Treatment of Gonorrhea: Current State and Future Considerations

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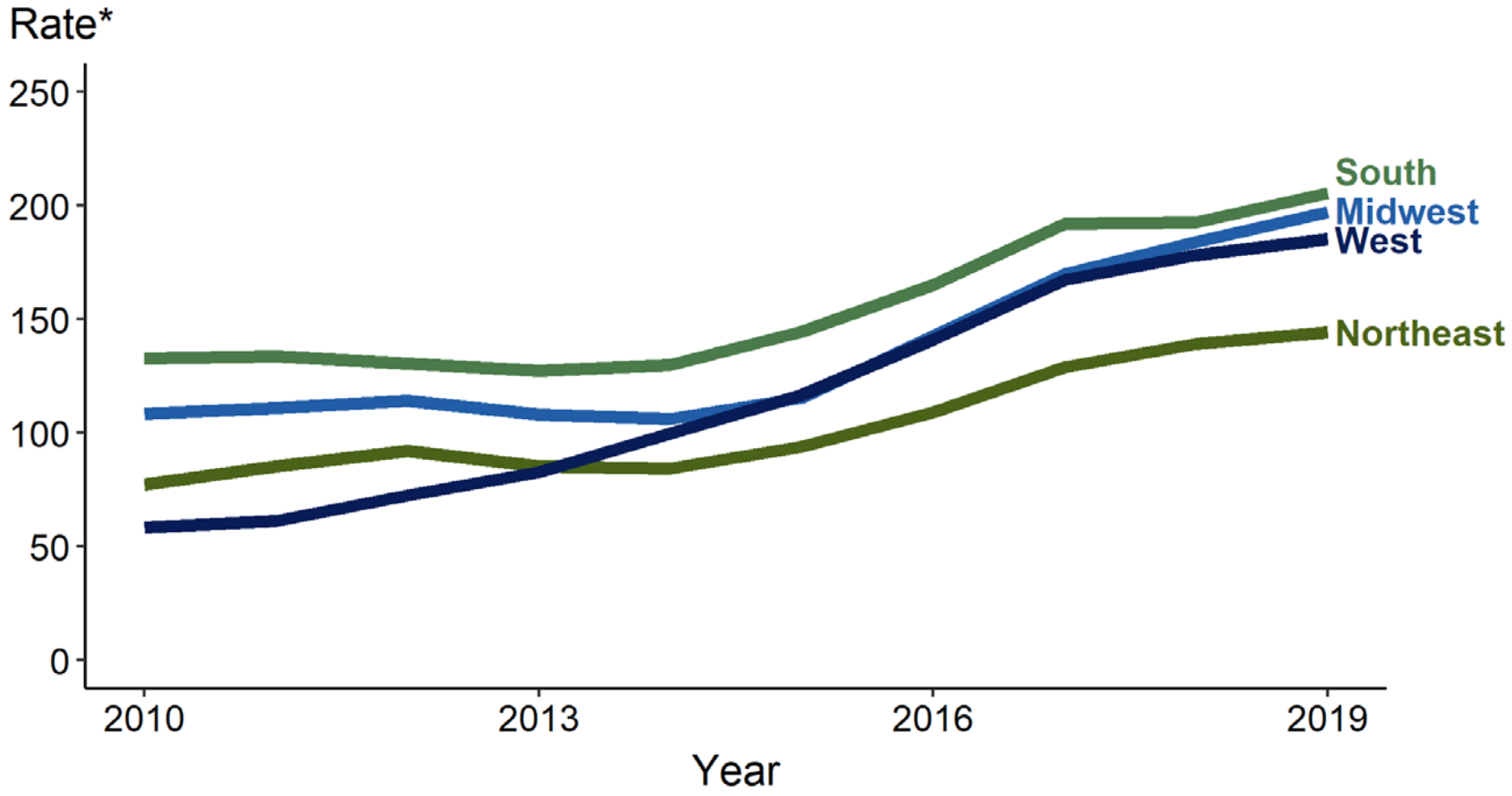
Development Considerations of Antimicrobial Drugs for the Treatment of Gonorrhea
FDA/NIAID/CDC Workshop Virtual Meeting
April 23, 2021

Outline

- Gonorrhea surveillance in the U.S.
  - Case trends
  - Monitoring susceptibility
- Antimicrobial stewardship
- Collateral impact and co-occurring pathogens
- Pharmacokinetic and pharmacodynamic considerations
- Updated gonorrhea treatment guidelines

