Containing Healthcare-Associated Infections through Antibiotic Stewardship

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Alliance for the Prudent Use of Antibiotics

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SHADOW EPIDEMIC

The Growing Menace of Antimicrobial Resistance

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Problems of Multidrug-Resistant Bacteria

Hospital

Gram-negative

- *Acinetobacter sp.*
- *Citrobacter sp.*
- *Enterobacter sp.*
- *Klebsiella sp.*
- *Pseudomonas aeruginosa*

Gram-positive

- *Clostridium difficile*
- *Enterococcus sp.*: VRE
- Coagulase-negative *Staphylococcus*
- *Staphylococcus aureus*: MRSA/ VRSA

Community

Gram-negative

- *Escherichia coli*
- *Neisseria gonorrhoeae*
- *Salmonella typhi*
- *Salmonella typhimurium*

Gram-positive

- *Enterococcus sp.*: VRE
- *Mycobacterium tuberculosis*
- *Staphylococcus aureus*: MRSA
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

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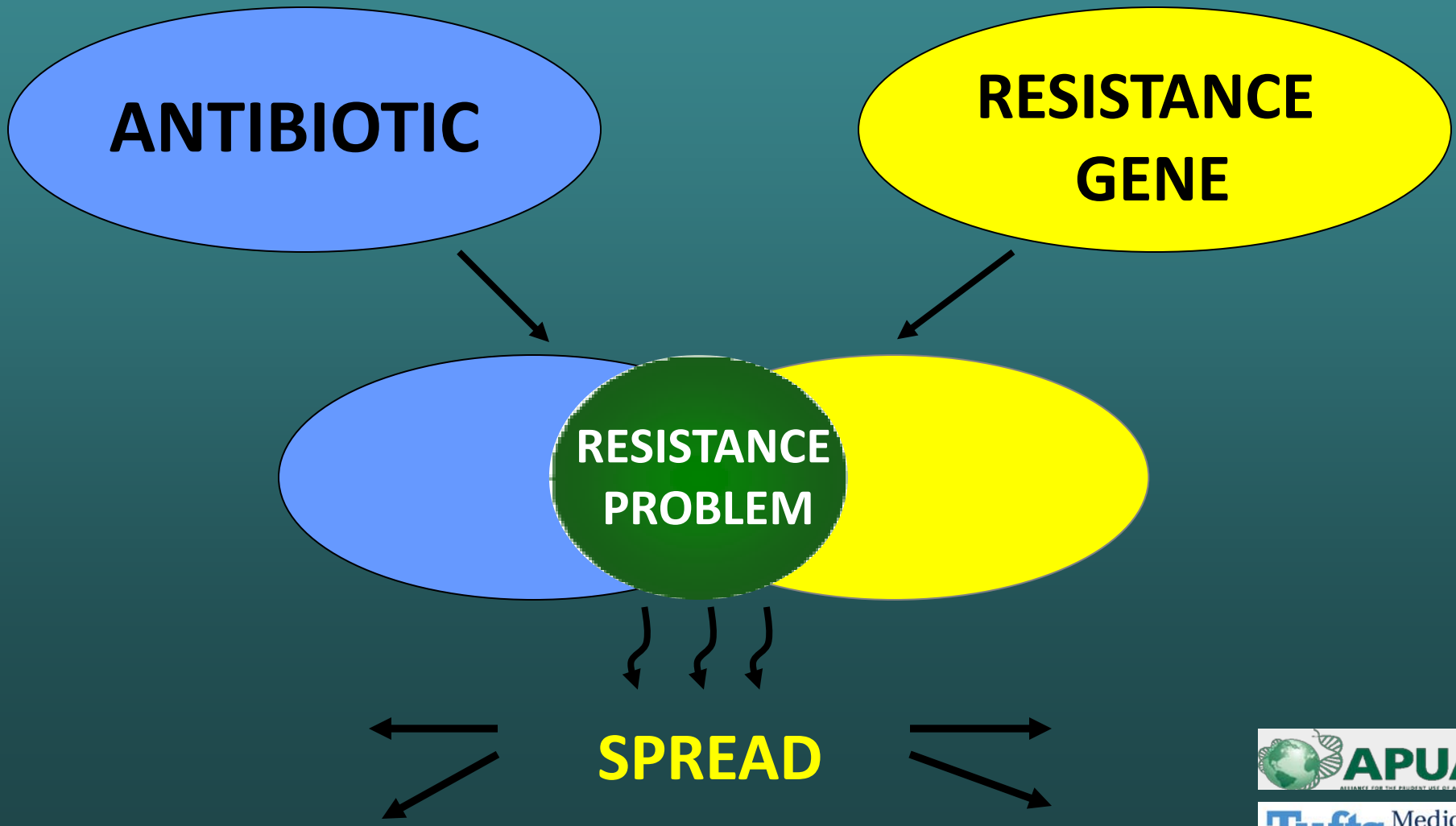
Drug Resistance Equation



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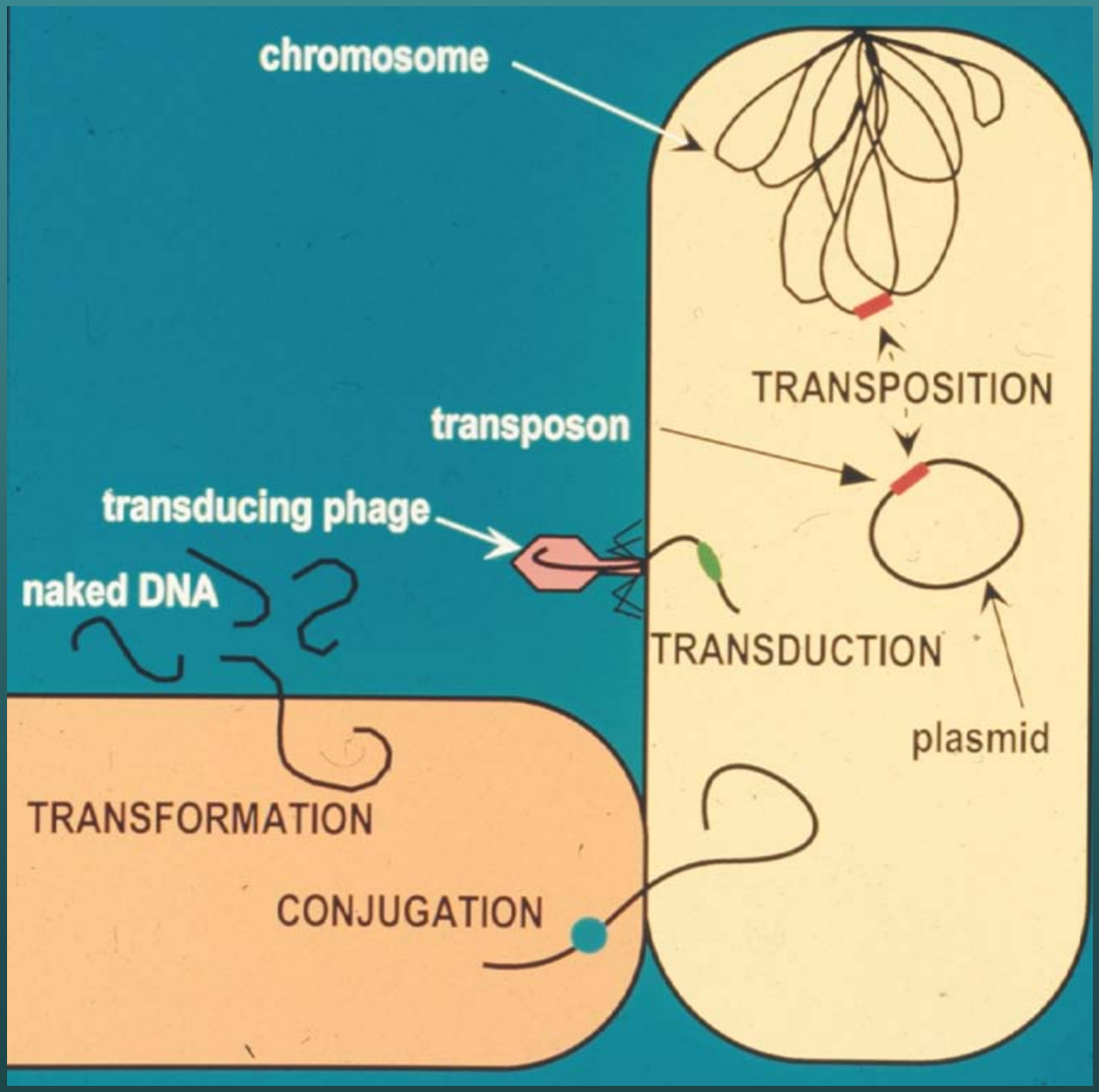
DNA Transfer Mechanisms



