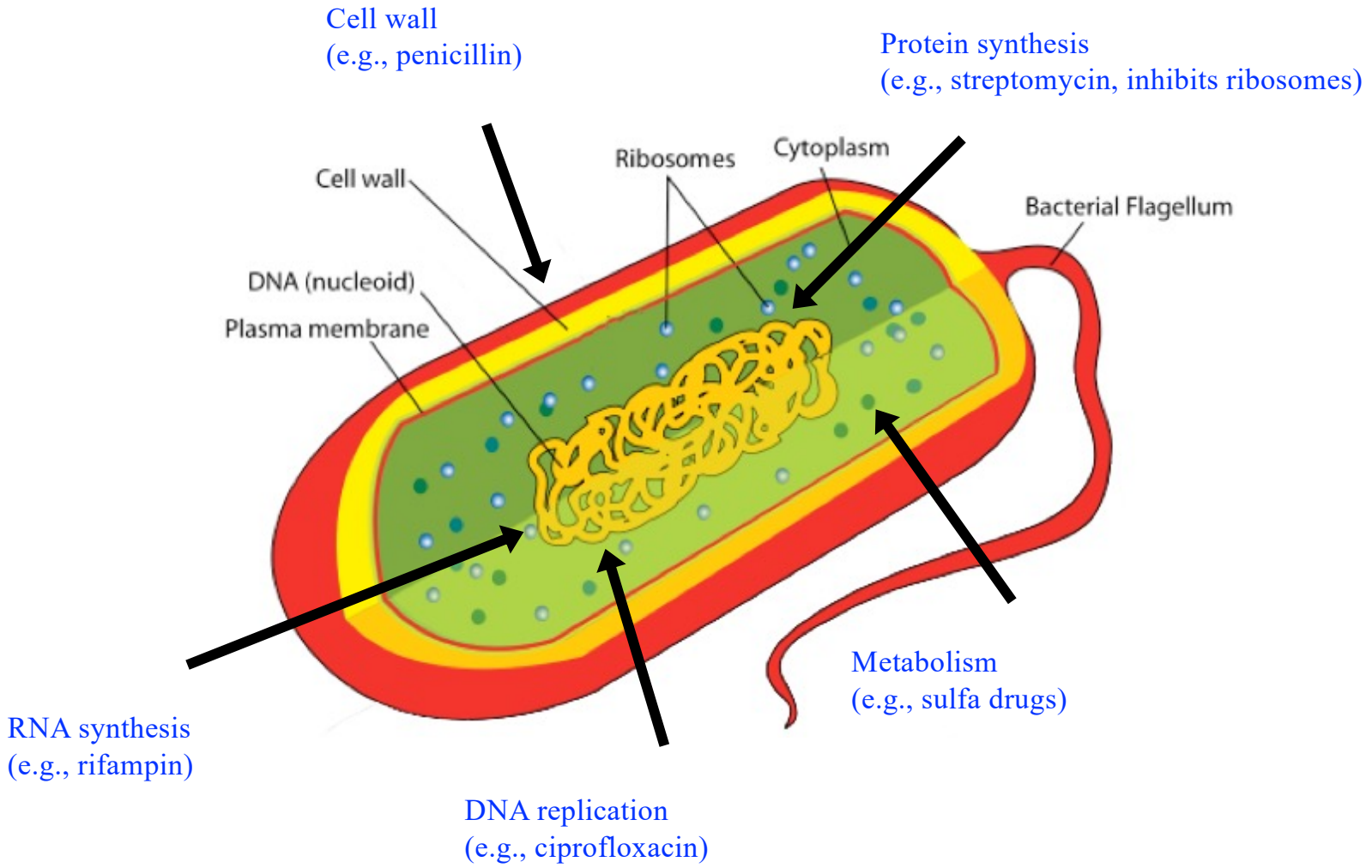
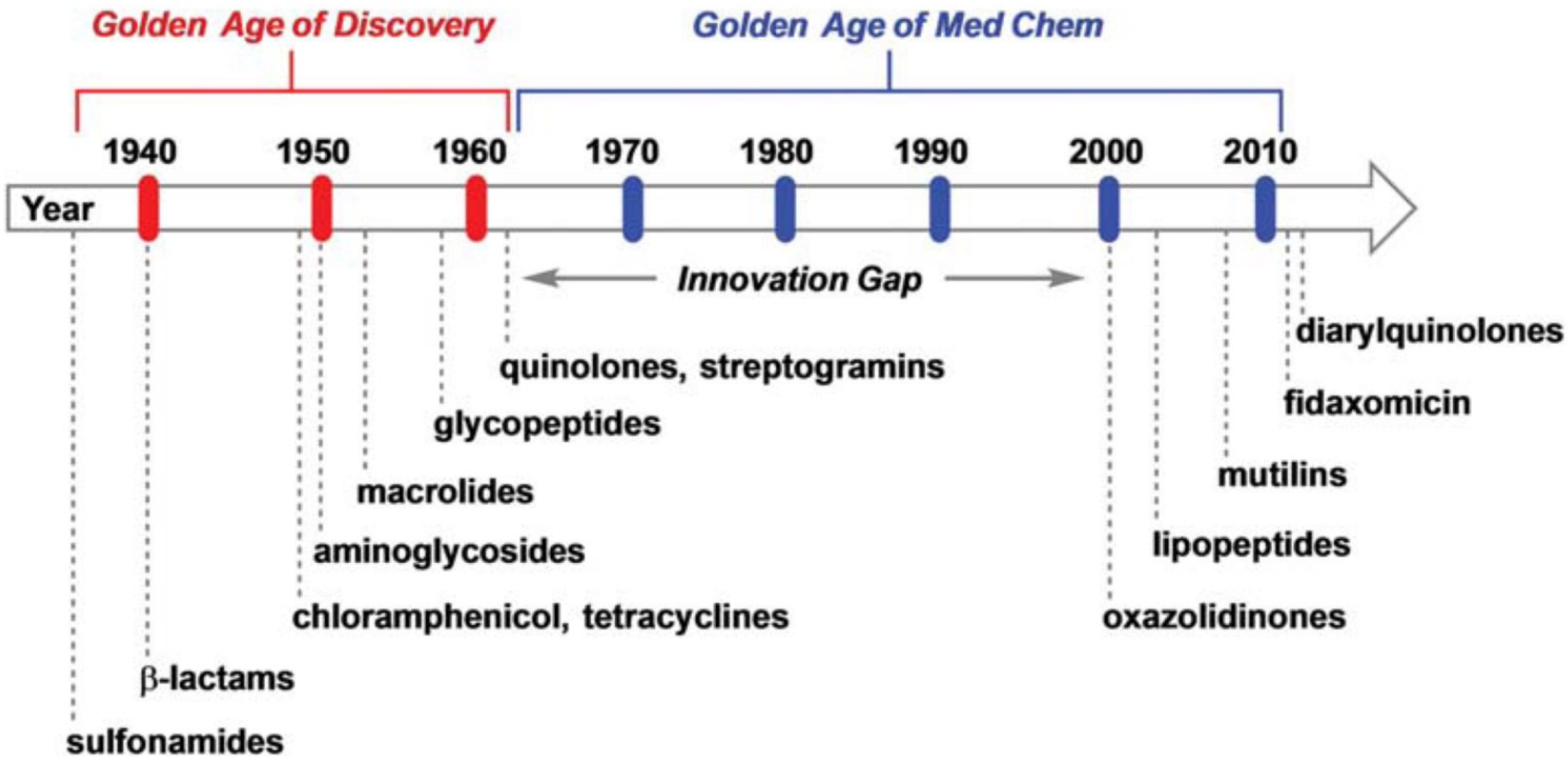
What do antibiotics target in bacteria?

