Antimicrobial Resistance

The Case for Diagnostics to Better Direct Therapy

Objectives

- Explain the medical significance of antibiotic resistance
- Assess the medical impact of disease, such as pneumonia and C. *difficile*
- Describe the diagnostic option available for pneumonia and C. *difficile*

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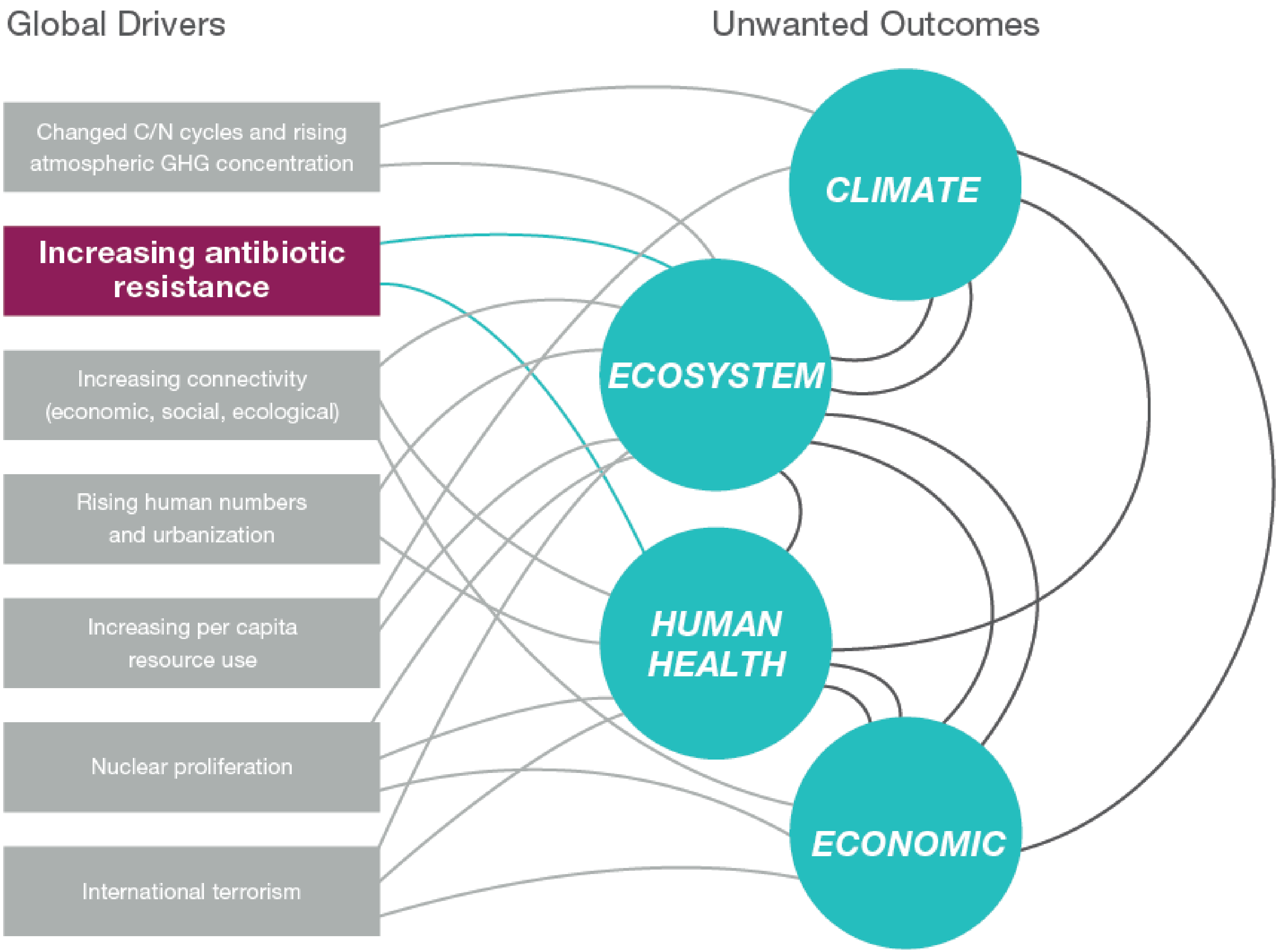
What do you think are the top 7 threats to the human race?

One of the top 7 issues that threatens the human race



Source adapted from: Science, Vol 325, September 2009
Available at: http://www.sciencemag.org/content/325/5948.cover-expansion

Infectious Disease in the US

1970: William Stewart, the Surgeon General of the United States declared the U.S. was “ready to close the book on infectious disease as a major health threat”; modern antibiotics, vaccination, and sanitation methods had done the job.

1995: Infectious disease had again become the third leading cause of death, and its incidence is still growing!

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The Problem – Drug Resistance Rates Can Occur Quickly

1928 Alexander Fleming announces the discovery of Penicillin

Antibiotic resistance was first seen in 1947 – only 4 years after the drug started being mass produced

1945 (17 years later) Fleming wrote:

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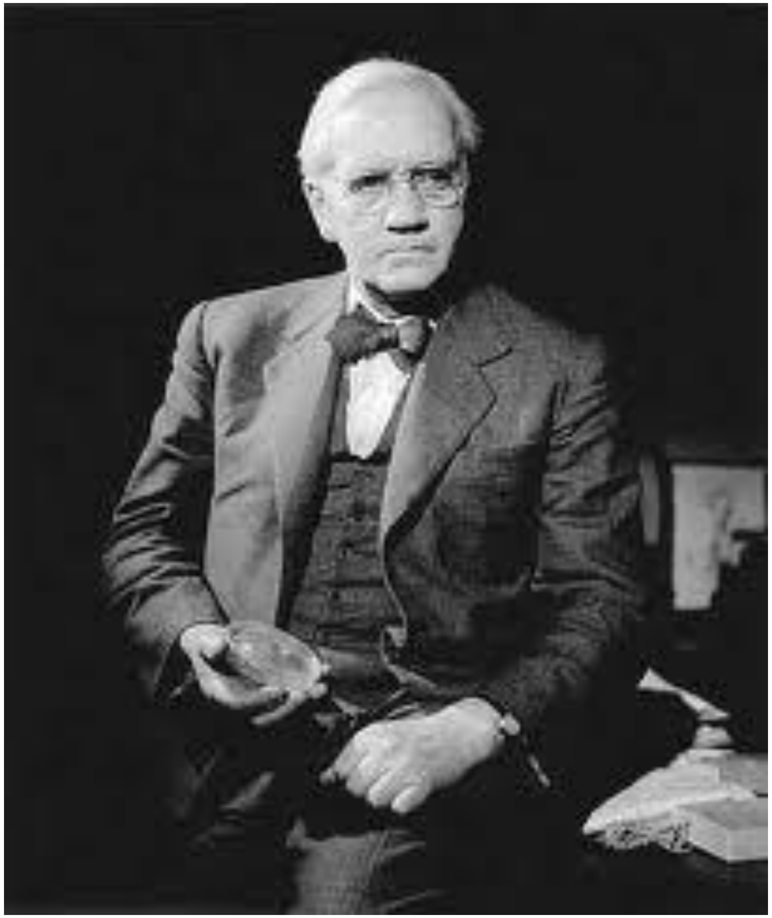
Sir Alexander Fleming



The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under dose himself and, by exposing his microbes to non-lethal quantities of the drug, educate them to resist penicillin.

