Management of Antibiotic-Resistant Pathogens

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Disclosures

I have the following financial relationships with the manufacturer(s) and/or provider(s) of commercial services discussed in this activity:

- Research Support from:
  - Pfizer (pediatric nirmatrelvir-ritonavir, maternal RSV vaccine)
  - Merck (monoclonal antibody for RSV prevention)

I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

2

Overview

- Introduction
  - Burden of antibiotic resistance (AR) – focus on inpatient settings
  - Critical antibiotics – current and under development
  - Diagnosis
- AR pathogens of epidemiologic significance
  - Gram-positive: *S. aureus*, *Enterococcus*
  - Gram-negative bacilli: ESBL, carbapenem resistance
  - Non-fermenters: *Acinetobacter*, *Pseudomonas*, etc.
  - Fungi: *Candida auris*

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Learning Objectives

- Antimicrobial Resistance
  - How it develops
  - How it's detected
  - How it spreads
- Specific and emerging antimicrobial resistance problems
  - Gram-positive: MRSA, VRE
  - Gram-negative: ESBL, carbapenemases, polymyxin resistance
  - Fungal: *Candida auris*
- Preventing AR infections

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Disclaimers

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- I am not a clinical microbiologist
- There's way more than we can cover in an hour

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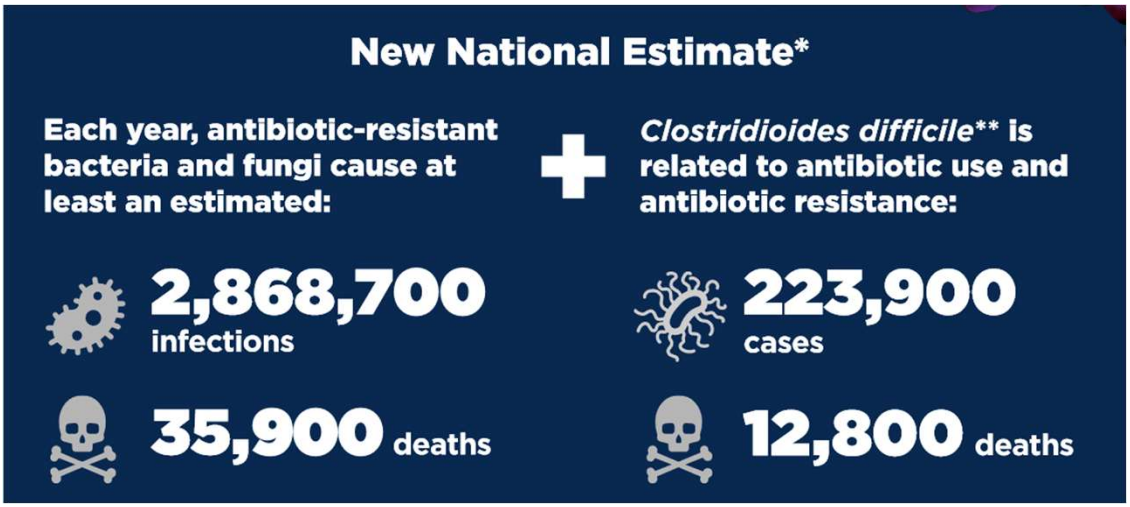

Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States*. 2019

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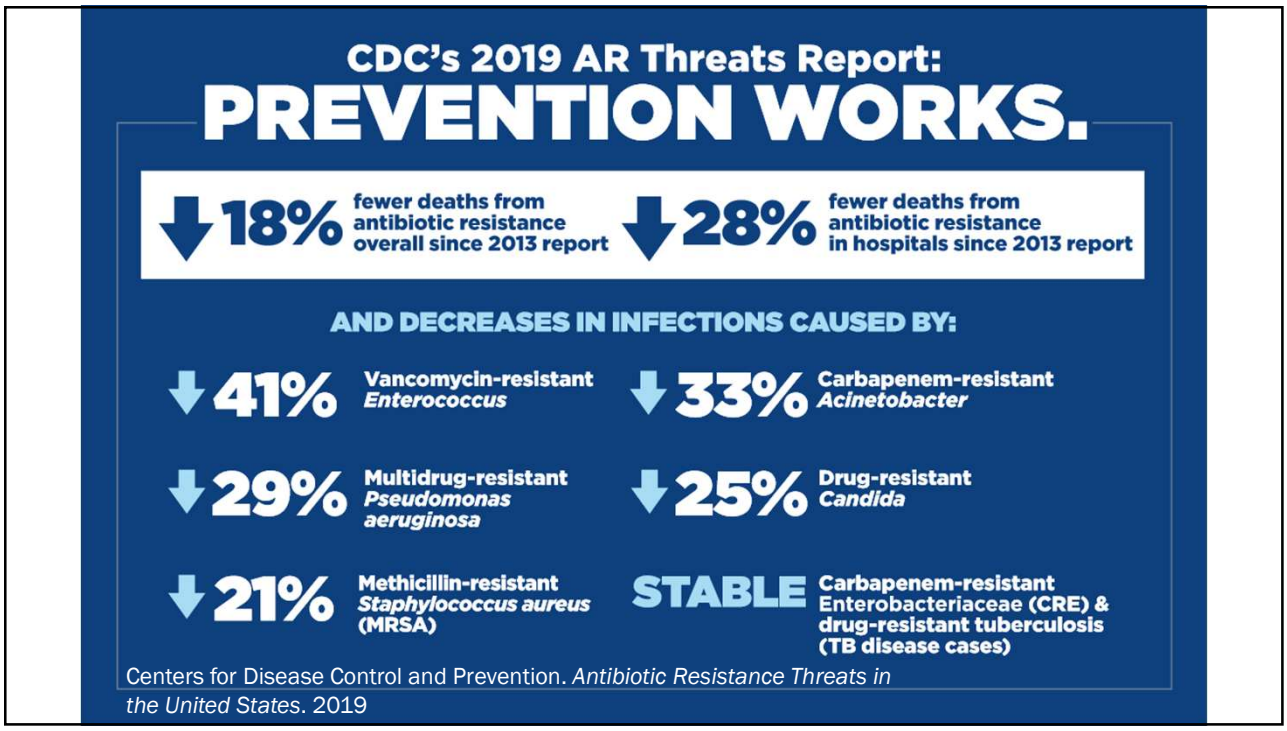

