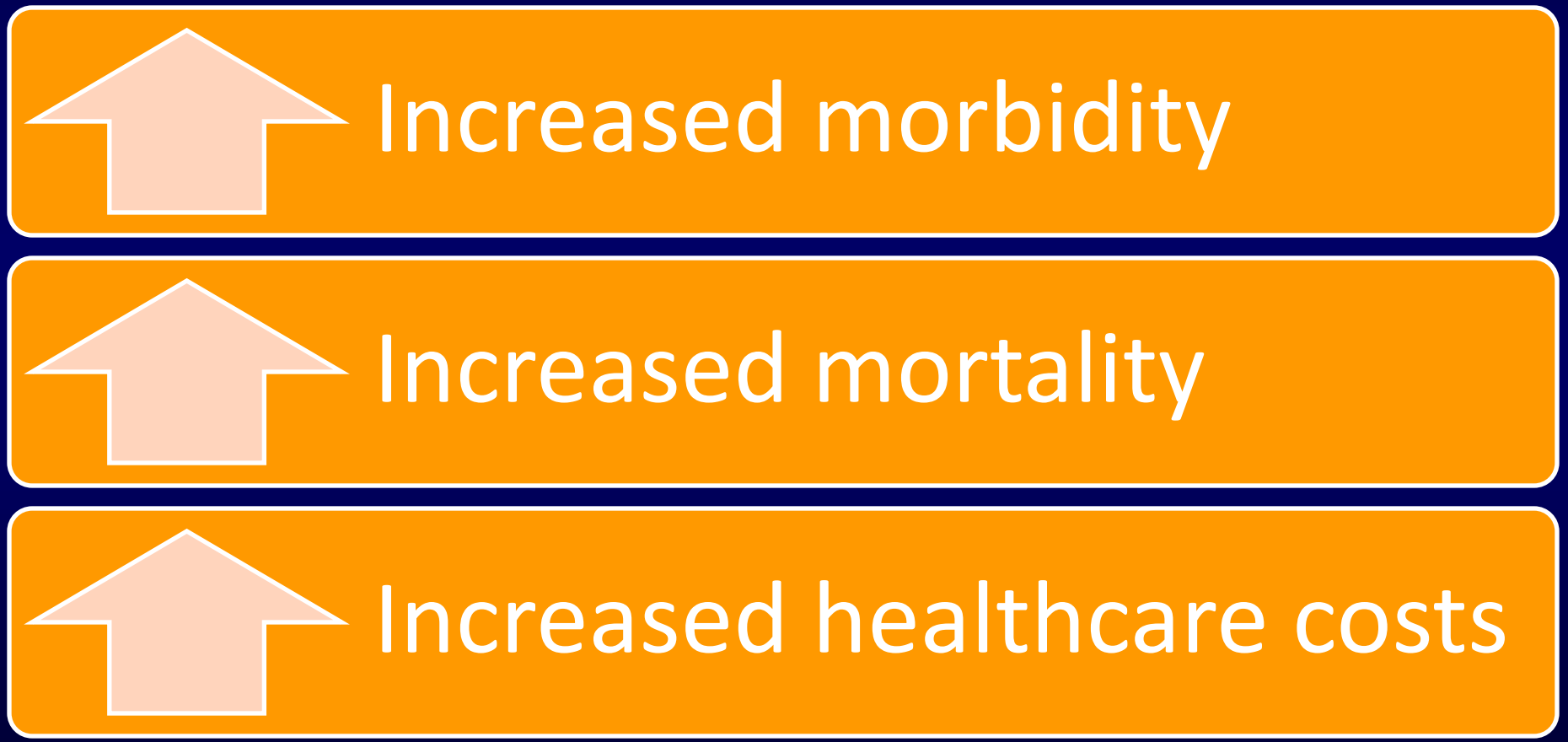
Centers for Disease Control and Prevention. Get Smart for Healthcare. Availble at: http://www.cdc.gov/getsmart/healthcare/

Selection for Antimicrobial-Resistant Strains



CDC
Centers for Disease Control and Prevention

Consequences of Resistance



SHEA/IDSA/PIDS. Infect Control Hosp Epidemiol 2012;33(4): 322-327.

