Antimicrobial stewardship

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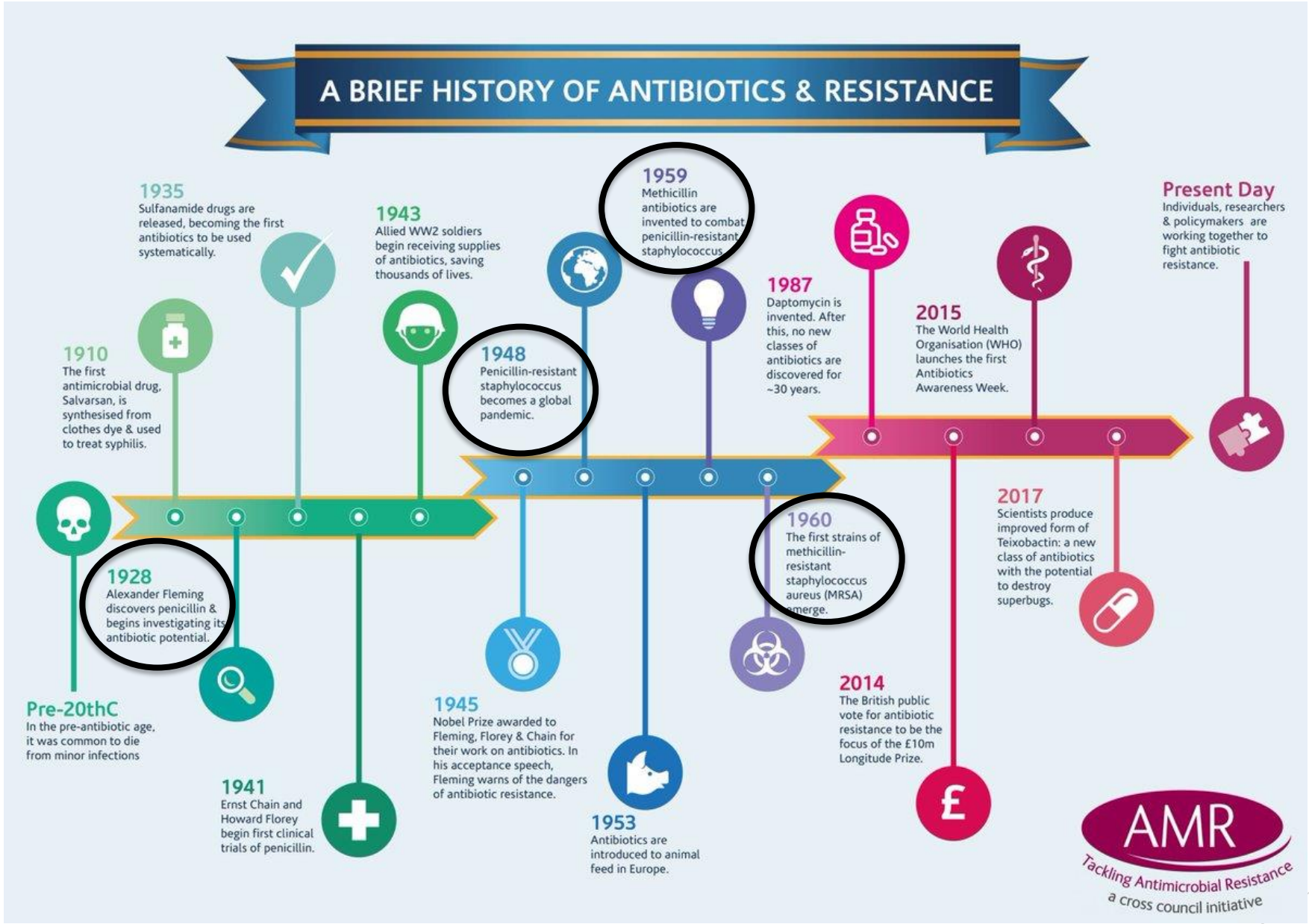
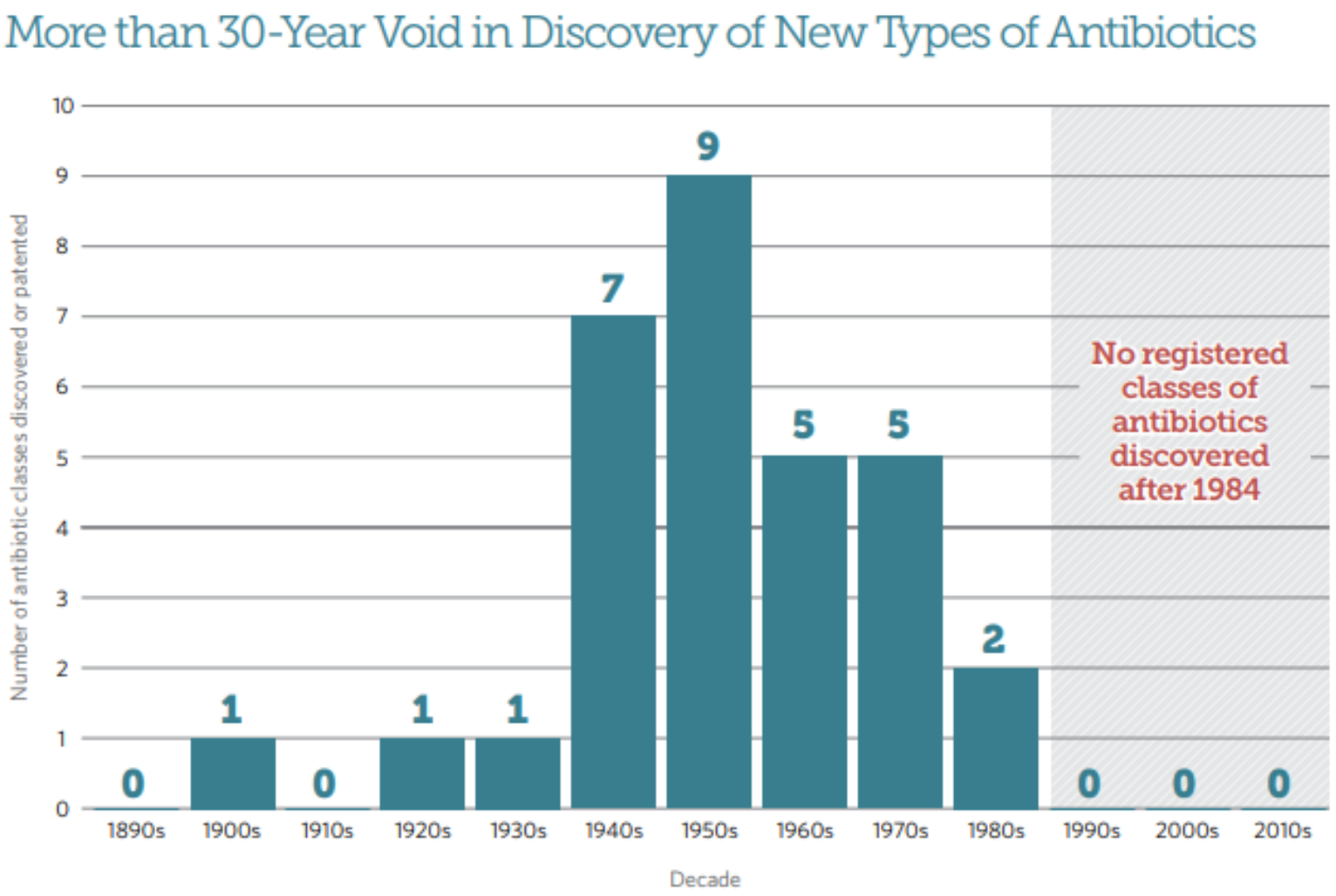
Objectives

- Discuss timeline of antimicrobials as they relate to antibiotic resistance
- Define antimicrobial stewardship
- Present real world cases of antimicrobial stewardship


A BRIEF HISTORY OF ANTIBIOTICS & RESISTANCE
Pre-20thC
In the pre-antibiotic age, it was common to die from minor infections
1910
The first antimicrobial drug, Salvarsan, is synthesised from clothes dye & used to treat syphilis.
1928
Alexander Fleming discovers penicillin & begins investigating its antibiotic potential.
1935
Sulfanamide drugs are released, becoming the first antibiotics to be used systematically.
1941
Ernst Chain and Howard Florey begin first clinical trials of penicillin.
1943
Allied WW2 soldiers begin receiving supplies of antibiotics, saving thousands of lives.
1945
Nobel Prize awarded to Fleming, Florey & Chain for their work on antibiotics. In his acceptance speech, Fleming warns of the dangers of antibiotic resistance.
1948
Penicillin-resistant staphylococcus becomes a global pandemic.
1953
Antibiotics are introduced to animal feed in Europe.
1959
Methicillin antibiotics are invented to combat penicillin-resistant staphylococcus.
1960
The first strains of methicillin-resistant staphylococcus aureus (MRSA) emerge.
1987
Daptomycin is invented. After this, no new classes of antibiotics are discovered for ~30 years.
2014
The British public vote for antibiotic resistance to be the focus of the £10m Longitude Prize.
2015
The World Health Organisation (WHO) launches the first Antibiotics Awareness Week.
2017
Scientists produce improved form of Teixobactin: a new class of antibiotics with the potential to destroy superbugs.
Present Day
Individuals, researchers & policymakers are working together to fight antibiotic resistance.
AMR
Tackling Antimicrobial Resistance
a cross council initiative

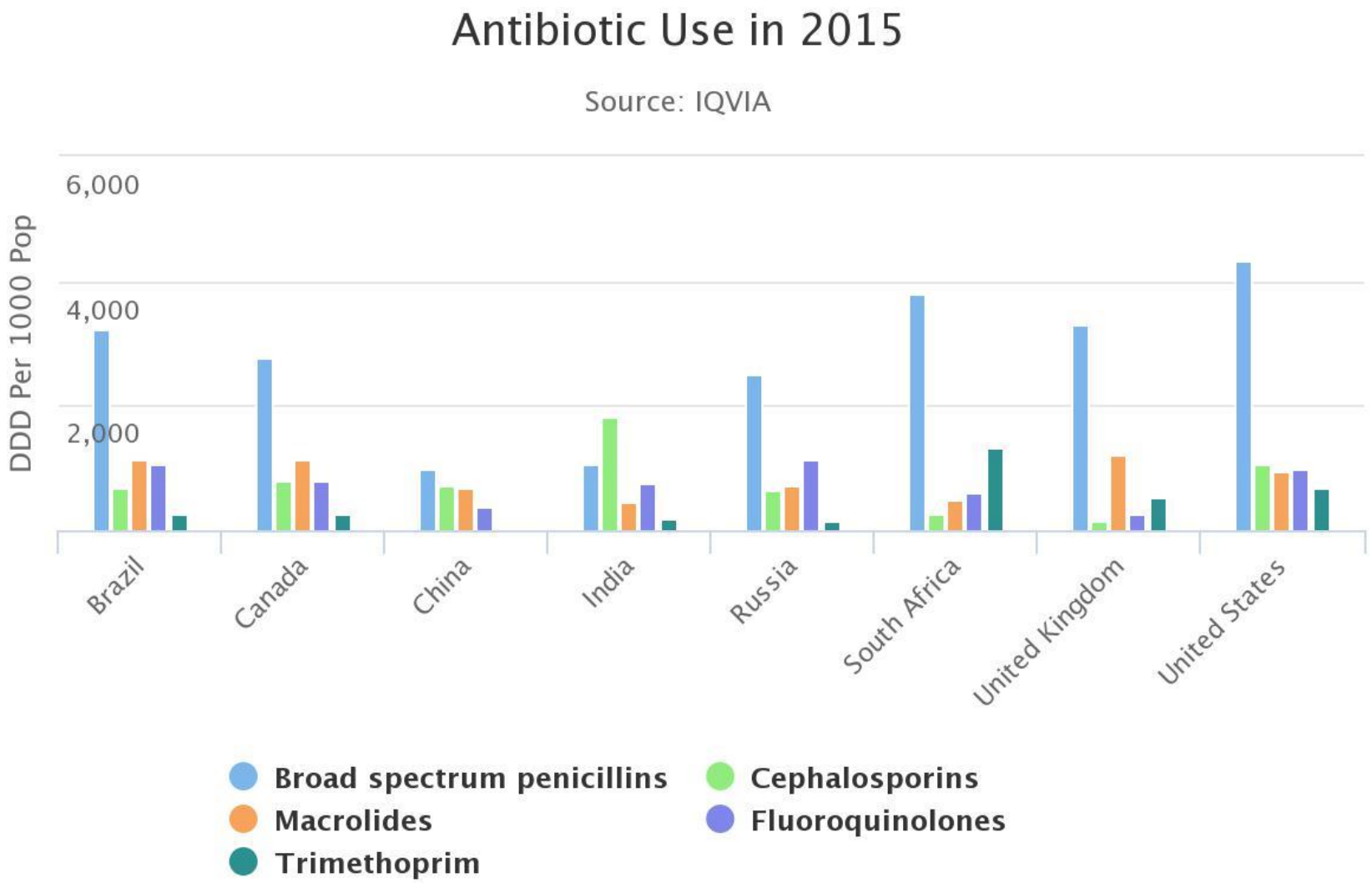
Age of antibiotics



New antibiotics since 2010:

- Omadcycline (2018)
- Eravacycline (2018)
- Plazomicin (2018)
- Meropenem/vaborbactam (2017)
- Ceftazidime/avibactam (2015)
- Dalbavancin (2014)
- Oritavancin (2014)
- Tedizolid (2014)
- Ceftolozane/tazobactam (2014)
- Televancin (2013)
- Bedaquiline (2012)
- Fidaxomicin (2011)
- Ceftaroline (2010)

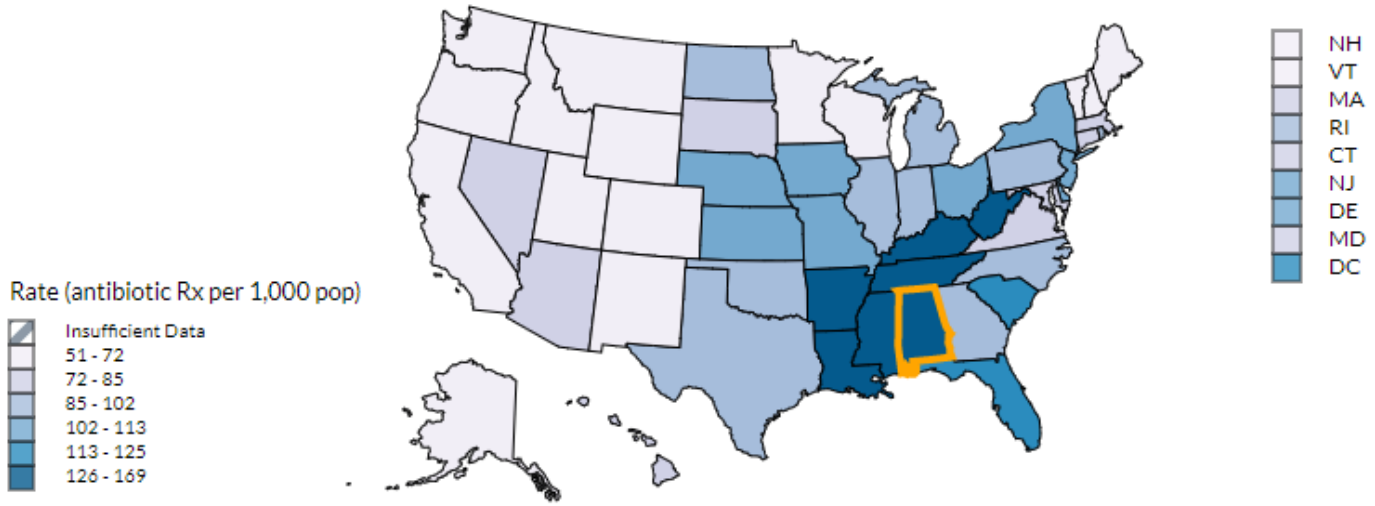
Antibiotic use in the United States



Antibiotic Prescriptions per 1000

Antibiotic Prescriptions Dispensed in U.S. Community Pharmacies Per 1000 Population | Fluoroquinolones | 2016

Map | Table | Bar Chart | Download



NATIONAL

92

Antibiotic prescriptions dispensed
PER 1000 POPULATION

ALABAMA

145

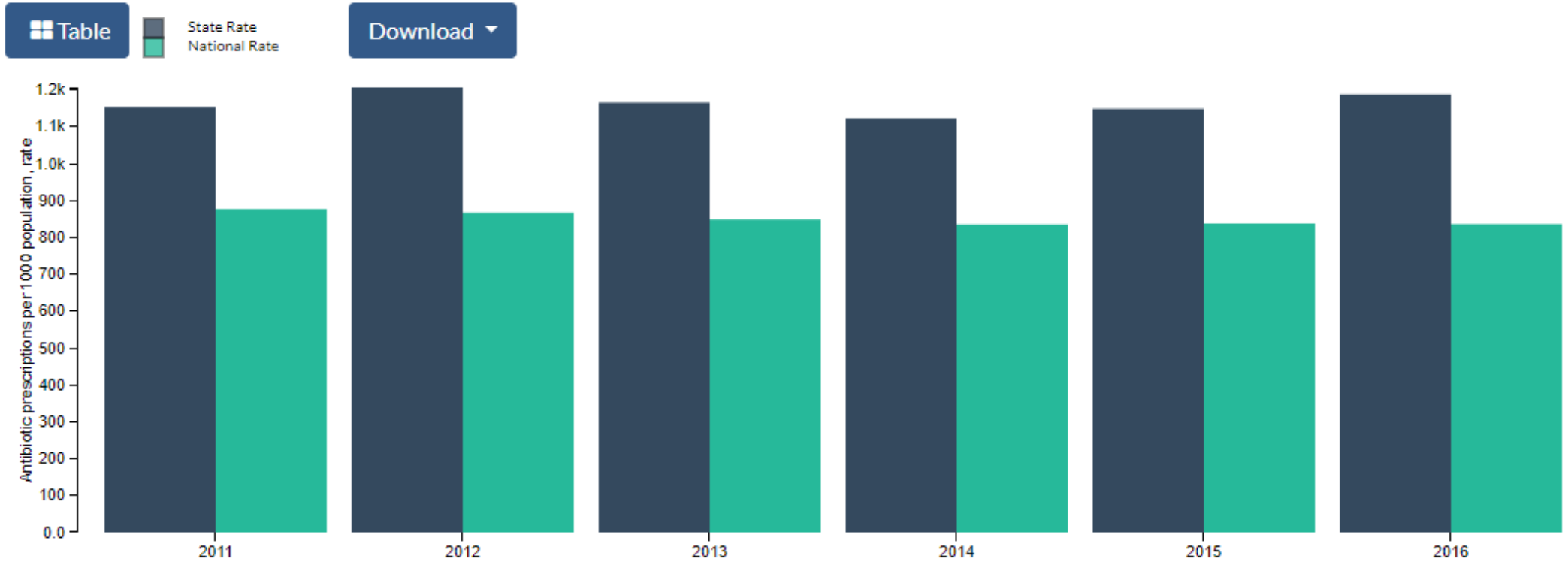
Antibiotic prescriptions dispensed
PER 1000 POPULATION

Alabama Antibiotics Dispensed in U.S. Community Pharmacies Per 1000 Population

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

Alabama Antibiotics Dispensed in U.S. Community Pharmacies Per 1000 Population

All Antibiotic Classes | Over Time



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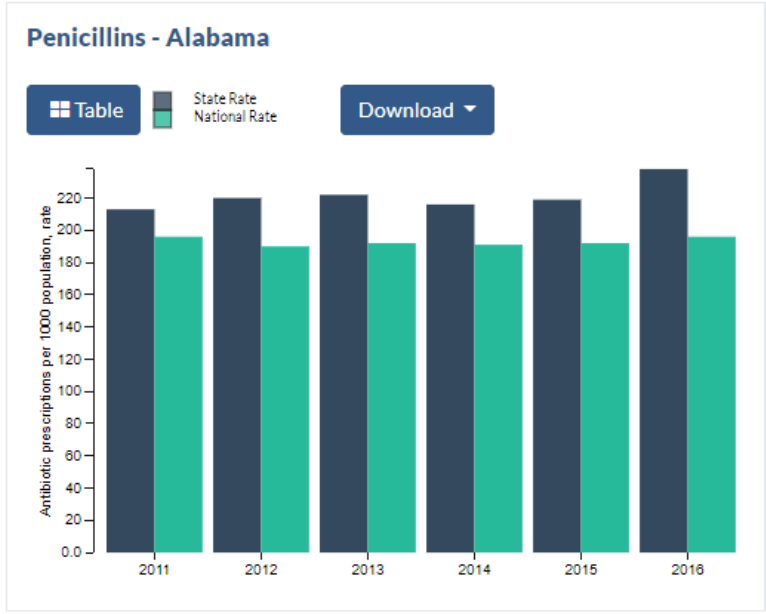