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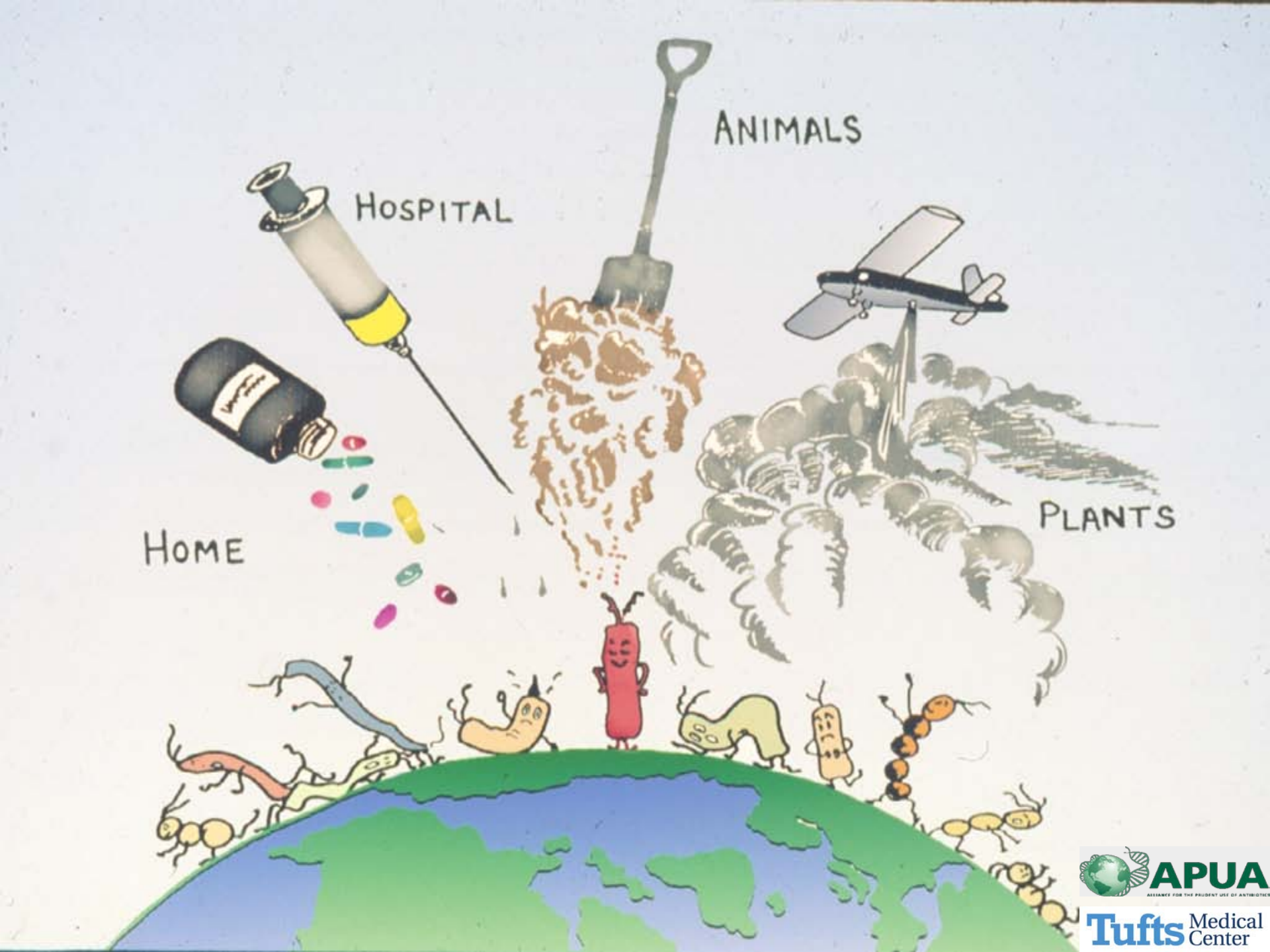
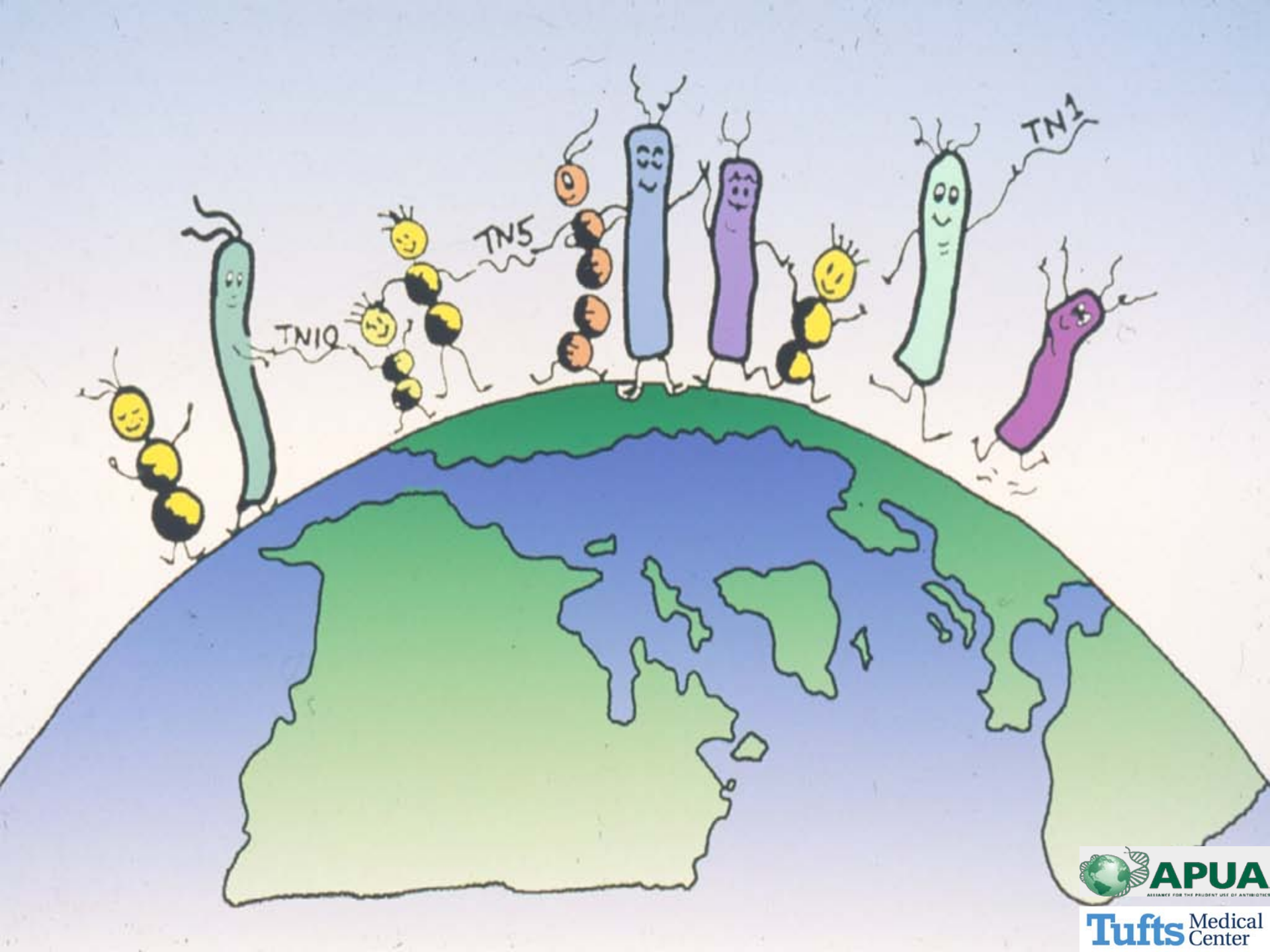

ANIMALS
HOSPITAL
HOME
PLANTS



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Antibiotics are Societal Drugs

Individual Usage Affects Family, Community, Society

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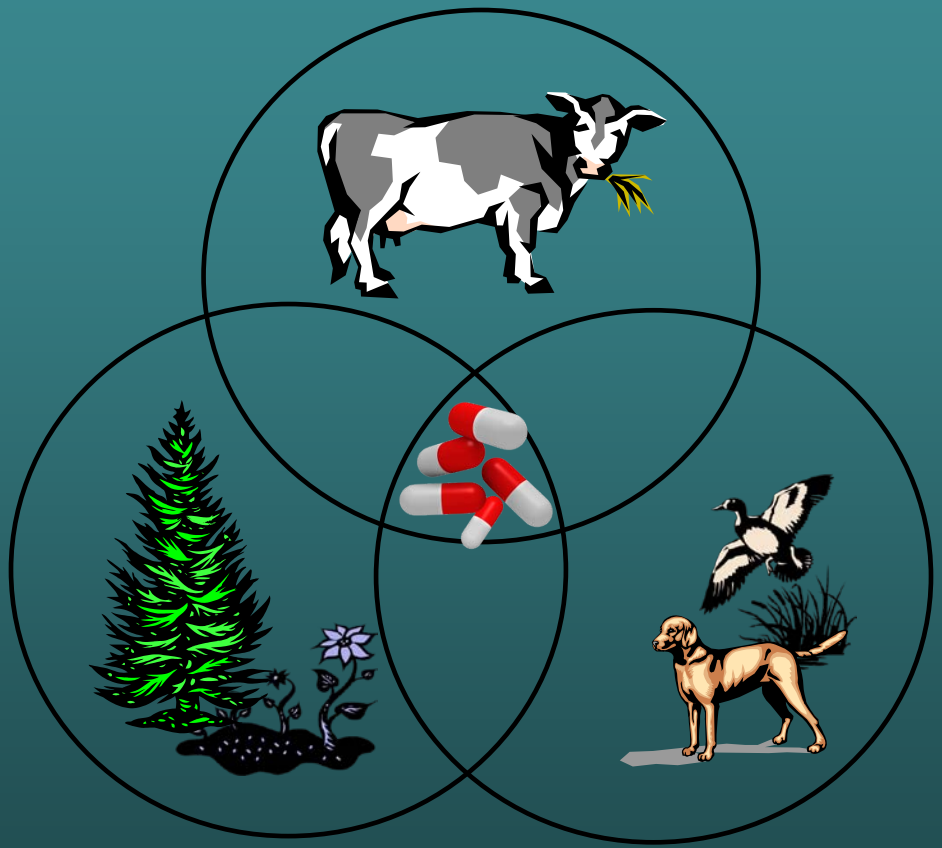
Antibiotics are also ecologic drugs



A drug-resistant flora emerges and spreads under antibiotic selection

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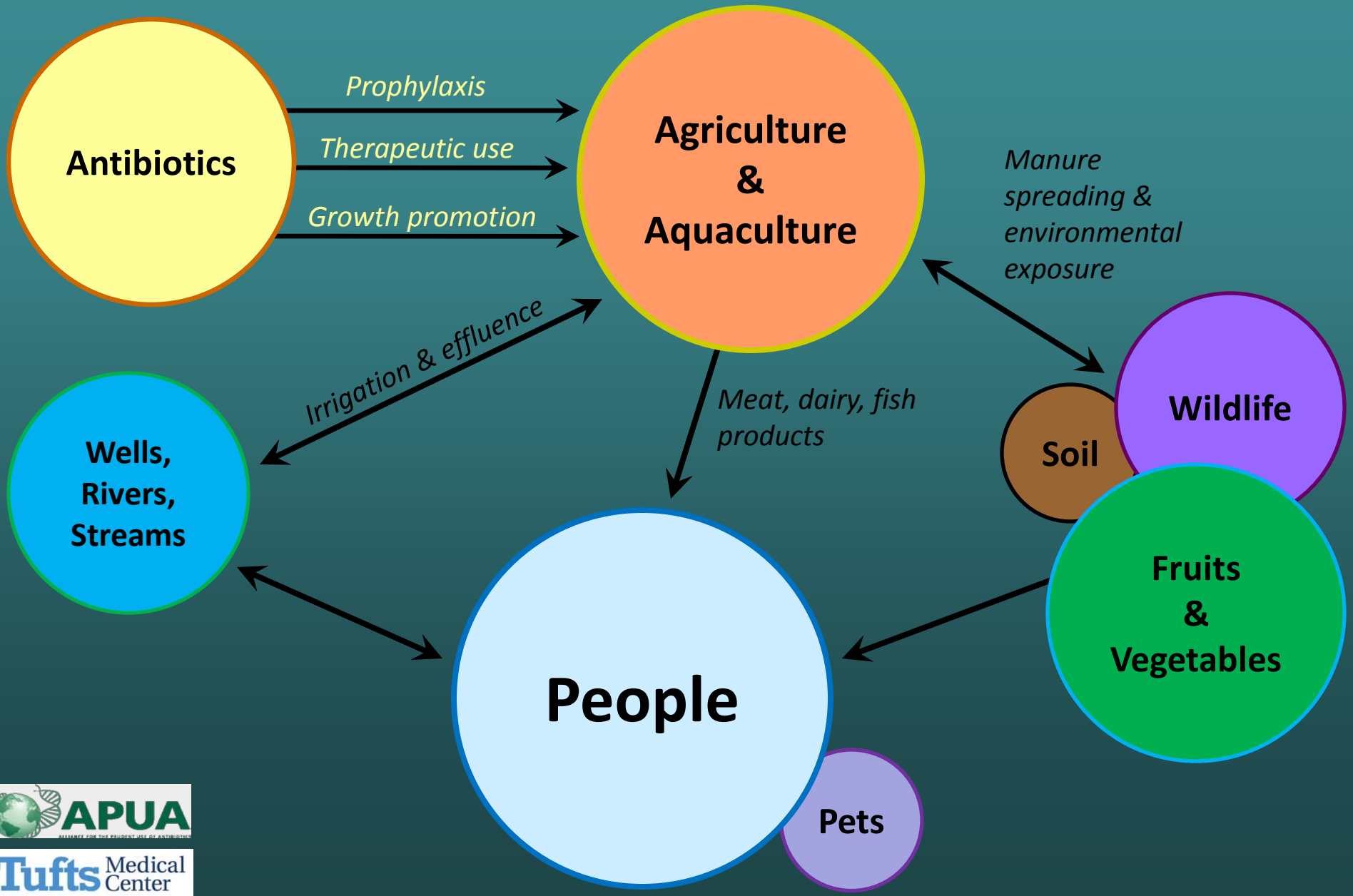
Ecologic impact of antibiotics in agriculture:

