Management of Antibiotic-Resistant Pathogens

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I have no disclosures

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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
  - Fungi: *Candida* spp

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*
- Strategies to prevent AR infections

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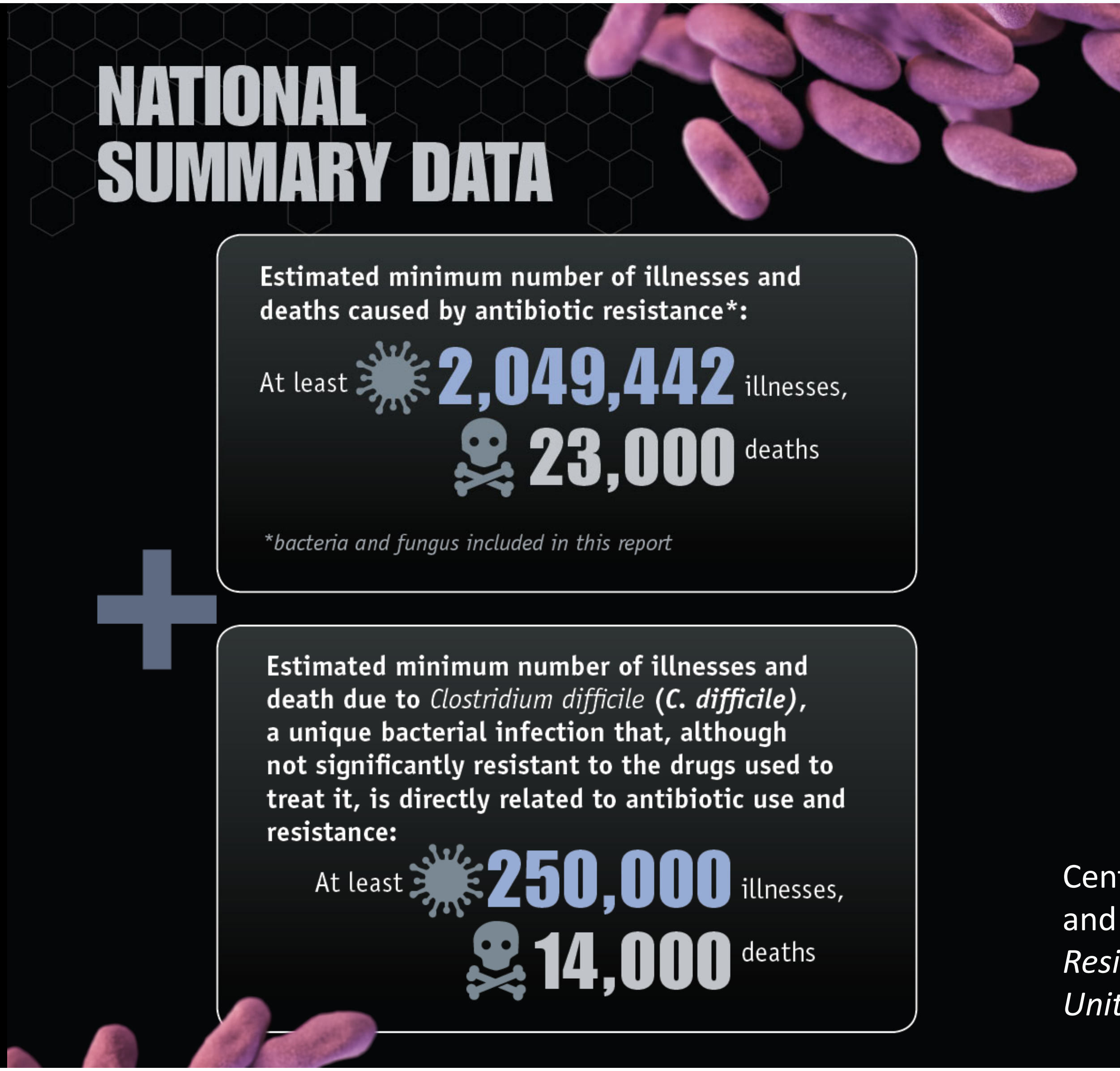
Disclaimers

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



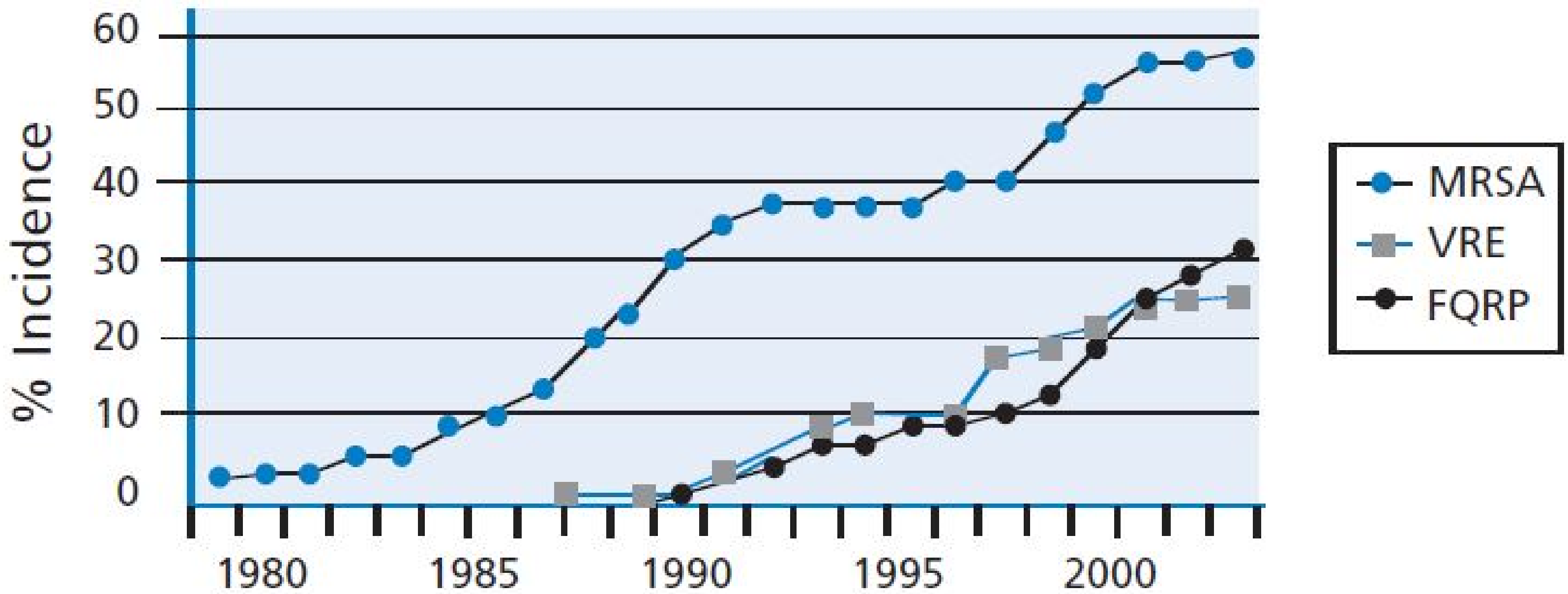
Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States*. 2013

Factors Contributing to Spread in Hospitals

- Patient Factors:
  - Severity of illness
  - Immunocompromising conditions
  - Medical technology and procedures (LDA, open wounds)
- Infection Control:
  - Increased introduction of resistant organisms from the community (and residential facilities)
  - Ineffective infection control & isolation practices (esp. compliance)
- Antibiotic Overuse:
  - 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.

