I HAVE NO DISCLOSURES OR CONFLICTS RELATED TO THIS LECTURE

Neil Fishman, MD

ANTIMICROBIAL MANAGEMENT: DESIGN, IMPLEMENTATION, AND EFFICACY

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Evolution of Terminology

- Antibiotic Control

Evolution of Terminology

- ~~Antibiotic Control~~
- Antimicrobial Management

Evolution of Terminology

- ~~Antibiotic Control~~
- ~~Antimicrobial Management~~
- Antimicrobial Stewardship

ANTIMICROBIAL STEWARDSHIP INTERVENTIONS: DESIGN, IMPLEMENTATION, AND EFFICACY

You can’t always get what you want . . .

HISTORY OF ANTIMICROBIAL USE IN INFECTIOUS DISEASES

2000 B.C.

- "Here, eat this root."

1000 A.D.

- "That root is heathen. Here, say this prayer."

1850 A.D.

- "That prayer is superstition. Here, drink this potion."

1940 A.D.

- "That potion is snake oil. Here, take this penicillin; it's a miracle drug."

1985 A.D.

- "Penicillin is worthless. Here, take this new antibiotic; it's bigger and better."

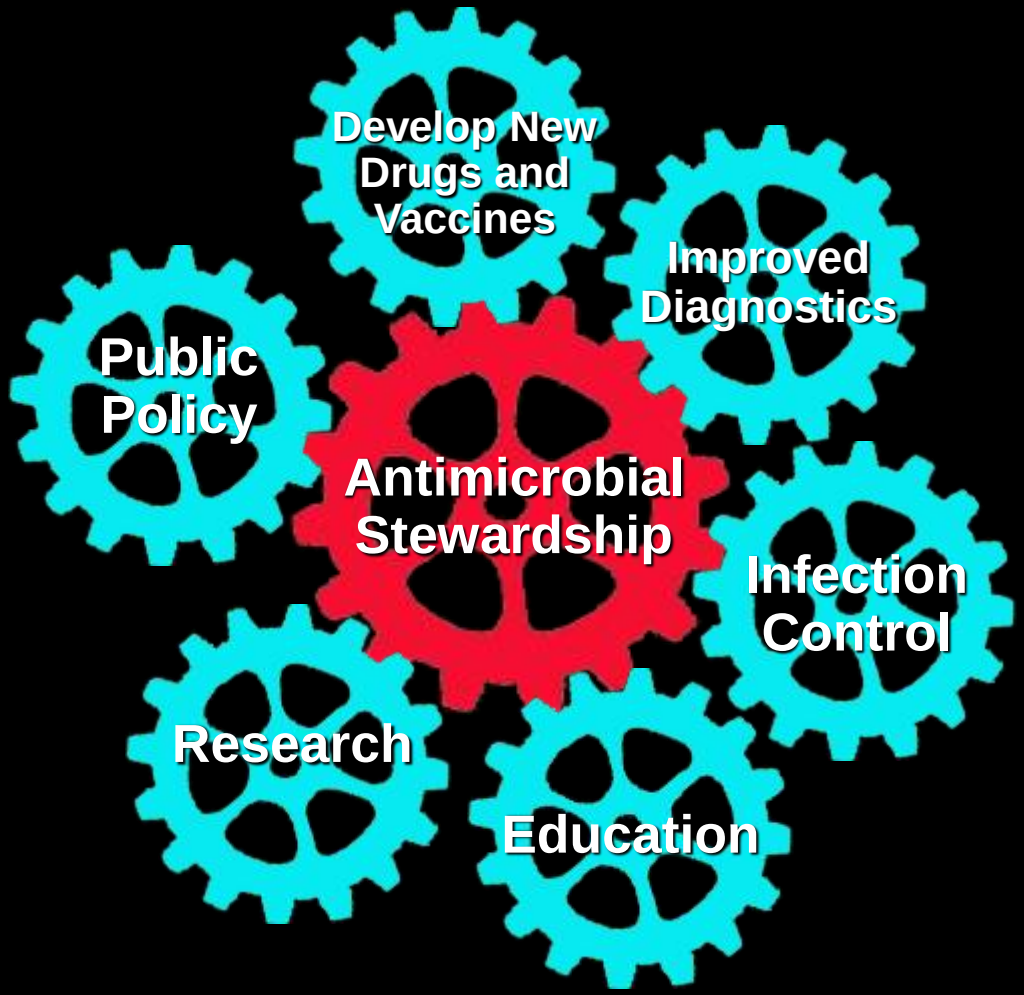
2013 A.D.

- "Those antibiotics don't work any more. Here eat this root."

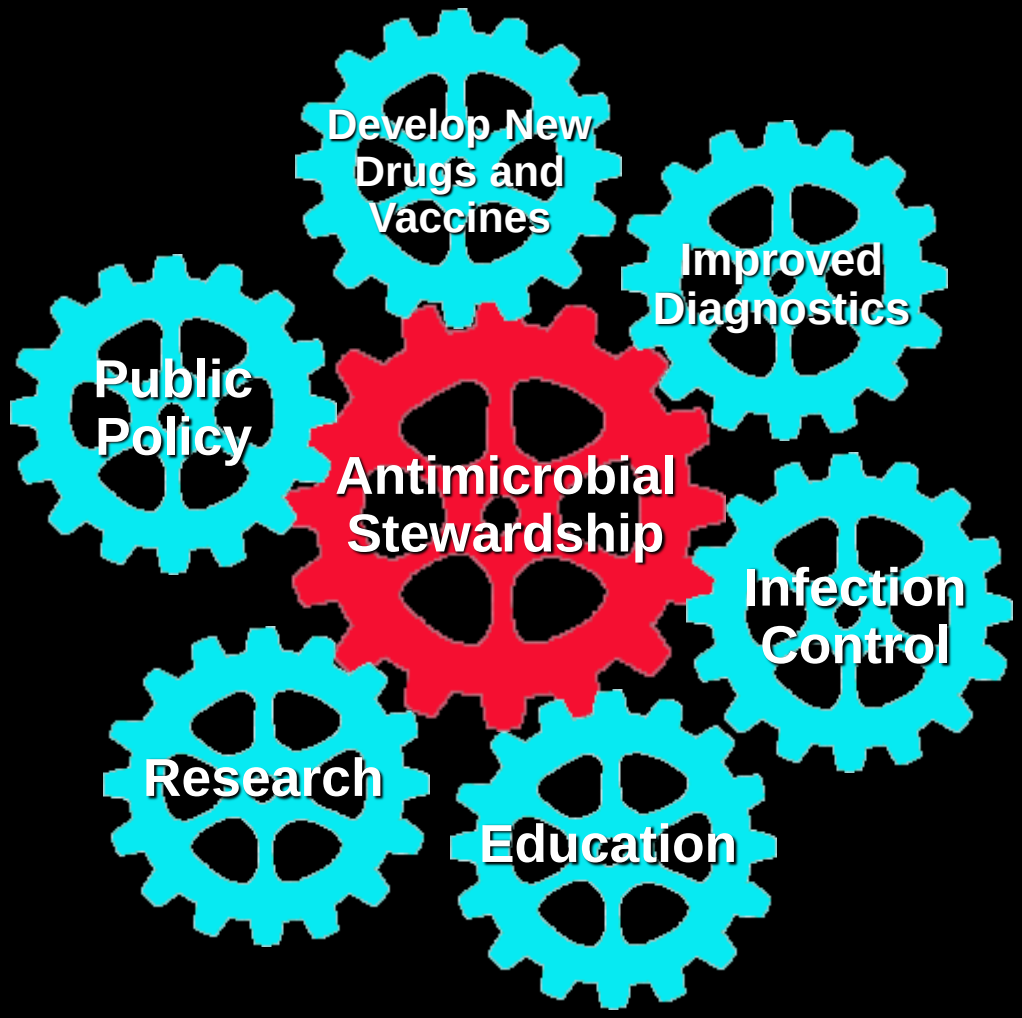
Antimicrobial Stewardship: Design, Implementation and Efficacy

- Background
- Conceptual framework for use of antibiotics
- Strategies to improve antibiotic use
- HUP Antimicrobial Stewardship Program
  - Evaluation
- Impact analysis
  - Microbial ecology
  - CRE

Efforts to Control Resistance



Efforts to Control Resistance



Why Are We Having This Conversation?

- A lot of in-patient antibiotic prescriptions are unnecessary or sub-optimal.
- We are running out of antibiotics.
- We won't get new ones anytime soon.
- Antimicrobial resistance is a significant clinical issue
- It is not just about resistance:
  - *C. difficile* infection
  - Increased toxicity and other adverse events
  - Increased morbidity and mortality
  - Increase length of stay
  - Increased cost of care

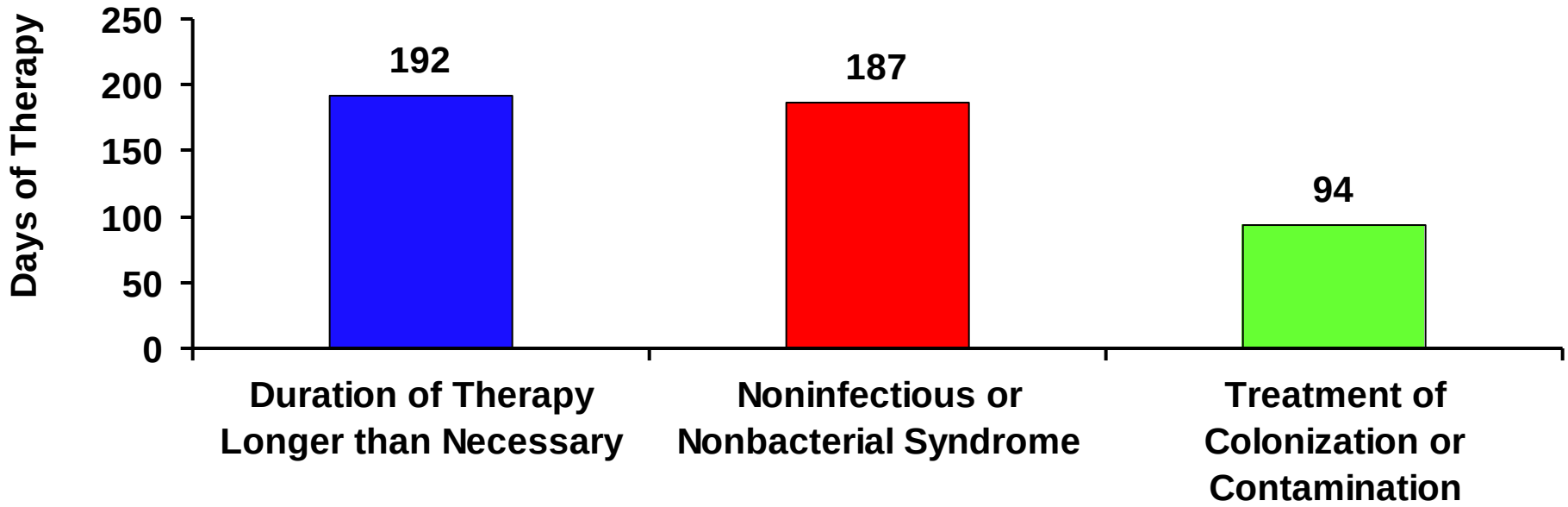
50% of antimicrobial use is either unnecessary or inappropriate

Reimann & D'Ambola. JAMA 1968;205:537

Unnecessary Use of Antimicrobials in Hospitalized Patients

- Prospective observational study in ICU
- 576 (30%) of 1941 antimicrobial days of therapy deemed unnecessary

Most Common Reasons for Unnecessary Days of Therapy



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

Why Does This Matter?

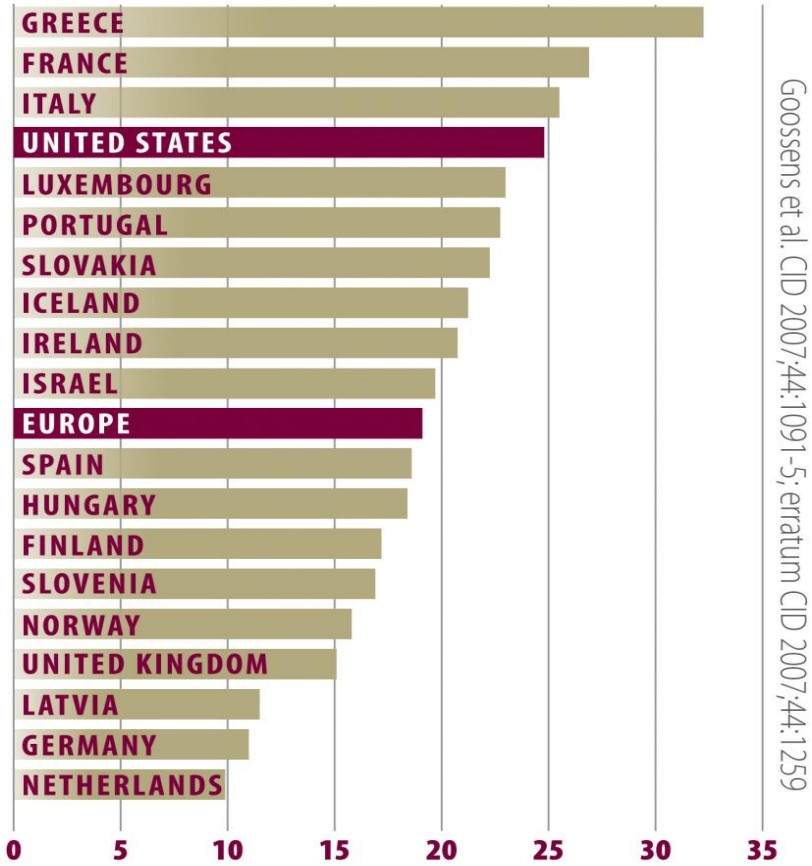
- 200-300 million antibiotics are prescribed annually
  - 45% for outpatient use
- 25-40% of hospitalized patients receive antibiotics
  - At least 30% are unnecessary or sub-optimal
  - 5% of hospitalized patients experience an adverse reaction
- >$1.1 billion spent annually on unnecessary adult antibiotic prescriptions for URI
  - 50-80% of outpatient antibiotic use is inappropriate
- **Antibiotics are unlike any other drug:** use of the agent in one patient can compromise efficacy in another

Outpatient antibiotic use: U.S.A. compared to Europe (2004)

Defined Daily Dose / 1,000 Inhabitants per day

United States: 24.9

Europe: 19.0



Goossens et al. CID 2007;44:1091-5; erratum CID 2007;44:1259

"Don't forget to take a handful of our complimentary antibiotics on your way out."

IS ANTIBIOTIC ABUSE A PROBLEM?

- Contributes to rising cost of medical care
- Increased adverse drug effects/reactions
  - 5% of hospitalized patients who receive antibiotics experience an adverse reaction
  - 20% of patients who require medical care have a history of an adverse drug effect
- Emergence of resistance

TABLE 4. Distribution and Rank Order of Selected Pathogens Associate to the National Healthcare Safety Network, January 2006–October 2007,

Pathogen	Overall[a]		CLABSI	
	No. (%) of pathogenic isolates	Rank	No. (%) of pathogenic isolates	Rank
CoNS	5,178 (15.3)	1	3,900 (34.1)	1
Staphylococcus aureus	4,913 (14.5)	2	1,127 (9.9)	4
Enterococcus species		3		2
E. faecalis	1,177 (3.5)		627 (5.5)	
E. faecium	1,888 (5.6)		942 (8.2)	
NOS	1,028 (3.0)		265 (2.3)	
Candida species		4		3
C. albicans	2,295 (6.8)		673 (5.9)	
Other *Candida* spp. or NOS	1,333 (3.9)		669 (5.9)	
Escherichia coli	3,264 (9.6)	5	310 (2.7)	8
Pseudomonas aeruginosa	2,664 (7.9)	6	357 (3.1)	7
Klebsiella pneumoniae	1,956 (5.8)	7	31.9%	5
Enterobacter species	1,624 (4.8)	8		6
Acinetobacter baumannii	902 (2.7)	9	252 (2.2)	9
Klebsiella oxytoca	359 (1.1)	10	99 (0.9)	10
Other	5,267 (15.6)		1,201 (10.5)	
Total	33,848 (100)		11,428 (100)	

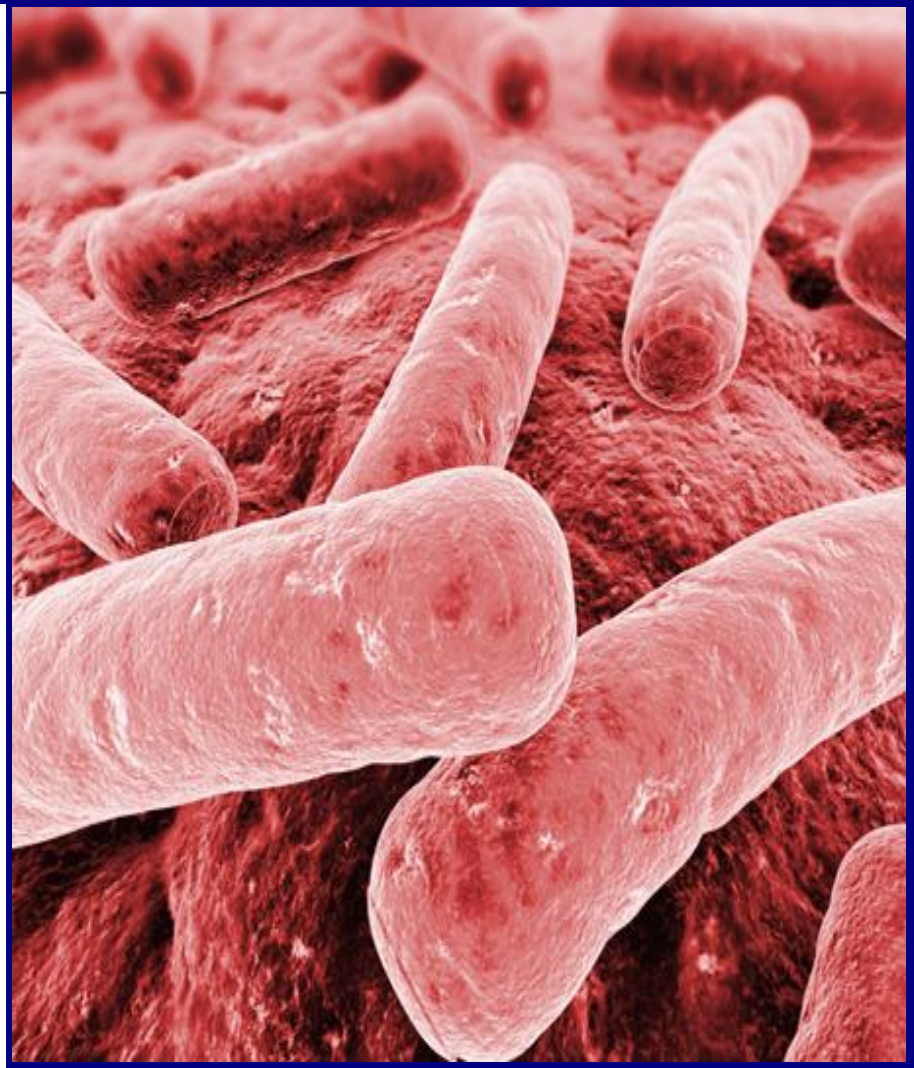
NOTE. Of the 28,502 cases of HAI reported, 4,671 (16.4%) were polymicrobial. associated bloodstream infection; CoNS, coagulase-negative staphylococci; NOS, no pneumonia.