The flow of antibiotics and antibiotic-resistant bacteria



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Antibiotic use in humans: The Prime Driver of Hospital Resistance

Antimicrobial Drugs Approved for Use in Food-Producing Animals: 2009 Sales and Distribution Data Reported by Drug Class

drug class	Kilograms	pounds	% of total
FOOD-ANIMAL USE			
aminoglycosides	339,678	748,862	2%
cephalosporins	41,328	91,113	0%
ionophores	3,740,627	8,246,671	23%
lincosamides	115,837	255,377	1%
macrolides	861,985	1,900,352	5%
penicillins	610,514	1,345,953	4%
sulfas	517,873	1,141,715	3%
tetracyline	4,611,892	10,167,481	28%
NIR	2,227,366	4,910,501	14%
sub-total	13,067,100	28,808,024	**79.8%**
HUMAN MED USE	3,300,000	7,275,255	**20.2%**
TOTAL	16,367,100	36,083,279	100%

Source: FDA

http://www.livablefutureblog.com/2010/12/new-fda-numbers-reveal-food-animals-consume-lion%E2%80%99s-share-of-antibiotics/fda-graph

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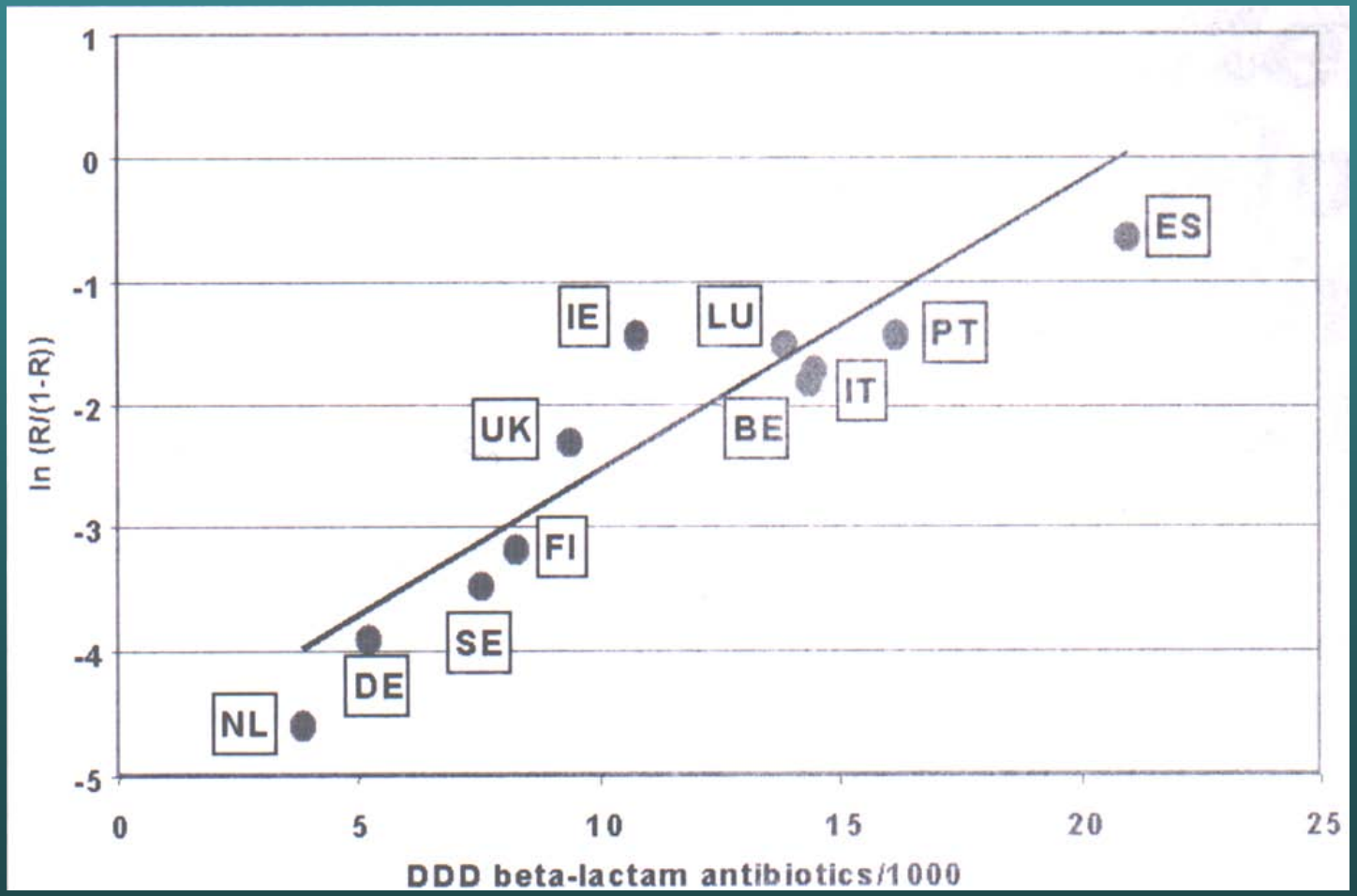
Relationship of ß-Lactam Use to Penicillin Resistance

(11 European Countries)



Source: Bronzwaer S.L.A.M., *et al* Emer. Inf. Dis. 8:278, 2002

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Antibiotic exposure increases the risks of resistance

Pathogen and Antibiotic Exposure	Increased Risk
Carbapenem-resistant *Enterobacteriaceae* and carbapenems	15 fold
ESBL-producing organisms and cephalosporins	6 - 29 fold

- Patel G et al. *Infect Control Hosp Epidemiol* 2008;29:1099-1106
- Zaoutis TE et al. *Pediatrics* 2005;114:942-9
- Talon D et al. *Clin Microbiol Infect* 2000;6:376-84

CDC

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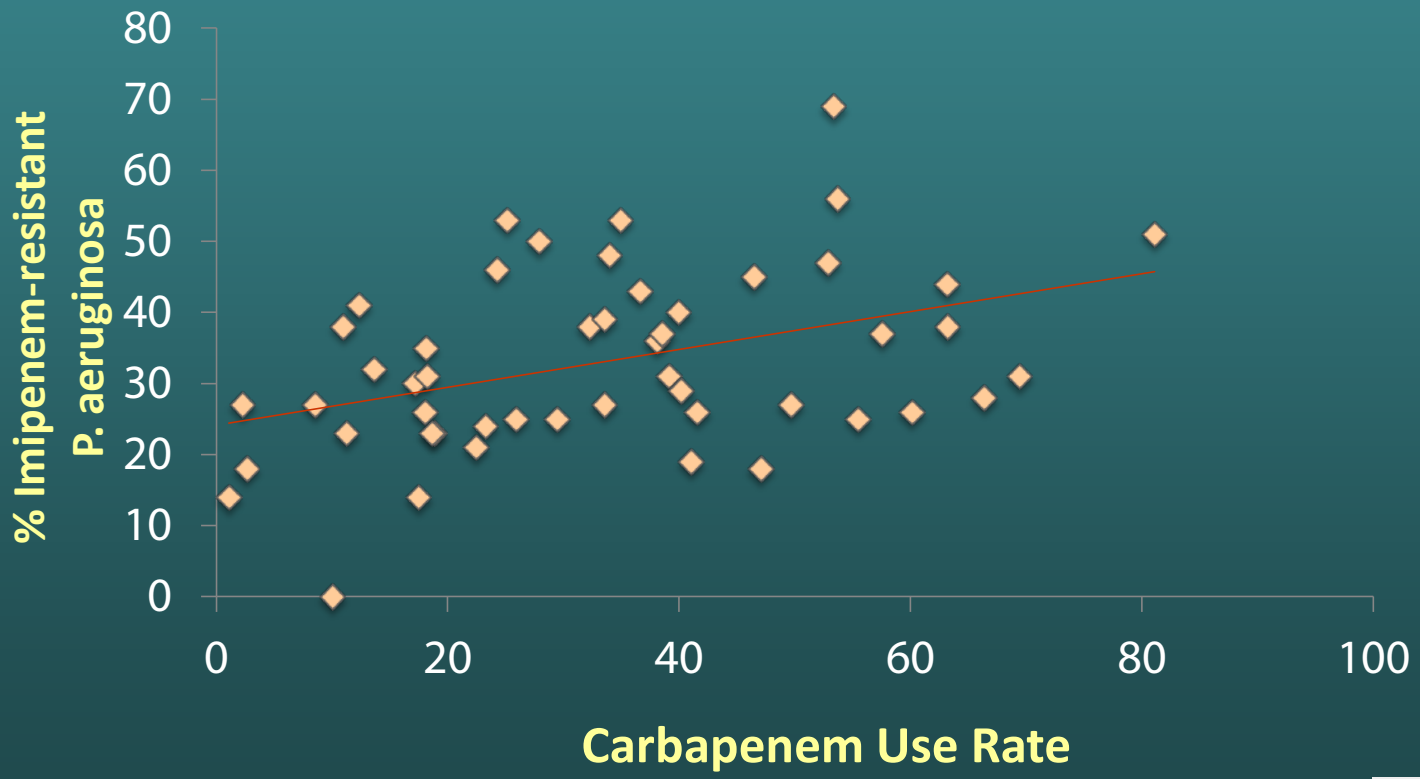
Annual prevalence of imipenem resistance in *P. aeruginosa* vs. carbapenem use rate



45 LTACHs, 2002-03 (59 LTACH years)

Gould et al. ICHE 2006;27:923-5

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Individual drug resistances are becoming increasingly associated with other drug resistances