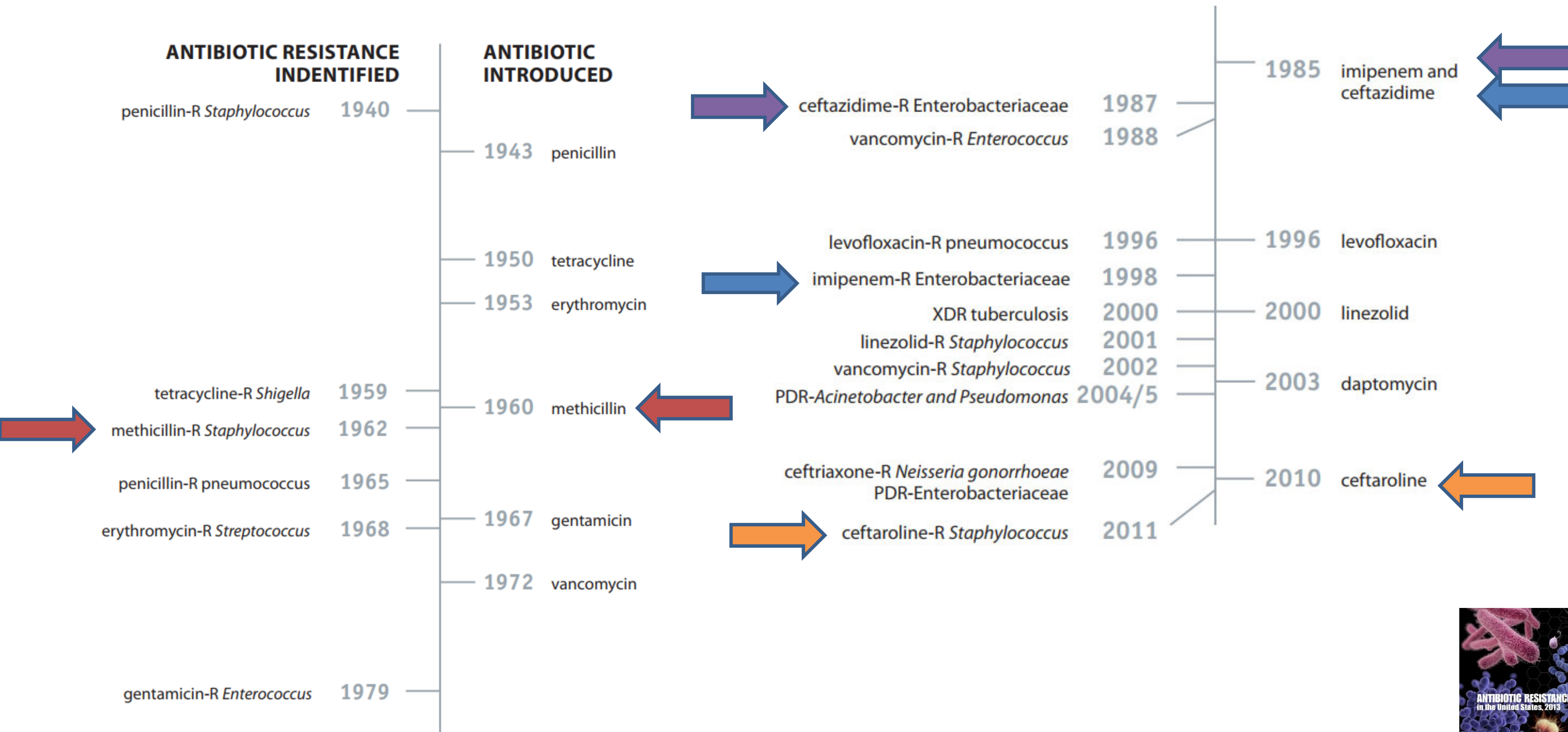
Chart 1: Resistant Strains Spread Rapidly

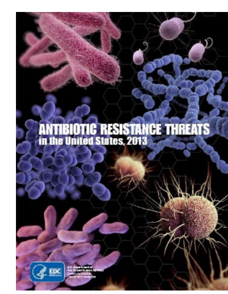


Source: Centers for Disease Control and Prevention

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


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


ANTIBIOTIC RESISTANCE THREATS
in the United States, 2013

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

Principles of Antibiotic Resistance

(Levy SB. NEJM, 1998)

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

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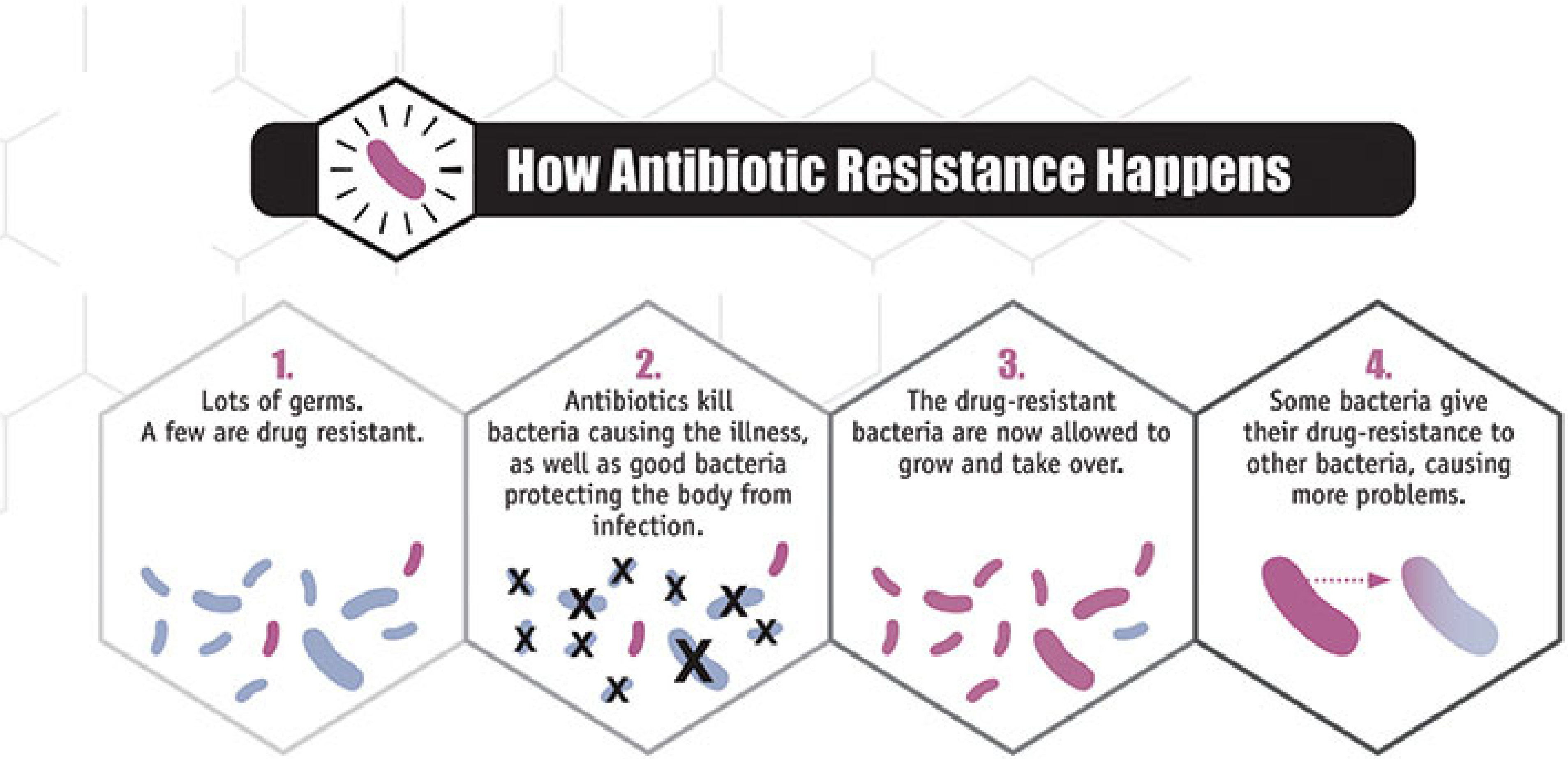
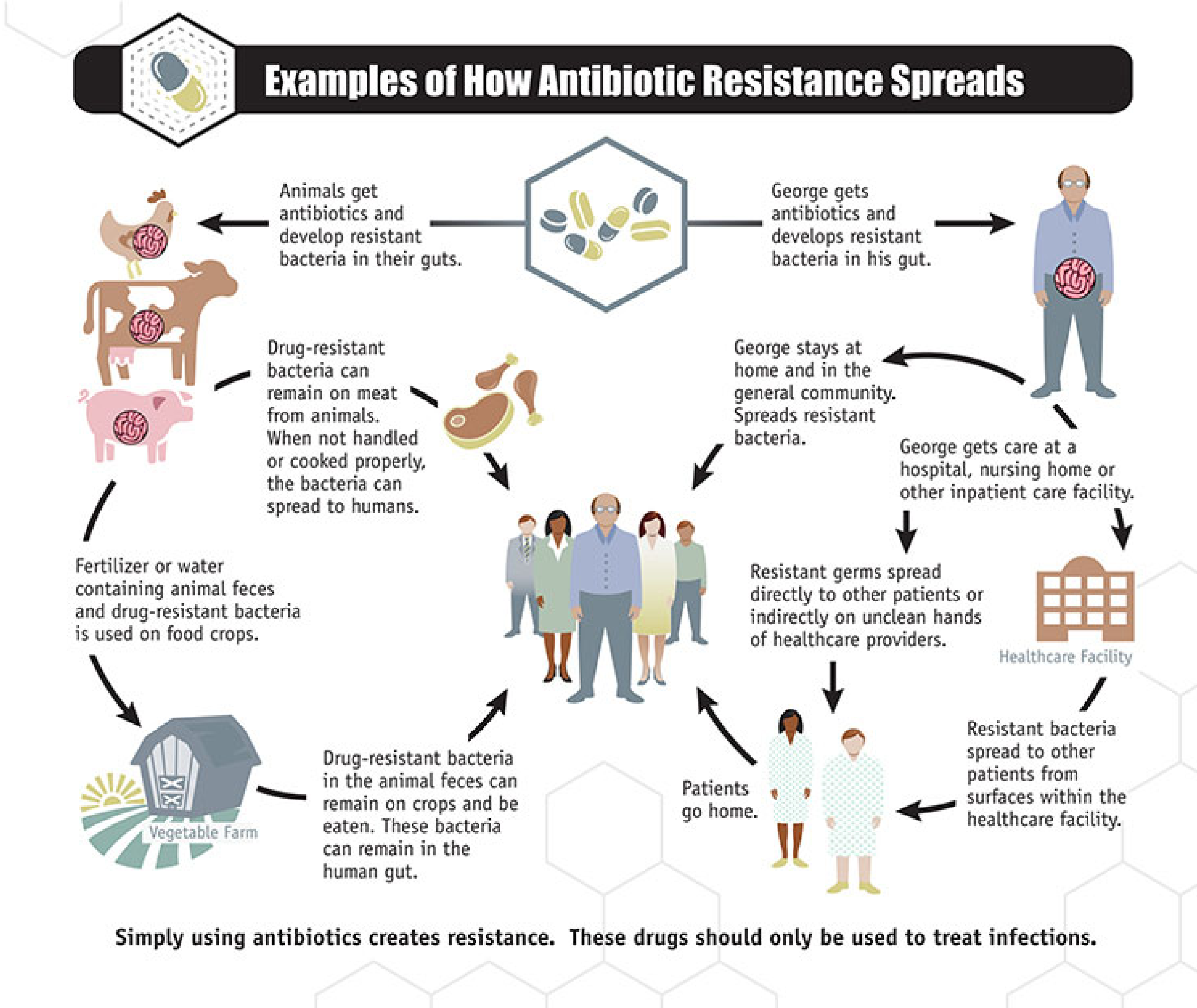
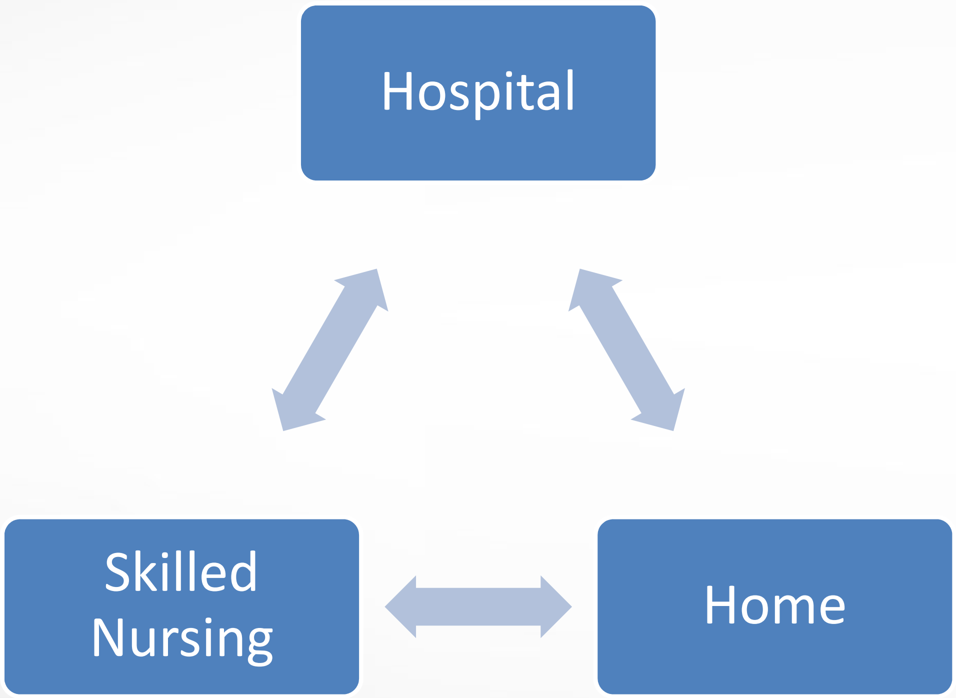