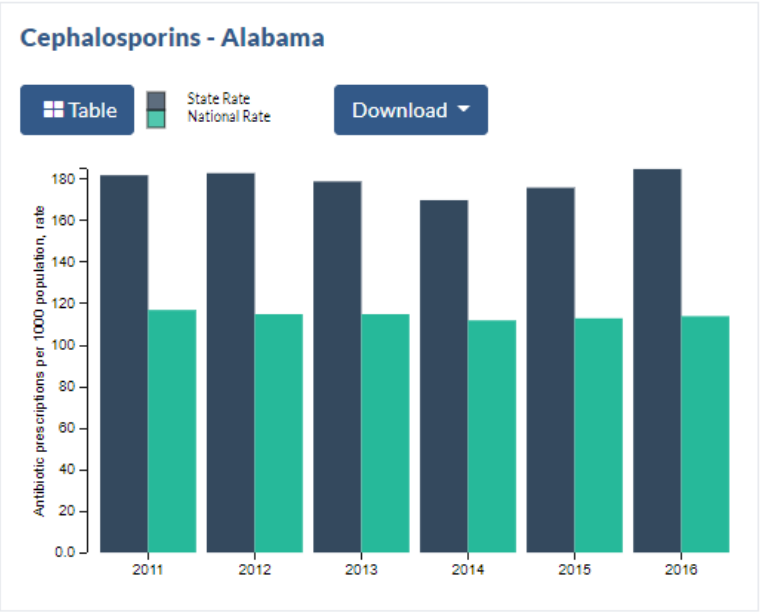

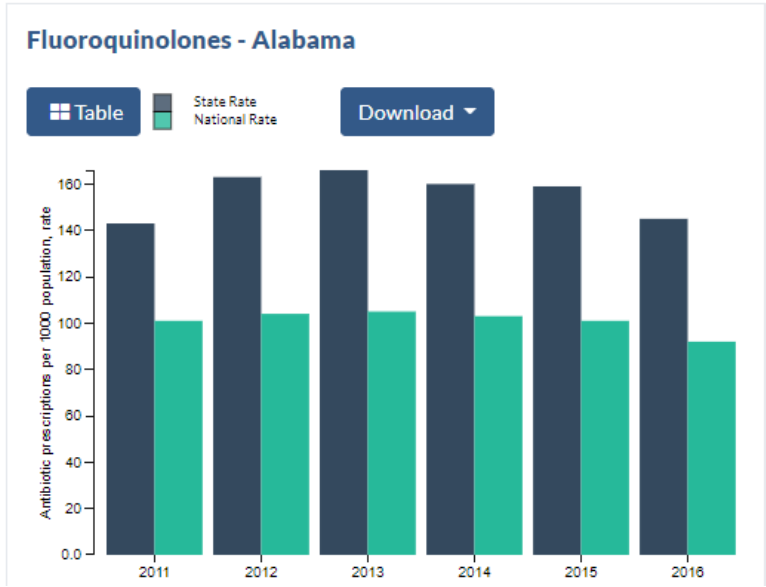

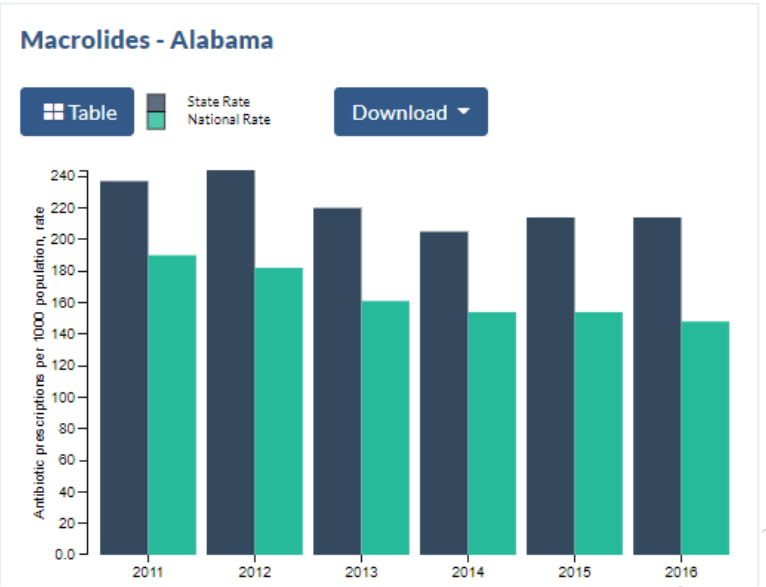

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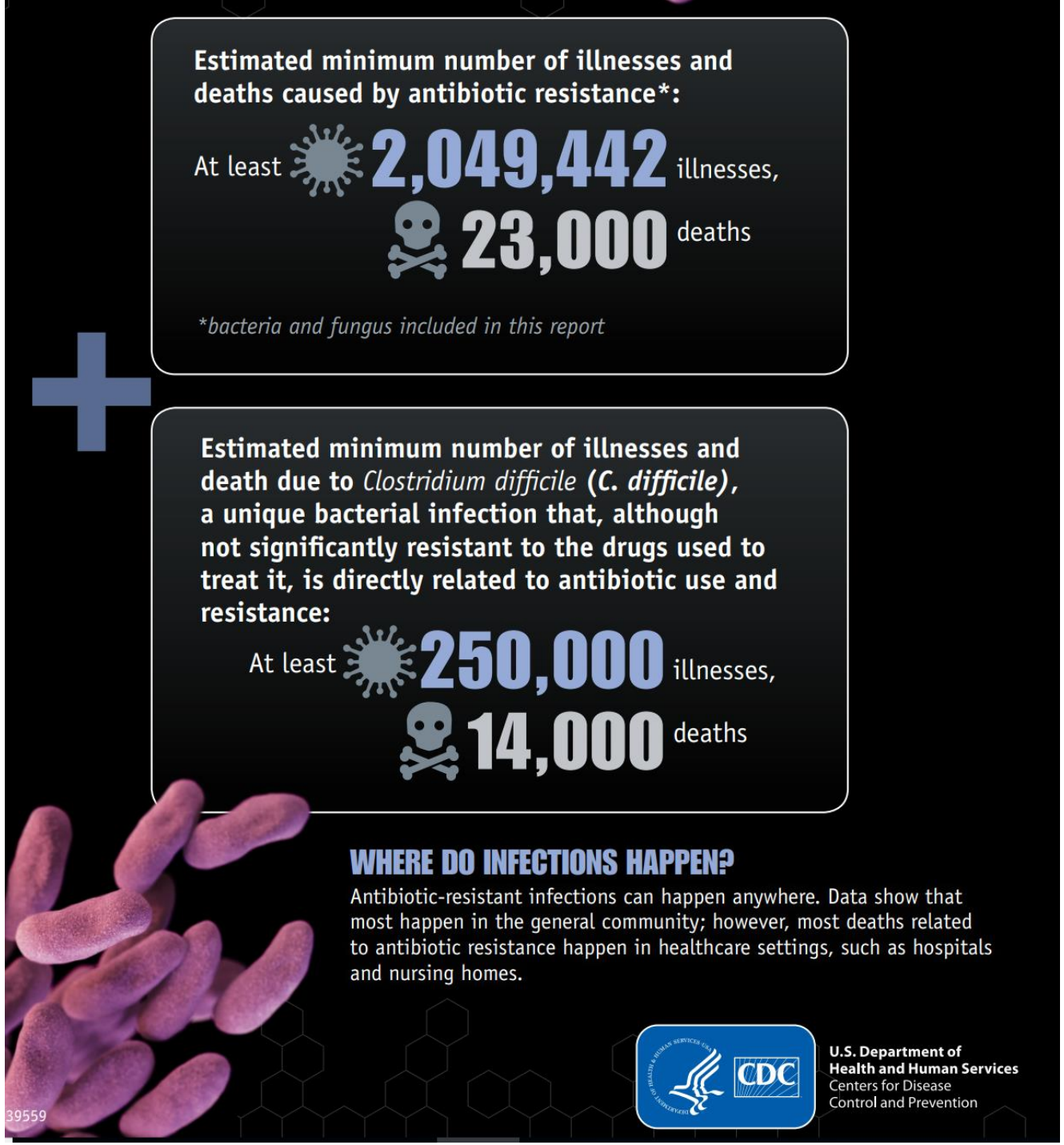


More recent evidence suggests >153,000 deaths related to MDROs annually in the United States

Why does antibiotic prescribing matter?

Pseudomonas aeruginosa				
	MBINT	KINT	EINT	MCFINT
Amikacin	R			
Ceftazidime	R			
Ciprofloxacin	R			
Gentamicin	R			
Imipenem	R			
Meropenem	R			
Tobramycin	R			
Cefepime		R		
Piperacillin/Tazobactam		R		
Ceftazidime/Avibactam			R	
Ceftolozane/ Tazobactam			R	
Colistin*				R c

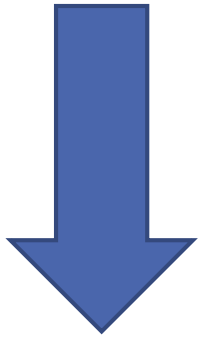
Klebsiella pneumoniae #2			
	MUINT	EINT	MDIL
Amikacin	R		
Ampicillin	R		
Cefepime	R		
Ceftazidime	R		
Ceftriaxone	R		
Cephalothin	R		
Ciprofloxacin	R		
Gentamicin	R		
Imipenem	R		
Meropenem	R		
Nitrofurantoin	R		
Piperacillin/Tazobactam	R		
Trimethoprim/Sulfa	R		
Tobramycin	R		
Ceftazidime/Avibactam		R	
Ceftolozane/ Tazobactam		R	
Colistin*			>4 c

Antibiotic prescriptions in hospitals

- >50% of patients in the hospital receive an antibiotic
  - Most common: pneumonia (22%), UTI (14%), suspected drug resistant infections (17%)
- Some doctors prescribe 3 times as many antibiotics as doctors in other hospitals
- Antibiotic use has well known unintended consequences
  - *Clostrioides difficile* infection (affects 500,000 patients with 15,000 deaths)
    - Reducing high use antibiotics by 30% can lower CDI by 26%
  - Drives antimicrobial resistance

Critical balance of antibiotic use

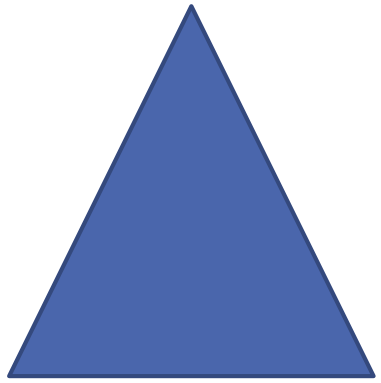
Infection Prevention and Antimicrobial Stewardship



Importance of appropriate empiric therapy

Effect of broad spectrum therapy on resistance

Mortality increases when initial therapy is inappropriate



Resistance increases when broad-spectrum agents are overused.

Resistance has negative impact on outcomes

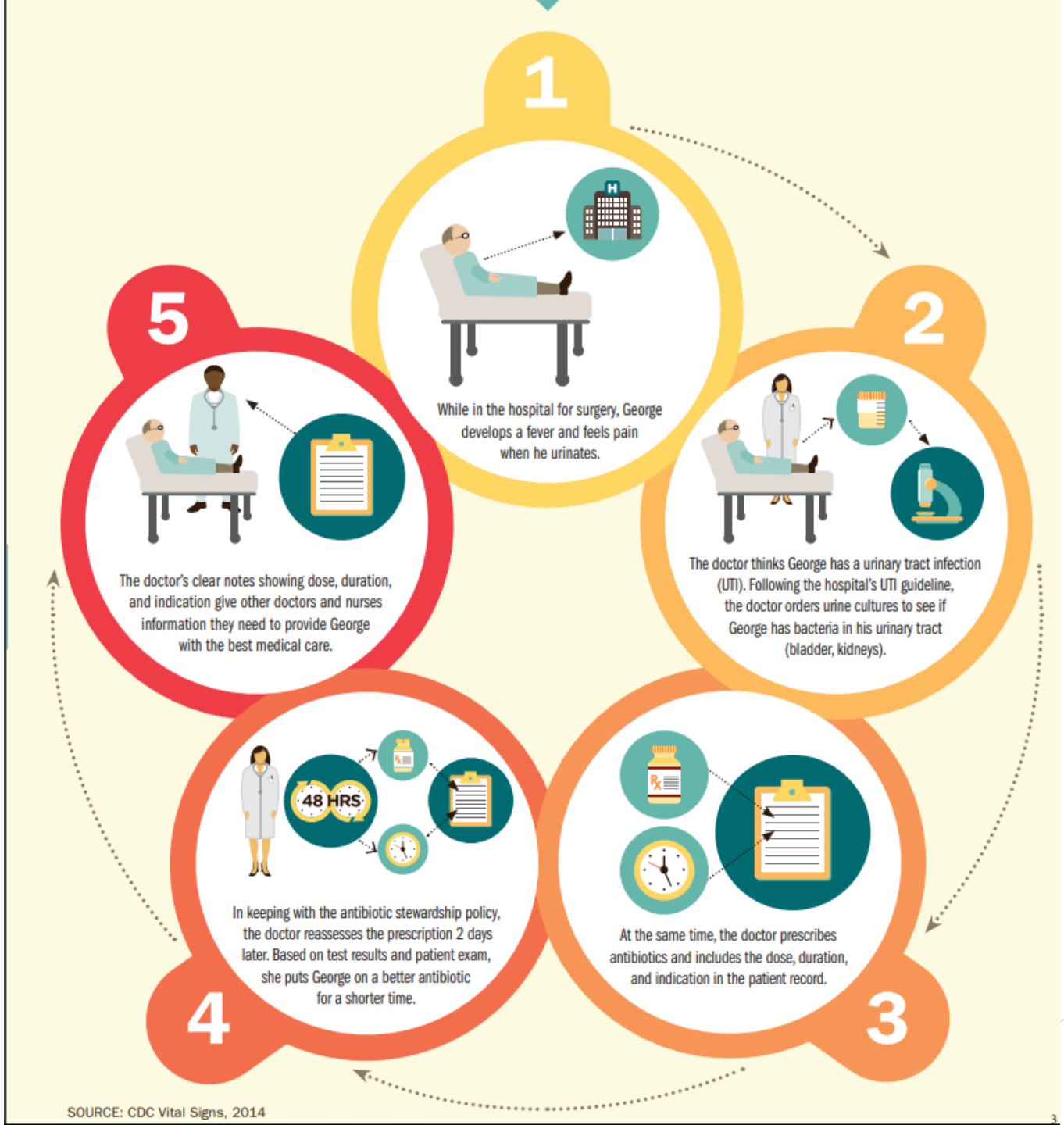
Common Misuses of Antibiotics

- Prolonged empiric treatment without evidence of infection
- Treatment of a positive clinical culture in the absence of disease
- Failure to narrow antimicrobial therapy when a causative organism is identified
- Prolonged prophylactic therapy
  - Ex. Until removal of surgical drains
  - excessive use of certain antimicrobials
    - Creates selective pressure

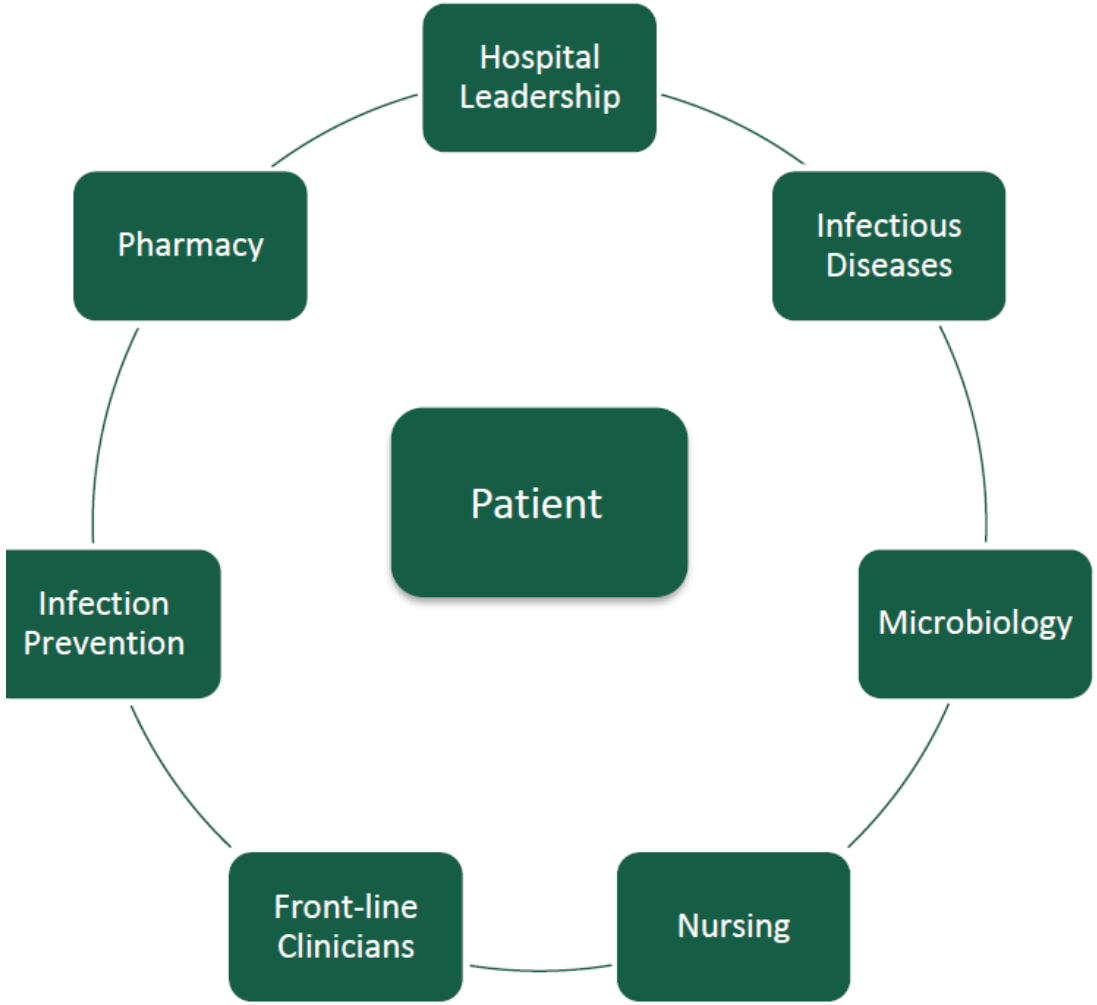
What is Antimicrobial stewardship?