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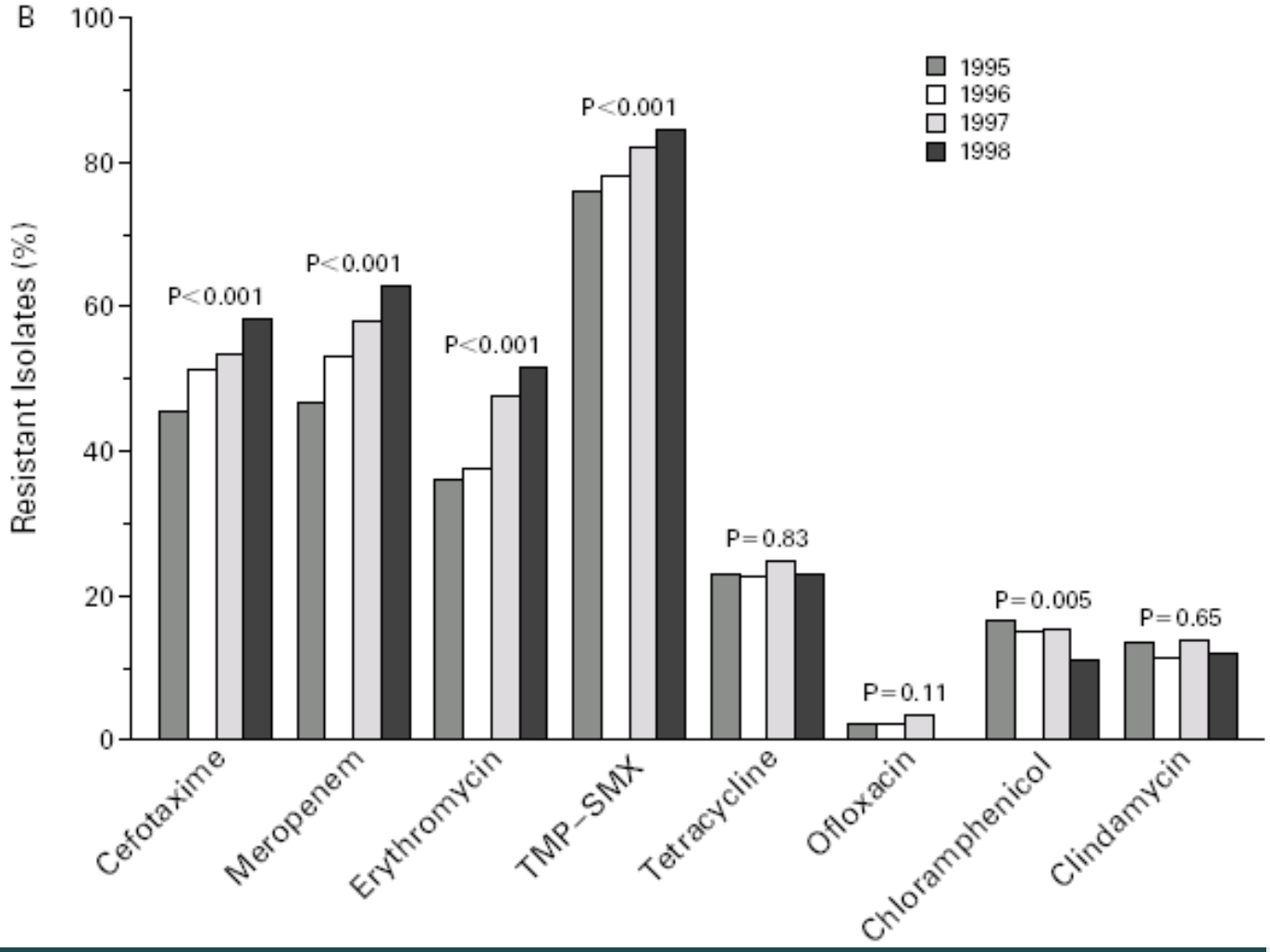
Penicillin Resistant *S. pneumoniae*
U.S.A. (co-resistances)



Whitney *et al* NEJM 343:1917 (2000)

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“Poster children” for antibiotic resistance

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Gram-Positive

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MRSA

- Most invasive organism that we face today; attacks healthy children and adults.

- Community -acquired and hospital -acquired

About 19,000 deaths from MRSA (U.S. 2005)

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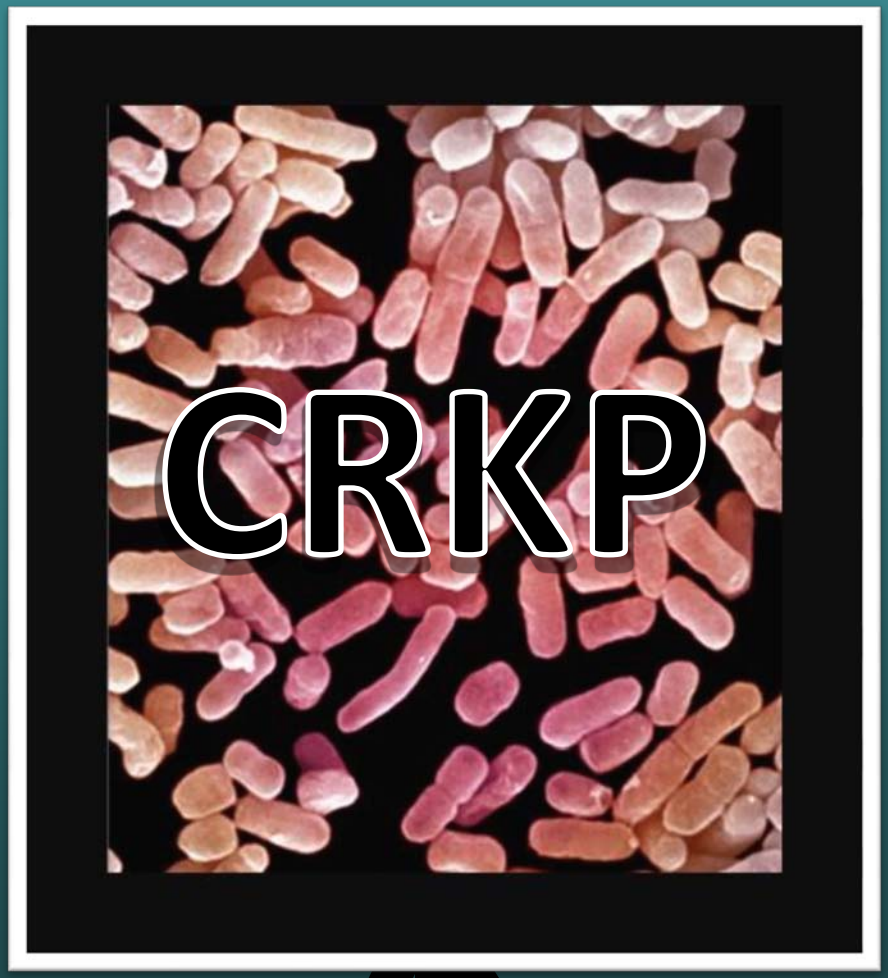
Gram-Negative



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Klebsiella pneumoniae

- **Carbapenem-resistant: KpC, CRKP**
- **NDM-1 carbapenemase**

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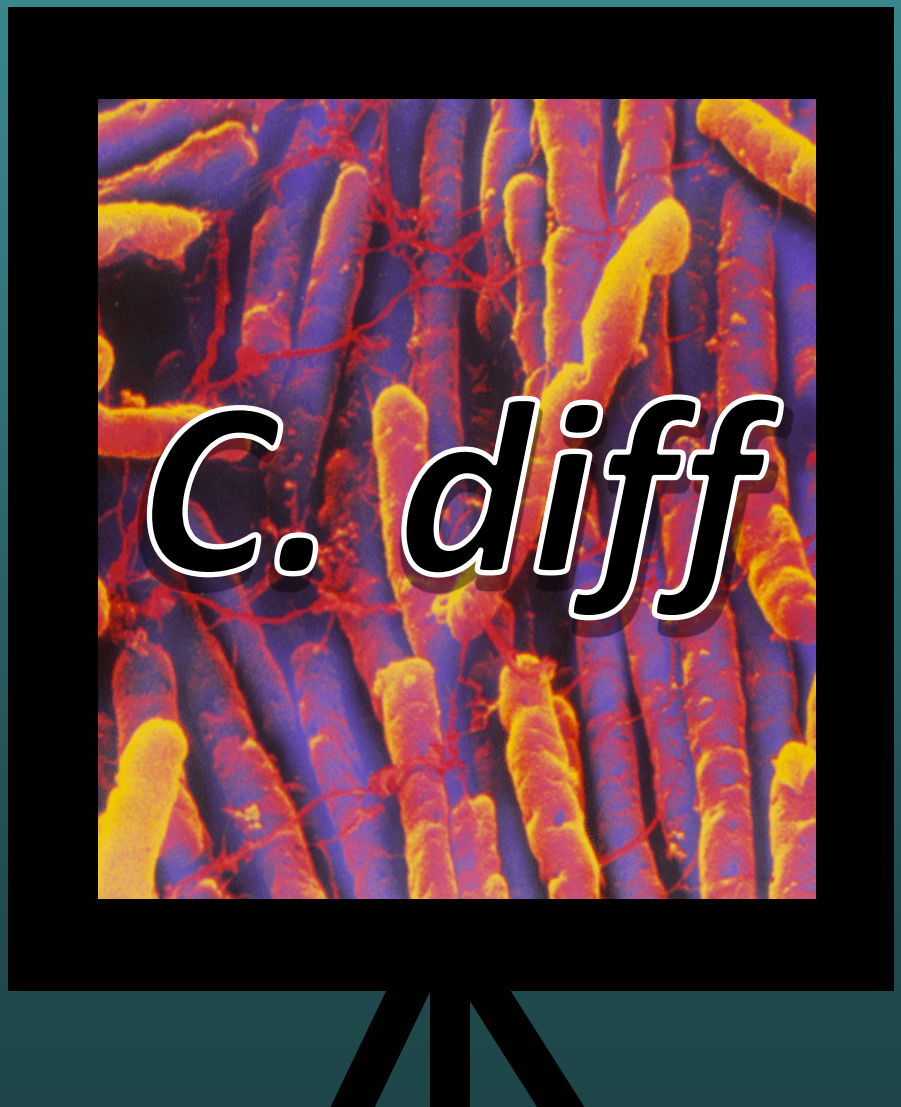
Gram-Positive Anaerobe



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Clostridium difficile

- Chiefly caused by antibiotic use
- Hospital discharges with *C. diff* disease doubled between 2000-2005
- Primary infection costs = $2871 - $4846/case
- Rapid detection is critical to optimal management

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The NEW ENGLAND JOURNAL of MEDICINE

Perspective

The Emerging Threat of Untreatable Gonococcal Infection

Gail A. Bolan, M.D., P. Frederick Sparling, M.D., and Judith N. Wasserheit, M.D., M.P.H.

N Engl J Med 2012; 366:485-487 | February 9, 2012 | DOI: 10.1056/NEJMp1112456

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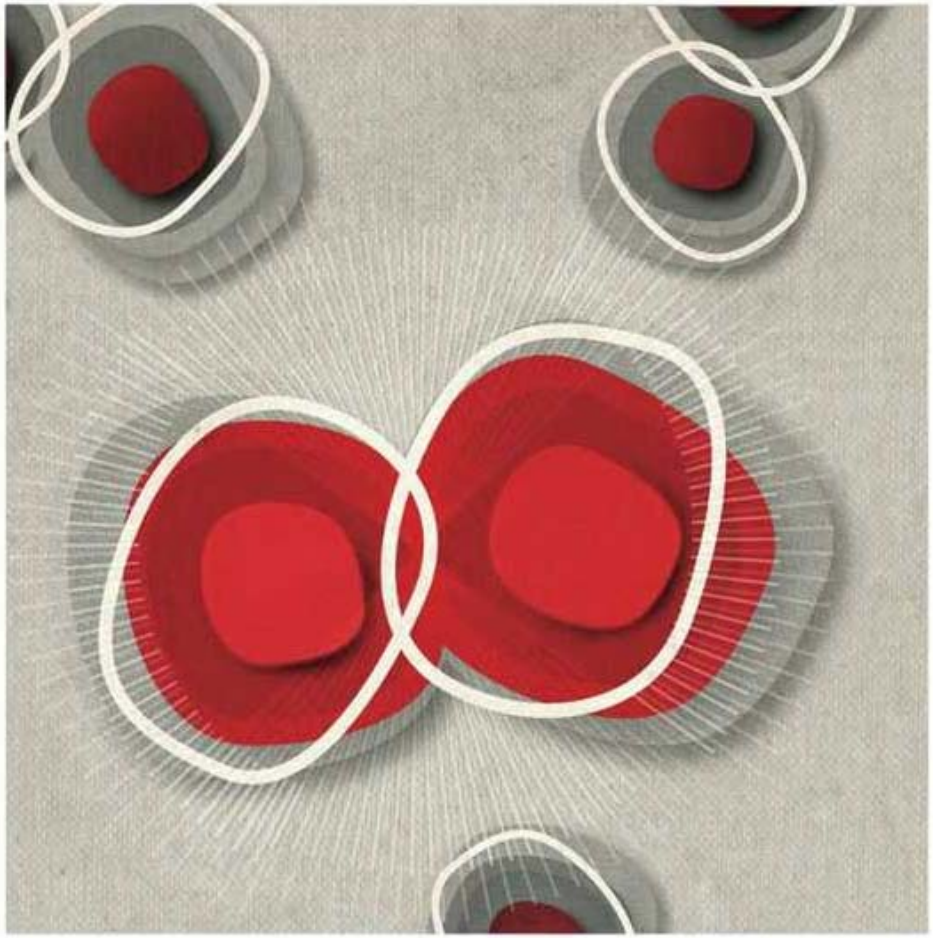
MEDICAL DISPATCHES

SEX AND THE SUPERBUG

The rise of drug-resistant gonorrhea.