How Antibiotic Resistance Happens
1.
Lots of germs.
A few are drug resistant.
2.
Antibiotics kill
bacteria causing the illness,
as well as good bacteria
protecting the body from
infection.
3.
The drug-resistant
bacteria are now allowed to
grow and take over.
4.
Some bacteria give
their drug-resistance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

Farm-to-~~Table~~
Hospital



Care Continuum



- Patients may cycle between inpatient facilities, skilled nursing facilities, and home
- AR pathogens can be acquired at any site and carried to the others
- Inadequate infection control and poor antibiotic stewardship at any one site can create problems at the others.

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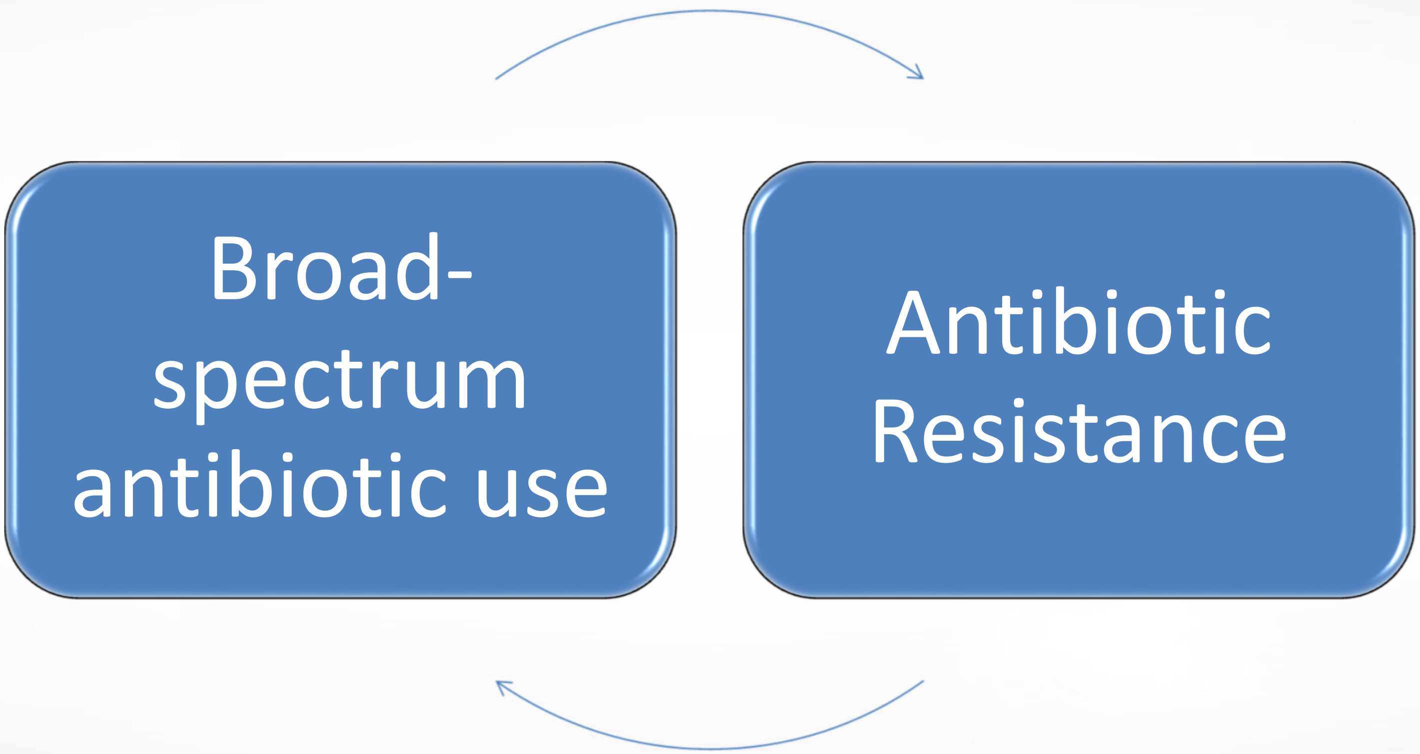