- Anything and Everything intended to improve patient outcomes and minimize the negative effects of antimicrobial use

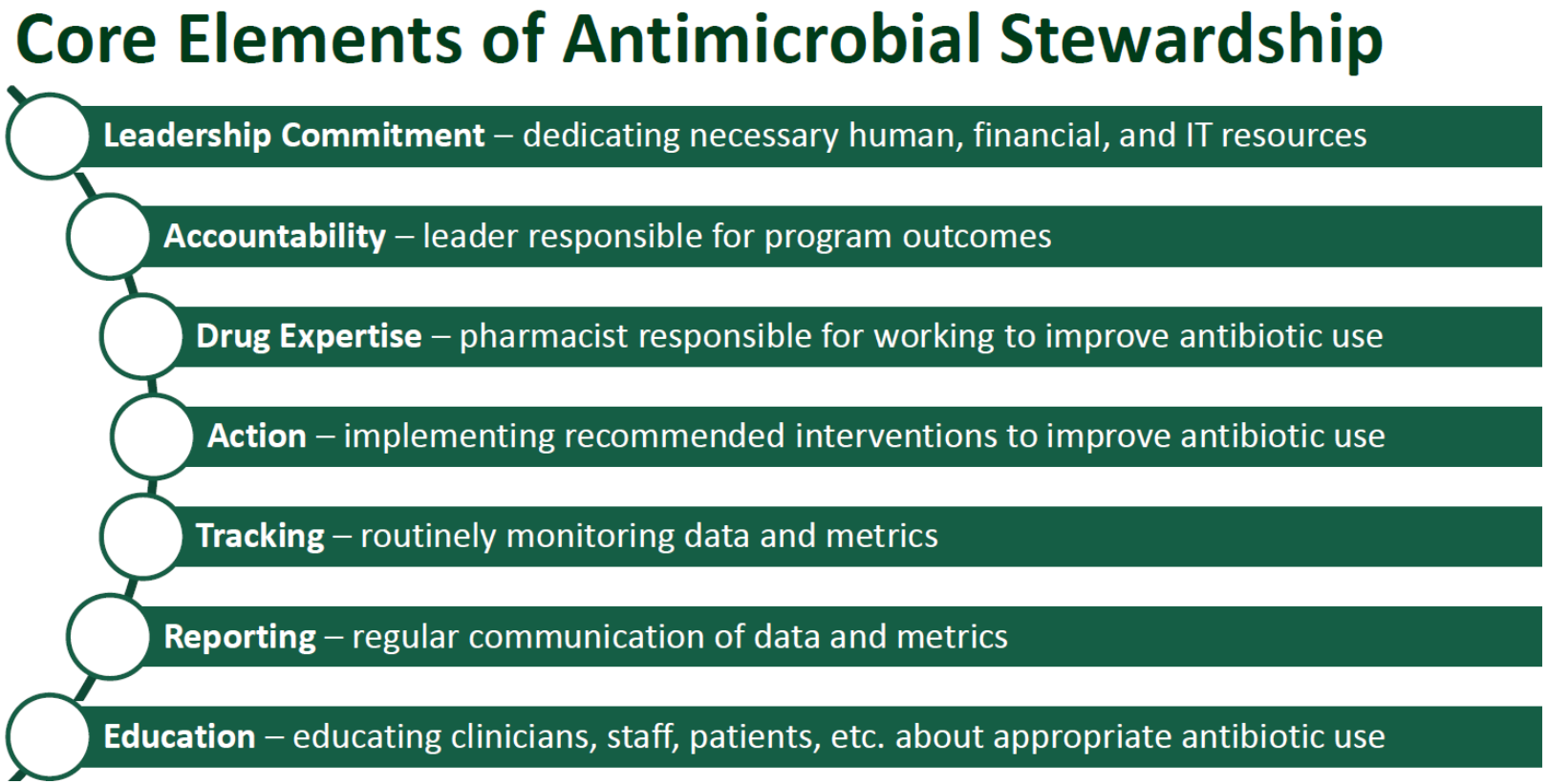
- “Antibiotics have a critical characteristic that makes them unique among all drugs…they suffer from transmissible loss of efficacy over time…” Brad Spellberg MD

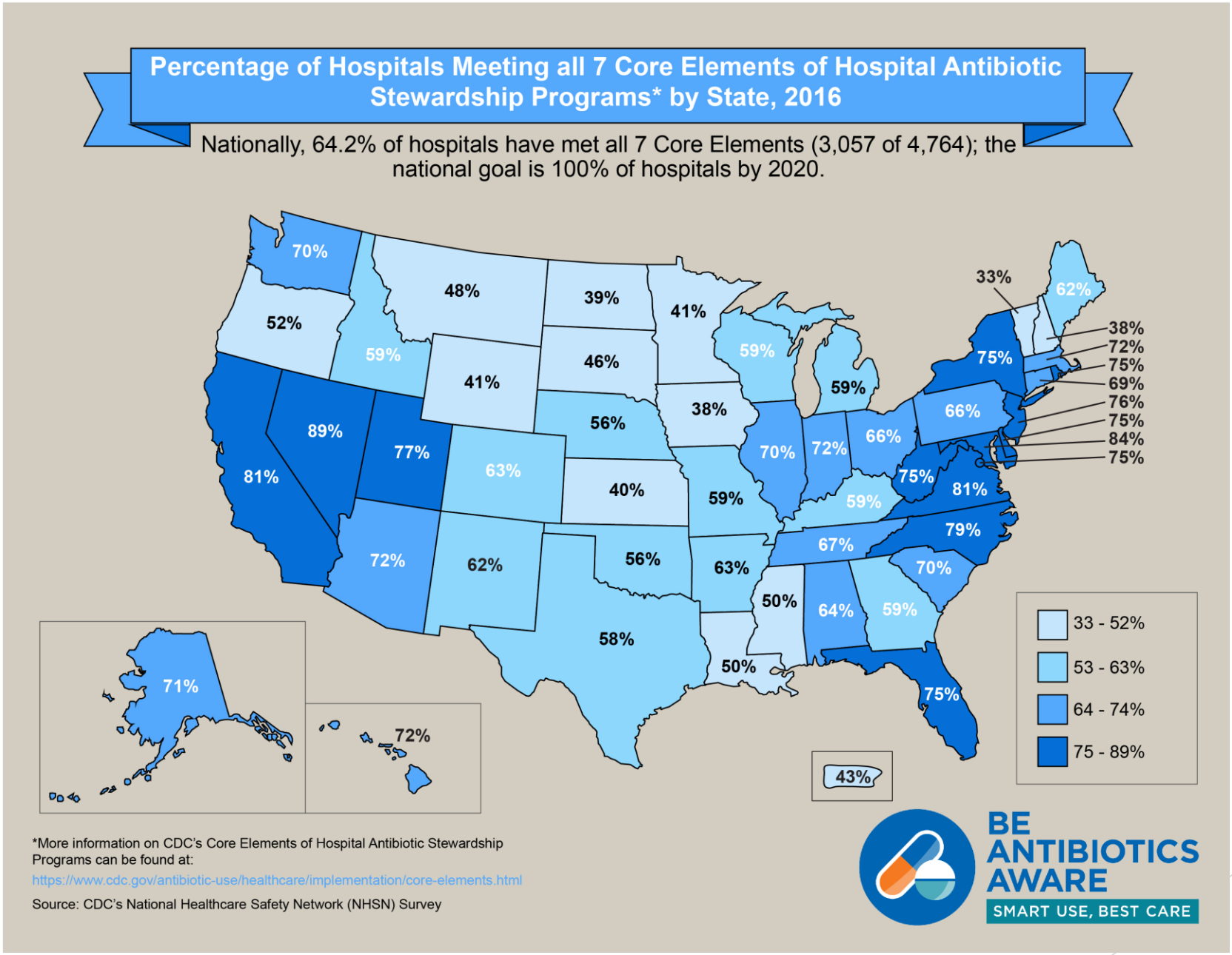

1
While in the hospital for surgery, George develops a fever and feels pain when he urinates.
2
The doctor thinks George has a urinary tract infection (UTI). Following the hospital's UTI guideline, the doctor orders urine cultures to see if George has bacteria in his urinary tract (bladder, kidneys).
3
At the same time, the doctor prescribes antibiotics and includes the dose, duration, and indication in the patient record.
4
48 HRS
In keeping with the antibiotic stewardship policy, the doctor reassesses the prescription 2 days later. Based on test results and patient exam, she puts George on a better antibiotic for a shorter time.
5
The doctor's clear notes showing dose, duration, and indication give other doctors and nurses information they need to provide George with the best medical care.
SOURCE: CDC Vital Signs, 2014

Antimicrobial Stewardship Programs



Core Elements




Percentage of Hospitals Meeting all 7 Core Elements of Hospital Antibiotic Stewardship Programs* by State, 2016
Nationally, 64.2% of hospitals have met all 7 Core Elements (3,057 of 4,764); the national goal is 100% of hospitals by 2020.
70%
52%
48%
59%
41%
39%
46%
41%
56%
38%
59%
59%
89%
81%
77%
63%
40%
59%
70%
72%
66%
33%
62%
38%
72%
75%
69%
76%
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84%
75%
66%
75%
59%
81%
79%
67%
72%
62%
56%
63%
70%
50%
64%
59%
58%
50%
75%
71%
72%
43%
33 - 52%
53 - 63%
64 - 74%
75 - 89%
*More information on CDC's Core Elements of Hospital Antibiotic Stewardship Programs can be found at:
https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html
Source: CDC's National Healthcare Safety Network (NHSN) Survey
BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

Stewardship in action

- Core strategies
  - Preauthorization
  - Prospective audit and feedback
- Supplemental strategies
  - Clinical pathways and guidelines
  - Dose optimization or adjustment
  - De-escalation or streamlining
  - IV to PO conversion
  - Education

Preauthorization

- Restrict the use of certain agents in a facility in order to prevent misuse
  - Daptomycin (cost)
  - Meropenem (prevent resistance)

Prospective audit and feedback

- Most beneficial in real time
  - Typically driven by pharmacy
  - Usually performed at 48-72 hours
  - Ensure appropriate therapy for the type of infection
  - Can assist in de-escalation
  - Can assist in IV→ PO conversion
    - Ex unasyn to augmentin

Guidelines and Education

- Guidelines from National Societies
- In house guidelines
  - What criteria to start treatment?
  - What to use?
  - How long?
  - Tailor to targeted population
    - Antibiogram

Antibiograms

- Laboratory report that displays overall susceptibility profile of a bacterial isolate to a variety of antibiotics
- Cumulative reports give percent of isolates susceptible to a variety of antibiotics over a period of time
  - Used to guide empiric therapy
  - Used to identify emergence of resistance over time

Gram Positive Bacteria	No. of Isolates	Ampicillin	Oxacillin(e)	Penicillin	Ceftriaxone	Vancomycin	Tetracycline	Erythromycin	Clindamycin	Trimethoprim/Sulfa	Gentamicin 500	Daptomycin(f)	Linezolid	Nitrofurantoin(*)	Fluconazole	Voriconazole	Micafungin
Staphylococcus aureus (MSSA)	569		100	22		99	93	56	71	100		99	99				
Staphylococcus aureus (MRSA)	653					99	90	15	61	96		98	98				
Staphylococcus lugdunensis	64		69	36		100	92	65	80	97		100	100				
Staphylococcus capitis	52		58	13		100	90	38	49	90		96	100				
Staphylococcus epidermidis	377		28	8		98	84	25	46	46		99	99				
Enterococcus faecalis (a)	499	98		98		95	28	23			76	99	95	99			
Enterococcus faecium (a)	216	13		13		26	15	2			91	74	87	44			
Streptococcus pneumoniae (b)	56			91	95	100	73	33	73								
GBS (Strep. agalactiae) (c)	41			98		100	19	32	51								
Viridans group streptococci	254			62	92	99	56	44	77								
Yeasts																	
Candida albicans	138														99	99	99
Candida glabrata (d)	74														88		99
Candida krusei	5														0 [9]	100	100
Candida parapsilosis	21														100	100	100
Candida tropicalis	16														75	81	100

Key ways to be an antibiotic steward

- 1. disease prevention through vaccination
  - Fewer infections = fewer antimicrobials needed
  - >20 vaccine preventable illnesses
  - Prevent 2-3 million deaths yearly

- Cross-reactivity <2%
- Most people outgrow PCN allergy @ rate of 10% per year
- 99% of patients found not to be TRULY allergic after testing

- Carrying a "PCN allergy" label on your EHR leads to:
  - ↑ morbidity & mortality
  - ↑ healthcare costs
  - ↑ hospital length of stay
  - ↑ use of broad-spectrum abx (with ↑ $$$)
  - ↑ antimicrobial resistance
  - ↑ rates C.diff, VRE
  - PCN Avoidance → suboptimal treatment

