Antibiotics: General Notions & Antimicrobial Stewardship

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Disclosures

- No conflict of interest

Objectives

- After this intervention, the participants will be able to:
  - Define the utility of antibiotics in medical practice using a case-based approach
  - Recognize the value of antimicrobial stewardship to reduce the emergence of antibiotic resistance

Alexander Fleming

Penicillium notatum

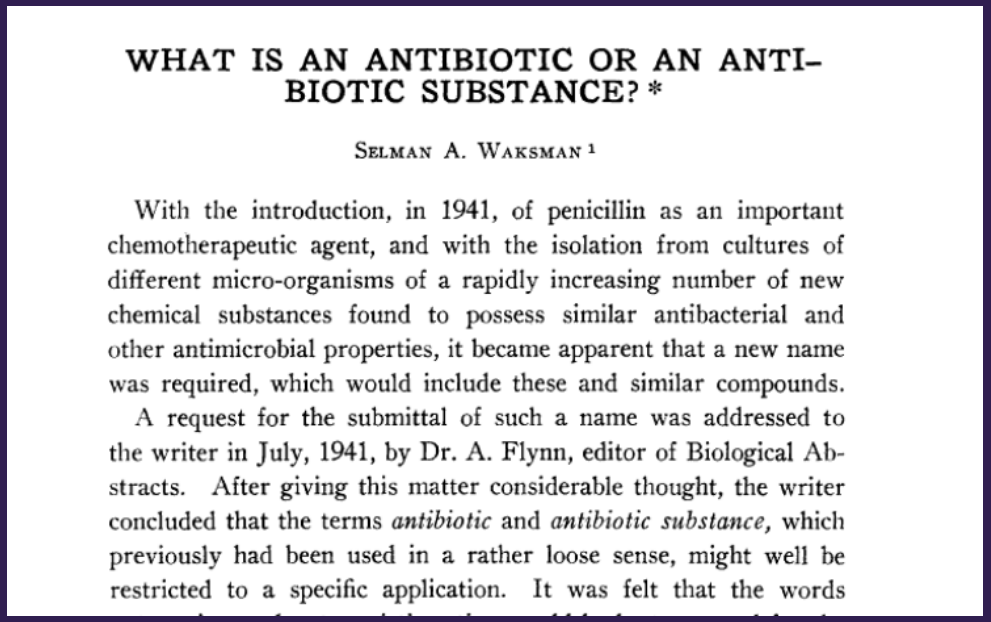
Staphylococcus aureus

September 22, 1928

Published in 1929 in the *British Journal of Experimental Pathology*

Antibiotics

- Any of a variety of substances, usually obtained from microorganisms, that inhibit the growth of or destroy certain other microorganisms.
- First definition in 1942 excluded synthetic agents like sulfonamides.



WHAT IS AN ANTIBIOTIC OR AN ANTI-BIOTIC SUBSTANCE? *

SELMAN A. WAKSMAN [1]

With the introduction, in 1941, of penicillin as an important chemotherapeutic agent, and with the isolation from cultures of different micro-organisms of a rapidly increasing number of new chemical substances found to possess similar antibacterial and other antimicrobial properties, it became apparent that a new name was required, which would include these and similar compounds.

A request for the submittal of such a name was addressed to the writer in July, 1941, by Dr. A. Flynn, editor of Biological Abstracts. After giving this matter considerable thought, the writer concluded that the terms *antibiotic* and *antibiotic substance,* which previously had been used in a rather loose sense, might well be restricted to a specific application. It was felt that the words

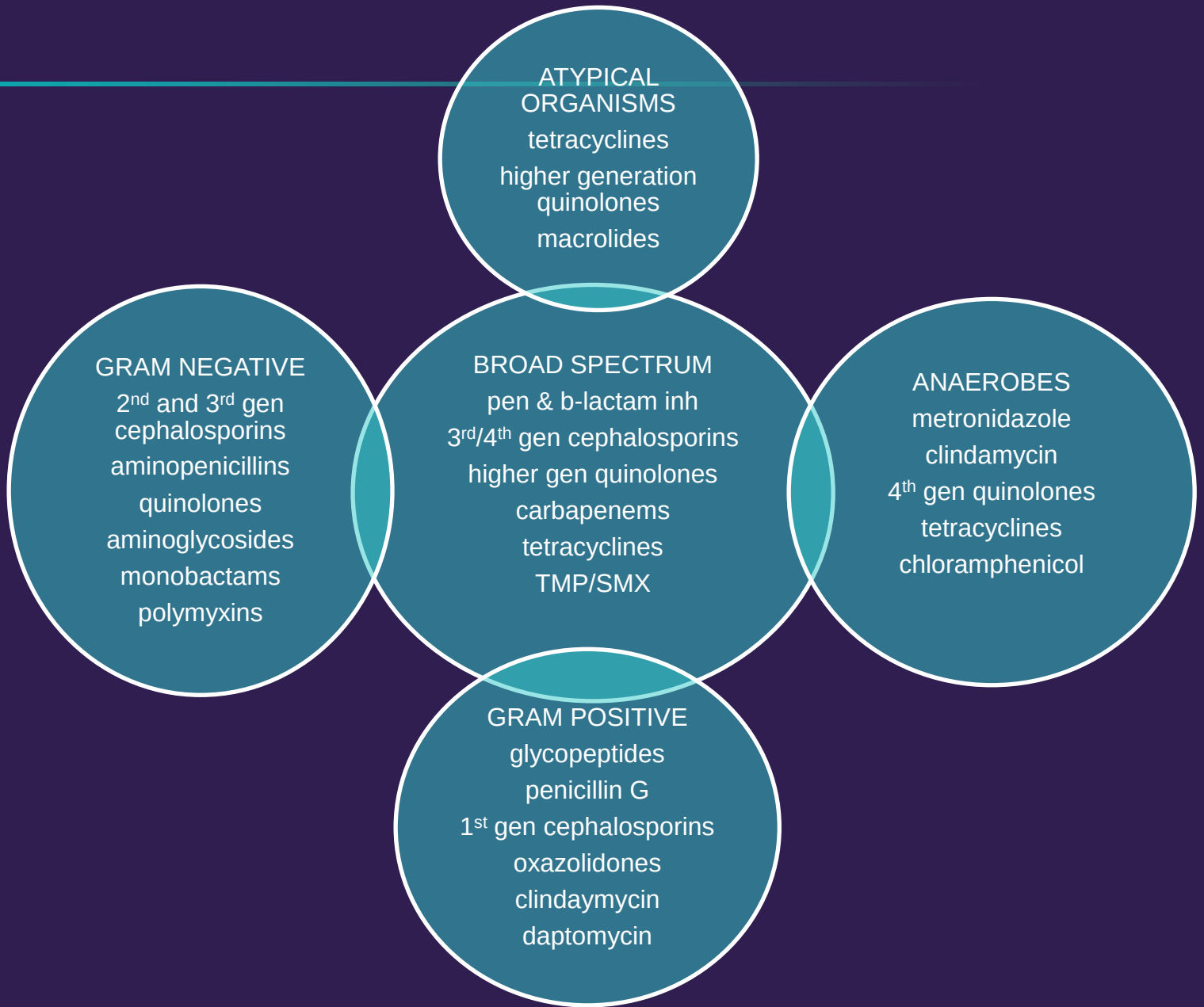
Selman A. Waksman. *Mycologia.* Vol. 39, No. 5 (Sep. - Oct., 1947), pp. 565-569

Classification of Antibiotics - I

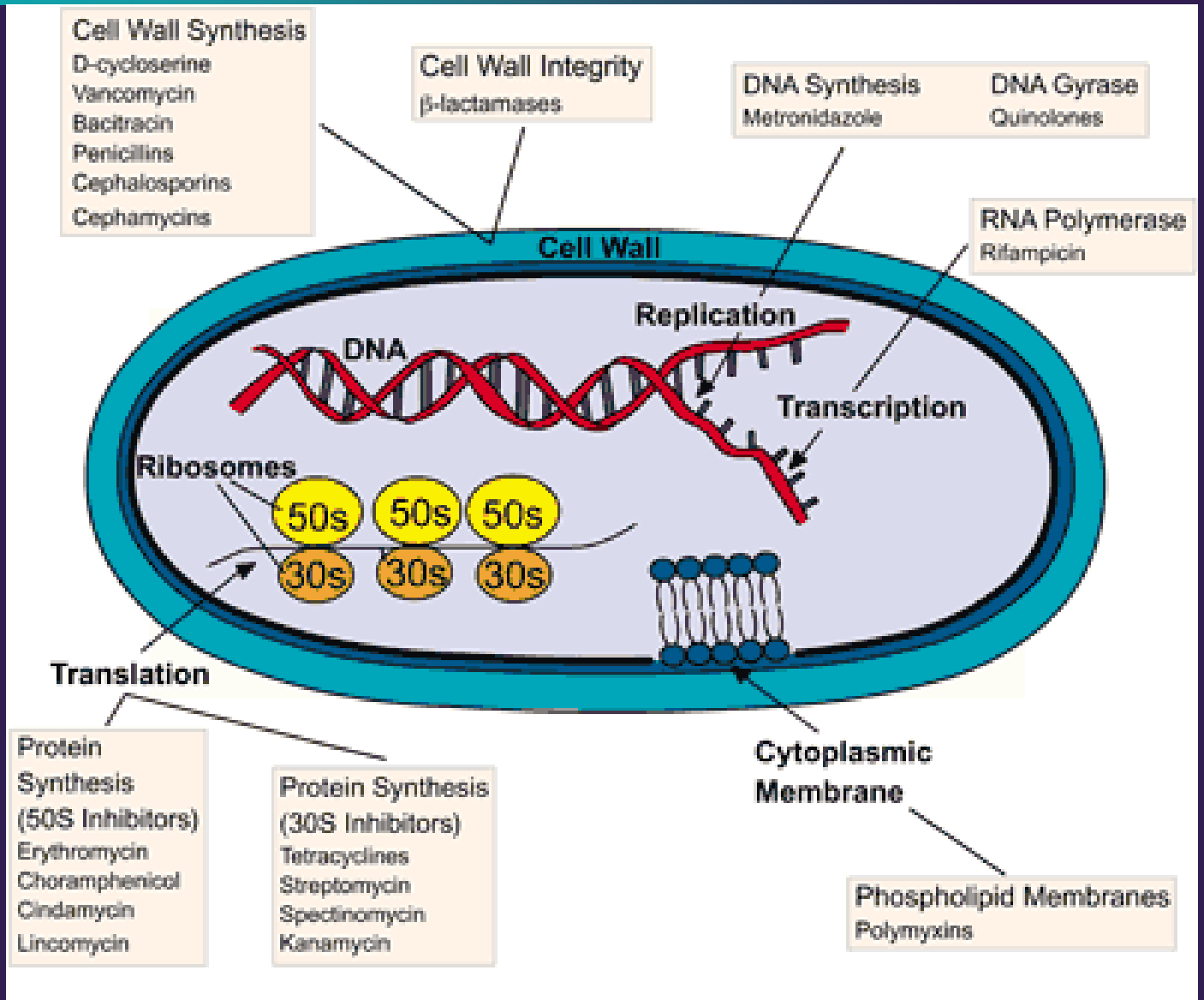
- According to their antimicrobial activity, can be divided into:

1. Bactericidal antibiotics
    1. Cell wall synthesis inhibition
    2. Cell wall alteration
2. Bacteriostatic antibiotics
    1. Protein synthesis (except aminoglycosides)
    2. Nucleic acid synthesis (except quinolones and metronidazole)
    3. Anti-metabolites