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CDC Four Core Activities to Fight Resistance

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

- 13 antibiotics approved since 2010
- Currently ~42 new antibiotics in development
  - Historically, about 1 in 5 will reach the market
- Barrier: limitations on sales
  - AR pathogens still uncommon
  - Brief courses
  - Antimicrobial stewardship
- Policy fixes:
  - GAIN Act extended patent protection for five years
  - 21^{st} Century Cures Act reduces the FDA approval burden for high-value antibiotics

Antibiotics Approved Since 2010

2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Ceftaroline		Telavancin	Tedizolid		Ceftazidime-Avibactam		Meropenem-Vaborbactam	Plazomicin	Lefamulin
			Dalbavancin				Delafloxacin	Eravacycline	Imipenem-Relebactam
			Oritavancin					Omadacycline	
			Ceftolozane-Tazobactam						

Emerging AR Pathogens of Importance in US Inpatient Settings

- *Enterococcus*:
  - Ampicillin, vancomycin
- *Staphyloccus aureus*:
  - Oxacillin, clindamycin, vancomycin?
- Gram-negative enterics:
  - ESBL, CRE
- *Pseudomonas, Stenotrophomonas, Acinetobacter*
- Fungi:
  - *Candida krusei, C. auris*

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ESKAPE Pathogens

Enterococcus faecium (VRE)

Staphylococcus aureus (MRSA)

Klebsiella and *Escherichia coli* producing ESBL

Acinetobacter baumannii

Pseudomonas aeruginosa

Enterobacteriaceace

Diagnosis of AR Pathogens

Culture

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

PCR

- 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

Mean Inhibitory Concentration (MIC)

- The MIC is a **phenotypic** test of a bacterial isolate's growth when exposed to a particular antibiotic
- 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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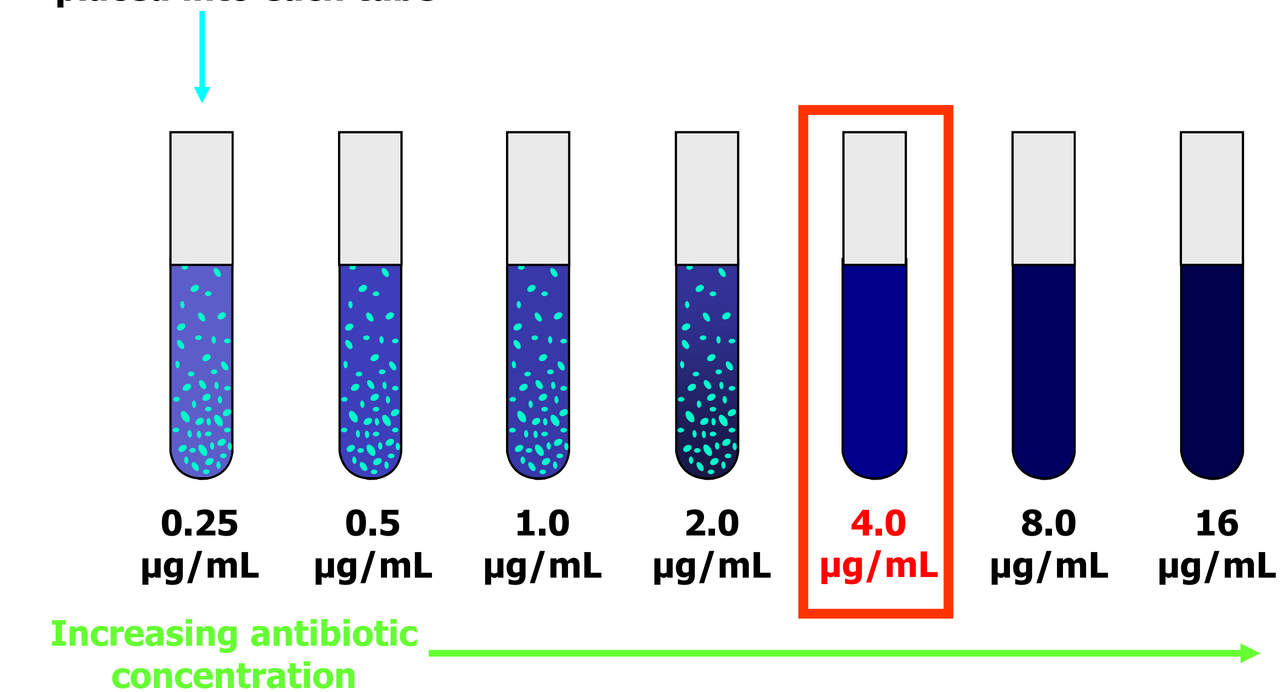
MIC Determination – Broth Microdilution

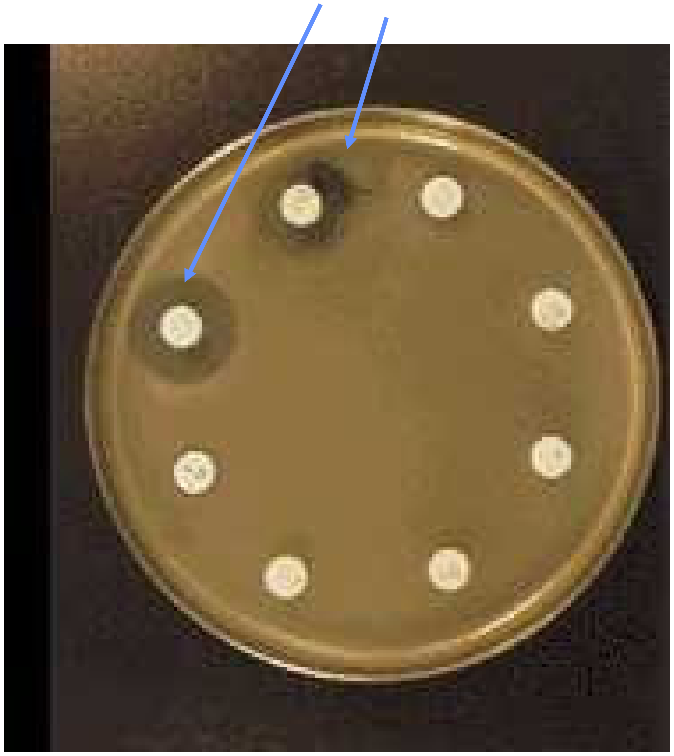
Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



Many Labs Use Automated Testing

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

MIC Determination – Plate-Based



Kirby-Bauer: zone of inhibition around disc predicts susceptibility

E-test: strip with gradient antibiotic concentration

MIC Interpretation

- For EVERY (relevant) combination of species and antibiotic, there is a breakpoint established by CLSI
- Requires understanding of pharmacology of antibiotic
- The breakpoint allows interpretation as susceptibleor resistant
  - For example: MIC=1, breakpoint=4 → susceptible
- Not all breakpoints are appropriate.
  - *S. aureus* vancomycin breakpoint is <=2. However, outcomes are worse if MIC=2 than if MIC<=1.