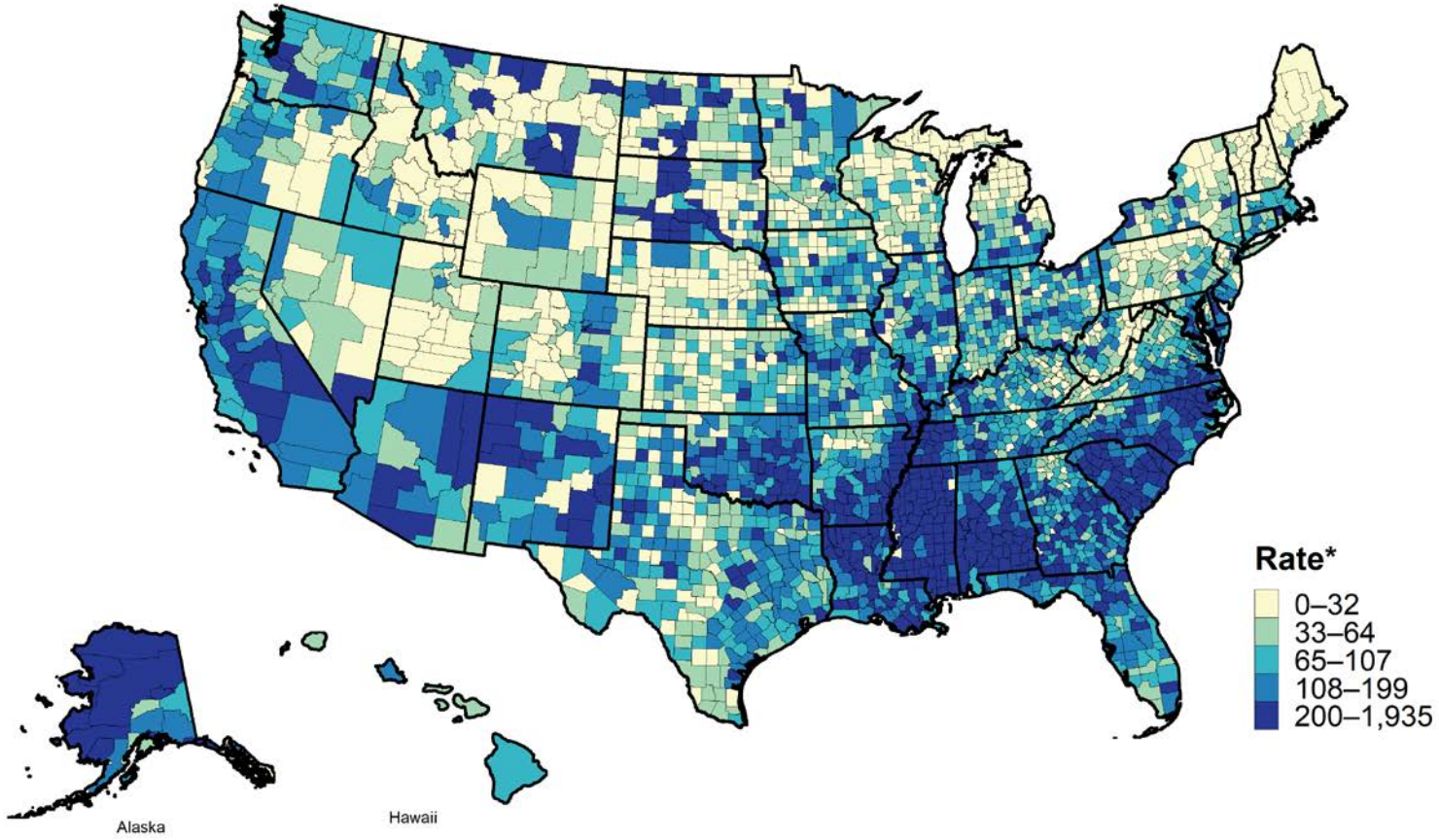
Gonorrhea — Rates of Reported Cases by Region, United States, 2010–2019