Classification of Antibiotics - II



Classification of Antibiotics - III



Vignette 1

- During a check-up for the employment yearly Health Certificate, a 26-year-old man from Puerto Rico was found with a positive VDRL test at 1:320 titers.
- 11 months ago, during the same screening, the patient had a negative VDRL test.
- Upon interview, he recalls an unprotected encounter with a sexual worker about 2 months, after which he had a penile ulcer. He did not seek for medical help because the ulcer was not painful and because it healed spontaneously.
- You request a FTA-ABS test, which is positive.
- The patient has no known drug allergies and is currently asymptomatic

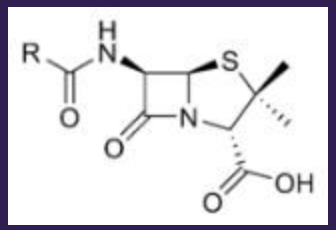
Vignette 1

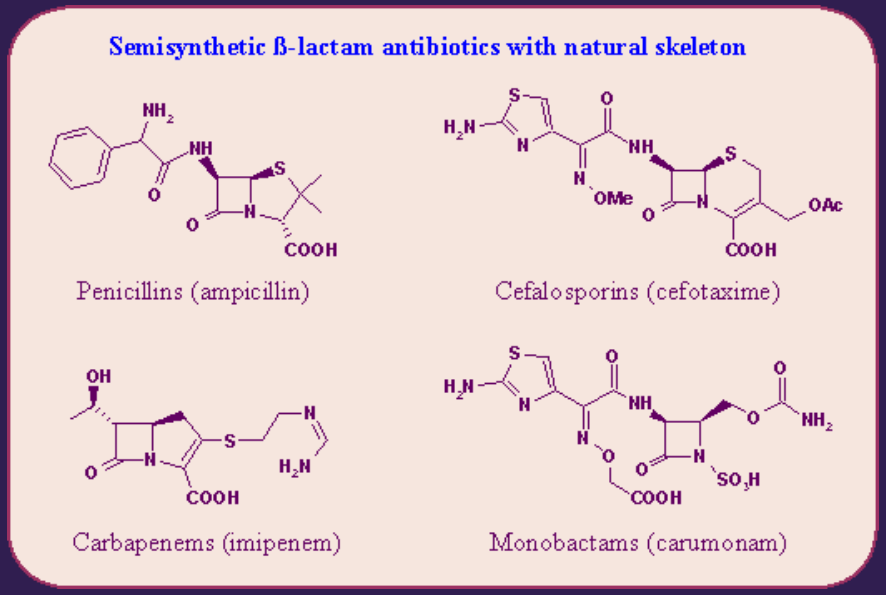
- What would be the best intervention for this patient?
  - A. Oral ciprofloxacin 500 mg twice daily x 14 days
  - B. Oral doxycycline 100 mg twice daily for 7 days
  - C. One dose of intramuscular benzathine penicillin G 2.4 million units
  - D. One dose of oral azithromycin 1g

CELL WALL SYNTHESIS AND INTEGRITY

Beta-lactams

- Beta-lactam antibiotics act at a target called (for some reason!) Penicillin-Binding Proteins (PBP).
- Penicillin-Binding Proteins causes peptidoglycan cross-linking.
- When bacteria is exposed to beta-lactam antibiotic, antibiotic binds to PBP, inhibiting cell wall synthesis and producing toxin release.
- Bacteria die. Hence, beta-lactams are bactericidal.





Cell wall synthesis inhibition: B-Lactam Antibiotics

- Penicillins
  - Natural penicillins (mostly GPC and anaerobes)
  - Amino penicillins (more GNB coverage)
  - Penicillinase – resistant penicillins (anti-Staph, methicillin-suscep)
  - B-lactamase inhibitor and penicillin combination
    - Broad spectrum; Active against B-lactamase-producing organisms
  - NEW! - B-lactamase inhibitor and cephalosporin combination
    - Activity against ESBL-producing GNB and carbapenemase-producing *Klebsiella*
- Cephalosporins – less susceptible to penicillinases
  - 1st Generation
  - 2nd Generation
  - 3rd Generation
  - 4th Generation
  - 5th Generation – anti-MRSA
- Monobactams
- Carbapenems – very broad spectrum

Generation	Gram +	Gram -	*Pseudomonas aeruginosa*	Anaerobes
First	+++	+	0	0/+
Second	++	++	0	++ (cephamycins only)
Third	+	+++	+++ (ceftazidime only)	0/+
Fourth	++	+++	+++	0/+

Adverse Reactions to Beta-Lactams

- Anaphylaxis
- Rash
- Diarrhea
- Platelet dysfunction
- Eosinophilia
- Neutropenia
- Elevated LFT’s

Allergic to PNC?

- The use of cephalosporins can be attempted in patients who had mild skin reactions with penicillin
- Patients who had ANAPHYLAXIS to penicillin can have 10-30% cross-reaction with the use of cephalosporins
  - The higher the generation of cephalosporin, the less is the risk of cross-reaction

Vignette 2

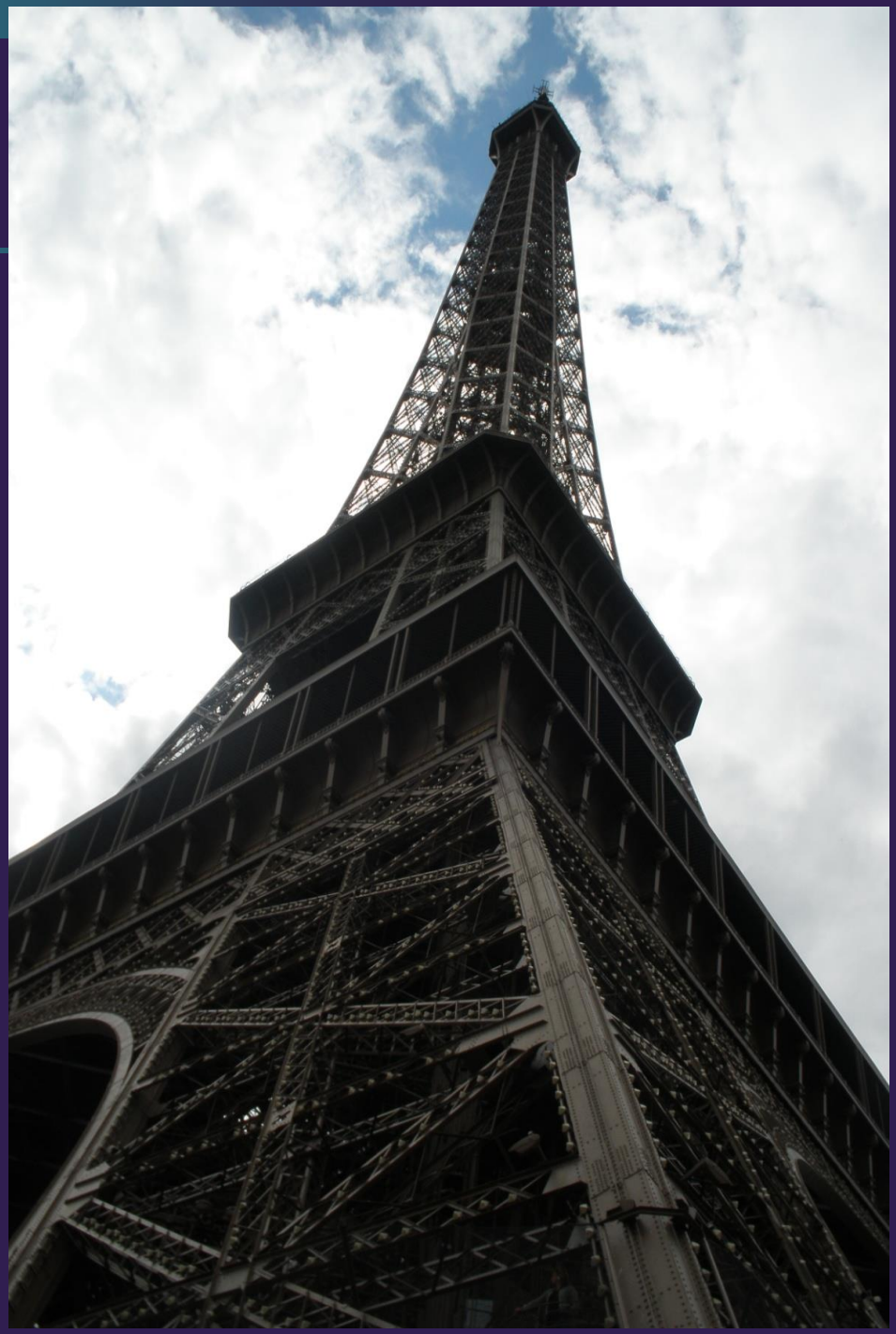
- A 17-year-old male patient has been experiencing skin lesions in his face as shown for the past 6 months.

- He has tried several topical over-the-counter remedies (salicylic acid) without success.

Vignette 2

- Which of the following treatments would be best to both improve the patient's condition and to prevent the emergence of resistance:
  - A. Continue topical salicylic acid alone
  - B. Add erythromycin 2% gel BID
  - C. Add systemic retinoid for 15-20 weeks
  - D. Oral doxycycline 100 mg PO BID + topical benzoyl peroxide

PROTEIN SYNTHESIS INHIBITION



Protein Synthesis Inhibition

- Aminoglycosides
- Tetracyclines
- Clindamycin
- Chloramphenicol
- Macrolides-Streptogramine-Lincosamide
- Ketolides
- Oxazolidones

Aminoglycosides

- Gentamicin
- Tobramycin
- Amikacin
- Streptomycin

- Coverage:
  - Infections Enteric GNB and *Pseudomonas*
  - Synergism for GPC (≥ *Enterococcus*)
  - Antimycobacterial (streptomycin, amikacin)
  - Plague
  - Tularemia
  - Brucellosis

Adverse Events of Aminoglycosides

- Ototoxicity
- Neuromuscular blockade
- Nephrotoxicity
  - Age, dehydration, hepatic dysfunction
  - Drugs: Vanco, Ampho B, Foscarnet, IV Dyes
  - Frequency of dosing and duration of treatment

Tetracyclines

- Doxycycline
- Oxytetracycline
- Minocycline

- Broad Spectrum: GPC, GNB, anaerobes, atypical

- Uses
  - Actinomycosis
  - Bartonellosis
  - Bite Wounds
  - Sexually Transmitted Diseases
  - Leptospirosis
  - Lyme Disease
  - *Plasmodium falciparum*
  - Plague
  - Rickettsial Disease
  - Rat Bite Fever
  - Syphillis
  - Tularemia
  - Vincent's Angina
  - Whipple's Disease
  - Jaws, Pinta
  - Relapsing Fever
  - Psittacosis

Adverse Effects Tetracyclines

- GI Intolerance
- Stains and deforms teeth in children up to 8 years
- Hepatotoxicity
- Candidiasis (thrush and vaginitis)
- Photosensitivity
- Phlebitis with IV injection
- Aggravation of Myastenia Gravis
- Increased Intracranial Pressure

Clindamycin (Cleocin)

- Spectrum:
  - mostly GPC, including MRSA
  - Anti-anaerobic coverage
  - Certain anti-parasitic activity and antifungal activity:
    - Cerebral Toxoplasmosis
    - ⊕ Primaquine for PCP
    - ⊕ Quinine for Babesiosis

Adverse Effects - Clindamycin

- *****Clostridium difficile*** colitis
- Allergic reactions
- Blood dyscrasias
- Esophageal ulceration
- Hepatotoxicity
- Neuromuscular blockade
- Fever
- Metallic taste
- Phlebitis at IV infusion sites

Macrolides

- Erythromycin
- Clarithromycin
- Azithromycin

- Spectrum:
  - some GPC
  - some GNB
  - coverage of atypical organisms

Adverse Effects of Macrolides

- Nausea, vomiting, abdominal pain
- Allergic reactions
- Cholestatic hepatitis
- Sensorineural hearing loss
- Prolongation of QT interval

Vignette 3

- A 23-year-old woman without systemic illnesses presents dysuria, change in urine odor, and an increased urinary frequency.
- She denies fever, low back pain or similar past episodes.
- U/A shows:
  - 48 WBC's, many bacteria, positive nitrites, positive leukocyte esterase, but no casts.
- She is prescribed an antibiotic for uncomplicated urinary tract infection (cystitis).
- 2 days into treatment, she experiences a sudden-onset excruciating ankle pain while doing her daily 3-mile fitness run.