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Modes of Antibiotic Therapy

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:
  - 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
- Threat of resistance → increased use of more toxic, less effective, more expensive, IV-only drugs in patients *without* resistant organisms

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Gram-positive AR Pathogens

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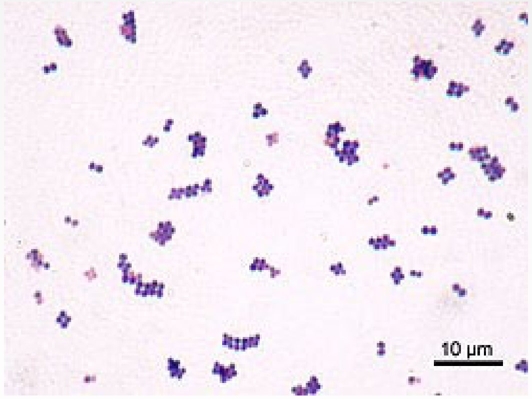
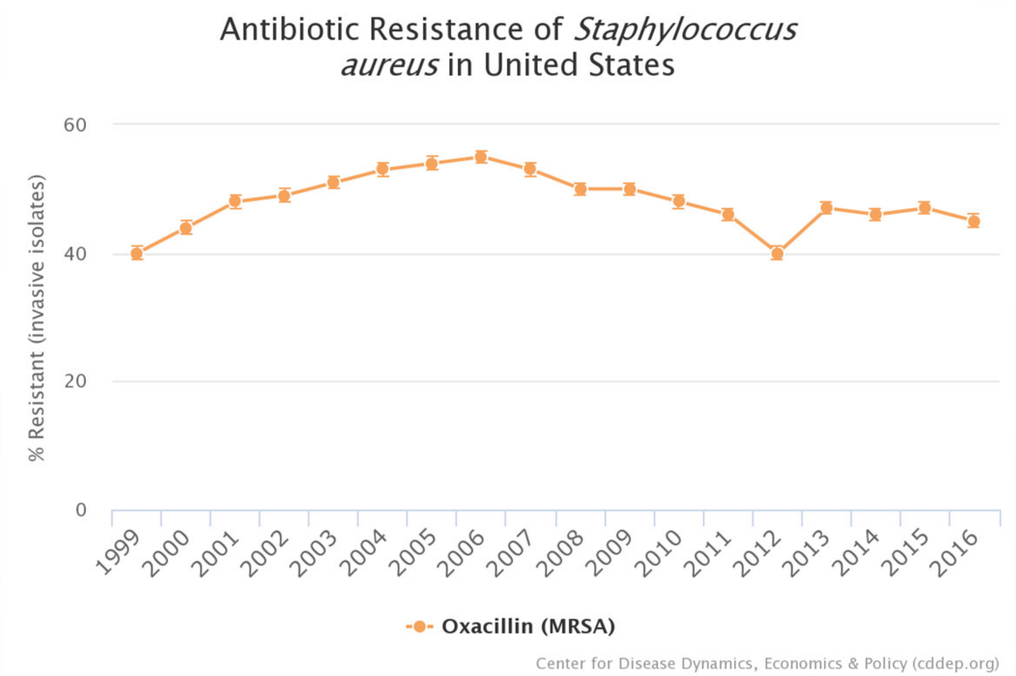
Gram-positive Principles

- Antibiotic resistance is often monogenic
  - 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*)

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**





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Staphylococcus aureus

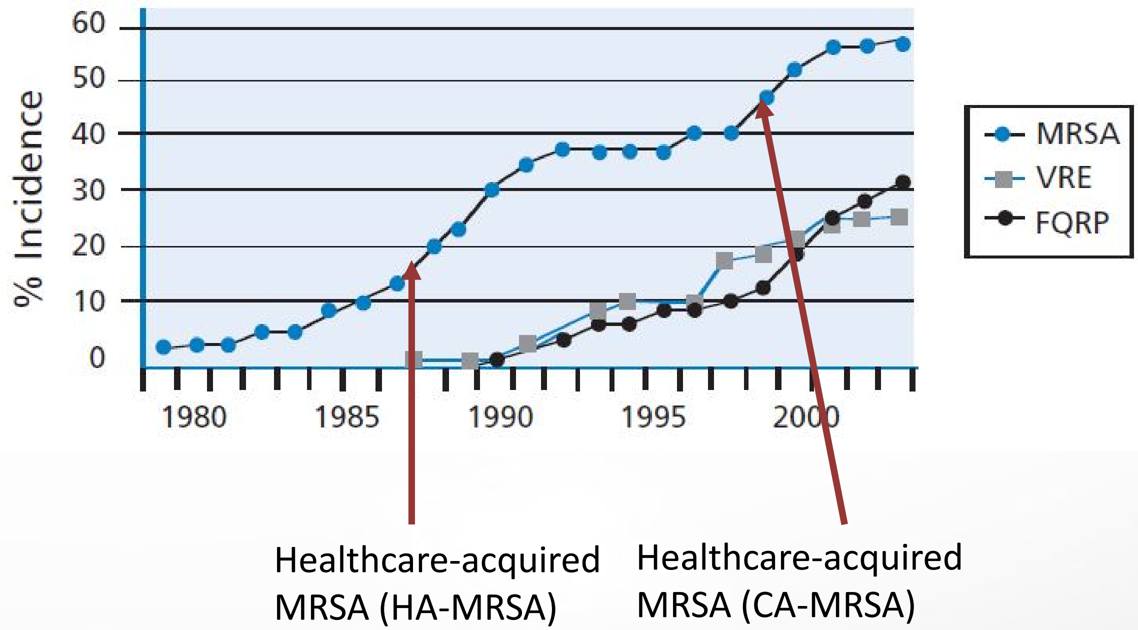
- Plain MSSA can be killed by most beta-lactams (nafcillin, oxacillin, cefazolin…)
  - MSSA may be just as invasive/virulent as MRSA
- Methicillin resistance is common
  - *mecA* gene alters the beta-lactam target (can detect by PCR)
  - Treatment: usually vancomycin
  - Options (severe infection): daptomycin, ceftaroline
  - Options (less severe): linezolid, clindamycin, doxycycline, TMP-SMX

Staphylococcus aureus

- Clindamycin resistance
  - Rising steadily over time with regional variance (high in NC)
  - Challenge in MRSA era
- Vancomycin resistance (VISA and VRSA)
  - Extremely rare (handful of cases of VRSA ever)
  - However, “MIC creep” is a well-described phenomenon in hospitals with heavy vancomycin use – the most common MIC may rise from 0.5 → 1 → 1.5 → 2

MRSA Evolution

- HA-MRSA was highly antibiotic-resistant
- CA-MRSA (USA300 strain) is highly virulent
- Less distinction between the two currently



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Staphylococcus aureus - Summary

- Causes a LOT of infections
  - Nosocomial and community-acquired
- Highly virulent
- We have options for dealing with MRSA
  - But usually more toxic and/or less effective than beta-lactams
  - The threat of MRSA → near-universal use of empiric vancomycin in severe acute infections
  - Can screen and isolate and decolonize patients
- VISA/VRSA are rare but can gradually be uncovered

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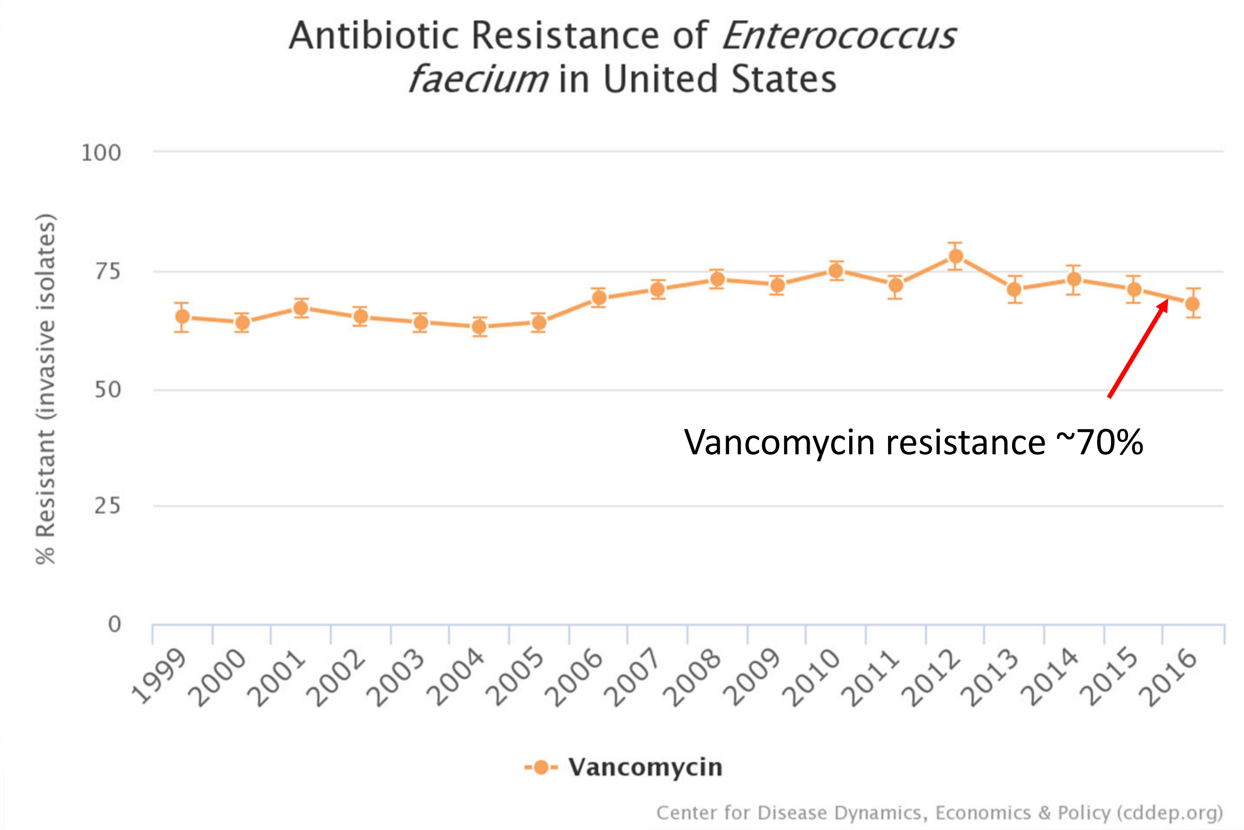
Enterococcus faecium