* Per 100,000



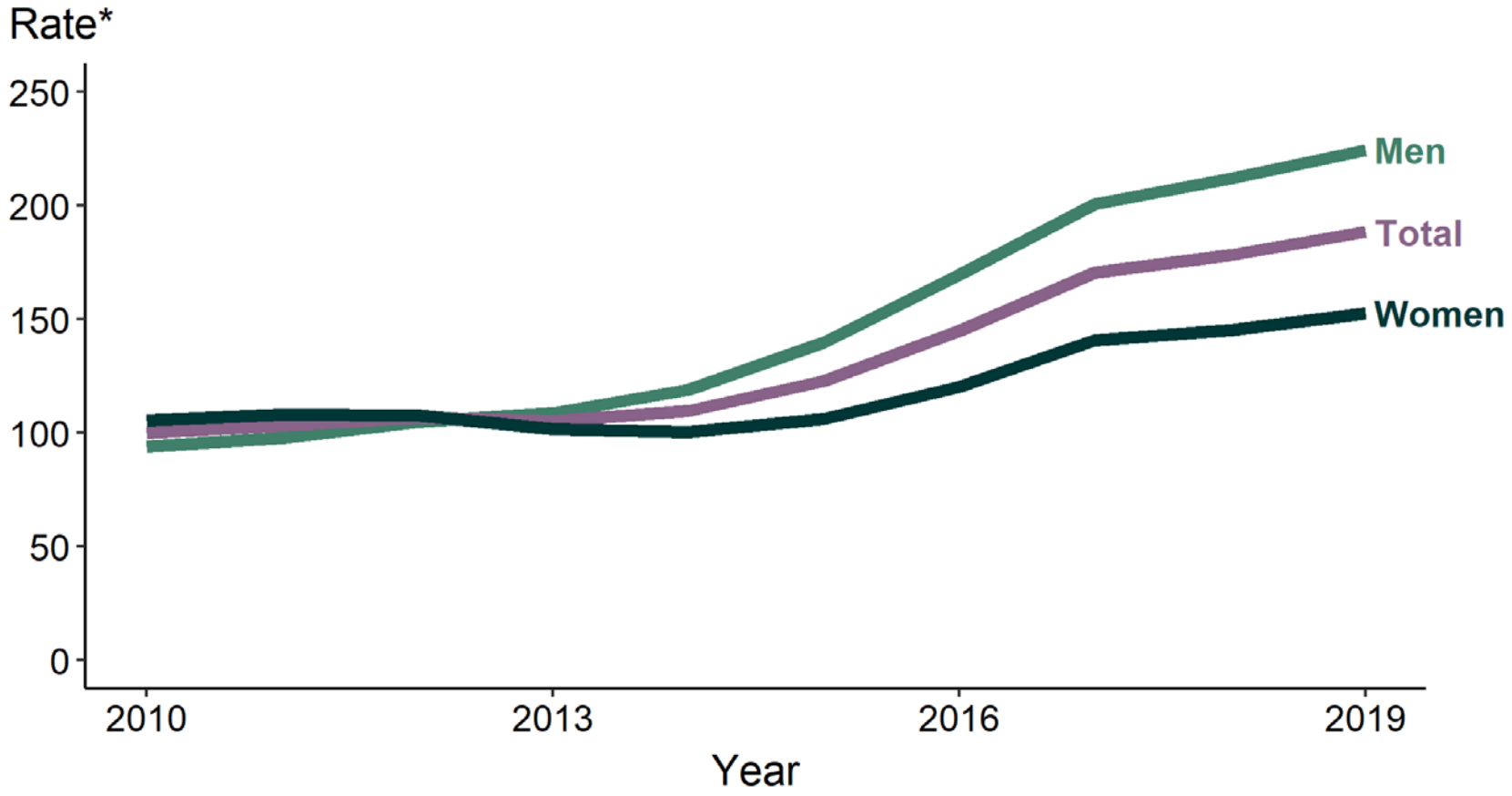
Gonorrhea — Rates of Reported Cases by County, United States, 2019

* Per 100,000



Gonorrhea — Rates of Reported Cases by Sex, United States, 2010–2019

* Per 100,000



Places Working to Combat Drug-Resistant Gonorrhea

AR Lab Network*
- Maryland
- Tennessee
- Utah
- Washington

SURRG†
- Denver
- Guilford County (NC)
- Honolulu
- Indianapolis
- Milwaukee
- New York City
- San Francisco
- Seattle

SSuN¥ Sites
- Baltimore
- California
- Columbus
- Florida
- Indiana
- Multnomah County (OR)
- New York City
- Philadelphia
- San Francisco
- Utah
- Washington