Vignette 3

- She is eventually diagnosed with an Achilles tendon rupture.
- What is the most likely etiology of the tendon rupture in this patient?
  - A) Trimethoprim/sulfamethoxazole
  - B) Nitrofurantoin
  - C) Ciprofloxacin
  - D) Ampicillin

NUCLEIC ACID INHIBITION

Nucleic acid inhibition

- DNA replication
  - 1. Quinolones:
    - a. Bind to DNA gyrase (mostly in gram negative)
    - B. Inhibit topoisomerase IV (mostly in gram positive)
    - Bactericidal
  - 2. Metronidazole:
    - Radicals derived from this antibiotic disrupt bacterial DNA
    - Bactericidal
- RNA synthesis: Prevent transcription at level of RNA synthesis
  - 1. Rifampin
  - 2. Rifabutin
  - 3. Rifapentin (Priftin)

Fluoroquinolones

- First Generation
  - Nalidixic Acid
- Second Generation
  - Norfloxacin
  - Ciprofloxacin
  - Ofloxacin
- Third Generation
  - Levofloxacin
  - Gatifloxacin
  - Gemifloxacin
- Fourth Generation
  - Moxifloxacin
  - Trovafloxacin

1st Generation
Gram-negative activity; urinary tract

2nd Generation
+ Gram-positive activity; systemic

3rd Generation
+ Gram-positive potency;
S pneumoniae

4th Generation
+ Anaerobes

Clinical Uses of Fluoroquinoles

- Urinary Tract Infections
- Prostatitis
- Sexually Transmitted Diseases
- Gastroenteritis
- Intra-abdominal infections
- Respiratory Tract Infections
- Bone and joint infections
- Anthrax
- Typhoid and enteric fever
- Prosthetic joint infections

Adverse Effects of Fluoroquinolones

- Gastrointestinal
  - Nausea, vomiting, diarrhea
- Central Nervous System
  - Dizziness, insomnia, seizures
- Cardiovascular
  - QT_c prolongation
- Hepatic
  - Idiosyncratic hepatitis
- Skin
  - Photosensitivity
- Musculoskeletal
  - Cartilage erosions, tendinitis/tendon rupture

Metronidazole

- Spectrum:
  - Anti-anaerobic
  - Anti-parasitic

- Uses:
  - *Clostridium difficile* colitis
  - Amebiasis, Giardiasis
  - Vaginitis: *Trichomonas, Gardenella*
  - Anaerobic Coverage

Adverse Effects of Metronidazole

- + Alcohol => Disulfiram-like reaction
- Inhibits metabolism of warfarin
- Nausea, vomiting, metallic taste
- Pancreatitis
- Neurotoxicity: Seizures, peripheral neuropathy
- Teratogenicity
- Carcinogenicity

Vignette 4

- A 45-year-old man living with AIDS has experienced shortness of breath, cough, low grade fever during the past 2 weeks.
- On physical examination, respiratory rate is 26 breaths/min and the lungs are clear to auscultation.
- Influenza rapid test is negative.
- ABG's shows pO2 at 53 mmHg.
- He is admitted and started on azithromycin, ceftriaxone, and trimethoprim/sulfamethoxazole, and prednisone.
- 6 days into treatment, he has shown clinical improvement, but creatinine levels have increased to 3.2 mg/dL (from a baseline of 1.2) and his K+ level is now 5.4 mEq/L

Vignette 4

- What is the most likely cause of increased renal parameters in this patient?
  - A) HIV
  - B) Prednisone
  - C) Azithromycin
  - D) Ceftriaxone
  - E) Trimethoprim/sulfamethoxazole

ANTIMETABOLITES

Antimetabolites

- Antibiotics that inhibit certain steps in metabolism include:

1. Sulfamides: inhibit folic acid synthesis
2. Trimethropim: interferes with folic acid metabolism
   -Prevent conversion from dehydrofolate to tetrahydrofolate
3. Dapsone: inhibits folic acid synthesis

Trimethoprim/Sulfamethoxazole

- Spectrum:
  - Some GPC
  - Some GNB
  - Some antiparasitic

- Uses: *Pneumocystis*, alternative for *Listeria*, *Cyclospora* and *Isospora,* UTI, MRSA
- Adverse reactions
  - Rash, SJS, Toxic epidermal necrolysis
  - Pancytopenia
  - Increased creatinine/hyperkalemia

Lessons learned

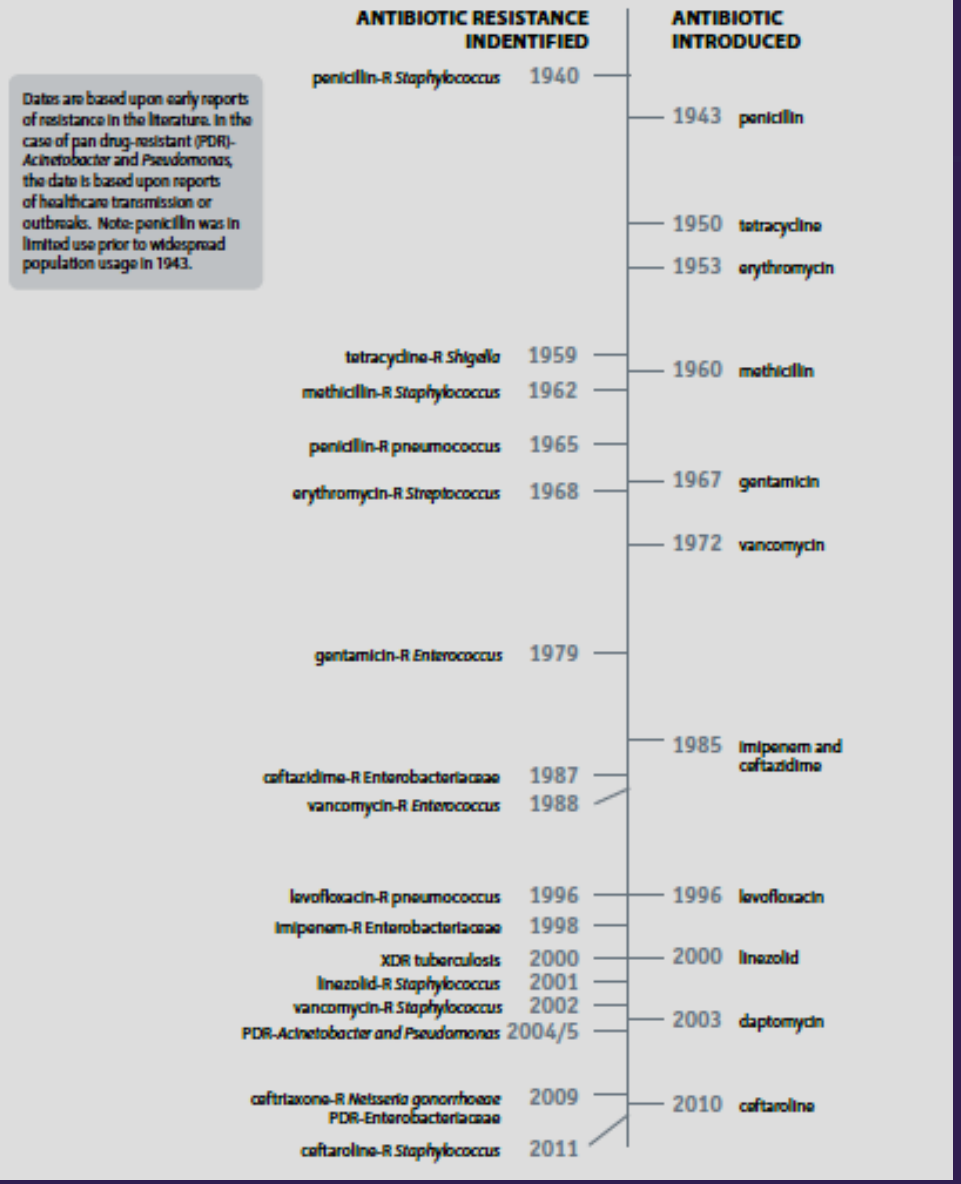
- There is a broad variety of antibacterial agents with different mechanisms of actions and antimicrobial spectrum
- Knowledge of the adverse events of each class of antibiotics will help us anticipate and identify complications during the treatment course
- Antibiotics can be life-saving, but their inappropriate use can lead to antibiotic resistance.

Antibiotic use for specific conditions

- There are numerous indications and approved use of antibiotics for hundreds of conditions.
- Proper use of antibiotics is granted in the setting of probable or confirmed infections by likely susceptible organisms.
- Preventive and empiric use of antibiotic therapy is also contemplated in several settings.

Developing Resistance

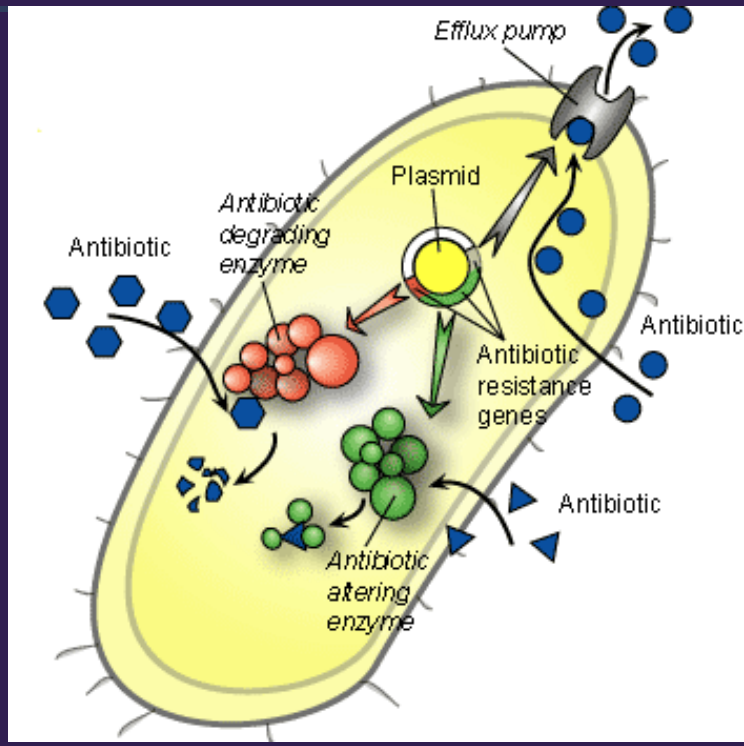
Timeline of Key Antibiotic Resistance Events



CDC. Antibiotic Resistance Threats in the US, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=11