BY JEROME GROOPMAN



Gonorrhea mutates in the pharynx, making oral sex far more risky than people think.

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The Cost of Antibiotic Resistance

Annual Cost of Antibiotic Resistance in U.S. Hospitals:

> 20 Billion Dollars

Roberts *et al.* CID 49:1175 (2009)

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Solutions require ecologic, multifaceted approaches

- New drug classes
- Education
- Surveillance and monitoring
- Policy modifications for agriculture
- Antibiotic stewardship interventions for healthcare

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Antimicrobial Resistance: An urgent need for Stewardship

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Controlling the spread of antimicrobial resistance in healthcare settings

Prevent disease

Infection Control

Antimicrobial Stewardship Programs (ASP)

Optimize Antibiotic Use

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Antimicrobial Stewardship Objectives

- Increase quality of patient care
- Reduce antimicrobial / hospital costs
- Improve hospital resistance rates

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Antimicrobial Stewardship Program Tools

Interventions customized to the needs and capabilities of the institution

- Education

  Rapid Diagnostics

- Antimicrobial restriction (front-end approach)

- Antimicrobial review and refinement (back-end approach)

- David L. Paterson

Clin Infect Dis. (2006) 42 (Supplement 2): S90-S95. doi: 10.1086/499407

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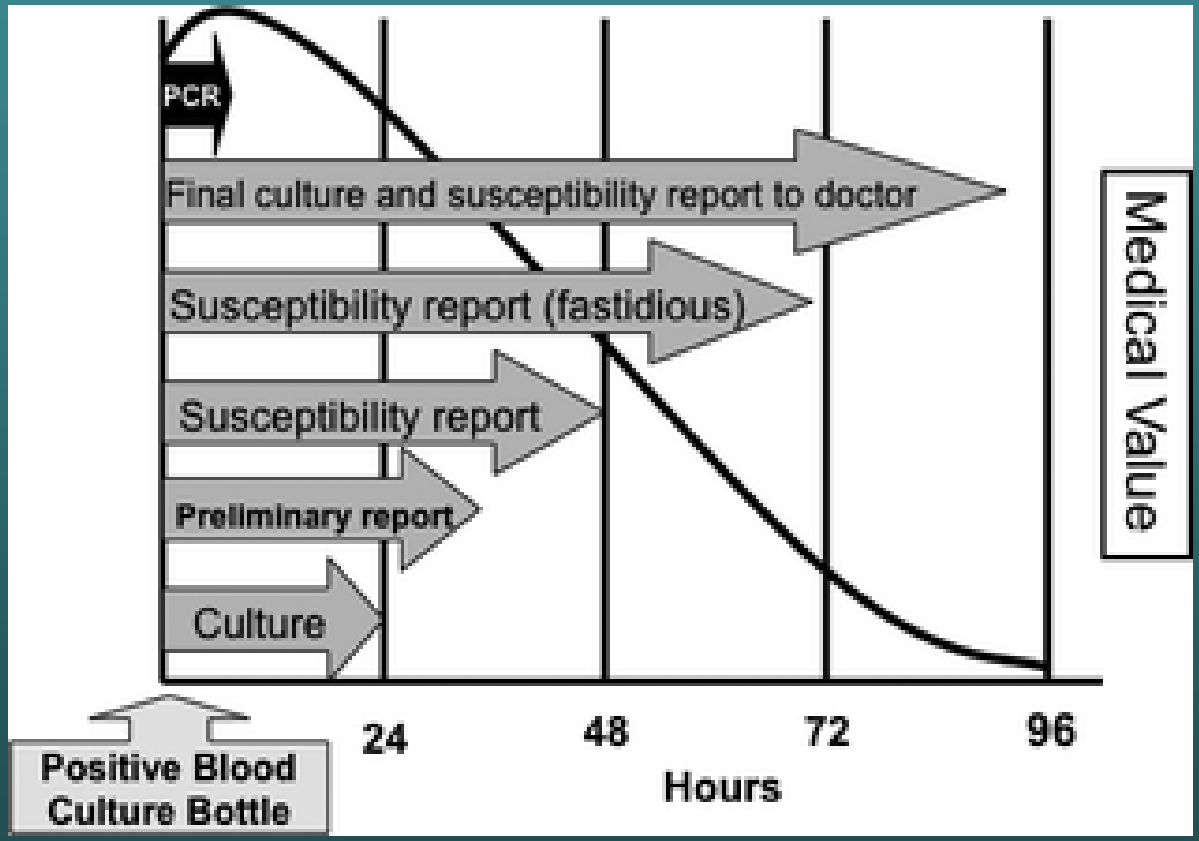
Using Rapid Diagnostic Tests to Optimize Antimicrobial Selection in Antimicrobial Stewardship Programs



Source: Goff, DA et al. Pharmacotherapy 2012. 32: 677-687

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Lessons Learned

- Given enough antibiotic and time, resistance will appear.
- Once selected, a drug resistance will not disappear, although it may drop in frequency.
- Resistance develops in steps: from *less susceptibility* to *resistance*.
- Resistant bacteria like to accumulate resistances.

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“Preserving the Power of Antibiotics”

http://www.apua.org

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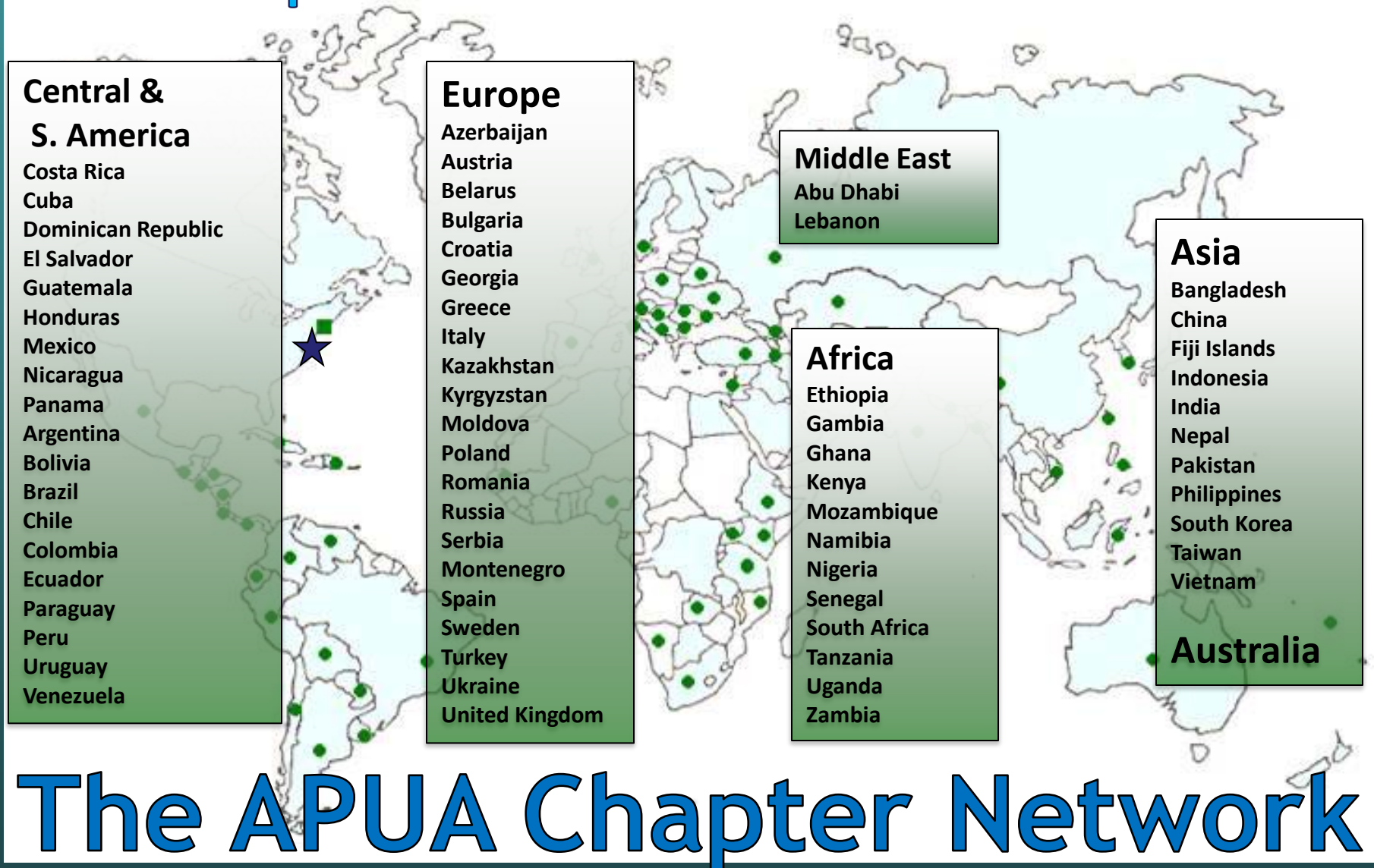
Global response to antibiotic access and resistance



The APUA Chapter Network


Think Globally

Act Locally

Get SMART: Optimizing Antibiotic Use in the Hospital

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Antimicrobial Steward
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Clinical Pharmacy Specialist
Department of Pharmacy

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Get Smart: Know When Antibiotics Work

Get Smart 2010 (focused on inpatient setting)

- Improve patient safety through better treatment of infections
- Reduce the emergence of antimicrobial resistant pathogens
- Encourage better use of antimicrobials in healthcare settings