Healthcare Associated Infections (HAIs) and Resistant Bacteria

- 16% of HAIs are associated with multidrug-resistant pathogens, including:
  - Methicillin-resistant *S. aureus* (MRSA)
  - Vancomycin-resistant *enterococcus faecium* (VRE)
  - *Pseudomonas aeruginosa (P. aeruginosa)*
  - *Klebsiella pneumoniae* (*K. pneumoniae)*

Centers for Disease Control and Prevention. Healthcare Associated Infections. Available at: http://www.cdc.gov/HAI/burden.html
Hidron et al. Infect Control Hosp Epidemiol 2008; 29:996-1011.

Clostridium difficile (C. Diff)

- 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

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

Bacteria Are Killing!

- HAIs are the 6th leading cause of death in the United States
  - 1.7 million HAIs annually
  - 34.4 million annual discharges
  - 99,000 resultant deaths
  - $28-33 billion excess healthcare costs

Klevens et al. Public Health Reports; 2007; 122:160-166. Available at: http://www.cdc.gov/HAI/pdfs/hai/infections_deaths.pdf

In Rhode Island…

- Every day, 17 people develop a HAI (6,266/365)
- Every day, someone dies from a HAI (365/365)
- Every day, 3 people develop a drug-resistant HAI (1,003/365)
- Once a week, someone dies from a drug-resistant HAI (59/52)

http://www.rimed.org/medhealthri/2010-09/2010-09.pdf

GUIDELINES

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

ANTIMICROBIAL STEWARDSHIP

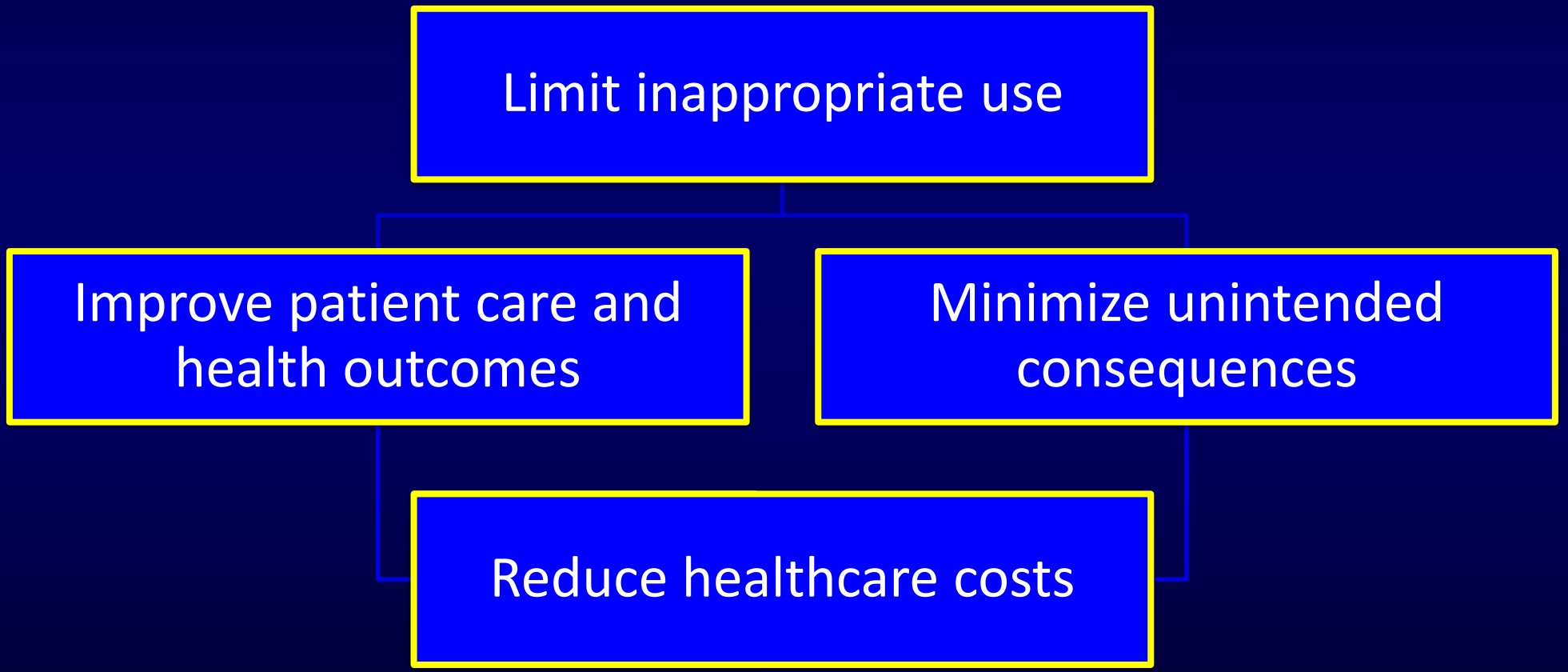
Dellit et al. Clin Infect Dis 2007; 44:159-77.