Nobel lecture, 1945

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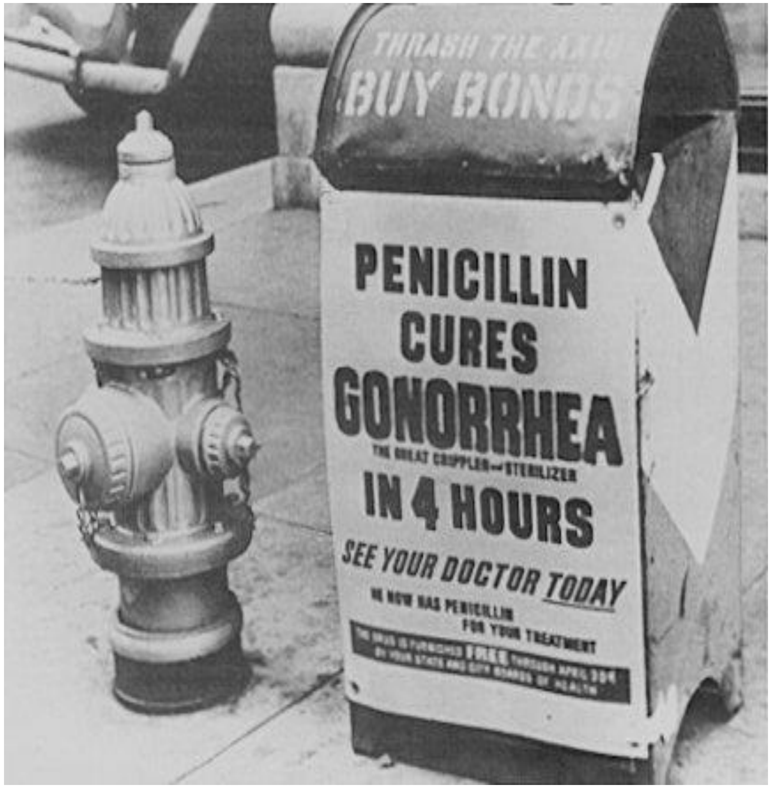
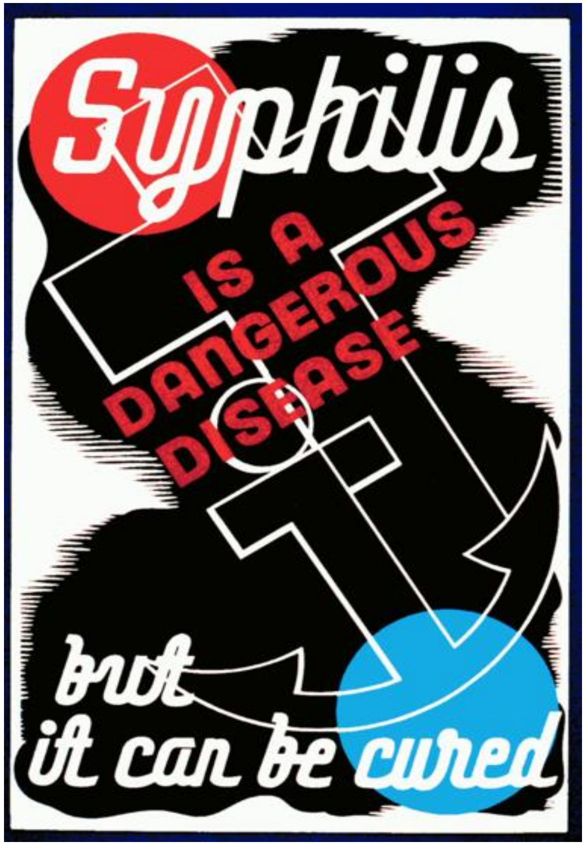
How it was





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Drug store in Mexico

The Costs of Antibiotic Resistance

Antibiotic resistance increases the economic burden on the entire US healthcare system

- Resistant infections cost more to treat and can prolong healthcare use

More than $1.1 billion is spent annually on unnecessary antibiotic prescriptions for respiratory infections in adults

In total, antibiotic resistance is responsible for:

- $20 billion in excess healthcare costs
- $35 billion in societal costs
- 8 million additional hospital days

CDC – Get Smart Campaign

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Inpatient Settings

One in every three patients will receive two or more antibiotics in the course of their hospital stay

Of the patients receiving antibiotics, three out of every four will receive unnecessary or redundant therapy, resulting in excessive use of antibiotics

CDC – Get Smart Campaign

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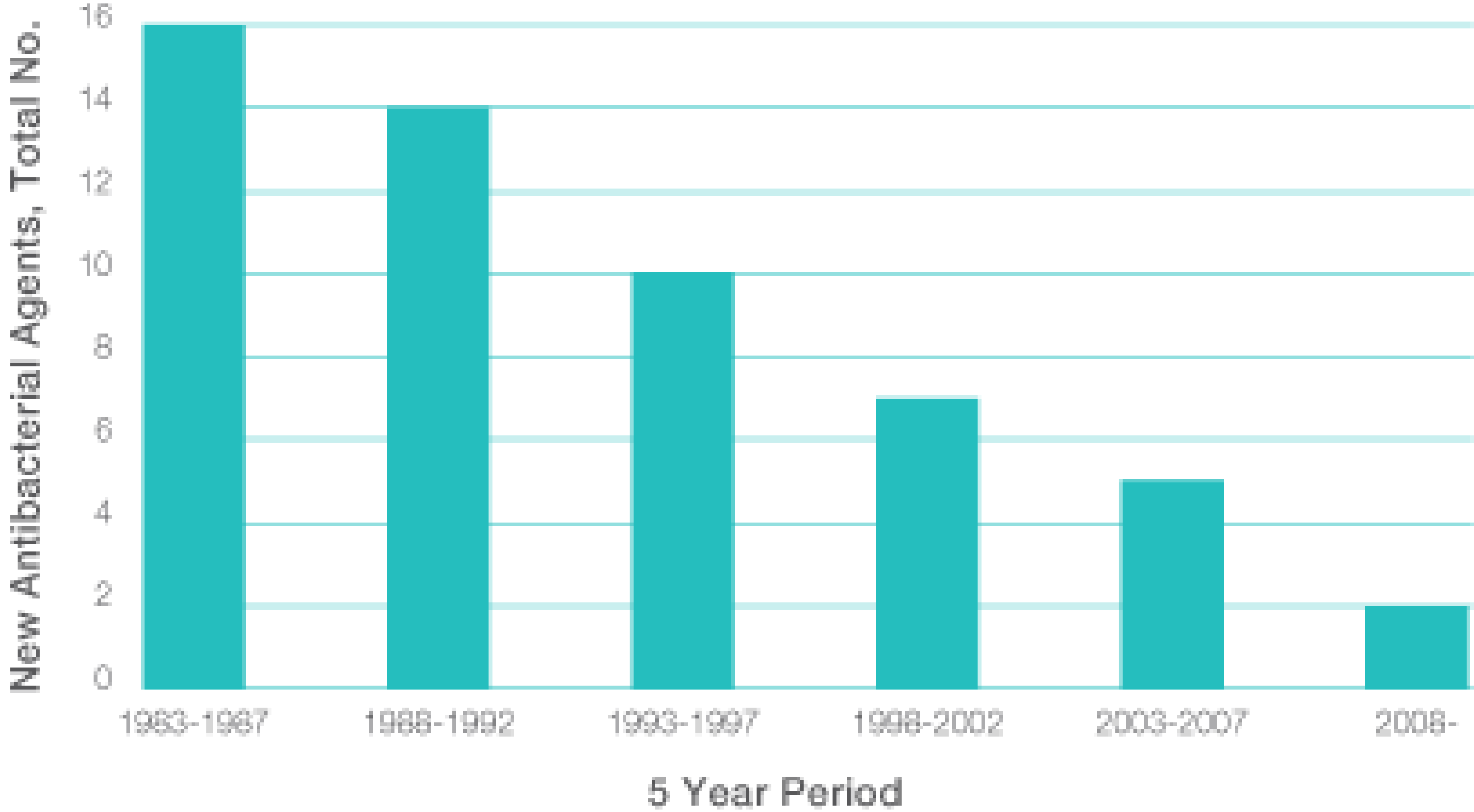
Outpatient Settings

Each year, tens of millions of antibiotics are prescribed unnecessarily for upper viral respiratory infections

Antibiotic use in primary care is associated with antibiotic resistance at the individual patient level

The presence of antibiotic-resistant bacteria is greatest during the month following a patient's antibiotics use and may persist for up to 1 year

New drugs



New antibacterial agents approved in the United States, 1983–2013, per 5-year period].
Source: adapted from Spellberg et al (2008) Clin Inf Dis 46:155-64

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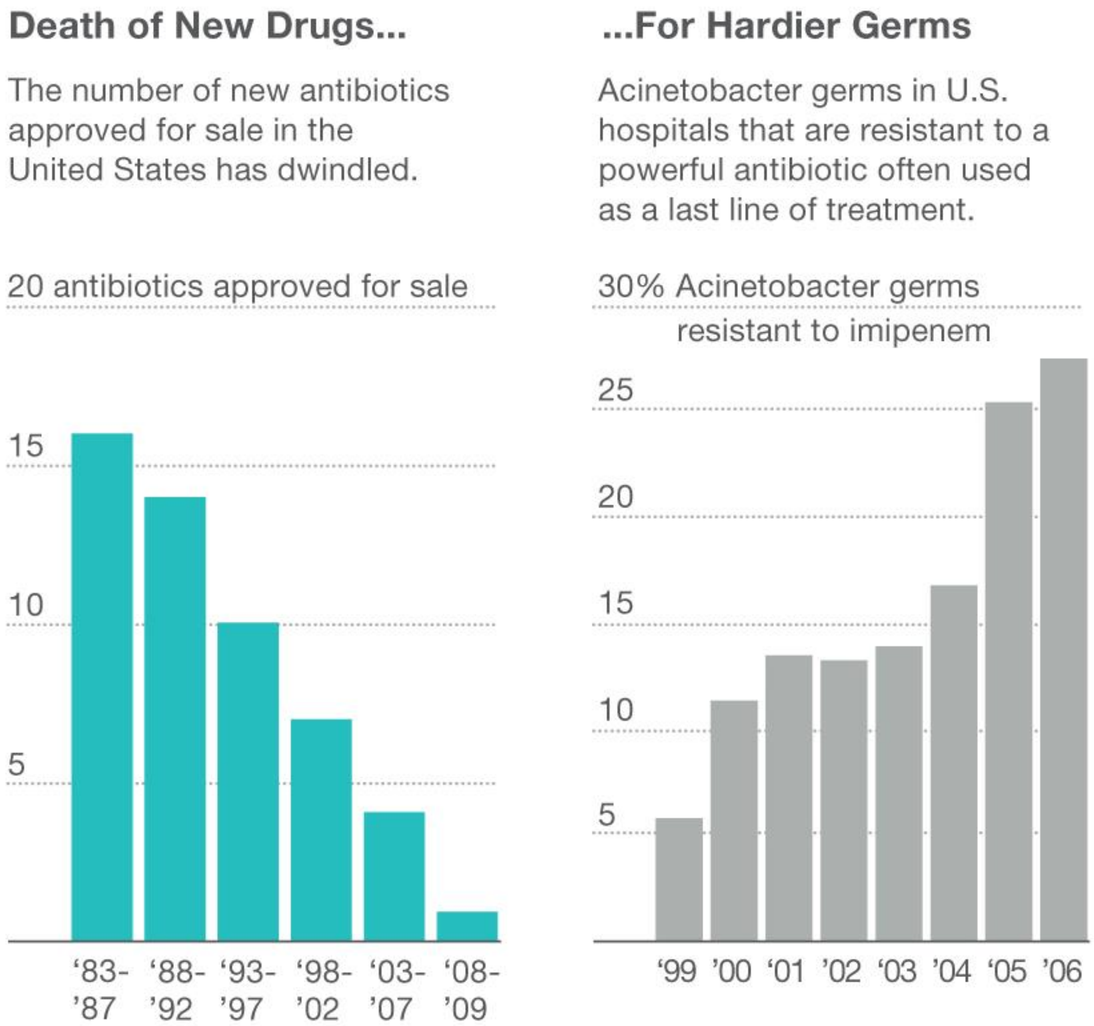
New drugs vs. Resistant organisms