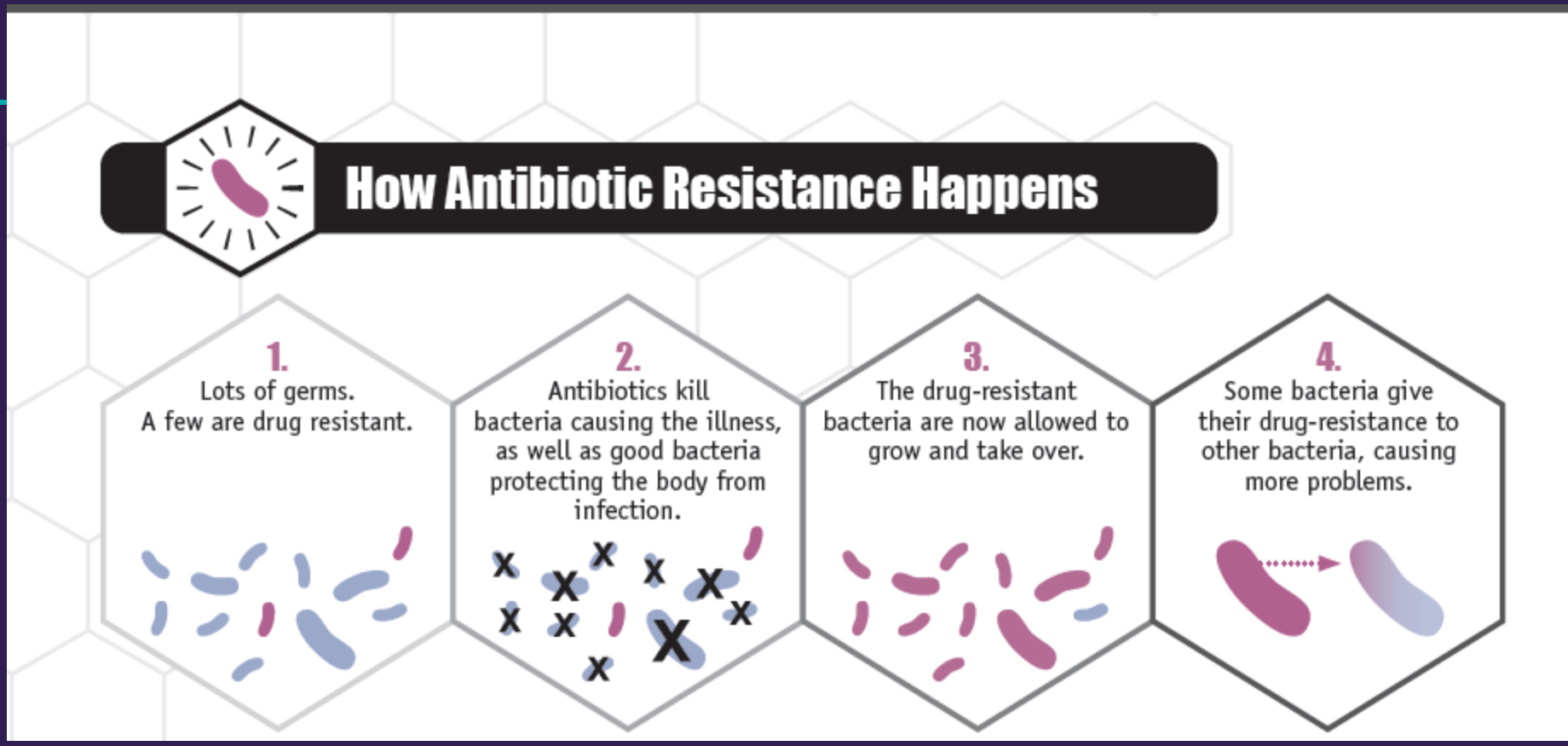
Mechanisms of resistance

- Most, encoded in plasmids:
  - Transmissible
- Efflux pumps
- Antibiotic altering enzymes
- Antibiotic degrading enzymes
  - penicillinases



- Also, change in binding site

Todar, K. Todar's Online Textbook of Bacteriology. 2011. Accessed: Nov 24, 2014. http://textbookofbacteriology.net/resantimicrobial_3.html



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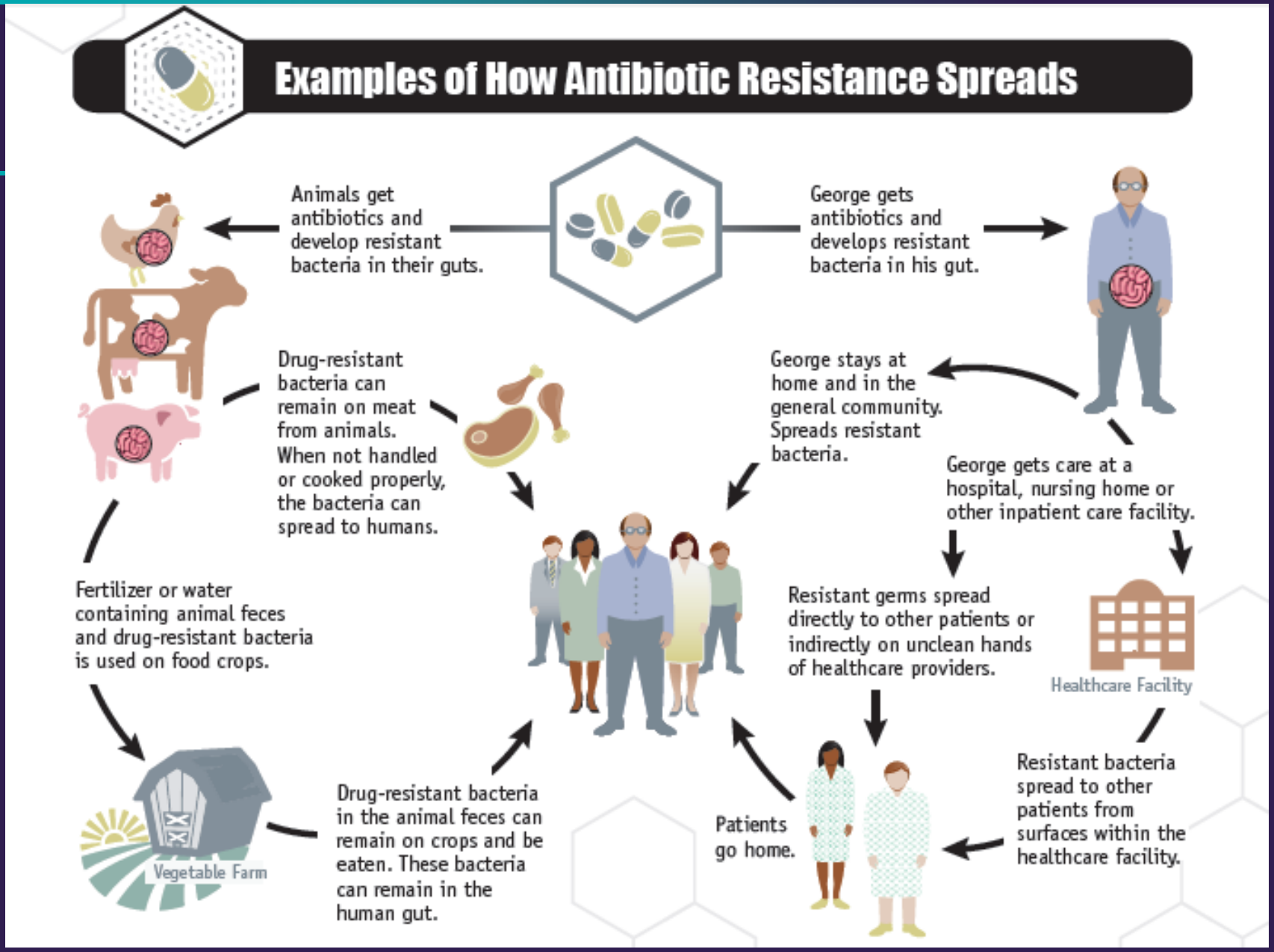

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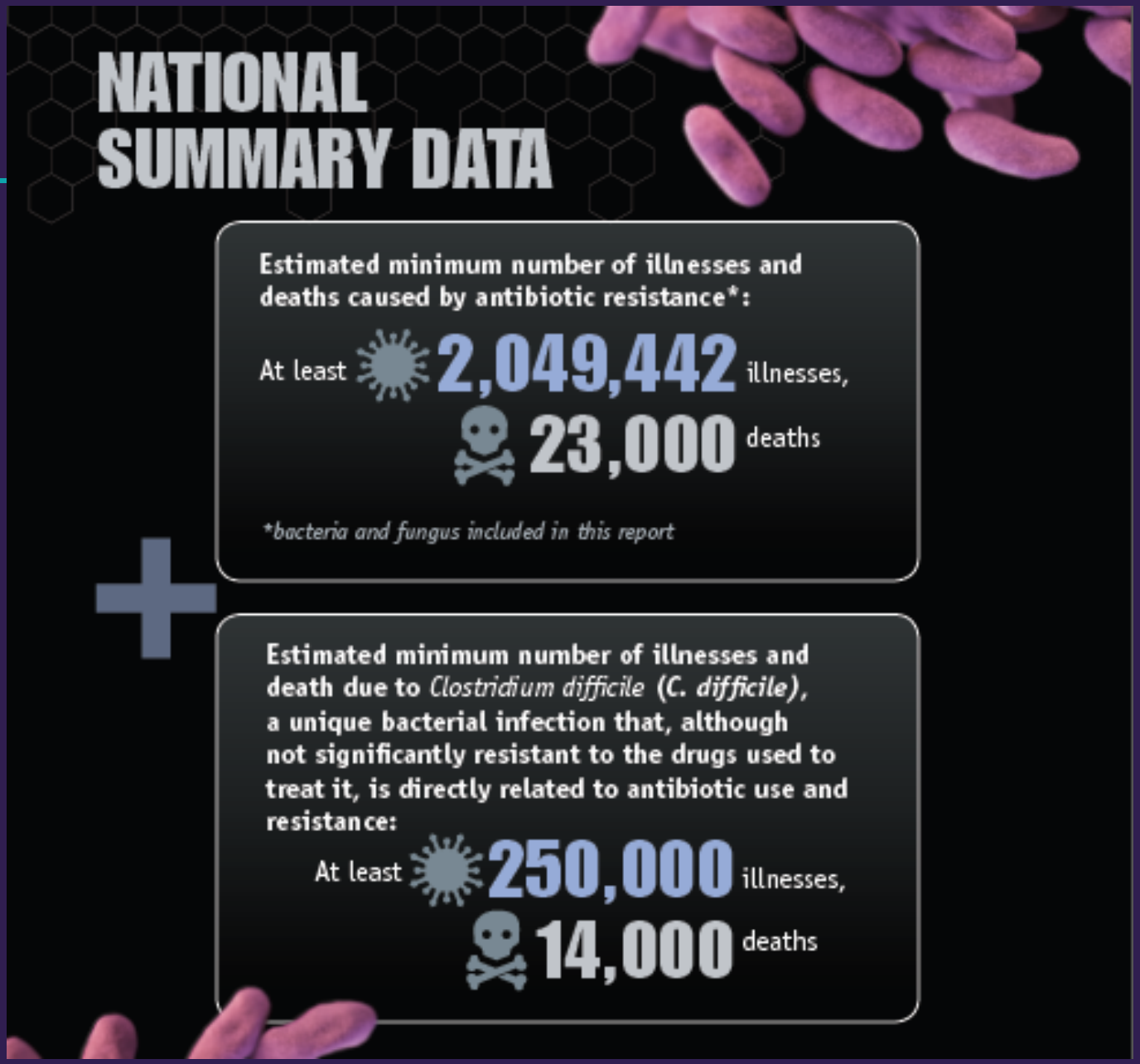