GISP€ Sentinel Sites
- Albuquerque
- Anchorage
- Baltimore
- Birmingham
- Buffalo
- Camden/Paterson
- Chicago
- Columbus
- Dallas
- Denver
- Greensboro
- Honolulu
- Indianapolis
- Jackson
- Kansas City
- Las Vegas
- Los Angeles
- Miami
- Milwaukee
- Minneapolis
- New Orleans
- New York City
- Orange County (CA)
- Philadelphia
- Phoenix
- Pontiac
- Portland
- San Diego
- San Francisco
- Seattle
- Tripler Army Medical Center (HI)
- Washington, DC

eGISP‡
- Chicago
- Columbus
- Las Vegas
- New Orleans
- Orange County (CA)
- Philadelphia
- Phoenix
- Pontiac
- San Diego

*AR Lab Network= AR Lab Network for Gonorrhea
†SURRG=Strengthening the U.S. Response to Resistant Gonorrhea
¥SSuN=STD Surveillance Network
€GISP=Gonococcal Isolate Surveillance Project
‡eGISP=Enhanced Gonococcal Isolate Surveillance Project

Revised October 30, 2019

GISP

1986

Core national sentinel **surveillance** system of ARGC

~ 25-30 clinical sites

Male only

Urethral isolates only

SURRG

2016

Rapid detection and response of ARGC

9 jurisdictions

Male and Female

Genital and extragenital isolates

ARLN

2016

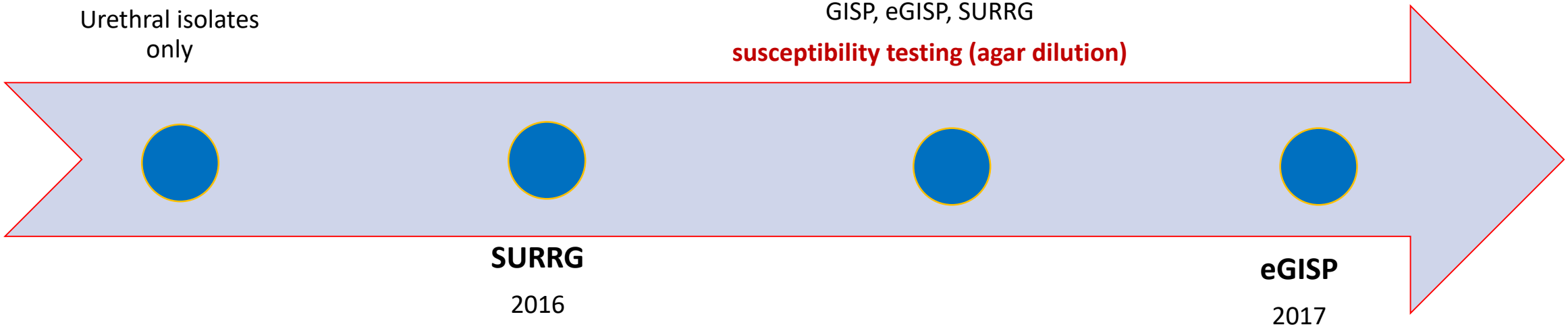
Nationwide laboratory infrastructure for antibiotic resistant organisms

7 regional laboratories (4 GC labs)

All isolates

GISP, eGISP, SURRG

susceptibility testing (agar dilution)



eGISP

2017

Surveillance system of expanded populations, infection sites and *Neisseria* species