Source adapted from New York Times (2010) Rising Threat of Infections Unfazed by Antibiotics. [Online]. Available at: http://www.nytimes.com/imagepages/2010/02/27/business/27germ_graphic.html

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Potential Reasons to Shift Focus of Drug Discovery from Antibiotics to Other Types

- Other types of drugs are more profitable
- Antibiotics become auto-obsolete
- Thought leaders advocating conservative use
- Increasing standards for efficacy and safety evaluation
- Increasingly complex patients in clinical trials
- Significantly increased costs in clinical trials

Edwards J, *ICAAC*, 2003

Slide from Ebbing Lautenback, University of Pennsylvania

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“A post-antibiotic era means, in effect, and end to modern medicine as we know it. Things as common as strep throat or a child’s scratched knee could once again kill.”

Margaret Chan, WHO Director General

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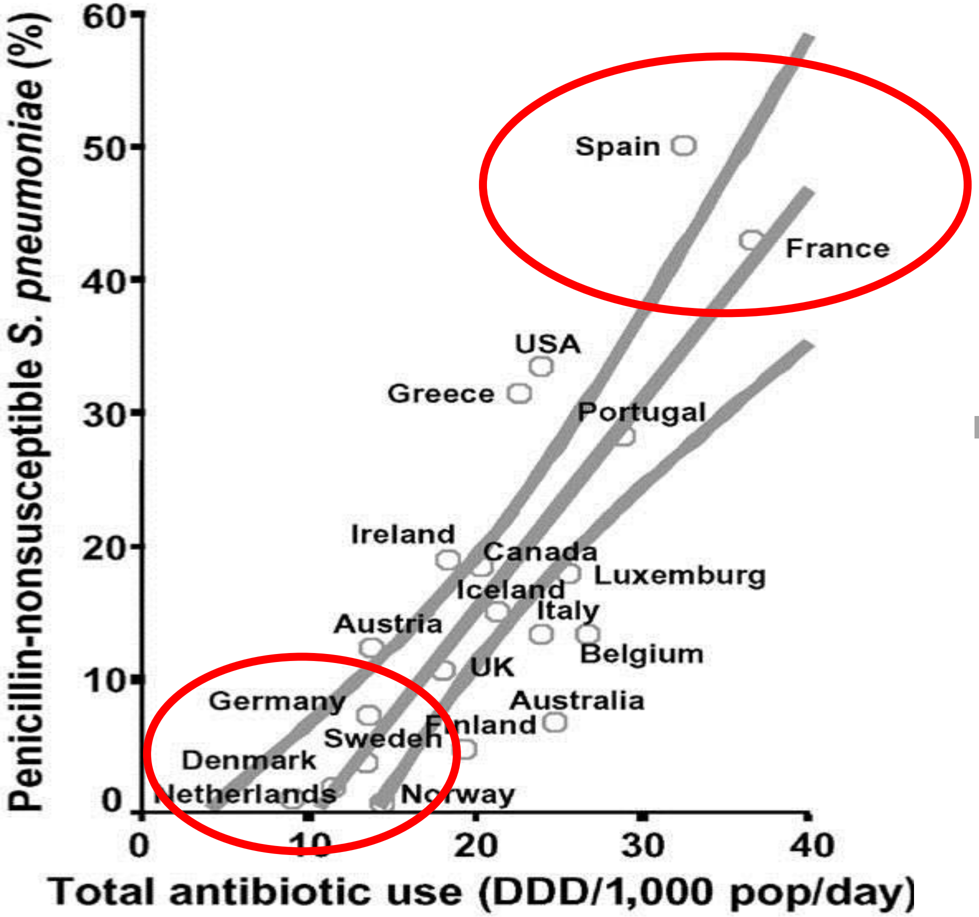
Penicillin Resistance in Pneumococci



- Correlation between the use of antibiotics and resistance

Test Target Treat model

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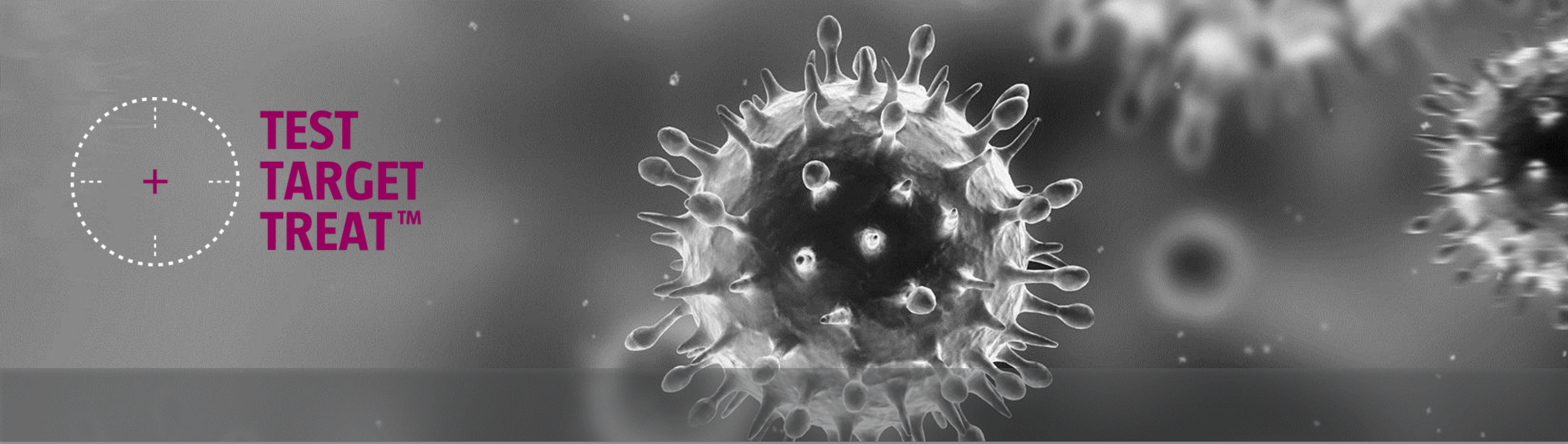
Why do providers give antibiotics when not certain?