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Bad Bugs No Drugs

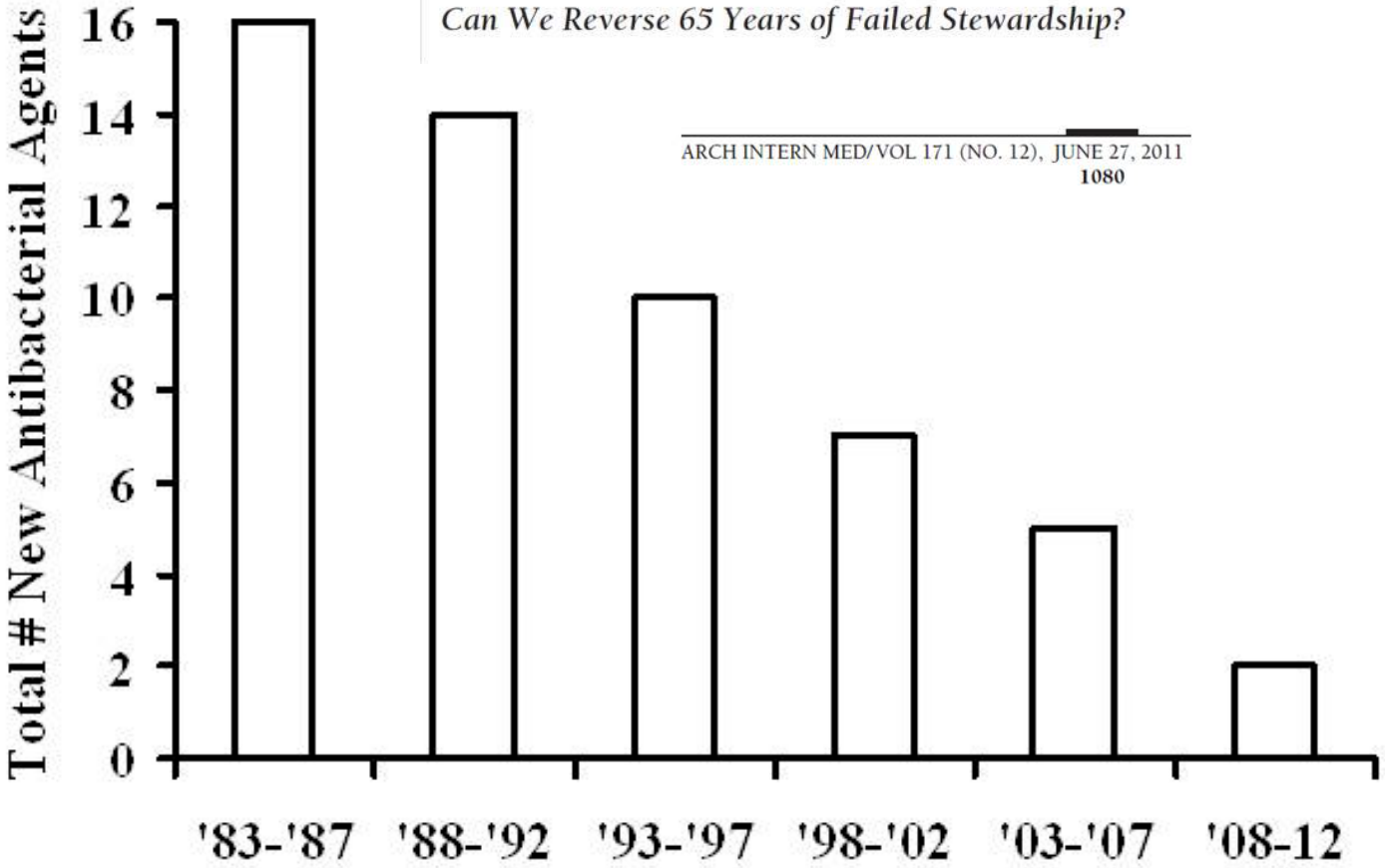
INVITED COMMENTARY

ONLINE FIRST

The Antibiotic Crisis

Can We Reverse 65 Years of Failed Stewardship?

ARCH INTERN MED/VOL 171 (NO. 12), JUNE 27, 2011
1080



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Get SMART in the hospital

- **S**tarting off – choosing the appropriate empiric regimen
- **M**aintenance of therapy: Targeting, de-escalating, and discontinuing therapy
- **A**re you treating infection or colonization?
- **R**oute: IV or PO
- **T**ime: Stop antibiotics as early as possible

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GET SMART – Mr. S

- Mr. S was admitted 4 days ago with an ST-elevation myocardial infarction and acute heart failure. He's been in the ICU on a ventilator.

- Today, he has increasing respiratory secretions, an increased oxygen requirement, fever, and an elevated white blood cell count.

- Chest x-ray shows development of a new infiltrate.

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What is the most appropriate initial antibiotic regimen for Mr. S with ventilator-associated pneumonia?

A. combination of vancomycin, piperacillin/tazobactam and ciprofloxacin
B. Ceftriaxone
C. Moxifloxacin
D. B or C

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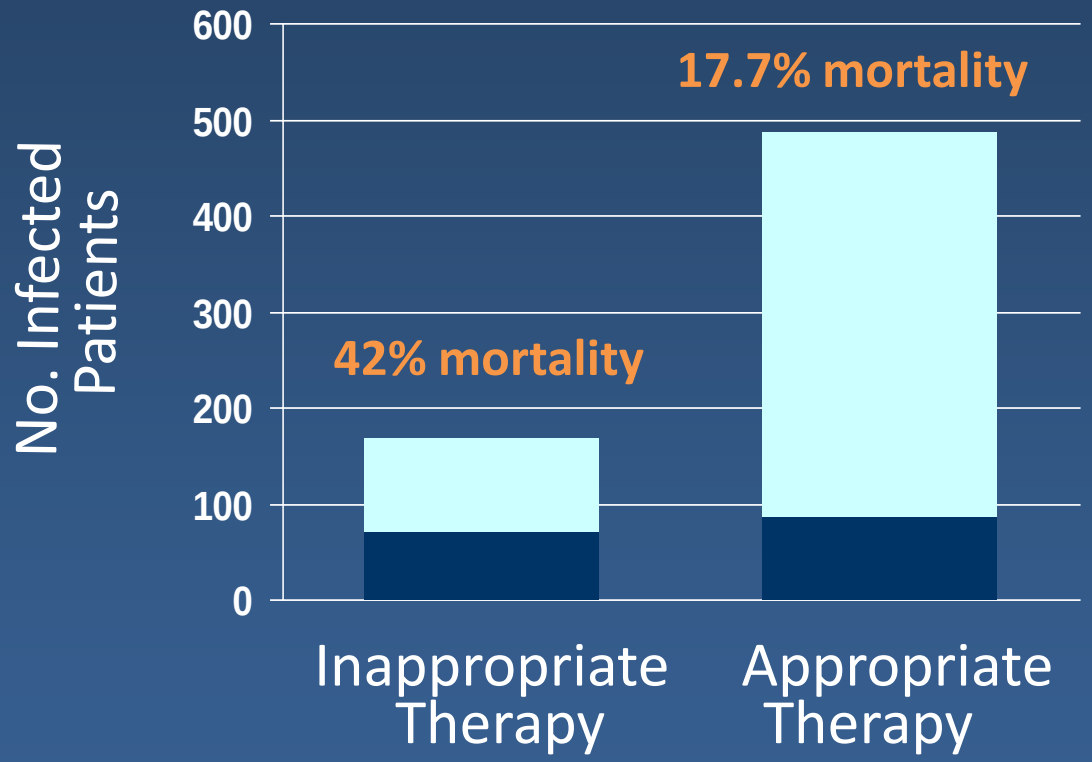
Inappropriate Antimicrobial Therapy: Impact on Mortality



Relative Risk = 2.37
(95% C.I. 1.83-3.08; p < .001)

Source: Kollef M,et al: Chest 1999;115:462-74

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Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

This official statement of the American Thoracic Society and the Infectious Diseases Society of America was approved by the ATS Board of Directors, December 2004 and the IDSA Guideline Committee, October 2004

CONTENTS

EXECUTIVE SUMMARY

Since the initial 1996 American Thoracic Society (ATS) guideline on nosocomial pneumonia, a number of new developments have appeared, mandating a new evidence-based guideline for hospital-acquired pneumonia (HAP), including healthcare-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP). This document, prepared by a joint committee of the ATS and Infectious Diseases Society of America (IDSA), focuses on the epidemiology and pathogenesis of bacterial pneumonia in adults, and emphasizes modifiable risk factors for infection. In addition, the microbiology of HAP is reviewed, with an emphasis on multidrug-resistant (MDR) bacterial pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus*. Controversies about diagnosis are discussed, emphasizing initial examination of lower respiratory tract samples for bacteria, and the rationale for both clinical and bacteriologic approaches, using either "semiquantitative" or "quantitative" microbiologic methods that help direct selection of appropriate antibiotic therapy. We also provide recommendations for additional diagnostic and therapeutic evaluations in patients with nonresolving pneumonia. This is an evidence-based document that emphasizes the issues of VAP, because there are far fewer data available about HAP in nonintubated patients and about HCAP. By extrapolation, patients who are not intubated and mechanically ventilated should be managed like patients with VAP, using the same approach to identify risk factors for infection with specific pathogens.

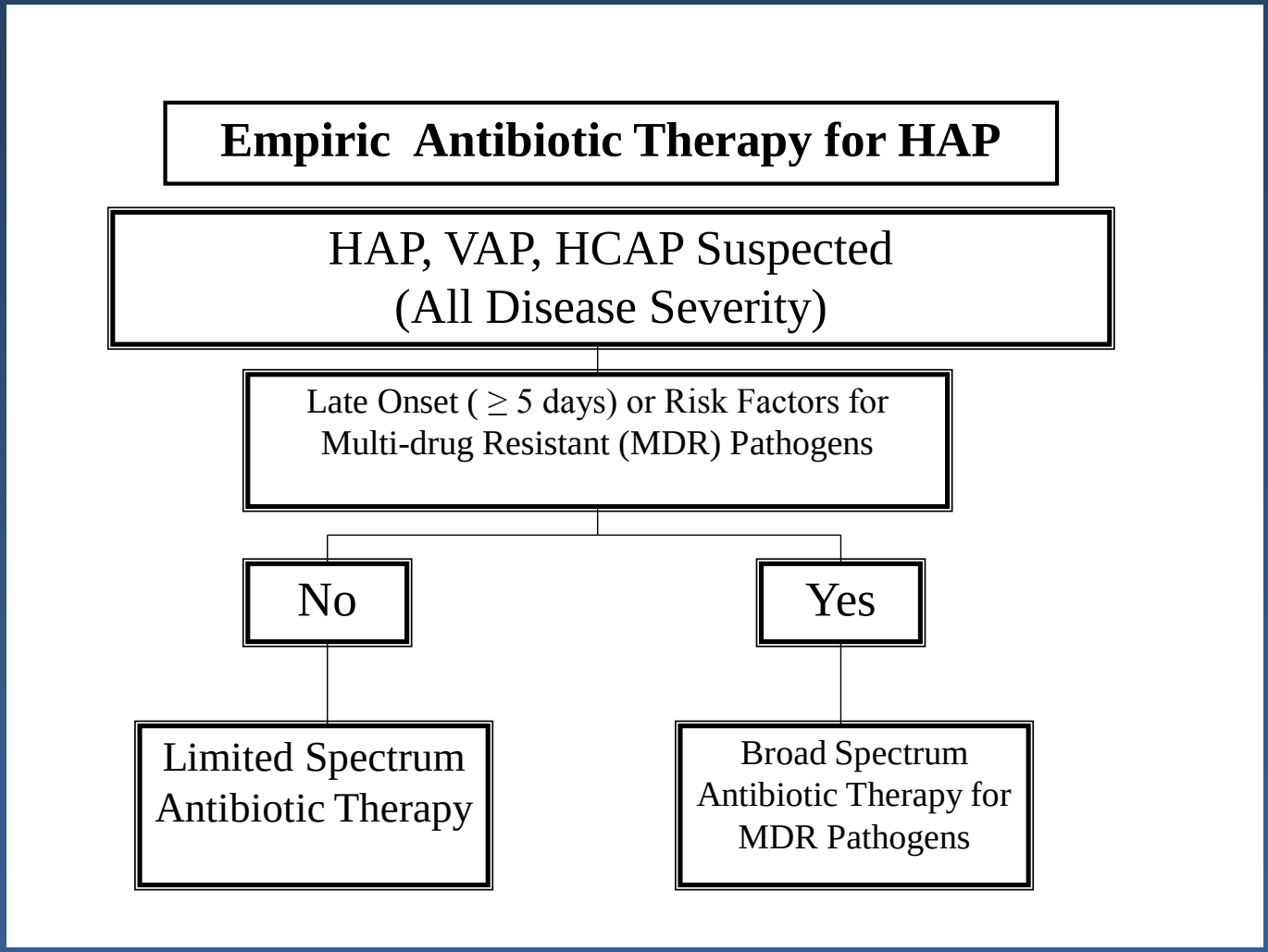
The major goals of this evidence-based guideline for the management of HAP, VAP, and HCAP emphasize early, appropriate antibiotics in adequate doses, while avoiding excessive antibiotics by de-escalation of initial antibiotic therapy, based on microbiologic cultures and the clinical response of the patient, and shortening the duration of therapy to the minimum effective period. The guideline recognizes the variability of bacteriology from one hospital to another and from one time period to another and recommends taking local microbiologic data into account when adapting treatment recommendations to any specific clinical setting. The initial, empiric antibiotic therapy algorithm includes two groups of patients: one with no need for broad-spectrum therapy, because these patients have early-onset HAP, VAP, or HCAP and no risk factors for MDR pathogens, and a second group that requires broad-spectrum therapy, because of late-onset pneumonia or other risk factors for infection with MDR pathogens.