Antimicrobial Stewardship: Definition

- Any activity that promotes appropriate antimicrobial:
  1. Drug
  2. Dosing
  3. Duration
  4. Route

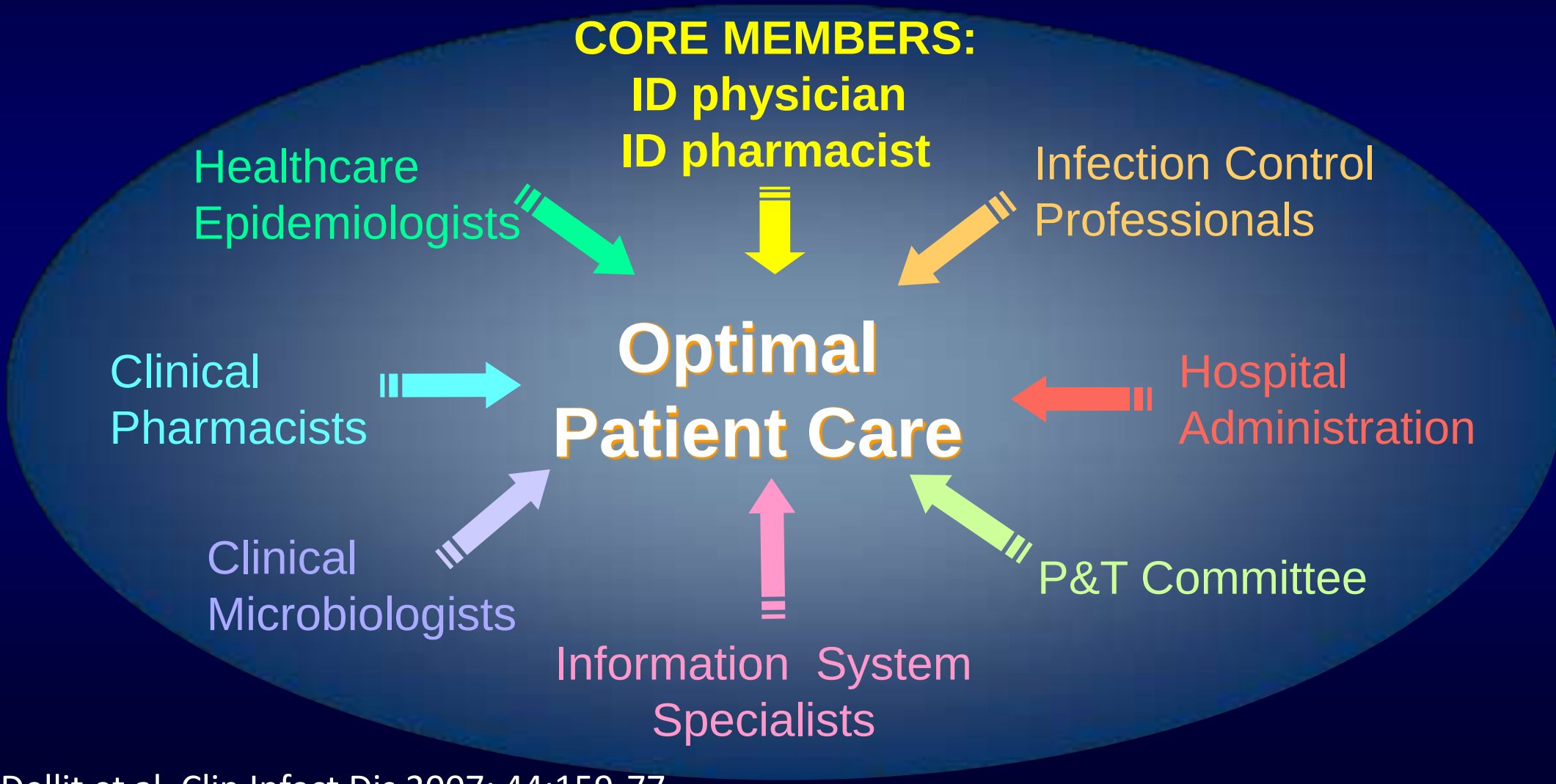
Dellit et al. Clin Infect Dis 2007; 44:159-77.