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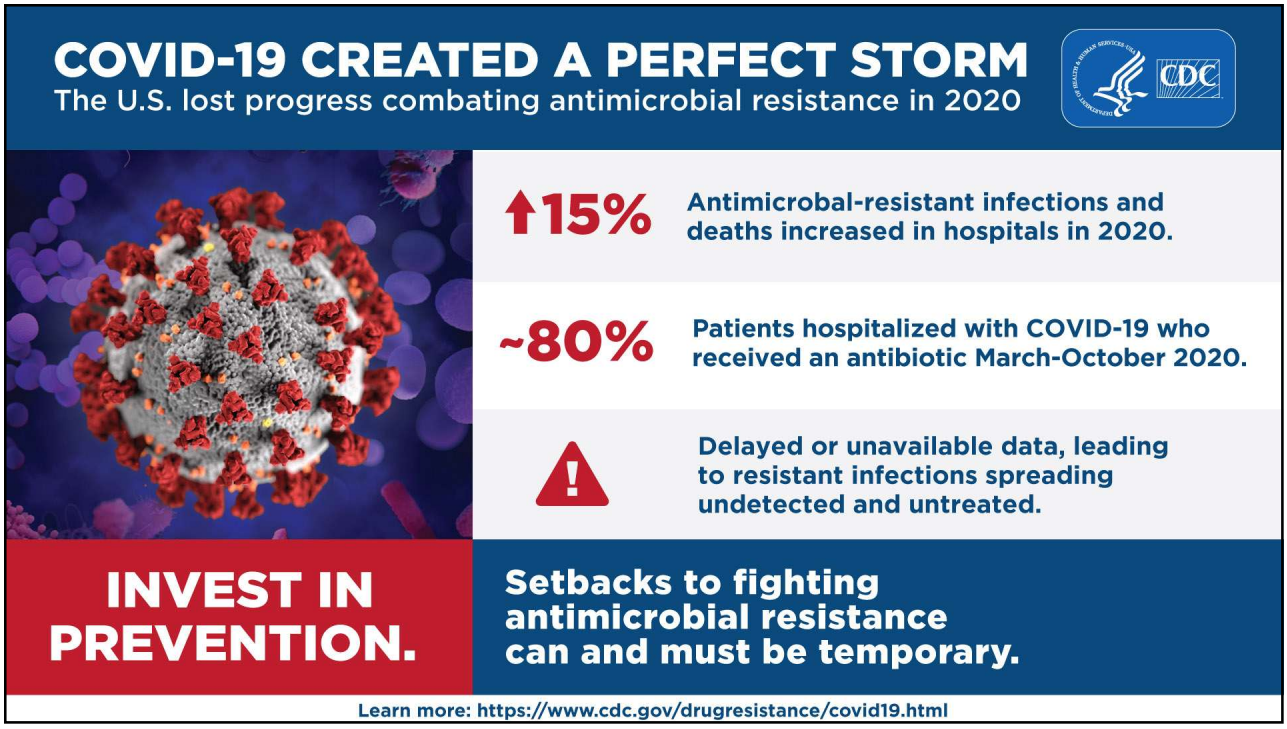
COVID-19 CREATED A PERFECT STORM
The U.S. lost progress combating antimicrobial resistance in 2020
CDC
↑15%
Antimicrobal-resistant infections and deaths increased in hospitals in 2020.
~80%
Patients hospitalized with COVID-19 who received an antibiotic March-October 2020.
Delayed or unavailable data, leading to resistant infections spreading undetected and untreated.
INVEST IN PREVENTION.
Setbacks to fighting antimicrobial resistance can and must be temporary.
Learn more: https://www.cdc.gov/drugresistance/covid19.html

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Antimicrobial Resistance in Hospitals

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Patient Factors	Infection Control	Antibiotic Overuse
• Severity of illness • Immunocompromising conditions • Medical technology and procedures (lines, airways, open wounds)	• Increased introduction of resistant organisms from the community (and residential facilities) • Ineffective infection control & isolation practices (esp. compliance)	• Increased use of antimicrobial prophylaxis • Increased use of polymicrobial antimicrobial therapy • High antimicrobial use in intensive care units

Source: Shlaes D, et al. Clin Infect Dis 1997;25:684-99.

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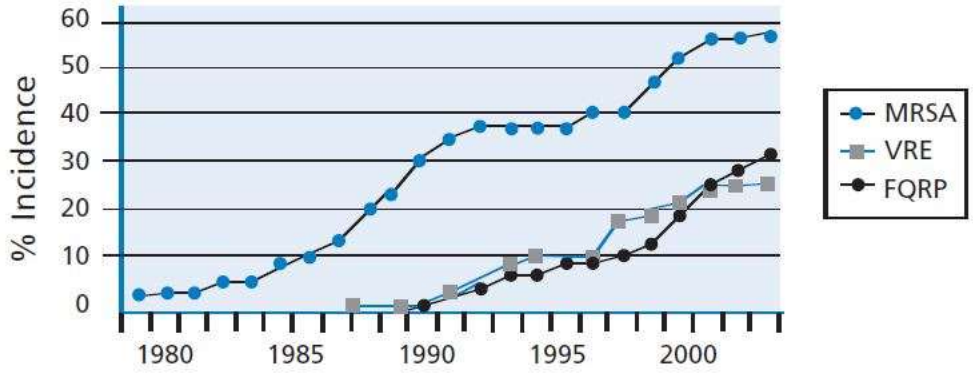
Chart 1: Resistant Strains Spread Rapidly



Source: Centers for Disease Control and Prevention

This chart shows the increase in rates of resistance for three bacteria that are of concern to public health officials: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.

IDSA. Bad Bugs No Drugs. 2004

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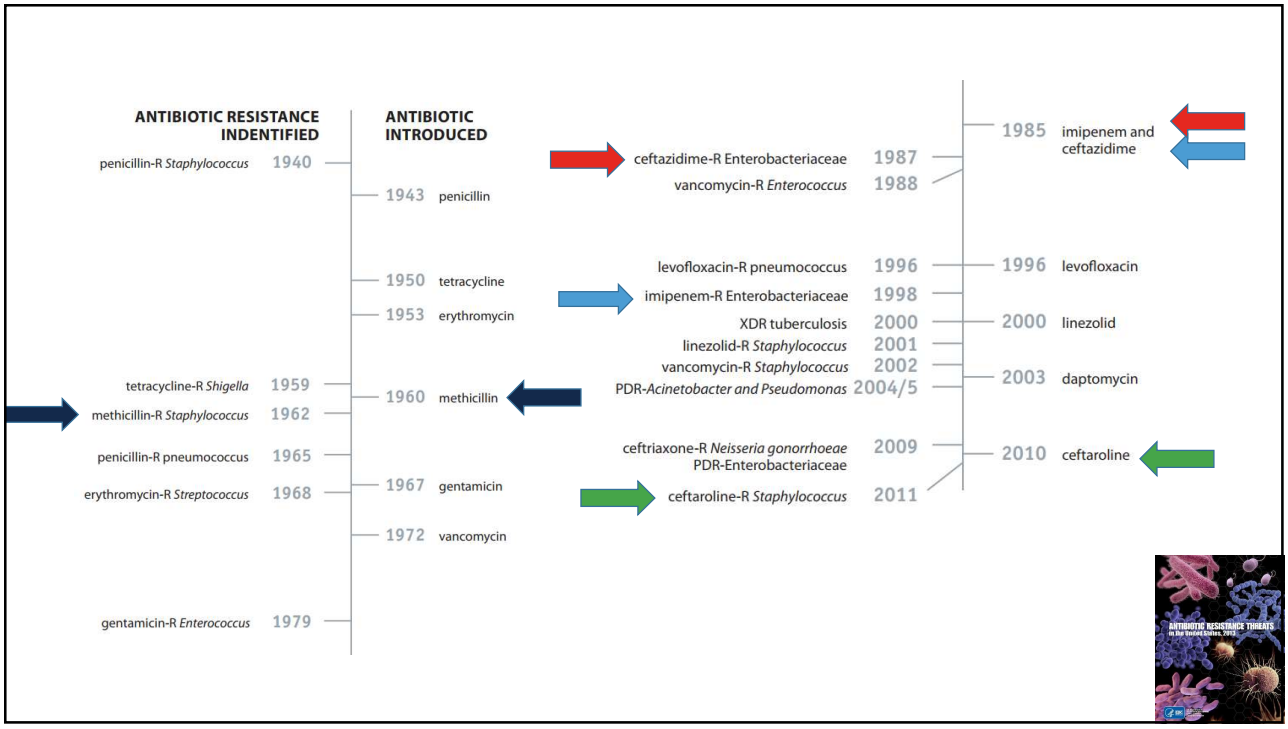
ANTIBIOTIC RESISTANCE INDENTIFIED
ANTIBIOTIC INTRODUCED
penicillin-R Staphylococcus 1940
1943 penicillin
1950 tetracycline
1953 erythromycin
tetracycline-R Shigella 1959
methicillin-R Staphylococcus 1962
1960 methicillin
penicillin-R pneumococcus 1965
erythromycin-R Streptococcus 1968
1967 gentamicin
1972 vancomycin
gentamicin-R Enterococcus 1979
ceftazidime-R Enterobacteriaceae 1987
vancomycin-R Enterococcus 1988
levofloxacin-R pneumococcus 1996
imipenem-R Enterobacteriaceae 1998
XDR tuberculosis 2000
linezolid-R Staphylococcus 2001
vancomycin-R Staphylococcus 2002
PDR-Acinetobacter and Pseudomonas 2004/5
ceftriaxone-R Neisseria gonorrhoeae 2009
PDR-Enterobacteriaceae
ceftaroline-R Staphylococcus 2011
1985 imipenem and ceftazidime
1996 levofloxacin
2000 linezolid
2003 daptomycin
2010 ceftaroline

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Why does this happen so fast?