Easy answer is they target essential features required for growth



History of antibiotic discovery

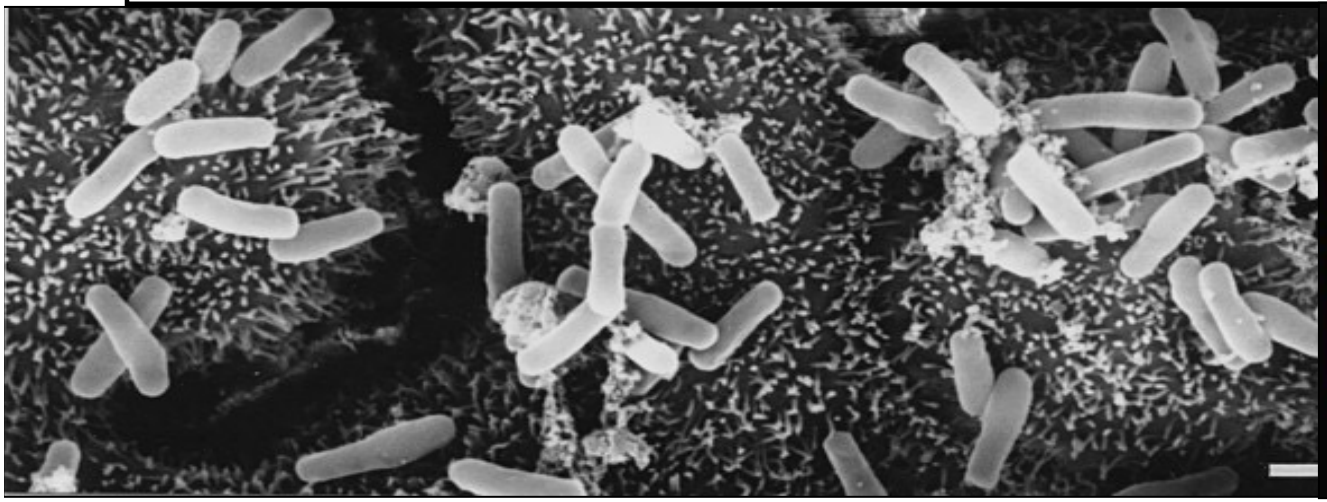


The golden age of antibiotic discovery encompassed 1940 to 1960, when most of the classes still in use today were introduced. The golden age of medicinal chemistry has ensued over the subsequent 50 years, involving tailoring of the periphery of each major antibiotic class while leaving the core scaffold intact and functional.