Hidron AI, et al. Infect Control Hosp Epidemiol 2008;29:996-1011

The Death of Antibiotics?

Klebsiella pneumoniae

Antibiotic	MIC	MIC interpretation
Ampicillin	>32	R
Ampicillin/sulbactam	>32	R
Piperacillin/tazobactam	512	R
Cefazolin	>32	R
Ceftriaxone	>32	R
Meropenem	>16	R
Ertapenem	>16	R
Imipenem	>16	R
Amikacin	32	I
Gentamicin	>10	R
Tobramycin	>10	R
Ciprofloxacin	>2	R
Trimethoprim/ sulfamethoxazole	>4/80	R
Colistin	>8	R
Tigecycline	2	S
Fosfomycin*	26 mm	S



Vital Signs

Vital Signs

- **Making Health Care Safer: Stop Infections from Lethal CRE Germs Now - NEW!**
- About Vital Signs
- Vital Signs Social Media
- Other Vital Signs Issues

Related Links

Download this factsheet [PDF - 1.62 MB]

Read the MMWR»

Vital Signs

Recommend 167 Tweet 42 Share

Making Health Care Safer

Stop Infections from Lethal CRE Germs Now

CDC Vitalsigns

March 2013

On this Page

- Introduction
- Problem
- Risk of CRE Infections (infographic)
- What Can Be Done
- Science Behind this Issue
- Related Links
- Social Media
- Read Associated MMWR

Untreatable and hard-to-treat infections from CRE germs are on the rise among patients in medical facilities. CRE germs have become resistant to all or nearly all the antibiotics we have today. Types of CRE include KPC and NDM. By following CDC guidelines, we can halt CRE infections before they become widespread in hospitals and other medical facilities and potentially spread to otherwise healthy people outside of medical facilities.

Health Care Providers can

- Know if patients in your facility have CRE.
  - Request immediate alerts when the lab identifies CRE.
  - Alert the receiving facility when a patient with CRE transfers, and find out when a patient with CRE transfers into your facility.
- Protect your patients from CRE.
  - Follow contact precautions and hand hygiene recommendations when treating patients with CRE.

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Early Release / Vol. 62

March 5, 2013

Vital Signs: Carbapenem-Resistant Enterobacteriaceae

Abstract

Background: Enterobacteriaceae are a family of bacteria that commonly cause infections in health-care settings as well as in the community. Among Enterobacteriaceae, resistance to broad-spectrum carbapenem antimicrobials has been uncommon. Over the past decade, however, carbapenem-resistant Enterobacteriaceae (CRE) have been recognized in health-care settings as a cause of difficult-to-treat infections associated with high mortality.

Methods: The percentage of acute-care hospitals reporting at least one CRE from health-care–associated infections (HAIs) in 2012 was estimated using data submitted to the National Healthcare Safety Network (NHSN) in 2012. The proportion of Enterobacteriaceae infections that were CRE was calculated using two surveillance systems: 1) the National Nosocomial Infection Surveillance system (NNIS) and NHSN (for 2001 and 2011, respectively) and 2) the Surveillance Network–USA (TSN) (for 2001 and 2010). Characteristics of CRE culture-positive episodes were determined using data collected as part of a population-based CRE surveillance project conducted by the Emerging Infections Program (EIP) in three states.

Results: In 2012, 4.6% of acute-care hospitals reported at least one CRE HAI (short-stay hospitals, 3.9%; long-term acute-care hospitals, 17.8%). The proportion of Enterobacteriaceae that were CRE increased from 1.2% in 2001 to 4.2% in 2011 in NNIS/NHSN and from 0% in 2001 to 1.4% in 2010 in TSN; most of the increase was observed in *Klebsiella* species (from 1.6% to 10.4% in NNIS/NHSN). In the EIP surveillance, 92% of CRE episodes occurred in patients with substantial health-care exposures.

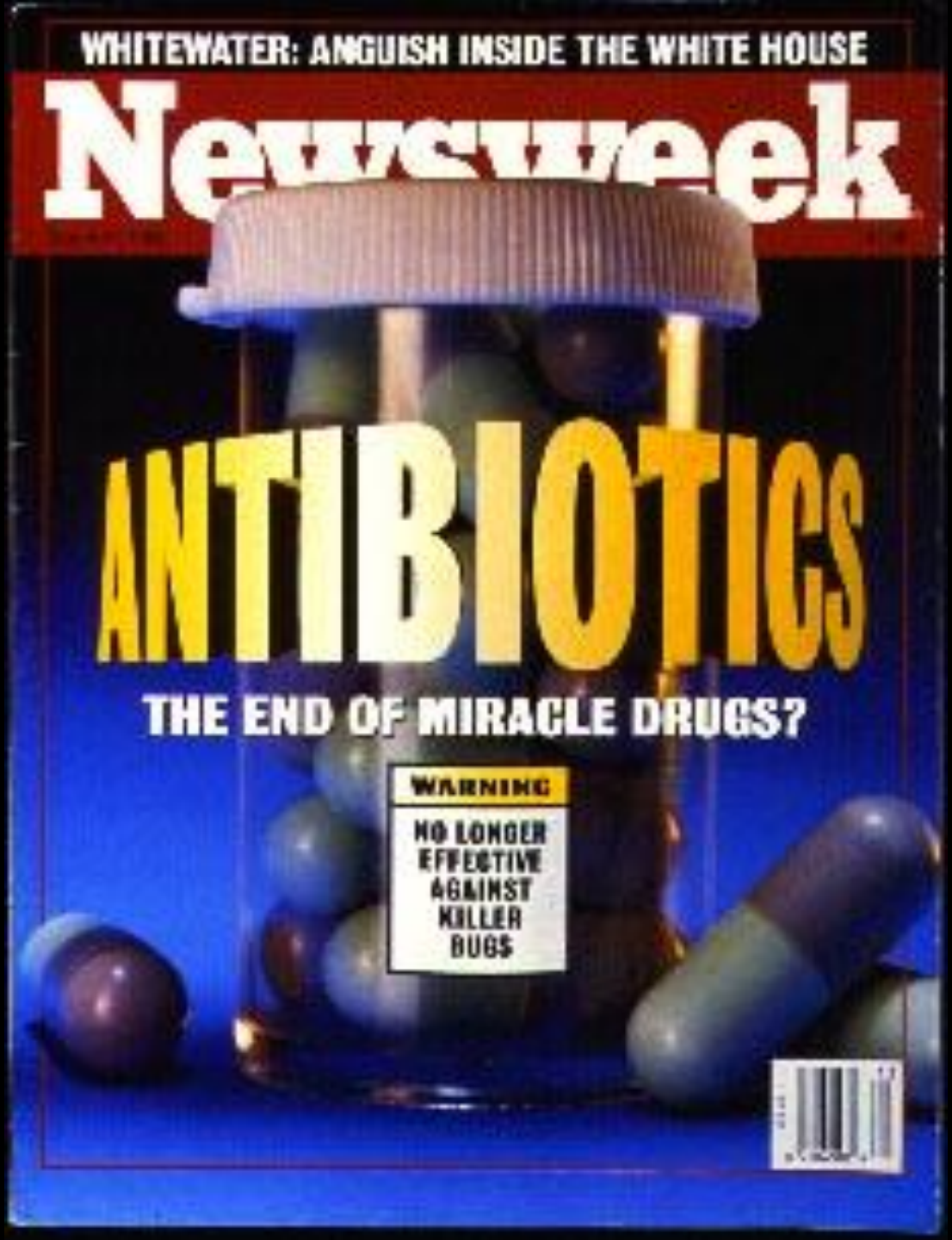
Conclusions: Carbapenem resistance among common Enterobacteriaceae has increased over the past decade; most CRE are associated with health-care exposures.

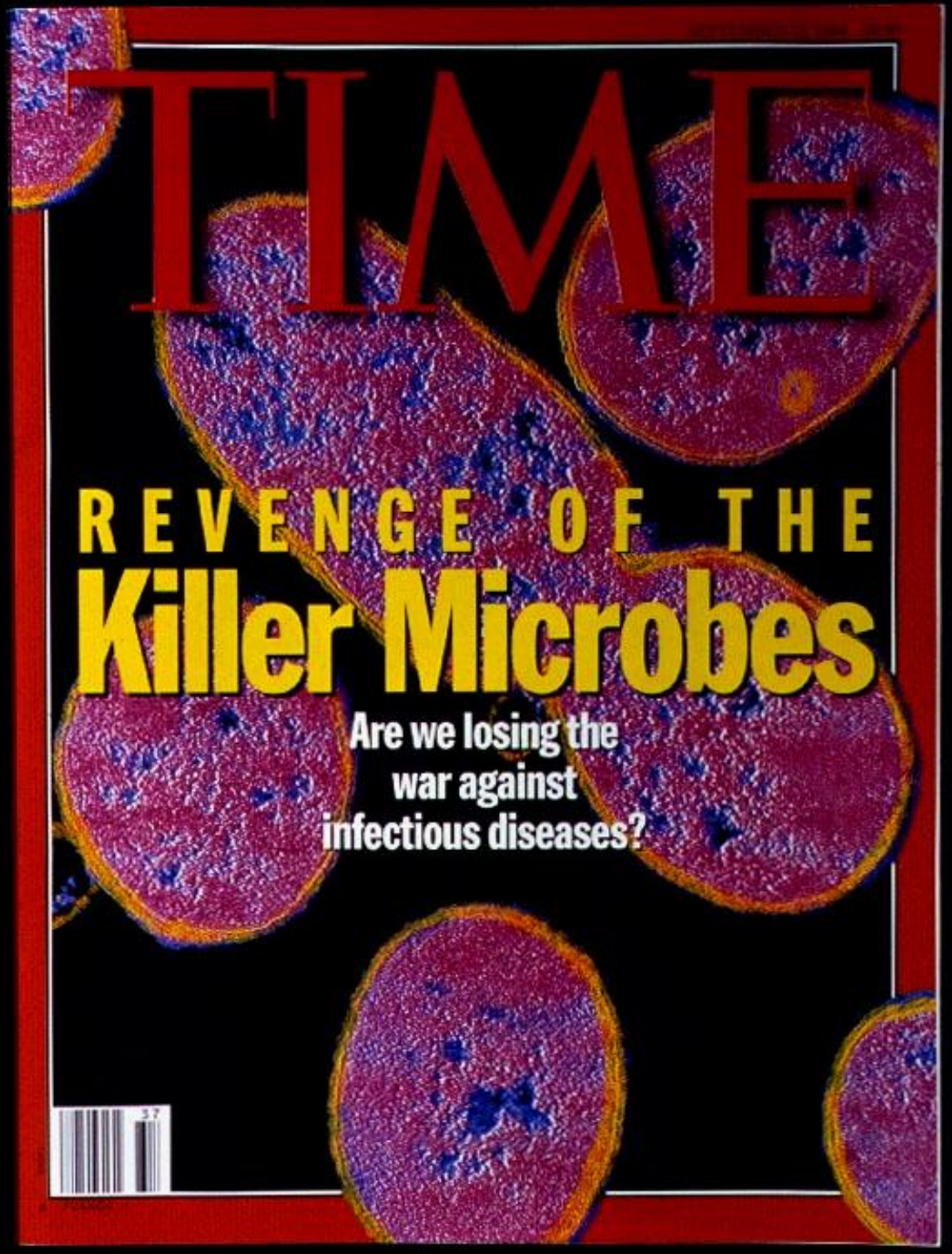
Implications for Public Health: Interventions exist that could slow the dissemination of CRE. Health departments are well positioned to play a leading role in prevention efforts by assisting with surveillance, situational awareness, and coordinating prevention efforts.

Introduction

The Enterobacteriaceae are a large family of gram-negative bacilli that are normal inhabitants of the gastrointestinal tract of humans and other animals (*1*). These organisms are

several decades have seen the spread of Enterobacteriaceae with resistance to broad-spectrum antimicrobials; however, clinicians in the United States have relied on the carbapenem antimicrobial class (imipenem, meropenem, doripenem,


WHITEWATER: ANGUISH INSIDE THE WHITE HOUSE
Newsweek
ANTIBIOTICS
THE END OF MIRACLE DRUGS?
WARNING
NO LONGER EFFECTIVE AGAINST KILLER BUGS


TIME
REVENGE OF THE
Killer Microbes
Are we losing the
war against
infectious diseases?

NOVEMBER 1997
SESAME STREET MAGAZINE SECTION ONE OF ONE

CTW

A Grab Bag of Great Autumn Activities

SESAME STREET PARENTS

Rating Children's TV
What Parents REALLY Need to Know

"I Can't Believe My Child Said That!"
Smart Comebacks for Embarrassed Moms and Dads

The Scary New Antibiotic Crisis

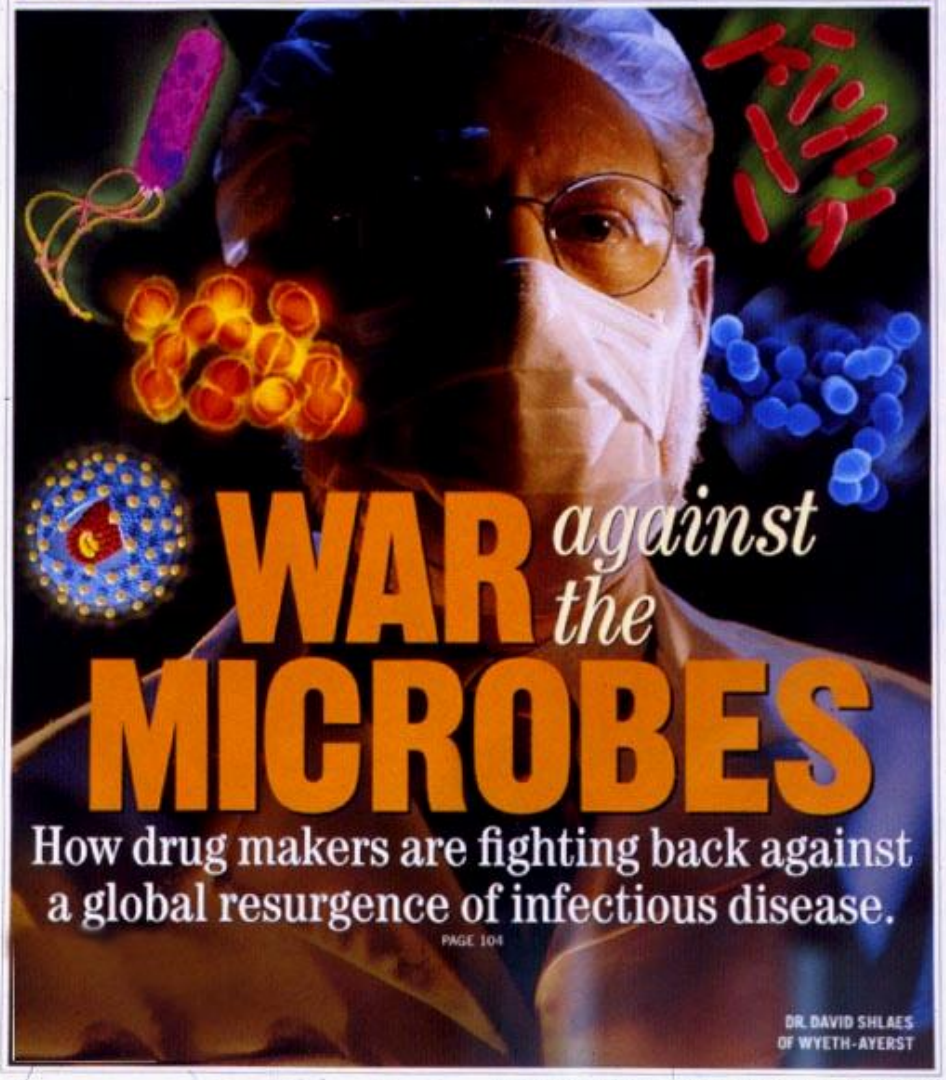
The Envelope, Please!
32 Terrific Toys
Our Annual Award Winners, Picked by Parents, Kids, and Other Experts

Finding the Perfect Baby Name...Again

SPECIAL REPORT TELECOM'S POWER PLAYERS **INVESTING** MUTUAL FUNDS: 1ST QUARTER STARS

BusinessWeek

APRIL 6, 1998 A PUBLICATION OF THE McGRAW-HILL COMPANIES $3.95



WAR *against the* MICROBES

How drug makers are fighting back against a global resurgence of infectious disease.

PAGE 104

DR. DAVID SHLAES OF WYETH-AYERST

Internet: www.businessweek.com America Online: Keyword: BW

Impact of Antibiotic Resistance

Organism	Increased risk of death (OR)	Attributable LOS (days)	Attributable cost
MRSA bacteremia	1.9	2.2	$6,916
MRSA surgical infection	3.4	2.6	$13,901
VRE infection	2.1	6.2	$12,766
Resistant Pseudomonas infection	3.0	5.7	$11,981
Resistant *Enterobacter* infection	5.0	9	$29,379

- Total cost of antimicrobial resistance is estimated to be **$30 billion annually.**

Cosgrove SE. *Clin Infect Dis*. 2006; 42:S82-9.

The Bottom Line

- Antimicrobial resistance is a critical patient safety issue
- Antimicrobial resistance is a public health threat
- Antibiotics should be viewed as a limited resource
- **Antimicrobial stewardship** provides the **infrastructure** to preserve antibiotics

Another Reason to Switch to Wegmans Pharmacy

Free
antibiotics*

Stop by the Pharmacy today! Switching only takes a minute.