- Most antibiotics are microbe-derived products
  - Penicillin: *Penicillium*
  - Cephalosporins: *Acremonium*
  - Carbapenems: *Streptomyces cattleya*
  - Vancomycin: *Amycolatopsis orientalis*
  - Also: tetracyclines, polymyxins, amphotericin B…
- Microbes have been fighting this war for billions of years
  - The genes for resistance are in the genetic pool

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Principles of Antibiotic Resistance
(Levy SB. NEJM, 1998)

- Given sufficient time and drug use, antibiotic resistance will emerge
- Resistance is progressive, evolving from low levels through intermediate to high levels
- Organisms resistant to one antibiotic are likely to become resistant to other antibiotics
- Once resistance appears, it is likely to decline slowly, if at all
- The use of antibiotics by any one person affects others in the extended as well as the immediate environment

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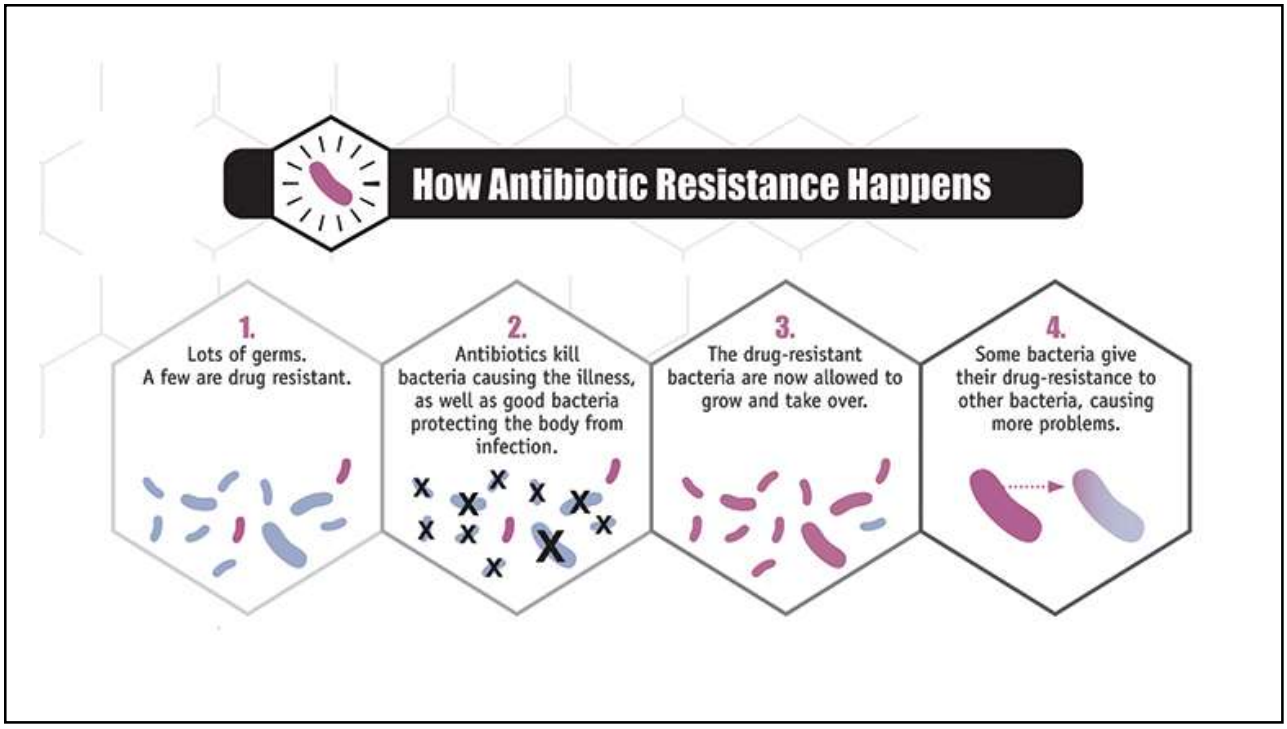
How Antibiotic Resistance Happens
1.
Lots of germs.
A few are drug resistant.
2.
Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.
3.
The drug-resistant bacteria are now allowed to grow and take over.
4.
Some bacteria give their drug-resistance to other bacteria, causing more problems.

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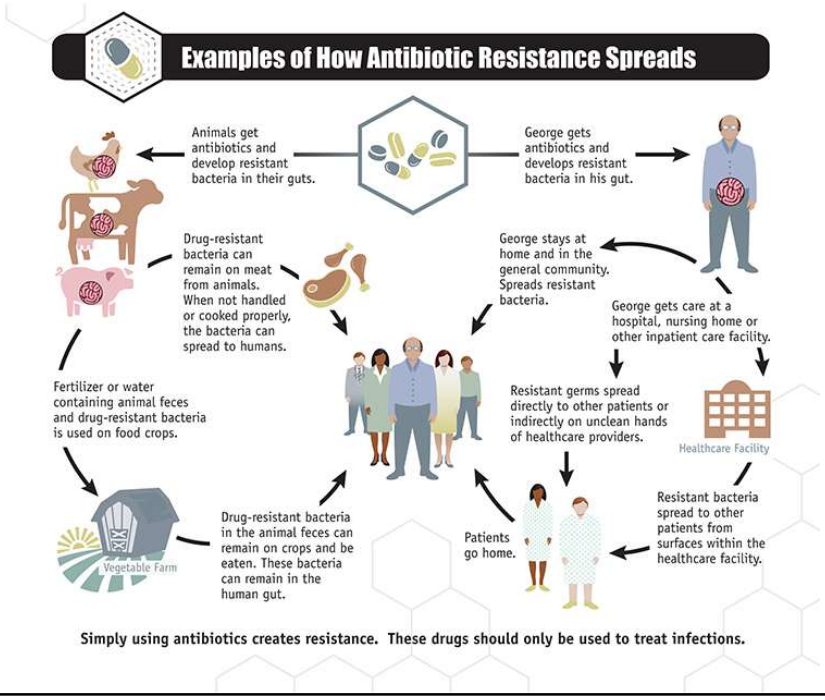
Farm-to-~~Table~~ Hospital



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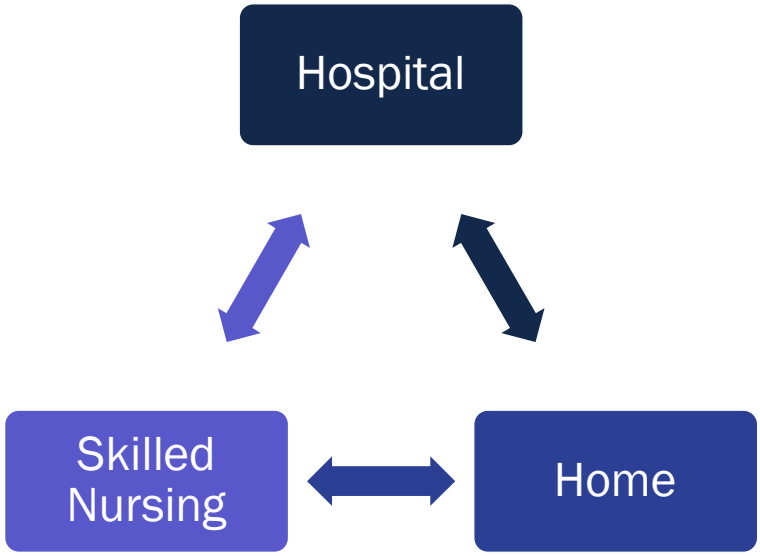
Care Continuum