Key ways to be an antibiotic steward

- 2. Allergy history taking and documentation
  - 9/10 people reporting penicillin allergies are not truly allergic, cross reactivity <2%
  - Up to 80% of those who were allergic lose their allergy after 10 years, 99% of patients found to not be truly allergy after testing
  - Prevent unnecessary use of second-line agents
  - Perform or refer for skin testing
- Carrying a “PCN allergy” label on your EHR leads to:
  - ↑ morbidity & mortality
  - ↑ healthcare costs
  - ↑ hospital length of stay
  - ↑ use of broad-spectrum abx (with ↑ $$$)
  - ↑ antimicrobial resistance
  - ↑ rates C.diff, VRE
  - PCN Avoidance → suboptimal treatment

Key ways to be an antibiotic steward

- 3. Comprehensive medication review
  - Right drug at right dose for right infection
  - Narrowest spectrum possible
- 4. Patient counseling on appropriate antibiotic use
- 5. Advocate for appropriate antibiotic use

Stewardship: Shorter = Better

Diagnosis	Short (d)	Long (d)	Result
CAP	3 or 5	7, 8, or 10	Equal
HAP	7	10-15	Equal
VAP	8	15	Equal
Pyelo	7 or 5	14 or 10	Equal
Intra-abd	4	10	Equal
Gram Neg Bacteremia	7	14	Equal
AECB	$\leq$5	$\geq$7	Equal
Cellulitis	5-6	10	Equal
Osteo	42	84	Equal
Neutropenic Fever	AF x 72 h	+ANC > 500	Equal

15

Stewardship in specialty areas

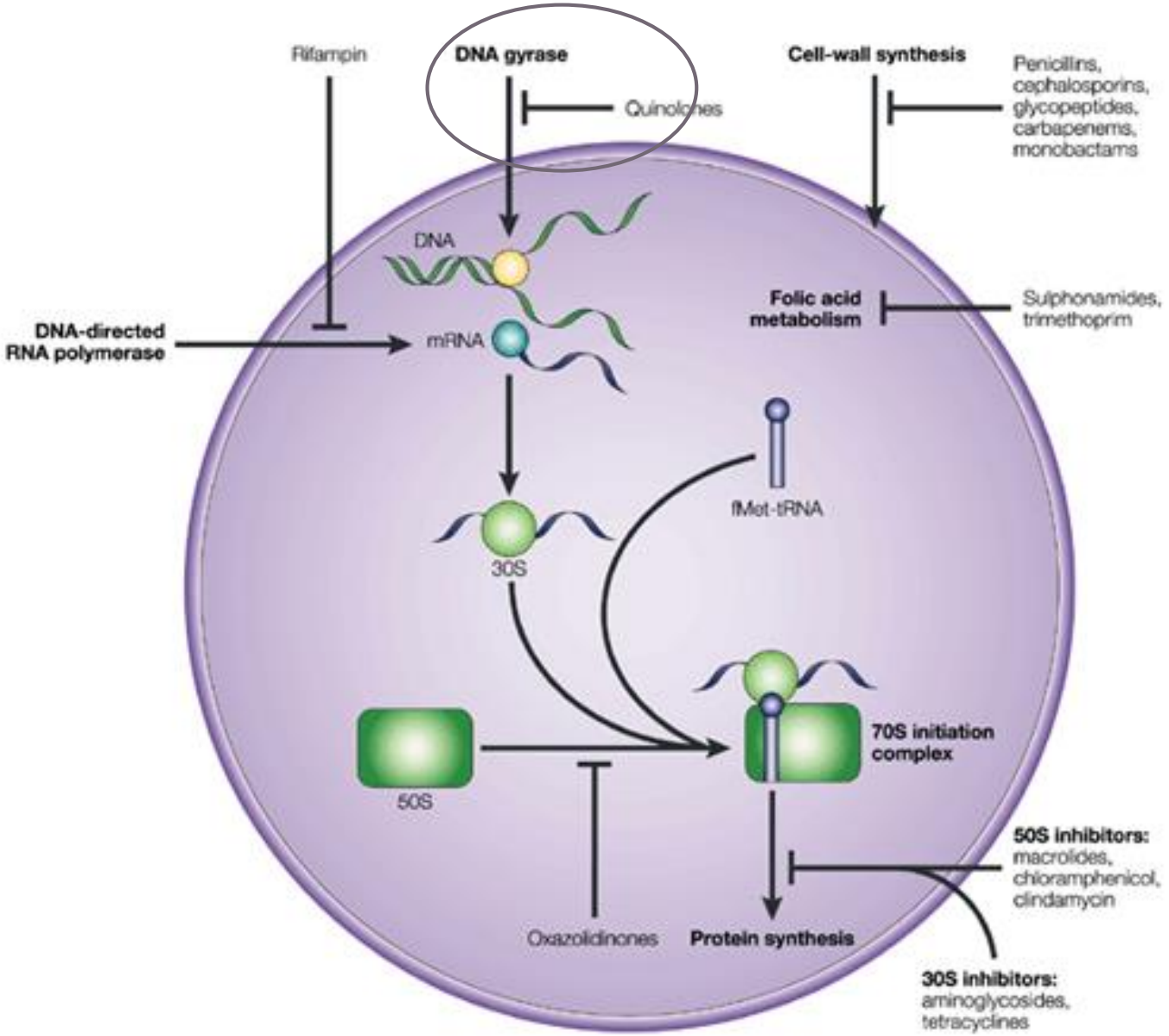
- Emergency Department
  - High volume, quick throughput
  - Challenge of follow up (patients and results)
  - Selection of appropriate drug, dose, route, duration
- Long term care facilities
  - Antibiotic overuse, suboptimal use, extended duration
  - Initial steps are least costly and intrusive
    - Monitor antibiotic use and resistance
    - Education of providers
  - Upfront guidelines
- ICU
  - Correct choices and durations (sepsis guidelines)
  - De-escalation, re-assessment, rapid testing, prevention

Stewardship in Action

Fluoroquinolone example

Fluoroquinolones

- Introduced in 1962
- Active against a wide variety of gram negative and gram-positive pathogens
- Good oral absorption and systemic distribution
- Broad clinical application
  - Lower respiratory tract infections
  - Skin and soft tissue infections
  - Sexually transmitted diseases
  - Urinary tract infections


Rifampin
DNA gyrase
Quinolones
Cell-wall synthesis
Penicillins, cephalosporins, glycopeptides, carbapenems, monobactams
DNA
DNA-directed RNA polymerase
mRNA
Folic acid metabolism
Sulphonamides, trimethoprim
fMet-tRNA
30S
70S initiation complex
50S
50S inhibitors: macrolides, chloramphenicol, clindamycin
Oxazolidinones
Protein synthesis
30S inhibitors: aminoglycosides, tetracyclines
Nature Reviews | Drug Discovery

Fluoroquinolone Prescribing Practices

- Fluoroquinolone (FQ) prescribing has increased threefold since the 1990s

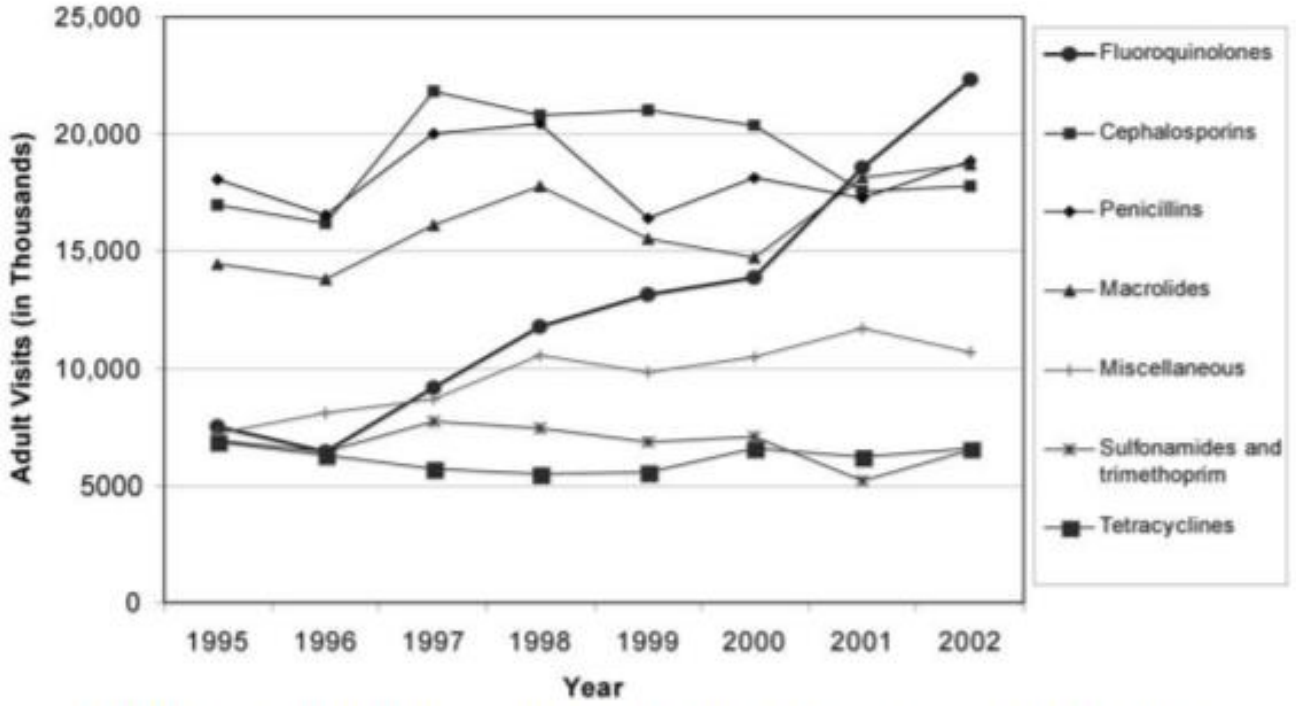
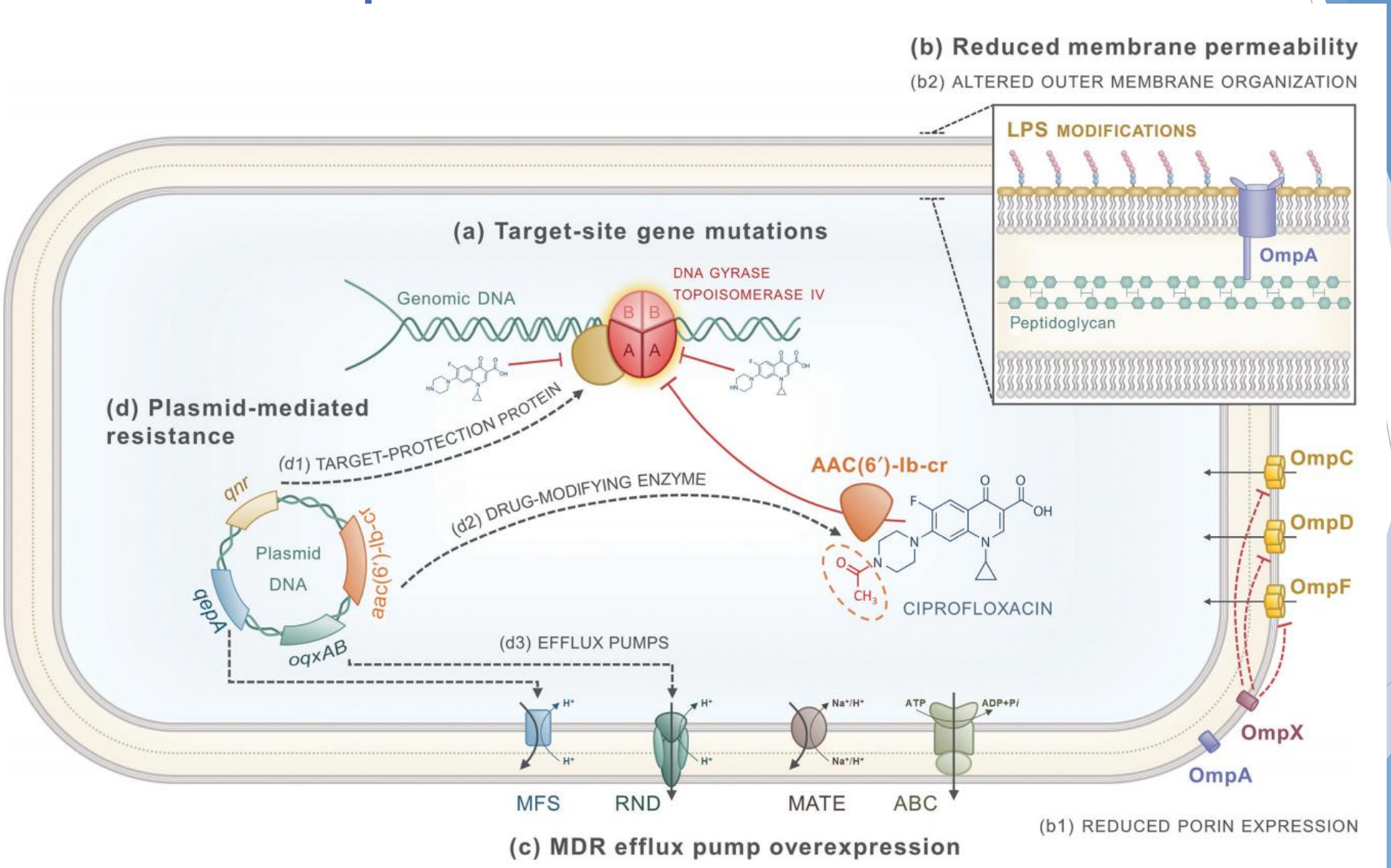


Figure 1 Antibiotic prescribing to adults in the United States: 1995 to 2002.

