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Changing Landscape of Antimicrobial Resistance: Primary Care Update from Antimicrobial Stewardship Perspective

2018 Infectious Diseases Symposium For Primary Care Providers

September 28, 2018

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Disclosures

- No conflicts of interest

Objectives

- Overview of burden of common antimicrobial resistance (AMR) patterns
  - Methicillin Resistant *Staphylococcus aureus* (MRSA)
  - Vancomycin Resistant *Enterococcus* (VRE)
  - Extended Spectrum β lactamase (ESBL), Amp-C, FQ-R
- Common syndromes with multidrug resistance (MDR)
  - Initial evaluation
- Antibiotic stewardship perspective
- Brief update on emerging drug resistance

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- **Overview of burden of commonly encountered antimicrobial resistance (AMR) patterns**
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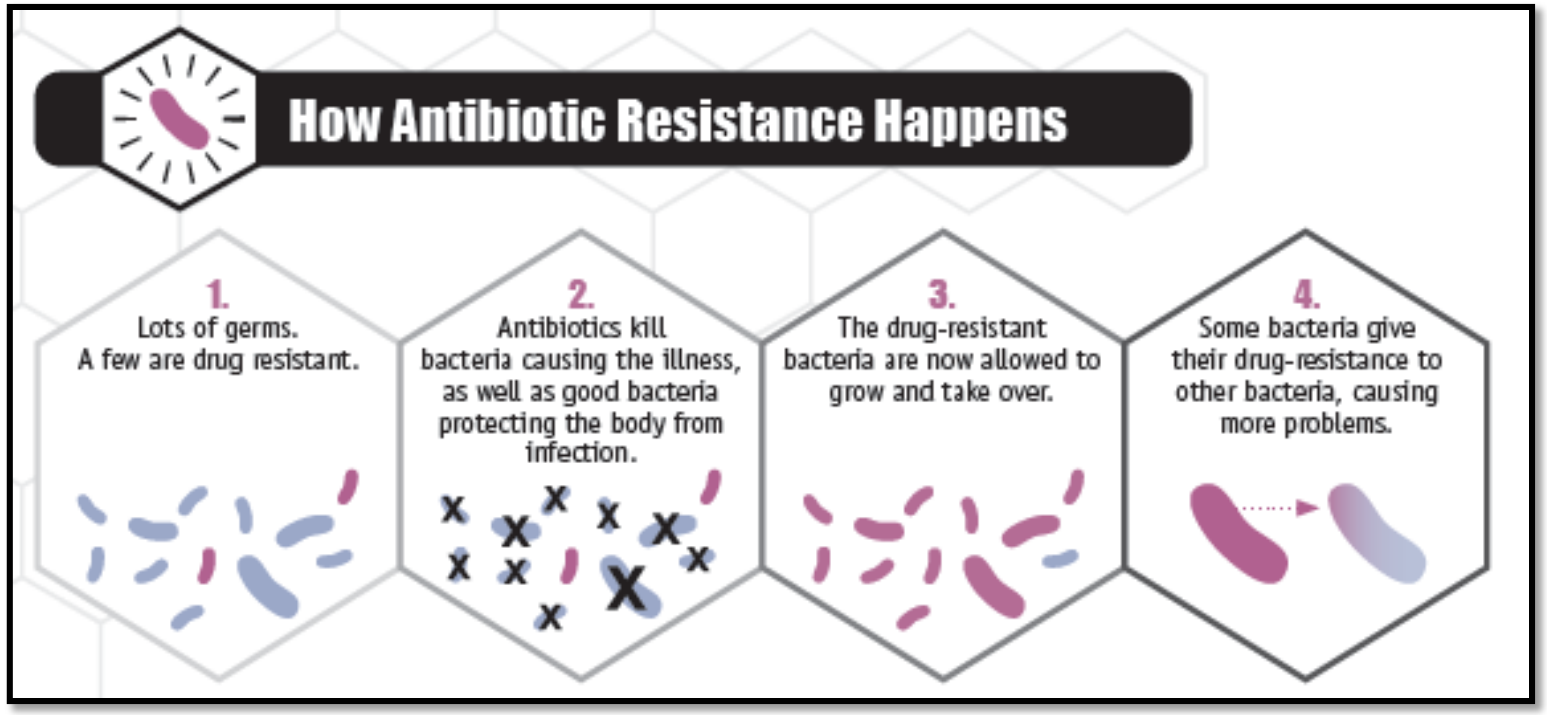
What Causes Antimicrobial Resistance?



Antibiotic pressure most important driver
Shown in both individual patients and populations
Up to 29 fold increase in AMR (drug, exposure, population dependent)

CDC. Antimicrobial resistance threats in the US, 2013

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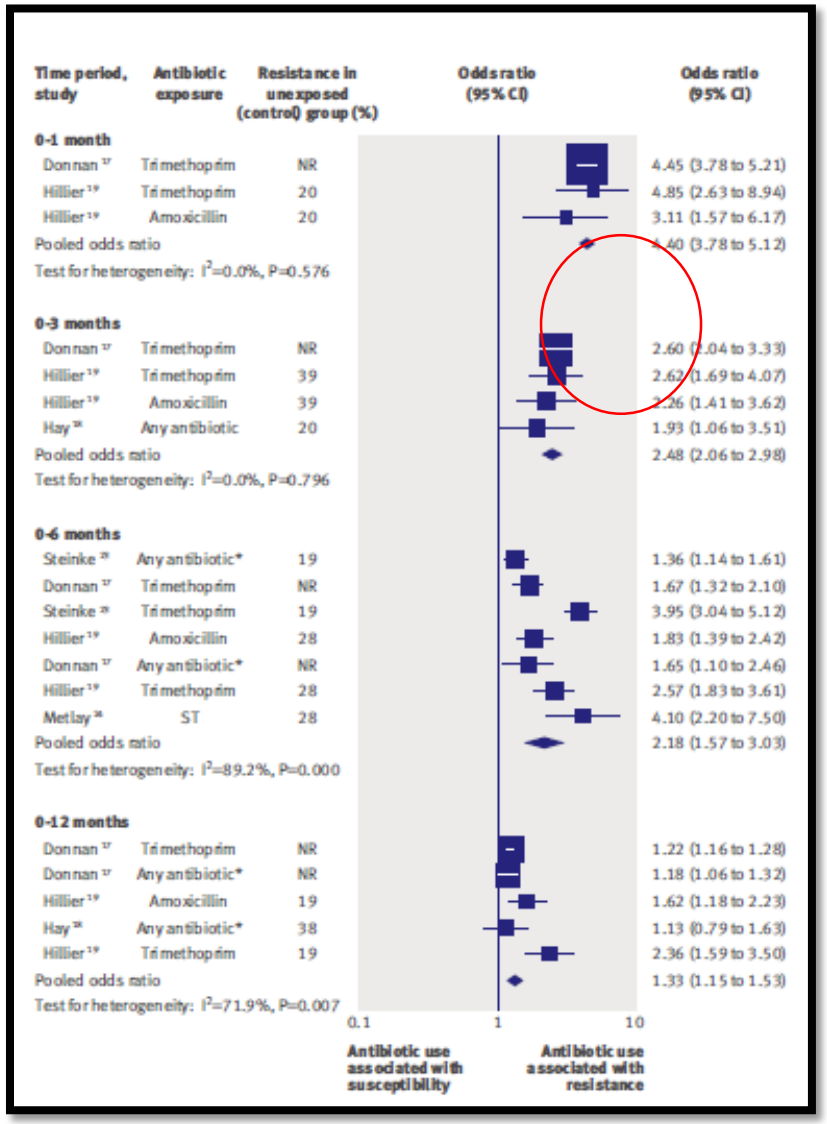
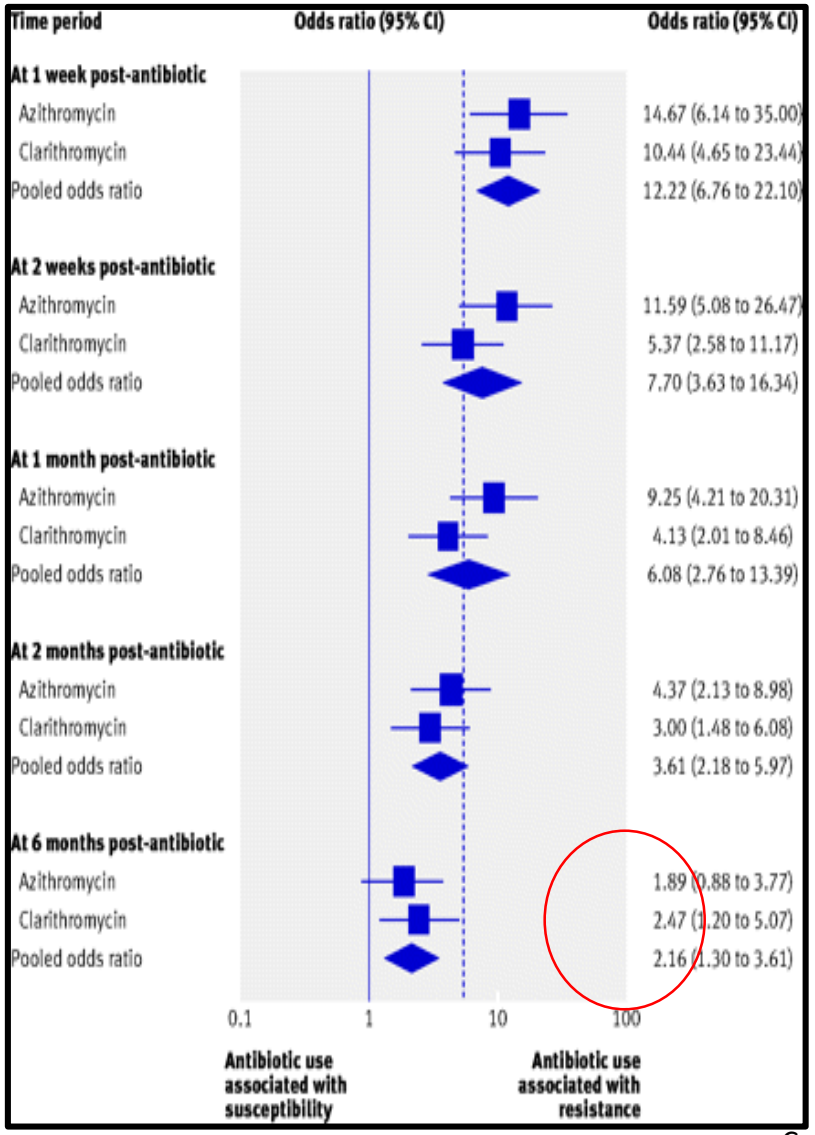
Resistance in Individual Patients

UTIs



URIs



Costelloe . BMJ 2010; 340

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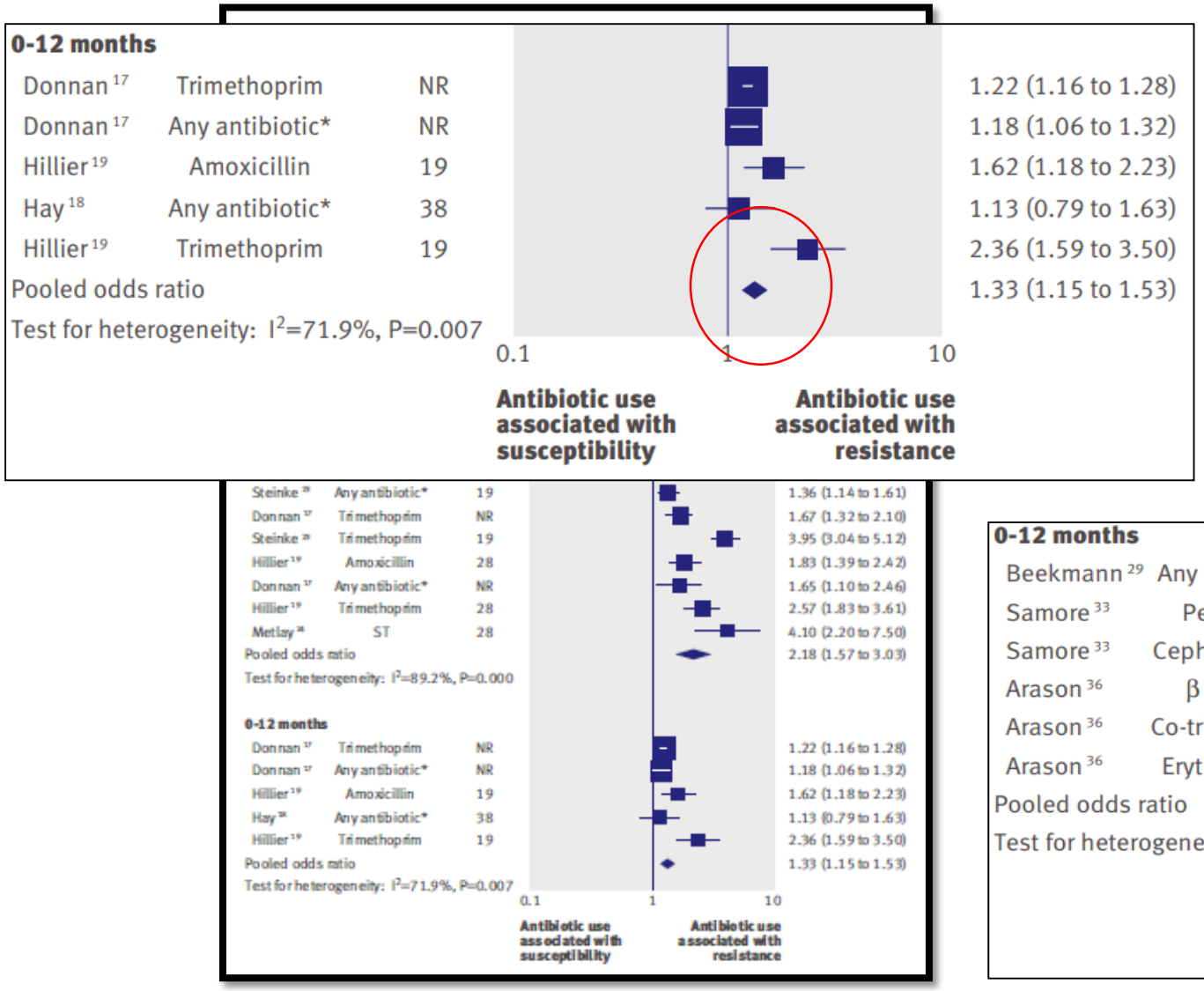
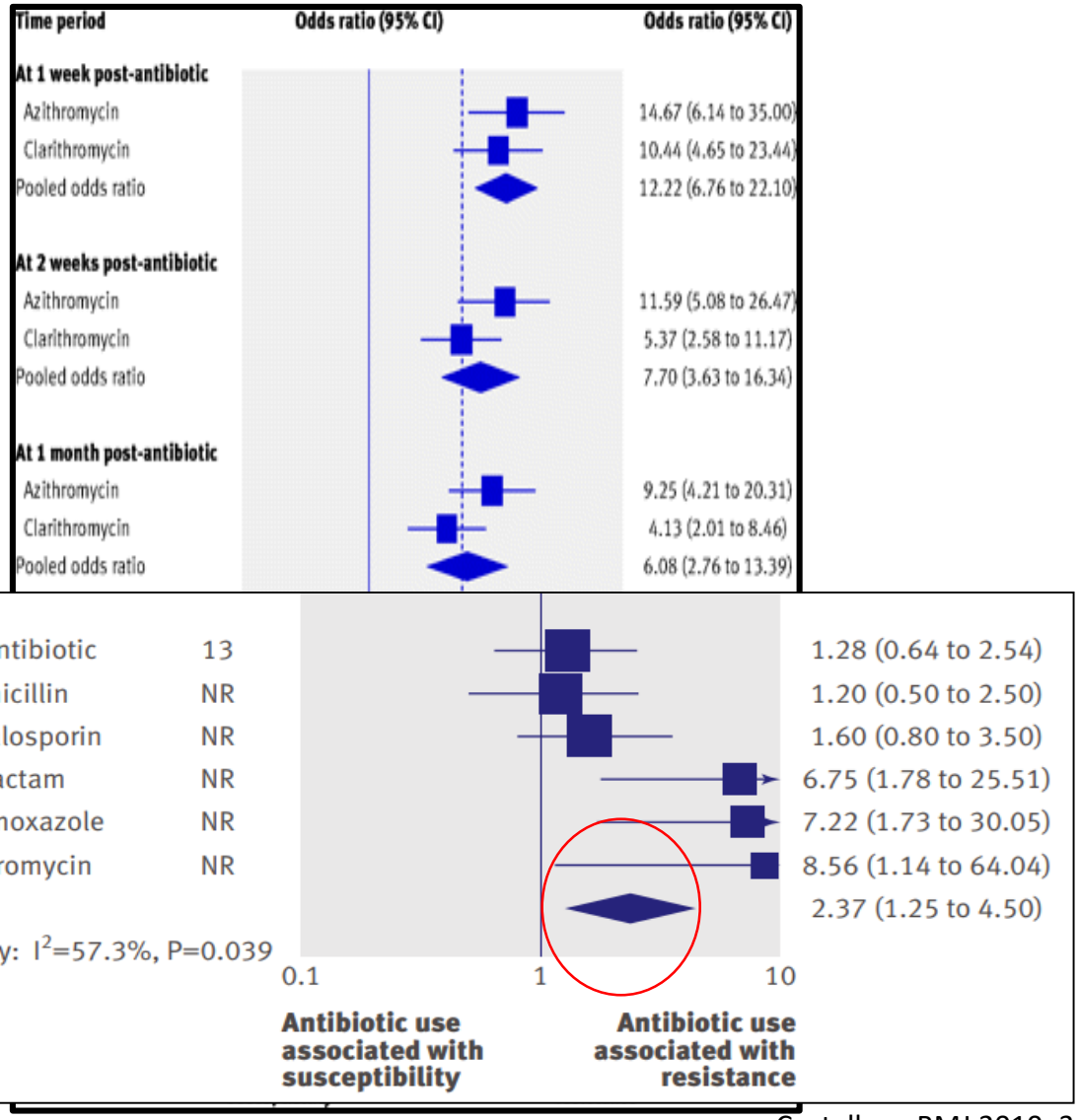
Resistance in Individual Patients