Goals of Antimicrobial Stewardship



Dellit et al. Clin Infect Dis 2007; 44:159-77.

Multi-disciplinary team



Dellit et al. Clin Infect Dis 2007; 44:159-77.

Strategies

CORE

- Prospective audit with intervention and feedback
- Formulary restriction and preauthorization

SUPPLEMENTAL

- Education
- Guidelines and clinical pathways
- Antimicrobial order forms
- Streamlining or de-escalation of therapy
- Dose optimization
- IV to PO conversion

Dellit et al. Clin Infect Dis 2007; 44:159-77.

Prospective Audit and Feedback

- Antimicrobial use reviewed and recommendations made to optimize use
- *Back-end* program - Antimicrobial use is reviewed AFTER antimicrobial therapy has been initiated
- "Unsolicited" feedback – unlike an ID consult
- Recommendations are voluntary

Owens et al. Diagnostic Microbiology and Infectious Disease 2008; 61:110–128.

PVAMC Audit With Feedback

- Print out a list of all patients on IV and PO antimicrobials
- Fill out patient templates (next slide)
- Identify potential interventions
- Discuss potential interventions with ID team
- Relay interventions to prescriber
- Document interventions in excel

Antimicrobial Stewardship Workup Template

Basic Info	DATE	LAST NAME/4	Age/39/Race	HT	WT	Loc/Att	Abx All
CC			Past Hosp/Abx/pathogens/ steroids/immunocompromise				
PMH							

Admission Details		Drug (route, dose, freq)	Days of Therapy						
			D1	D2	D3	D4	D5	D6	D7
From where									
On what day									
DX									
1st Intervention									
Documentation									
Date/Time									
ID		**Monitoring**							
Res/Int		CrCl: DATE							
✆ / ✉		WBC							
Limitations to communication		Baseline Cr: SCr/ BUN							
		Tmax							

Culture		
MRSA nares ☐ Y ☐ N	Date	Source/Results
	Date	Source/Results
	Date	Source/Results

Recommendations		Further Details						
☐	Vanc Dose/Mon							
☐	Asx UTI							
☐	Surg							
☐	IV to PO							
☐	Drug optimizati							
☐	De-escalation							
☐	Stop Abx	Daily time (minutes):						
☐	Other	D1	D2	D3	D4	D5	D6	
☐	No rec							

IV to PO Conversion		UTI	
☐	Low WBC	☐	Bacteriuria
☐	Afebrile	☐	Pyuria
☐	Pt Improving	☐	Symptoms
☐	On PO medicatio	☐	MSSA
☐	No GI problems	☐	Other
☐ Y ☐ N		☐ Y ☐ N	

Additional HPI and Notes	Result		Follow-Up
	Accepted	Why?	☐
	☐ Y ☐ N	☐ Unable to contact	
		☐ Loss to follow-up	☐
		☐ Clinical picture changed	
		☐ Other	☐

Impact of a Stewardship Program

- Process measures:
  - How did the intervention result in the desired change in antimicrobial use?
  - Accomplished a task?
  - Ex- Level of acceptance?
    - Types of recs
    - # recs mades
    - % recs implemented
- Outcome measures:
  - Did the process implemented reduce any unintended consequences of antimicrobial use?
  - Eg- Think of stewardship goals (next slide)

Dellit et al. Clin Infect Dis 2007; 44:159-77.

Outcomes Metrics Examples

- **Goal 1- Improve Pt Outcomes**
  - Clinical success
  - Microbiologic success
- **Goal 2- Improved Pt Safety**
  - Antibiotic adverse effects
  - *C. Difficile* infections
  - Nosocomial infection rates
  - Mortality
- **Goal 3- Reduced Resistance**
  - Changes is antimicrobial susceptibility among specific organisms
  - Antibiogram
- **Goal 4- Reduced Cost**
  - Antimicrobial Use
  - Length of Stay
  - Re-admissions

McGowan. Infect Control Hosp Epidemiol 2012; 33(4):331-337.