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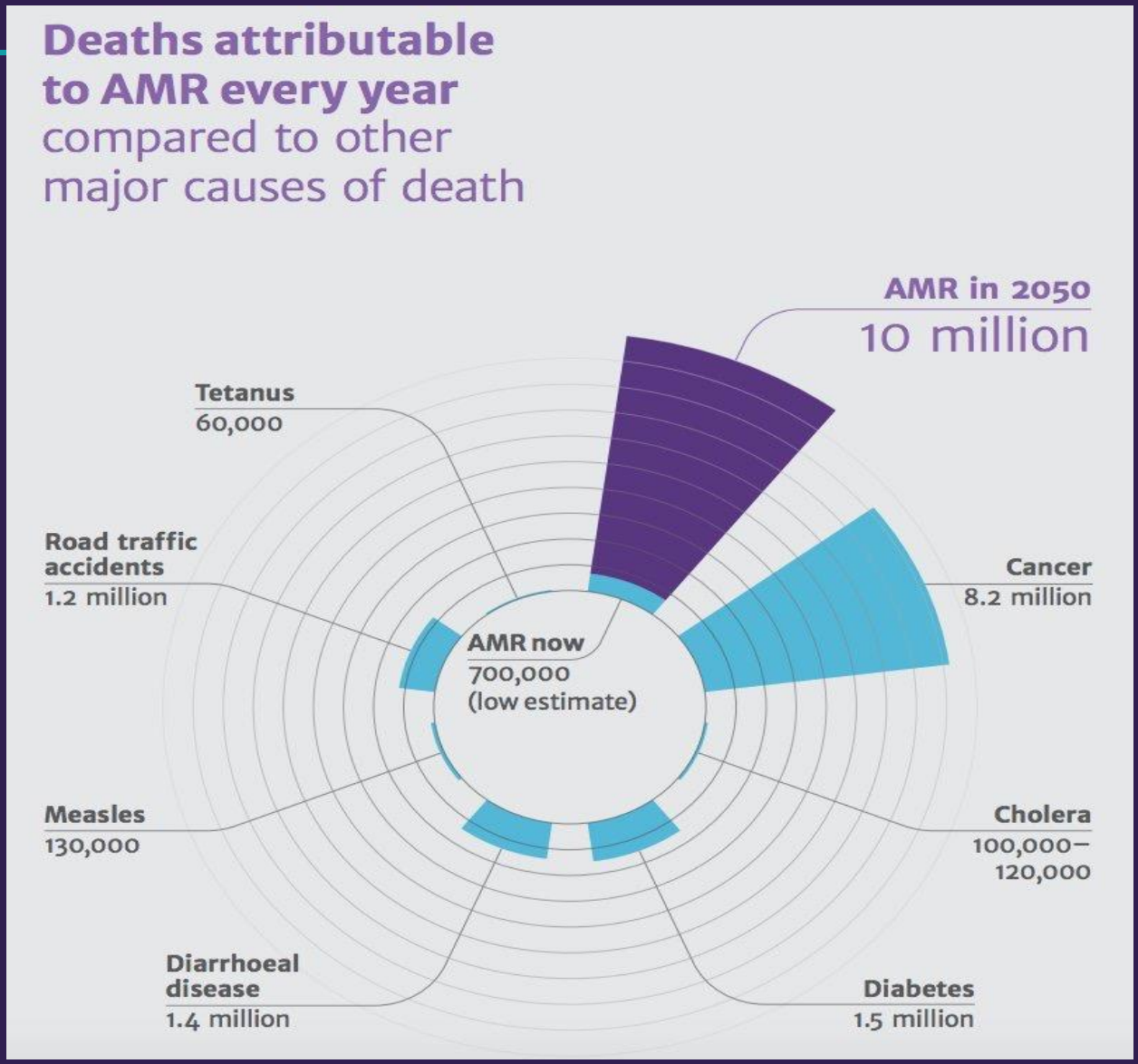
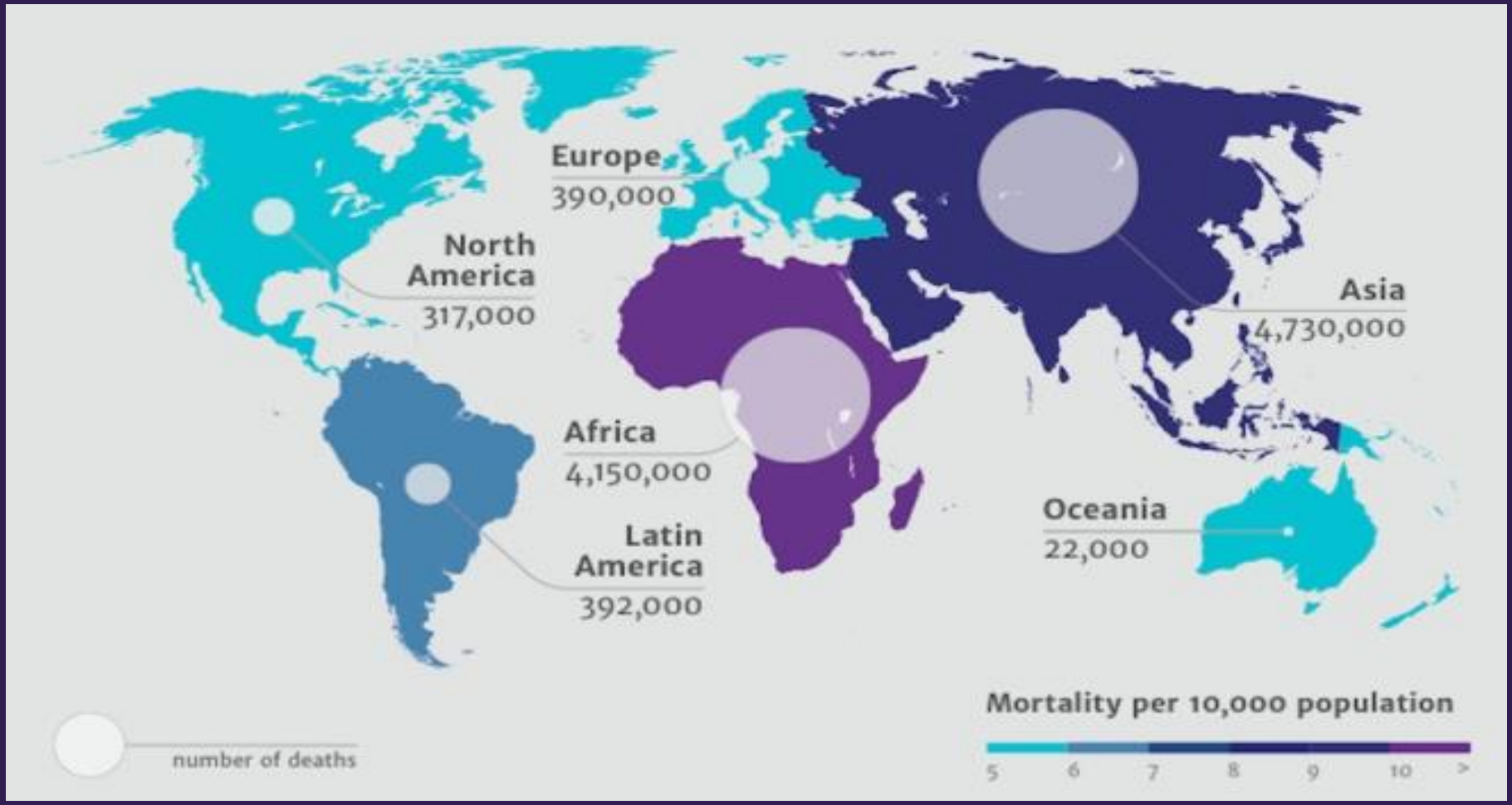
Question

- Which is expected to be the major cause of death by 2050?
  - A. Cancer
  - B. Trauma/Accidents
  - C. Diabetes mellitus
  - D. Resistant bacteria

ANTIMICROBIAL RESISTANCE FORECAST FOR 2050



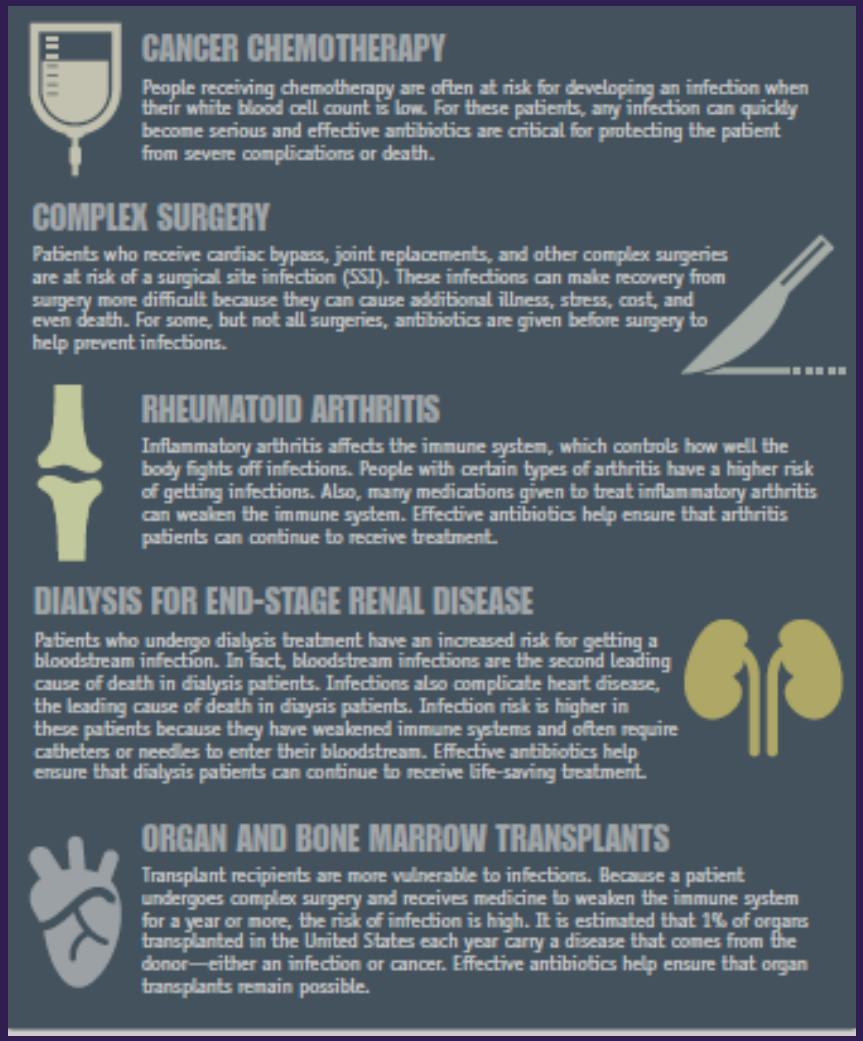
WORLDWIDE MORTALITY FORECAST FOR ANTIMICROBIAL RESISTANCE 2050



Burden of resistance

- Antibiotic-resistant bacteria could lead to the use of:
  - combination therapy
  - alternative agents which could promote more adverse events
  - more expensive options
  - antibiotics which could be less effective => higher mortality