12 clinical sites

Male and Female

Genital and extragenital isolates

Increased capacity of AST and WGS

Count of AST performed annually,

Prior 2016 ~5700

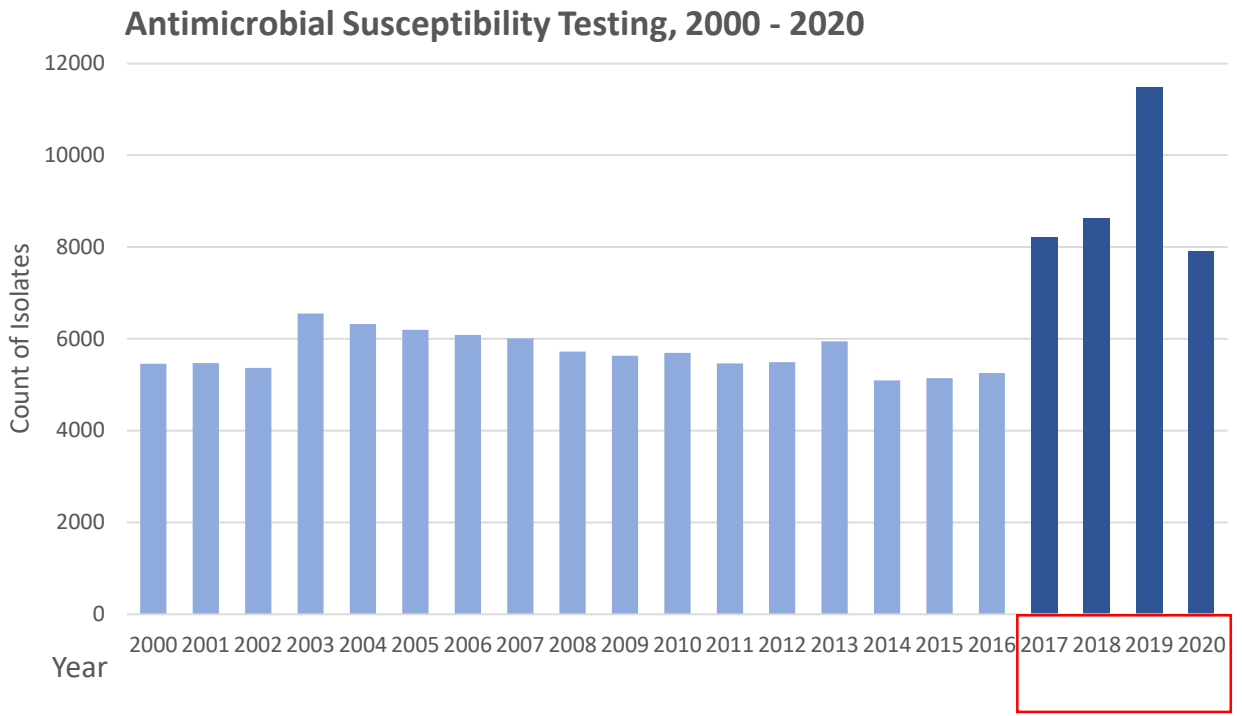
Post 2017 8500 – 12000