Antibiotics are great, but....

Antibiotic use can actually increase the chance of getting certain infections.

Clostridium difficile, an “opportunistic infection”, causes post-antibiotic diarrhea and intestinal pain.



C. difficile on epithelial cells

Intestinal inflammation caused by C. difficile

C. difficile infection can be a life-threatening inflammation of the colon.

Why does C. difficile disease increase after antibiotic use?

Antibiotics are not very selective

Our normal microbiota function to keep pathogens at bay (metabolic/space competition, shapes immune system)

Antibiotics kill many of these beneficial organisms as a side effect

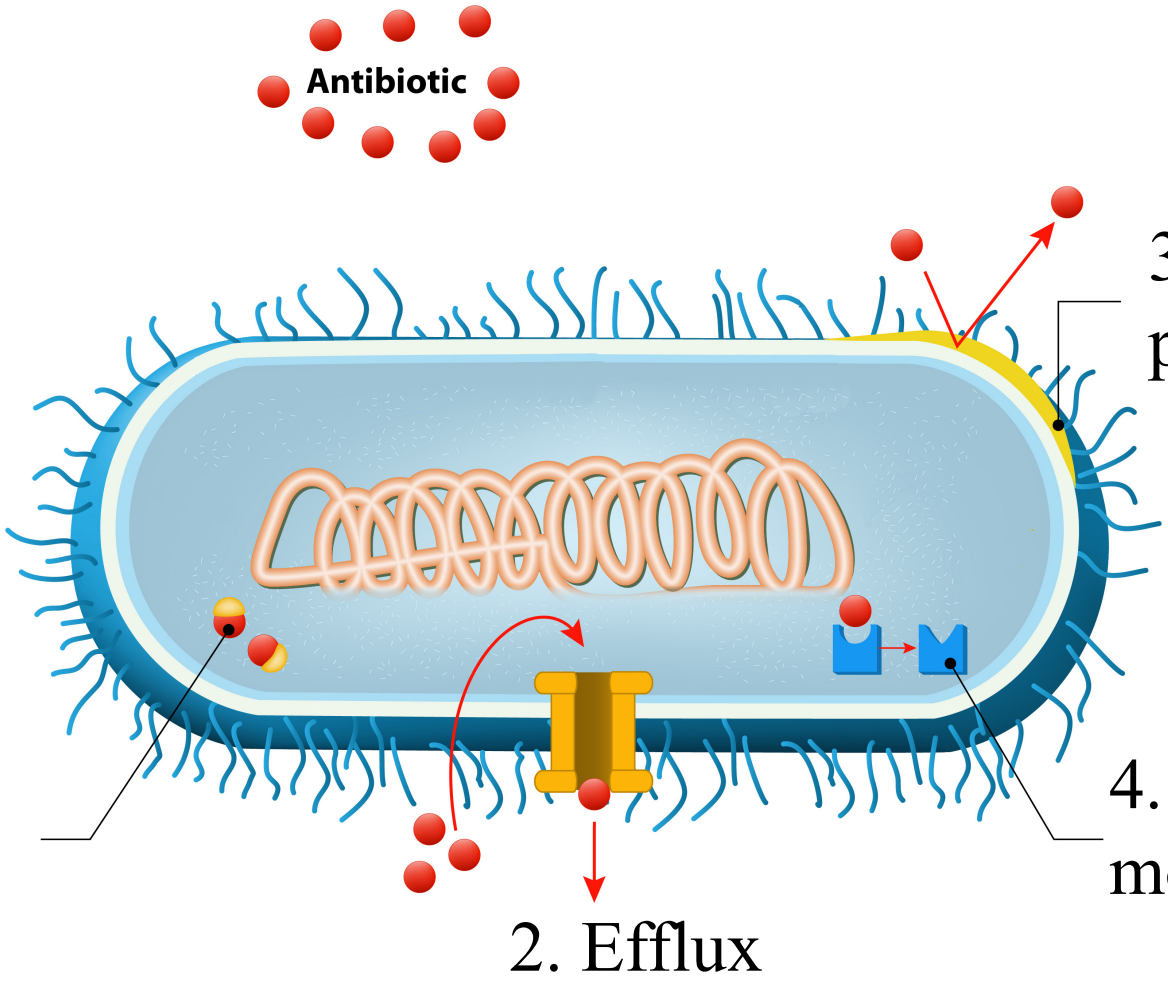
C. difficile is often a minor component of the microbiota, but is naturally resistant to many antibiotics, and thus takes over when its competitors are wiped out.

How did we get here?

Why has resistance to antibiotics become such a big problem?

