Antibiotic Stewardship in Primary Care
Puerto Rico ACP 2020

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Disclosures for speaker:

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- No relevant financial disclosures:
  - Daniel C. DeSimone, MD
- *Reference to off-label/investigational use(s) of pharmaceuticals or devices:*
  - None

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Learning Objectives

Upon conclusion of this program, participants should be able to:

- Discuss the issues surrounding antimicrobial resistance and lack of new ABX development
- Describe the underlying principles of antimicrobial stewardship
- Discuss common outpatient ID syndromes and appropriateness of ABX therapy

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Background

- 2002 survey: 1.7 million healthcare acquired infections (100,000 deaths) in the US annually.
  - ~$6.5 billion in annual healthcare expenditure
- Infection with a multidrug resistant (MDR) organism =
  - Increased cost
  - Longer length of hospitalization
  - Increased risk of mortality
- Antibiotic-resistant pathogens in the US result in:
  - An annual cost of $21-34 billion dollars
  - More than 8 million hospital days annually

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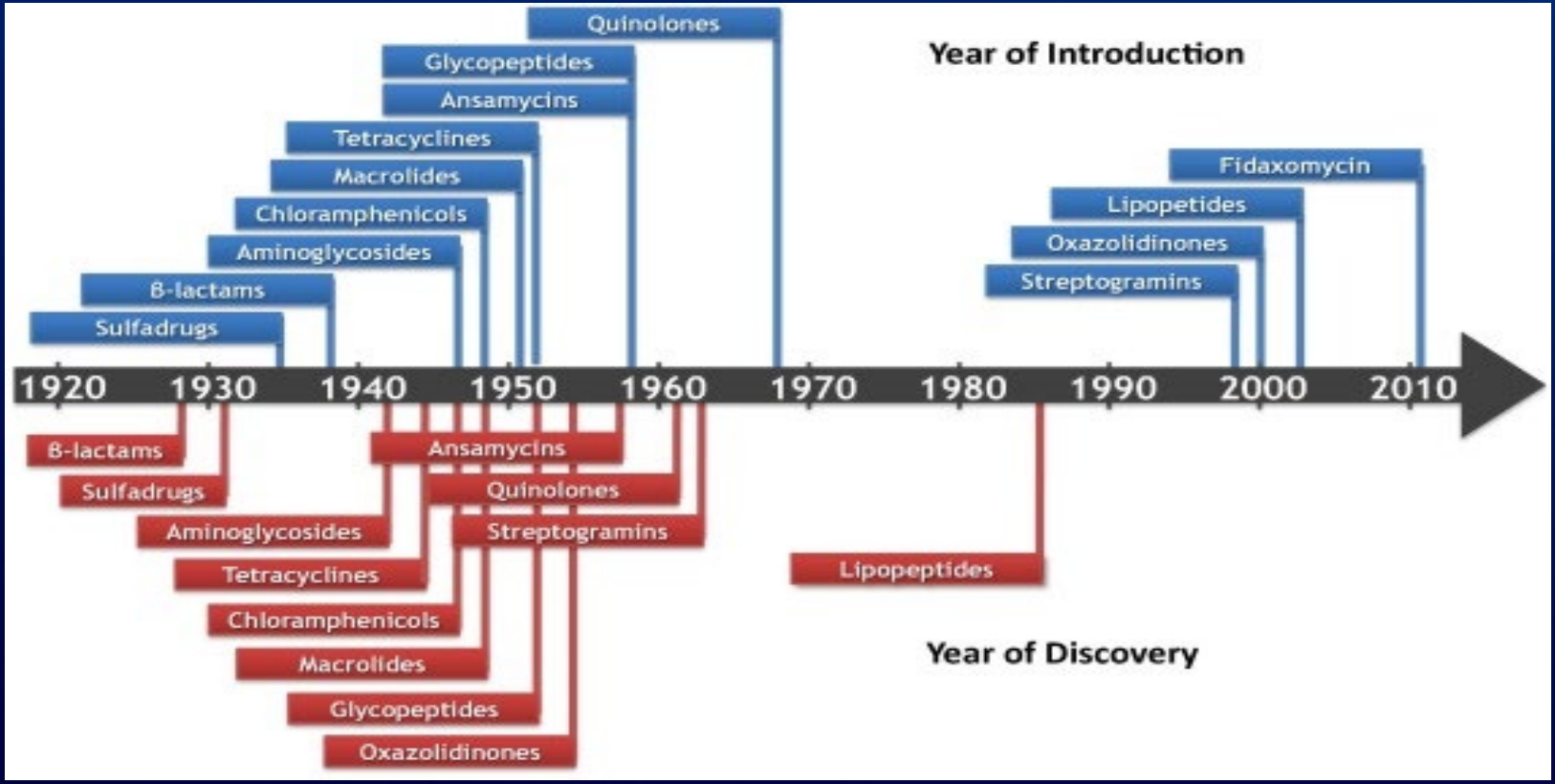
Background