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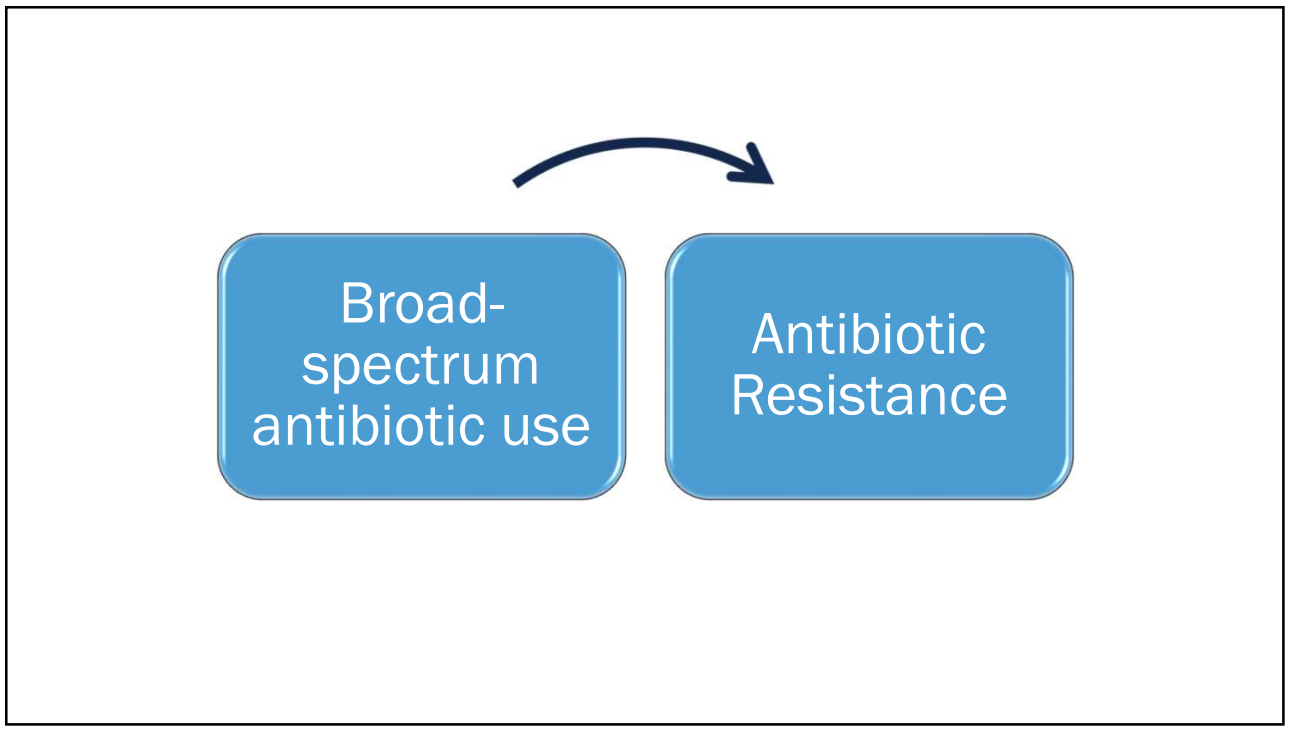

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CDC Four Core Activities to Fight Resistance

1. Prevent infections, prevent spread of resistance
2. Tracking
3. Improving antibiotic prescribing/stewardship
4. Developing new drugs and diagnostic tests

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Antibiotic Pipeline: Can Pharma Save Us?

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- Difficult to develop new antimicrobials
- Small markets → sales limitations:
  - Antimicrobial stewardship
  - Small populations with MDRO infections
- Improvements though: 14 antibiotics approved since 2014
  - Policy fixes incentivized new antimicrobial development: longer patent protection, lower thresholds for approval
- At any given time, ~40 antibiotics in development

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Identifying AR Pathogens

1. Screening specified patient populations – examples:
   - MRSA PCR (common)
   - Vancomycin-resistant *Enterococcus*
   - *C. difficile* screening (not routinely done)

2. Diagnostic cultures
   - Bacterial growth does not always mean clinical infection

Diagnosis of AR Pathogens

Culture

- "Gold standard"
- Requires sampling of site of infection prior to therapy
- Allows determination of antimicrobial susceptibility

PCR/molecular

- From blood, still requires an incubation step
- Rapid species identification
- Blood culture systems rapidly detect *some* resistance mechanisms (e.g., VRE, MRSA), but not 100%
- Direct detection of bacteria (e.g., from CSF or stool) can NOT provide resistance information

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Mean Inhibitory Concentration (MIC)

- The lowest concentration of the antibiotic needed to prevent the bacteria from growing
  - Expressed in mcg/mL
- Requires interpretation
  - Cannot just pick the lowest MIC from the Micro report

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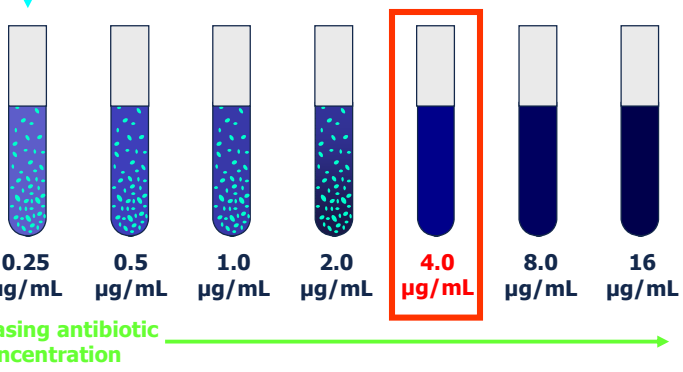
MIC Determination – Broth Microdilution

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism

Known quantity of bacteria placed into each tube



Many Labs Use Automated Testing

Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg*. 2000;123(1 Pt 2):S1.

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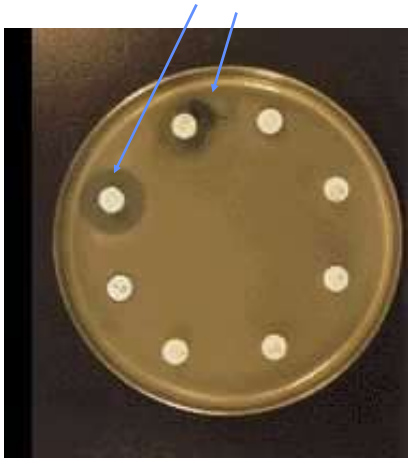
MIC Determination – Plate-Based



Kirby-Bauer: zone of inhibition around disc predicts susceptibility

E-test: strip with gradient antibiotic concentration

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MIC Interpretation

- For EVERY (relevant) combination of species and antibiotic, there is a breakpoint established by CLSI (Clinical Laboratory Standards Institute)
- Requires understanding of pharmacology of antibiotic
- The breakpoint allows interpretation as susceptible or resistant
  - For example: MIC=1, breakpoint=4 → susceptible
- Breakpoints occasionally require revision
  - Often due to treatment failures with antibiotics that are supposed to be active

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Molecular Diagnostics: Nucleic Acid Amplification Testing (NAAT)