1. Selection for antibiotic resistant bacteria
2. Spread of antibiotic-resistant bacteria
3. Spread of antibiotic resistance genes

Four fundamental ways bacteria become antibiotic resistant



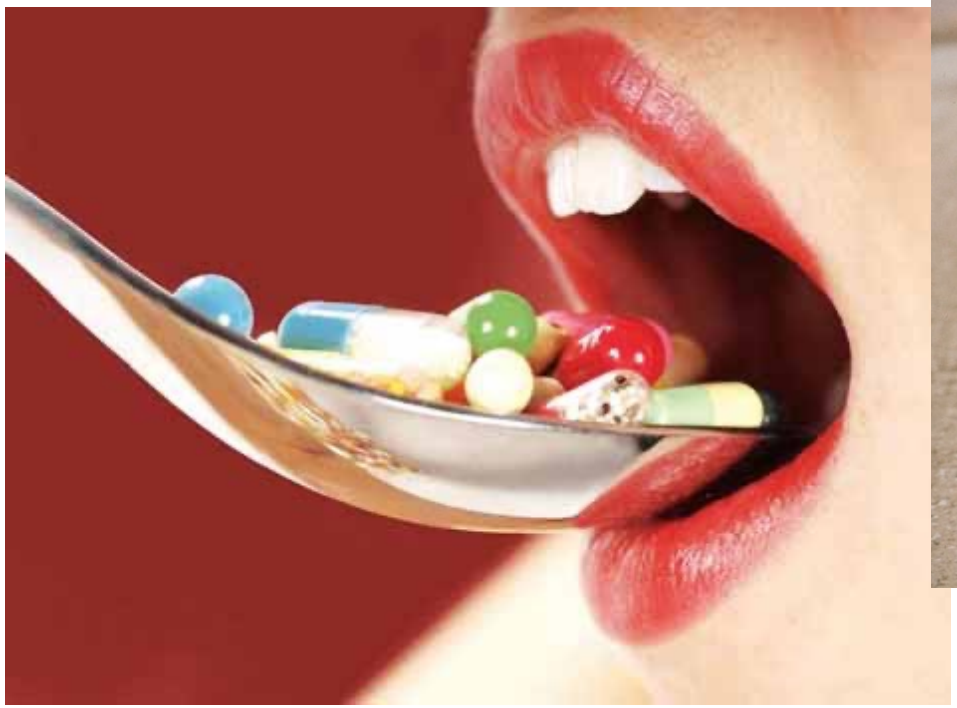
Bacteria can evolve new traits very quickly

Penicillin-resistance was discovered before penicillin was used clinically!