- The rate of new antimicrobial development has slowed significantly as of late.
  - FDA approval rate of new antimicrobial agents **decreased** by 56% between 1983 and 2002.



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Background:

- **Sir Alexander Fleming:**
  - Discovered penicillin in 1928
    - Nobel Prize in Physiology/Medicine in 1945
  - New York Times article from 1945:
    - "…the microbes are educated to resist penicillin and a host of penicillin-fast organisms are bred out…In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin resistant organism. I hope that this evil can be averted."

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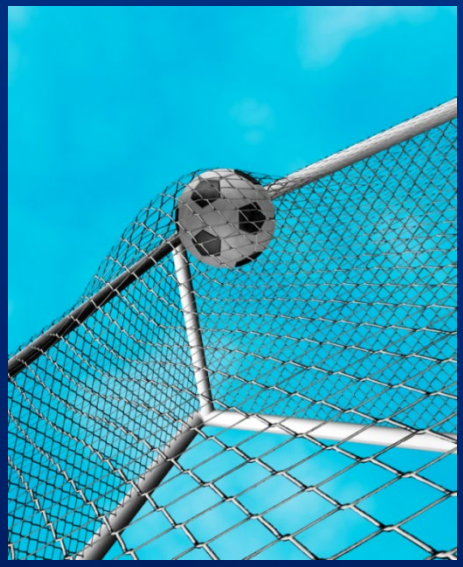
Infect Control Hosp Epidemiol 2012;33(4):322-327

Antimicrobial stewardship

- Coordinated interventions designed to promote the optimal use of antimicrobial agents including
  - Choice
  - Dosing
  - Route
  - Duration

Goals



- **Reduction in inappropriate use of antimicrobials and optimization of appropriate use (i.e. drug, dose, route, frequency, and duration)**
- Primary goals:
  - Optimize clinical outcomes
    - Improved patient outcomes
    - Shorter length of stay (LOS)
  - Minimizing unintended consequences
    - i.e. toxicity, emergence of resistance, and selection of resistant organisms.
- Secondary
  - Cost-savings
    - Pharmacy (Literature reports 22-36% reduction in antimicrobial use)
    - Other (i.e. length of stay)

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The Team:

- Recommended Team:
  - ID Pharmacist
  - ID Physician
  - Microbiology
  - Infection Control
  - Information Systems Specialist
  - Administration
  - Departmental Stakeholders