People at high risk



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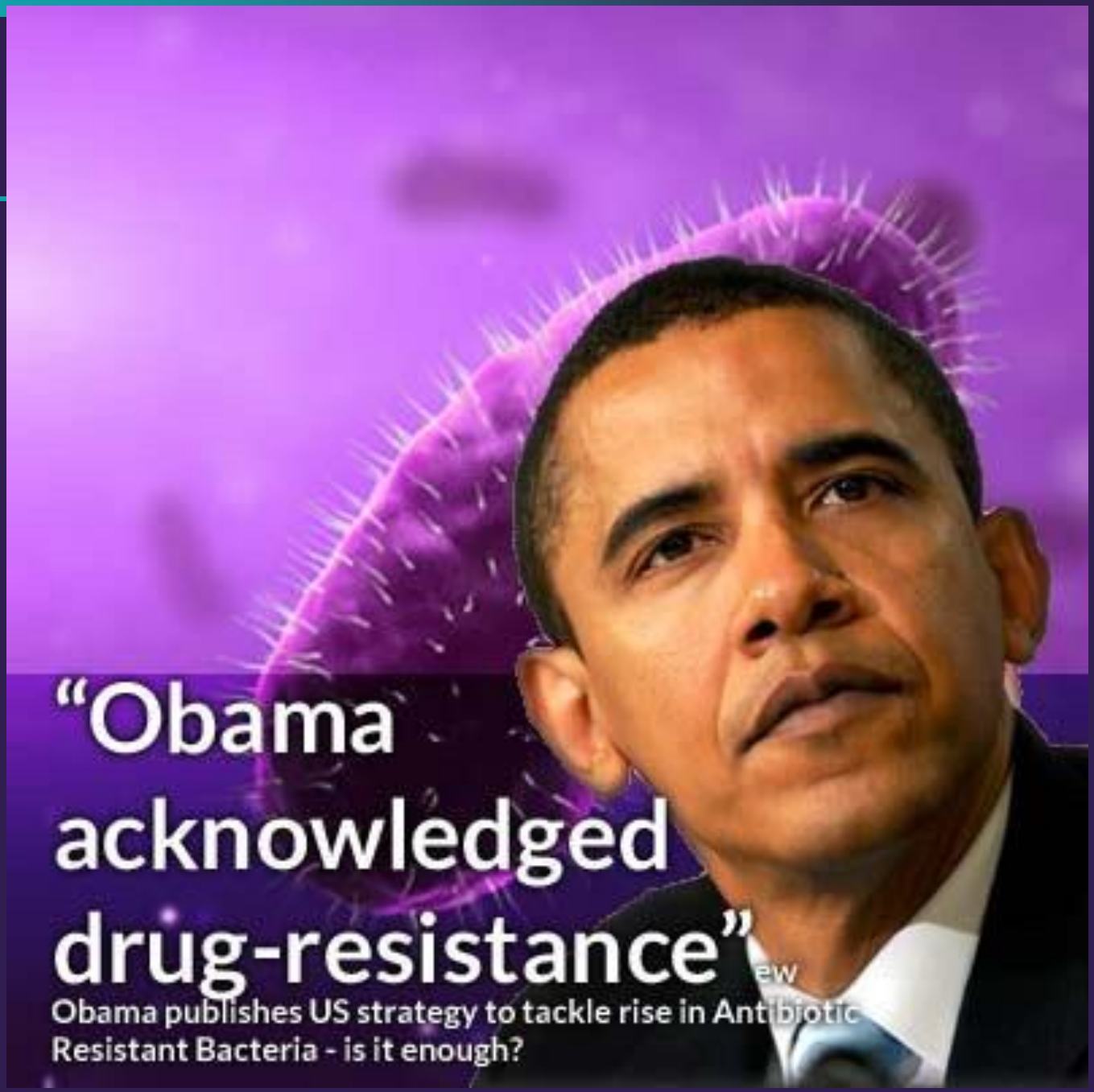
Question

- What is the most important factor contributing to antimicrobial resistance?

Antibiotics contribute to resistance!

- The use of antibiotics is the single most important factor leading to antibiotic resistance around the world.
- Antibiotics are among the most commonly prescribed drugs used in human medicine.
  - up to 50% of all the antibiotics prescribed for people are not needed or are not optimally effective as prescribed.
- Antibiotics are also commonly used in animals to prevent, control, and treat disease, and to promote the growth of food-producing animals.

CDC. Antibiotic Resistance Threats in the US, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=11


"Obama acknowledged drug-resistance"
Obama publishes US strategy to tackle rise in Antibiotic Resistant Bacteria - is it enough?

"The evolution of antibiotic resistance is now occurring at an alarming rate and is outpacing the development of new countermeasures capable of thwarting infections in humans."

- President Barack Obama, 2015

NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Vision: The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic- resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.

September 2014

THE WHITE HOUSE
WASHINGTON

http://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf

Preventing Antibiotic Resistance

1 PREVENTING INFECTIONS, PREVENTING THE SPREAD OF RESISTANCE

Avoiding infections in the first place reduces the amount of antibiotics that have to be used and reduces the likelihood that resistance will develop during therapy. There are many ways that drug-resistant infections can be prevented: immunization, safe food preparation, handwashing, and using antibiotics as directed and only when necessary. In addition, preventing infections also prevents the spread of resistant bacteria.

2 TRACKING

CDC gathers data on antibiotic-resistant infections, causes of infections and whether there are particular reasons (risk factors) that caused some people to get a resistant infection. With that information, experts can develop specific strategies to prevent those infections and prevent the resistant bacteria from spreading.

3 IMPROVING ANTIBIOTIC PRESCRIBING/STEWARDSHIP

Perhaps the single most important action needed to greatly slow down the development and spread of antibiotic-resistant infections is to change the way antibiotics are used. Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe. Stopping even some of the inappropriate and unnecessary use of antibiotics in people and animals would help greatly in slowing down the spread of resistant bacteria. This commitment to always use antibiotics appropriately and safely—only when they are needed to treat disease, and to choose the right antibiotics and to administer them in the right way in every case—is known as antibiotic stewardship.

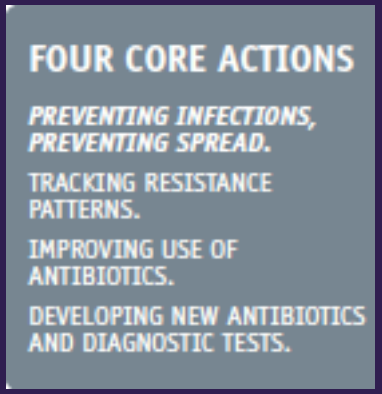
4 DEVELOPING NEW DRUGS AND DIAGNOSTIC TESTS

Because antibiotic resistance occurs as part of a natural process in which bacteria evolve, it can be slowed but not stopped. Therefore, we will always need new antibiotics to keep up with resistant bacteria as well as new diagnostic tests to track the development of resistance.

CDC. Antibiotic Resistance Threats in the US, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=11

Preventing Antibiotic Resistance

- Promoting proper handwashing
- Vaccination
  - *S. pneumonia*
- Adhering to Treatment Guidelines
  - *Mycobacterium tuberculosis*
- Promotion of Safer Sex
  - *Neisseria gonorrhoeae*



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2. TRACKING RESISTANCE PATTERNS

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FOUR CORE ACTIONS

PREVENTING INFECTIONS, PREVENTING SPREAD.

TRACKING RESISTANCE PATTERNS.

IMPROVING USE OF ANTIBIOTICS.

DEVELOPING NEW ANTIBIOTICS AND DIAGNOSTIC TESTS.

CDC's Antibiotic Resistance and Antibiotic-Resistant Infections Tracking Platform

Tracking Networks	Data Collected	Resistant Bacteria/Fungus[3]
EIP Emerging Infections Program There are three main programs within the EIP: ■ **ABCs:** Active Bacterial Core surveillance ■ **HAIC:** Healthcare-Associated Infections-Community Interface ■ **FoodNet:** Foodborne Diseases Active Surveillance Network	A network of public health-academic-hospital collaborations in 10 states. It provides access to bacterial and fungal samples for testing and detailed clinical case data. The three main programs within EIP collect different types of resistance data: ■ ABCs provides clinical information and resistance data for bacteria that cause infections predominately in the community. ■ The HAIC provides clinical information and resistance data for bacteria and fungi that cause infections at the intersection of healthcare and the general community. ■ FoodNet supplies clinical and epidemiologic data on some human isolates in the National Antimicrobial Resistance Monitoring System (NARMS).	**ABCs:** *Streptococcus pneumoniae* Groups A and B *Streptococcus* Methicillin-resistant *Staphylococcus aureus* **HAIC:** *C. difficile* *Candida* (a fungus) Carbapenem-R Enterobacteriaceae MDR *Acinetobacter* FoodNet: (see NARMS list)
NARMS National Antimicrobial Resistance Monitoring System	A national public health surveillance system that tracks changes in the susceptibility of foodborne and other enteric bacteria to antibiotics of human and veterinary medical importance. NARMS is a collaboration among CDC, FDA, USDA, and state and local health departments. CDC tests bacterial isolates from humans, while FDA and USDA test isolates from retail meats and food animals.	*Salmonella* *Campylobacter* *Shigella*

CDC. Antibiotic Resistance Threats in the US, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=11

FOUR CORE ACTIONS

PREVENTING INFECTIONS, PREVENTING SPREAD.

TRACKING RESISTANCE PATTERNS.

IMPROVING USE OF ANTIBIOTICS.

DEVELOPING NEW ANTIBIOTICS AND DIAGNOSTIC TESTS.

Tracking Networks	Data Collected	Resistant Bacteria/Fungus[3]
NHSN National Healthcare Safety Network	A system that collects and provides data on infections and drug-resistance in healthcare settings. Since NHSN collects data directly from healthcare facilities, it can provide facility-level information on healthcare-associated infections and antibiotic resistance (and in the future, on antibiotic use).	*Staphylococcus aureus* *Enterococcus* Enterobacteriaceae *Acinetobacter* *Pseudomonas aeruginosa* *Candida* (a fungus)
GISP Gonococcal Isolate Surveillance Program	A program to track antibiotic resistance data for gonococcal isolates. Isolates are collected from sexually transmitted disease clinics in approximately 28 cities.	*Neisseria gonorrhoeae*
NTSS National Tuberculosis Surveillance System	National Electronic Disease Surveillance System (NEDSS)-based reporting of tuberculosis cases including resistance data. Public health departments from 50 states and the US territories contribute data.	*Mycobacterium tuberculosis*

CDC. Antibiotic Resistance Threats in the US, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=11

Question

- What can be done to diminish antimicrobial resistance?
  - A. Nothing
  - B. Wait until the CDC and the White House take further actions
  - C. Stop using antibiotics
  - D. Use antibiotics wisely

FOUR CORE ACTIONS

PREVENTING INFECTIONS, PREVENTING SPREAD.

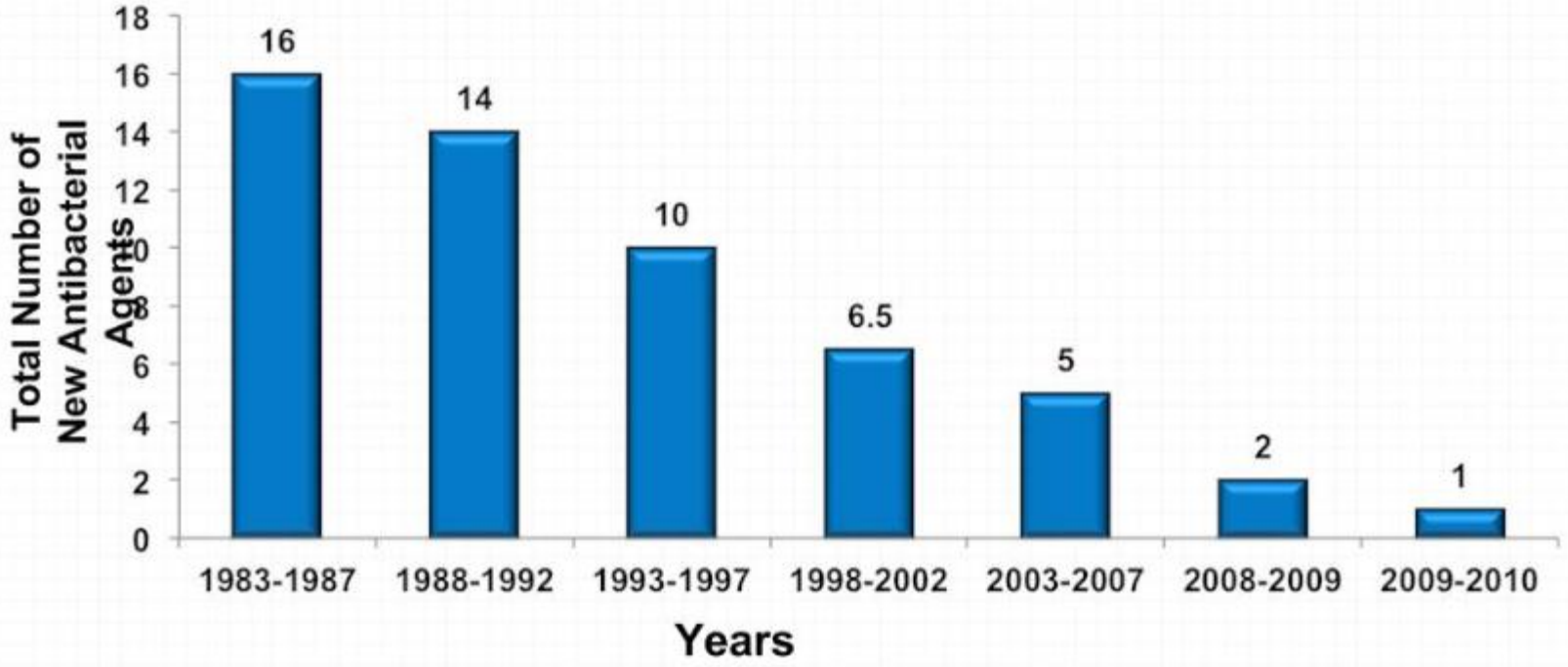
TRACKING RESISTANCE PATTERNS.