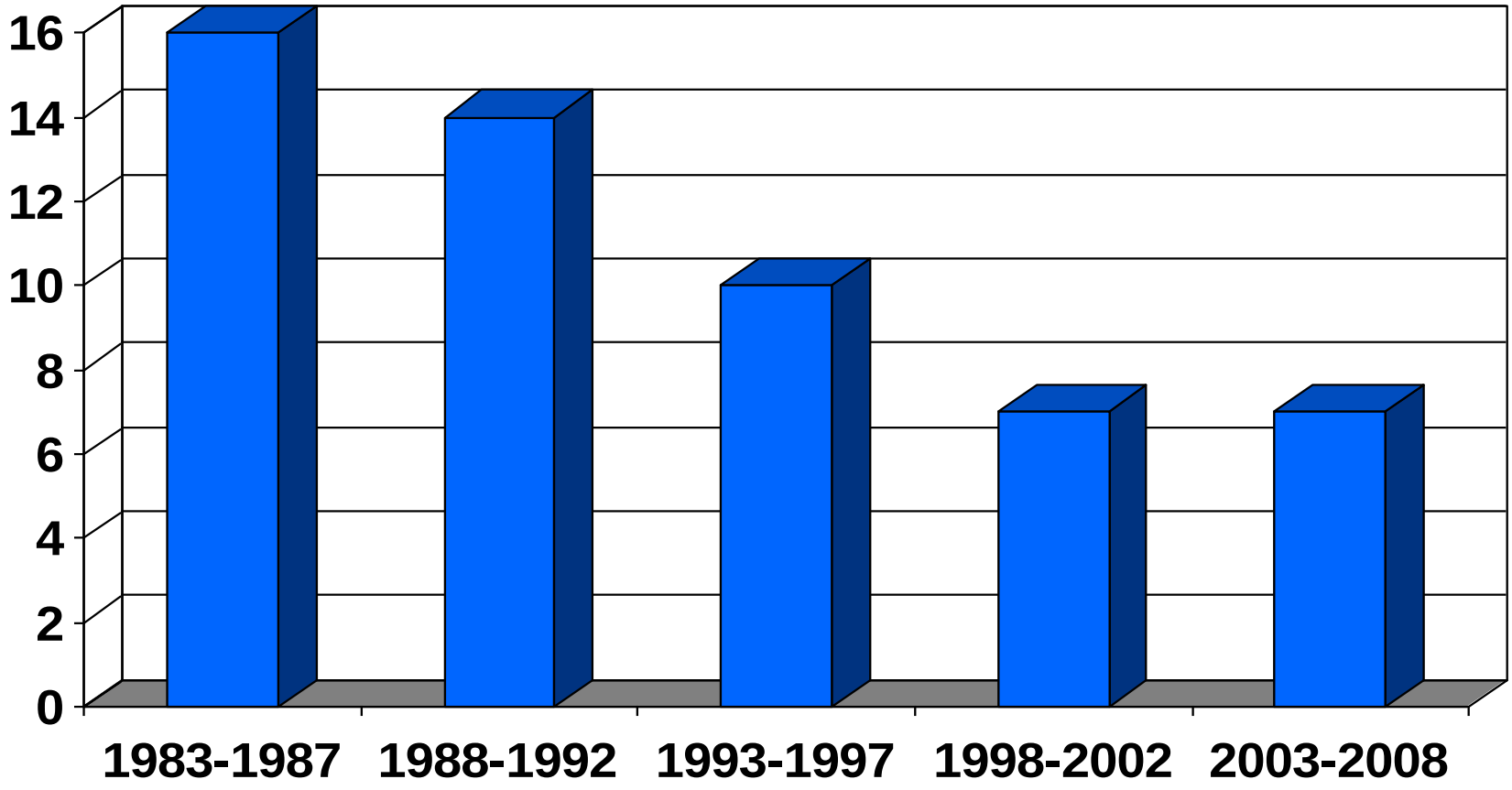
Shoppers Club

* Select generics only, with Shoppers Club Card and prescription. Antibiotics are not effective for viral infections, such as the common cold and the flu. See store or wegmans.com for list of items.

Wegmans pharmacy


FREE
Antibiotics
Up to a 14-day supply of the most commonly prescribed generic antibiotics with a valid prescription*
Your Neighborhood
Drugstore
at GIANT
LIMITED TIME ONLY!
Earn
5X
GAS
ON PARTICIPATING PRODUCTS

New Antibacterial Drugs Approved By FDA



Spellberg, *CID* 2004, Modified

The Pipeline is Dry

- Only 15-16 antibiotics are in development
- Only 8 of these have activity against key Gram negative bacteria
- None have activity against bacteria resistant to all current drugs

Boucher HW et al. Clin Infect Dis 2009; 48:1–12
European Centre for Disease Prevention and Control/European Medicines Agency Joint Technical Report
http://www.emea.europa.eu/pdfs/human/antimicrobial_resistance/EMEA-576176-2009.pdf

“The development of new antibiotics without having mechanisms to insure their appropriate use is much like supplying your alcoholic patients with a finer brandy.”

-Dennis Maki, 1998

Antimicrobial Stewardship: Definition

- Processes designed to measure and optimize the appropriate use of antimicrobials
- Achieved by selecting the appropriate agent, dose, duration of therapy and route of administration

Antimicrobial Stewardship: Objectives

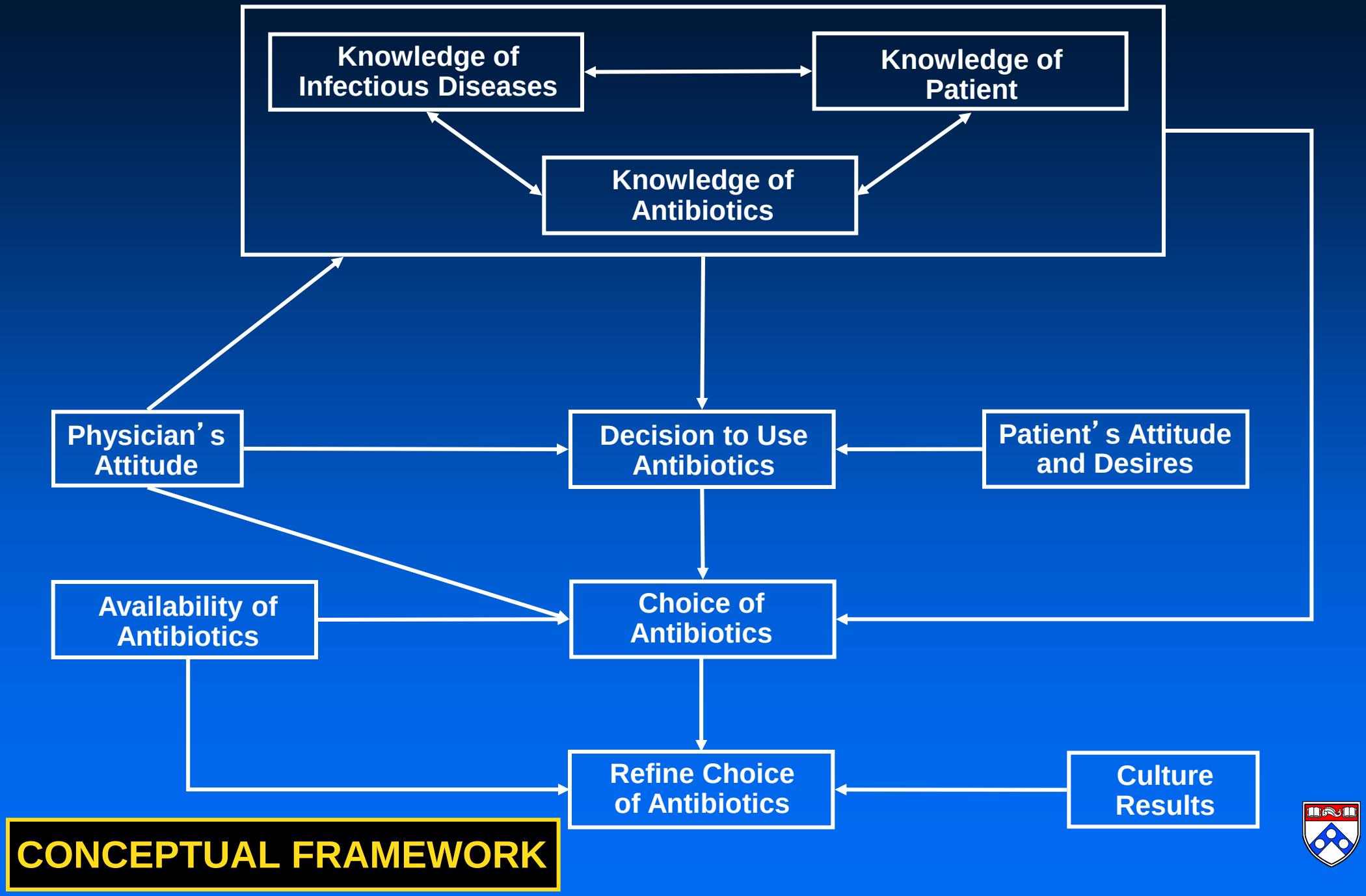
- Achieve optimal clinical outcomes
- Minimize toxicity and other adverse events
- Minimize development of antimicrobial resistance

May also reduce excessive costs attributable to:

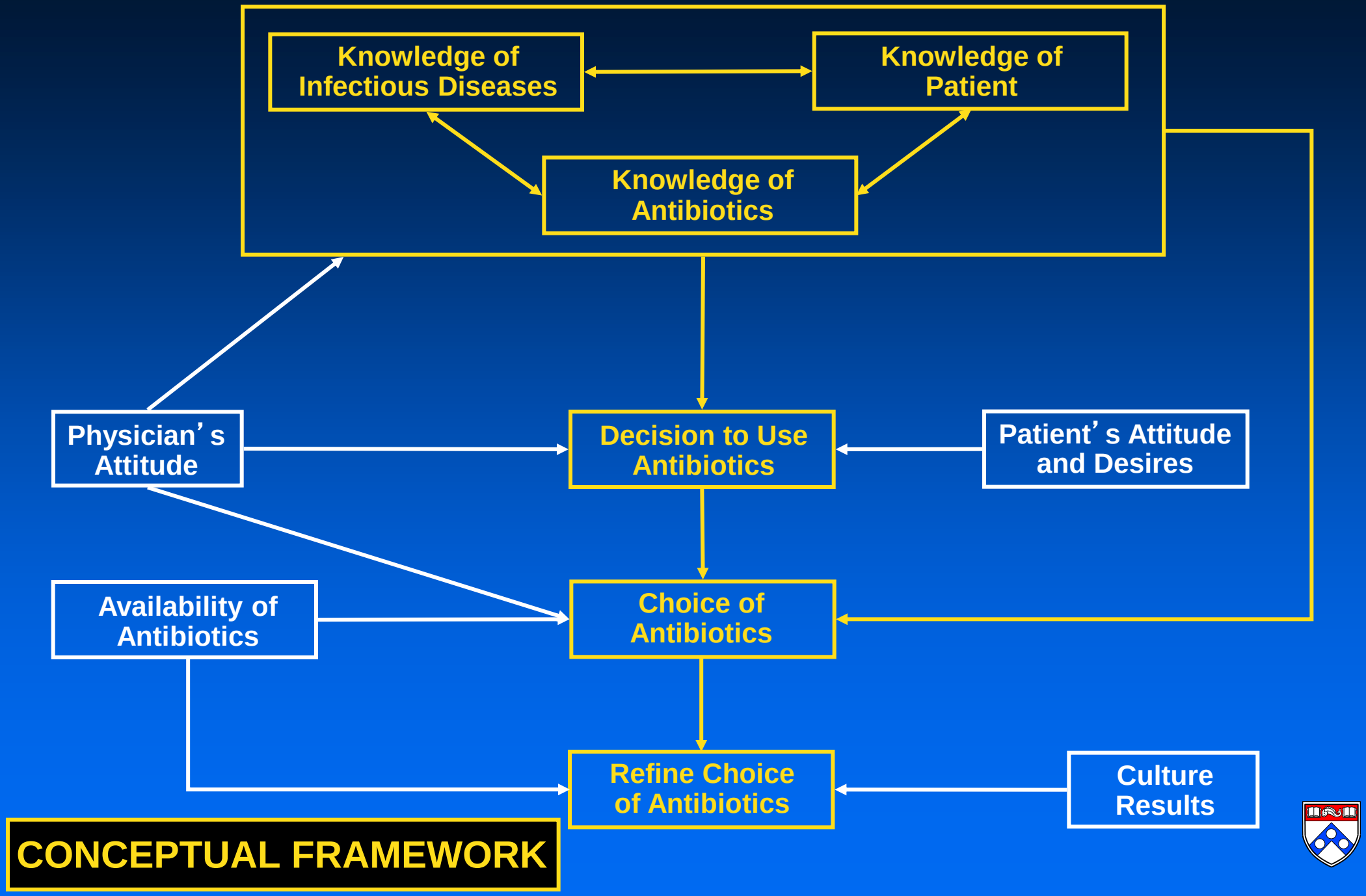
- Inappropriate/unnecessary therapy
- Suboptimal outcomes
- Toxicity and other adverse events
- Antimicrobial resistance

Antimicrobial Stewardship Interventions

- Education
- Formulary restriction
- Prior approval
- Prospective Audit with Feedback (Streamlining)
- Cycling/rotation
- Computer-assisted programs
- Comprehensive programs



CONCEPTUAL FRAMEWORK



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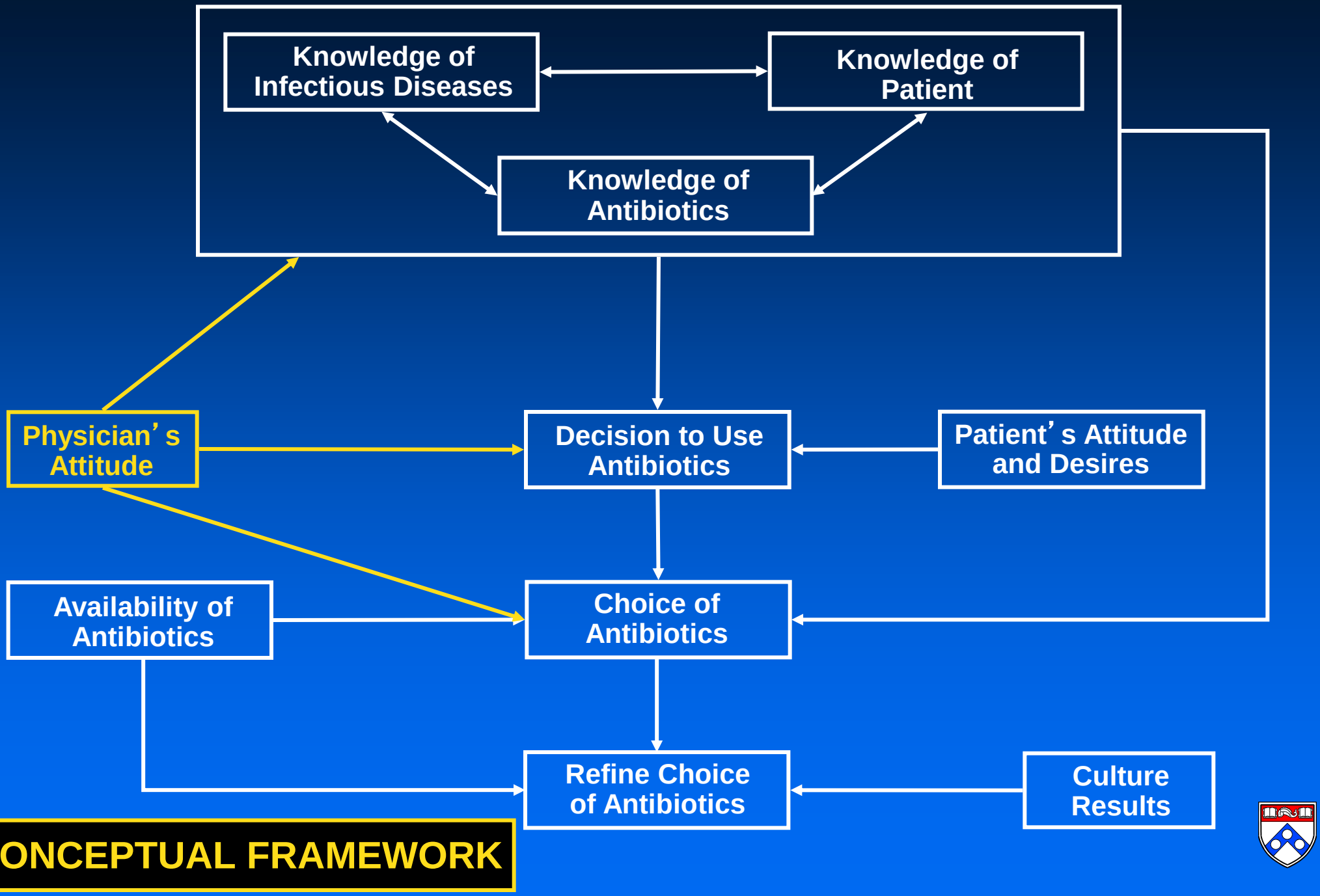

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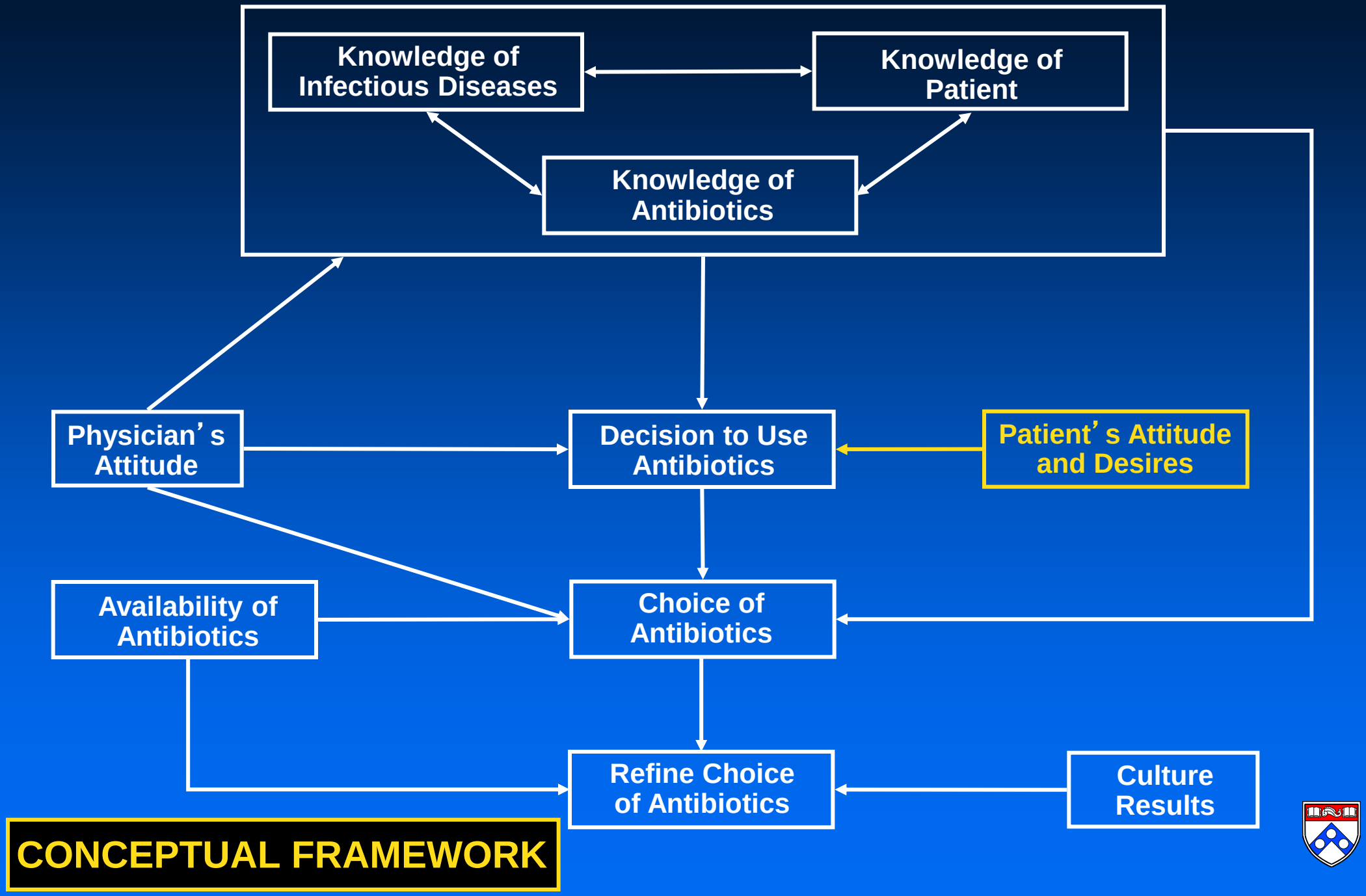