UTIs



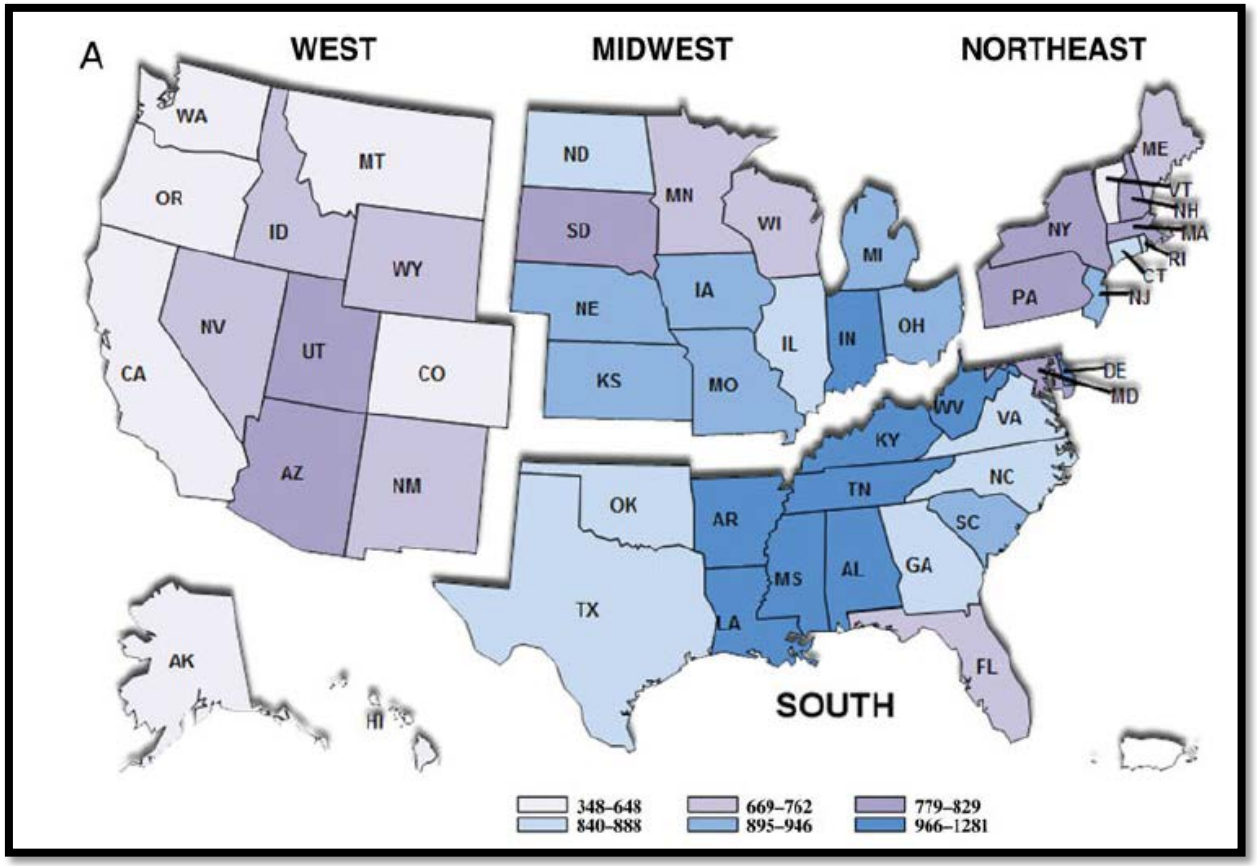
URIs



Costelloe . BMJ 2010; 340

Outpatient Antibiotic Use

- At least **30%** of antibiotics in outpatient setting **unnecessary**
- Total inappropriate use approaches **50%**
  - Considering agent, dose, duration
- >60% use in outpatients
- Southeast U.S. highest rates



CDC. Threat Report. 2013
Fleming-Dutra . JAMA. 2016;315(17):1864-1873
Hicks. CID. 2015;60(9):1308–16

Impact of Antibiotic Resistance

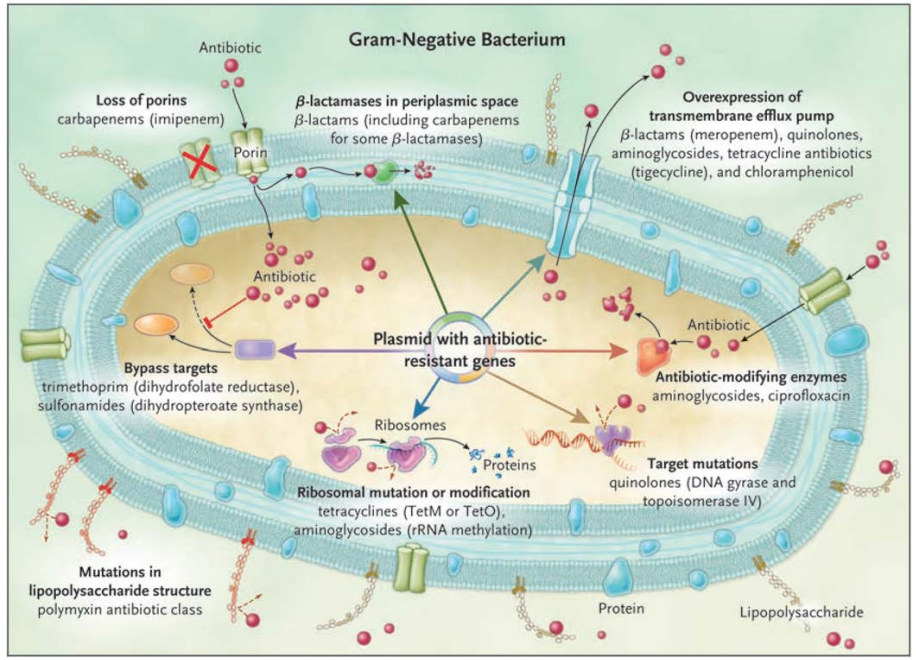
Organism	**Increased risk of death (OR)**	Attributable LOS (days)	Attributable cost
MRSA bacteremia	**1.9**	2.2	$6,916
MRSA surgical infection	**3.4**	2.6	$13,901
VRE infection	**2.1**	6.2	$12,766
Resistant *Pseudomonas* infection	**3.0**	5.7	$11,981
Resistant *Enterobacter* infection	**5.0**	9	$29,379
Carbapenem-R Enterobactereciae**	**1.12**	5.0	$10,312

Every study, regardless of organism and AMR

Cosgrove. *CID*. 2006; 42:S82-9
**Zilberberg. BMC Infet Dis. 2017; 17: 279

MDR- No ESKAPE!

- ESKAPE pathogens most significant multidrug-resistant (MDR) hospital pathogens
  - ***E****nterococcus faecium*
  - ***S****taphylococcus aureus*
  - ***K****lebsiella pneumoniae*
  - ***A****cinetobacter baumannii*
  - ***P****seudomonas aeruginosa*
  - ***E****nterobacter species*



Peleg and Hooper. NEJM 2010 May 13;362(19):1804-13

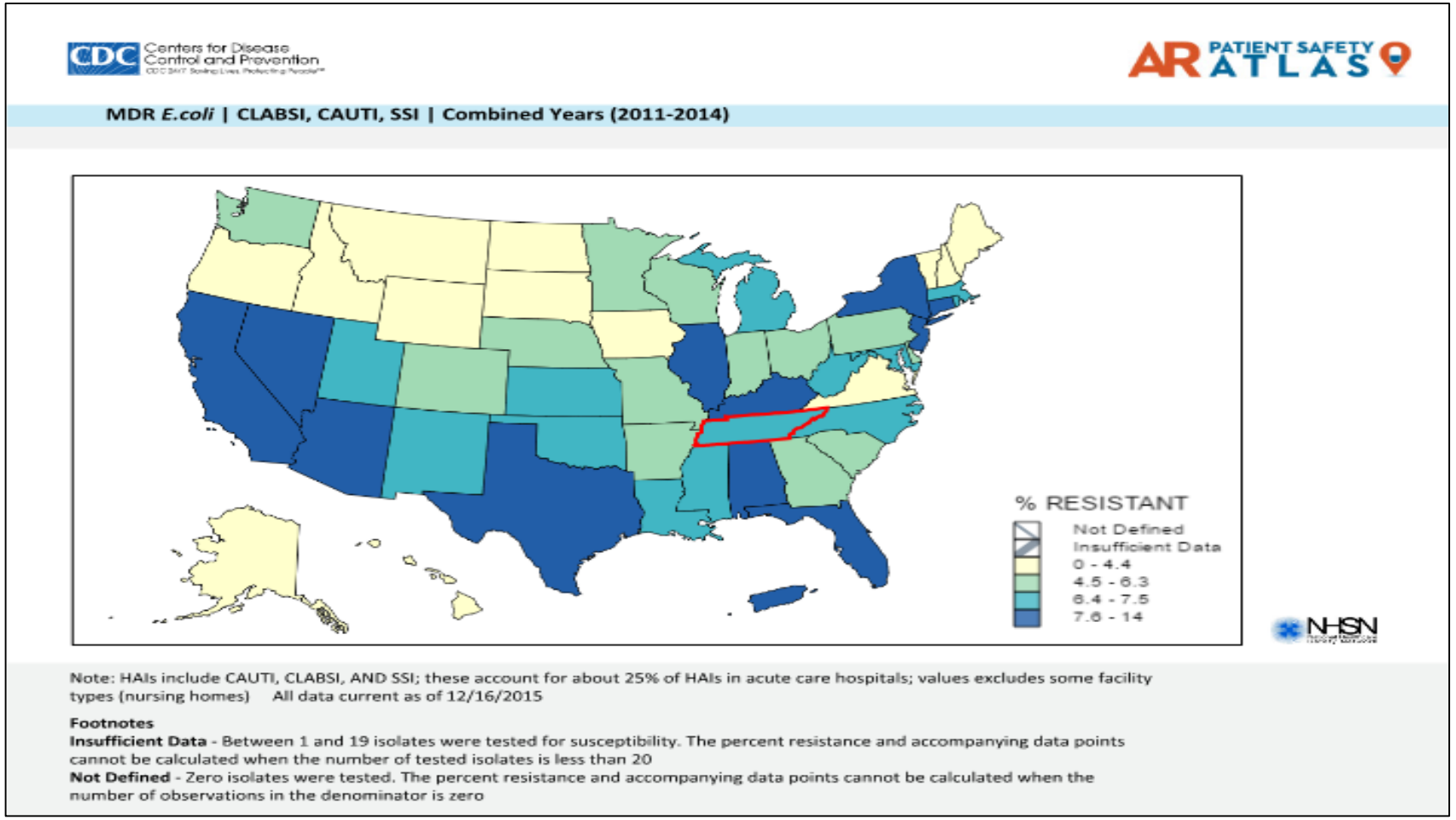
Rice. *JID*. 2008;197:1079-1081
Boucher. *CID*. 2009;48:1-12

How Much Antibiotic Resistance in TN?

- Patient Safety Atlas (CDC)
- CLABSI, CAUTI, and SSI in U.S. hospitals
- Other infections/carriage not addressed
- Reported to CDC
- Not representative of US population
- Most recent data 2014

Found at: https://gis.cdc.gov/grasp/PSA/MapView.html

Regional MDR *E. coli*



Found at: https://gis.cdc.gov/grasp/PSA/MapView.html

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Patient Atlas Summary

Organism	Phenotype	National (%)	Tennessee (%)	TN isolates
All	CRE	3.5	1.3	33/2466
Enterobacter	MDR	7.9	9.5	40/423
Klebsiella	MDR	14.2	6.1	46/750
E. coli	MDR	7.5	7.1	116/1625
Acinetobacter	MDR	54.8	51.5	53/115

TN below national average
Isolate counts low

https://gis.cdc.gov/grasp/PSA/MapView.html

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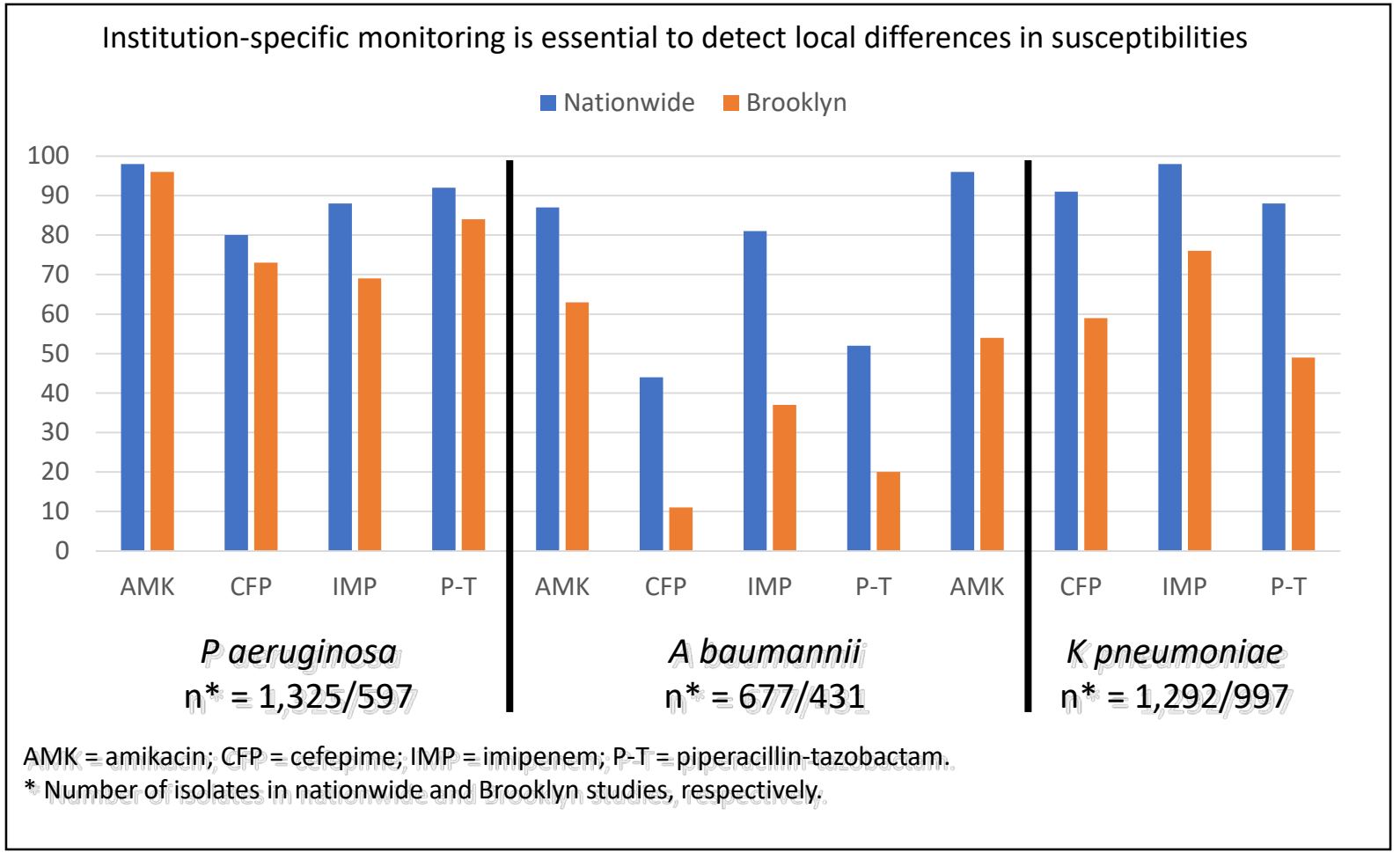
Local Differences Matter