Measuring Antimicrobial Use

Defined Daily Dose (DDD):

- Developed by the WHO
  - Grams used / WHO DDD
- Advantages-
  - Easier data collection
- Disadvantages-
  - Actual doses often differ from WHO-approved DDD (ie levofloxacin DDD= 500mg
    - Pt 1- 750mg x 10 days = 7500mg/500mg = 15 DDD
    - Pt 2- 500mg x 10 days= 5000mg/500mg = 10 DDD

Days of Therapy (DOT):

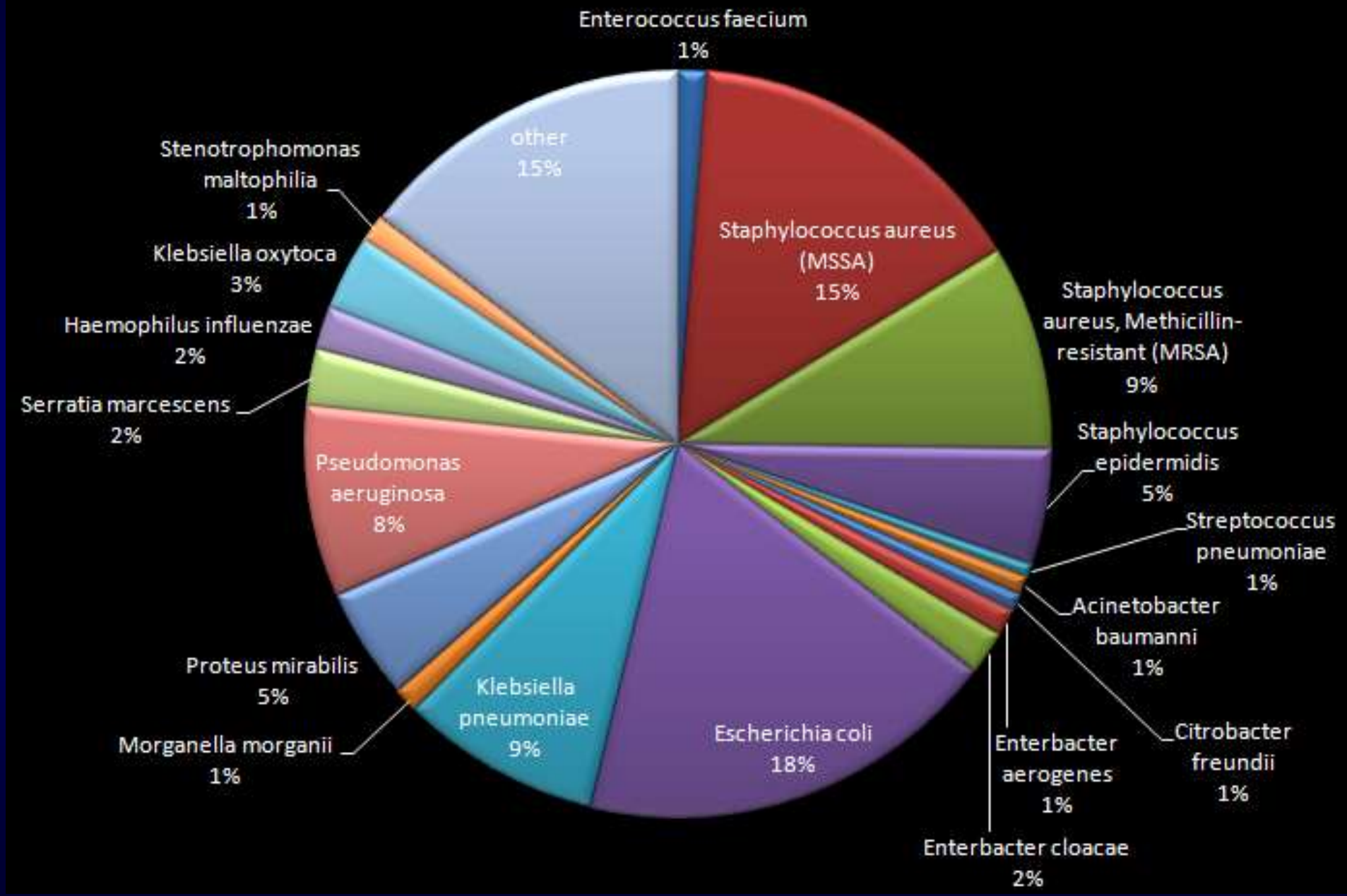
- Calendar day on which a pt received the drug in question
- Advantages-
  - May be more accurate when hospitals use doses that differ from the WHO specified doses (ie impaired renal function, pediatric patients)
- Disadvantages-
  - More difficult to measure
  - Number of doses per day not measured

Polk RE et al. Clin Infect Dis 2007; 44: 664-70.