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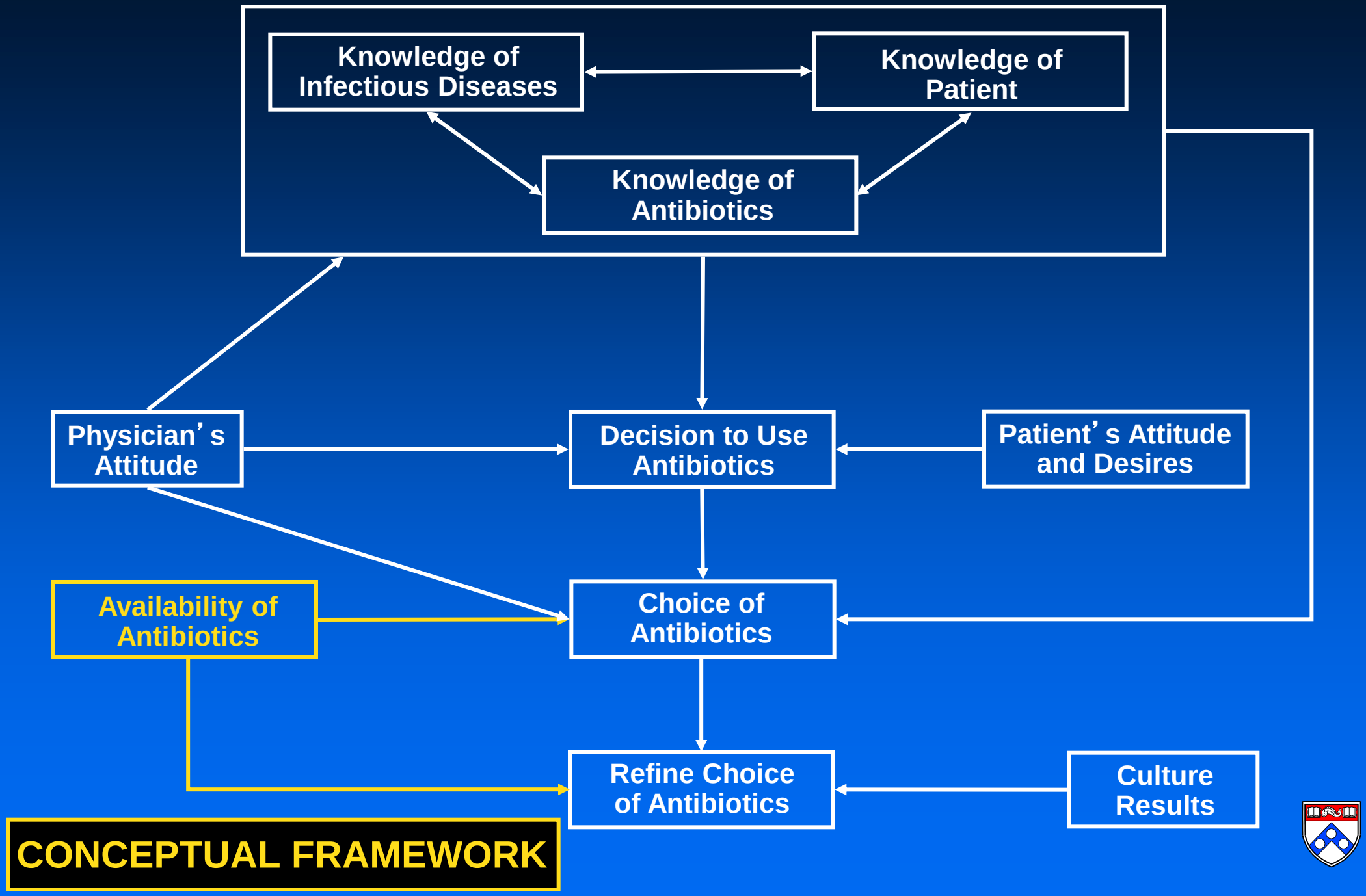

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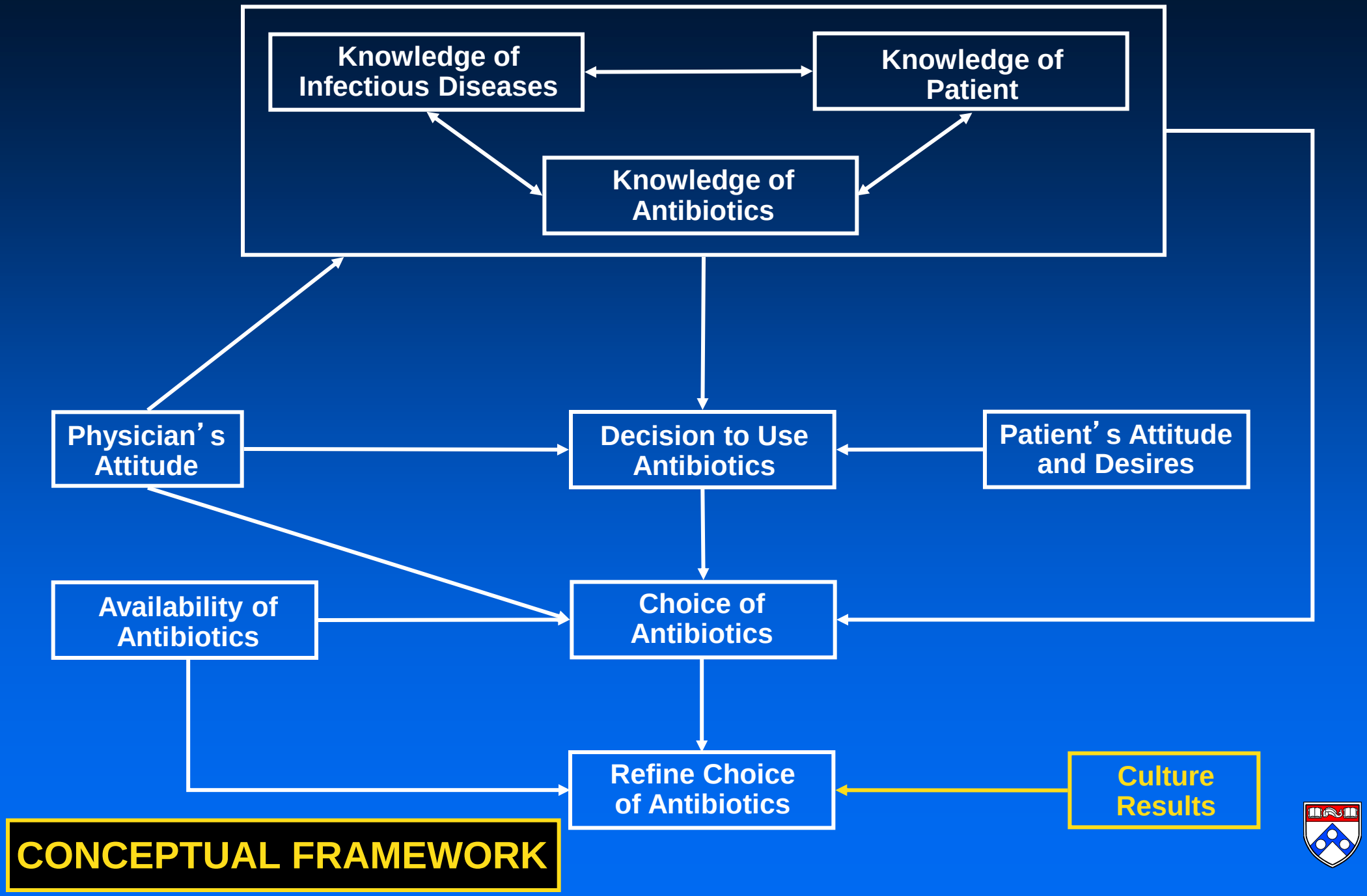
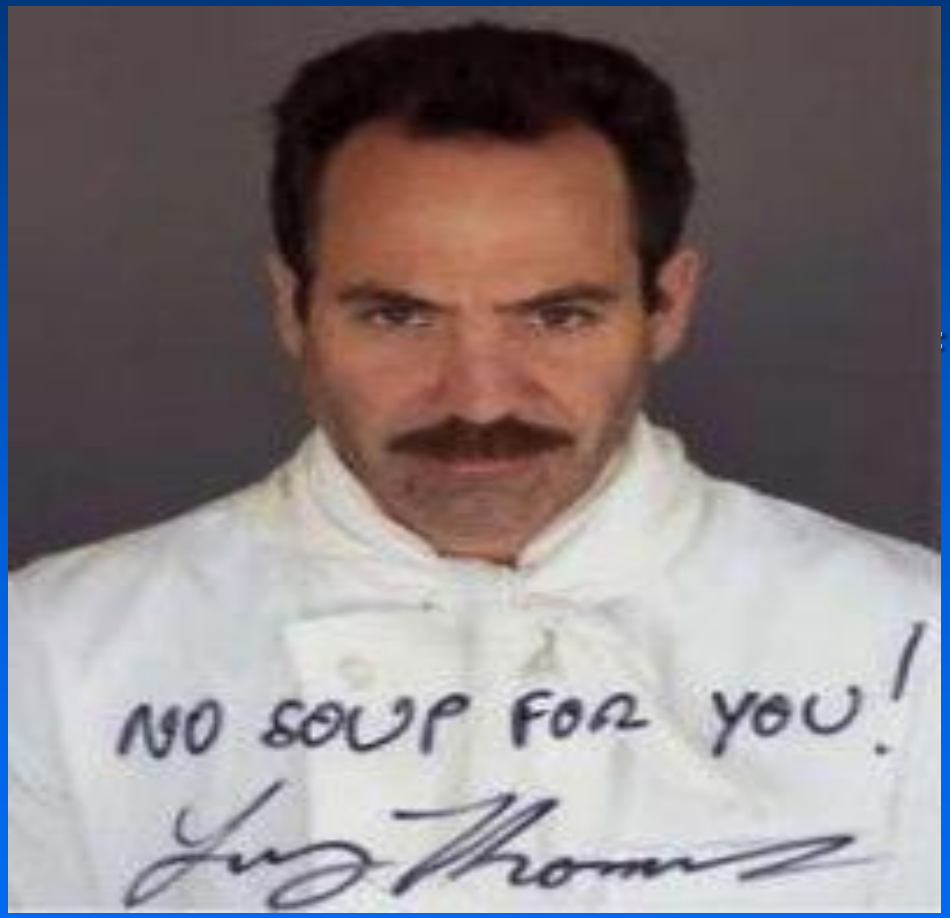


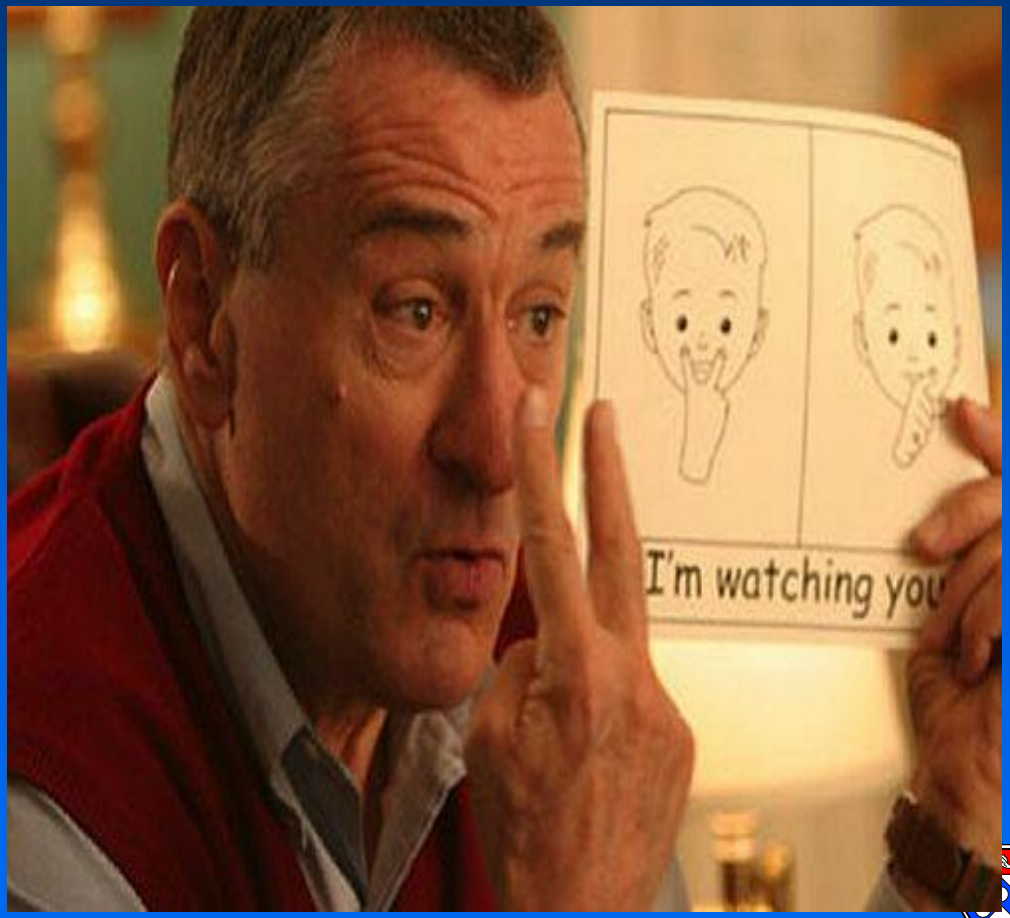
CONCEPTUAL FRAMEWORK

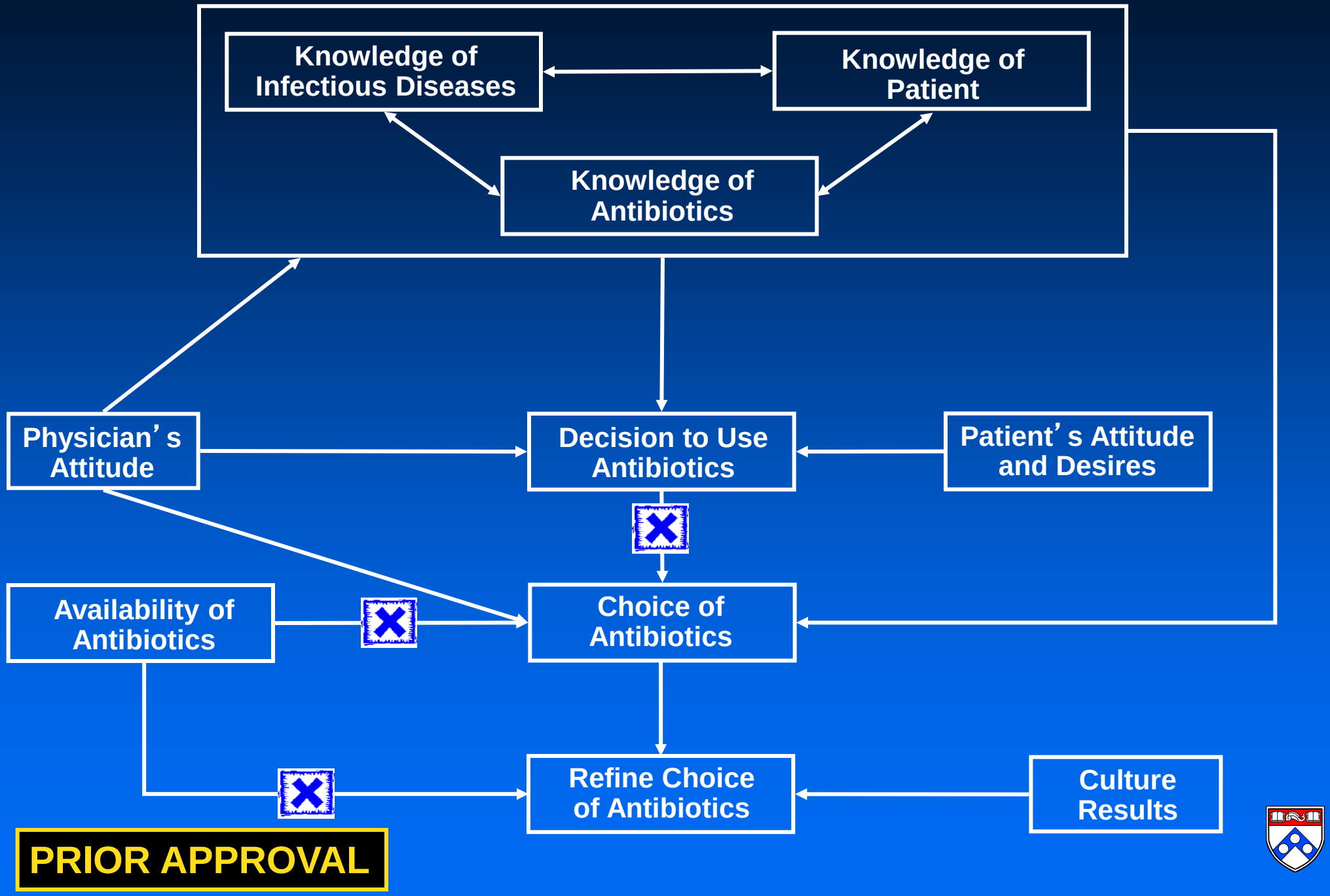
Antimicrobial Stewardship

Prior Approval



Post-Prescription Review




Knowledge of Infectious Diseases
Knowledge of Patient
Knowledge of Antibiotics
Physician's Attitude
Decision to Use Antibiotics
Patient's Attitude and Desires
Availability of Antibiotics
Choice of Antibiotics
Refine Choice of Antibiotics
Culture Results
PRIOR APPROVAL