Institution-specific monitoring is essential to detect local differences in susceptibilities

Dowzicky. *Clin Ther*. 2008;30:2040-2050
Landman. *JAC*. 2007;60:78-82

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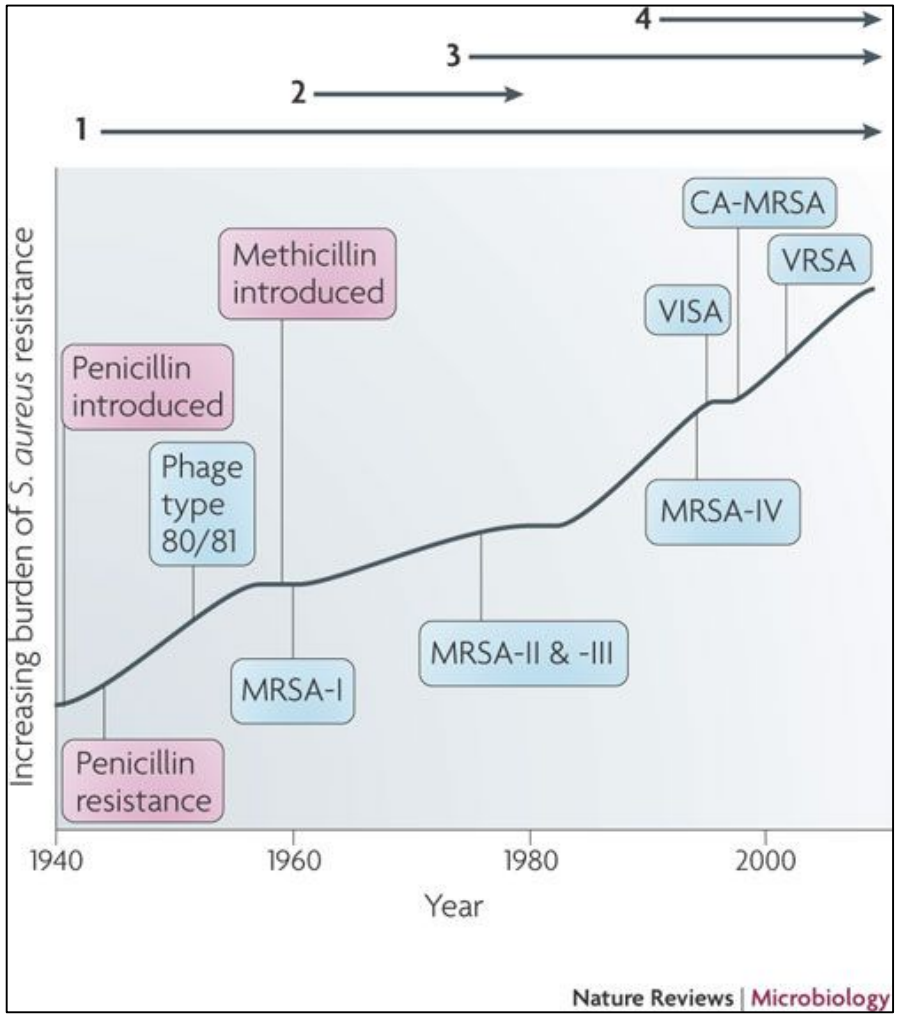
Emerging Community MRSA

- Waves of Staphylococcal Resistance
- MRSA emerged in 1960s
  - Initially elderly patients in healthcare facilities
- MRSA eventually found in healthy individuals in community
  - Designated community-associated MRSA (CA-MRSA)



Jevons. BMJ, 1 (1961), pp. 124-125
Udo. J Hosp Infect, 25 (1993), pp. 97-108
Chambers. Nat Rev Microbiol. 2009 Sep;7(9):629-41

Is This Skin Infection MRSA?

- Clinical/epidemiologic factors
  - Poor MRSA predictors
- Is there purulence??
  - Probably most helpful
- Risk Factors exist
  - Healthcare exposure, nursing home residence, recent surgery, dialysis, HIV infection, IVDU, prior antibiotics, exposure related (incarceration, etc)
- Cultures may be difficult to interpret
  - If abscess drained can provide useful info (Clinda, FQ, TMP/SMX, Doxy susceptibility)

Outpatient† management of skin and soft tissue infections in the era of community-associated MRSA‡

Patient presents with signs/ symptoms of skin infection:

- Redness
- Swelling
- Warmth
- Pain/tenderness
- Complaint of "spider bite"

YES

Is the lesion purulent (i.e., are any of the following signs present)?

- Fluctuance—palpable fluid-filled cavity, movable, compressible
- Yellow or white center
- Central point or "head"
- Draining pus
- Possible to aspirate pus with needle and syringe

NO

Possible cellulitis without abscess:

- Provide antimicrobial therapy with coverage for *Streptococcus* spp. and/or other suspected pathogens
- Maintain close follow-up
- Consider adding coverage for MRSA (if not provided initially), if patient does not respond

YES

1. Drain the lesion
2. Send wound drainage for culture and susceptibility testing
3. Advise patient on wound care and hygiene
4. Discuss follow-up plan with patient

† For severe infections requiring inpatient management, consider consulting an infectious disease specialist.

‡ Visit ***www.cdc.gov/mrsa*** for more information.

Abbreviations:
I&D—incision and drainage
MRSA—methicillin-resistant *S. aureus*
SSTI—skin and soft tissue infection

If systemic symptoms, severe local symptoms, immunosuppression, or failure to respond to I&D, consider antimicrobial therapy with coverage for MRSA in addition to I&D. (See below for options)

Options for empiric outpatient antimicrobial treatment of SSTIs when MRSA is a consideration*

Drug name	Considerations	Precautions**
Clindamycin	■ FDA-approved to treat serious infections due to *S. aureus* ■ D-zone test should be performed to identify inducible clindamycin resistance in erythromycin-resistant isolates	■ *Clostridium difficile*-associated disease, while uncommon, may occur more frequently in association with clindamycin compared to other agents.
Tetracyclines ■ Doxycycline ■ Minocycline	■ Doxycycline is FDA-approved to treat *S. aureus* skin infections.	■ Not recommended during pregnancy. ■ Not recommended for children under the age of 8. ■ Activity against group A streptococcus, a common cause of cellulitis, unknown.
Trimethoprim-Sulfamethoxazole	■ Not FDA-approved to treat any staphylococcal infection	■ May not provide coverage for group A streptococcus, a common cause of cellulitis ■ Not recommended for women in the third trimester of pregnancy. ■ Not recommended for infants less than 2 months.
Rifampin	■ Use only in combination with other agents.	■ Drug-drug interactions are common.
Linezolid	■ Consultation with an infectious disease specialist is suggested. ■ FDA-approved to treat complicated skin infections, including those caused by MRSA.	■ Has been associated with myelosuppression, neuropathy and lactic acidosis during prolonged therapy.

■ MRSA is resistant to all currently available beta-lactam agents (penicillins and cephalosporins)
■ Fluoroquinolones (e.g., ciprofloxacin, levofloxacin) and macrolides (erythromycin, clarithromycin, azithromycine) are not optimal for treatment of MRSA SSTIs because resistance is common or may develop rapidly.

https://www.cdc.gov/mrsa/pdf/flowchart_pstr.pdf

SSTI Microbiology

>50% MRSA

>50% MRSA patients received **ineffective** antibiotics

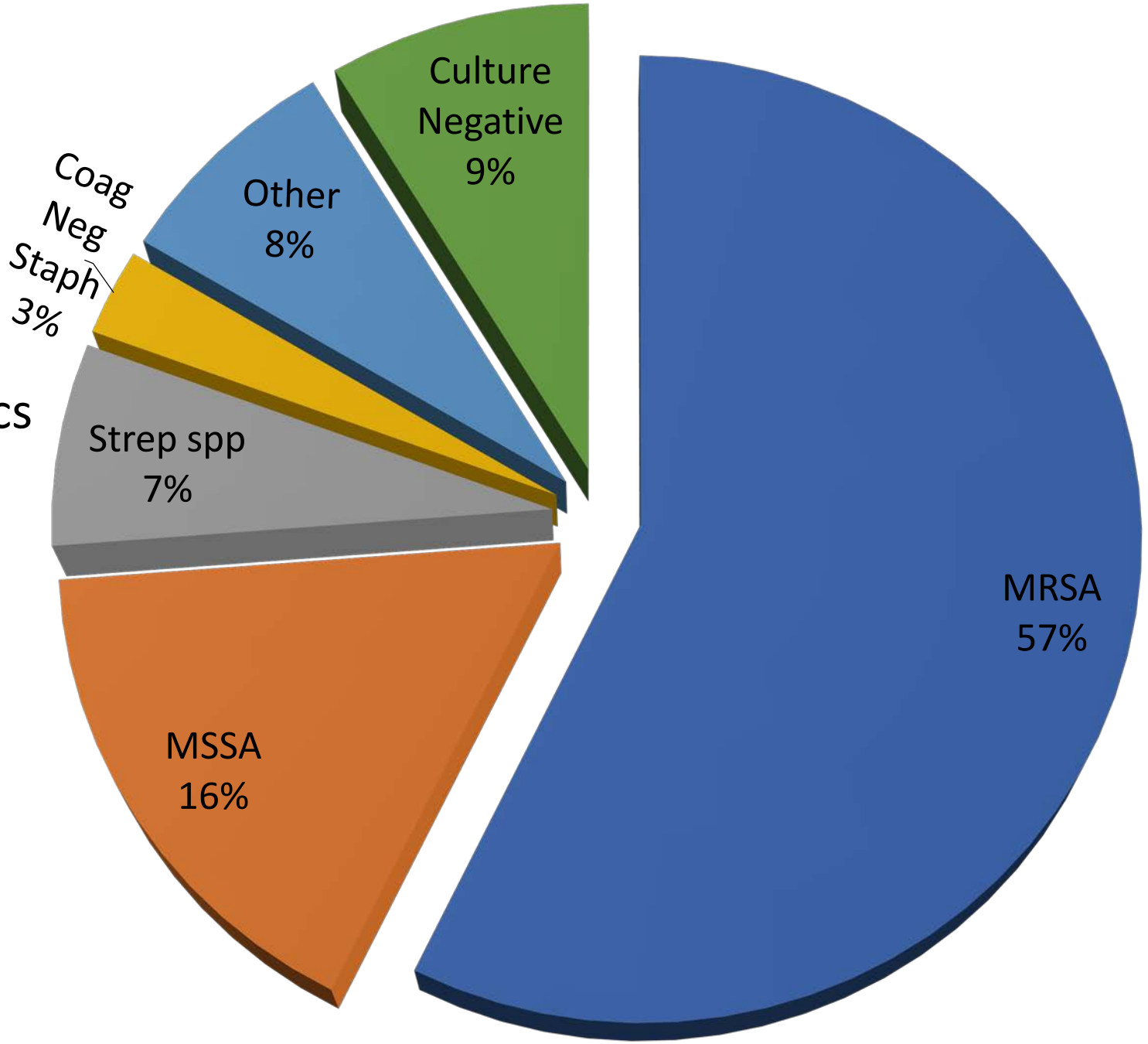
<u>Susceptibilities (2006)</u>

TMP/SMX 100%

Clindamycin 95%

Doxycycline 92%

Quinolones 60%



Moran. NEJM. 2006 Aug 17;355(7):666-74

Do we need to rethink cellulitis treatment?

- Empiric MRSA coverage typically reasonable given high prevalence
- Purulence present, then MRSA coverage indicated!
- If no purulence, may not require MRSA coverage
  - Prospective study: non-purulent SSTI with >70% due to Strep, >95% response to β-lactam
  - Retrospective study: ↑ treatment failure with TMP/SMX vs β-lactam

Jeng. Medicine 2010; 89:217-26
Elliott. Pediatrics 2009; 123:e959-66

What antibiotic do I choose?

- This is where antibiogram important

Antibiotics[a,b,c]	2014 (*n* = 3112), %
Ciprofloxacin	80.5
Clindamycin	86.0
Erythromycin	49.7
Gentamicin	99.2
Oxacillin	68.4
Penicillin	8.0
Rifampin	99.7
Tetracycline	95.3
TMP/SMX	98.4

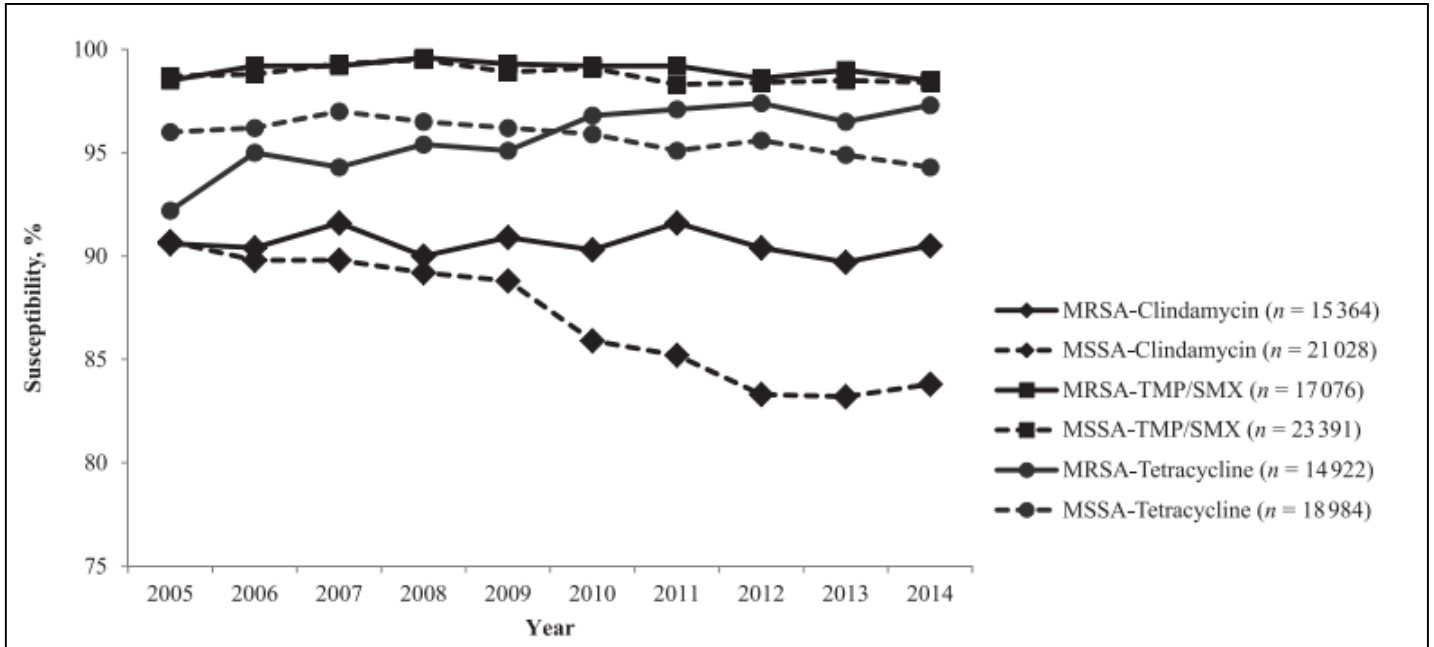


FIGURE 1
Antibiotic susceptibilities to MRSA and MSSA among pediatric patients in 2005–2014.