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- Multiple molecular techniques make microbiologic diagnosis faster
- NAAT/PCR can quickly detect epidemiologically important AR:
  - MRSA (nasal swab)
  - VRE (rectal swab)
  - Carbapenemase production (rectal swab, culture samples)

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Modes of Antibiotic Therapy

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Empiric

- Infection suspected
- Pathogen not yet known (may never be found)
- Cover most common possibilities
- Broad, multiple agents, more toxicity

Directed

- Infection proven, pathogen identified, susceptibility known or predicted
- Almost always single-agent
- As narrow as possible
- Almost always less toxic

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Impact of Antimicrobial Resistance

- Empiric therapy may be inadequate. Delays in providing effective antibiotic therapy increase risk of mortality.
- Drugs used for antibiotic-resistant infections are:
  - Usually more toxic (e.g., vancomycin vs. cefazolin)
  - Usually more expensive
  - Often less effective (e.g., vancomycin vs. cefazolin)
  - Often not available PO → increased LOS, increased central-line use
  - Often broader spectrum → future AMR, higher risk of C-diff
- Threat of resistance → increased use of more toxic, less effective, more expensive, IV-only drugs in patients *without* resistant organisms

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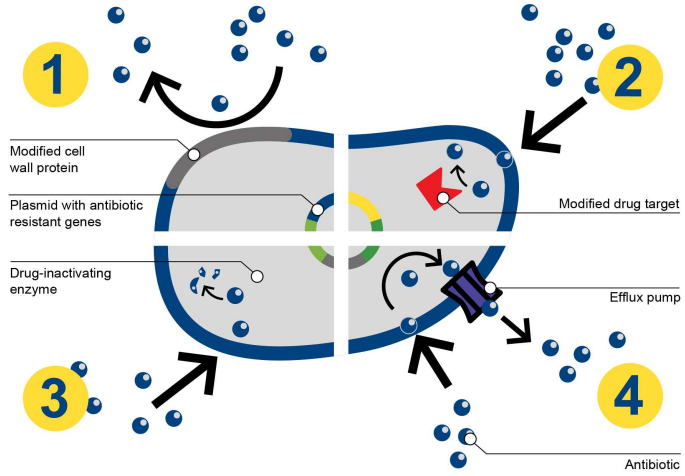

Resistance mechanisms : how do bacteria resist antibiotics?

1. Impermeable barrier: the bacterial cell membrane develops an impermeable barrier which blocks antibiotics.

2. Target modification: modification of components of the bacteria which are targeted by the antibiotic, meaning the antibiotic can no longer bind properly to its target in order to destroy the bacteria.

3. Antibiotic modification: the cell produces substances (usually a protein called an "enzyme") that inactivate the antibiotic before it can harm the bacteria.

4. Efflux pump mechanism: the antibiotic is actively pumped out of the bacteria so that it cannot harm the bacteria.

https://amr.biomerieux.com/en/about-amr/what-is-antibiotic-resistance/

Accessed 10/13/21

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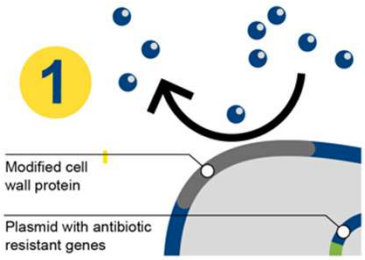
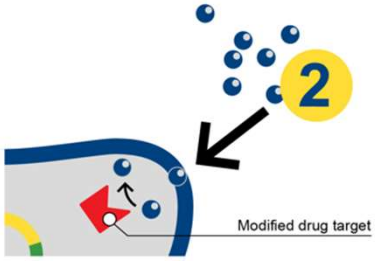
AR Mechanisms





https://amr.biomerieux.com/en/about-amr/what-is-antibiotic-resistance/

Accessed 10/13/21

Modified cell-wall protein

- Antibiotic can't bind to cell-wall target
- **MRSA, VRE**

Modified drug target

- Antibiotic can't inhibit cellular process
- Examples: Resistance to fluoroquinolones, clindamycin

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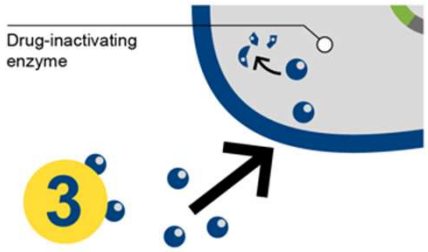
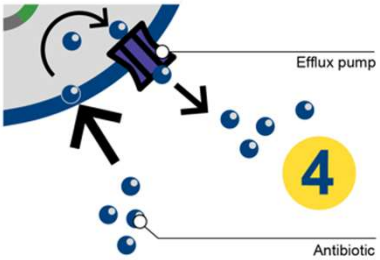
AR Mechanisms



Drug-inactivating enzyme

- Bacteria breaks down the antibiotic before it can act
- ESBL, CRE



https://amr.biomerieux.com/en/about-amr/what-is-antibiotic-resistance/

Accessed 10/13/21

Efflux pump

- Bacteria pumps the antibiotic back out
- Multi-drug resistant *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*

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Gram-positive AR Pathogens

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Gram-positive Principles

- Antibiotic resistance is often a single gene
  - MRSA is predicted by a single gene → facilitates accurate rapid detection
- Less inter-species sharing of resistance mechanisms than Gram-negatives
- Colonization is skin and nasopharynx (*Staphylococcus aureus*) and GI tract (*Enterococcus*)

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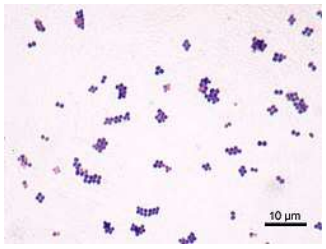
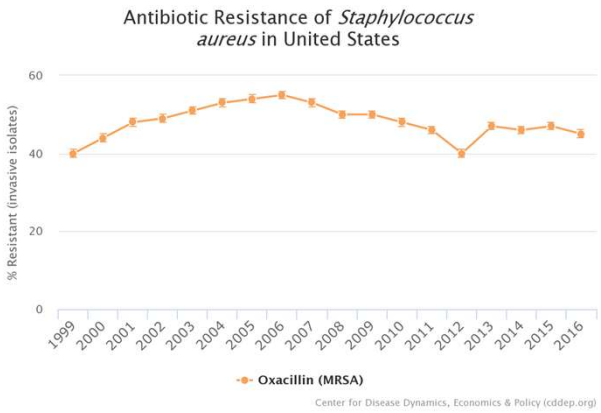
Staphylococcus aureus

- Community and nosocomial
- Infection types:
  - Skin and soft-tissue
  - Bone/joint
  - Nosocomial and postviral pneumonia
  - Wound infections
  - Bacteremia, CRBSI
  - Endocarditis/endovascular
  - **Metastatic infection**
- Bacteremia mortality rate: 20-40%





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Staphylococcus aureus

- Plain MSSA susceptible to most beta-lactams (penicillins and cephalosporins)
  - MSSA may be just as invasive/virulent as MRSA
- MRSA resistant to (almost) all beta-lactams
  - *mecA* gene alters the beta-lactam target (can detect by PCR)
  - Treatment: usually vancomycin
  - Options (severe infection): daptomycin, ceftaroline
  - Options (less severe): linezolid, clindamycin, doxycycline, TMP-SMX
- Most hospitals isolate patients colonized with MRSA

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Staphylococcus aureus

- Clindamycin resistance
  - Rising steadily over time with regional variance (high in NC)
  - Challenge in MRSA era
- Vancomycin resistance (VISA and VRSA)
  - VRSA extremely rare
  - Heavy vancomycin use can cause VISA (intermediate) – vancomycin may lose efficacy gradually