1. Selection for antibiotic resistant bacteria

Extensive use of antibiotics in agriculture

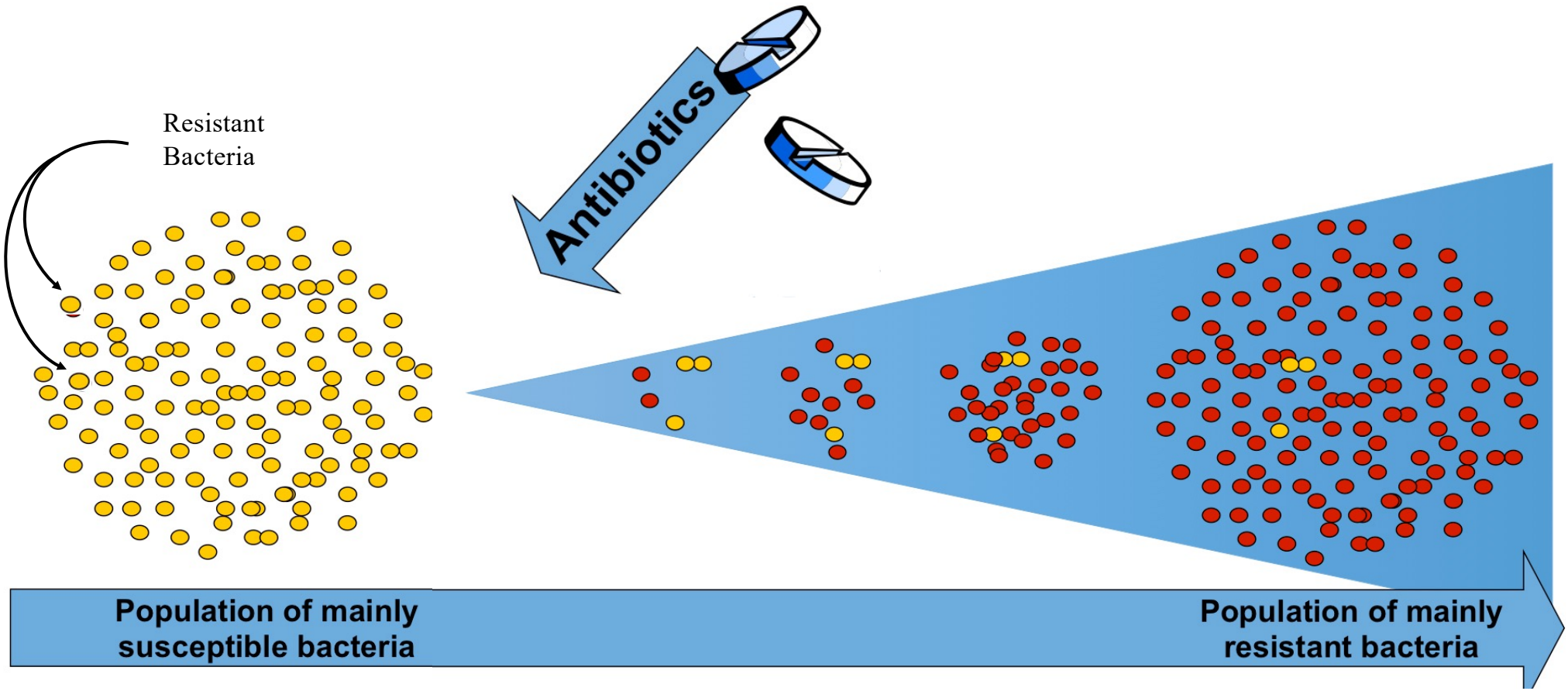
Misuse of antibiotics



Overuse of antibiotics

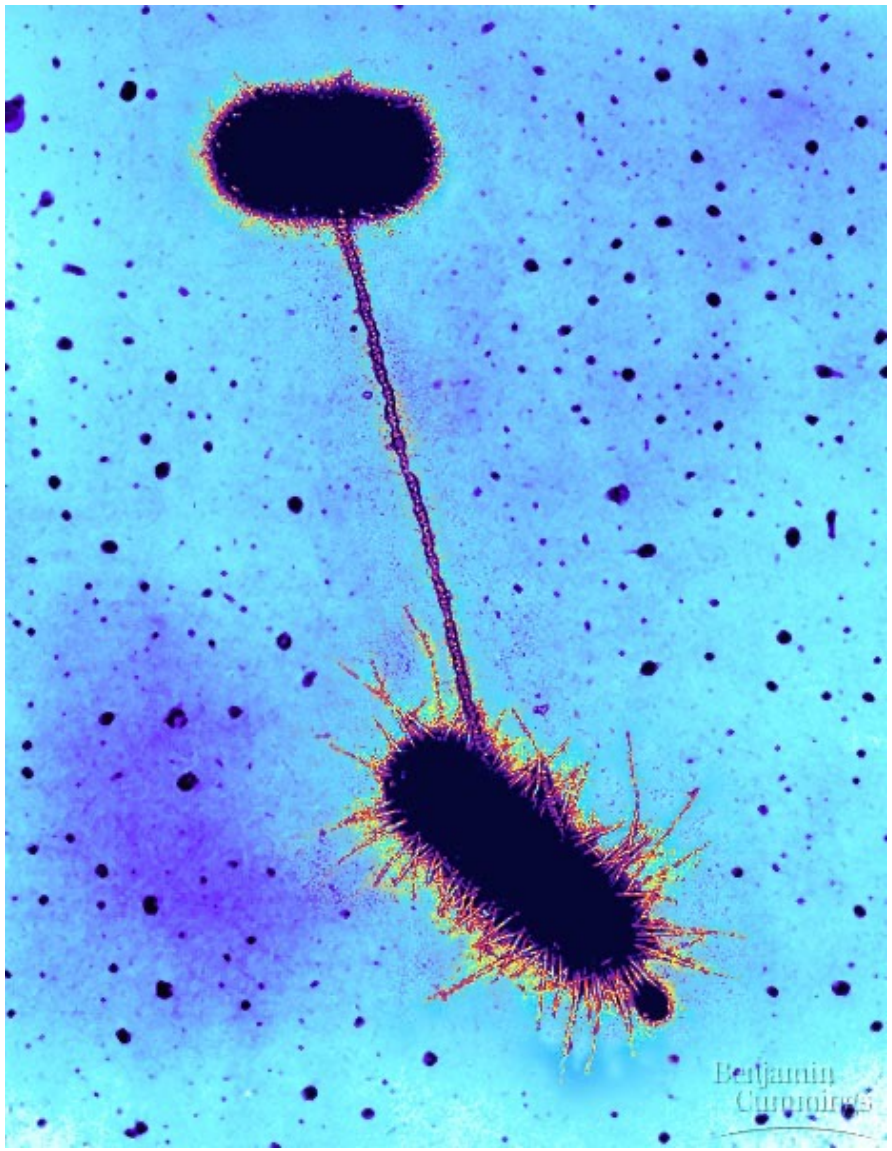
Not following instructions (default)