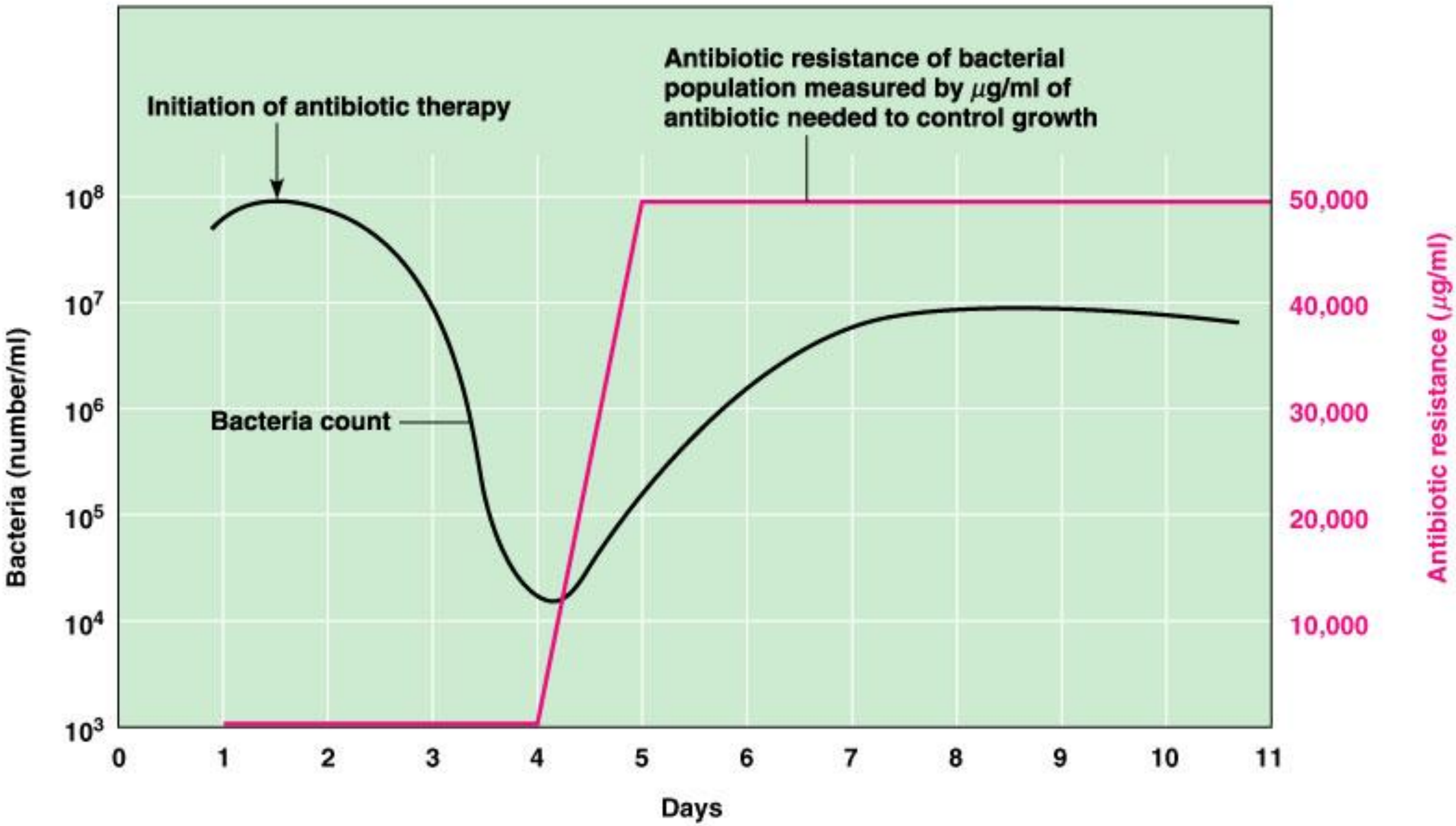
Medscape survey

- 53% - Prescriptions written when “certain enough”
- 42% - Worry that it could be bacterial
- 31% - Lab work takes too long
- 30% - Infection didn’t appear to be bacteria or viral
- 19% - Patient didn’t want or couldn’t afford test
- 15% - Malpractice concerns