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



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Enterococcus faecium

- Generally, 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
- High-risk populations (neonates, immunocompromised) can be screened with perirectal swabs

Treatment of VRE

- Vancomycin resistance encoded by genes *vanA* or *vanB*
  - Change in structure of target → complete resistance
- Daptomycin is often active
  - Requires high-dose daptomycin
- Linezolid is almost always active
- Others: tigecycline, quinupristin-dalfopristin, telavancin

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Gram-negative AR Pathogens

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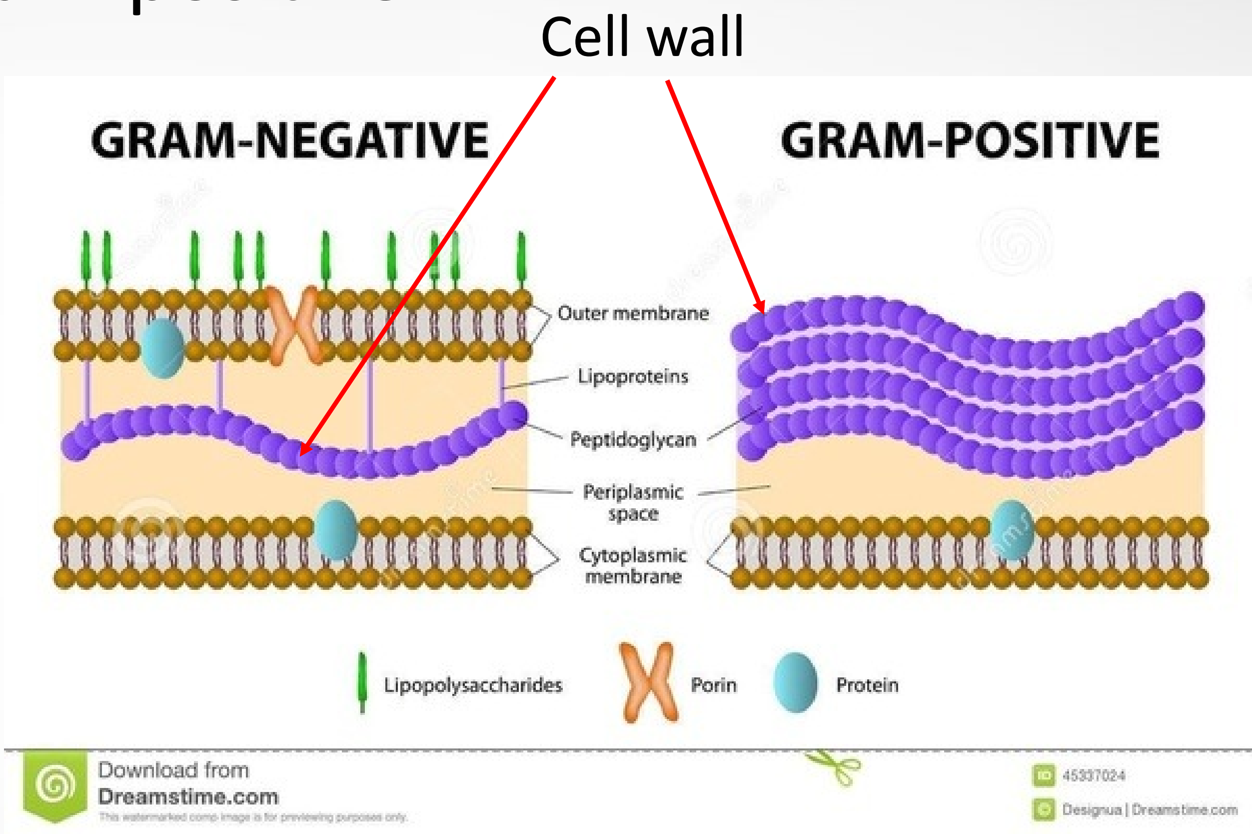
Gram-negative vs Gram-positive

- 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

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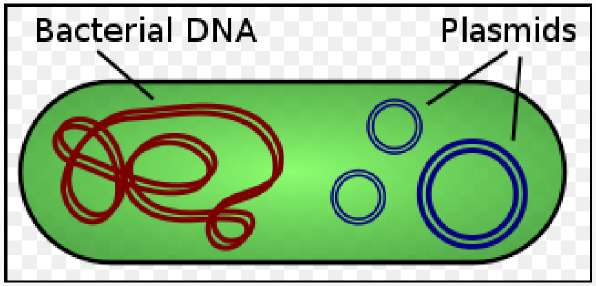
Gram-negative Rods – General Principles

- Genotype may not predict phenotype
- Lab phenotype may not predict clinical phenotype
- 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

Extended-Spectrum Beta-lactamases (ESBL)

- Large heterogeneous family of enzymes
- “Extended spectrum” generally means activity against penicillins, cephalosporins (including 4th-gen), and aztreonam
- Labs may use 3rd-gen cephalosporin resistance as proxy
- NOT active against carbapenems
- Inhibited by beta-lactamase inhibitors (e.g., tazobactam)

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
- In general, one single type tends to predominate in a region or hospital

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ESBL – Clinical Strategies

- Often resistant to other antibiotic classes as well (aminoglycosides and fluoroquinolones)
- Beta-lactam strategies
  - **Carbapenems** have given the best outcomes
  - **Avoid cephalosporins** (even if reported susceptible)
  - For patients with ESBL bacteremia, mortality higher if treated with pip-tazo compared to meropenem (12.3% vs 3.7%)

Carbapenem Resistance

- Carbapenems are the last-line beta-lactams
- In Enterobacteriaceae (e.g., *E. coli, Klebsiella*, *Enterobacter*), carbapenem resistance is mediated by carbapenemases
  - CRE = Carbapenem-resistant Enterobacteriaceae
- Non-carbapenemase mechanisms: altered porins, efflux pumps
  - Less concern for healthcare epidemiology
  - Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
  - Carbapenem-resistant *Acinetobacter baumanii* (CRAB)

Carbapenemases

- Major infection control concern
- Most are **plasmid-mediated**
- In general, active against all beta-lactams
- Generally not inhibited by beta-lactamase inhibitors
  - Novel BLIs can target them
- For years, no good antibiotic strategies