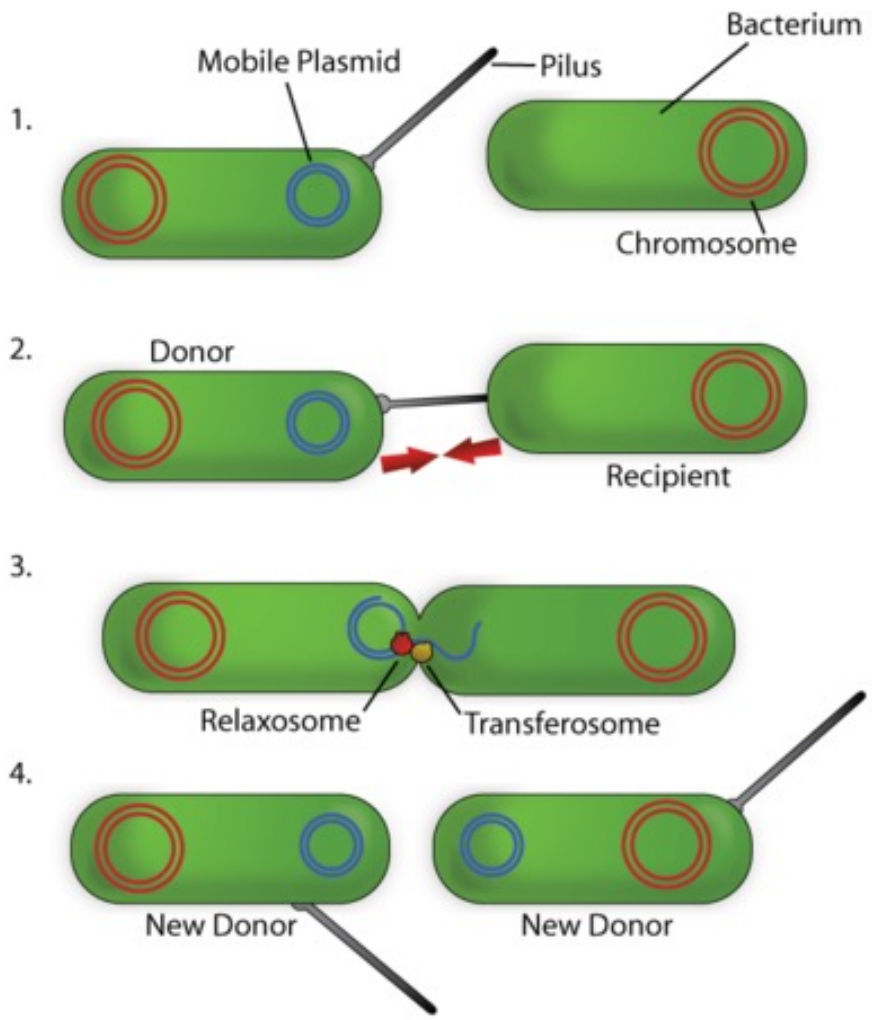
2. Selection and spread of antibiotic-resistant bacteria



Just as antibiotics evolved in microbes as a weapon, so too has resistance to antibiotics evolved as a defense strategy.

3. Spread of antibiotic resistance genes
Horizontal Gene Transfer - Conjugation





E-S-K-A-P-E pathogens

ESKAPE bacteria are the most common **nosocomial** (hospital acquired) infections. They also have high rates of antibiotic resistance which presents even more serious problems.