PRIOR APPROVAL PROGRAMS

- Multiple approaches
  - Phone approval
  - Antibiotic order forms
  - Automatic stop orders
  - Direct interaction
  - Control categories
  - Simple chart entry
- Most onerous to physicians
- Most effective single intervention
  - McGowan and Finland. J Infect Dis 1974;130:165-8
  - Recco et al. JAMA 1979;241:2283-6
  - Coleman et al. Am J Med 1991;90:439-44

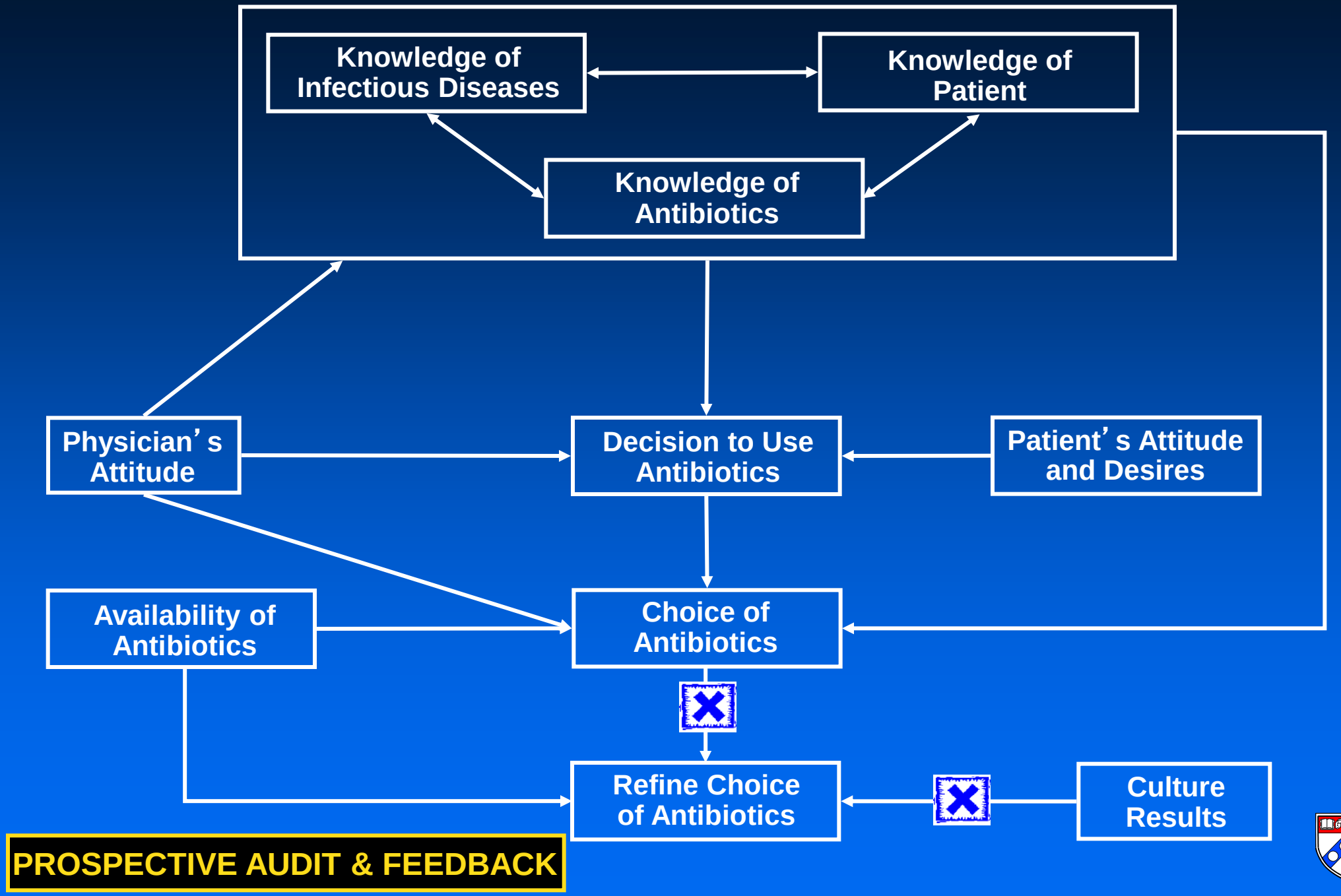
PRIOR APPROVAL: MICROBIOLOGICAL OUTCOMES

- Prior approval for selected parenteral agents
- Antimicrobial expenditures decreased 32%
- Susceptibilities to all β-lactam and fluoroquinolone antibiotics increased
  - Most dramatic in ICUs
- No change in survival
- No change in LOS
- No delay in appropriate therapy

White AC et al. *Clinical Infectious Diseases* 1997;25:230-9

Prior Approval

- The most widely implemented and evaluated approach to improving in-patient antimicrobial use
- The one true hard stop intervention
- Very effective and very quickly effective
- Relatively easy to implement
- Labor intensive
- Requires subject matter expertise
- Can create ill-will among providers
- Can lead to quick burnout of approvers


Knowledge of Infectious Diseases
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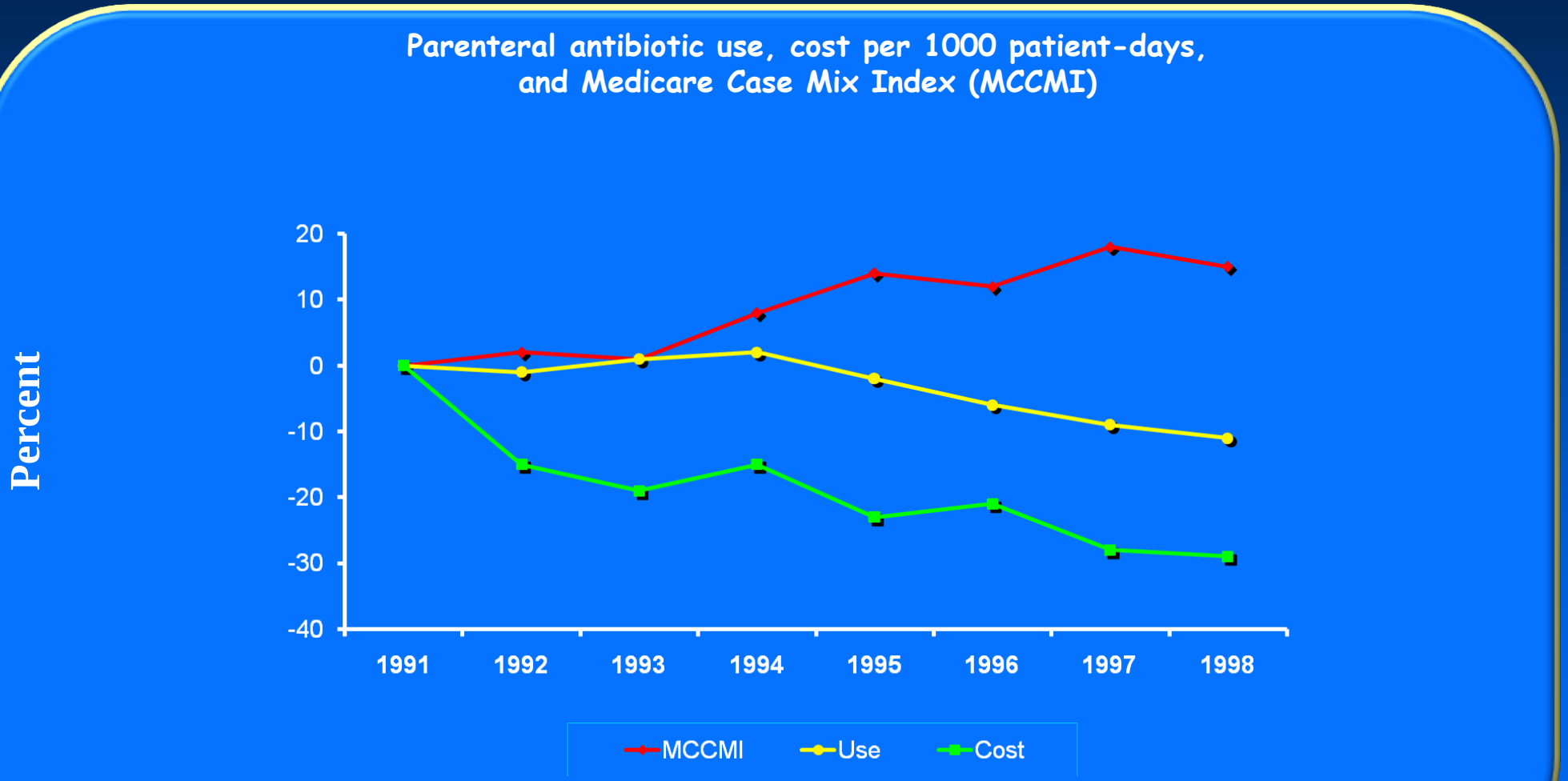
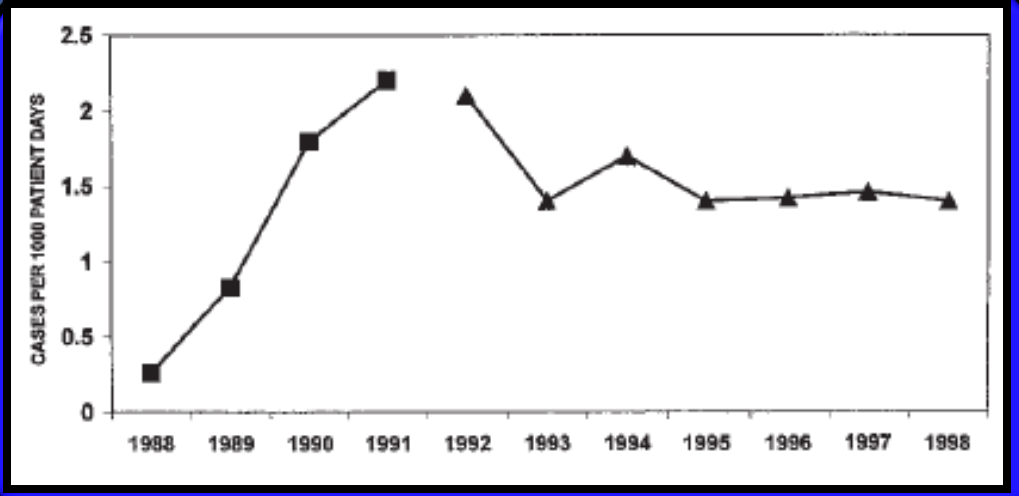
Choice of Antibiotics
Refine Choice of Antibiotics
Culture Results
PROSPECTIVE AUDIT & FEEDBACK

Prospective Audit & Feedback Example



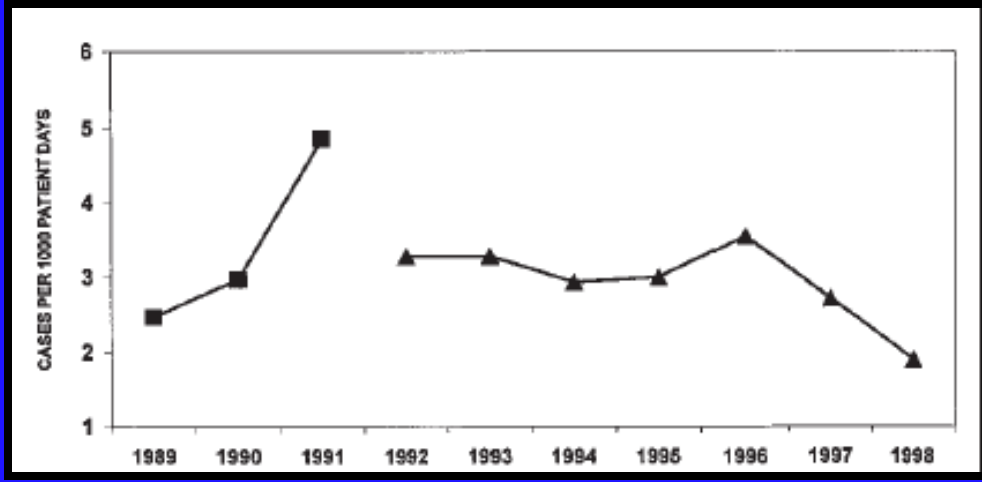
Carling P et al. *Infect Control Hosp Epidemiol.* 2003;24(9):699-706.

Measurable, Sustained Outcomes



Rates of CDI

Rates of Resistant Enterobacteriaceae



Carling P et al. *Infect Control Hosp Epidemiol.* 2003;24(9):699-706.

Stewardship Optimizes Patient Safety: Improved Use of Antibiotics

- Cluster randomized trial over 10 months
  - 6 IM teams received academic detailing regarding appropriate use of vancomycin, levofloxacin, piperacillin/tazobactam
  - 6 IM teams received guidelines only

Variable	Proportion (%) of prescriptions		Risk ratio (95% CI)	*P*
	Intervention group	Control group		
Antibiotic use deemed appropriate				
Initial (<72 hours)	305/390 (78)	229/394 (58)	1.35 (1.22–1.49)	<.001
Empirical	242/294 (82)	211/291 (73)	1.14 (1.04–1.24)	.005
Definitive	92/112 (82)	60/138 (43)	1.89 (1.53–2.33)	<.001
Appropriate cultures obtained	188/270 (70)	193/286 (67)	1.03 (0.92–1.15)	.59
Changed to recommended antibiotics[a]	168/186 (90)	85/199 (43)	2.11 (1.79–2.50)	<.001
Appropriate end antimicrobial usage	367/390 (94)	277/394 (70)	1.34 (1.25–1.43)	<.001

Camins BC et al. Infect Control Hosp Epidemiol. 2009;30:931-8.

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

ORIGINAL ARTICLE

Evaluation of Postprescription Review and Feedback as a Method of Promoting Rational Antimicrobial Use: A Multicenter Intervention

Sara E. Cosgrove, MD, MS;[1] Susan K. Seo, MD;[2] Maureen K. Bolon, MD, MS;[3] Kent A. Sepkowitz, MD;[2] Michael W. Climo, MD;[4] Daniel J. Diekema, MD;[5] Kathleen Speck, MPH;[6] Vidhya Gunaseelan, MS;[7] Gary A. Noskin, MD;[3] Loreen A. Herwaldt, MD;[5] Edward Wong, MD;[4] Trish M. Perl, MD, MSc;[1] for the CDC Prevention Epicenter Program

- **Quasi-experimental before-after study of postprescription review**
- **5 academic medical centers**
- **Adults receiving at least 48 hrs of study antibiotics**

Results of Multicenter Intervention

TABLE 1. Rate of Study and Total Antimicrobial (ABX) Use and Incidence Rate Ratios (IRR) in Each Study Period

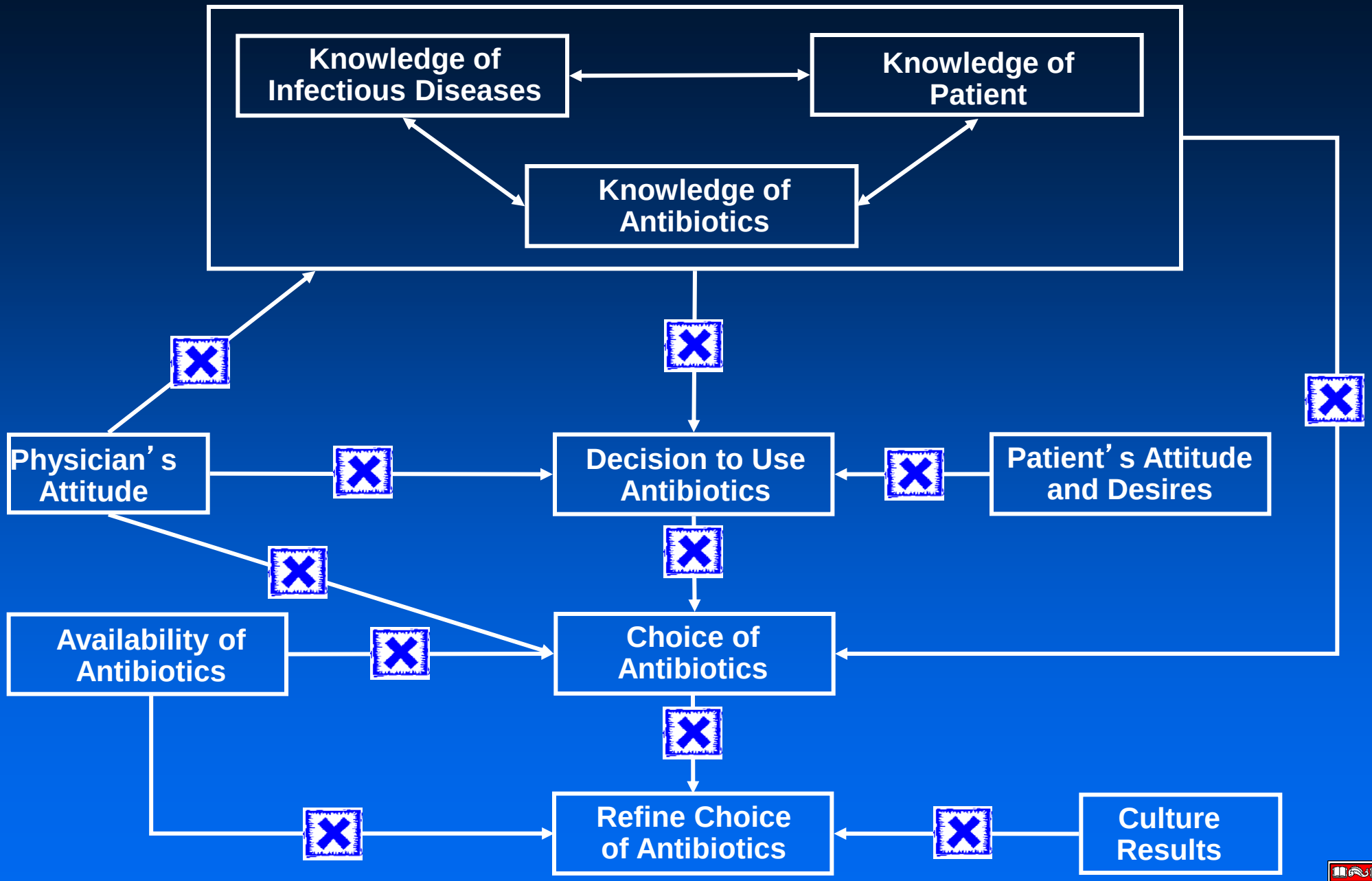
	Hospital A	Hospital B[a]	Hospital C	Hospital D	Hospital E
ABX-days/1,000 patient-days					
Study ABX					
Baseline	419.56	574.37	509.03	615.59	519.85
Intervention	469.62	533.84	497.28	512.62	596.07
Follow-up	446.33	...	476.67	602.72	642.47
Total ABX					
Baseline	395.63	548.02	474.07	522.25	473.46
Intervention	443.30	484.01	460.80	421.42	560.87
Follow-up	397.36	...	425.20	500.57	605.77
IRR (95% CI)					
Study ABX					
Intervention vs baseline	1.12 (1.05–1.19)	0.93 (0.88–0.98)	0.98 (0.91–1.04)	0.83 (0.79–0.88)	1.14 (1.08–1.22)
Intervention vs follow-up	0.95 (0.89–1.01)	...	0.96 (0.90–1.02)	1.18 (1.12–1.24)	1.08 (1.01–1.15)
Total ABX					
Intervention vs baseline	1.12 (1.06–1.18)	0.88 (0.85–0.92)	0.97 (0.92–1.03)	0.81 (0.77–0.84)	1.18 (1.13–1.25)
Intervention vs follow-up	0.90 (0.85–0.95)	...	0.92 (0.87–0.97)	1.19 (1.14–1.24)	1.08 (1.03–1.13)

NOTE. CI, confidence interval.