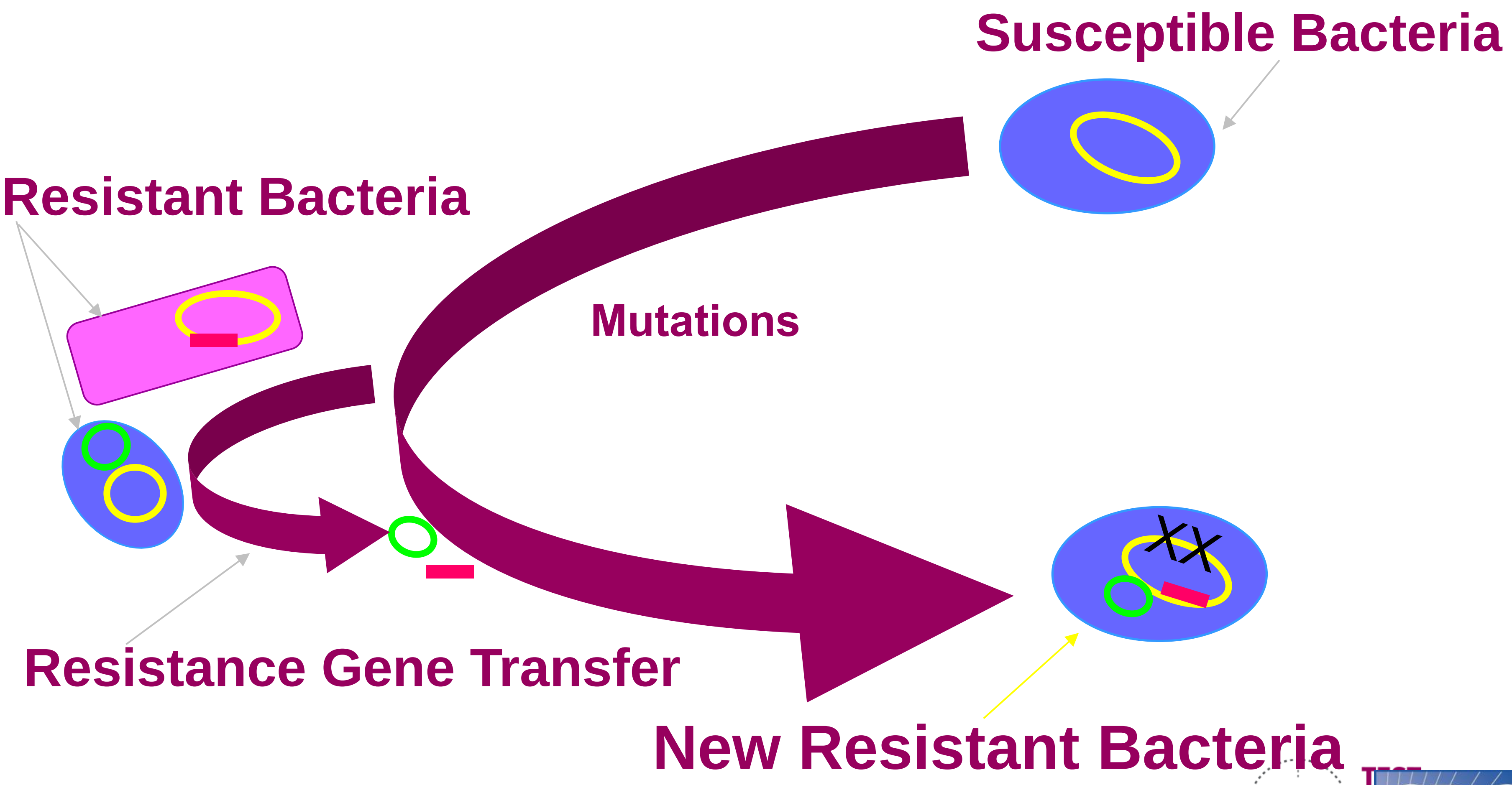


How Resistance Is Transmitted

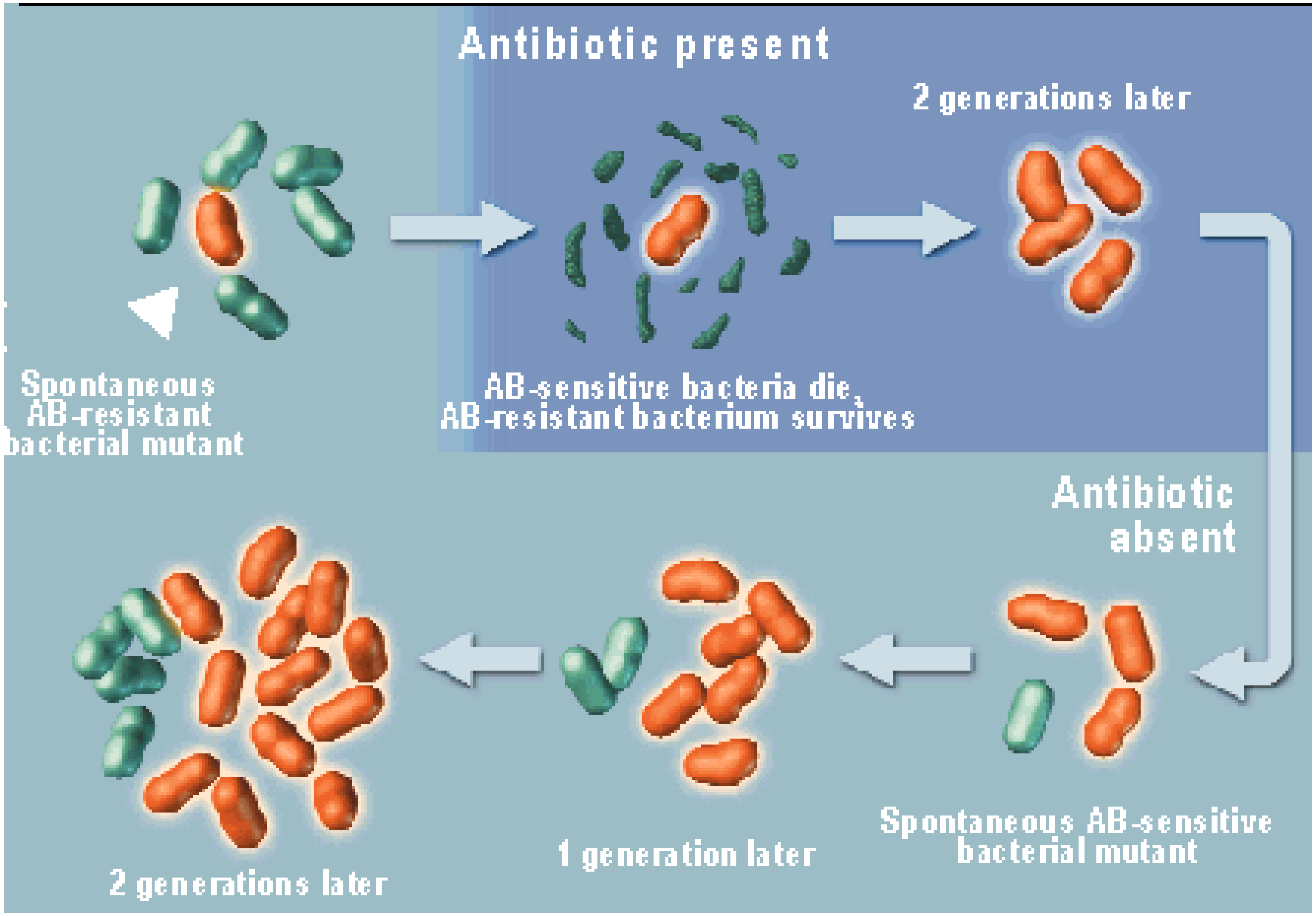
ANTIBIOTIC RESISTANCE



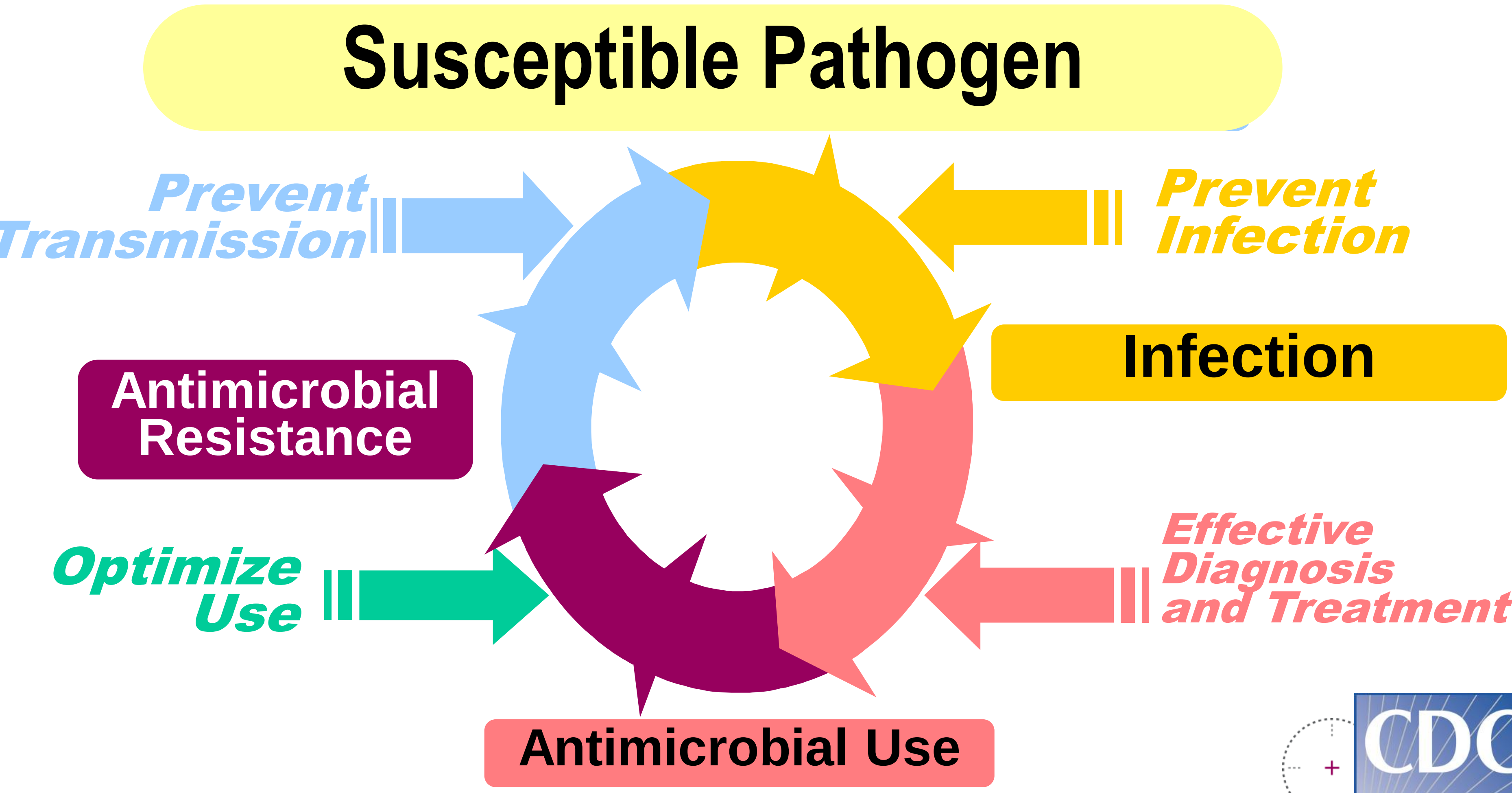
EMERGENCE OF ANTIMICROBIAL RESISTANCE



ANTIBIOTIC SELECTION FOR RESISTANT BACTERIA



ANTIMICROBIAL RESISTANCE: KEY PREVENTION STRATEGIES



Antibiotic Resistance Mechanisms

Bacteria can inactivate the antibiotic

- B-lactamase can cleave molecule, rendering it inactive

The bacteria can modify the target the antibiotic binds to

- Penicillin binding protein in MRSA

The bacteria can actively pump the antibiotic outside of the cell

- Eflux pumps keep the antibiotic level below what would kill cell

Bacterial pathways can be inhibited, such as metabolic pathway

- Alternative pathway can be used

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

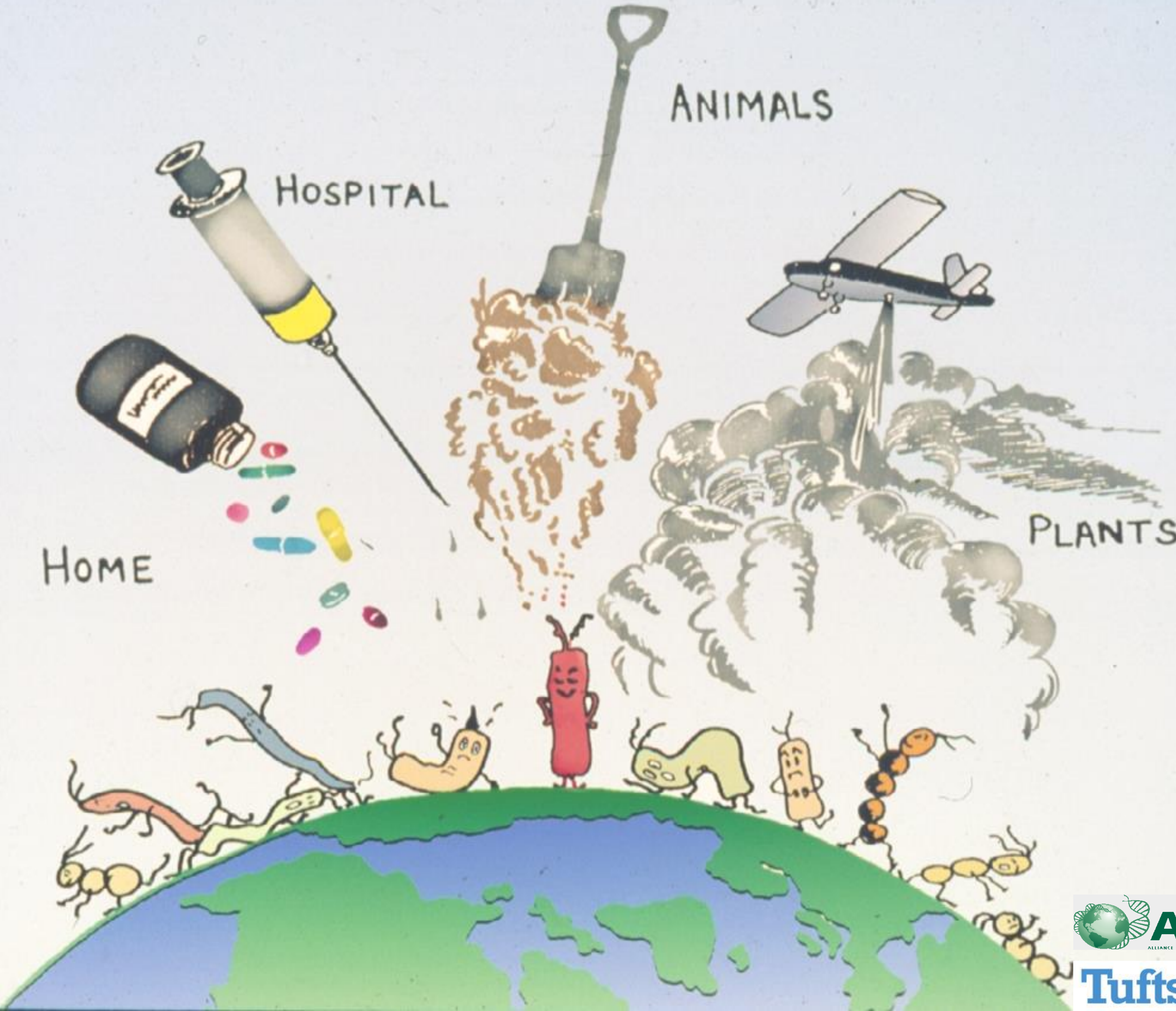
Community

Gram-negative

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

Gram-positive

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


ANIMALS
HOSPITAL
HOME
PLANTS

What percent of antibiotics made in this country goes into animal feed?

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What percent of antibiotics made in this country goes into animal feed?

80%

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“Poster children” for antibiotic resistance

Gram-Positive

MRSA

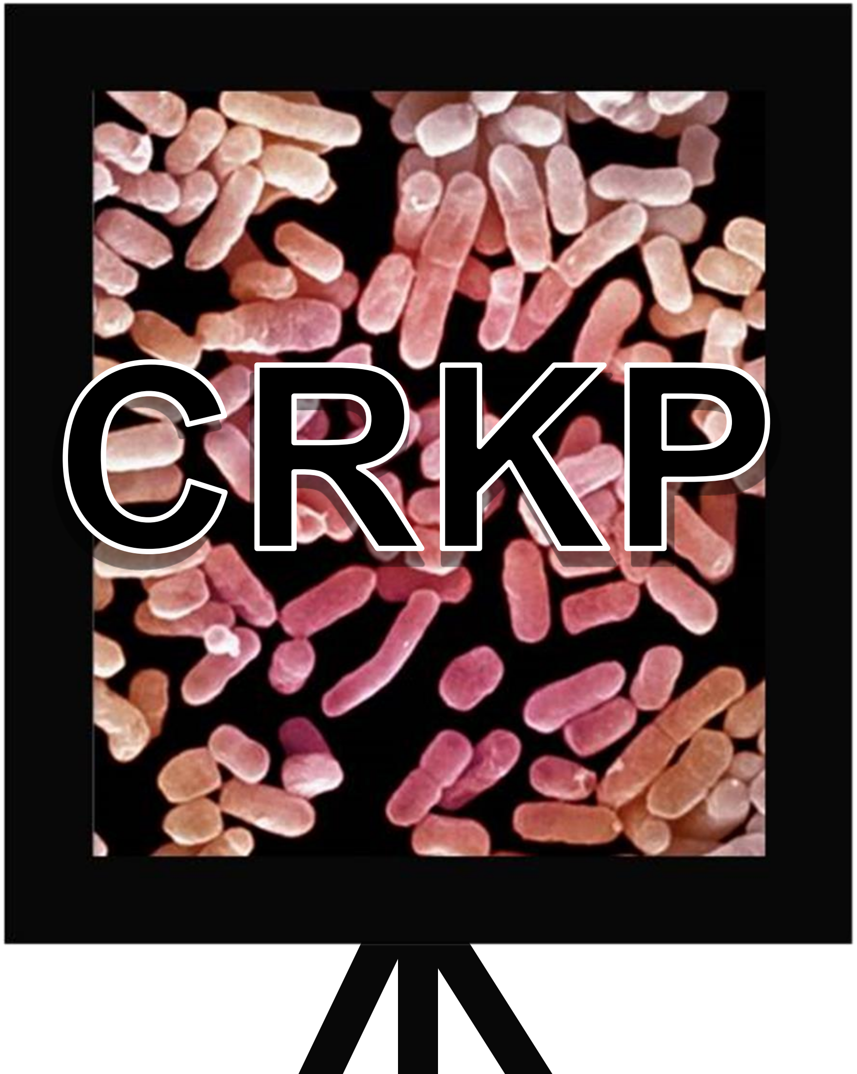
Most invasive organism that we face today

Attacks all groups regardless of age