Enterococcus faecium

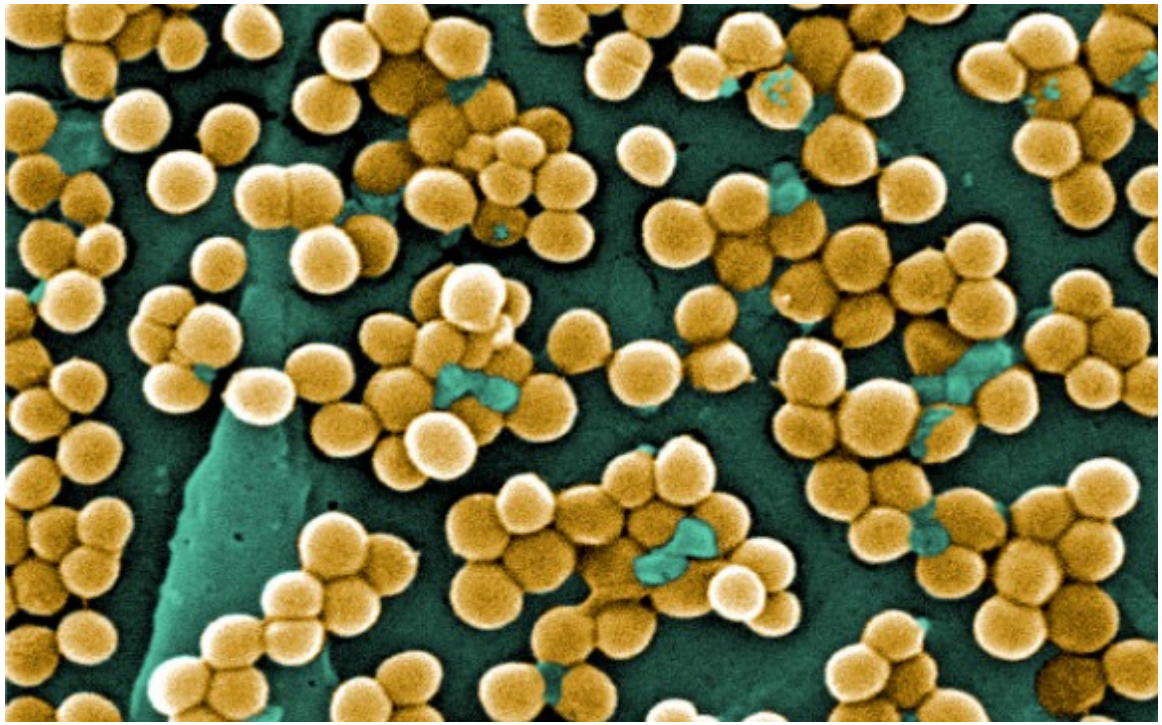
Staphylococcus aureus

Klebsiella pneumoniae

Acinetobacter baumannii

Pseudomonas aeruginosa

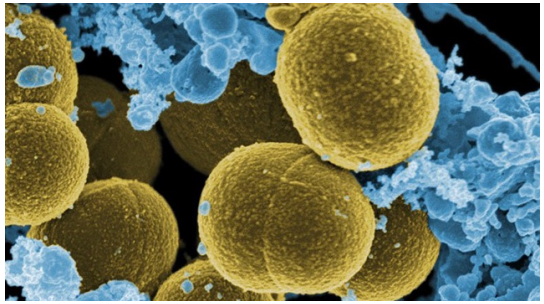
Enterobacter species



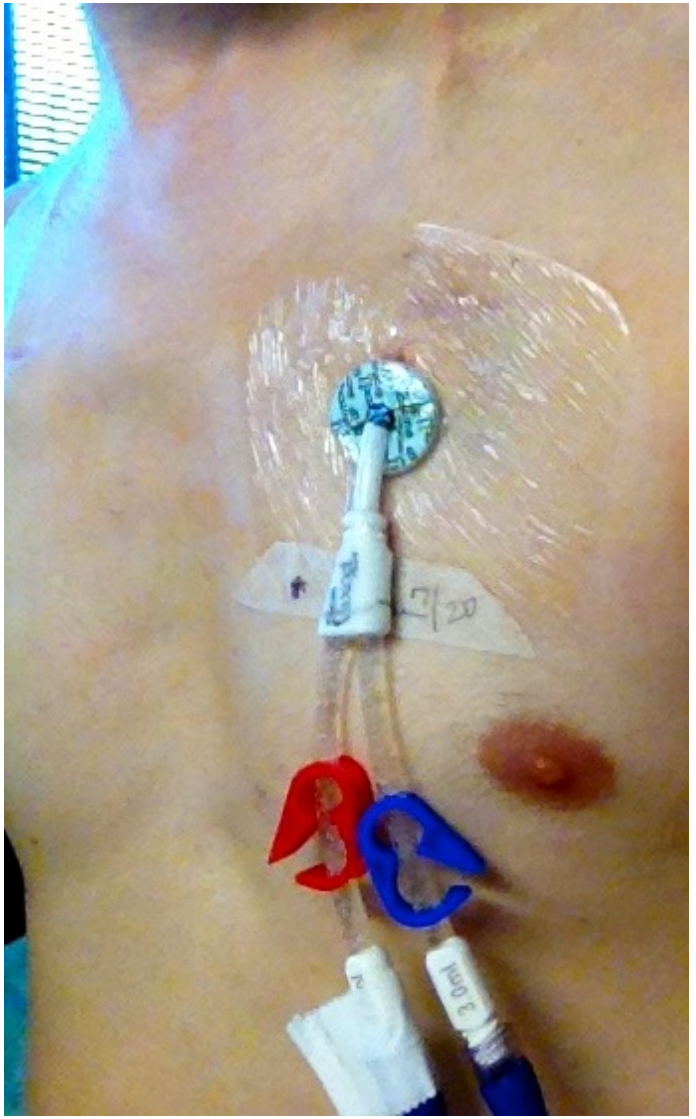
The CDC estimates antibiotic resistant ESKAPE pathogens cause over 2 million illnesses and approximately 23,000 deaths per year in the US alone.

REMEMBER
Healthcare-associated infections
Staphylococcus aureus

- **Bacteremia** or sepsis when bacteria spread to the bloodstream.
- **Pneumonia,** usually found in patients with underlying lung disease and/or on mechanical ventilators.
- **Endocarditis** (infection of the heart valves), which can lead to heart failure or stroke.
- **Osteomyelitis** (bone infection), can happen after bacteremia or surgery/injury.



Staphylococcus aureus



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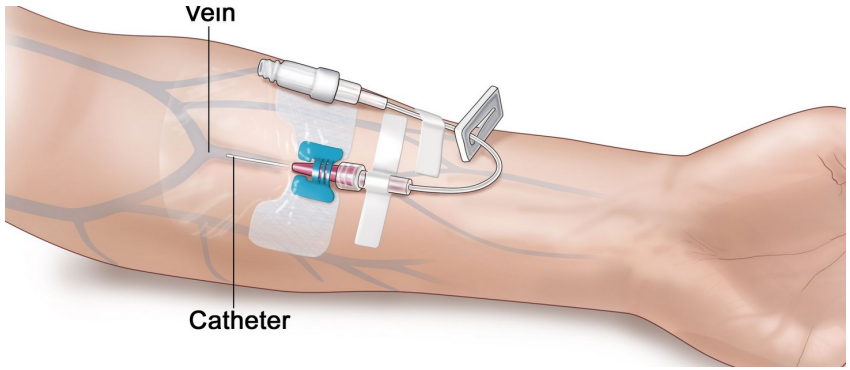
Major cause of nosocomial (healthcare-acquired) infections

- Catheter infections
- Surgical site infections
- Cancer treatments
- Hemodialysis
- Ventilators



S. aureus in health care settings

- Before antibiotics there was a mortality rate of 82% for patients with S. aureus bacteremia.
- Penicillin (1942) decreased these deaths.
- By 1950 almost 25% of hospital-associated S. aureus strains were resistant to penicillin.
- Methicillin and oxacillin were developed to overcome this resistance problem in the 1960s, one year after their introduction, **resistant strains of S. aureus emerged.**

MRSA=methicillin resistant *Staphylococcus aureus*
MRSA is responsible for 30% of hospital-acquired infections.
MRSA is often acquired in hospital/clinical settings.