Some of the key recommendations and principles in this new, evidence-based guideline are as follows:

- HCAP is included in the spectrum of HAP and VAP, and patients with HCAP need therapy for MDR pathogens.
- A lower respiratory tract culture needs to be collected from all patients before antibiotic therapy, but collection of cultures should not delay the initiation of therapy in critically ill patients.
- Either "semiquantitative" or "quantitative" culture data can be used for the management of patients with HAP.
- Lower respiratory tract cultures can be obtained broncho-

Am J Respir Crit Care Med Vol 171. pp 388–416, 2005
DOI: 10.1164/rccm.200405-644ST
Internet address: www.atsjournals.org

Treatment algorithm



Bonten MJ, Chastre J, Craig WA, et al: Am J Respir Crit Care Med 2005; 171: 388-416.

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TABLE 2. RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS CAUSING HOSPITAL-ACQUIRED PNEUMONIA, HEALTHCARE-ASSOCIATED PNEUMONIA, AND VENTILATOR-ASSOCIATED PNEUMONIA

- Antimicrobial therapy in preceding 90 d
- Current hospitalization of 5 d or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

Bonten MJ, Chastre J, Craig WA, et al: Am J Respir Crit Care Med 2005; 171: 388-416.

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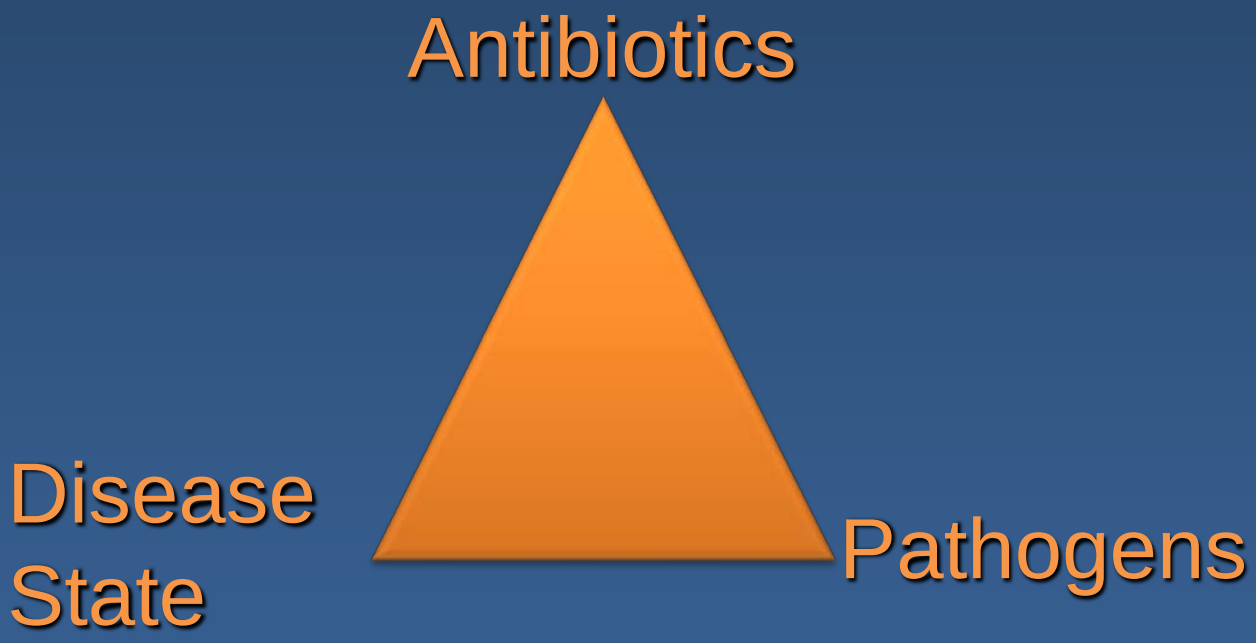
Starting off – choosing the most appropriate empiric regimen



Get SMART – Ms. M

- Ms. M is a 45 year old woman with breast cancer who has been in the hospital for 1 week for complications of chemotherapy
- On day 6, she develops low-grade fevers and UA is positive, so she is started on cefepime
- Today, her blood pressure is low and the lab reports urine is growing *Acinetobacter spp.*
- It will be another 24 hours before they have susceptibility testing results

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What is the most appropriate approach to the treatment of Mrs. M with UTI?

A. Keep her on cefepime because it is an excellent gram negative agent

B. Switch to something with a broader spectrum, since that will be more likely to cover a resistant organism

C. Check the antibiogram to see which drug is most likely to cover *Acinetobacter spp.*

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Hospital Antibiogram

Gram Negative Organisms		Percent Susceptible																
IN-PATIENT, all sources (adult and pediatric combined)		Penicillins & Related Antibiotics							Cephalosporins 1st 3rd 4th generation				Aminoglycosides			Quinolones			UTI Agent
ORGANISM	(# of isolates)	AMPICILLIN	AMPICILLIN / SULBACTAM	PIPERACILLIN / TAZOBACTAM	AZTREONAM	IMIPENEM	MEROPENEM	ERTAPENEM	CEFAZOLIN	CEFTRIAXONE	CEFEPIME	TIGECYCLINE	AMIKACIN	GENTAMICIN	TOBRAMYCIN	CIPROFLOXACIN	MOXIFLOXACIN	TRIMETHOPRIM/ SULFA	NITROFURANTOIN
Acinetobacter baumannii	(56)	0	74		0	59			0	0	32			66	96	29	40	73	
Enterobacter aerogenes	(27)	0	0	77	77	100	100	100	0	74	60		100	96	95	96		100	
Enterobacter cloacae	(108)	0	0	60	58	87	87	76	0	56	69	71	100	76	81	68	66	72	
E. coli	(516)	42	54	95	91	99	99	99	81	92	93	98	98	82	84	66	58	66	93
Klebsiella oxytoca	(28)	0	96	100	96	100	100	100	78	96	96		100	92	92	100		92	
Klebsiella pneumoniae	(276)	0	63	84	71	95	94	92	68	72	72	92	94	84	73	68	69	66	13
Proteus mirabilis	(68)	70	82	98	89		100	100	91	94	94		100	88	97	69		79	0
Pseudomonas aeruginosa (CF sputum by Kirby-Bauer In and out patients	(273) (48)			93 96	 73	71 90	77 80				81 79		96 60	76 72	83 92	53 54			
Serratia marcescens	(62)	0	0	95	91	90	96	96	0	91	93	100	95	95	91	95	97	98	
S. maltophilia	(41)																	95	
OUT-PATIENT URINE																			
E. coli	(738)	55	67						89							81		76	94

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Antimicrobial Prescribing

Empiric

- Initial administration of a broad-spectrum antibiotic regimen that attempts to improve outcomes and minimize resistance.

Defined or Targeted

- Modification of antimicrobial therapy once the cause of infection is identified. Therapy may also be discontinued if the diagnosis of infection becomes unlikely.[1]
- Focus on de-escalation of antibiotic therapy with the goal of minimizing resistance and toxicity, and improving cost-effectiveness.

1. Kollef MH. *Drugs.* 2003;63:2157–2168.
2. Kollef MH. *Crit Care Med.* 2001;29:1473–1475.
3. Evans RS et al. *N Engl J Med.* 1998;338:232–238.

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Maintenance of therapy: Targeting, de-escalating, and discontinuing therapy

- Empiric regimen is often NOT the regimen that needs to be continued for the full treatment course

- GET CULTURES and use the data to target therapy using the most narrow spectrum agent possible.