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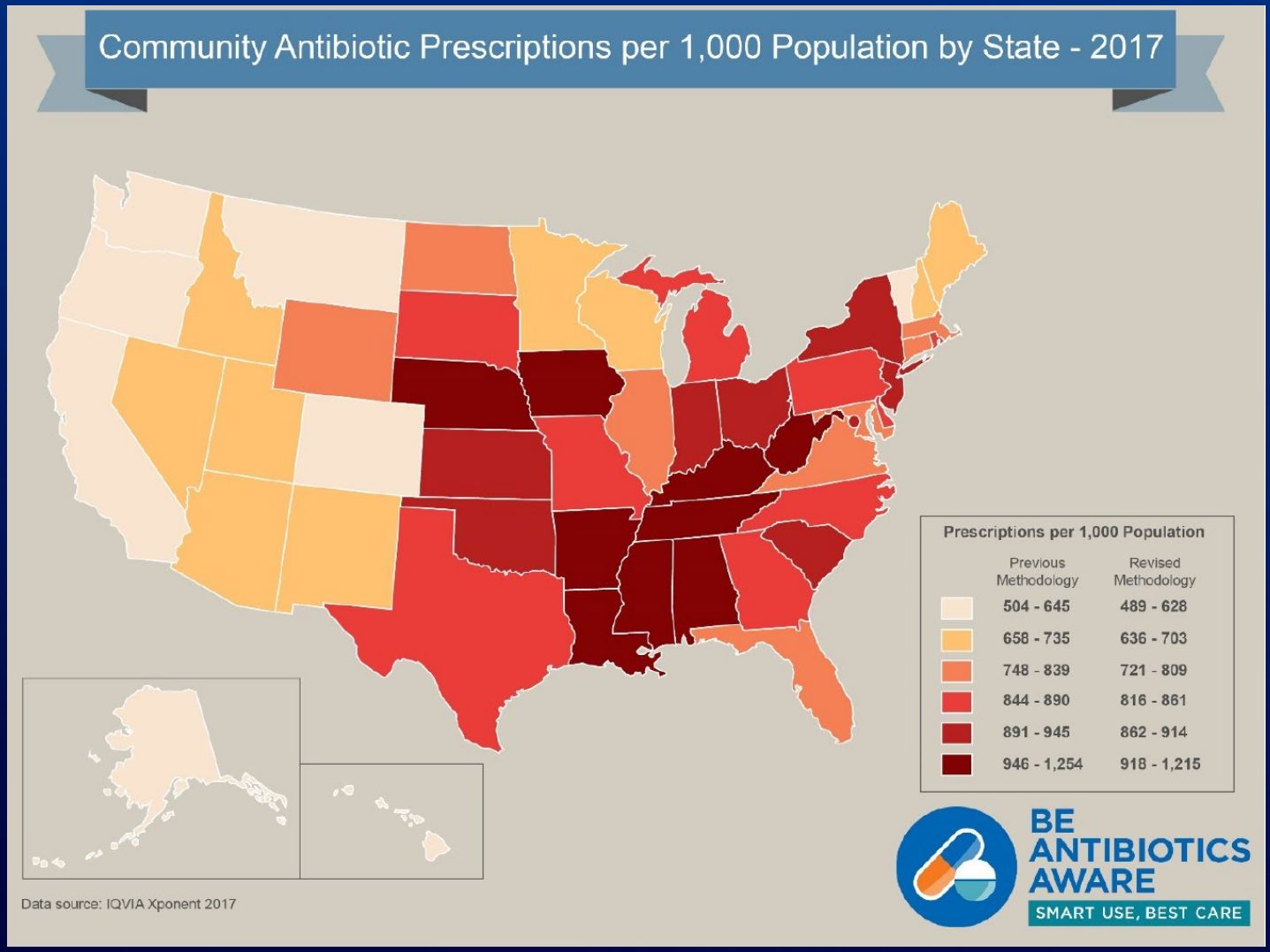
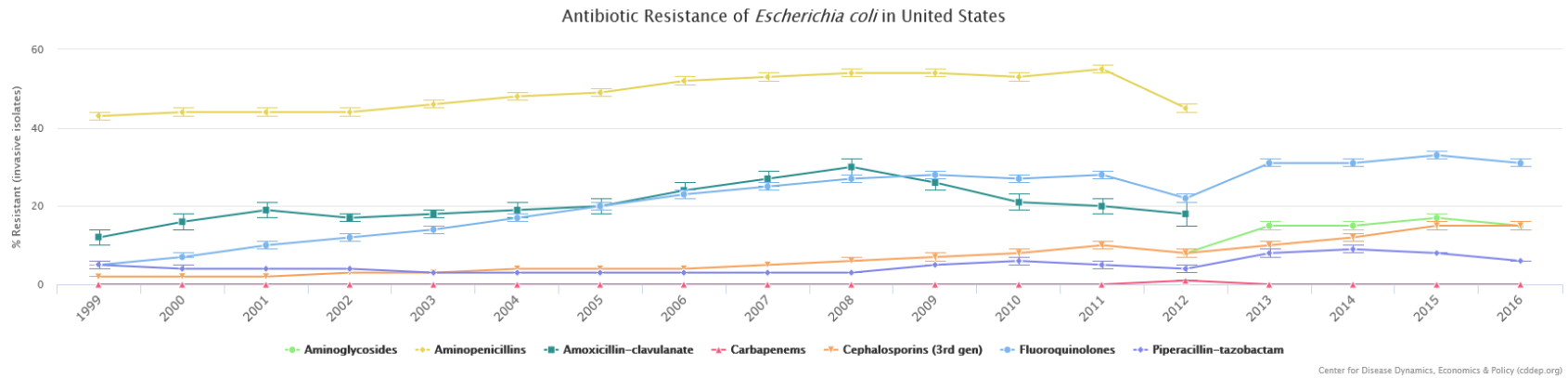
Outpatient Antimicrobial Stewardship:



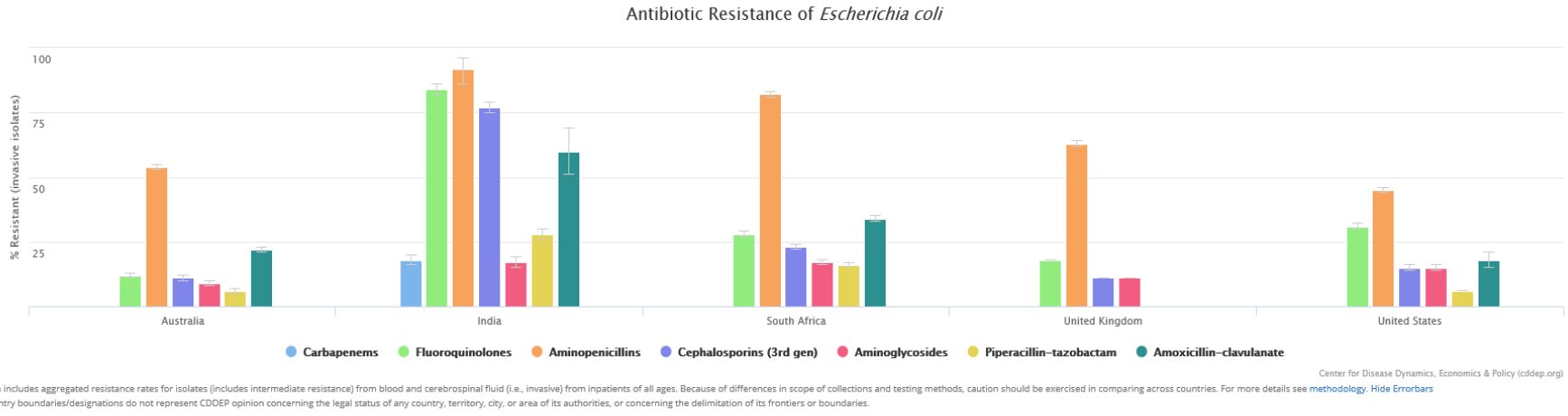
CDC Annual Outpatient Antibiotic Prescription Report. 2017.

Antimicrobial Resistance: *E. coli*

Antibiotic Resistance



Antibiotic Resistance



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The Center for Disease Dynamics, Economics & Policy. ResistanceMap: Antibiotic Resistance in Eschericia coli. 2019. https://resistancemap.cddep.org/AntibioticResistance.php. Date accessed: *12/17/2019*

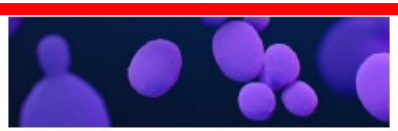
Concerning Threats

ERYTHROMYCIN-RESISTANT
GROUP A *STREPTOCOCCUS*

CLINDAMYCIN-RESISTANT
GROUP B *STREPTOCOCCUS*

Urgent Threats

CARBAPENEM-RESISTANT
ACINETOBACTER



CANDIDA AURIS

CLOSTRIDIOIDES DIFFICILE

CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE

DRUG-RESISTANT
NEISSERIA GONORRHOEAE

Serious Threats

DRUG-RESISTANT
CAMPYLOBACTER

DRUG-RESISTANT
CANDIDA

ESBL-PRODUCING
ENTEROBACTERIACEAE

VANCOMYCIN-RESISTANT
ENTEROCOCCI

MULTIDRUG-RESISTANT
PSEUDOMONAS AERUGINOSA

DRUG-RESISTANT
NONTYPHOIDAL *SALMONELLA*

DRUG-RESISTANT
***SALMONELLA* SEROTYPE TYPHI**

DRUG-RESISTANT
SHIGELLA

METHICILLIN-RESISTANT
STAPHYLOCOCCUS AUREUS

DRUG-RESISTANT
STREPTOCOCCUS PNEUMONIAE

DRUG-RESISTANT
TUBERCULOSIS

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CDC. Antibiotic Resistance Threats in the US, 2019: U.S. Department of Health and Human Services, CDC; 2019

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No ESKAPE!