[a] Hospital B lacks follow-up data because the intervention was continued as hospital policy.

Conclusions

- **Postprescription review and feedback intervention most effective in institutions with established ASPs**
  - Institutional support
  - Dedicated resources
- **Acceptance rates equal**
  - Greater case-finding and intervention
  - Increased contact with healthcare providers



COMPREHENSIVE AND COMPUTER-ASSISTED PROGRAMS

The New England Journal of Medicine

Special Article

A COMPUTER-ASSISTED MANAGEMENT PROGRAM FOR ANTIBIOTICS AND OTHER ANTIINFECTIVE AGENTS

R. Scott Evans, Ph.D., Stanley L. Pestotnik, M.S., R.Ph., David C. Classen, M.D., M.S., Terry P. Clemmer, M.D., Lindell K. Weaver, M.D., James F. Orme, Jr., M.D., James F. Lloyd, B.S., and John P. Burke, M.D.

NEJM 1998;338:232

Table 1. Patient-Specific and Disease-Specific Issues Addressed by the Computerized Antiinfectives-Management Program.

Monographs for antiinfective agents in formulary
5-Year antibiograms
Patient infections in the previous 5 years
Outpatient models for treatment of infections
Costs of antiinfective agents
Review of radiologic, pathological, and laboratory findings
Alternative therapies
Patient allergies
Alerts, suggestions, and interpretation regarding laboratory-test results
Contraindications
Alerts and suggestions regarding dose, route, and duration of therapy
Drug–drug interactions
Drug–laboratory-test interactions
Drug–nutrient interactions
Drug-therapy omission
Indication for drug use
Therapeutic duplication
Pharmacokinetic consultation

IHC ANTIBIOTIC ASSISTANT & ORDER PROGRAM

00000000 Doe, John Q. E615 77yr M Dx:PANCREATITIS
Max 24hr WBC=26.3 ↑ (21.1) **Admit:06/21/96.17.50** Max 24hr Temp=38.3 ↑ (37.8)
RENAL FUNCTION: Impaired, CrCl= 28, Max 24hr Cr=2.0 ↑ (2.2) IBW: 77kg
Patient's Diff shows a left shift, Max 24hr Bands = 20 ↑ (8)
ANTIBIOTIC ALLERGIES: Ofloxacin
CURRENT ANTIBIOTICS:
1. 07/14/96.17:23 AMPHOTERICIN B, VIAL 45 Q 24hrs
2. 07/18/96.12:19 VANCOMYCIN (VANCOCIN), VIAL 1000 Q 72hrs
Total amphotericin given = 181mg

IDENTIFIED PATHOGENS	SITE	COLLECTED
Enterococcus	T-Tube	07/17/96.10:57
Staphylococcus aureus	Blood	07/17/96.10:28
Candida albicans	Abdomen	07/14/96.06:23

ABX SUGGESTION	DOSAGE	ROUTE	INTERVAL	
Vancomycin	*1000mg	IV	*q72h	(infuse over 1hr)
Amphotericin B	45mg	IV	q24h	(infuse over 2-4hr)

Suggested Antibiotic Duration: 28 days
*** Adjusted based on patient's renal function**
<1>Micro, <2>OrganismSuscept, <3>Drug Info, <4>ExplainLogic, <5>Empiric Abx
<6>Abx Hx, <7>ID Rnds, <8>Lab/Abx Levels, <9>Xray, <+ or F12>Change Patient
<Esc>EXIT, <F1>Help, <0>User Input, <.>OutpatientModels
ORDERS: <*>Suggested Abx, <Enter>Abx List, </>D/C Abx, <->Modify Abx

Figure 1. Example of the Type of Information Initially Displayed When the Computerized Antiinfectives-Management Program Is Used.

Dx denotes diagnosis, max maximal, WBC white-cell count, CrCl creatinine clearance, Cr serum creatinine, IBW ideal body weight, Diff differential, arrows direction of change, IV intravenous, Abx antiinfective, Hx history, ID Rnds infectious-disease rounds, Lab laboratory, and D/C discontinue.

Computerized Antibiotic Assistant

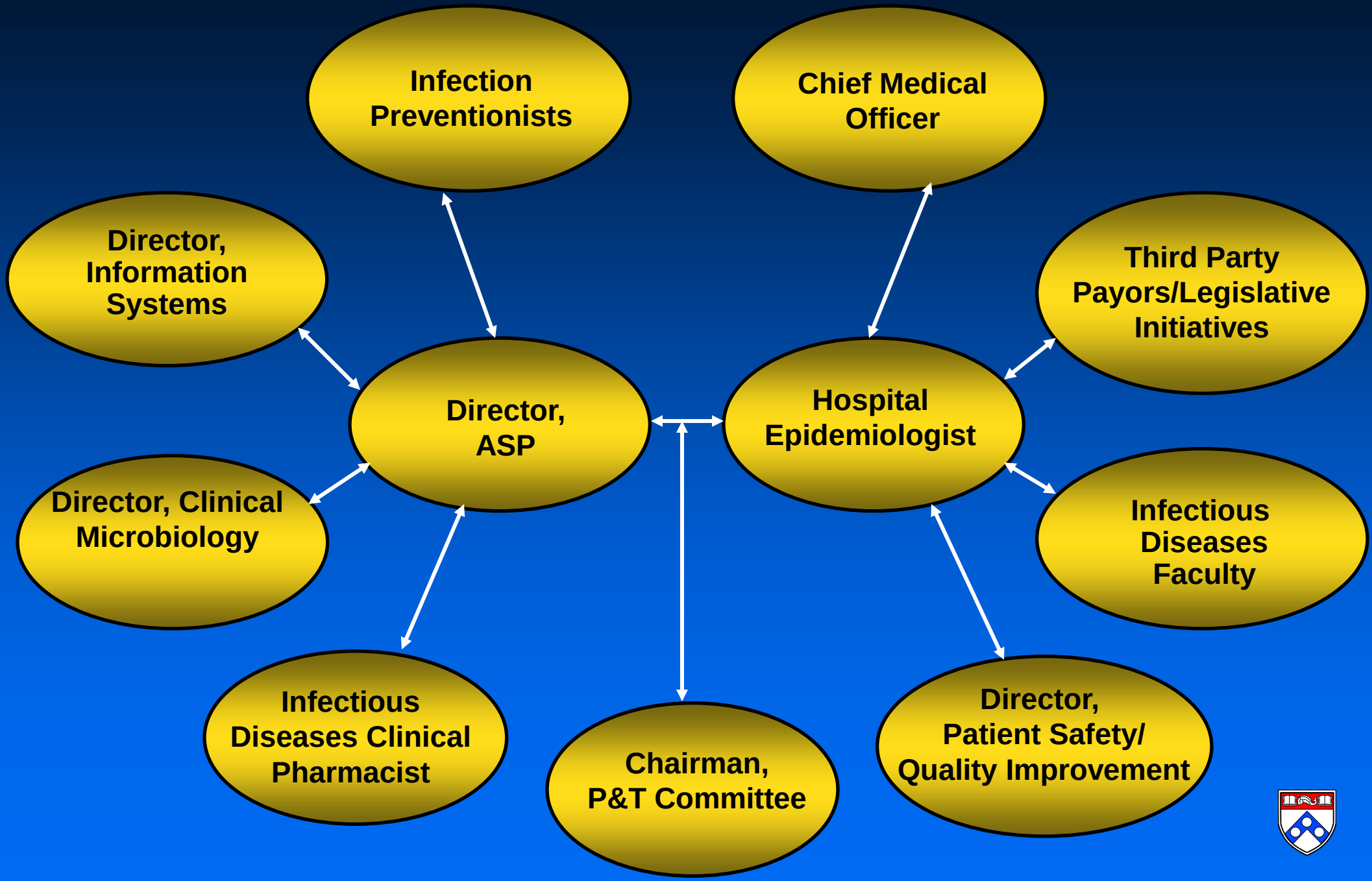
- **Significant reductions in:**
  - Orders for drugs with reported allergies (35 vs. 146)
  - Excess drug dosages (87 vs.405)
  - Antibiotic-susceptibility mismatches (12 vs. 206)
  - Mean number of days of excessive dosages (2.7 vs. 5.9)
  - Adverse events (4 vs. 28)

Evans et al. N Engl J Med 1998;338:232

Computerized Antibiotic Assistant

VARIABLE	PREINTERVENTION PERIOD	INTERVENTION PERIOD	
		Regimen Followed	Regimen Overridden
LOS - ICU (days)	4.9	2.7	8.3
Total LOS (days)	12.9	10.0	16.7
Cost of antiinfective ($)	340	102	427
Total cost ($)	35,283	26,315	44,865

Evans et al. N Engl J Med 1998;338:232


Infection Preventionists
Chief Medical Officer
Director, Information Systems
Third Party Payors/Legislative Initiatives
Director, ASP
Hospital Epidemiologist
Director, Clinical Microbiology
Infectious Diseases Faculty
Infectious Diseases Clinical Pharmacist
Chairman, P&T Committee
Director, Patient Safety/ Quality Improvement

GUIDELINES FOR ANTIMICROBIAL THERAPY

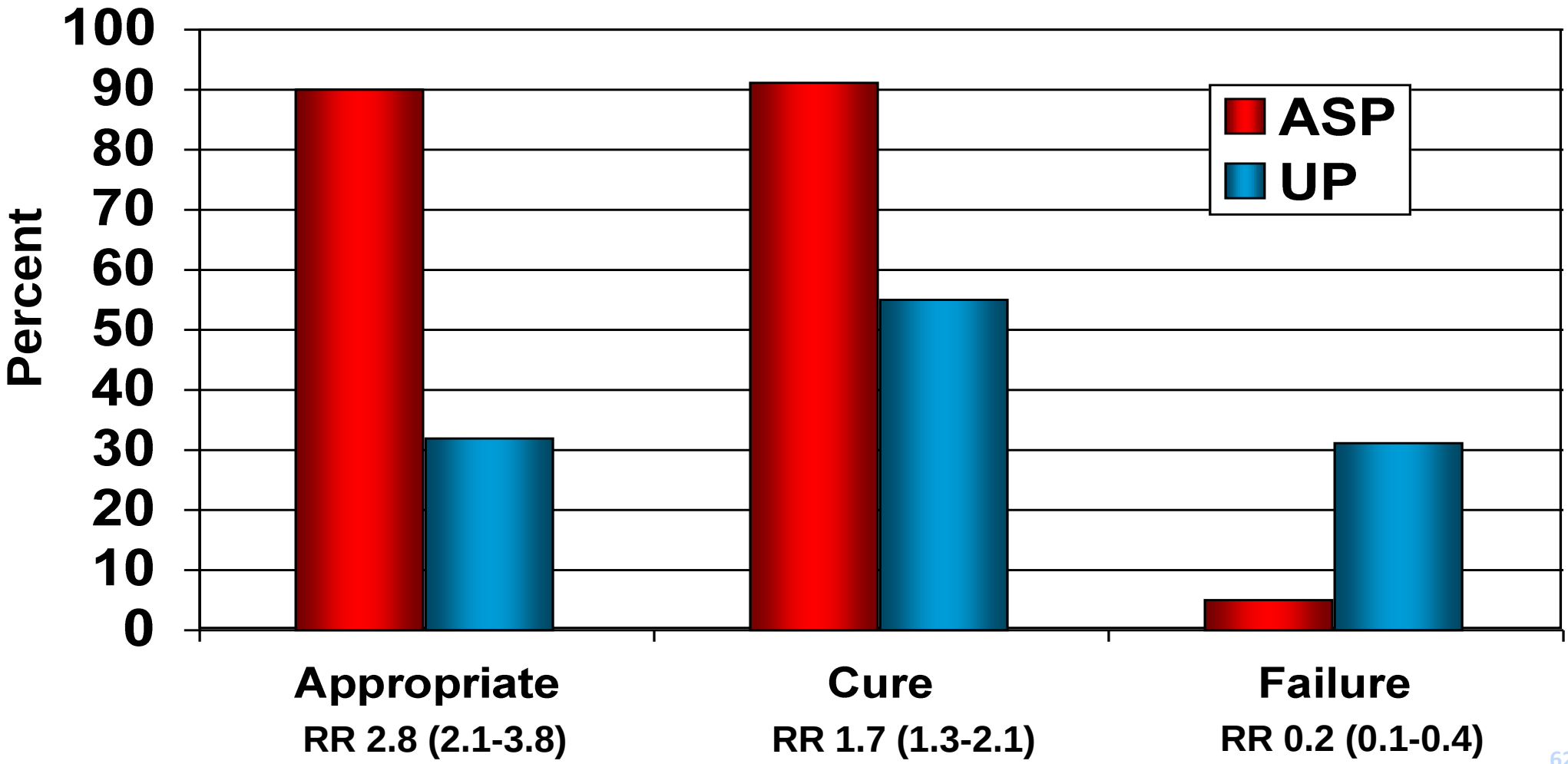
WEB ADDRESS

www.uphs.upenn.edu/antibiotics


COSMOPOLITAN
November 1995
At Last! Something Pleasurable That's Good for You.
The Health Benefits of Sex
The Heart-Pounding Bawdiness of Brad Pitt, Who Couldn't Care Less
Cosmo's Update on Antibiotics. What's Okay and What's Dangerous
Why Marry Instead of Just Fooling Around?
Makeup Tricks
$2.95
74820 08233

Fishman N. Am J Med 2006;119:S53

Clinical Outcomes



UPHS ECONOMIC OUTCOMES

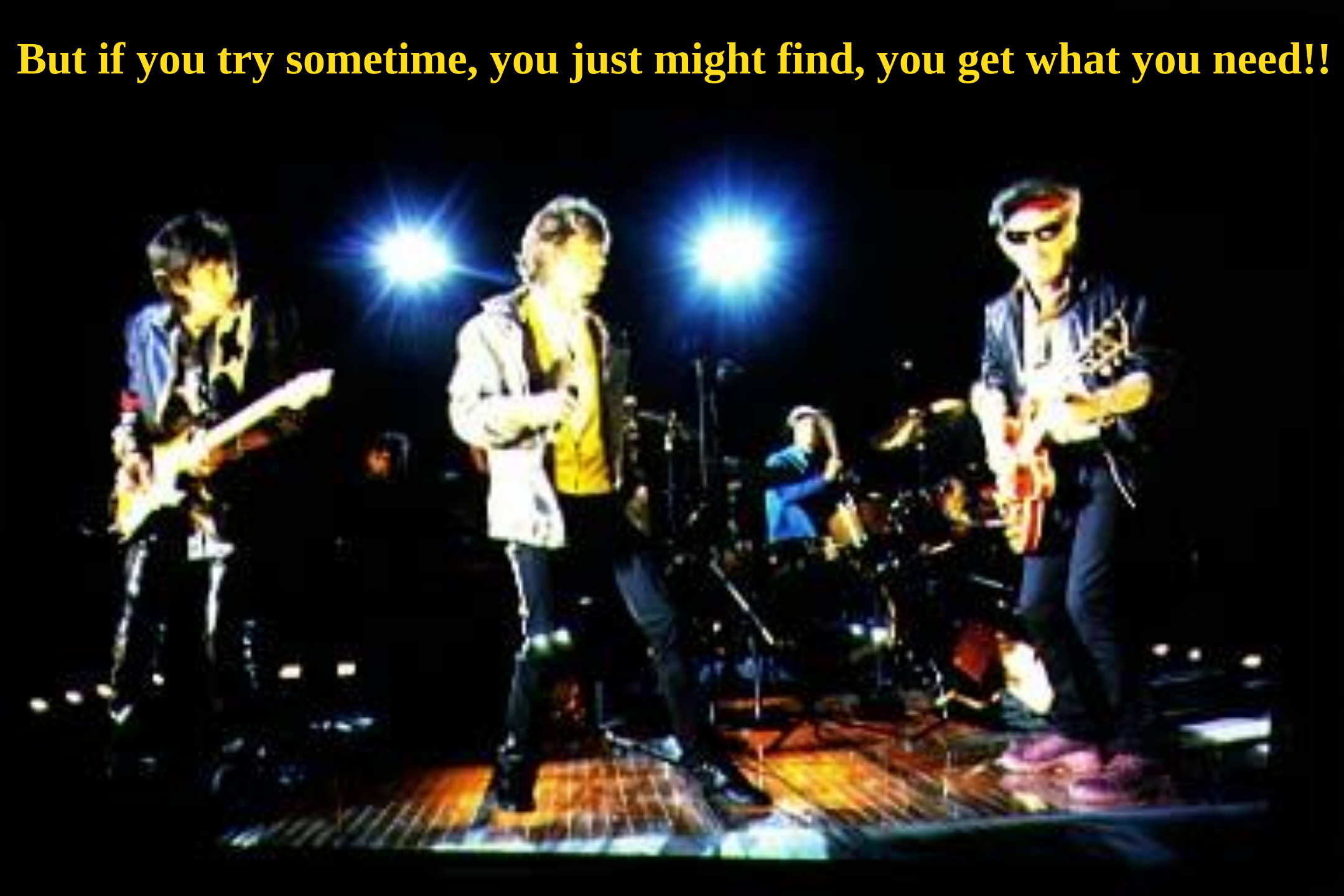
RANDOMIZED CONTROLLED TRIAL

Annual savings (600 interventions/month)

- Antibiotics: $302,400.00
- Infx-assoc costs: $533,000.00
- **Total costs: $4,277,000.00**

You can’t always get what you want . . .

But if you try sometime, you just might find, you get what you need!!