Community-acquired and hospital-acquired

About 19,000 deaths from MRSA in US in 2005 alone

Gram-Negative



Carbapenem-Resistant Enterobacteriaceae

Klebsiella are normally found in intestines

May cause pneumonia, bloodstream infections, wound or surgical site infections, and meningitis

Mortality rates can be as high as 40%-50%

National Healthcare Safety Network found in 2009-2010 that 13% of *Klebsiella* species from catheter-associated UTI's and central line associated bloodstream infections were resistant

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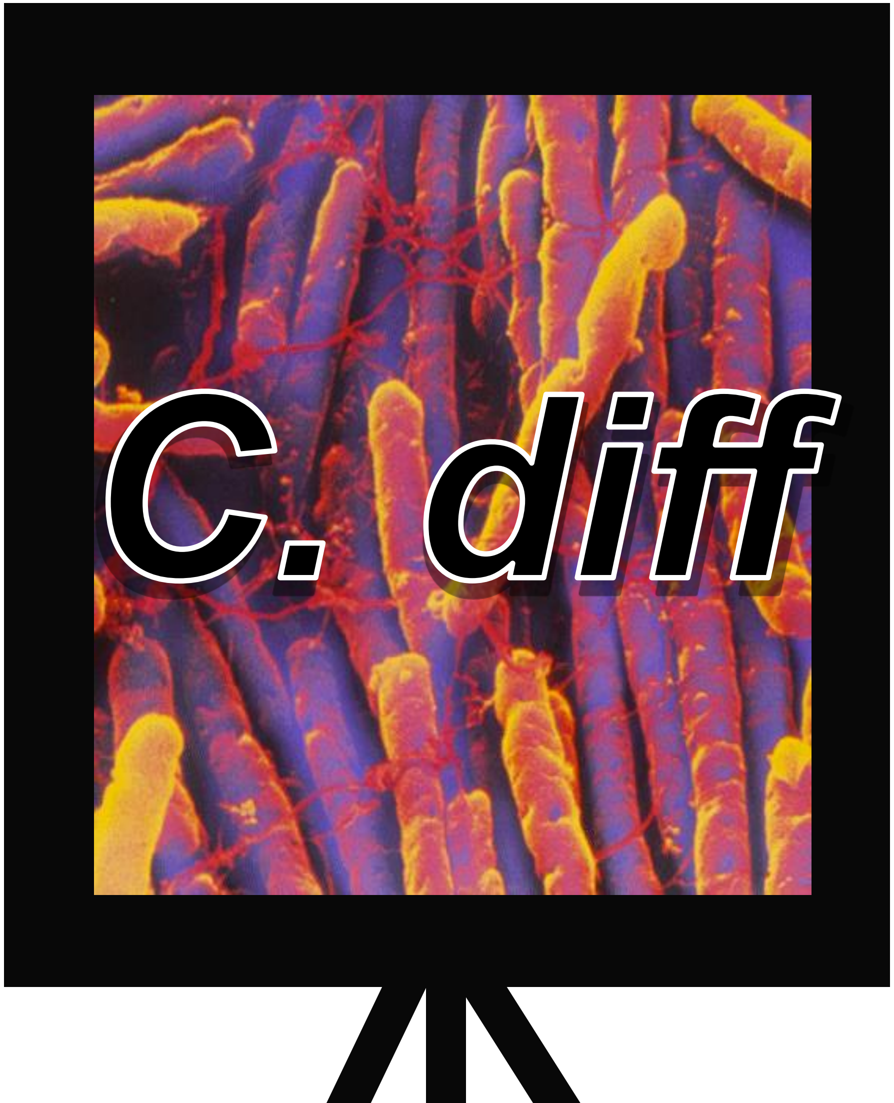
Gram-Positive Anaerobe



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Tufts Medical Center

Clostridium difficile

Gram positive spore former – the most common cause of healthcare-associated diarrhea

Spread by health care workers - spores difficult to eradicate

Causes 25% of antibiotic associated diarrhea and 90-99% of pseudomembranous colitis

Disease is caused by the toxins the organism produces

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Treating Respiratory Diseases in the Emergency Department

- **Is the pathogen bacterial or viral?** — Influenza and pneumonia symptoms can overlap dramatically
- **Who do you test?** — If it is flu season, do you test for other pathogens?
- **What do you test them for?** — Different age groups are linked to different pathogens.
- **Can treatment be impacted if the appropriate testing is done?** — Stop indiscriminate use broad spectrum antibiotics.