Sutter. Pediatrics. 2016 Apr;137(4). pii: e20153099

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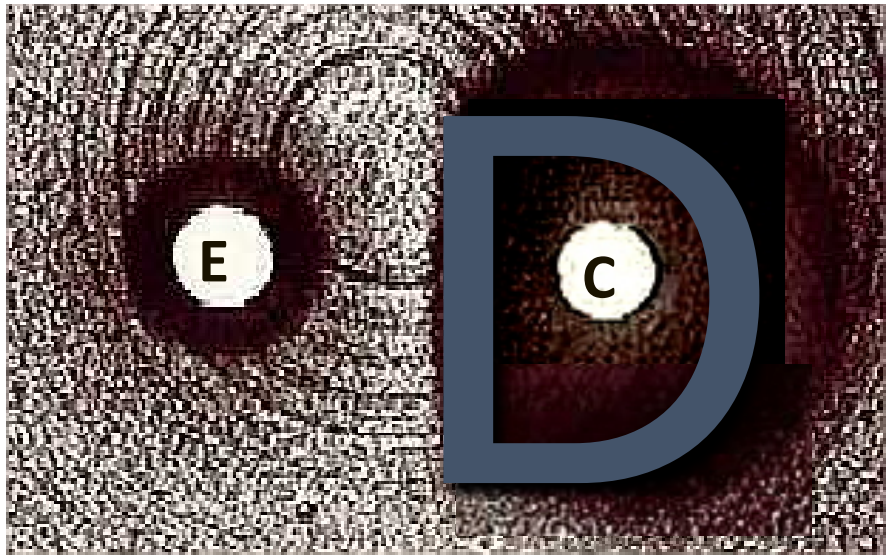
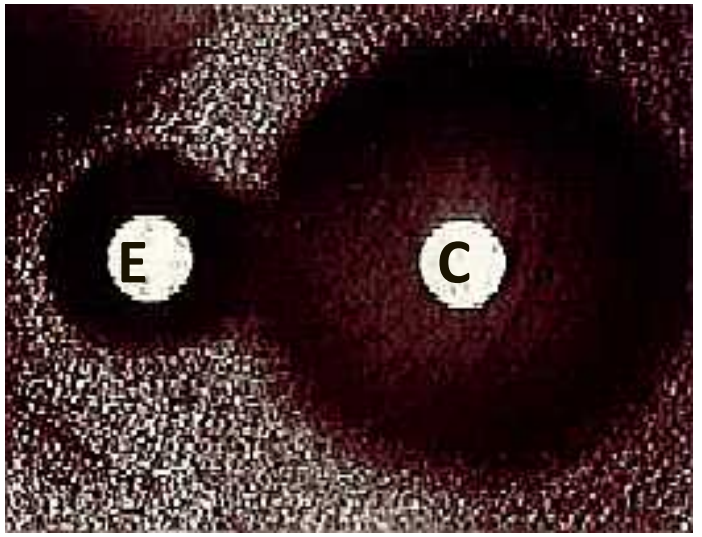
Inducible Clindamycin-R: D-Test



Positive test for inducible resistance. **Resistant to erythromycin and clindamycin.**



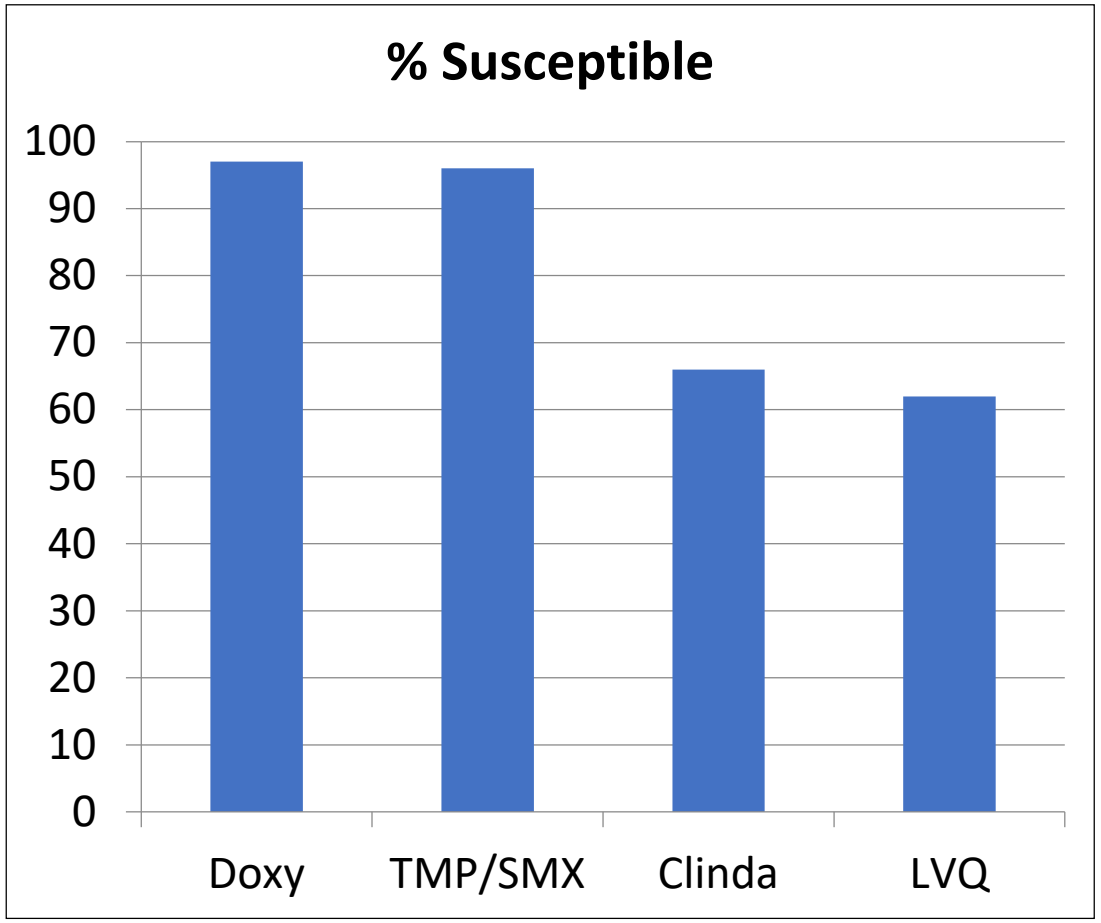
Negative test for inducible resistance. Erythromycin-R but **Clindamycin-S.**

Rich. Vet Microbiol. 2005 Dec 20;111(3-4):237-40

Local MRSA Susceptibility Patterns

- TMP/SMX 96%
- Doxycycline 97%

- Clindamycin 66-70%
- Levofloxacin 62-70%



Antibiotics Needed After I&D?

- Several studies completed
- Current IDSA guidelines (last updated, 2014)
  - For simple abscesses or boils, I&D alone likely adequate
  - Recommended for high risk groups (severe infection, elderly, prior failure, etc)
  - High cure rates regardless of approach→ difficult to discern difference
- Likely reduction in recurrent lesions
- Guidelines only followed ~20% in US EDs

Rajendran. AAC 2007; 51:4044-8
Duong. Ann Emerg Med 2009;55:401-7
Schmitz . Ann Emerg Med 2010; 56:283-7
Talan. Ann Em Med 2010; 55:412-14
Spellburg. Ann Em Med 2011; 57:183-4
Kamath. OFID. 2018 Jan 12;5(1):ofx188

Antibiotics Needed After I&D?

- Newer, large RCTs → benefit with TMP/SMX
  - Primarily in *S. aureus*
- Newer European guidelines suggest TMP/SMX or clinda (not cephalosporin) after I/D
  - Must balance SE profile
- RCT of cephalexin + TMP/SMX vs cephalexin alone = no difference

Vermandere. BMJ. 2018; 360: k243
Talan. Ann Emerg Med. 2018 Jan;71(1):21-30
Talan. NEJM. 374 (2016), pp. 823-832
Daum. NEJM. 376 (2017), pp. 2545-2555
Moran. JAMA.2017 May 23;317(20):2088-2096

MRSA Treatment Considerations

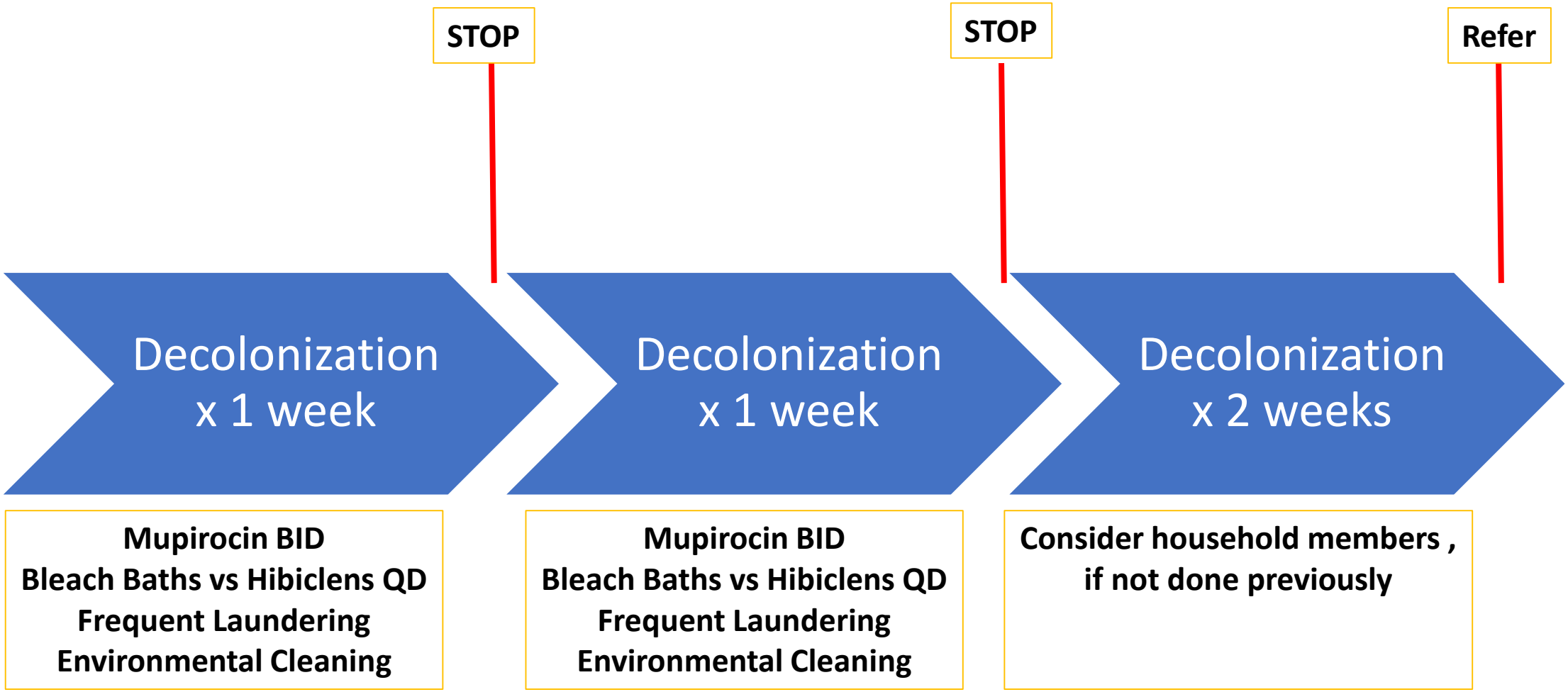
Drug name	
Clindamycin	→ Inducible Clinda-R
Tetracyclines ■ Doxycycline ■ Minocycline	→ Very Reasonable
Trimethoprim-Sulfamethoxazole	→ Very Reasonable (allergy/kidney function OK)
Rifampin	→ Avoid (drug-drug interaction, never sole agent)
Linezolid	→ $$ issues, interactions with many psych meds, likely unnecessary

Recurrent Furunculosis (boils)

- Almost always *S. aureus*
- Oral agents NOT recommended
- Dilute bleach baths, intranasal mupirocin, and hygiene education
  - Effective over four months
- Durability of decolonization limited
  - Recolonization at 12 months 50-75% (healthcare workers & dialysis patients, respectively)

Creech. Infect Dis Clin North Am. 2015 Sep;29(3):429-64
Fritz. ICHE. 2011 Sep;32(9):872-80

Several Strategies



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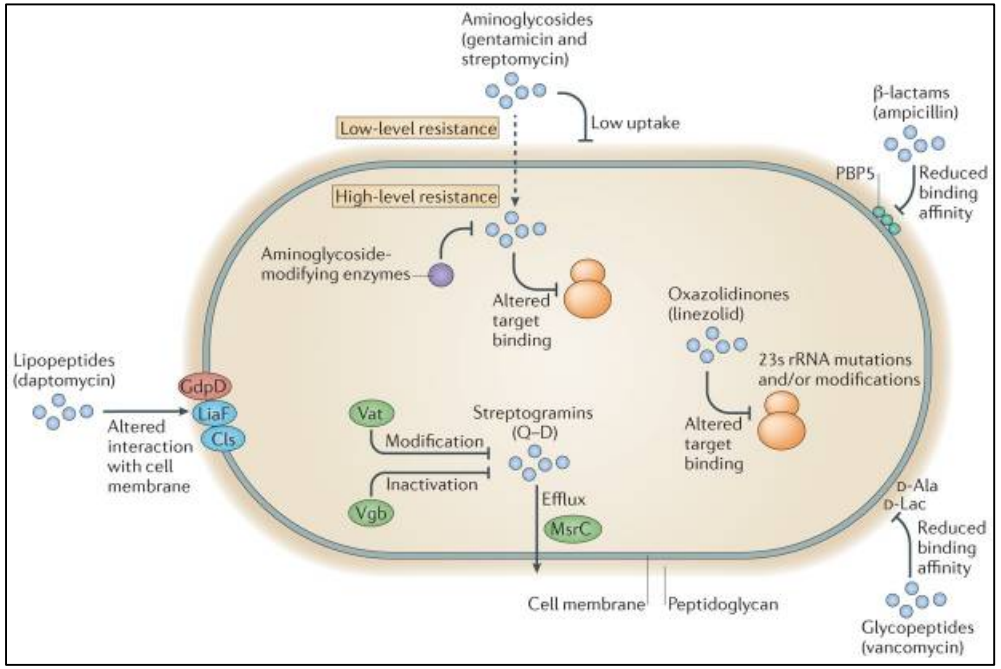
Vancomycin Resistant *Enterococcus*

- *E. faecalis* more virulent than *E. faecium*
- *E. faecalis* more likely ampicillin-S
- Urine most common site recovered
  - Colonization vs infection
- Diagnostic evaluation:
  - Obtain Urinalysis (with microscopy) amount of pyuria (>10WBC/hpf?)
  - THEN interpret Urine Culture (>100,000 CFU?)

Mechanisms of Enterococcal Resistance



Arias. Nat Rev Microbiol. 2012 Mar 16; 10(4): 266–278

Do they need to be treated at all?

- Subject of controversy
- Enterococci are GI/GU tract commensals
  - Presence ≠ infection
  - Commonly recovered, commonly polymicrobial
- 6 trials: no treatment failures w/o enterococcal Rx (20-30% enterococcus present)
- Many studies demonstrate treatment failure/poor outcome 2/2 enterococcus

Harbarth. Eur J Clin Microbiol Infect Dis 2004; 23: pp. 73-77
Gorbach. CID 1993; 17: pp. 961-965
Onderdonk. Infect Immun 1976; 13: pp. 22-26
Burnett. Surgery 1995; 118: pp. 716-721

Do they need to be treated at all?