Colonization and disease of *S. aureus* or MRSA

- About **30%** of the population are persistently colonized with any single *S. aureus* strain in the nose.
- The pooled prevalence of MRSA colonization is **1.3%.**

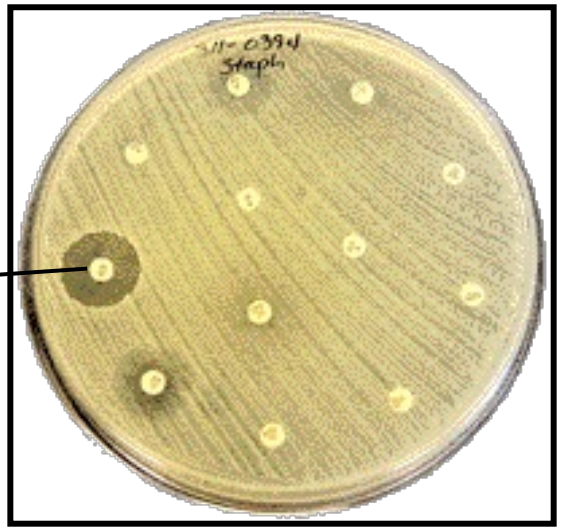
- *S. aureus* was the most prevalent pathogen in ventilator-associated pneumonia and surgical site infections.
- 43 to 58% of these *S. aureus* were MRSA strains.

- 120,000 *S. aureus* bloodstream infections and 20,000 associated deaths occurred in the United States in 2017.
- The 20,000 deaths are mostly from MRSA strains of *S. aureus*.

Bacteria can acquire resistance to multiple antibiotics

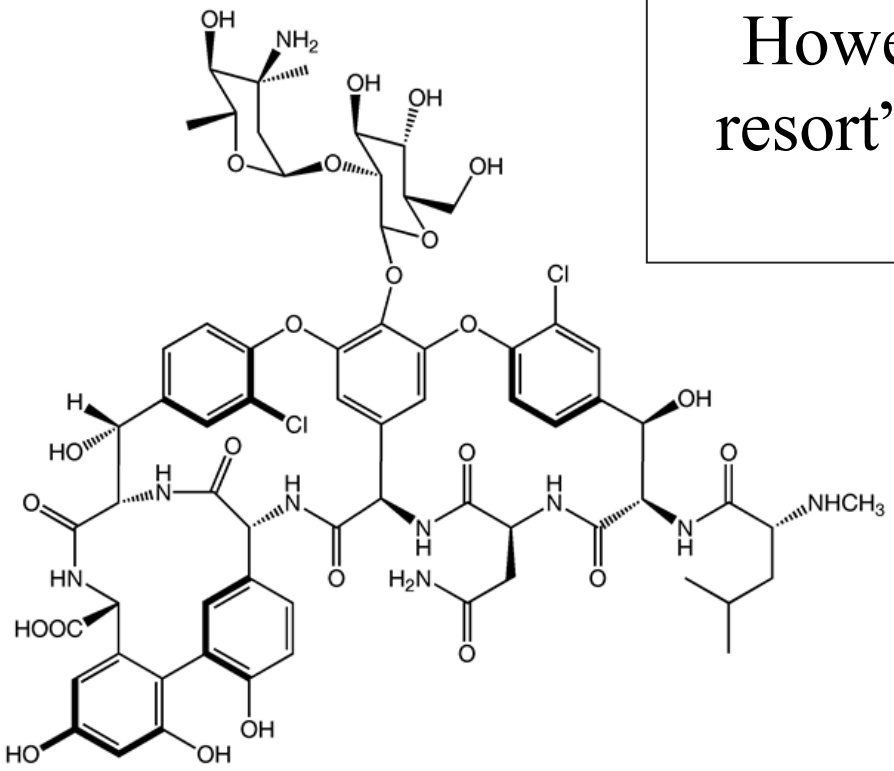
MRSA strains are frequently resistant to methicillin, but are also often resistant to ciprofloxacin, clindamycin and other drugs.

vancomycin disk



This MRSA disk diffusion assay shows a MRSA strain that has resistance to 11 of the 12 antibiotics tested. The MRSA is ONLY sensitive to (killed by) vancomycin.

Vancomycin is considered the "antibiotic of last resort"



However, if we are using the "last resort" antibiotic more frequently is resistance inevitable?

Some bacteria exhibit resistance even to vancomycin.
This resistance appears to have been transmitted to Staphylococcus.