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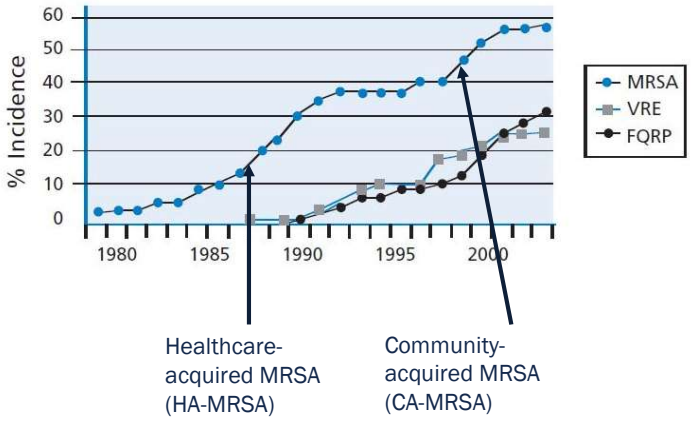
MRSA Evolution

- HA-MRSA was highly antibiotic-resistant
- CA-MRSA (USA300 strain) is highly virulent
- Currently – mix of MRSA and MSSA, similar virulence



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Staphylococcus aureus - Summary

- Highly virulent, causes a LOT of infections
  - Nosocomial and community-acquired
- MRSA is treatable
  - But antibiotics more toxic and/or less effective than beta-lactams
  - MRSA threat → near-universal use of empiric vancomycin in severe acute infections → nephrotoxicity, increased risk of VRE
  - Can screen and isolate and decolonize patients
- Vancomycin resistance is very rare

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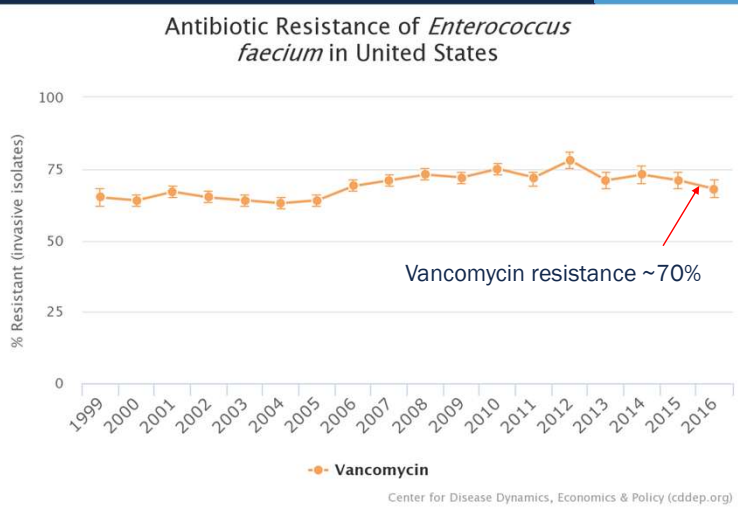
Enterococcus faecium

- Infections:
  - UTI
  - CRBSI
  - Endocarditis
  - Wounds
- Less virulent than *S. aureus*, but difficult to treat



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Enterococcus faecium

- Most enterococci are susceptible to penicillins and vancomycin
  - Tend to be hard to kill and synergistic approaches are used
- *E. faecium* is nearly universally resistant to ampicillin and **usually resistant to vancomycin (VRE)**
- Rarely encountered outside of healthcare settings
- Screening high-risk populations (neonates, immunocompromised): perirectal swabs
- Isolation of patients with VRE is highly recommended

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Treatment of VRE

- Vancomycin resistance encoded by genes *vanA* or *vanB*
  - Change in structure of target → complete resistance
- **Mainstays:** high-dose daptomycin, linezolid
- Others: tigecycline, telavancin
- Clearance is often challenging, and recurrence is common

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Notes from the Field

Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae* — Washoe County, Nevada, 2016

Lei Chen, PhD[1]; Randall Todd, DrPH[1]; Julia Kiehlbauch, PhD[2,3]; Maroya Walters, PhD[4]; Alexander Kallen, MD[4]

- 70 y/o F returned to Reno, NV, after prolonged stay in India, during which she was hospitalized multiple times for a femur fracture and subsequent infection.
- She presented with sepsis and a wound culture grew pan-resistant *Klebsiella pneumoniae* (intermediate to tigecycline)
- ~2 weeks after admission, she died of septic shock

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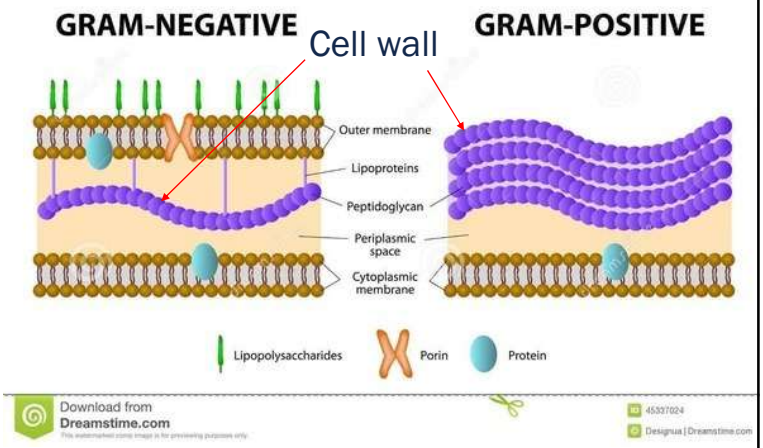
Gram-negative vs Gram-positive

- Both have a cell wall
- Gram-negatives have an outer membrane
- Able to regulate what comes in and out → much more complex



https://www.dreamstime.com/stock-illustration-gram-positive-gram-negative-bacteria-difference-bacterial-image45337024, accessed 5/8/2018

Gram-negative Rods – General Principles

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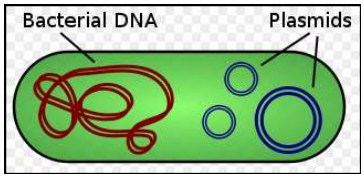
- Genotype less predictive – PCR may miss resistance
- May behave differently in infection than in lab
  - May develop resistance on therapy – not seen in lab
- Different mechanisms interact (e.g., moderate expression of a beta-lactamase plus an efflux pump may act synergistically)
- Gram-negatives may share plasmid DNA promiscuously
- Colonize GI tract very densely



https://en.wikipedia.org/wiki/Plasmid, accessed 5/8/18

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Gram-negative Rods: Common Infections

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- Healthy, ambulatory people: UTIs, intra-abdominal infections (diverticulitis, appendicitis), bacterial diarrhea (i.e., *Salmonella*, traveler's diarrhea)
- Colonize medical devices → nosocomial infections:
  - HAP/VAP
  - CLABSI
  - CAUTI
  - SSI

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Key Antibiotics for Resistant Gram-Negatives

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- Beta-lactam family – highly effective, less toxicity
  - Penicillins: Piperacillin-tazobactam
  - Cephalosporins: Ceftazidime, cefepime
  - Carbapenems: meropenem, imipenem
  - Aztreonam
  - New antibiotics: cefiderocol, ceftazidime-avibactam
- Aminoglycosides: gentamicin, tobramycin, amikacin
  - Nephrotoxicity, ototoxicity
- Fluoroquinolones: ciprofloxacin, levofloxacin
  - Can be taken by mouth
  - Easy for resistance to develop

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IDSA Treatment Guidelines

6 major groups of AR Gram-negative Infections

1. Extended-spectrum Beta-Lactamase-Producing Enterobacterales (ESBL)
2. AmpC Beta-Lactamase-Producing Enterobacterales
3. Carbapenem-Resistant Enterobacterables (CRE)
4. *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-PA)
5. Carbapenem-resistant *Acinetobacter baumanii* (CRAB)
6. *Stenotrophomonas maltophilia*

https://www.idsociety.org/practice-guideline/amr-guidance/

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Enterobacterales Vs Non-fermenters