- Subject of controversy
- Enterococci are GI/GU tract commensals
  - Presence ≠ infection

TAKE HOME:

Enterococcus can cause disease, must be thoughtful if true pathogen

If modest pyuria (WBC/hpf), colony counts (CFUs) reconsider

Could retest

If patient has foley catheter → remove, replace, retest

Harbarth. Eur J Clin Microbiol Infect Dis 2004; 23: pp. 73-77
Gorbach. CID 1993; 17: pp. 961-965
Onderdonk. Infect Immun 1976; 13: pp. 22-26
Burnett. Surgery 1995; 118: pp. 716-721

I've decided treatment needed --now what?

- Uncomplicated UTIs
  - Antibiotics that concentrate in urine useful

- If Amp-S *Enterococcus*, ampicillin (or amoxicillin) will work
  - Amoxicilin may be useful if ampicillin MICs <128 µg/ml

- Cannot assume PCN sensitivity
  - Usually works, but must request sensitivity or monitor response

Kristich. Enterococci: From Commensals to Leading Causes of Drug Resistant Infection. Available: https://www.ncbi.nlm.nih.gov/books/NBK190420/

Options for VRE

- Fosfomycin
  - FDA approved for UTIs from vancomycin-susceptible enterococci, but not for VRE or any *E. faecium*
- Nitrofurantoin
- Linezolid
  - Previous pros/con discussion
  - Beware of developing resistance (must ensure linezolid is active [MIC<4]!!)
    - Daptomycin-linezolid-vanc R enterococcus (DLVRE) emerging [Greene. OFID. *In press*]

Kristich. Enterococci: From Commensals to Leading Causes of Drug Resistant Infection. Available: https://www.ncbi.nlm.nih.gov/books/NBK190420/

VRE: Be Aware

- Other antibiotics increase VRE risk!
  - Clindamycin, metronidazole, pip-tazo, and cephalosporins
  - Disrupt gut flora, VRE emerges

- VRE colonization can last, and last, and last (up to a year!)
  - Consider if persistent

Donskey . NEJM. 2000;343(26):1925–1932
Sullivan. Lancet. 2001;1(2):101–114
Baden. CID. 2001;33(10):1654–1660

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Risk Factors for Community ESBL infection

- Recurrent UTI
- Previous antibiotic usage
- Diabetes
- Prior urinary tract instrumentation
- Age > 65 years
- Prior ESBL infection/colonization

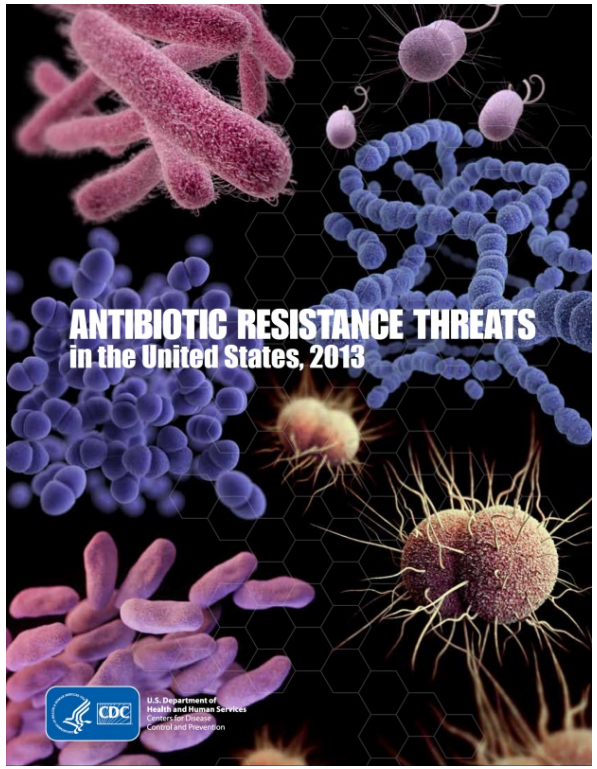
No reliable way to predict ESBL

Rodríguez-Baño . Arch Intern Med. 2008 Sep 22;168(17):1897-902
Dhillon. Crit Care Res Pract. 2012;2012:625170

UTIs

- Most commonly encountered MDR GNR*
  - Also intrabdominal processes
  - Less common in community: CAP, SSTI, etc

- UTI evaluation
  - *(discussed previously: UA w/ micro & UCx)*

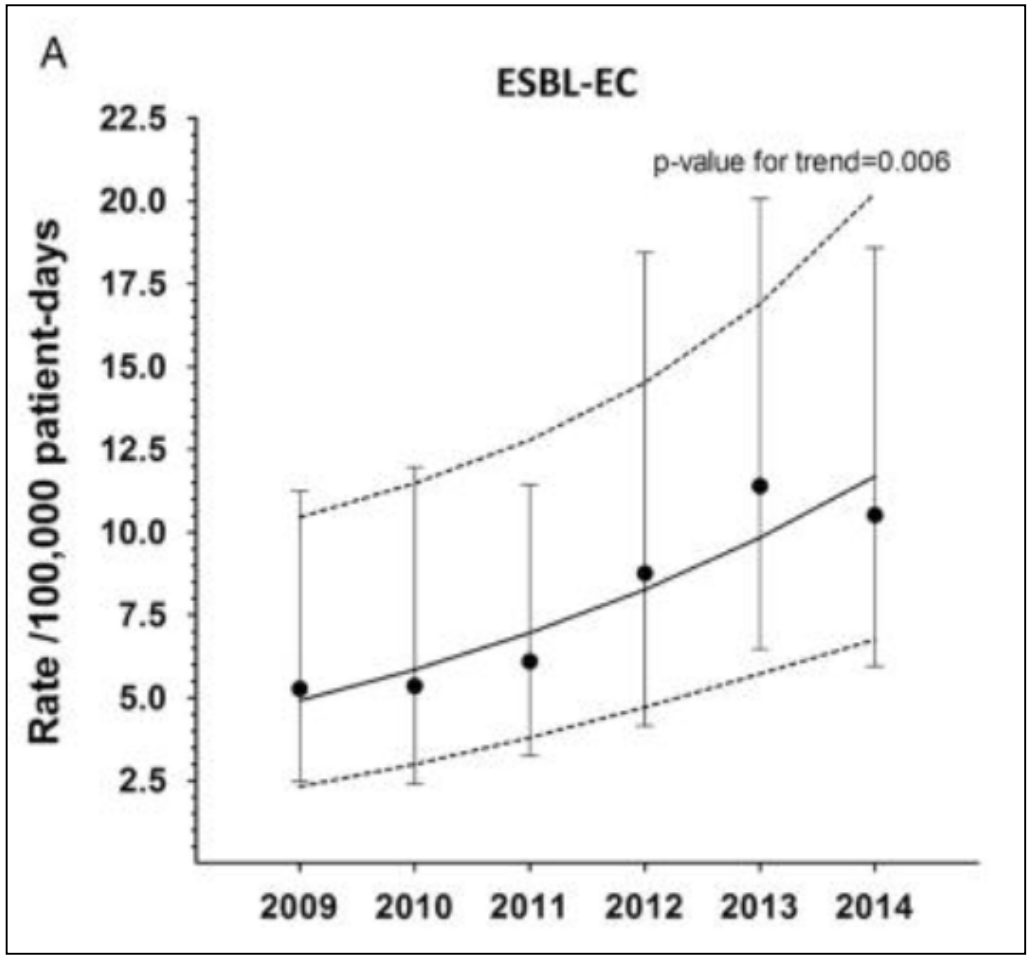


- IF MDR GNR recovered (esp. ESBL, MDR) → request Fosfomycin sensitivity (not routinely done)

*MDR GNR= Mulit-drug resistant gram negative rod

Are ESBLs becoming more common?

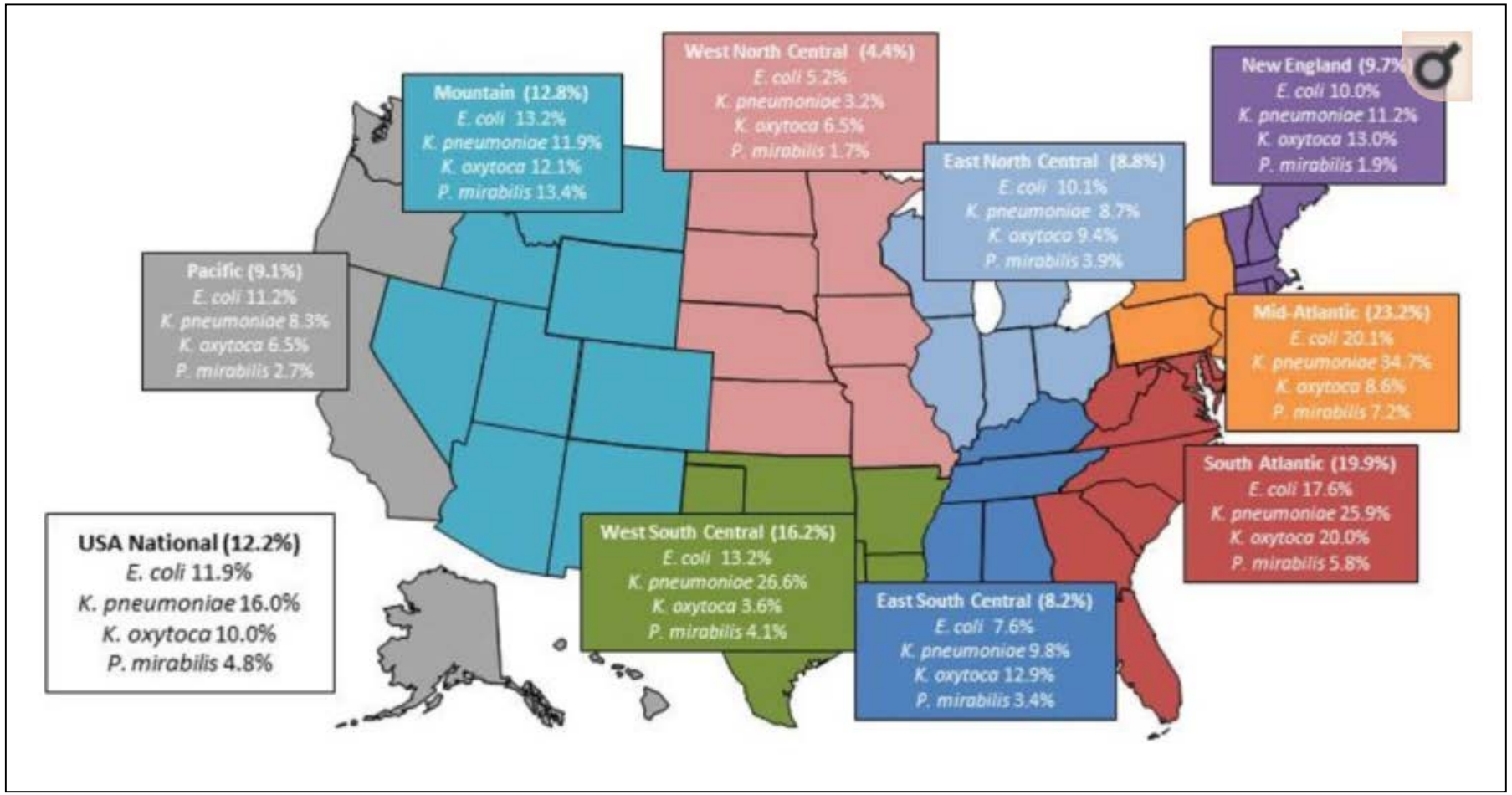
- **Yes!!**
- In both community and hospital
- ESBL *E.coli* infections doubled in community hospitals
  - Healthcare exposure common
  - Community infections drove increase
- 26 community hospitals in Southeast US



McDanel. ICHE. 2017;38:1209–1215
Thaden. ICHE. 2016;37:49-54
Freeman. CID. 2009 Jul 15;49(2):e30-2

ESBL Geographic Variation

National: 12%
2012 Data
72 Hospitals
INPATIENTS Only



Castanheira. AAC. 2014;58(2):833-8

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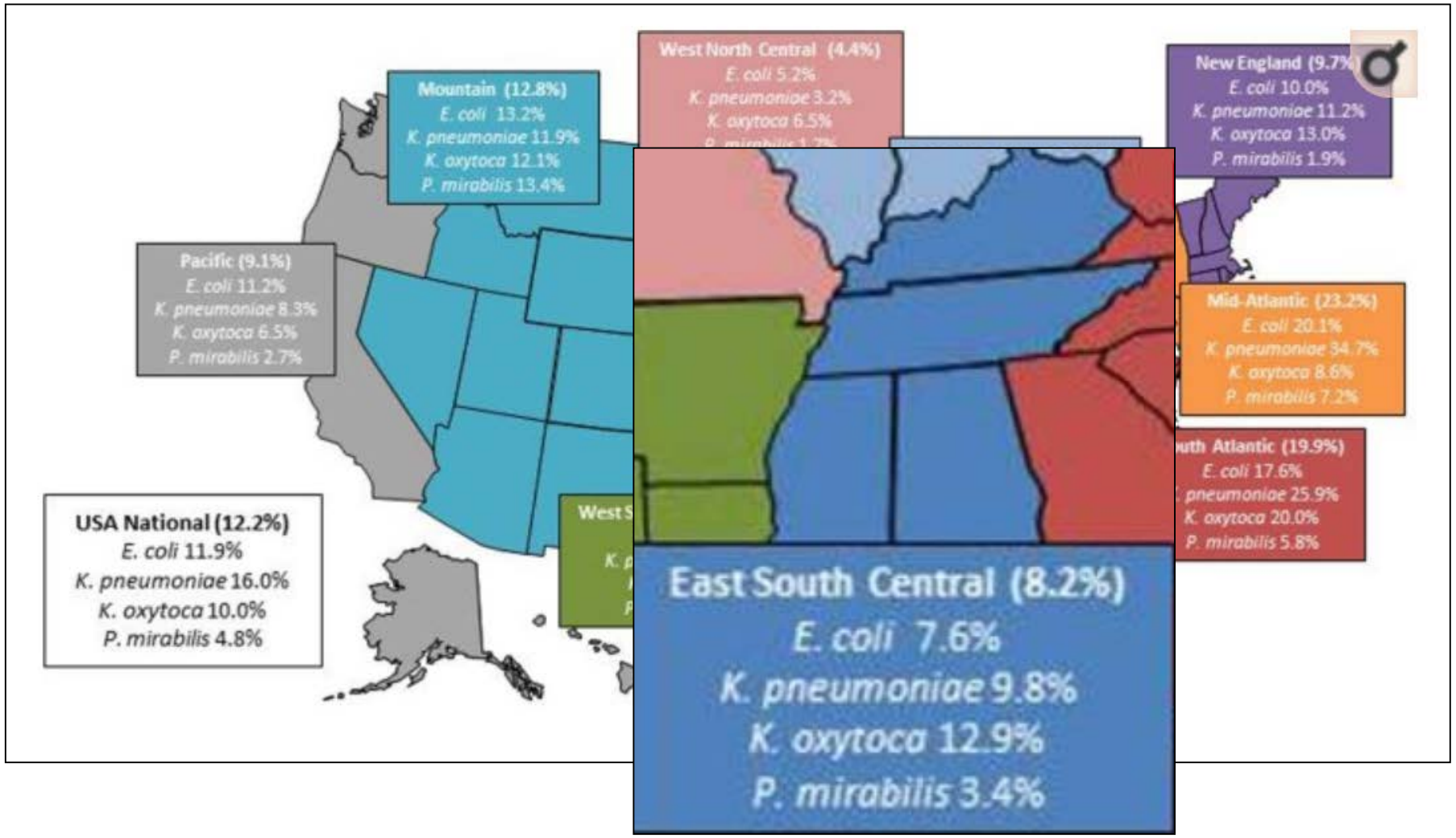
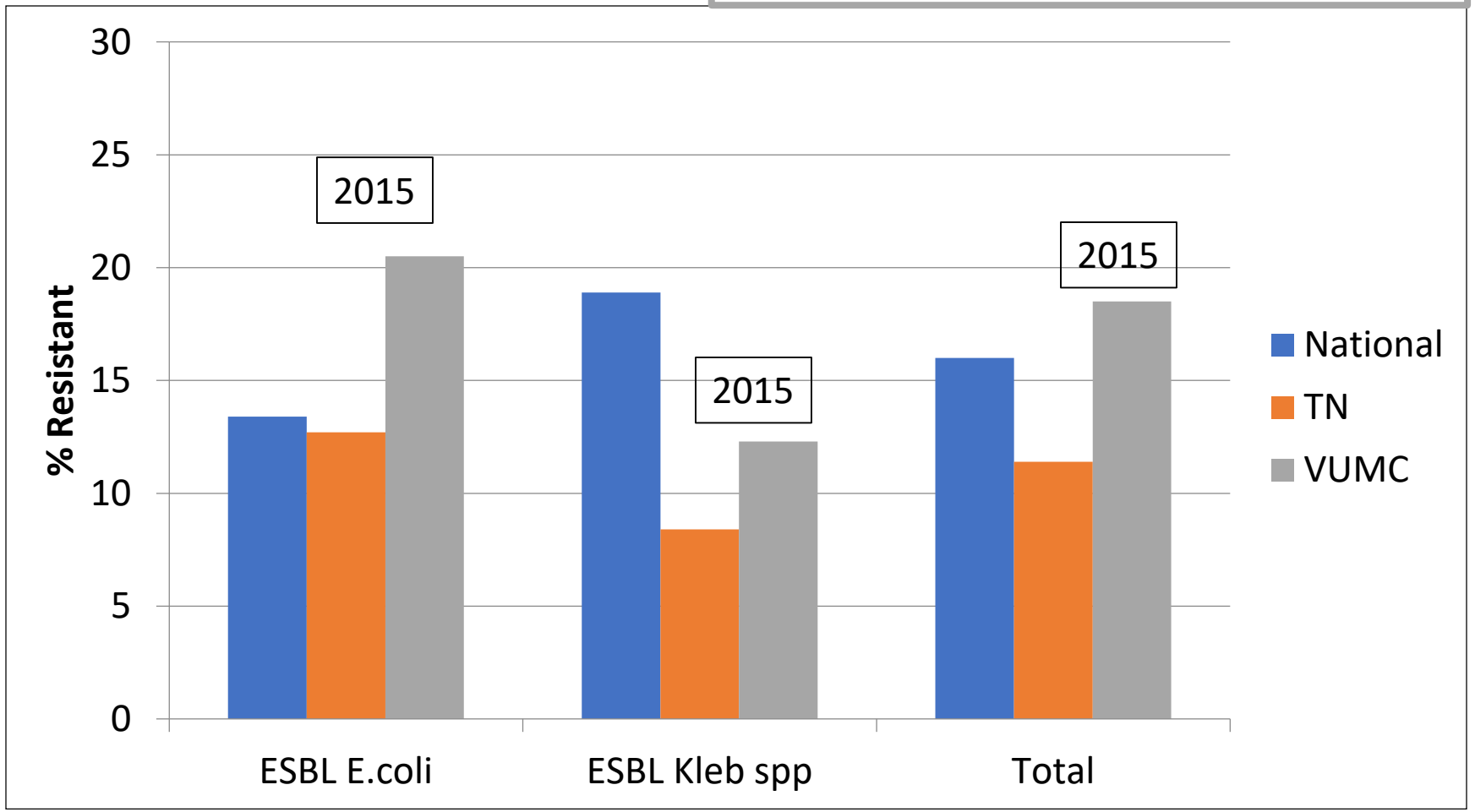