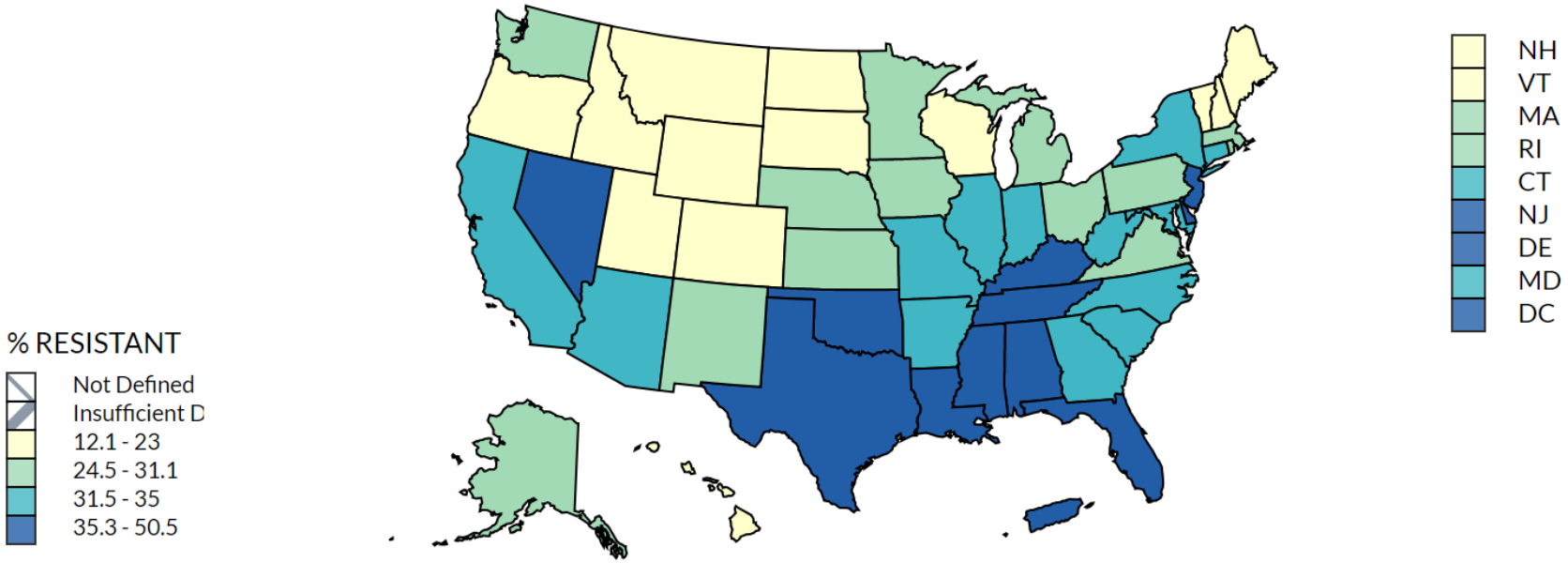
1. Linder JA, Huang ES, Steinman MA, Gonzales R, Stafford RS. Fluoroquinolone prescribed in the United States 1995 to 2002. Am. J. Med. 2005;118:259-268

Fluoroquinolone resistance



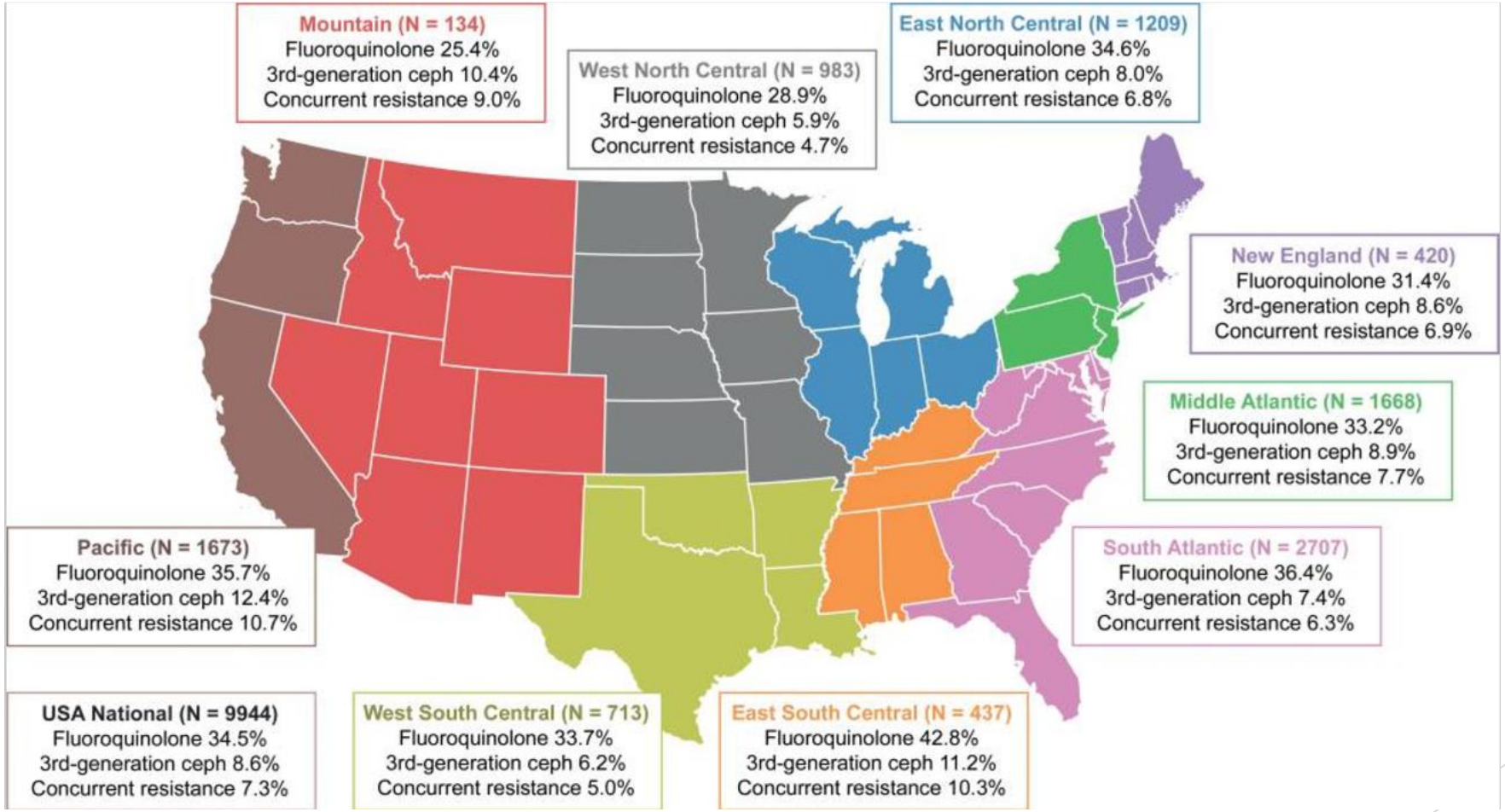
Correia et al., Journal of Medical Microbiology 2017;66:551–559

Fluoroquinolone resistant E. coli, Healthcare associated infections



National resistance rate is 33%

Urinary *Escherichia coli* Isolates Percent Resistance



1. Bidell MR, Palchak M, Mohr J, Lodise T: Fluoroquinolone and third generation-cephalosporin resistance among hospitalized patients with urinary tract infections due to *Escherichia coli*: do rates vary by hospital characteristics and geographic region?. *Antimicrob. Agents Chemother*. 2016;60:3170-3173.

Prior authorization of antimicrobials

- Common intervention employed by stewardship programs
- Fluoroquinolone restriction was implemented at UAB Hospital in October 2006 by Division of Infectious Diseases and Department of Pharmacy
- Hospital formulary consolidated to ciprofloxacin and moxifloxacin only
- All physicians required ID approval for inpatient FQ use outside set guidelines
  - Pharmacy regulated
  - EMR alert

Hypothesis

- Requiring prior authorization for inpatient fluoroquinolone prescriptions will improve gram-negative bacteria fluoroquinolone susceptibility rates

Methods

Organism	2003	2004	2005	2006
CIPROFLOXACIN Susceptibility	%	%	%	%
Acinetobacter baumannii	42	30	35	47
Citrobacter freundi	74	73	67	70
Citrobacter koseri	86	98	90	96
Enterobacter aerogenes	81	80	85	79
Enterobacter cloacae	54	48	55	59
Escherichia coli	88	80	71	69
Klebsiella oxytoca	86	72	71	76
Klebsiella penumoniae	90	85	80	89
Morganella morganii	66	77	69	75
Proteus mirablils	70	74	69	66
Providencia stuartii	38	39	13	29
Pseudomonas aeruginosa	60	54	50	56
Serratia marcescens	81	80	85	80

Methods

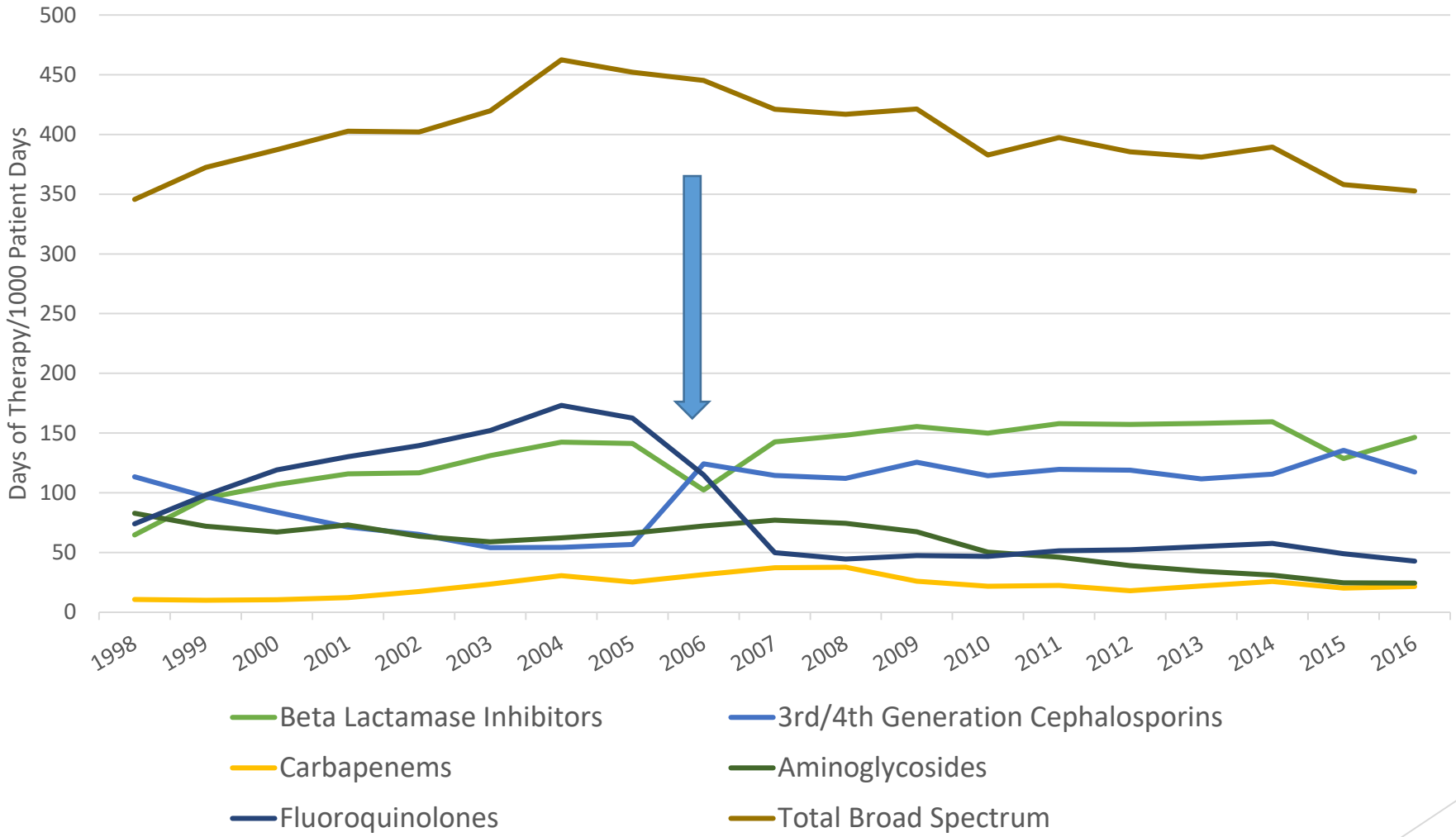
- Collected MIC data for clinical isolates from all body sites on 5 gram negative bacteria from 1998-2016
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Acinectobacter baumannii/haemolyticus*
  - *Pseudomonas aeruginosa*
  - *Enterobacter cloacae*
- Pre-intervention: 1998-2005
- Post-intervention: 2006-2016