IMPROVING USE OF ANTIBIOTICS.

DEVELOPING NEW ANTIBIOTICS AND DIAGNOSTIC TESTS.

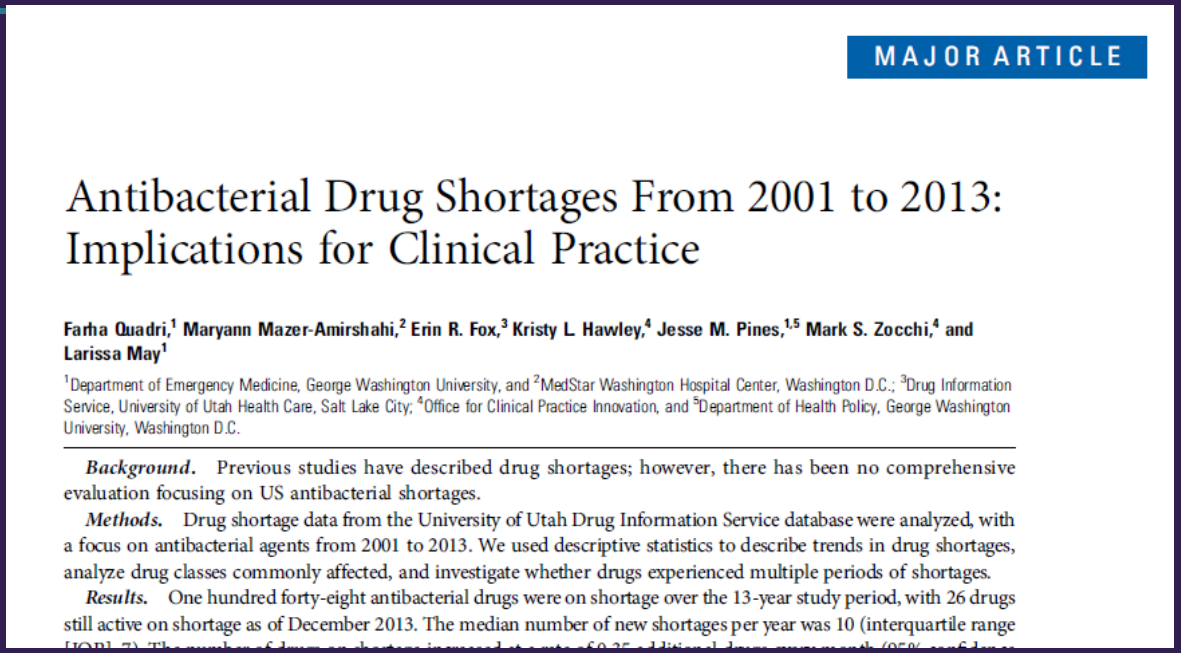
Antimicrobial stewardship

Declining Antibacterial Approvals (1983-2010)[1-3]



1. Spellberg B et al. *Clin Infect Dis*. 2008;46(2):155-164.
2. Theravance and Astellas announce FDA approval of VIBATIV(TM) (telavancin) for the treatment of complicated skin and skin structure infections [press release]. South San Francisco, CA: Theravance Inc; September 11, 2009.
3. Forest announces FDA approval of Teflaro™ (ceftaroline fosamil) for the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infection [press release]. New York, NY: Forest Laboratories, Inc; October 29, 2010.

Antibiotic shortage



MAJOR ARTICLE

Antibacterial Drug Shortages From 2001 to 2013: Implications for Clinical Practice

Farha Quadri,[1] Maryann Mazer-Amirshahi,[2] Erin R. Fox,[3] Kristy L. Hawley,[4] Jesse M. Pines,[1,5] Mark S. Zocchi,[4] and Larissa May[1]

[1]Department of Emergency Medicine, George Washington University, and [2]MedStar Washington Hospital Center, Washington D.C.; [3]Drug Information Service, University of Utah Health Care, Salt Lake City; [4]Office for Clinical Practice Innovation, and [5]Department of Health Policy, George Washington University, Washington D.C.

Background. Previous studies have described drug shortages; however, there has been no comprehensive evaluation focusing on US antibacterial shortages.

Methods. Drug shortage data from the University of Utah Drug Information Service database were analyzed, with a focus on antibacterial agents from 2001 to 2013. We used descriptive statistics to describe trends in drug shortages, analyze drug classes commonly affected, and investigate whether drugs experienced multiple periods of shortages.

Results. One hundred forty-eight antibacterial drugs were on shortage over the 13-year study period, with 26 drugs still active on shortage as of December 2013. The median number of new shortages per year was 10 (interquartile range

- "Analyzing data from the University of Utah Drug Information Service database, a national database of drug shortages, the researchers found that 148 antibiotics experienced shortages during the study period, with an upward trend starting in 2007."
- "Thirty-two antibiotics (22 percent) experienced multiple shortages, with a median duration of more than six months. At the end of the study period in December 2013, 26 antibiotics were still in short supply or not available."

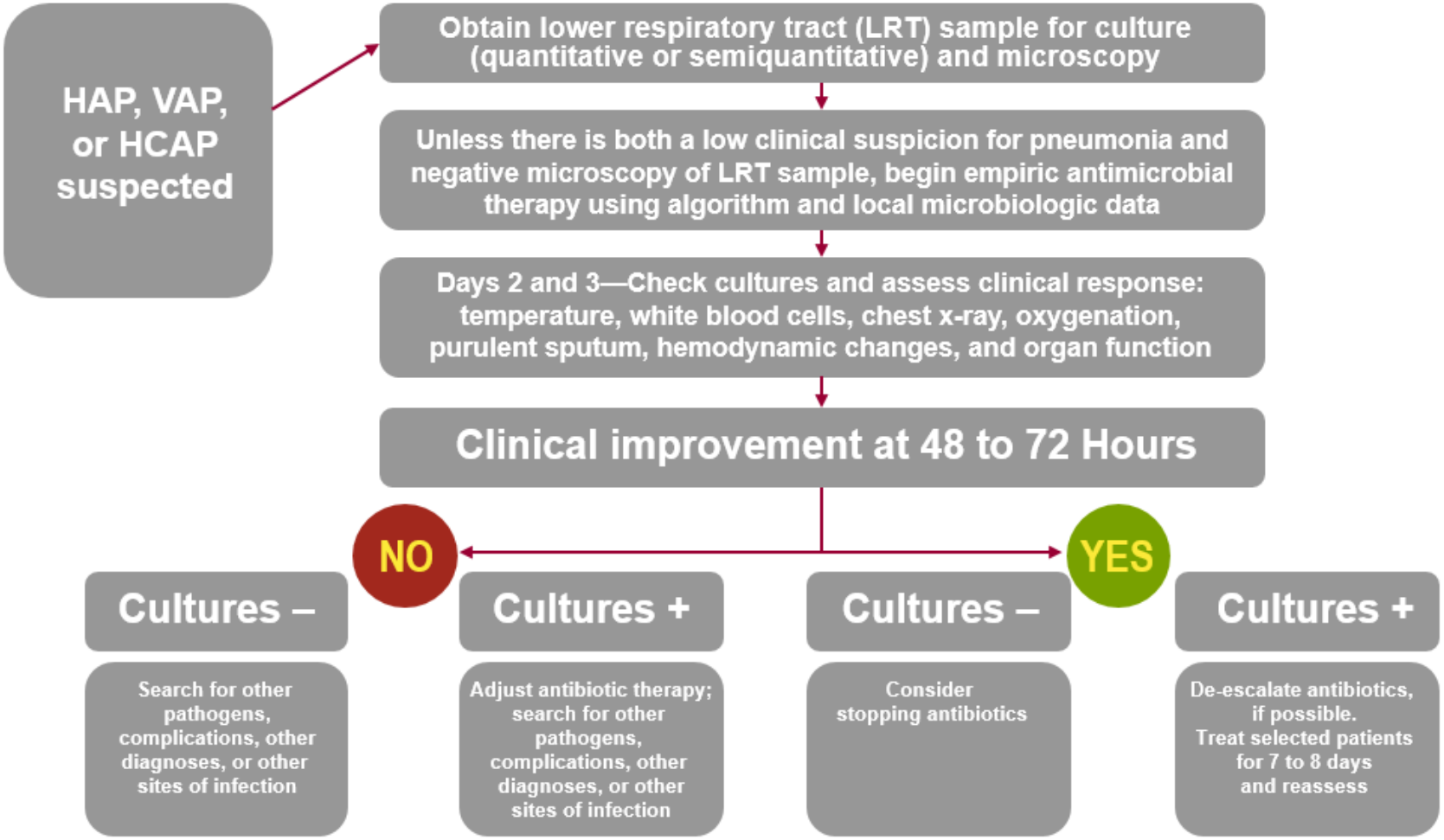
Antibiomicrobial stewardship

- Multidisciplinary intervention that involves:
  - Selection of appropriate agents
  - Correct dosing
  - Adequate route and duration
  - Marriage between infection control and antimicrobial management
  - Effective de-escalation (when feasible)

De-escalation

- Only possible when:
  - Appropriate broad spectrum antibiotic therapy is initiated
  - Adequate cultures are obtained
  - Effective laboratory resources are available
  - Rapid flow of information occurs

ATS/IDSA Guidelines: Initial Management Strategies for Patients With Suspected HAP, VAP, or HCAP



ATS=American Thoracic Society; IDSA=Infectious Diseases Society of America; HAP=hospital-acquired pneumonia; VAP=ventilator-associated pneumonia; HCAP=healthcare-associated pneumonia.

The provision of this information is not meant to imply or otherwise suggest that ZYVOX® (linezolid) should be used to treat each of these infections or microorganisms. Pfizer recommends that ZYVOX be used only in accordance with its approved indications.

Adapted from American Thoracic Society/Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2005;171:388-416.

How to implement an Antimicrobial Stewardship Program?

EIGHT KEY STEPS
for implementing an Antimicrobial Stewardship Program (ASP)

1. Assess the motivations
2. Ensure accountability and leadership
3. Set up structure and organization
4. Define priorities and how to measure progress and success
5. Identify effective interventions for your setting
6. Identify key measurements for improvement
7. Educate and Train
8. Communicate

1. Assess the motivations

- **Analyse your situation** and what problems you want to address. There are many international guidelines available (see page 38), but you will need to adapt them to your local situation.
- Define **where you are** and **where you want to go**, with **quantitative figures**. One of the ways of obtaining these data is to measure the quantity and quality of antibiotic use (see Chapter 6).
- What can be implemented will depend on local needs/issues, geography, available skills/expertise and other resources.