Castanheira. AAC. 2014;58(2):833-8

AMR Comparisons

Caveat:
VUMC newer, all comers (not just HAI)



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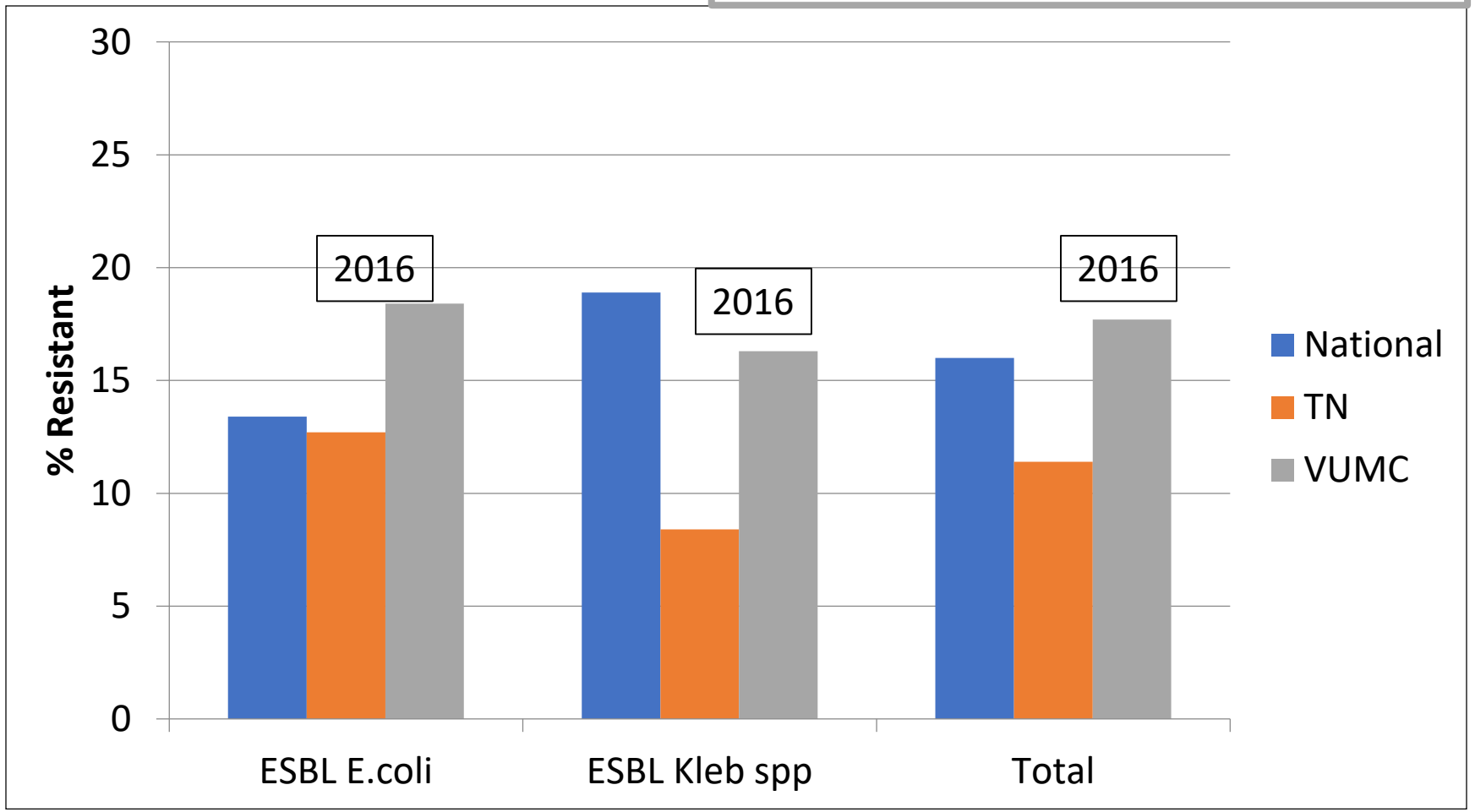
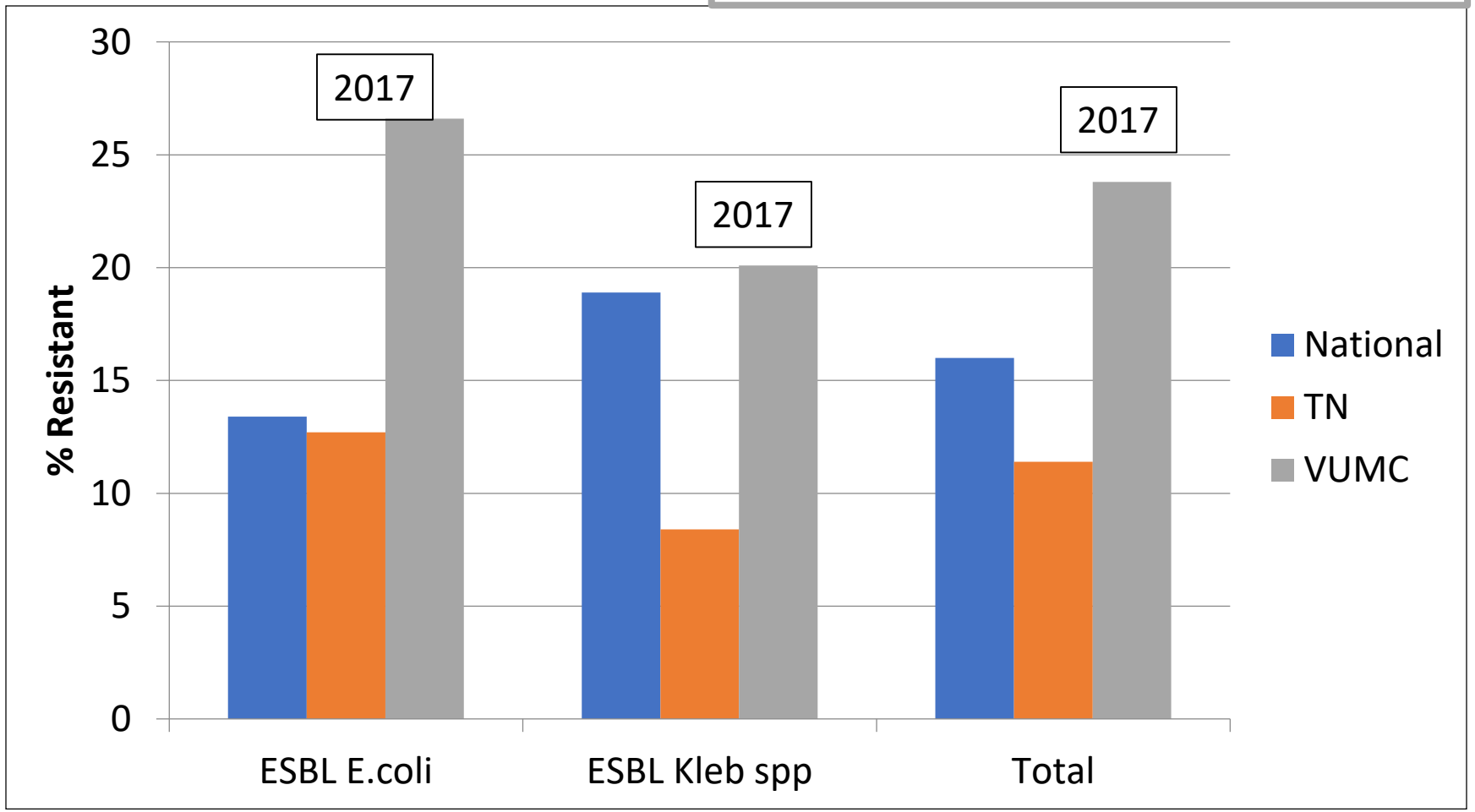
Caveat:
VUMC newer, all comers (not just HAI)



AMR Comparisons

Caveat:
VUMC newer, all comers (not just HAI)



ESBL Treatment

- Confers resistance to **PCNs, 3rd gen cephalosporin, monobactams**
- Empiric severe infection: Hospitalization/IV ABX

- Uncomplicated UTI options:
  - Fosfomycin
  - Quinolone (different resistance mechanisms)
  - Nitrofurantoin
  - TMP/SMX

- **MUST** confirm sensitivities

Gutierrez-Gutierres. AAC 2016 epub
Lee. CID 2013:488-95
Lee. AAC 2015: 7558-63
Nguyen. JAC 2014:871-880
Harris. Lancet ID 2015:475-85
Wang. OFID 2016, 20;3(3)
Muhammed . OFID. 2017. 4(2):ofx099

Does Fosfomycin treat ESBL UTIs?

- FOS may be option for UNCOMPLICATED UTIs
- Excellent *in vitro* activity against ESBL
- Systematic review showed ~90% ESBL susceptible
  - 97% of *E. coli*
  - 81% *Klebsiella*
- Resistance developing during therapy reported
  - Re-evaluate if clinical response unclear
- Increased FOS use promoting FOS-resistance
  - One study 4% (2005) to 11% (2009) to ?? 2018…

Rx: 3gm PO q2-3 days for UTI
Not indicated for pyelonephritis
(poor tissue penetration)
Must request sensitivities

Falgas. Lancet ID. 2010 Jan;10(1):43-50
de Cueto. AAC. 2006 Jan;50(1):368-70
Perez. Curr Opin Pharmacol 2007 Oct;7(5):459-69
Paterson. Clin Micro Rev. 2005 Oct;18(4):657-86
Rodríguez-Baño. Arch IM. 2008 Sep 22;168(17):1897-902
Neuner. AAC. 2012 Nov;56(11):5744-8
Oteo. JAC. 2010 Nov;65(11):2459-63

Any other options?

- Nitrofurantoin
  - Contraindicated with CrCl < 60 mL/min
  - May still be effective at lower CrCl
  - Treatment of cystitis only
- Rarely TMP/SMX
- Cephalosporins??
  - Cannot use even if reported as susceptible (*in vitro)*
  - ESBL enzyme inactivates drug *(in vivo)*
  - AND…promotes ESBL production….

Paterson. J Clin Microbiol. 2001 Jun;39(6):2206-12

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  - AND…promotes ESBL production….

No appreciable systemic concentrations achieved
C/I in pregnancy at term
Hemolytic anemia risk

Paterson. J Clin Microbiol. 2001 Jun;39(6):2206-12

Any other options?

- Nitrofurantoin
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If susceptibility confirmed

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Paterson. J Clin Microbiol. 2001 Jun;39(6):2206-12

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NO

Paterson. J Clin Microbiol. 2001 Jun;39(6):2206-12

Can you use Quinolones for ESBLs?