Statistical analysis

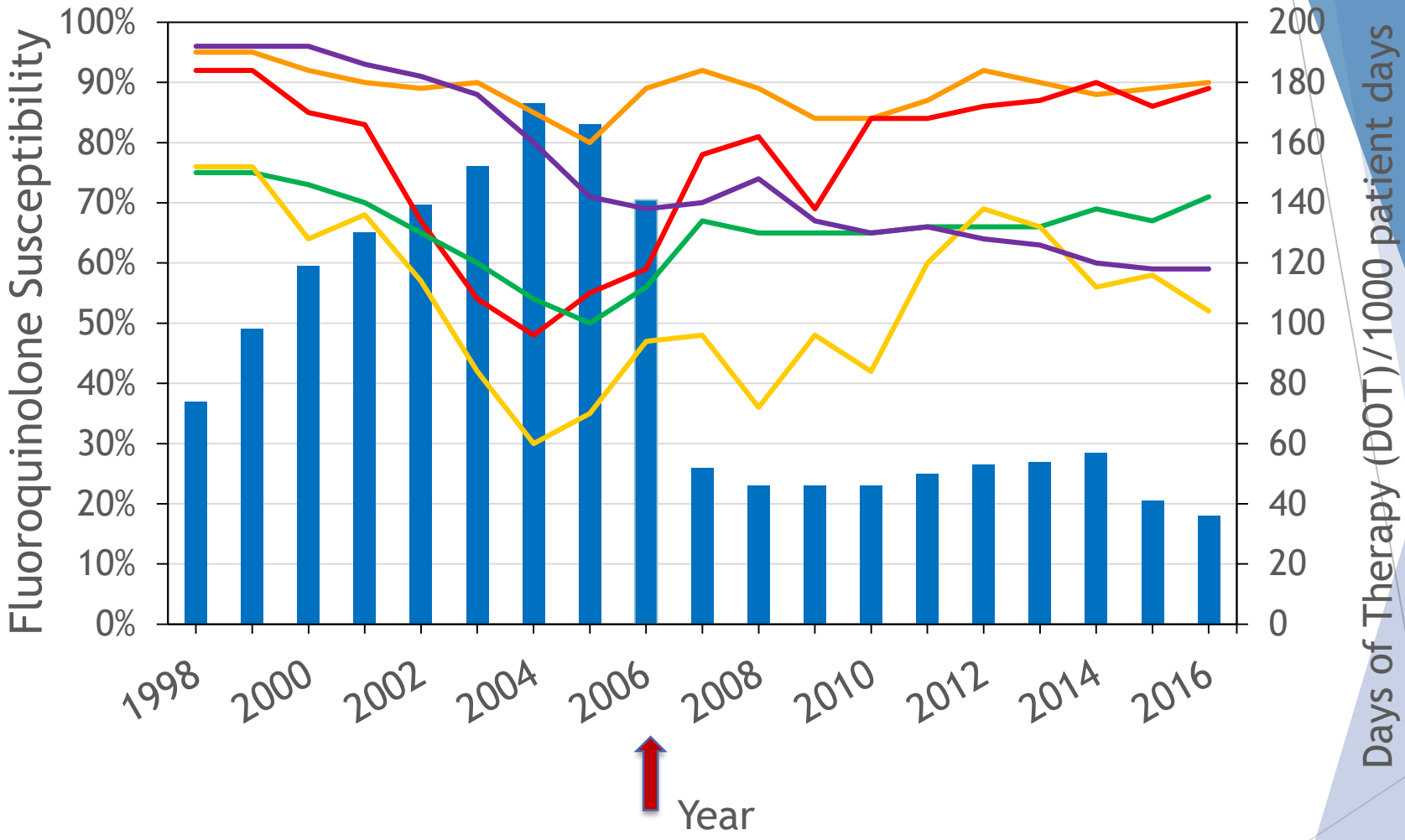
- To determine whether the annual trends in susceptibility were different in the periods prior to and following implementation of the stewardship program, we utilized Poisson regression
  - Calculated rate ratios (RRs) and associated 95% confidence intervals (CIs) for the annual rate of change in susceptibility for each of the 2 time periods.

Results

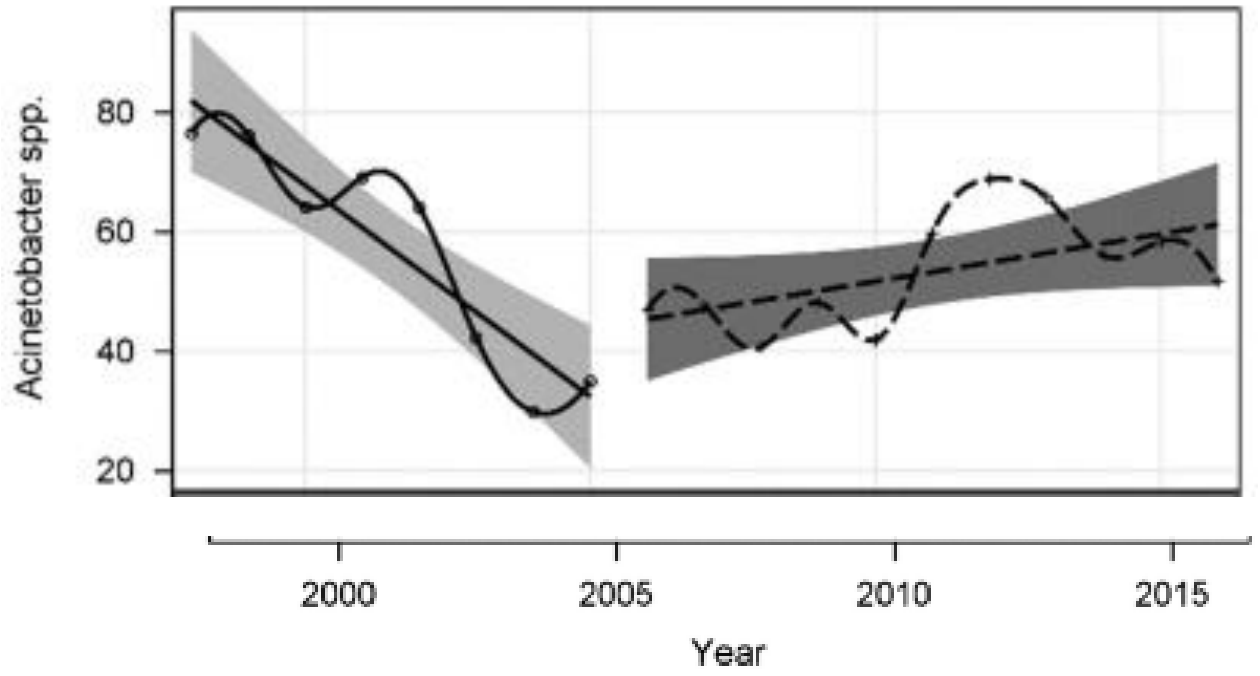
Days of Therapy at UAB per 1000 patient days



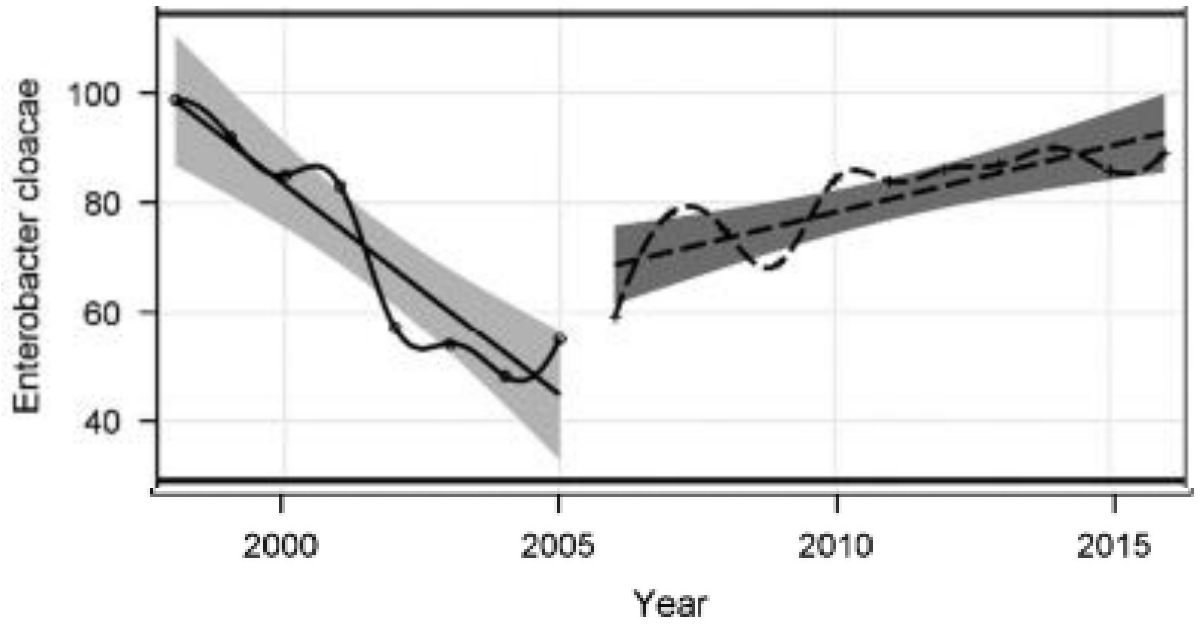
Gram Negative Fluoroquinolone Sensitivity