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Importance of FQ Resistance

- One of the most commonly used antibiotic classes[1,2]
- Most common antibiotic used in nursing homes[3]
- Broad spectrum
- Oral bioavailability
- Long half-life
- Well tolerated

1. Thomson, J Antimicrob Chemother, 1994
2. Lee, Am J Infect Control, 1998
3. Steinman, Ann Intern Med, 2003

Slide from Ebbing Lautenback, University of Pennsylvania

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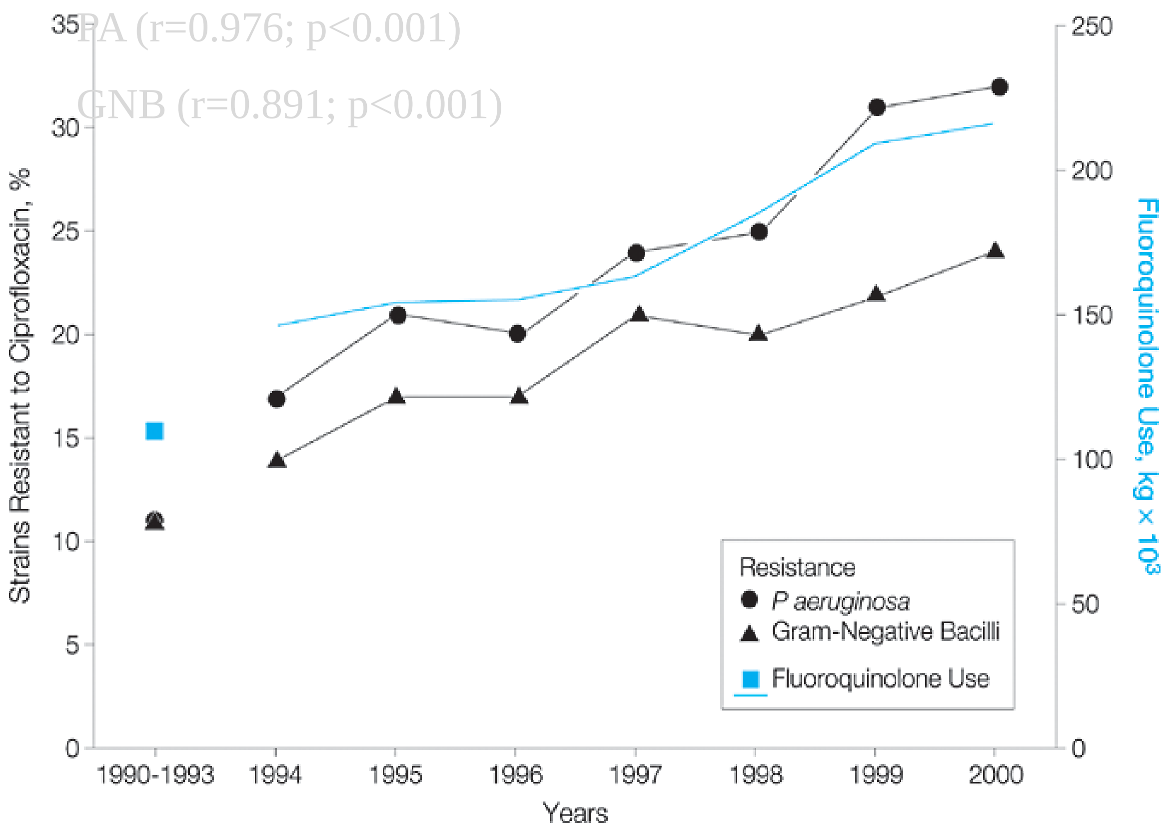
FQ Resistance vs. FQ Use



Neuhauser MM, *JAMA* 2003;289:885

Slide from Ebbing Lautenback, University of Pennsylvania

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Implications: Addressing FQ Overuse/Misuse

On whom/Where are they being used?

- Inpatient
- Outpatient
- Emergency Departments

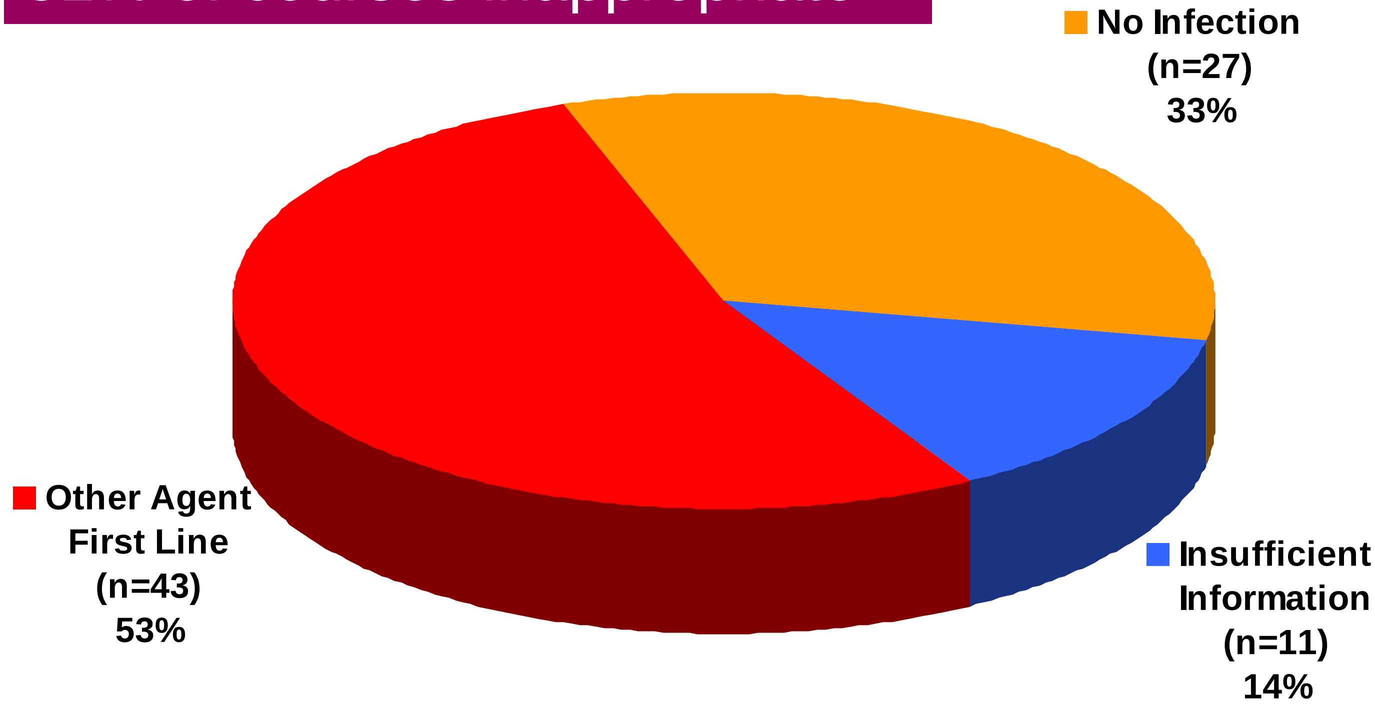
Why/How are they being used?

- Indications
- Dose/duration

Slide from Ebbing Lautenback, University of Pennsylvania

Appropriateness of ED FQ Use

81% of courses inappropriate



Lautenbach, *Arch Intern Med* 2003;163:601

Slide from Ebbing Lautenback, University of Pennsylvania

Appropriateness of FQ Use: EDs

19/100 (19%) patients received appropriate FQ therapy (judged by indication)

- 14 received both an incorrect dose & duration
- 4 received either an incorrect dose or duration
- 1 received the correct dose and duration

Lautenbach, *Arch Intern Med* 2003;163:601

Slide from Ebbing Lautenback, University of Pennsylvania

Study on CAP Patients and Therapy

Retrospective study on 175 CAP patients in New York	Rate of multidrug resistant organism detected within 90 days

• Exclusion criteria
  • Hospitalization ≥ 2 days within 90 days
  • Residence in nursing home
  • Prior isolation of MDR organism
	• 15% patients on fluoroquinolone
	• 4% of patients on cephalosporin/macrolide