- MAYBE
- Different resistance mechanism, BUT frequently seen together
- Quinolones are appropriate AFTER susceptibility confirmed

Lo. J Microbiol Immunol Infect. 2017 Jun;50(3):355-361

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AmpC β-lactamases

- Primarily *Enterobacter*, *Serratia*, *Citrobacter*
  - SPICE or SPACE organisms
- **Inducible**
  - *Initially sensitive* **Abx exposure** → *resistant*
- Seen in UTIs primarily

"SPICE"	OR	**"SPACE"**
Serratia		*Serratia*
Pseudomonas		*Pseudomonas*
Indole + *Proteus*		*Acinetobacter*
Citrobacter		*Citrobacter*
Enterobacter		*Enterobacter*

AmpC Treatment

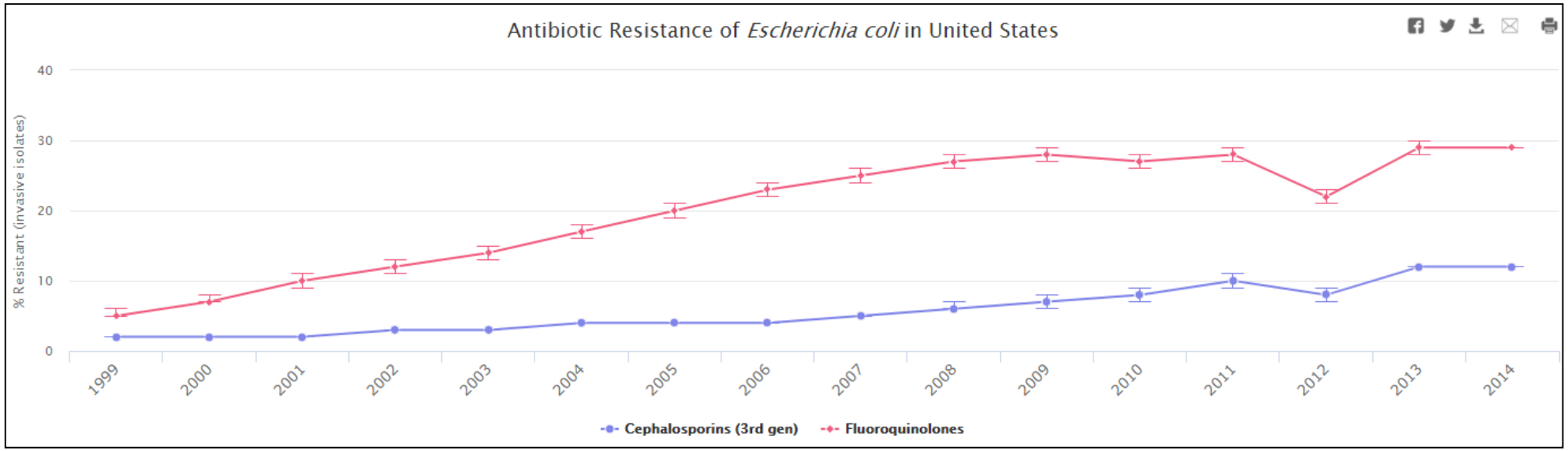
- Empiric severe infection
  - Hospitalize/IV ABX
- **Prevalence data scarce**
  - Depressed mutations (i.e. always present)
- *Inducible* mutations of more interest
  - Data variable (pathogen, abx exposure) 0-20%
  - Likely low occurrence during therapy (~5%)
- Usually won't know (not typically reported)
  - Cefoxitin/cefotetan-R gives clue (if see on micro report, avoid cephalosporins)
  - Monitor response (i.e. failure to improve/worsening at 72hrs)

"SPICE"	OR	**"SPACE"**
Serratia		*Serratia*
Pseudomonas		*Pseudomonas*
Indole + *Proteus*		*Acinetobacter*
Citrobacter		*Citrobacter*
Enterobacter		*Enterobacter*

Park. AAC. 2012 Apr;56(4):1870-6
Jacoby. Clin Microbiol Rev. 2009 Jan; 22(1): 161–182

Fluoroquinolone (FQ) Resistance

- "Scarier Than We Thought"
- Not recommended for empiric tx
- Must culture and follow



https://resistancemap.cddep.org/AntibioticResistance.php

Spellberg. JID. 2015 Dec 15; 212(12): 1853–1855
Sanchez. JAC. 2013; 68:1838–41
Bouchillon. Clin Ther 2013; 35:872–7

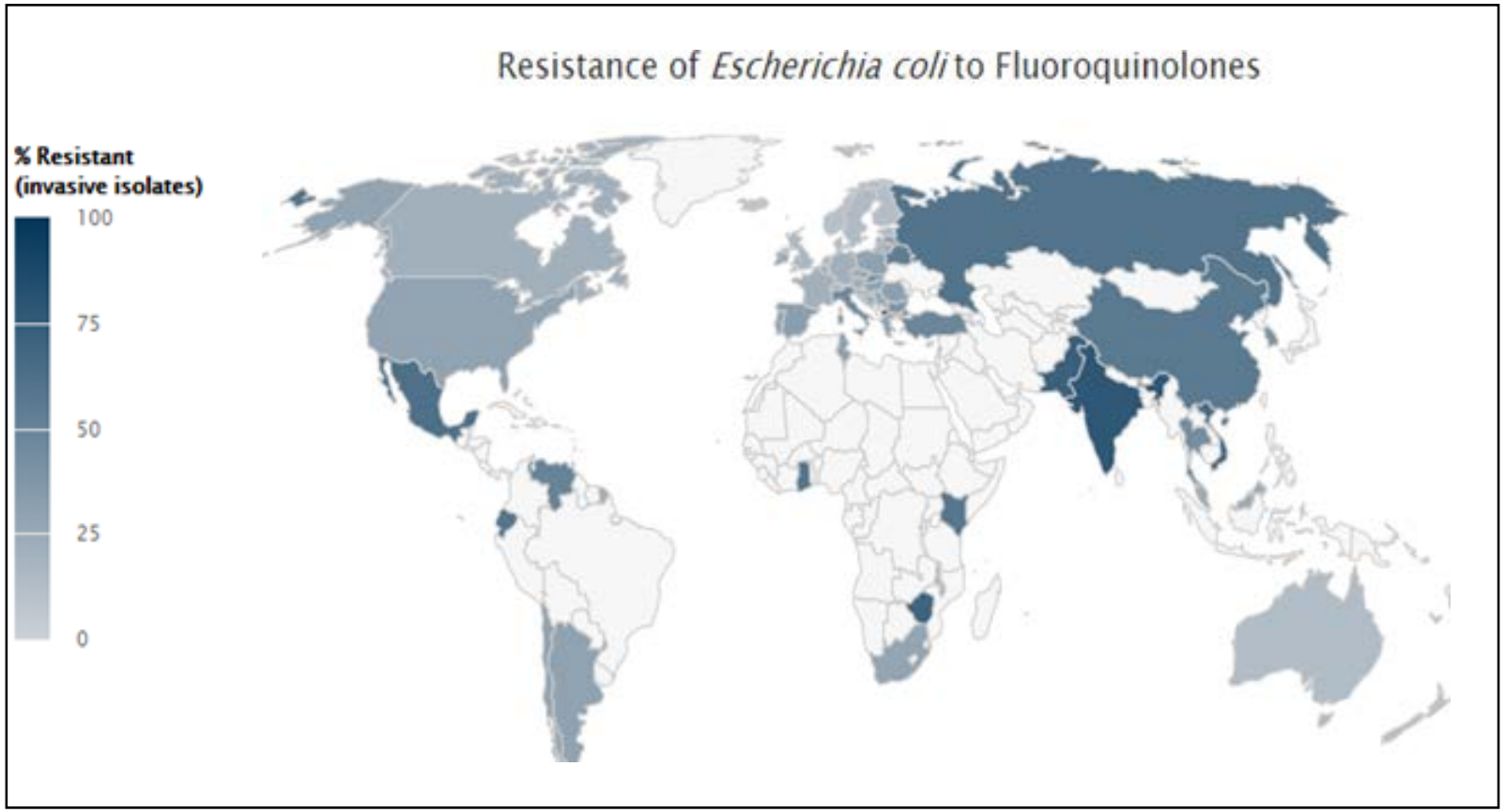
FQ-R Increasing *Worldwide*

United States

<1% (1990s)

As low as 3% (2008)

Currently ≥ 29%

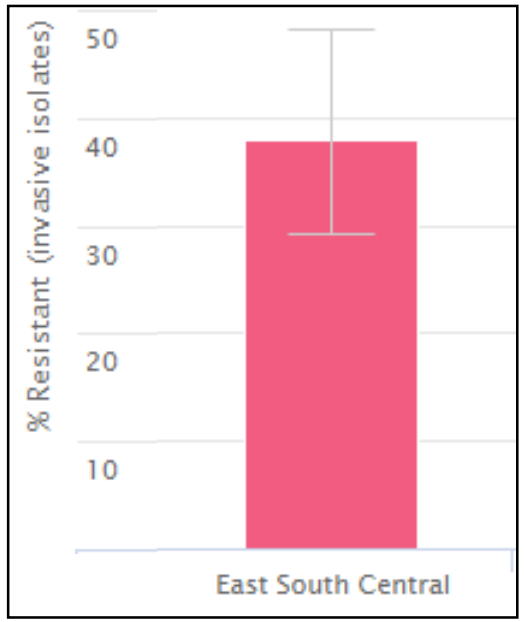


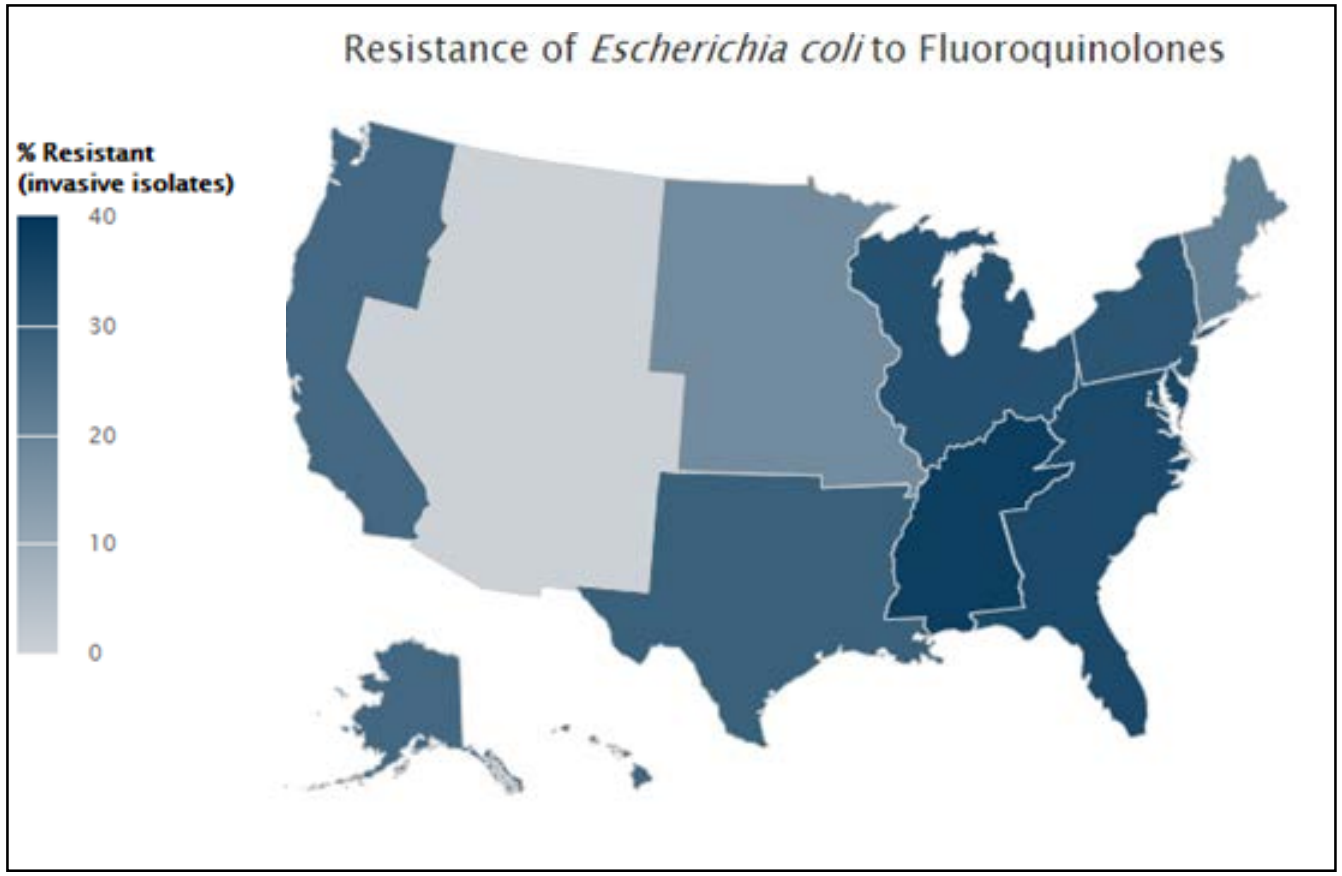
https://resistancemap.cddep.org/AntibioticResistance.php

Spellberg. JID. 2015 Dec 15; 212(12): 1853–1855
Sanchez. JAC. 2013; 68:1838–41
Bouchillon. Clin Ther 2013; 35:872–7

FQ-R Increasing *Nationally*

- Southeast US
- 38% *E. coli* FQ-R





https://resistancemap.cddep.org/AntibioticResistance.php

Local Rates: E. Coli Resistant to FQ ~40%

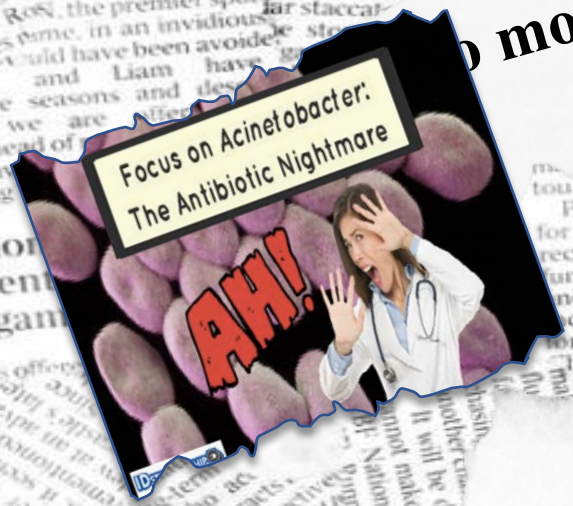
Additional FQ Considerations

- New FDA warning
- QTc prolongation
  - ✓ECG if other QT agents
- *Very* C.diff- o-genic
- Other AEs
  - Arthopathy/arthralgia
  - Tendinitis/tendon rupture
  - Seizures

Objectives

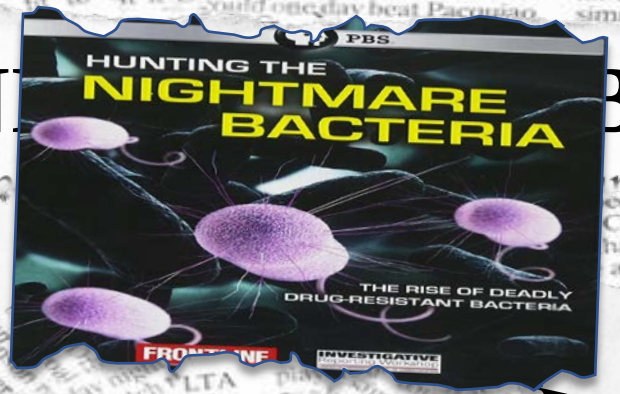
- Overview of burden of commonly encountered antimicrobial resistance (AMR) patterns
  - MRSA
  - VRE
  - ESBL
- Common syndromes associated with multidrug resistance (MDR)
  - Initial evaluation
- Antibiotic stewardship perspective
- **Brief update on emerging drug resistance**


No more antibiotics?
IS THIS THE END?
SUPER BUG FOUND
NIGHTMARE BACTERIA
OVERUSE
NDM-1 Found in U.S.
Post antibiotic era?
CDC THREAT REPORT

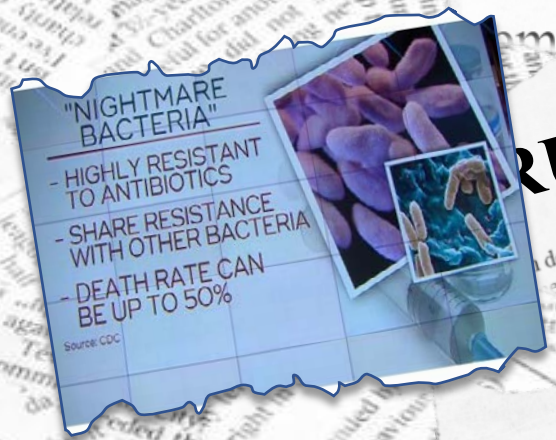

Focus on Acinetobacter: The Antibiotic Nightmare
AH!


'Nightmare Bacteria' a Rising Threat in US Hospitals


SuperBugs'


PBS
HUNTING THE NIGHTMARE BACTERIA
THE RISE OF DEADLY DRUG-RESISTANT BACTERIA


FRONTLINE
HUNTING THE NIGHTMARE BACTERIA


"NIGHTMARE BACTERIA"
- HIGHLY RESISTANT TO ANTIBIOTICS
- SHARE RESISTANCE WITH OTHER BACTERIA
- DEATH RATE CAN BE UP TO 50%
Source: CDC


HEALTHCHECK
200 CASES OF 'NIGHTMARE BACTERIA' IN 2017

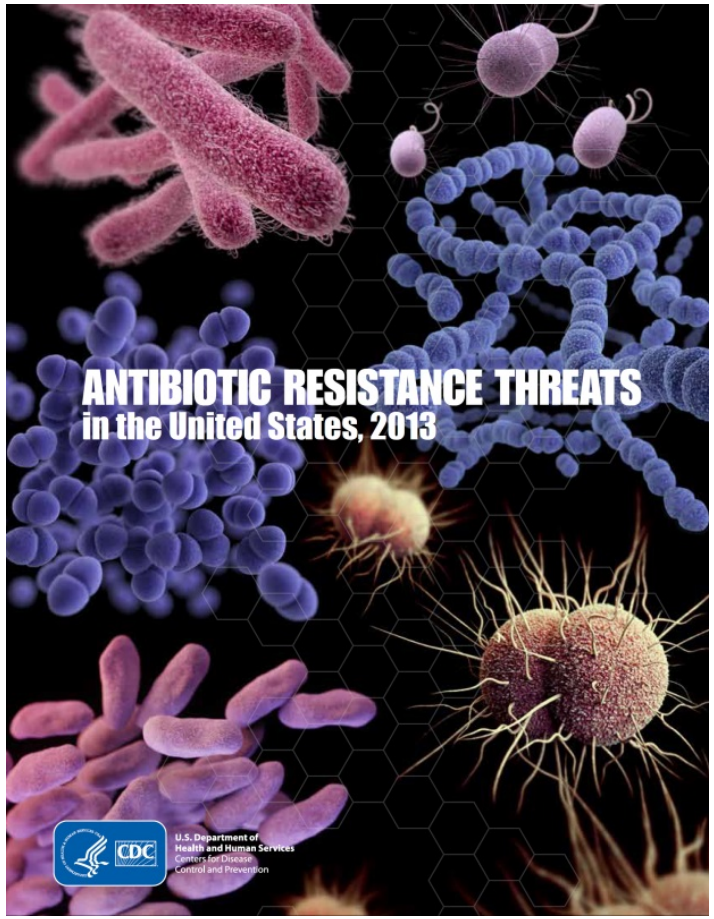

'NIGHTMARE BACTERIA' SPREADING ACROSS U.S. HOSPITALS
SCI&TECH

Carbapenem-R Enterobacteriaceae (CRE), U.S.