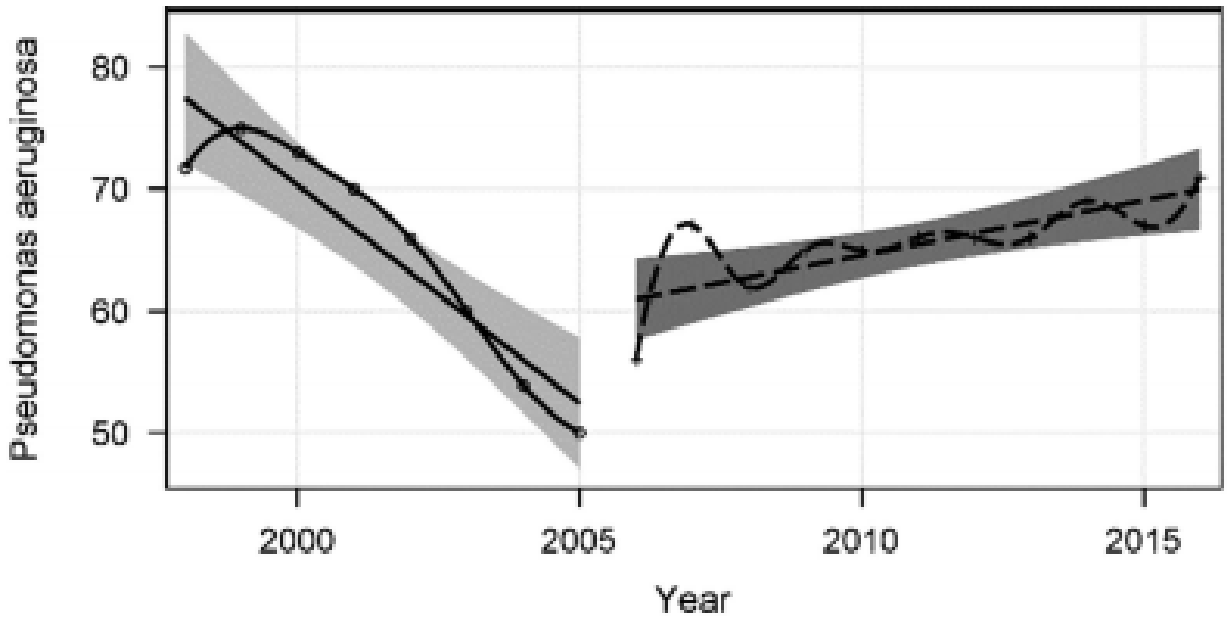
Acinetobacter species



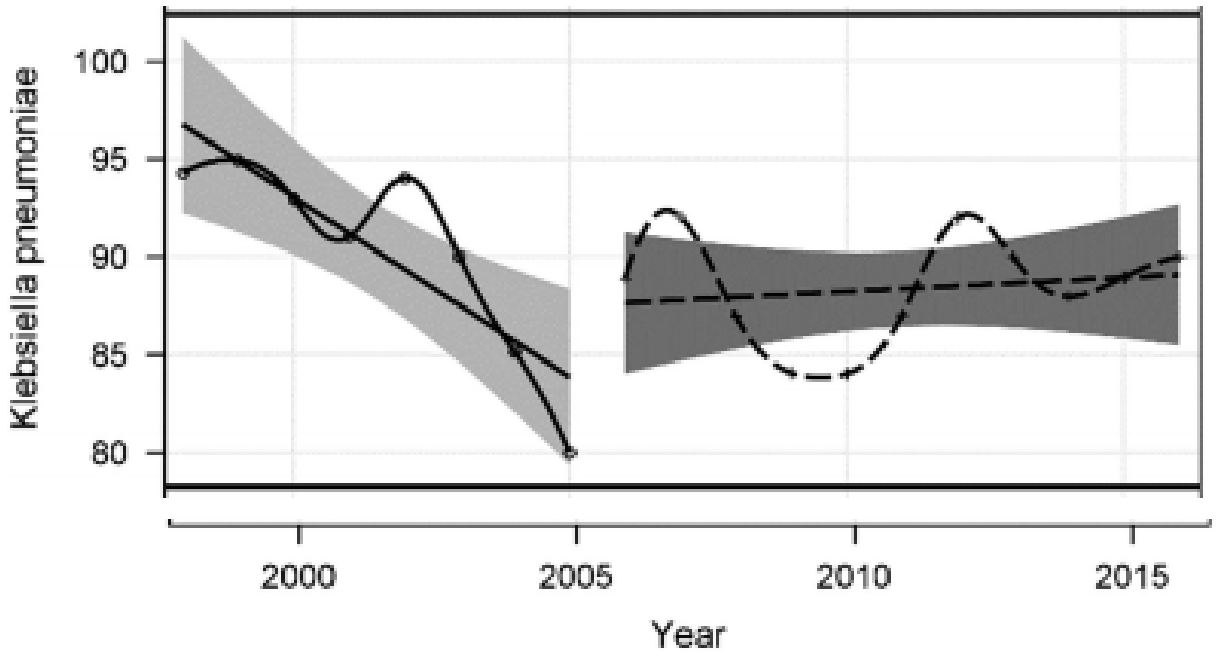
Enterobacter cloacae



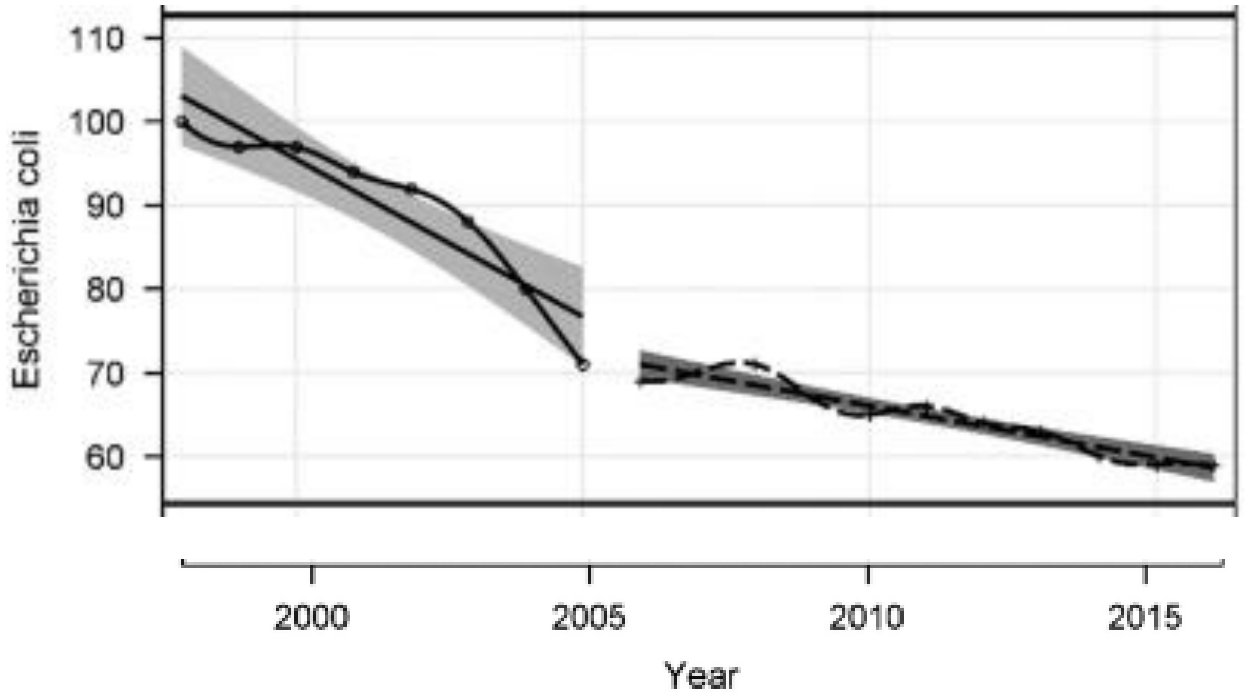
Pseudomonas aeruginosa



Klebsiella pneumoniae



E. coli



Results

- Fluoroquinolone Use
  - Peaked 173 days of therapy (DOT)/1000 patient days in 2004
  - Largest drop 2006-2007
    - 141 to 52 DOT/1000 patient days
- Fluoroquinolone Susceptibility
  - *Enterobacter cloacae* largest improvement: 42% to 89% susceptible
  - *Pseudomonas aeruginosa* improved: 54% to 71% susceptible
  - *Klebsiella pneumonia* halted downward trend: remained above 84%
  - *Acinectobacter spp*. Improved: 30% to 69% susceptible
    - 2012 began to decline again to 52% susceptible
  - *E. coli* did not improve but continued to have declining sensitivity

Organism		Preintervention								Postintervention										
		1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Acinetobacter spp	Isolates	62/81	135/177	106/165	83/120	109/170	95/225	87/291	157/449	115/245	98/205	75/184	78/162	149/355	181/302	128/186	121/184	74/132	66/113	45/87
	%	76	76	64	69	64	42	30	35	47	48	36	48	42	60	69	66	56	58	52
Enterobacter cloacae	Isolates	25/25	291/316	216/254	216/260	184/322	162/300	126/262	206/375	155/262	266/341	258/344	187/271	276/328	293/349	340/395	325/374	279/310	280/326	319/358
	%	99	92	85	83	57	54	48	55	59	78	81	69	84	84	86	87	90	86	89
Escherichia coli	Isolates	85/86	1,065/1,098	960/990	857/912	846/920	774/879	438/547	887/1,249	649/941	739/1,055	816/1,149	707/1,055	752/1,157	1,111/1,683	1,054/1,647	944/1,499	884/1,473	915/1,550	823/1,395
	%	99	97	97	94	92	88	80	71	69	70	74	67	65	66	64	63	60	59	59
Klebsiella pneumoniae	Isolates	33/35	546/575	502/540	446/490	456/485	459/510	298/350	440/550	465/523	613/666	614/706	549/653	637/758	625/718	934/1,015	755/839	673/765	797/896	693/770
	%	94	95	93	91	94	90	85	80	89	92	89	84	84	87	92	90	88	89	90
Pseudomonas aeruginosa	Isolates	66/92	666/888	495/678	406/580	362/549	399/665	276/512	379/758	444/793	655/977	592/955	580/892	590/908	527/798	774/1,172	733/1,110	619/897	712/1,062	692/975
	%	72	75	73	70	66	60	54	50	56	67	65%	65	65	66	66	66	69	72	75
Total isolates		319	3,054	2,627	2,362	2,446	2,479	1,962	3,381	2,564	3,244	3,338	3,033	3,506	3,850	4,415	4,006	3,577	3,947	3,585

Effect of Community Antibiotic Use

- Multiple studies demonstrate *E. coli* FQ resistance is correlated to community use and not hospital use
- Mixed success with other stewardship programs
  - Improvement in susceptibility often small
  - UK study with improved susceptibility was noted to include stewardship in long term care facilities as well as concurrent community decreasing FQ use [1].
- Focus on community prescribing may be needed to improve *E. coli* susceptibility

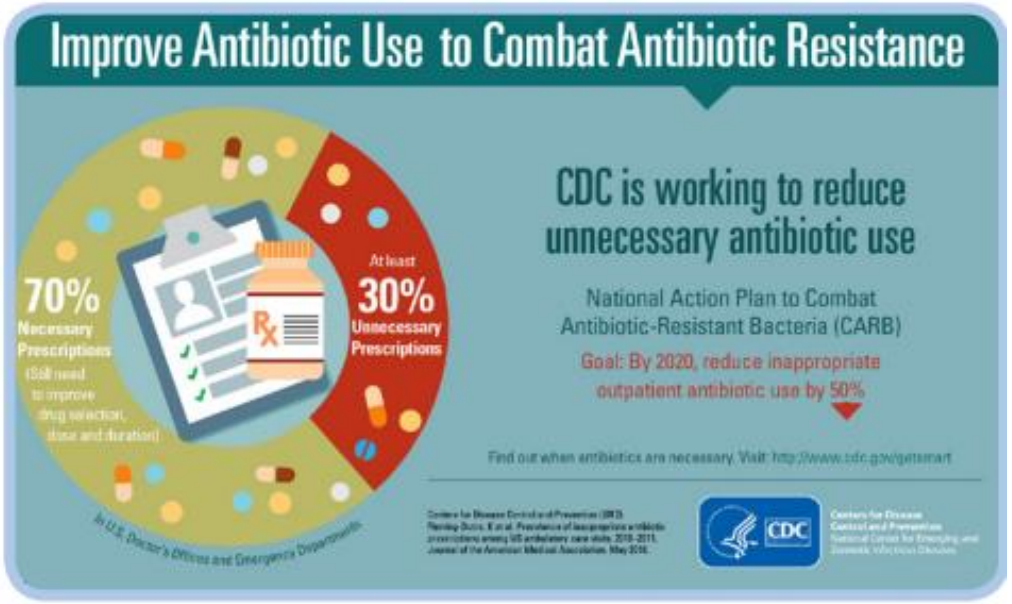
1. Sarma JB, Marshall B, Cleeve V, Tate D, Oswald T, Woolfrey S. Effects of fluoroquinolone restriction (from 2007 to 2012) on resistance in Enterobacteriaeceae: interrupted time-series analysis. *J Hosp Infect*. 2015;91:68-73.

Implications

- Limited antibiotic choice vs. approval policy
  - Levofloxacin induces resistance faster than Cipro
- Decrease in FQ use consistently obtained
- Contribution of unrelated antimicrobials
- Role of community prescribing practices
- Importance of long-term data
- Evaluation of stewardship efforts

Key Take Home Points for Stewardship

Reduce inappropriate antibiotic use



PERCENT OF ANTIBIOTIC PRESCRIPTIONS THAT WERE UNNECESSARY		
	All conditions*	Acute respiratory conditions**
0-19 year olds	29%	34%
20-64 year olds	35%	70%
≥65 year olds	18%	54%
All ages	30%	50%

*All conditions included acute respiratory conditions, urinary tract infections, miscellaneous bacterial infections, and other conditions.

**Acute respiratory conditions included ear infections, sinus infections, sore throats, pneumonia, acute bronchitis, bronchiolitis, upper respiratory infections (i.e., common colds), influenza, asthma, allergy, and viral pneumonia.

Reduce inappropriate antibiotic use

- In 2014, 266.1 million courses of antibiotics are dispensed to outpatients in U.S. community pharmacies. This equates to more than 5 prescriptions written each year for every 6 people in the United States
- At least 30% of antibiotics prescribed in the outpatient setting are unnecessary, meaning that no antibiotic was needed at all.
- Total inappropriate antibiotic use, inclusive of unnecessary use and inappropriate selection, dosing and duration, may approach 50% of all outpatient antibiotic use.
- Local outpatient prescribing practices contribute to local resistance patterns.
- Outpatient antibiotic prescribing is greatest in the winter months.
- The majority (>60%) of antibiotic expenditures are associated with the outpatient setting.
- An estimated 80-90% of the volume of human antibiotic use occurs in the outpatient setting.
- Azithromycin and amoxicillin are among the most commonly prescribed antibiotics.

Outpatient stewardship

Condition	Epidemiology	Diagnosis	Management
Acute rhinosinusitis	1/8 adults (12%) 98% of rhinosinusitis cases are viral	Acute bacterial: • Severe (>3-4 days) fever, purulent drainage • Persistent (>10 days) • Worsening (3-4 days)	• Watchful waiting • Amoxicillin/ augmentin is first line • Macrolides not recommended
Acute bronchitis	Cough is the most common symptom for seeing a primary care doctor	• Evaluation should rule out pneumonia • Colored sputum does not indicate bacterial infection	• Antibiotics not recommended • Symptomatic treatment only
Upper respiratory infection	>200 viruses can cause common cold	• Cold symptoms include fever, cough, rhinorrhea, nasal congestion	• Decongestants • NSAIDs
Pharyngitis	Group A streptococcus is the only infection requiring antibiotics Only 5-10% of adult sore throat are caused by GAS	• Clinical features cannot distinguish • Centor criteria	Amoxicillin is first line
Acute uncomplicated cystitis	Usually caused by E. coli	• Dysuria, frequency, urgency	Nitrofurantoin Bactrim fosfomycin

Questions?