- Take an "Antibiotic Time Out" – reassess after 48-72 hours

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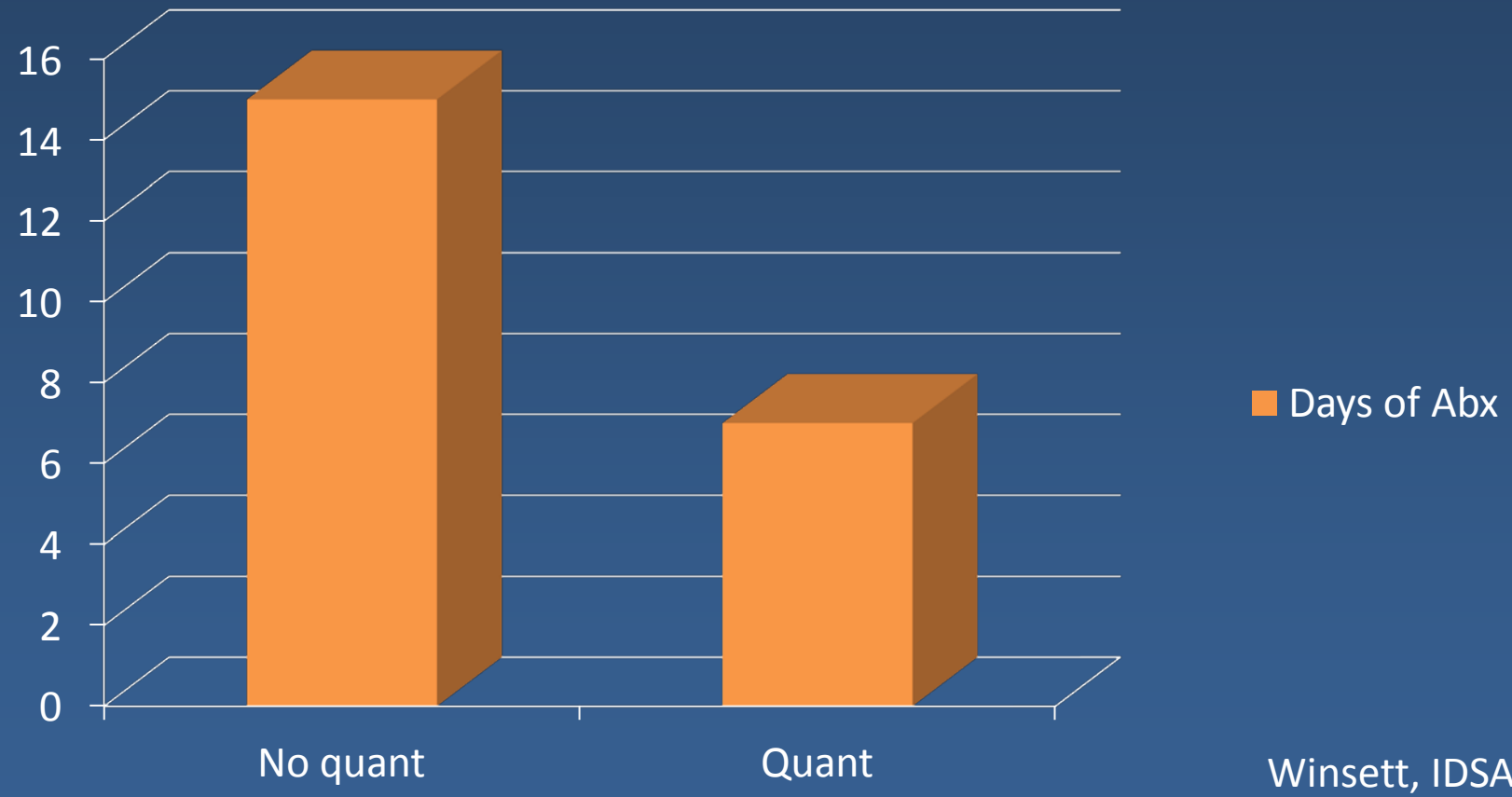
HAP/HCAP/VAP Protocol at Tufts Medical Center: a model for de-escalation

Use of mini-BAL and quantitative respiratory cultures

Antibiotic usage before and after implementation of quantitative lower respiratory cultures



Winsett, IDSA 2008

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Diagnostics

Highly sensitive, specific and rapid diagnostics

- Support stewardship
- Improve care
- Optimize antimicrobial clinical trials

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Get SMART – Mrs. A

- Mrs. A has been in the coronary care unit with heart failure for over 2 weeks
- She is on a ventilator, has a central line, and has an indwelling bladder catheter
- Her blood pressure has been tenuous
- Concerned that she may be septic, her physicians order a "pan-culture"
- She has no fever or leukocytosis, she is oxygenating well and her UA has no WBCs

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Get SMART – Mrs. A

- Her blood cultures drawn through the central line are growing coagulase-negative staph (peripheral blood cultures are not)
- Her urine culture is growing VRE
- Her tracheal aspirate is growing Candida

What is the most appropriate therapy for this Mrs. A with multiple positive cultures?

A. Vancomycin for Staph bacteremia
B. Fluconazole for Candida pneumonia
C. Linezolid for VRE UTI
D. All of the above
E. No treatment

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What is the most appropriate therapy for this Mrs. A with multiple positive cultures?

A. Vancomycin for Staph bacteremia
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D. All of the above

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Are you treating infection or colonization?

- **Colonization** = bacteria or fungi are present at the site sampled, but are not causing disease

- **Contamination** = bacteria or fungi are present in the laboratory sample, but not at the site

- **NEITHER** requires antibiotics!

- Cultures drawn through a central line should be avoided
- WBCs in the urine ≠ UTI; NO WBCs in the urine = NO UTI
- Candida is a frequent colonizer

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Get SMART – Mr. R

- Mr. R is admitted with a surgical site infection of a saphenous vein graft site
- He has a history of Stevens Johnson Syndrome to IV vancomycin
- Cultures are growing MRSA
- His vital signs are stable and he is taking his usual PO meds and a regular diet

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What is the most appropriate regimen for Mr. R with surgical site infection?

A. IV Linezolid
B. PO Linezolid
C. IV Bactrim
D. PO Vancomycin

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What is the most appropriate regimen for Mr. R with surgical site infection?

A. IV Linezolid

B. PO Linezolid

C. IV Bactrim

D. PO Vancomycin

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Route: IV or PO

- Many drugs are highly bioavailable in the PO form
- The oral route is less expensive, allows for earlier removal of lines and decreased length of stay
- Patients on oral antimicrobials with clearly documented reasons for continued hospital stay are not at risk for claims rejection by payors

Get SMART – Ms. T

- Ms. T is a 70-year-old admitted for community acquired pneumonia and started on moxifloxacin
- Cultures were not obtained on admission
- She is afebrile by hospital day 3 with normal vital signs and is tolerating room air and a regular diet, so you decide to discharge her

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Which of the following is the most appropriate discharge regimen for Ms. T with CAP?

A. Moxifloxacin 400mg PO once daily for the next 2 days for total of 5 days
B. Moxifloxacin 400 mg PO once daily for total of 7 days
C. Moxifloxacin 400 mg PO once daily for total of 10 days
D. No further antibiotic therapy

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Which of the following is the most appropriate discharge regimen for Ms. T with CAP?

A. Moxifloxacin 400mg PO once daily for the next 2 days for total of 5 days

B. Moxifloxacin 400 mg PO once daily for total of 7 days

C. Moxifloxacin 400 mg PO once daily for total of 10 days

D. No further antibiotic therapy

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Time: Stop antibiotics as early as possible

- "*We know everything about antibiotics except how much to give*."— Maxwell Finland (one of the forefathers of antibiotic therapy)
- Longer is not better
- CAP guidelines and clinical trials suggest good results with 5 days of antibiotics if patient meets clinical criteria
- Intra-abdominal infection guidelines: 4-7 days unless difficult to control the source of infection

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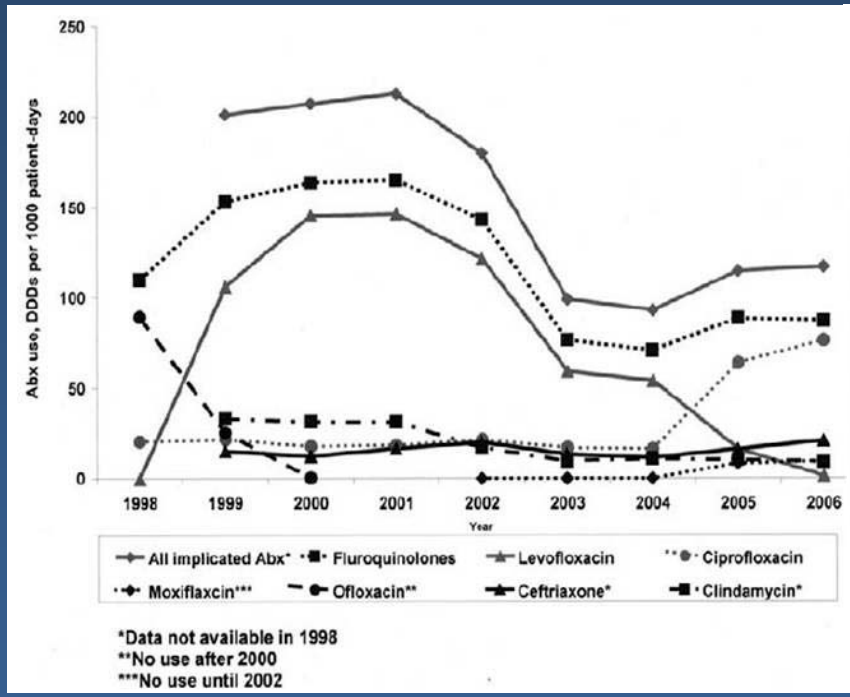
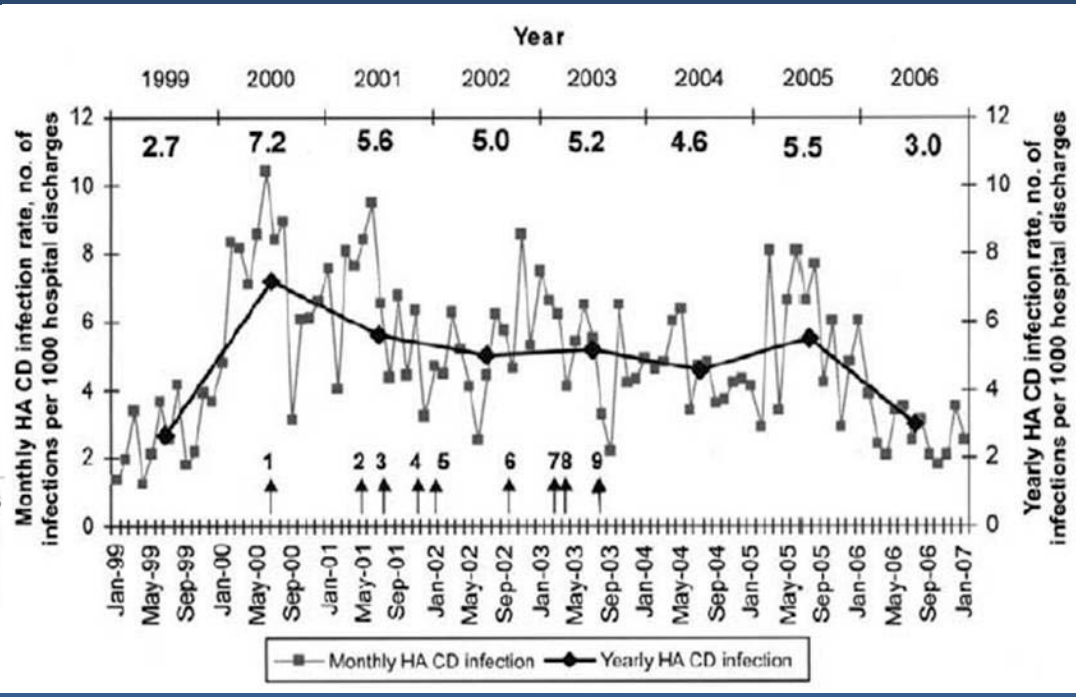
SomeTimes, less is more

"The single most important modifiable risk factor for the development of *Clostridium difficile* infection is exposure to antimicrobial agents"





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The Future of Stewardship

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

Nobel prize winner Dr. Joshua Lederberg

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The Future of Stewardship = YOU

- Appropriate antibiotic use is a patient safety priority
- Antibiotics are a shared resource – and becoming a scarce resource.
- Inappropriate antibiotic use and resistant infections = Billions of $$ in excess healthcare costs
- To combat resistance: Think globally, act locally

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Coming soon…

- Strategies for reversing resistance trends and examples of successes
- How to implement or improve your antimicrobial stewardship program
- Antimicrobial stewardship strategies that will work for your facility
- How to measure the success of your stewardship program

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