- ESKAPE Pathogens
  - **E**nterococcus faecium, **S**taphylococcus aureus, **K**lebsiella pneumoniae, **A**cinetobacter baumanii, **P**suedomonas aeruginosa, and **E**nterobacter species

- Increasing resistance
  - Pan-ABX resistance has been identified (P. aeruginosa / A. Baumanii)
    - New resistance mechanisms: Metalo-beta-lactamase 1 (NDM-1)
  - Decreasing antibiotic development
    - CDC, FDA, IDSA, NIH, and Congress all working together to encourage development of new drugs

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Resistance: A few basic truths

- Change in antimicrobial use = change in resistance patterns
- Resistance is more common in healthcare/hospital acquired infections vs. community acquired
- Patients with resistant, healthcare associated infections are more likely to have received previous antimicrobial therapy than control patients
- Even within an institution, higher antimicrobial use = higher rates of resistance in hospital-acquired infections
- The longer a patient is exposed to an antimicrobial the more likely they will become colonized with an organism resistant to that antimicrobial

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Antimicrobial Stewardship:

- **Primary Interventions:**
  - Prospective audit with intervention and feedback
  - Formulary restriction
- **Secondary Interventions:**
  - IV to PO switch
  - De-escalation
  - Guidelines/clinical pathways
  - Ordersets/Order forms
  - Education

- **5 D's of Antimicrobial Stewardship:**
  - Diagnosis
  - Drug regimen (empiric)
  - Dosing
  - De-escalation (targeted)
  - Duration of therapy

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CID 2007;44(2):159-177
Exp Opin Pharmacother 2008;9:561-75

Core Elements of Outpatient Antimicrobial Stewardship:

CDC Core Elements:

The Joint Commission Standard Elements:

1. Identifying an antimicrobial stewardship **leader**
2. Establishing an annual antimicrobial stewardship **goal**
3. Implementing **evidence-based practice guidelines** related to the antimicrobial stewardship goal
4. Providing clinical staff with **educational resources** related to the antimicrobial stewardship goal
5. Collecting, analyzing, and reporting **data** related to the antimicrobial stewardship goal

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MMWR 2016;65(RR-6):1-12.
R^{3}Report 2019;23:1-3

Outpatient Antimicrobial Stewardship:

- Scoping the problem:
  - Estimated 80-90% of human antibiotics = outpatient
  - In 2017:
    - 258.2 million antibiotic prescriptions written
      - 30% unnecessary: 77.46 million prescriptions
      - 50% inappropriate/unnecessary: 129.1 million prescriptions

Age:
<20 y/o: 23.4%
≥20 y/o: 76.4%

Sex:
Male: 39.1%
Female: 60.9%

Top Classes:
1) Penicillins (23.7%)
2) Macrolides (17.3%)
3) Cephalosporins (14%)
4) Fluoroquinolones (10.3%)
5) Beta-lactam, increased activity (9.5%)

Region:
West: 17.3%
Northeast: 18.2%
Midwest: 22%
South: 42.5%

Amoxicillin, azithromycin, Augmentin, cephalexin, and Bactrim accounted for ~64% of all Rx.

CDC Annual Outpatient Antibiotic Prescription Report. 2017

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AR Solutions *In Action*

CDC's Investments to Combat Antibiotic Resistance Threats

FISCAL YEAR **2019**

PUERTO RICO

$2,955,541

Funding for AR Activities
Fiscal Year 2019

FUNDING TO STATE HEALTH DEPARTMENTS

$212,270

RAPID DETECTION & RESPONSE: State, territory, and local public health partners fight antibiotic resistance in healthcare, the community, and food. Programs use the AR Lab Network to rapidly detect threats and implement prevention, response, and antibiotic stewardship to stop the spread of resistant germs.