PVAMC Stewardship Program

- Prospectively audit all antimicrobial use (IV and PO) daily (Mondays-Fridays)
- Reviewed 420 patients since September 2012
  - 272 reviewed by PharmD fellow
  - 103 reviewed by pharmacy student
  - 45 reviewed by PharmD resident
- Mean time spent per patient = 18.8 minutes (+/- 14.7)

Total Isolates 2011



Antibiotics with Usage				
GRAMS PER YEAR	2008	2009	2010	2011
Piperacillin/tazobactam	19,336	28,125	33,281	35,260
Vancomycin (IV only)	2,081	4,898	5,796	9,303
Metronidazole (IV only)	1,539	1,843	4,823	1,185

Patient Characteristics

Characteristic	n (%)
Age in years (mean ± SD)	70.8 (+/-14.3)
Male gender	404 (96.2)
Caucasian	388 (92.4)
Service Admitted	
General Medicine	310 (73.8)
ICU	43 (10.2)
Surgery	58 (13.8)
Psychiatry	9 (2.1)
Length of stay in days (mean ± SD)	6.5(+/-8.4)

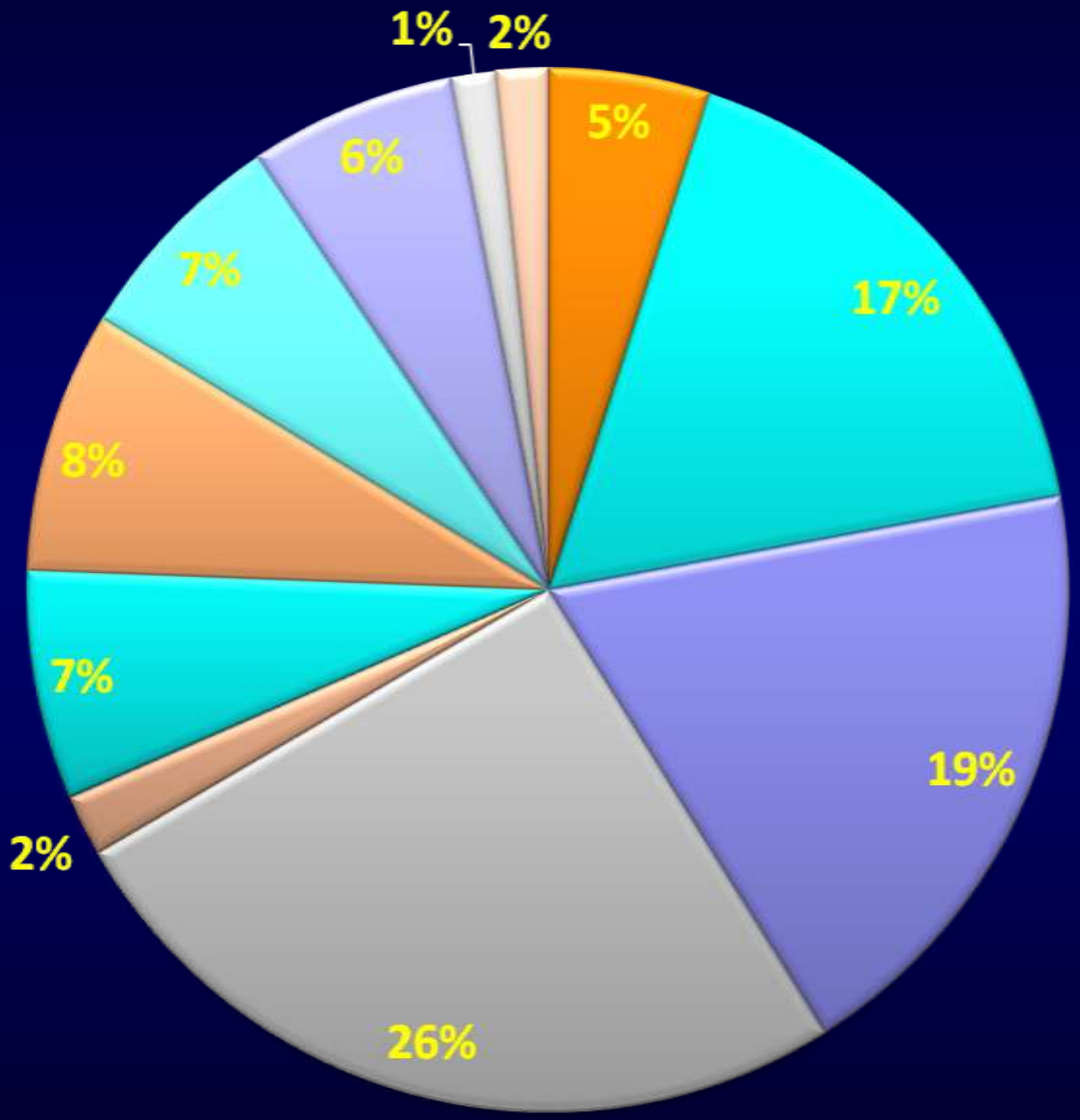
*N = 420

Most Frequently Involved Antibiotics

Rank	Antibiotic	n (%)
1	Vancomycin IV	141 (33.6 %)
2	Piperacillin/ Tazobactam	139 (30.7%)
3	Azithromycin	86 (20.5%)
4	Ceftriaxone	69 (16.4%)
5	Oseltamivir	41 (9.8%)
6	Metronidazole	40 (9.5%)

*N = 420

Antimicrobial Indication



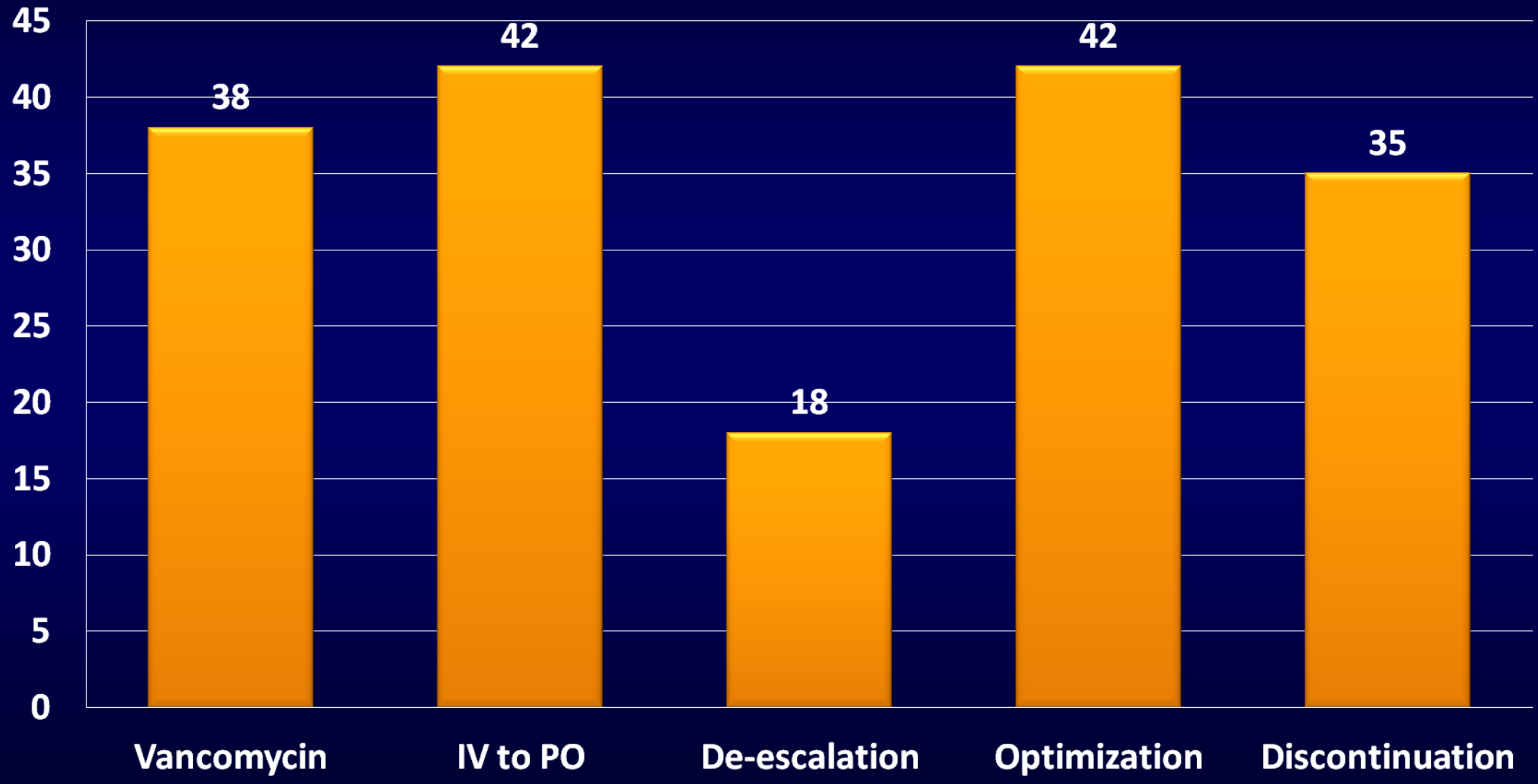
- Bloodstream
- Urinary Tract Infection
- Skin/ Soft Structure
- Pneumonia
- Surgical Prophylaxis
- C. Diff
- COPD exacerbation
- Intra-abdominal
- Influenza
- Bone and Joint
- Other