With increase in ESBLs and subsequent reliance on carbapenems, CRE emerged

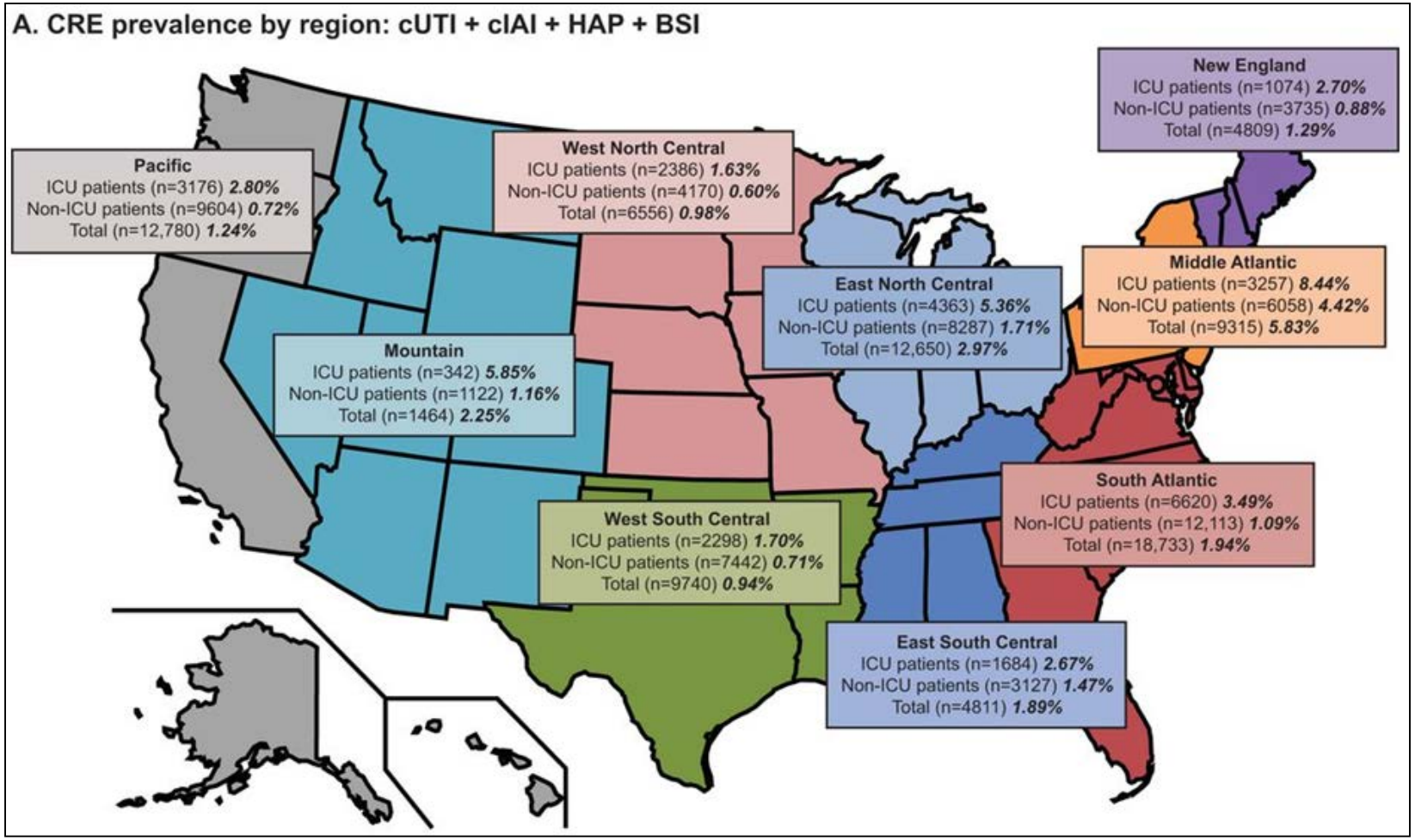
CRE: 9000 infections; 600 deaths

- Underestimate
- *Klebsiella* and *E. coli* most common
- CRE in 44 states (2013)
  - Widespread



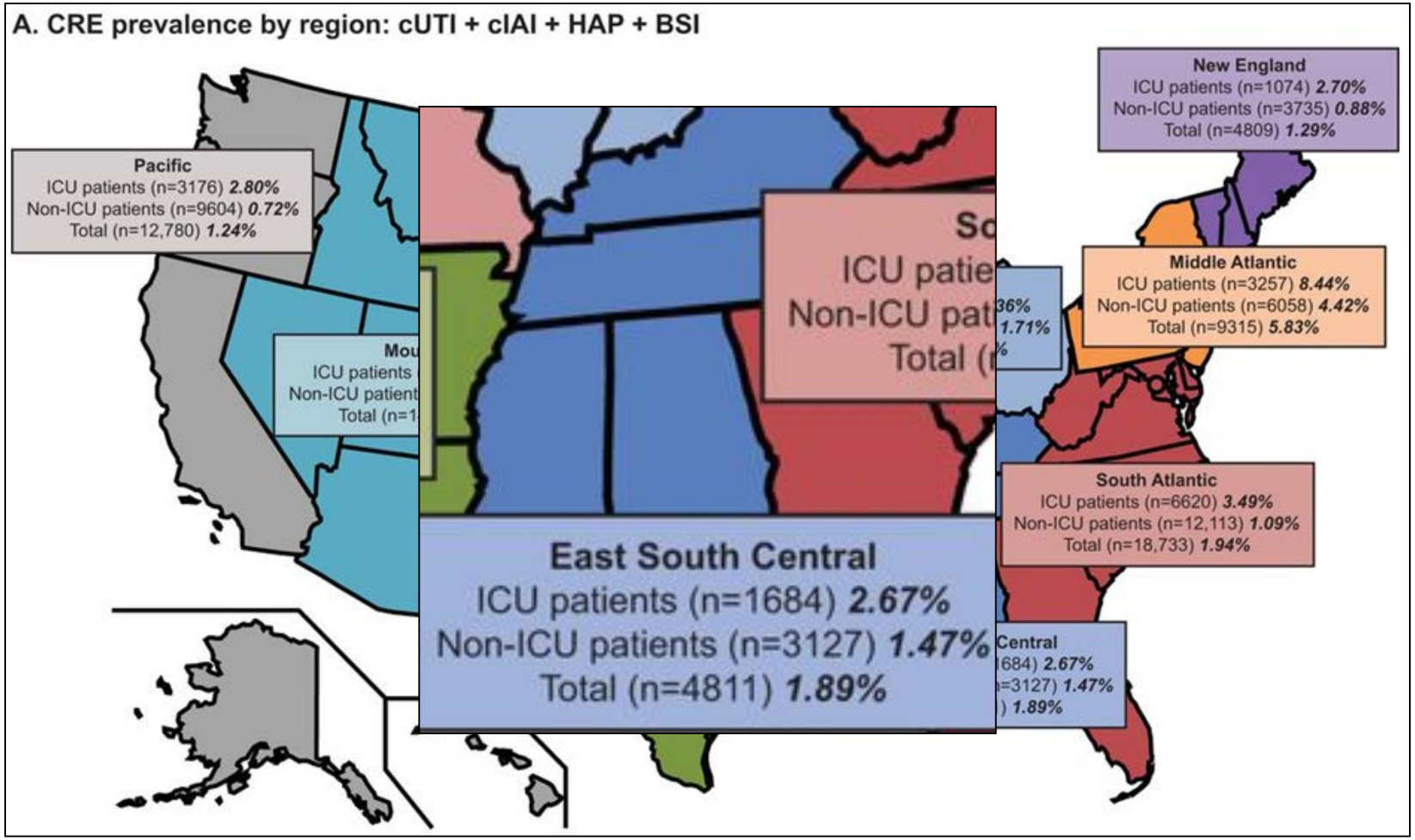
CDC. Antibiotic resistance threats in the United States, 2013

Regional CRE Prevalence



Lodise. AAC. 2017 Jul 25;61(8)

Regional CRE Prevalence

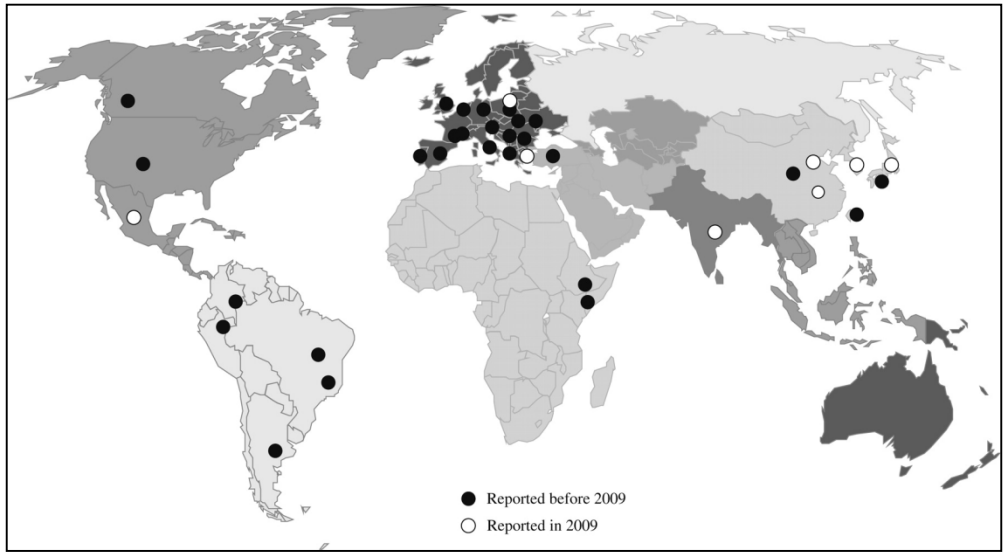


Lodise. AAC. 2017 Jul 25;61(8)

New Delhi Metallo β-lactamase (NDM-1)

- First described in 2009
  - Traced to India
  - Unpopular name politically
  - *Klebsiella pneumoniae most common*
- Confers resistance to most antibiotics
  - Usually colistin and tigecycline susceptible
  - Colistin-resistant NDM-1 reported
- Subsequent global spread
  - Identified in drinking/runoff water
- Highlighted scarcity of systematic AMR data
- Plasmid-mediated, easily transferable

Enzyme produced by the gene *bla*$_{\text{NDM-1}}$



Yong. AAC. 2009 December; 53(12): 5046–5054
Kumarasamy. Lancet ID. 2010;10:597–602
Sidjabat. *CID.* 2011;52:481-4
Walsh. *Lancet ID.* 2011;11:355-62

MCR-1 (Mechanism of Colistin Resistance 1)

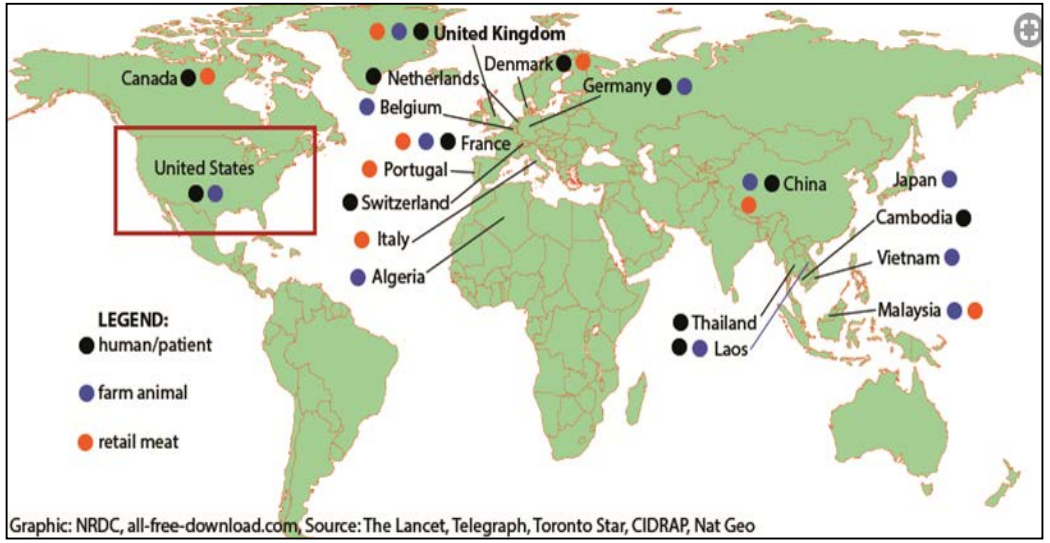
- Colistin resistance traditionally chromosomal
  - Not horizontal transfer (sharing between bacteria)
- *E. coli s*urveillance in livestock in China
  - Major increase colistin resistance
- Colistin-resistant *E. coli* strain with ability to transfer
- Concern that *mcr-1* could share colistin-R
  - Create pan-resistance

https://www.fwi.co.uk/livestock/antibiotic-usage-halved-pig-industry-two-years

Liu. Lancet ID. 2016 Feb;16(2):161-8

Major Concern Followed…

- CDC responded
  - Screened 55,000 samples (no MCR1 detected)
- Since found worldwide
- *E. coli with MCR-1* in Pennsylvania woman
  - No recent travel outside the U.S.
- CDC's Antibiotic Resistance Lab Network
  - 7-8 regional labs
  - Labs in all states and 7 major cities to detect resistant organisms from human samples



As of 2016….

McGann. AAC. doi:10.1128/AAC.01103-16

And then ….

- September 2016 Nevada woman died CRE *Klebsiella*
  - History of recent, prolonged hospitalizations in India
- New Delhi metallo-β-lactamase (NDM) confirmed
- CDC testing revealed resistant to 26 antibiotics
  - Only Intermediately susceptible to tigecycline
  - MCR-1 gene not found
- Investigation on patient's unit without any transmission
- What's next superbug?


The Atlantic

HEALTH

A Woman Was Killed by a Superbug Resistant to All 26 American Antibiotics

She won't be the last.

SARAH ZHANG JAN 13, 2017

npr set station news arts & life music programs

INFECTIOUS DISEASE

A Superbug That Resisted 26 Antibiotics

January 17, 2017 · 3:01 PM ET

SUSAN BRINK

CDC. *MMWR* January 13, 2017 / 66(1);33

Conclusions

- Antibiotic resistance is increasing
- Antibiotics #1 driver
- MRSA, VRE, ESBL, FQ resistance commonly encountered in primary care
- Emerging drug resistance continues
- Stratify by risk factors, clinical presentation and epidemiology
- Know treatment options

VANDERBILT UNIVERSITY
MEDICAL CENTER

THANK YOU!!

Changing Landscape of Antimicrobial Resistance: Primary Care Update from Antimicrobial Stewardship Perspective

2018 Infectious Diseases Symposium For Primary Care Providers

September 28, 2018

George Nelson, MD

Assistant Professor and Director Antimicrobial Stewardship Program

Vanderbilt University Medical Center