With 2018 funds, Puerto Rico implemented antibiotic stewardship programs at more than 65% of hospitals. Using community AR surveillance data, Puerto Rico identified populations at increased risk for infection due to incorrect use of antibiotics and piloted an educational program to prevent inappropriate antibiotic use in outpatient settings. As of July 2019, Puerto Rico has engaged 60% of the ambulatory care centers selected to participate in the pilot program.

$2,711,578

NATURAL DISASTERS can increase the risk for injuries and infections.

With 2019 funds, the Puerto Rico Department of Health hired nurses to support healthcare-associated infection activities in hurricane-damaged hospitals, safety officers to conduct facility infrastructure assessments, and regional nurses to support facilities. CDC provided training and assessment materials to newly hired nurses. Twenty-two facility assessments were completed, eleven training plans were developed, and twenty staff were trained for Certification of Infection Control.

$31,693

FOOD SAFETY projects protect communities by rapidly identifying drug-resistant foodborne bacteria to stop and solve outbreaks and improve prevention.

Puerto Rico uses whole genome sequencing to track and monitor local outbreaks of *Listeria*, *Salmonella*, *Campylobacter*, and *E. coli* and uploads sequence data into PulseNet for nationwide monitoring of outbreaks and trends. In Fiscal Year 2020, Puerto Rico will continue monitoring these isolates for resistance genes. When outbreaks are detected, local CDC-supported epidemiologists investigate the cases to stop spread.

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RESPIRATORY TRACT INFECTIONS

Acute Bronchitis

- Rhinovirus, enterovirus, influenza A/B, parainfluenza, coronavirus, metapneumovirus, RSV
- Bacteria (1-10%). Atypical bacteria, such as *M. pneumoniae*, *C. pneumoniae*, *B. pertussis* are rare

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Strategies to reduce antibiotic use

- Use delayed prescription strategies
- Describe the infection as a viral illness or chest cold
- Discuss the expected course of illness and cough duration (2-3 weeks)
- Explain that antibiotics do not significantly shorten illness duration and are associated with adverse effects and resistance
- Non-antibiotic medications: dextromethorphan, guaifenesin, beta$_2$ agonists only if wheezing

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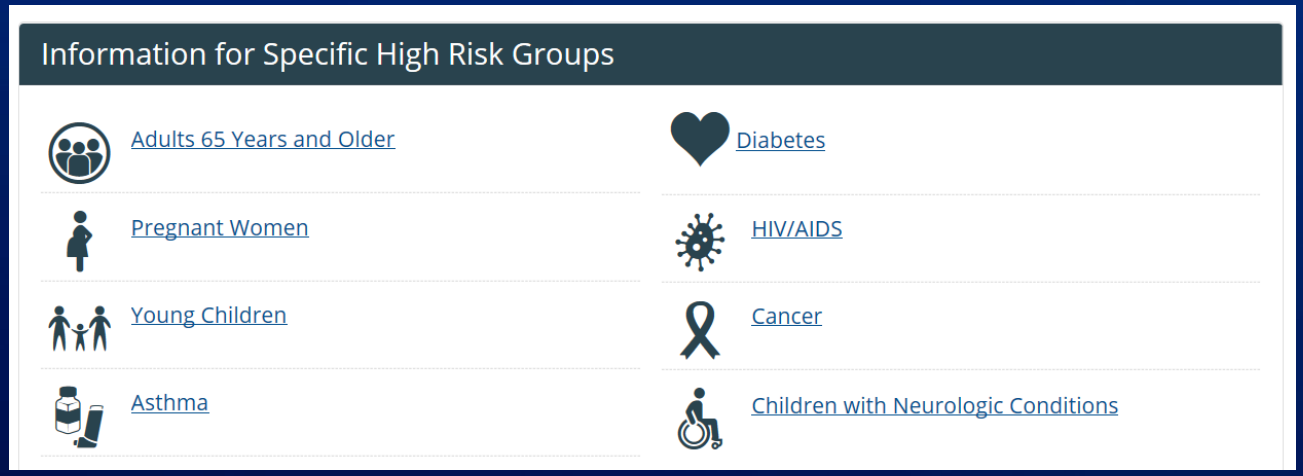
Indications for Antimicrobial Use