For example, **easier or less costly approaches** can include:

- Simple clinical algorithms
- Prescribing guidance for treatment, surgical prophylaxis
- Intravenous (IV) to oral conversion
- Provision of microbiological support
- Restricting availability of certain antibiotics (formulary restriction)
- Automatic therapeutic substitution
- IV antimicrobial batching
- Promoting education.

[Gaff et al., 2012]

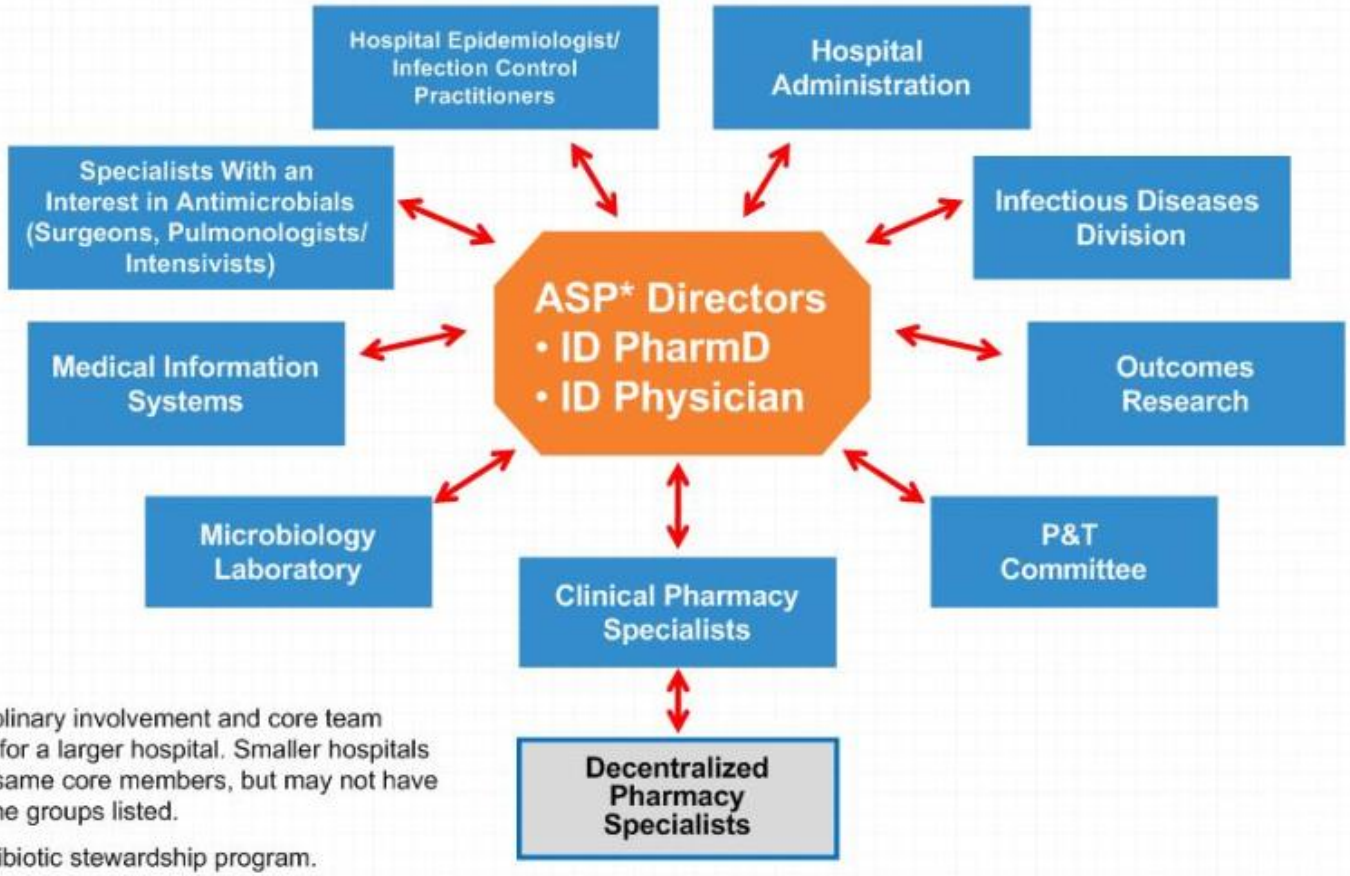
2. Ensure accountability and leadership

To ensure a successful Antimicrobial Stewardship Program:

- The program should be supported by the **senior hospital management**, who are accountable for the outcomes.
- A **team of people and resources** should be allocated by the head of the organization to implement and evaluate the program.
- The ASP team members must possess **power, expertise, credibility and leadership**. These individuals need to convince managers and healthcare staff of the added value of the program.

A key component of a stewardship program is **leadership and culture of antibiotic use**. This can be set out as a **driver diagram** (see pages 14 and 16 for more details).

Antibiotic Stewardship Team Interaction



Multidisciplinary involvement and core team members for a larger hospital. Smaller hospitals need the same core members, but may not have some of the groups listed.

*ASP=antibiotic stewardship program.

Figure reprinted from *Diagnostic Microbiology and Infectious Disease*, Vol 61, Owens RC Jr, Antimicrobial stewardship: concept and strategies in the 21st century, pp 110-128, copyright 2008 with permission from Elsevier.

IDSA Guidelines. *CID* 2007; 44:159-77.

Antimicrobial Stewardship Program

Key Elements	Core Strategies	Supplementary Strategies
Multidisciplinary Team	Restriction and/or pre-authorization	Guidelines / Order Forms
Collaboration and Support	Prospective Audit with Intervention and Feedback	De-escalation or Streamlining
Education		Dosage Optimization
Microbiology		Re-evaluation / Automatic Stop Orders
Information Technology		IV to PO
		Antimicrobial Cycling and Mixing

Antimicrobial stewardship programs (ASP)

CDC Recommends All Nursing Homes Implement Core Elements to Improve Antibiotic Use

Urged to implement at least one core element immediately

Press Release

For Immediate Release: Tuesday, September 15, 2015

Contact: Media Relations

(404) 639-3286

New recommendations from the Centers for Disease Control and Prevention (CDC) advise all nursing homes to improve antibiotic prescribing practices and reduce their inappropriate use to protect residents from the consequences of antibiotic-resistant infections, such as *C. difficile*.

- "The Centers for Medicare & Medicaid Services (CMS) recently proposed a rule that would require long-term care facilities to incorporate an antibiotic stewardship program, including antibiotic use protocols and antibiotic monitoring, into their infection prevention and control program."

Improving diagnostic tests

- Procalcitonin as a biomarker in the diagnosis and management of sepsis[1,2]
- PCR for diagnosis of Tb vs mycobacterial culture
- Rapid diagnostic test for *Strep* throat[3]
- RT PCR for the detection of health-care associated bloodstream infections in critical care[4]
- Depressed monocytic activity as a marker of sepsis[5]
- Lactate levels as a marker of hypoperfusion

[1]Riedel S. *Diagn Microbiol Infect Dis*. 2012 Jul; 73(3): 221-7.
[2]Schuetz P et al. *Cochrane Database Syst Rev*. 2012 Sep 12;9:CD007498.
[3]Lean WL. *Pediatrics*. 2014 Oct;134(4):771-81
[4]Warhurst G et al. *Health Technol Assess*. 2015 May;19(35):1-142.
[5]Bhardwaj P et al. *J Lab Physicians*. 2015 Jan-Jun;7(1):26-31

Educating patients

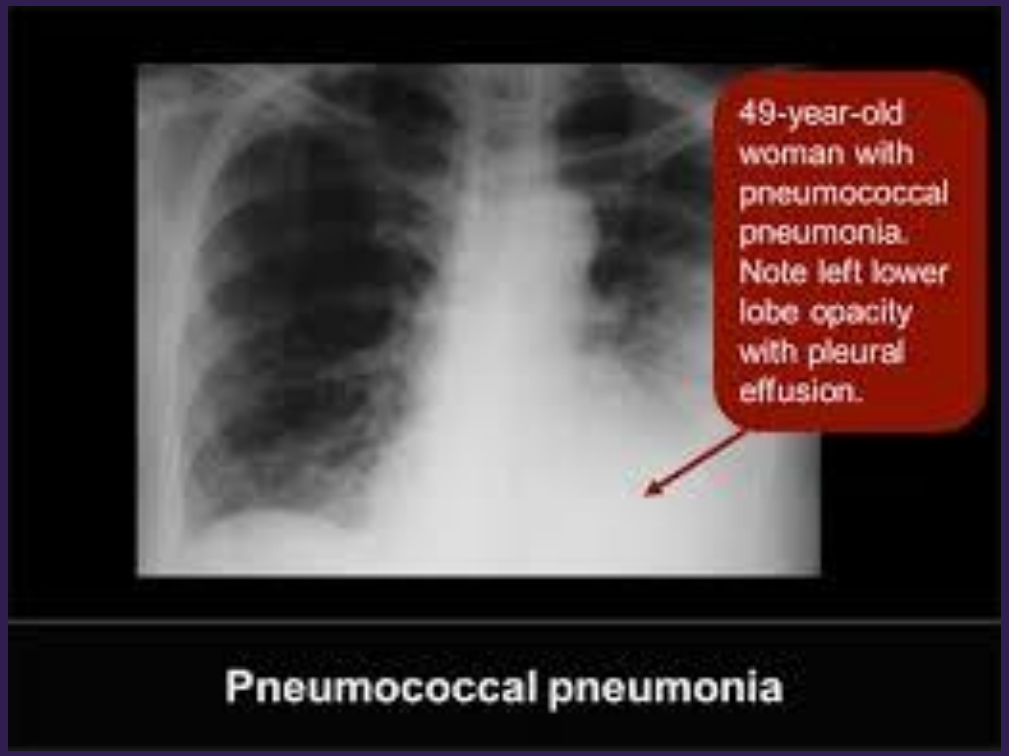
- Antibiotics are required only for bacterial infections
- Antibiotics should only be taken by a specific patient when prescribed for that patient
- Patients should be instructed to take the antibiotics as indicated for the complete course

Conclusions

- Antibiotics can be life-saving, but their inappropriate use can lead to antibiotic resistance.
- Antibiotic resistance has a high impact on morbility, mortality and costs
- An interdisciplinary approach can diminish antibiotic resistance

Vignette 1

- A 49-year-old woman with bronchial asthma is admitted with shortness of breath, sputum production, fever (39 degrees), and leukocytosis (22,000 WBC's).
- Her Chest X-ray was as follows:



Vignette 1

- She underwent a bronchoscopy and was started on ceftriaxone, vancomycin and azithromycin.
- Two days later, she has no fever, sputum production has decreased and WBC are now at 9,000 cells.
- Culture from bronchoscopy reveals a *Streptococcus pneumonia* with the following susceptibility:
  - ampicillin S
  - erythromycin R
  - cefazolin S
  - cefotaxime S
  - vancomycin S

Vignette 1

- What is the most appropriate action now?
  - A. Continue current therapy
  - B. Discontinue cetriaxone
  - C. Discontinue azithromycin and vancomyin
  - D. Switch from vancomycin to linezolid

Vignette 1: Learning Point

- De-escalate if the patient has improved in 48-72 hours and results from appropriate cultures are available

Conclusions

- An interdisciplinary approach, such an antibiotic stewardship team, can diminish antibiotic resistance

“For better or worse, life would not be the same without microbes”…