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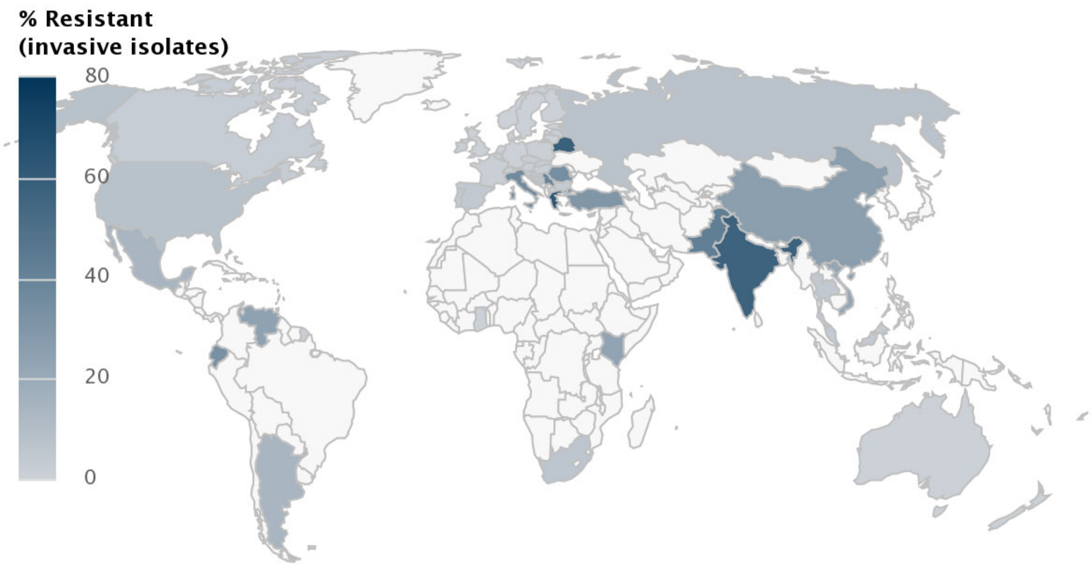
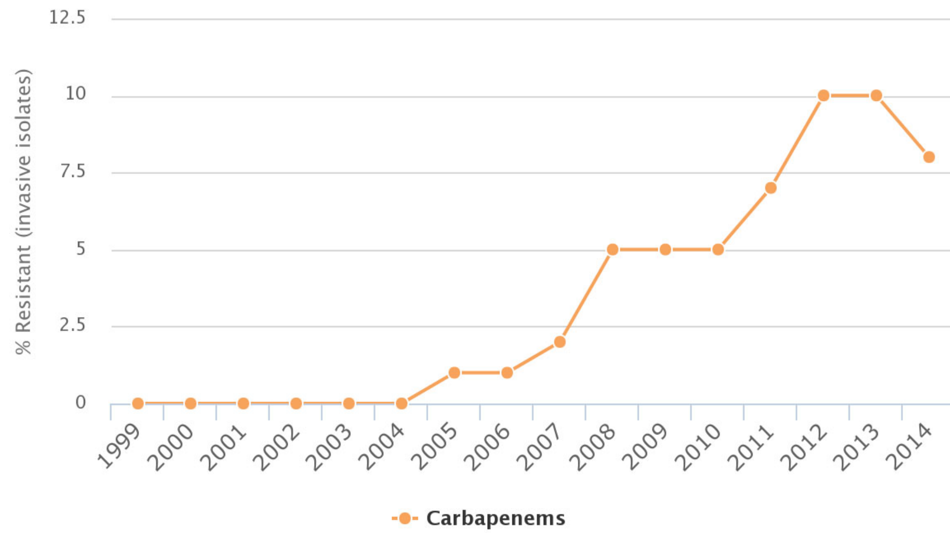
Resistance of *Klebsiella pneumoniae* to Carbapenems



Center for Disease Dynamics, Economics & Policy (cddep.org) © Natural Earth

Antibiotic Resistance of *Klebsiella pneumoniae* in United States



Center for Disease Dynamics, Economics & Policy (cddep.org)

Treatment

- Often have resistance to other classes (fluoroquinolones, aminoglycosides); sometimes on same plasmid
- Other options
  - Tigecycline (bad for bloodstream infections and pneumonia)
  - Polymyxins: colistin, polymyxin B (extraordinarily toxic)
  - Generally used in combination
- Newer beta-lactam combinations are a revolution

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

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

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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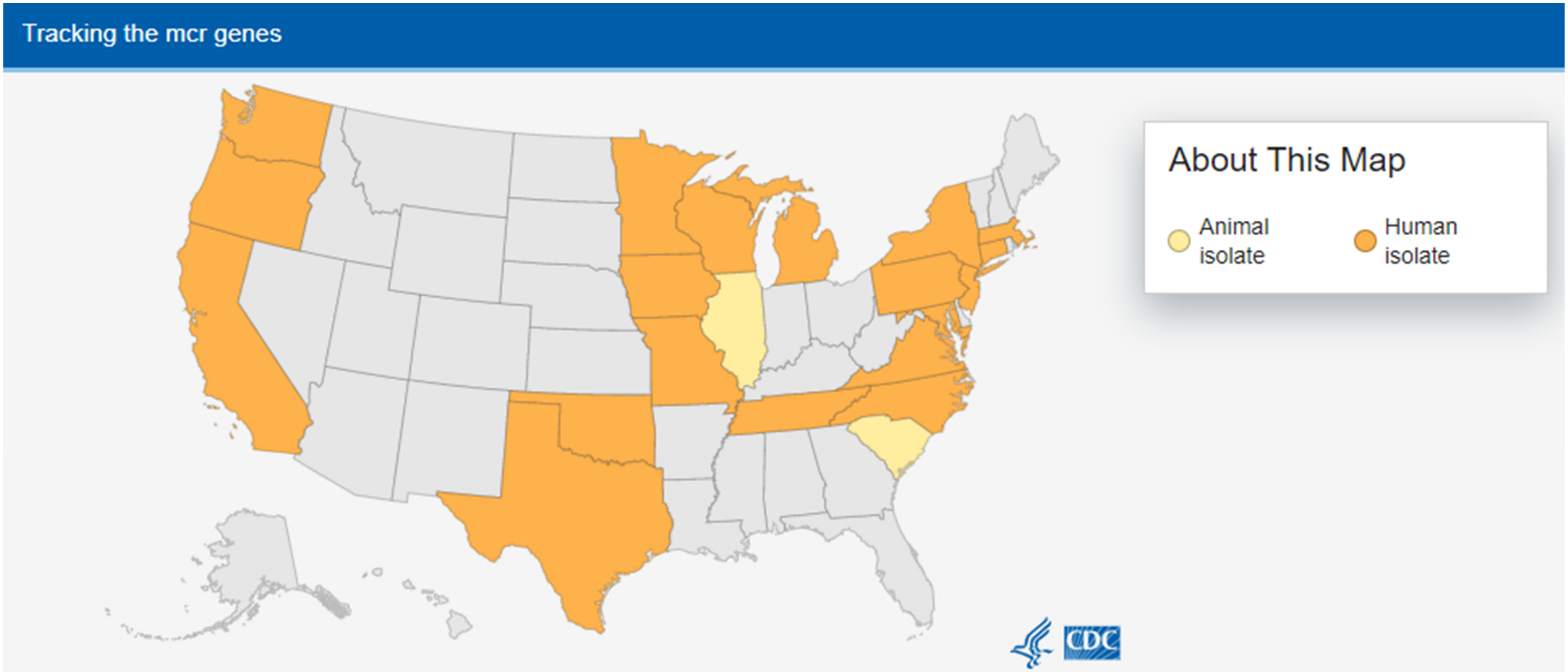

https://www.cdc.gov/drugresistance/biggest-threats/tracking/mcr.html

Pseudomonas aeruginosa

- Important cause of VAP (20 percent), CLABSI (18 percent), CAUTI, SSI
- Can accumulate multiple mechanisms of resistance
  - Often mediated at the outer membrane: porins and efflux pumps
- If *Pseudomonas* is suspected, consider double-coverage for **empiric** therapy: e.g., add tobramycin to cefepime to cover cefepime-resistant isolates
- Double-coverage is generally *not* recommended for **targeted** therapy

Acinetobacter baumanii

- Important nosocomial bacterial pathogen: VAP (8.4 percent), 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
- Resistant infections treated with polymyxins + tigecycline or minocycline

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

Prevention of Resistant Gram-negative infections

- High-risk populations:
  - Trauma, diabetes, malignancy, organ transplantation
  - Mechanical ventilation, indwelling Foley, CVCs
  - Poor functional status, severe illness
- Strategies
  - Antibiotic stewardship
  - Contact precautions
  - During CRE outbreaks, screening for rectal colonization

Antifungal-Resistant *Candida*

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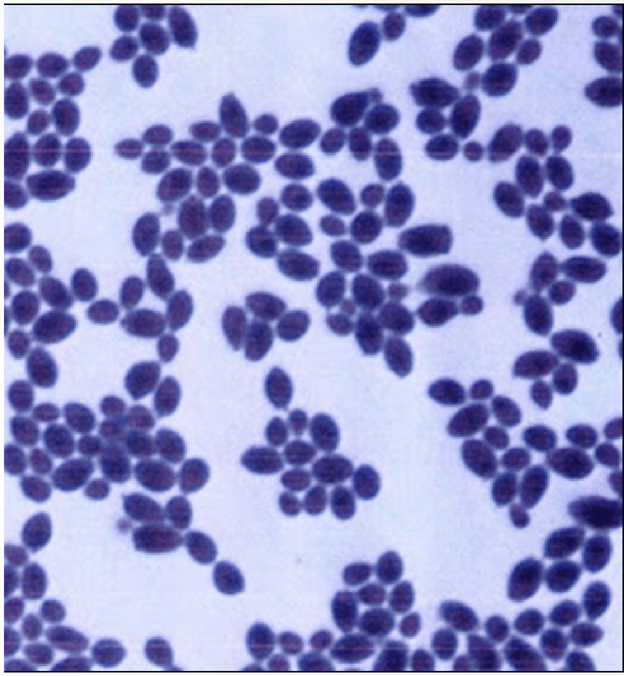
Invasive Candidiasis

- 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.