- *Enterobacterales*
  - Generally species are pretty similar to each other
  - Can ferment glucose. Normal habitat: GI tracts
  - *E. coli, Klebsiella, Enterobacter, Citrobacter, Serratia, Proteus…*
- Non-fermenters
  - Usually have complex mechanisms of resistance
  - Normal habitat: soil, wet/aquatic areas
  - *Pseudomonas, Stenotrophomonas, Acinetobacter, Burkholderia…*

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Extended-Spectrum Beta-lactamases (ESBL)

- Large heterogeneous family of enzymes
- "Extended spectrum" generally means resistant to penicillins, cephalosporins (including 4th-gen), and aztreonam
- Labs may use 3rd-gen cephalosporin resistance as proxy
- Susceptible to carbapenems
- Usually inhibited by beta-lactamase inhibitors (such as tazobactam in pip-tazo/Zosyn)

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Epidemiology of ESBL

- Frequently found in:
  - ***Klebsiella*** *pneumoniae* and *oxytoca*, ***E. coli***
- Less commonly: *Acinetobacter, Burkholderia, Citrobacter, Enterobacter, Morganella, Pseudomonas, Salmonella, Serratia, Shigella*
- **Plasmid**-based, mobile
- Contact precautions generally recommended

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ESBL – Clinical Strategies

- Plasmids often carry resistance genes for other drug classes (fluoroquinolones, aminoglycosides)
  - Big problem
- Beta-lactam strategies
  - **Carbapenems** have given the best outcomes
  - **Avoid cephalosporins** (even if reported susceptible)

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AmpC Beta-Lactamase Producers

- AmpC Beta-lactamases
  - Can be resistant to all beta-lactams except carbapenems and cefepime
  - **Susceptibility testing may miss inducible resistance**
- Important species:
  - *Enterobacter cloacae*
  - *Klebsiella aerogenes*
  - *Citrobacter freundii*
- Limited epidemiologic significance; no isolation recommended

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Carbapenem Resistance

- Carbapenems are considered the last-line beta-lactams
- Two major types of carbapenem resistance:
  1. Carbapenemases
     - More common in *Enterobacterales.* CRE = Carbapenem-Resistant Enterobacterales
     - Bigger Infection Prevention concern
  2. Non-carbapenemases
     - Non-fermenters – *Pseudomonas aeruginosa, Acinetobacter baumanii*
     - Not a beta-lactamas – altered porins, efflux pumps

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Carbapenemases

- Major infection control concern
  - Definitely isolate!
- Most are **plasmid-mediated** (Infection Prevention!)
  - Families: KPC, OXA-48-like, VIM, IMP, NDM
    - KPC most common in US; others often associated with international travel
- In general, active against all beta-lactams
- Generally not inhibited by beta-lactamase inhibitors
- For years, no good antibiotic strategies

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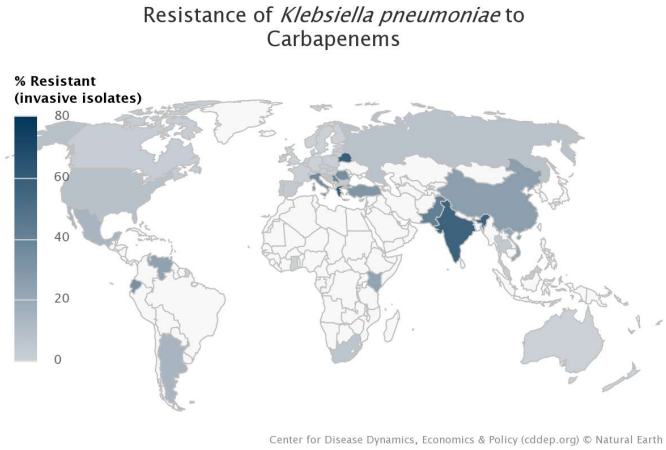
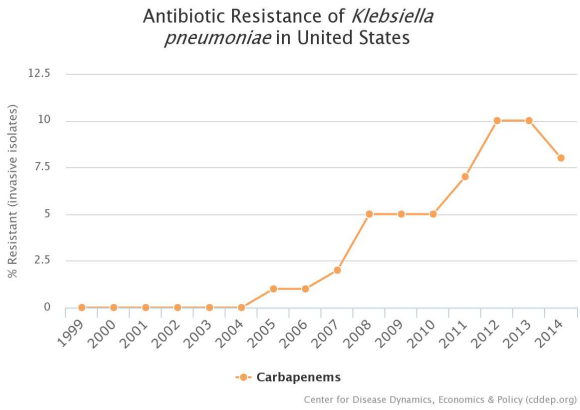

Resistance of *Klebsiella pneumoniae* to Carbapenems
% Resistant (invasive isolates)
80
60
40
20
0
Center for Disease Dynamics, Economics & Policy (cddep.org) © Natural Earth


Antibiotic Resistance of *Klebsiella pneumoniae* in United States
% Resistant (invasive isolates)
12.5
10
7.5
5
2.5
0
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Carbapenems
Center for Disease Dynamics, Economics & Policy (cddep.org)

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Treatment

- Often have resistance to other classes (fluoroquinolones, aminoglycosides); sometimes on same plasmid
- Other options (colistin, advanced tetracyclines) very toxic and/or ineffective
- Antibiotics approved since 2016 have been revolutionary
  - Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol
  - VIM, IMP, NDM most challenging
- CRE: still very bad, but new treatment options
  - Empiric treatment will almost always be inadequate

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Pseudomonas aeruginosa

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- Important cause of VAP (20 percent), CLABSI (18 percent), CAUTI, SSI
- May have multiple mechanisms of resistance
  - Porins, efflux pumps, beta-lactamases
- Double-coverage is generally *not* recommended for **targeted** therapy
  - Used for empiric therapy to hedge against resistance

https://www.cidrap.umn.edu/news-perspective/2016/11/drug-resistant-pseudomonas-sharply-us-kids. Accessed 10/19/2022.

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Difficult to Treat *Pseudomonas aeruginosa* (DTR-PA)

- Defined by resistance to all of:
  - Pip-tazo, ceftazidime, cefepime, aztreonam, meropenem, imipenem, ciprofloxacin, levofloxacin
- Treatment: cefiderocol, ceftolozane-tazobactam
  - Aminoglycosides for UTIs (if active)

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Stenotrophomonas maltophilia

- Closely related to *Pseudomonas*
- Colonizes airway devices, may cause pneumonia (usually VAP)
  - May also cause CLABSI
- Intrinsic resistance to most beta-lactams and aminoglycosides
- Active antibiotics:
  - TMP-SMX (best), levofloxacin, minocycline
  - If resistant → aztreonam+avibactam
  - Dual therapy recommended for significant infections
- Relatively low virulence, but significant intrinsic resistance

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Acinetobacter baumanii

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- Important nosocomial bacterial pathogen: VAP, CLABSI, CAUTI, SSI
- Intrinsically resistant to many agents
- Definitions:
  - MDR: non-susceptible >= 1 agent in >= 3 categories (9 total)
  - XDR: non-susceptible to >= 1 agent all but <=2 categories
  - PDR: non-susceptible to all possibly active drugs
- Combination therapy recommended
- Resistant infections treated with polymyxins + tigecycline or minocycline
- New antibiotic in development: sulbactam-durlobactam

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Polymyxin Resistance

- Colistin and Polymyxin B: last-line antibiotics for resistant Gram-negative infections
  - Abandoned in the 1970s due to toxicity, revived in 2000s
- Resistance is mediated by *mcr* genes
  - Plasmid-mediated (transmissible)
- Emerged in food animals in China in 2014
  - Now spread across the globe
- Colistin is commonly used in agriculture, especially in China