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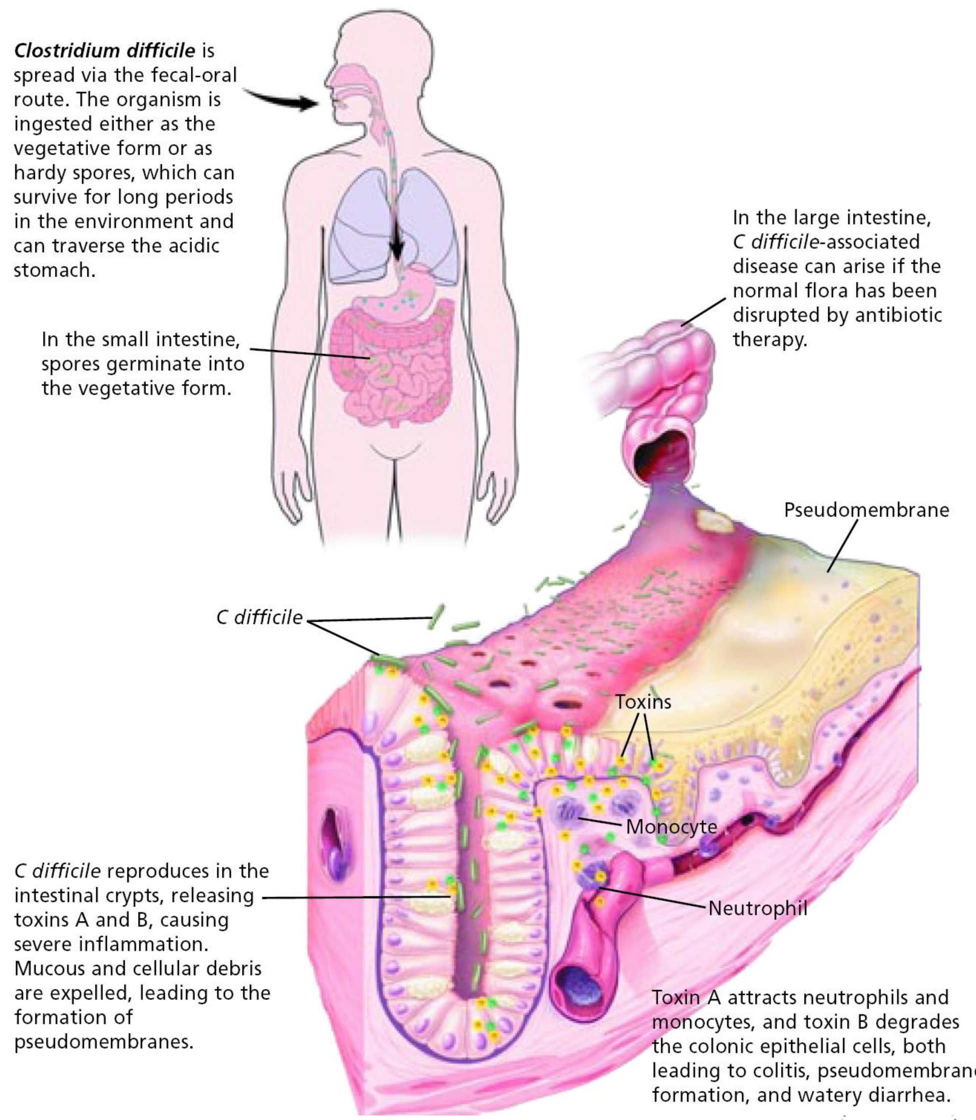
Misuse of Antibiotics Can Lead to Other Medical Issues

Pneumonia may be treated with fluoroquinolone

Disrupts normal intestinal flora

O27 strain of *C. difficile* is specifically resistant to fluoroquinolone

Pathogenesis of CDAD



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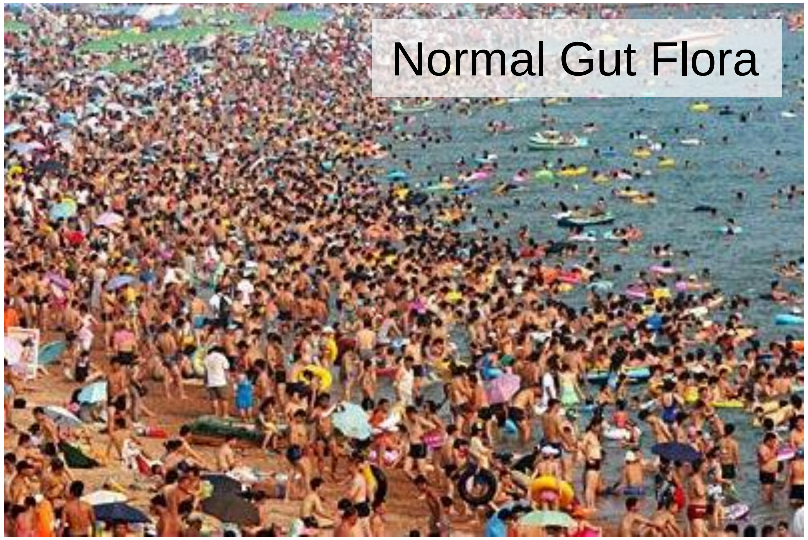
Antibiotic-Associated Diarrhea:
Life's a Beach with *C. difficile*



Clinical Manifestations of CDAD

Increasing disease severity

Asymptomatic Colonisation	Diarrheal illness	PMC Toxic megacolon
No Symptoms	• **Diarrhea- Mild to severe (explosive)** • **Abdominal Pain** • **Fever**	

Treatment for relapsing *C. difficile* Fecal transplant

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Pneumonia in the United States

Estimated 4.5 million cases of pneumonia annually. Approximately 1.1 million are hospitalized.[1]

Pneumonia, along with influenza, is the eighth leading cause of death in the United States.[2]

Third in the top 20 hospital discharge diagnosis groups for emergency department visits.[3]

1. Niederman MS, McCombs JS, Unger AN, et al. *The Cost of Treating Community-Acquired Pneumonia.* Clin. Ther. 1998; 20:820-837.
2. CDC Website: Deaths Preliminary Data for 2011
3. National Hospital Ambulatory Medical Care Survey: 2010 Emergency Department Summary Tables

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Etiological Agents of Respiratory Disease

Newborns (0 to 30 days)

- Group B *Streptococcus*, *Lysteria monocytogenes*, or Gram negative rods are common
- RSV in premature babies

Infants and toddlers

- 90% of lower respiratory tract infections are viral with the most common being RSV, Influenza A&B, and parainfluenza. Bacterial infections are rare, but could be *S. pneumoniae*, Hib, or *S. aureus*.

Etiological Agents

Outpatient

- *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, and respiratory viruses

Inpatient (non-ICU)

- With the above agents, add *L. pneumophila*

Inpatient (ICU)

- *S. pneumoniae*, *S. aureus*, *L. pneumophila*, Gram-negative bacteria, and *H. influenzae*

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IDSA/ATS CAP Guidelines

Recommended by the 2007 IDSA/ATS Community-Acquired Pneumonia (CAP) Guidelines for all adult patients with severe pneumonia

- Recommended Diagnostic Tests for Etiology (page S39)
  - Patients with CAP should be investigated for specific pathogens that would significantly alter standard (empirical) management decisions, when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues. (Strong recommendation; level II evidence.)
  - The spectrum of antibiotic therapy can be broadened, narrowed, or completely altered on the basis of diagnostic testing.

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Recommended by the 2007 IDSA/ATS Community-Acquired Pneumonia (CAP) Guidelines for all adult patients with severe pneumonia (con’t)

- Patients with severe CAP should have blood samples drawn for culture, urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* performed, and expectorated sputum samples collected for culture.

Importance of Testing During Respiratory Season

S. pneumoniae: A secondary complication to flu

- 2009 pandemic influenza A (H1N1) & Spanish flu 1918
  - Many deaths were attributed to the flu combined with the secondary complication of pneumonia.[1]
- Testing for both flu <u>and</u> *S. pneumoniae* will enable appropriate antibiotic therapy.
  - Is it flu? Is it pneumonia? Is it both?
  - Is it bacterial or viral?

1. Bacterial Coinfections in Lung Tissue Specimens from Fatal Cases of 2009 Pandemic Influenza A (H1N1) — United States, May–August 2009. CDC MMWR, September 29, 2009; Vol. 58.

Are there other issues with the abuse of antibiotics?

Data suggests link between antibiotic use and obesity in children

Yeast infections

Antibiotic Stewardship Programs

These programs focus on:

- Proper use of antibiotics to provide the best patient outcomes
- Lessen the risk of adverse effects (*C. diff*, toxicity damage to organs, etc.)
- Promote cost-effectiveness
- Reduce or stabilize levels of resistance

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Antibiotic Stewardship Programs

- IDSA/SHEA Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship – 2006
  - http://www.idsociety.org

- Core members include:
  - Infectious Disease Physician
  - Emergency Department Physician / Manager
  - Clinical Pharmacist – ideally with infectious disease training
  - Clinical Microbiologist
  - Infection Control Professional
  - Information System Specialist

Program components:

- Education
- Guidelines and **clinical pathways**
  - Includes diagnostic testing
- Antimicrobial cycling
- Antimicrobial order forms
- Combination therapy
- Streamlining or de-escalation of therapy
- Dose optimization
- Parenteral to oral conversion

Conclusions

Treating for one condition may lead to unintended consequences

Diagnostic testing can help direct the appropriate therapy

Directed therapy can prolong the effectiveness for broad spectrum antibiotics

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Discussion