Antifungal Resistance

- *C. albicans* is usually fully susceptible
  - Historically the most common cause of infection
- With increasing use of antifungals, shift to more 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

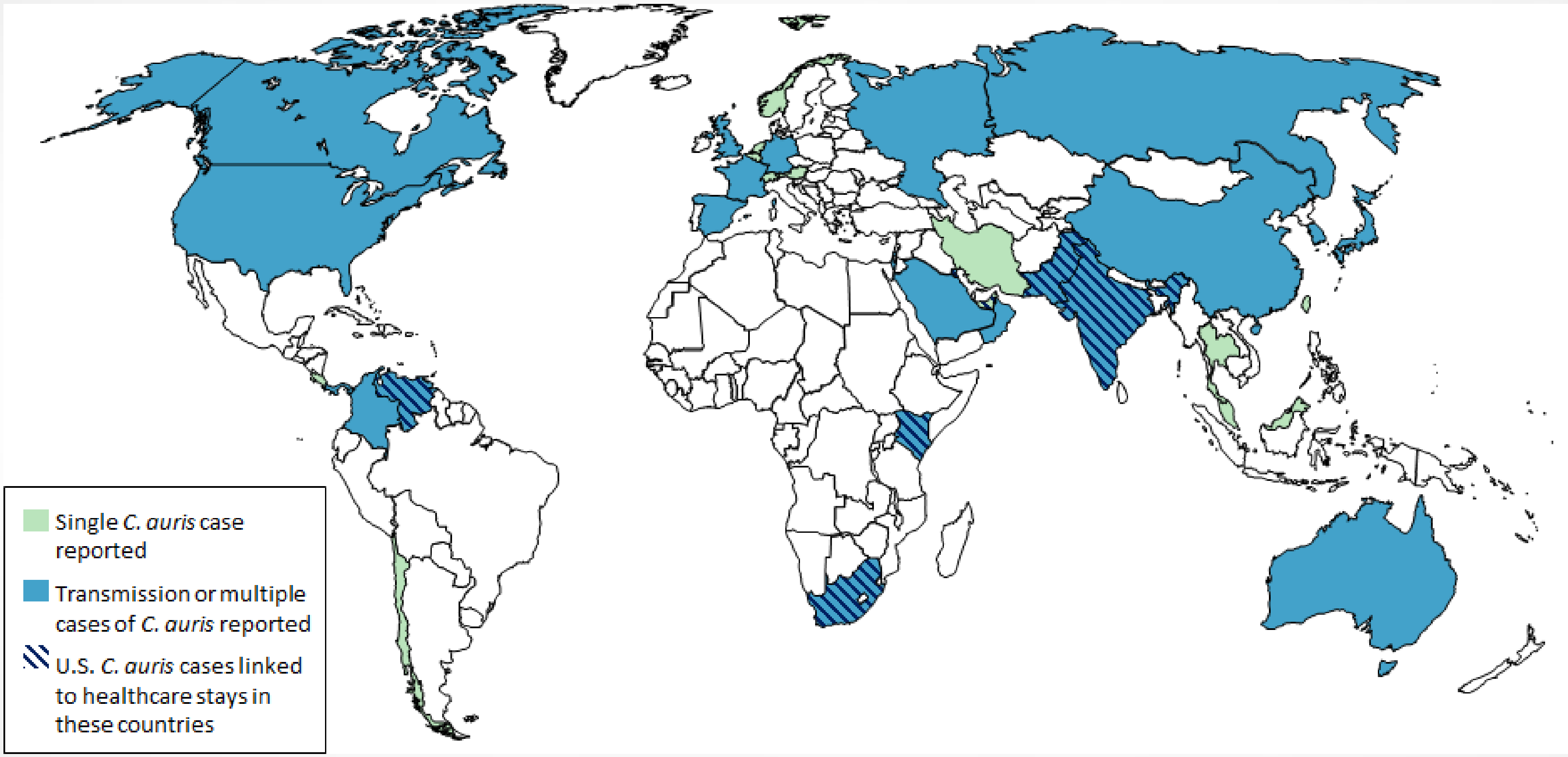
- Emerging *Candida* species
  - 799 total cases in the US (153 in 2017, 427 in 2018)
- Important concern for Infection Prevention
  - Prolonged patient colonization
  - Prolonged survival on surfaces

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

Candida auris



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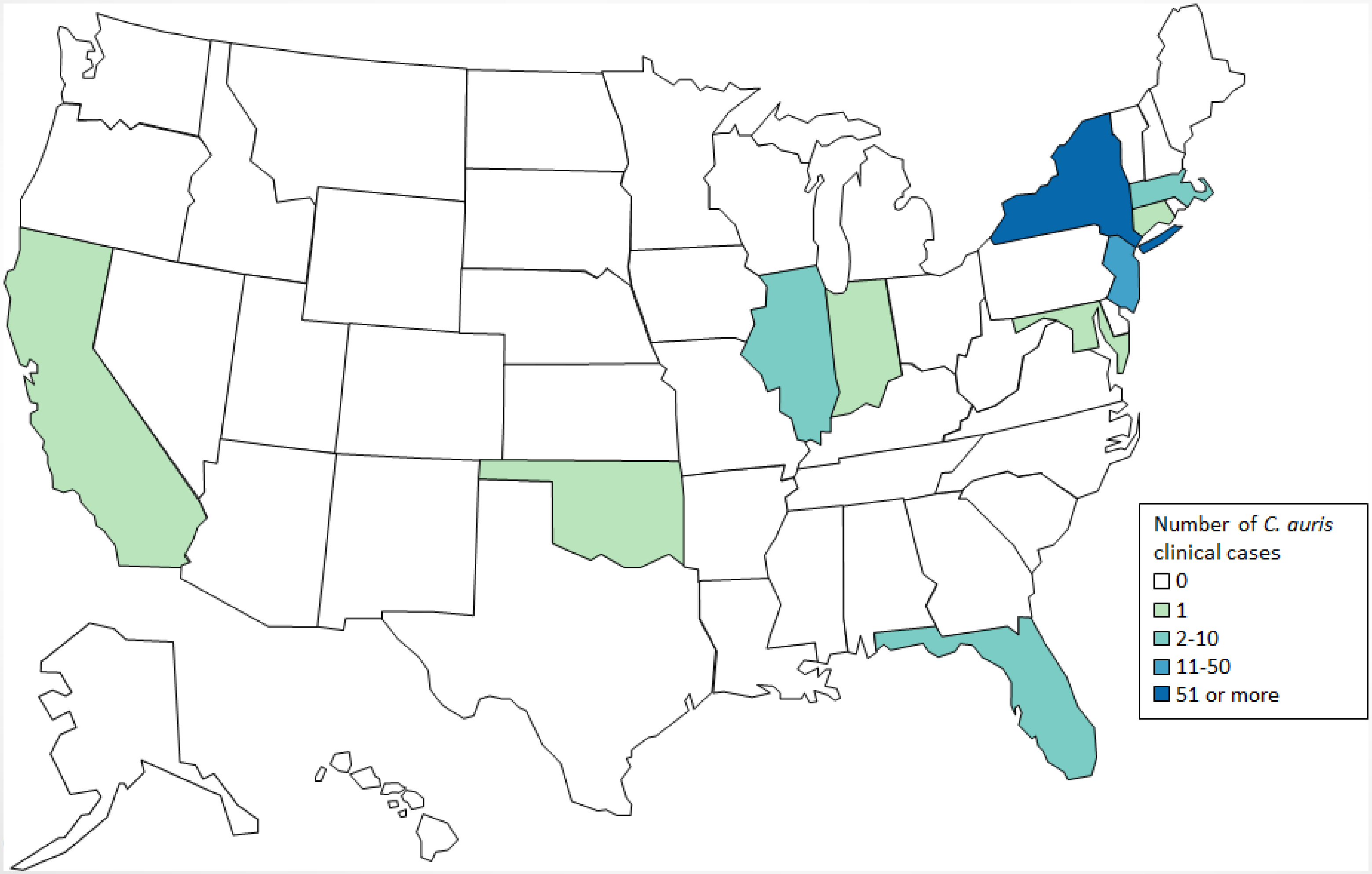
Centers for Disease Control and Prevention

Candida auris



Centers for Disease Control and Prevention

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

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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