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New Drugs for Carbapenem-Resistant Organisms

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- Beta-lactam/beta-lactamase combinations (Beta-lactamase engineered to bind to carbapenemase)
  - Ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, aztreonam-avibactam
- Novel beta-lactam
  - Cefiderocol: stable against beta-lactamases, actively transported through the outer membrane
- Tetracycline derivatives
  - Eravacycline, omadacycline - generally not thought to be as effective
- Aminoglycoside: plazomicin
- Since ~2016, significant improvements in antibiotic armamentarium to keep up with this threat

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New Antibiotics for Carbapenem-Resistant Organisms

Antibiotic	Active Against	No or Limited Activity
Ceftazidime-avibactam	KPC, OXA-48	NDM, CRPA, CRAB
Meropenem-vaborbactam	KPC	OXA-48, NDM, CRPA, CRAB
Imipenem-relebactam	KPC, CRPA	NDM, OXA-48
Aztreonam-avibactam	KPC, NDM, OXA-48	CRPA, CRAB
Eravacycline	KPC, NDM, OXA-48, CRAB	CRPA
Cefiderocol	KPC, OXA-48, NDM, CRAB, CRPA	

Adapted from Tamma PD and Hsu AJ, *JPIDS*, 2019

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Prevention of Resistant Gram-negative infections

- Identifying high-risk populations:
  - Trauma, diabetes, malignancy, organ transplantation
  - Mechanical ventilation, indwelling Foley, CVCs
  - Poor functional status, severe illness
  - Healthcare exposure in high-risk international regions (South and Southeast Asia, Middle East, Eastern Europe)
- Strategies
  - Antibiotic stewardship
  - Contact precautions
  - During CRE outbreaks, screening for rectal colonization

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Antifungal-Resistant Candida

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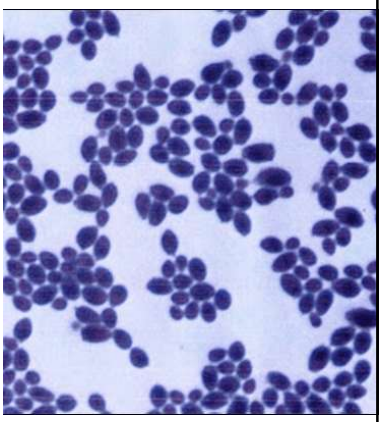
Invasive Candidiasis

- Risk factors
  - Trauma, burns
  - Extremes of age
  - Venous catheter
  - TPN
  - Broad-spectrum antibiotic exposure
  - Renal failure
  - Abdominal surgery, GI tract perforations
  - Immunocompromise



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Antifungal Agents

1. Triazoles
   - Fluconazole – fairly safe, effective against most *Candida*
   - Voriconazole – slightly broader-spectrum against *Candida*, lots of toxicities and challenging PK
2. Echinocandins (micafungin, caspofungin, anidulafungin)
   - Very broad coverage of virtually all *Candida*. Minimal toxicity.
3. Amphotericin B
   - Very broad coverage. Very toxic.

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Antifungal Resistance

- *C. albicans* is usually fully susceptible
  - Historically the most common cause of infection
- Common resistant species:
  - *C. krusei* is intrinsically resistant to fluconazole
  - *C. lusitaniae* is usually resistant to amphotericin B
  - *C. glabrata* is often resistant to azoles
- Echinocandin (micafungin, caspofungin) resistance is increasingly seen

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Candida auris

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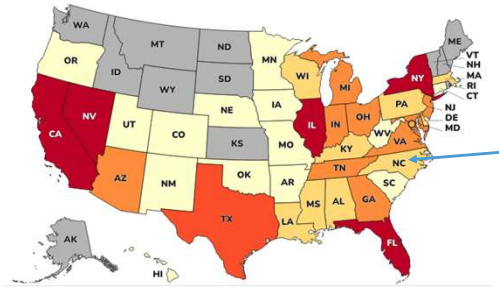
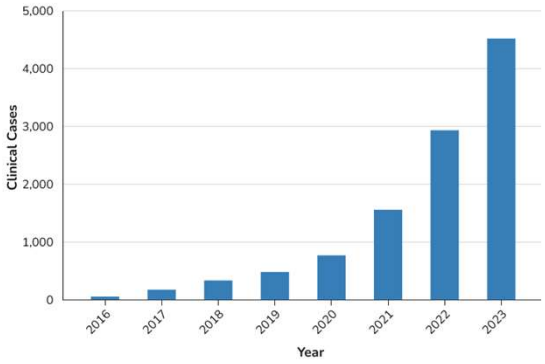
- Important concern for Infection Prevention
  - Prolonged patient colonization
  - Prolonged survival on surfaces



NC: 20 cases



https://www.cdc.gov/candida-auris/tracking-c-auris/index.html, accessed 10/17/25

Candida auris - Significance

- Infections have tended to be severe
- Antifungal resistance
  - 90% are resistant to fluconazole/voriconazole
  - 30% are resistant to amphotericin B
  - 5% resistant to echinocandins
  - 2 cases of pan-resistant *Candida auris* in US

https://www.cdc.gov/fungal/candida-auris/index.html

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Candida auris Spread

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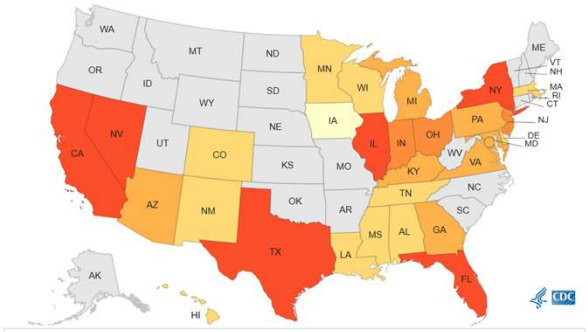
2022

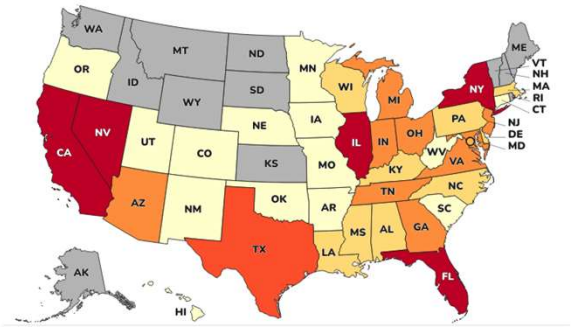


Number of *C. auris* clinical cases through December 31, 2022

In the most recent 12 months, there were 2,377 clinical cases and 5,754 screening cases (January 2022 - December 2022).

- 0 clincial cases and at least 1 screening case
- 1 to 10
- 11 to 50
- 51 to 100
- 101 to 500
- 501 to 1000
- 1001 or more

2023



Centers for Disease Control and Prevention, "Tracking *Candida auris*" accessed 10/17/2025 https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html

Infection Control for *Candida auris*

- CDC requests immediate reporting (candidaauris@cdc.gov)
- Single-patient room, contact precautions
- Screen index patient's contacts for colonization
- Disinfection: disinfectants effective against C-diff spores

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Conclusions

1. Antibiotic resistance continues to worsen
   - Positive feedback loops
   - Treatment remains challenging
   - Some significant antibiotic breakthroughs will improve outcomes
2. Populations vulnerable to antibiotic resistance continue to grow
   - Elderly, medically fragile, immunocompromised, critical illness, prolonged hospitalization
3. Local spread of antibiotic resistance can be significantly slowed through Infection Prevention and Antibiotic Stewardship

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