- Influenza: Oseltamivir



- Pertussis: Macrolides

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COPD Exacerbation

- Outpatients with a moderate or severe exacerbation
- Having at least 2 of the following 3 symptoms:
  - Increased dyspnea
  - Increased sputum volume
  - Increased sputum purulence
- Antibiotic coverage: *S. pneumoniae, H. influenzae, M. catarrhalis*
  - Azithromycin, doxycycline, TMP/SMX, cefdinir

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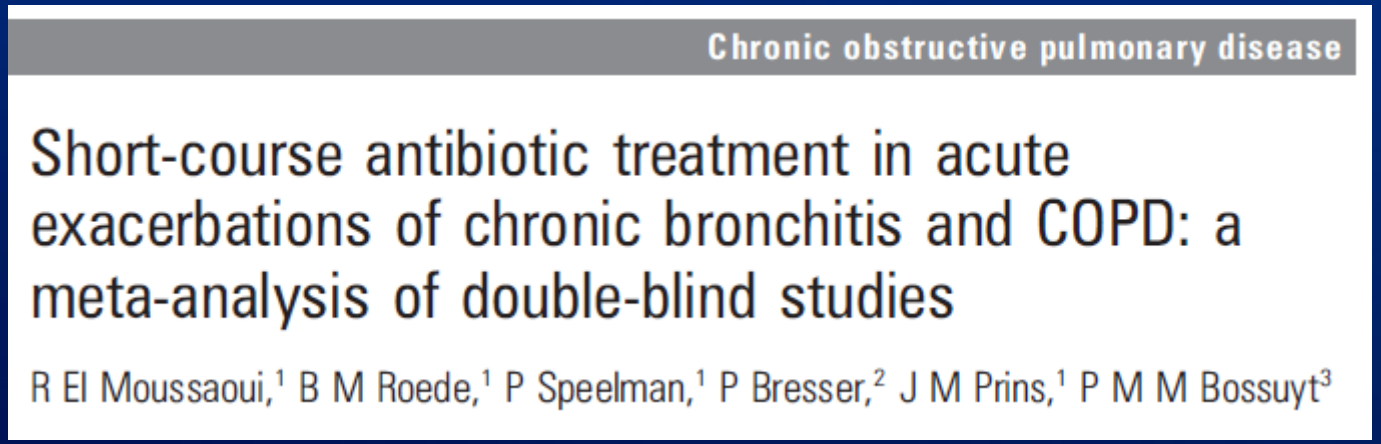
COPD Exacerbation



Chronic obstructive pulmonary disease

Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies

R El Moussaoui,[1] B M Roede,[1] P Speelman,[1] P Bresser,[2] J M Prins,[1] P M M Bossuyt[3]

For mild to moderate COPD exacerbations, **no difference between short course** (≤5 days) **and long course** (≥7) days of antibiotic therapy

Thorax. 2008 May;63(5):415-22

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Pneumonia

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

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Updates

Recommendation	2007 ATS/IDSA Guideline	2019 ATS/IDSA Guideline
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients based on resistance
Empiric therapy for severe CAP	Beta-lactam/macrolide and beta-lactam/fluoroquinolone given equal weighting	Stronger evidence in favor of beta-lactam/macrolide combination
Use of HCAP Category	Accepted as per 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines	Abandon the category and focus on local epidemiology and validated risk factors to determine need for MRSA or *P. aeruginosa*

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Antibiotics Recommended for Empiric Treatment

Adults with comorbidities (chronic heart, lung, liver, renal disease, diabetes mellitus, alcoholism, malignancy, or asplenia):

- Combination therapy with amoxicillin/clavulanate or a cephalosporin PLUS macrolide or doxycycyline

OR

- Monotherapy with a respiratory fluoroquinolone (levofloxacin, moxifloxacin, or gemifloxacin)

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What Is the Appropriate Duration of Antibiotic Treatment?