*N = 420

Intervention Description

- In 133 patients (31.7%) an intervention was made
- Total number of interventions made = 198
- Total number of interventions accepted = 145
- Acceptance Rate = 73.2%
- Avg. # Interventions per week = 9

Types of Interventions



*N = 198

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY APRIL 2012, VOL. 33, NO. 4

SHEA/IDSA/PIDS POLICY STATEMENT

Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS)

Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society

FUTURE ANTIMICROBIAL STEWARDSHIP NEEDS

SHEA/IDSA/ PIDS. Infect Control Hosp Epidemiol 2012;33(4):322-327.

ASPs Should Be Required

- No national or coordinated legislative or regulatory policies mandating antimicrobial stewardship at this time
- Pending legislation - Strategies to Address Antimicrobial Resistance (STARR) Act
  - Creates an antimicrobial task force and advisory board
    - Gather data on emergence of AMR, recommend prevention strategies, develop a public health action plan to combat spread of antimicrobial resistance
  - Requires a pharmacist to serve on the advisory board

IDSA's Efforts to Promote Antimicrobial Stewardship. Available at: http://www.idsociety.org/Stewardship_Policy/.

Stewardship Policy

- DHHS and the Healthcare Infection Control Practices Advisory Committee - **Top 5 Campaign Messages**
  - Since 2010, antimicrobial stewardship has been one of the top five messages for a healthcare worker and consumer awareness campaign
- The Joint Commissions - **National Patient Safety Goal 07.03.01**
  - Implement evidence-based practices to prevent health-care associated infections due to multidrug-resistant organisms
  - Prevention and control strategies should be tailored to the specific needs of each hospital
  - Includes: Periodic risk assessments, education, surveillance program, process/outcomes measures, implement policies and procedures to reduce transmission of MDROs, alerts

http://www.hhs.gov/ash/initiatives/hai/actionplan/hhs_hai_action_plan_final_06222009.pdf
http://jointcommission-lms.org/1900_00_HAI_NPSG_7/player.html

Stewardship Education

- "Significant knowledge deficits in the areas of antimicrobial stewardship and antimicrobial resistance among healthcare providers in the US"
  - Shortage of trained personnel for ASPs
  - All prescribing clinicians
- ASP certificate programs
- ASP education should be a **required** curriculum component for medical and pharmacy students, and postgraduate residents and fellows

SHEA/IDSA/ PIDS. Infect Control Hosp Epidemiol 2012;33(4):322-327.

Antimicrobial Use Data

- Antimicrobial use data to track and benchmark is lacking
  - Both inpatient and outpatient settings
- Need a reliable and accurate national system for collecting data on antimicrobial use

SHEA/IDSA/ PIDS. Infect Control Hosp Epidemiol 2012;33(4):322-327.

Antimicrobial Stewardship Research

- Knowledge gaps exist in understanding:
  - Antimicrobial resistance
  - Interventions to limit emergence and transmission of resistance
  - Our ability to measure associated impacts and clinical outcomes

SHEA/IDSA/ PIDS. Infect Control Hosp Epidemiol 2012;33(4):322-327.

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