Impact Analysis

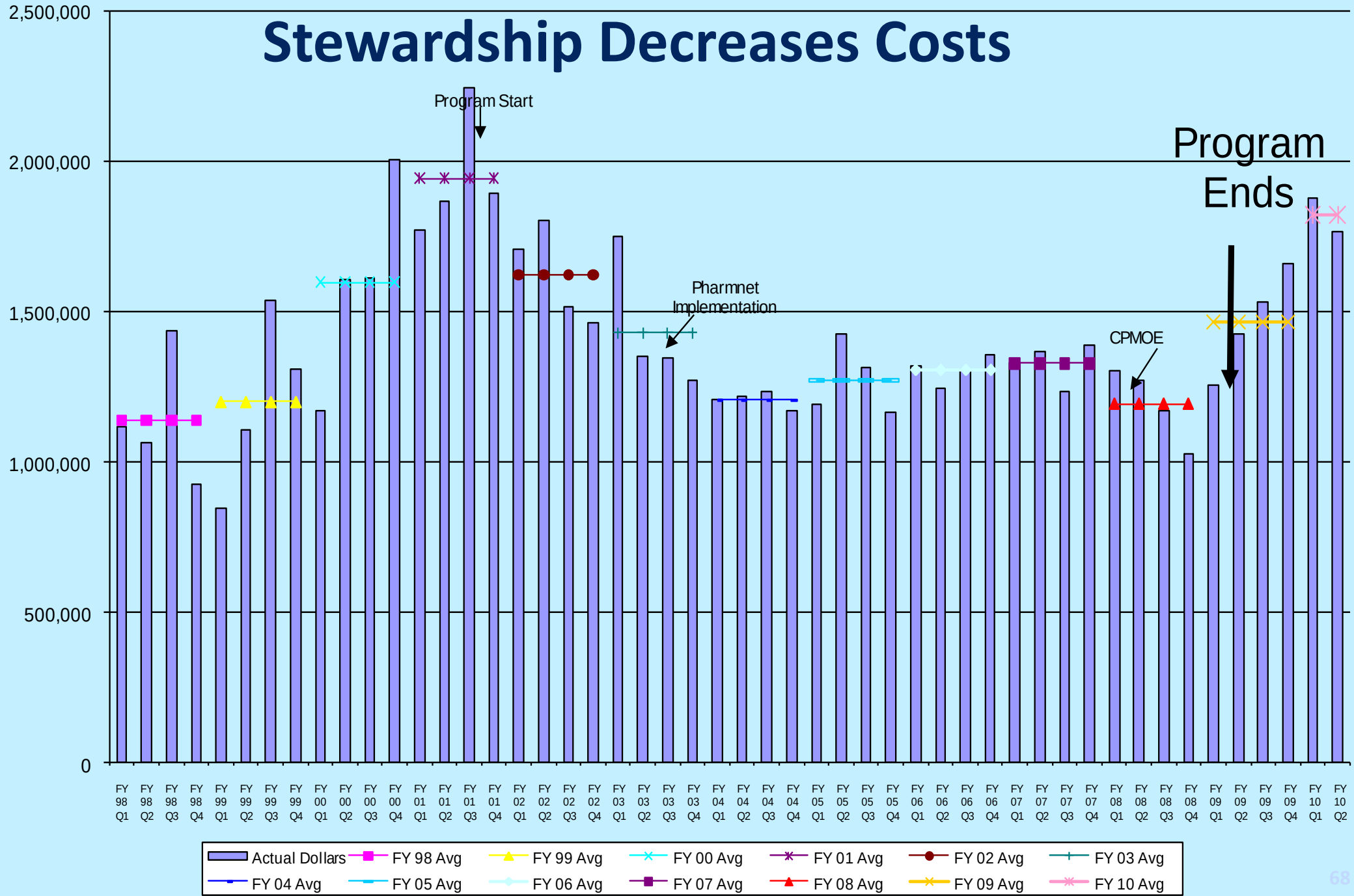
A Cautionary Tale

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

ORIGINAL ARTICLE

Antimicrobial Stewardship at a Large Tertiary Care Academic Medical Center: Cost Analysis Before, During, and After a 7-Year Program

Harold C. Standiford, MD;[1,2] Shannon Chan, PharmD;[3] Megan Tripoli, BA;[1]
Elizabeth Weekes, PharmD;[4] Graeme N. Forrest, MBBS[5]


Stewardship Decreases Costs
Program Start
Pharmnet Implementation
CPMOE
Program Ends
2,500,000
2,000,000
1,500,000
1,000,000
500,000
0
FY 98 Q1
FY 98 Q2
FY 98 Q3
FY 98 Q4
FY 99 Q1
FY 99 Q2
FY 99 Q3
FY 99 Q4
FY 00 Q1
FY 00 Q2
FY 00 Q3
FY 00 Q4
FY 01 Q1
FY 01 Q2
FY 01 Q3
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FY 02 Q1
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FY 02 Q3
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FY 03 Q1
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FY 04 Q1
FY 04 Q2
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FY 04 Q4
FY 05 Q1
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FY 06 Q2
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FY 08 Q1
FY 08 Q2
FY 08 Q3
FY 08 Q4
FY 09 Q1
FY 09 Q2
FY 09 Q3
FY 09 Q4
FY 10 Q1
FY 10 Q2
Actual Dollars
FY 98 Avg
FY 99 Avg
FY 00 Avg
FY 01 Avg
FY 02 Avg
FY 03 Avg
FY 04 Avg
FY 05 Avg
FY 06 Avg
FY 07 Avg
FY 08 Avg
FY 09 Avg
FY 10 Avg

Duration of Therapy

The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 124, No. 10 — CHICAGO, ILLINOIS — MARCH 4, 1944

THE CLINICAL USE OF PENICILLIN

OBSERVATIONS IN ONE HUNDRED CASES

MARTIN HENRY DAWSON, M.D.
AND
GLADYS L. HOBBY, PH.D.
NEW YORK

of cases of this disease was therefore abandoned until such time as larger supplies might become available. In the light of subsequent work it became obvious that the amount of penicillin given in this early group of cases was totally insufficient to secure a significant result.

During this stage of the investigation 3 cases of acute pneumococcic endocarditis came under observation. Since it was known that pneumococci were much more

prompt in 2 and more gradual in the other 2. In general the results were satisfactory with doses of 10,000 units every four hours for one and a half to two days, but in 1 instance there was a dramatic response with a dose of 5,000 units every three hours for one and a half days.

The New England
Journal of Medicine

Volume 232 JUNE 28, 1945 Number 26

TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH PENICILLIN*

MANSON MEADS, M.D.,† H. WILLIAM HARRIS, M.D.,‡ AND MAXWELL FINLAND, M.D.§
WITH THE TECHNICAL ASSISTANCE OF CLARE WILCOX
BOSTON

Severity before penicillin:
Grade 2 (moderately ill)
Grade 3 (acutely ill and irrational)
Grade 4 (shock or congestive failure, or both)

TABLE 2. *Average Total Dosage of Penicillin and Duration of Treatment in Recovered Cases.*

TYPE OF CASE	AVERAGE TOTAL DOSAGE OF PENICILLIN	AVERAGE DURATION OF TREATMENT
	units	*hr.*
Group I	411,000	86
Group II	728,000	162
Severity:		
Grade 2	317,000	66
Grade 3	477,000	107
Grade 4	735,000	148
All cases	507,000	107

Duration of Antibiotics

- Some studies indicate that shorter courses of antibiotics are sufficient
  - Ventilator associated pneumonia
  - Community acquired pneumonia
  - Septic arthritis
- Regardless, duration of antibiotics in many cases longer than most would consider sufficient
  - Average duration of antibiotics for SSTI is 14 days (range 10-16 days)
  - Average duration for VAP is 15 days (range 10-21 days)

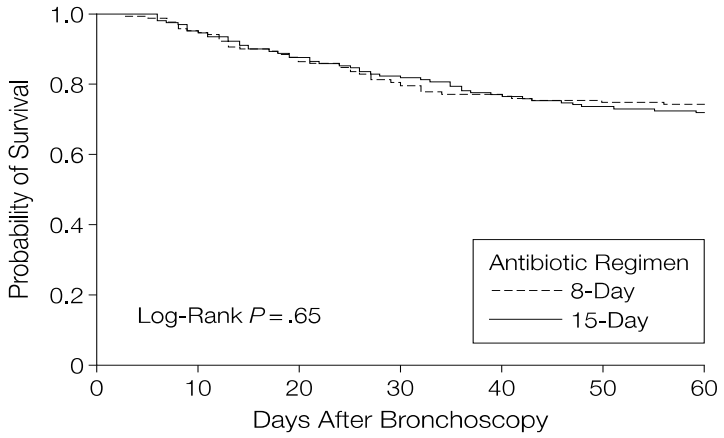
Hayashi, CID, 2011.
Chastre, JAMA, 2003.
El Moussaoui, BMJ 2006.
Peltola, CID 2009.

Treatment of VAP

JAMA®
The Journal of the American Medical Association

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial



No. at Risk							
8-Day Antibiotic Regimen	197	187	172	158	151	148	147
15-Day Antibiotic Regimen	204	194	179	167	157	151	147

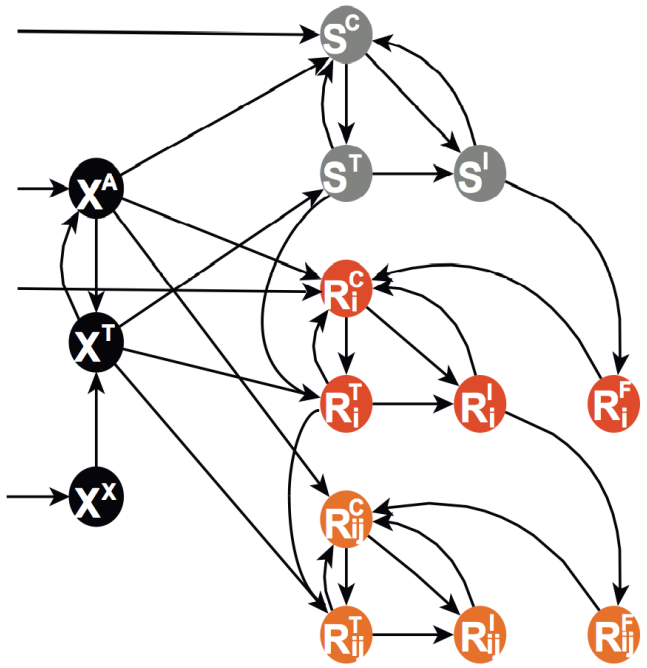
- **8 day course equal to 15 day course in RCT**

Chastre J. JAMA 2003;290:2588

Mathematical Modeling of ASP Interventions

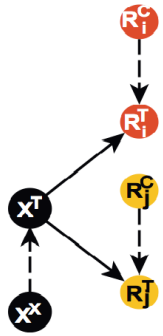
A

Mathematical model

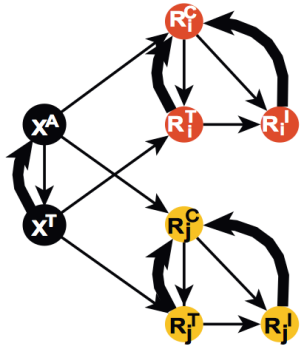


B

Fewer uninfected patients are prescribed antimicrobials (FP)



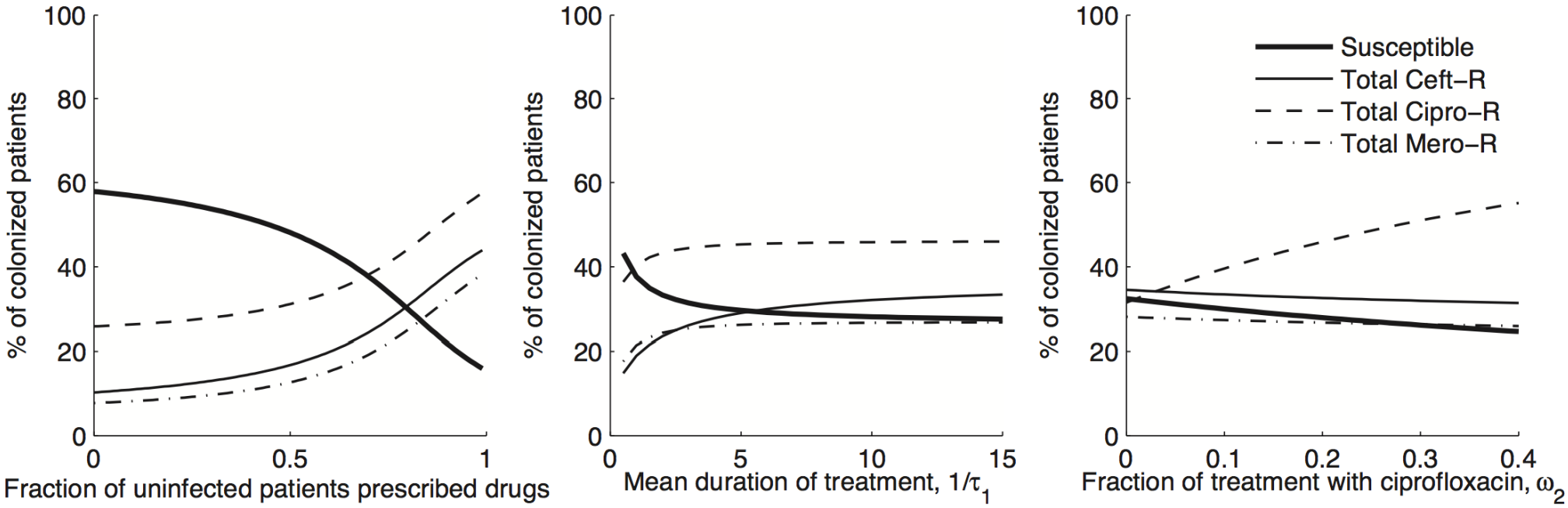
The duration of treatment is shortened (SD)

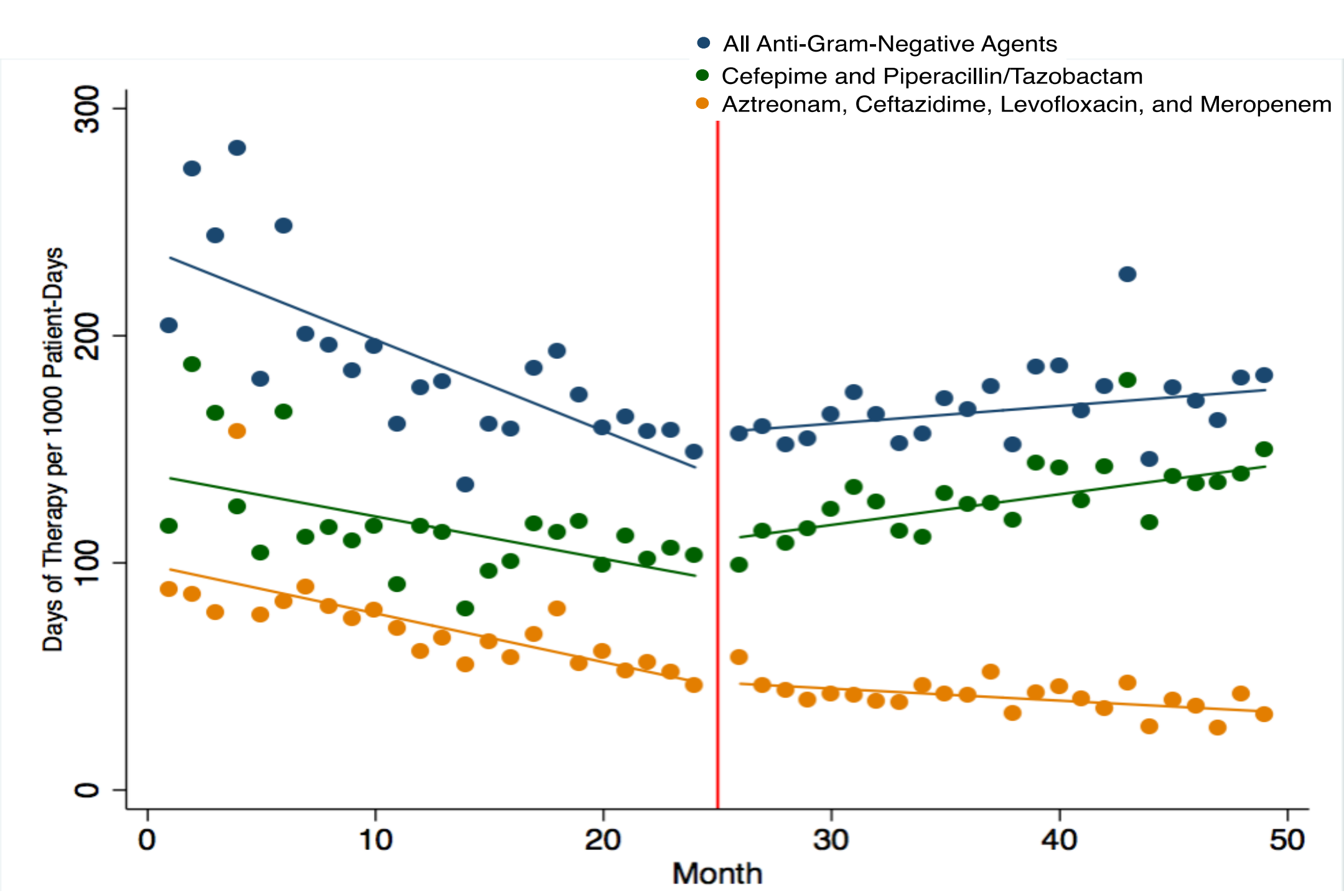


Fewer uninfected treated patients are prescribed the antimicrobial *j* (AT)

Mathematical Modeling of ASP Interventions

A. Hurford et al. / Epidemics 4 (2012) 203–210




All Anti-Gram-Negative Agents
Cefepime and Piperacillin/Tazobactam
Aztreonam, Ceftazidime, Levofloxacin, and Meropenem
Days of Therapy per 1000 Patient-Days
0
100
200
300
0
10
20
30
40
50
Month

Impact on Antimicrobial Resistance

Impact of ASPs on Antimicrobial Resistance

Ecological Data

- Changes in antimicrobial use are paralleled by changes in the prevalence of resistance
- Antimicrobial resistance is more prevalent in healthcare-associated bacterial infections
- Patients with infections caused by MDROs are more likely to have received prior antimicrobials
- Hospital units with highest antimicrobial use also have highest resistance rates
- Increased duration of exposure (time at risk) increases likelihood of colonization with MDRO

Impact of ASPs on Antimicrobial Resistance

Epidemiological Data

- Majority of data from control of outbreaks
  - CDI
  - ESBL
  - VRE
- Limited data demonstrating impact on endemic resistance

POOR STUDY DESIGN ISSUES

- Selection biases
- Insufficient power
- Varying duration of intervention
- Failure to deal with confounders
  - Cause of resistance is multifactorial
  - Community vs. nosocomial pathogens
  - Multiple concurrent control measures
  - Colonization pressure
- Generalizability
  - Bug/drug combinations
  - Setting