- Until the patient achieves stability and for no less than 5 days
- Duration of therapy due to suspected or proven MRSA or *Pseudomonas aeruginosa* should be 7 days

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URINARY TRACT INFECTIONS

Asymptomatic Bacteriuria

- Pregnant women
  - Treatment reduces the risk of pyelonephritis and may reduce the risk of low birth weight and preterm labor
- Patients undergoing endoscopic urologic procedures associated with mucosal trauma
  - Substantial risk of postoperative sepsis

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Asymptomatic Bacteriuria

- Screening and treatment **not** recommended for:
  - Infants and children
  - Healthy nonpregnant women of any age
  - Elderly persons living independently or in a long-term care facility
  - Diabetes
  - Renal transplant recipients >1 month after surgery
  - Patients with spinal cord injury
  - Patients with indwelling urinary catheters

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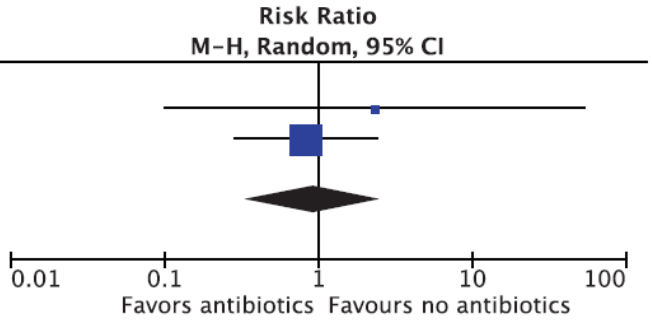
Asymptomatic Bacteriuria

- Risk of prosthetic joint infection in treated vs untreated asymptomatic bacteriuria

Study or Subgroup	Antibiotics Events	Total	No antibiotics Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cordero-Ampuero 2013	0	1	0	1		Not estimable
Drekonja 2013	1	26	0	20	10.3%	2.33 [0.10, 54.42]
Sousa 2014	6	154	7	149	89.7%	0.83 [0.29, 2.41]
Total (95% CI)		**181**		**170**	**100.0%**	**0.92 [0.34, 2.53]**
Total events	7		7			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.37$, df = 1 (P = 0.54); $I^2 = 0\%$

Test for overall effect: Z = 0.16 (P = 0.88)



CID 2019; 68(10):e83-75

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Duration of Treatment

MALE	FEMALE
• Nitrofurantoin 100 mg bid for 7 days	• Nitrofurantoin 100 mg bid for 5 days
• TMP-SMX 160/800 mg bid for 7 days	• TMP-SMX 160/800 mg bid for 3 days
• Cefdinir 300 mg bid for 7 days	• Cefdinir 300 mg bid for 5 days
• Limited data for fosfomycin use in men	• Fosfomycin 3 g once

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Recurrent UTIs

- ≥2 infections in 6 months or ≥3 infections in a year
- Typically acute simple cystitis rather than complicated UTI
- Vast majority of recurrences of simple cystitis appear to be reinfections

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Preventive Measures

- ↑ fluid intake (2-3 L/day)
- Avoid use of spermicides
- Early postcoital voiding
- Wiping from front to back
- Vaginal estrogen for postmenopausal women
- Cranberry products
- Probiotics
- Methenamine salts (Hiprex)
- D-mannose

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Stewardship: Shorter = Better

Diagnosis	Short (d)	Long (d)	Result	#RCTs
CAP	3 or 5	7-14	Equal	9
VAP	8	15	Equal	2
Pyelo	7 or 5	14 or 10	Equal	7
Intra-abd	4	10	Equal	2
GNB Bacteremia	7	14	Equal	1*
AECB	≤5	≥7	Equal	>20
Cellulitis	5-6	10	Equal	4*
Chronic Osteomyelitis	42	84	Equal	2
Septic Arthritis	14	28	Equal	1
Ortho Implant w/removal	28	42	Equal	1
Neutropenic Fever	AFx72 h	+ANC>500	Equal	1
P. vivax Malaria	7	14	Equal	1

*GNB bacteremia also in UTI/cIAI RCTs; 3 cellulitis RCTs equal, 1 (low dose oral flucox) ↑relapses; refs at https://www.bradspellberg.com/shorter-is-better

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Outpatient Antimicrobial Stewardship

- Antimicrobial resistance is a growing concern.
- Antibiotics in the outpatient care setting make up a bulk of human antibiotic use.
- Opportunity exists for optimization of outpatient antibiotic prescribing.
- The most common indications for outpatient antibiotic prescribing are:
  1. Respiratory tract infections
  2. Skin and soft tissue infections
  3. Genitourinary tract infections

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Thank You

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