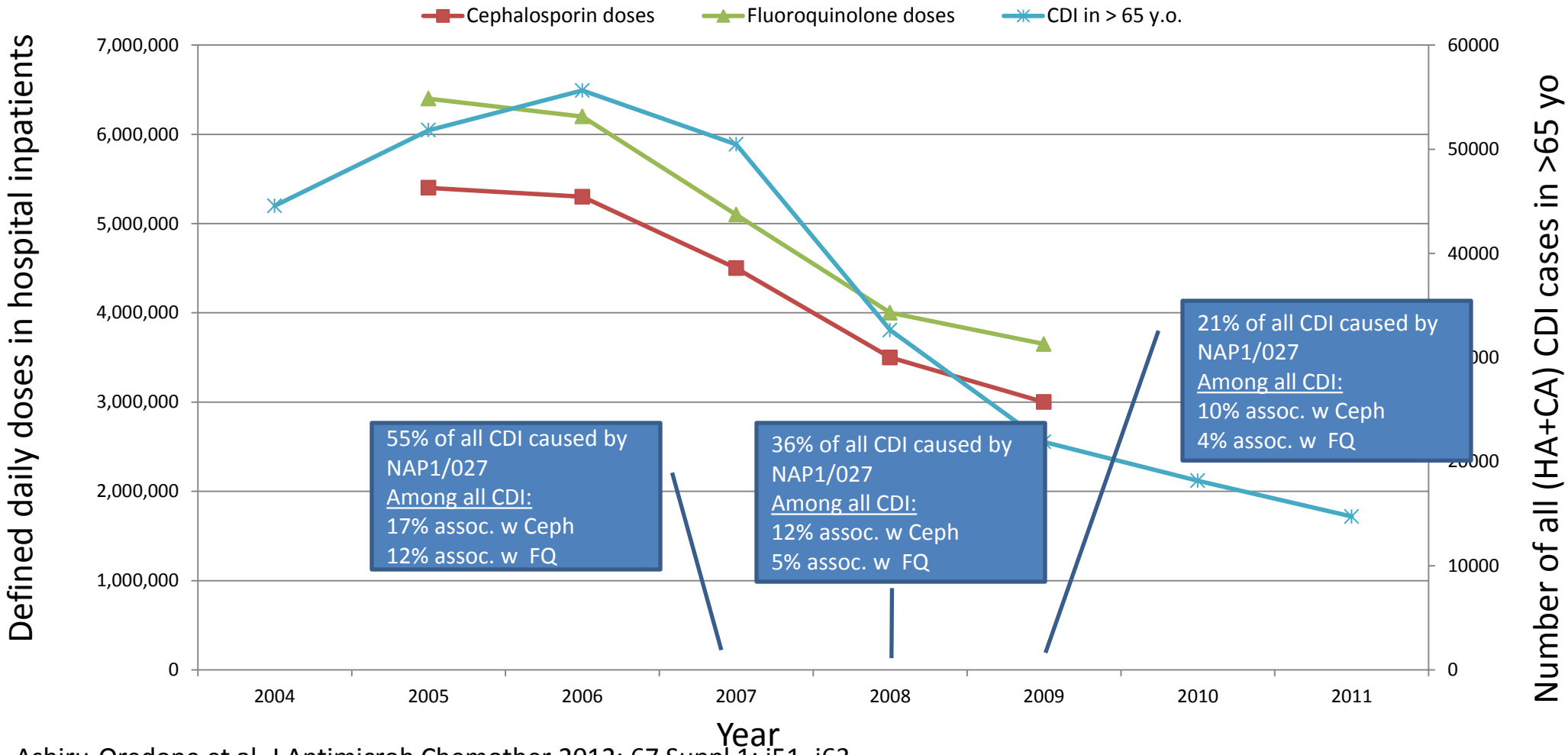
Can Antimicrobial Stewardship Limit Resistance?

Best Evidence

- Decreased CDI
- Decreased resistant GNB
- Decreased VRE
- Decreased LOS (particularly in the ICU)

Carling et al. ICHE 2003;24:699-706
Climo et al. Ann Intern Med 1998;128:989-95
Khan et al. J Hosp Infect 2004;54:104-8
Meyer et al. Ann Intern Med 1993;119:353-8
Pear et al. Ann Intern Med 1994;120:272-7
Bradley et al. J Antimicrob Chemother 1997;40:707-11
de Man et al. Lancet 2000;355:973-8
Singh et al. Am J Respir Crit Care Med 2000;162:505-11

Impact of Changes in Antibiotic Prescribing on CDI in England



Ashiru-Oredope et al. J Antimicrob Chemother 2012; 67 Suppl 1: i51–i63

Wilcox MH et al. Clinical Infectious Diseases 2012;55(8):1056–63

http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1179745282388

Conclusions: *C. difficile* as an ASP Endpoint

- **Data is compelling**
- **As much as 60% of healthcare-associated CDI may be attributable to antibiotic use**
- **Many published studies, using good methods, show an association between reduced antibiotic use and reduced *C. difficile* infections**
- **Results can be demonstrated within a year**
- **Targeting key antibiotics can be very effective**
  - Fluoroquinolones
  - Cephalosporins

Antibiotic Resistance: What Does the Data Show?

- **There are many published studies looking at the impact of reductions in antibiotic use on resistance**
- **Most of them do show favorable impacts**
  - Reduced use leads to reduced resistance
  - Could be publication bias
  - Commonly in an outbreak setting
- **Some common limitations**

Overall Impressions

- **The data supporting reducing antibiotic use as a way to impact resistance are not as weak as I thought**
- **Some studies are pretty compelling**
  - CRE
- **Few studies look at the impact of stewardship interventions on resistance among patients who were actually eligible to get the intervention**
  - Case-case-control studies

Antimicrobial Stewardship and CRE

TABLE 2. Multivariable Models of Risk Factors for Enterobacteriaceae Isolation, Detroit Medical Center, September 1, 2008, to August 31, 2009

	CRE vs uninfected[b]		ESBL vs uninfected[b]		Susceptible vs uninfected[b]		CRE vs ESBL		CRE vs susceptible		CRE vs all controls combined	
Variable[a]	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Any antibiotic exposure in previous 3 months	11.4 (2–64.3)	.006	1.7 (0.7–4.1)	.24			5.2 (1.4–19.4)	.015	12.3 (3.3–45)	<.001	7.1 (1.9–25.8)	.003
Permanent residency in institution	1.04 (0.2–4.5)	.96	1.3 (0.5–3.6)	.56	0.15 (0.05–0.5)	.002	2.1 (1–4.2)	.05	5.3 (2.1–12.9)	<.001	2.6 (1.3–5.3)	.01
Isolation of resistant bacteria in previous 6 months[c]	15.3 (4.2–55.6)	<.001	8.25 (2.7–25.7)	<.001	6.6 (1.9–23.3)	.003	1.7 (0.76–3.7)	.2	1.8 (0.7–4.7)	.23	2.9 (1.4–5.7)	.003
Dependent functional status in background	1.4 (0.5–4.4)	.55	5.6 (2.1–14.7)	.001	2.6 (1.1–6.4)	.03			2.0 (0.7–6.2)	.2	1.6 (0.6–4)	.33
ICU stay in previous 3 months	3.9 (1.3–12.4)	.02	5.2 (2.1–13.2)	.001	3.0 (1.2–7.2)	.02			1.6 (0.6–4)	.34	1.36 (0.7–2.7)	.37
Recent (6 months) invasive procedure	4.2 (1.2–15)	.03	1.2 (0.4–3.4)	.76	3.2 (1.3–8)	.01	2.8 (1.1–7.6)	.04			2.7 (1.1–7.1)	.04
Charlson weighted index comorbidity ≥3	3.1 (0.8–11.8)	.1	1.1 (0.4–2.7)	.87	2.2 (0.94–5)	.07	2.4 (1.03–5.6)	.04	4.8 (1.9–12.5)	.001	3.1 (1.4–7)	.006

NOTE. CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; ICU, intensive care unit; OR, odds ratio.

[a] If a variable was not significant in bivariate analysis, it was not forced into the multivariable model.

[b] Part of the case-case-control analysis.

[c] Includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ESBL-producing Enterobacteriaceae, *Acinetobacter baumanni*, and *Pseudomonas aeruginosa*.

Marchaim D. et. al. Infect Control Hosp Epidemiol 2012;33:817-30.

Antimicrobial Stewardship and CRE

Table 3. Six separated multivariable models of risk factors for *Enterobacteriaceae* isolation, including enforcement of cephalosporin exposure into models (Detroit Medical Center, MI, USA, September 2008–September 2009).

Variable	CRE versus uninfected		ESBL versus uninfected		Susceptible versus uninfected		CRE versus ESBL		CRE versus susceptible		CRE versus all controls combined	
	OR (95% CI)	*p-value*	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*
Cephalosporin exposure in previous 3 months	3.6 (1.4–8.8)	0.006	1.8 (1.1–3.2)	0.03	0.8 (0.5–1.4)	0.4	1.7 (0.8–3.9)	0.18	4.9 (2.1–11.4)	<0.001	4.7 (2.0–11.0)	<0.001
Permanent residency in institution	1.0 (0.5–1.8)	0.95	0.9 (0.6–1.5)	0.7	0.6 (0.3–1.1)	0.08	1.5 (0.8–2.6)	0.21	1.8 (1.0–3.3)	0.08	1.7 (0.9–3.1)	0.09
Isolation of resistant bacteria in previous 6 months[†]	1.9 (1.0–3.7)	0.06	1.6 (0.9–2.6)	0.09	1.6 (0.9–2.6)	0.1	1.4 (0.8–2.5)	0.3	1.4 (0.8–2.6)	0.27	2.0 (1.1–3.6)	0.03
Dependent functional status in background	1.1 (0.5–2.4)	0.8	2.0 (1.0–4.0)	0.04	1.5 (0.9–2.4)	0.2	0.6 (0.3–1.2)	0.17	0.7 (0.3–1.4)	0.3	0.6 (0.3–1.3)	0.2
ICU stay in recent 3 months	1.2 (0.7–2.0)	0.6	1.5 (0.9–2.5)	0.09	1.3 (0.8–2.1)	0.3	0.9 (0.5–1.6)	0.8	1.0 (0.6–1.7)	0.9	1.1 (0.6–1.8)	0.8
Recent (6 months) invasive procedure	1.9 (0.8–4.6)	0.14	1.0 (0.6–1.7)	0.9	2.0 (1.1–3.4)	0.02	1.9 (0.8–4.3)	0.14	1.1 (0.5–2.5)	0.8	1.9 (0.8–4.3)	0.15
Charlson's combined condition score ≥4	1.4 (0.6–3.1)	0.42	1.0 (0.6–1.7)	0.9	0.8 (0.5–1.3)	0.5	1.8 (0.8–4.2)	0.15	1.7 (0.8–3.8)	0.2	2.2 (1.0–4.9)	0.06

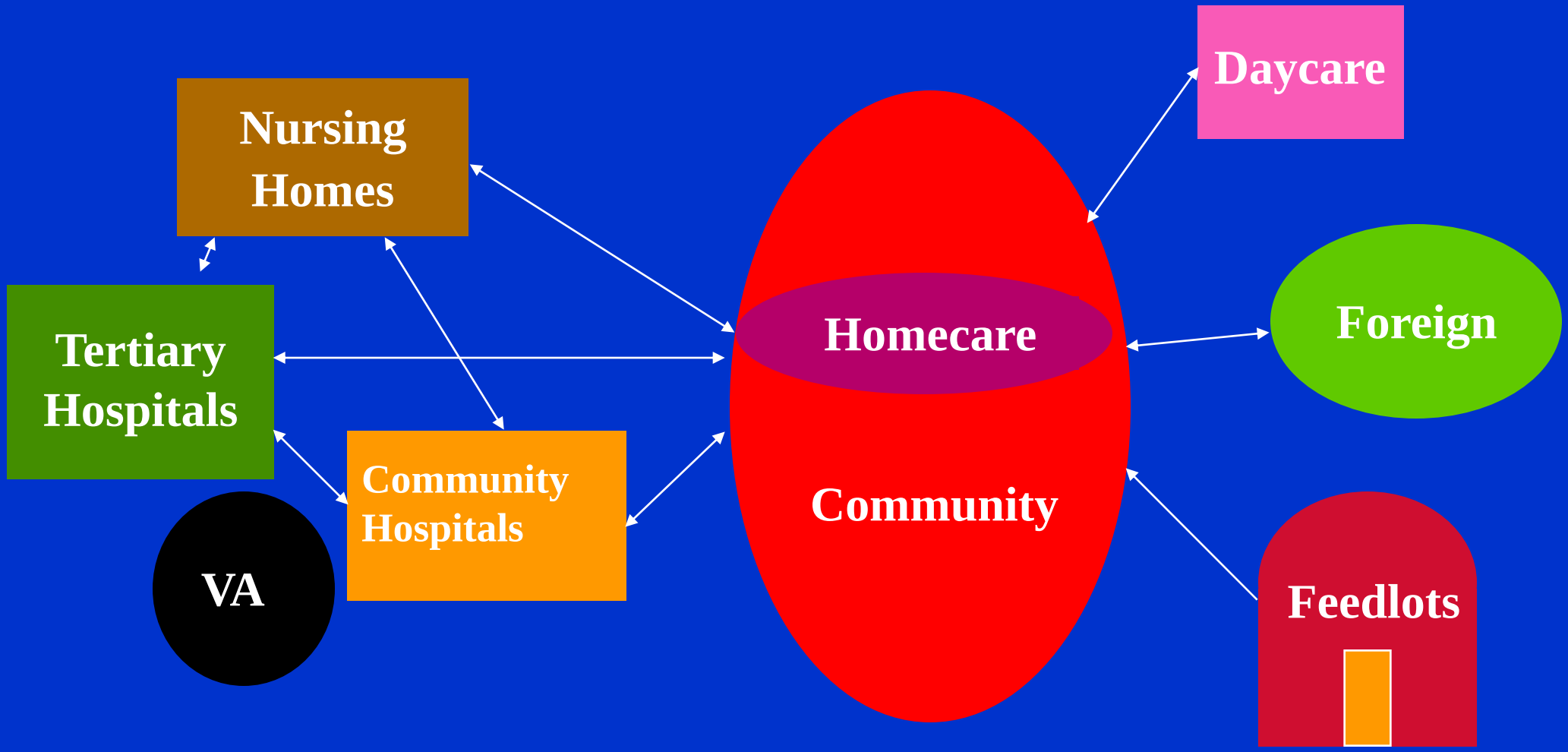
If a variable was not significant in bivariate analysis, it was not forced into the multivariable model.
[†]*Includes methicillin-resistant* Staphylococcus aureus, *vancomycin-resistant* Enterococcus, Acinetobacter baumannii, Pseudomonas aeruginosa *and ESBL-producing* Enterobacteriaceae.
CRE: Carbapenem-resistant Enterobacteriaceae; *ESBL: Extended-spectrum β-lactamase-producing* Enterobacteriaceae; *ICU: Intensive-care unit; OR: Odds ratio.*

Bogan C, Marchaim D. Future Microbiol 2013;8:979-91.

Conclusions

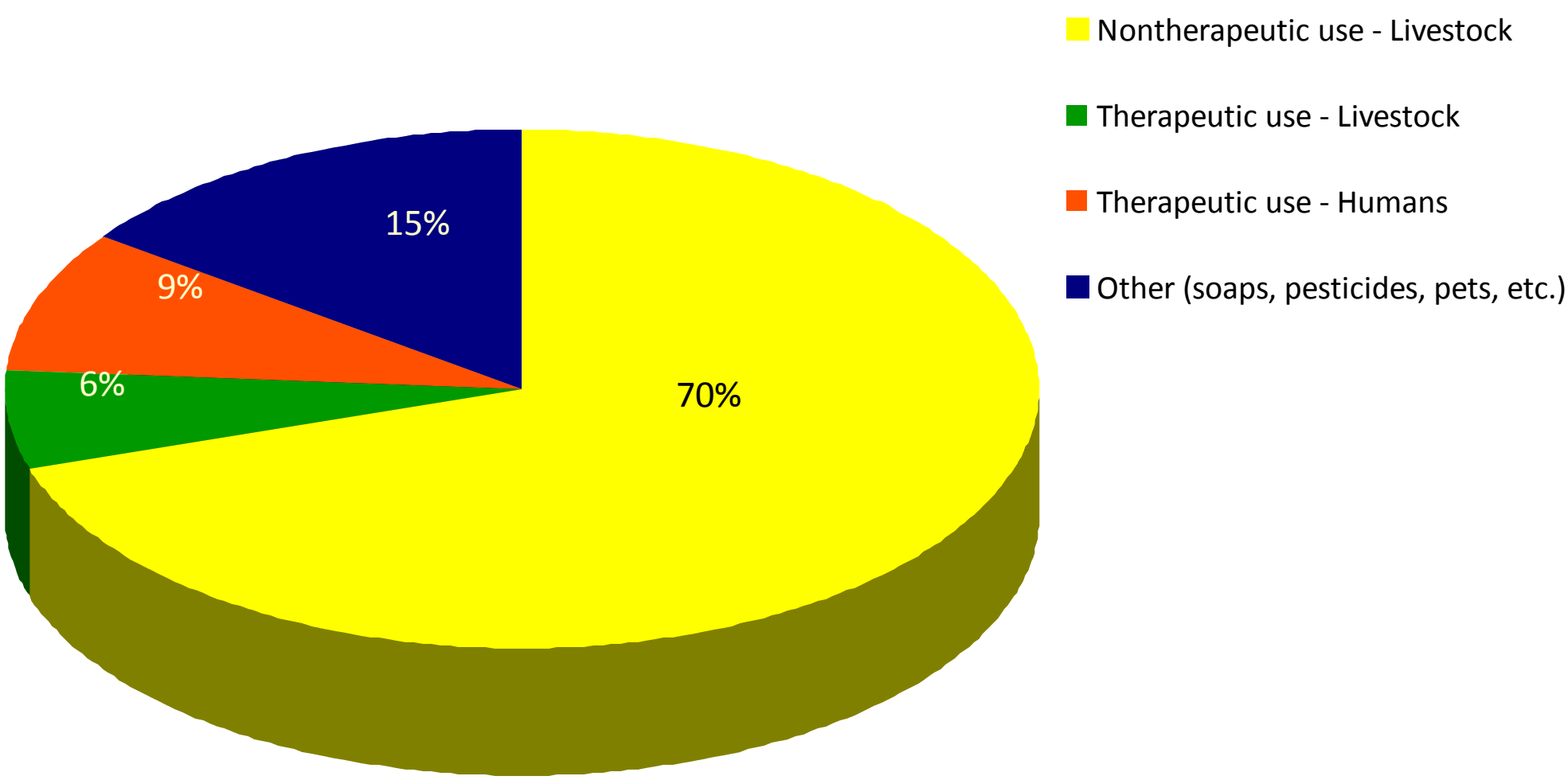
- **Antimicrobial stewardship interventions can arrest outbreaks of MDROs**
  - CDI
  - ESBL
  - VRE
- **Overall data demonstrating impact on antimicrobial resistance is improving**
  - Correct study design critical
  - Must study impact on patients eligible to receive intervention
- **Fewer data supporting effect of ASPs on endemic resistance**
  - Impact on antibiogram unlikely to be an effective outcome measure
- **Prior approval may be a more effective AS intervention with respect to preventing emergence of antimicrobial resistance**

Environments Where Antibiotic Resistance Develops and Their Relationships



Adapted from B. Murray

Antibiotic Use in the United States



Union of Concerned Scientists, January 2001