Count of WGS completed annually,

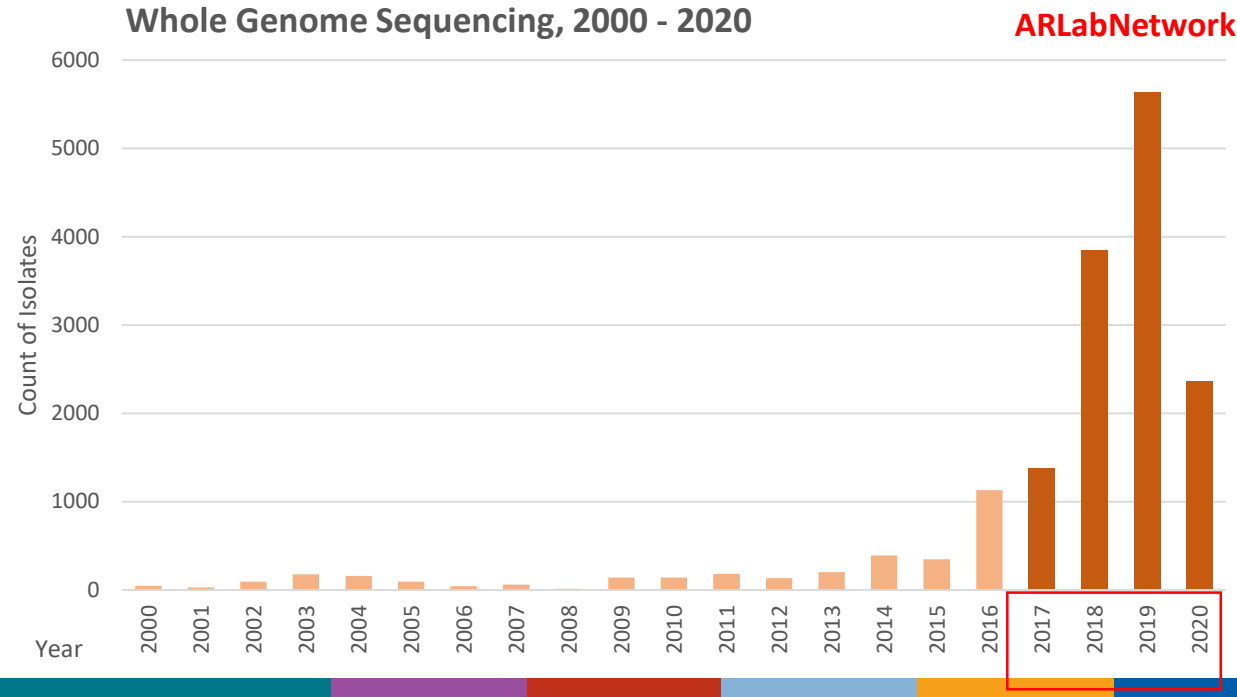
Prior 2016 10 – 200

Post 2017 3500 – 5500

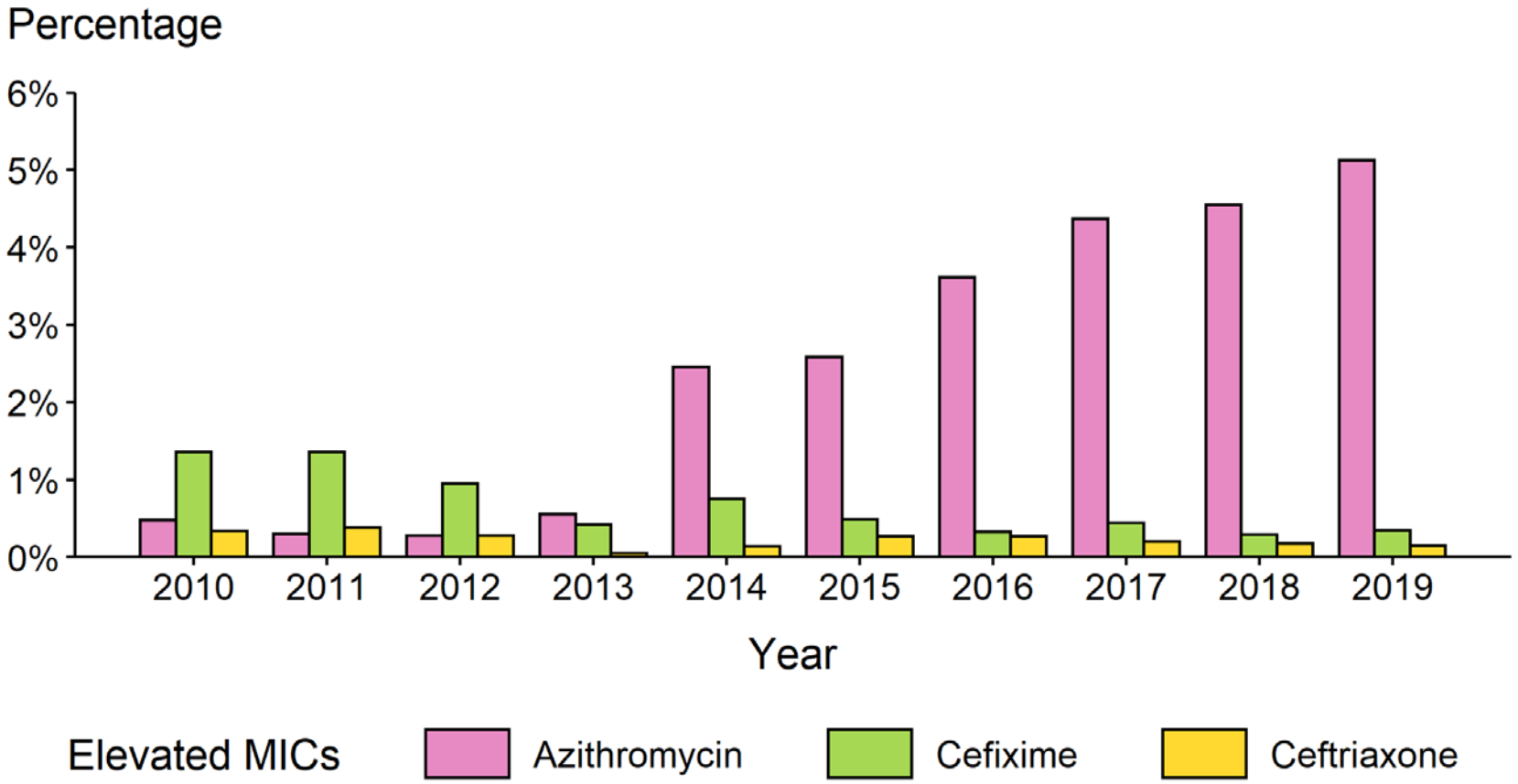
By 2020, over 9200 NG sequences submitted to public archive, NCBI SRA.



ARLabNetwork

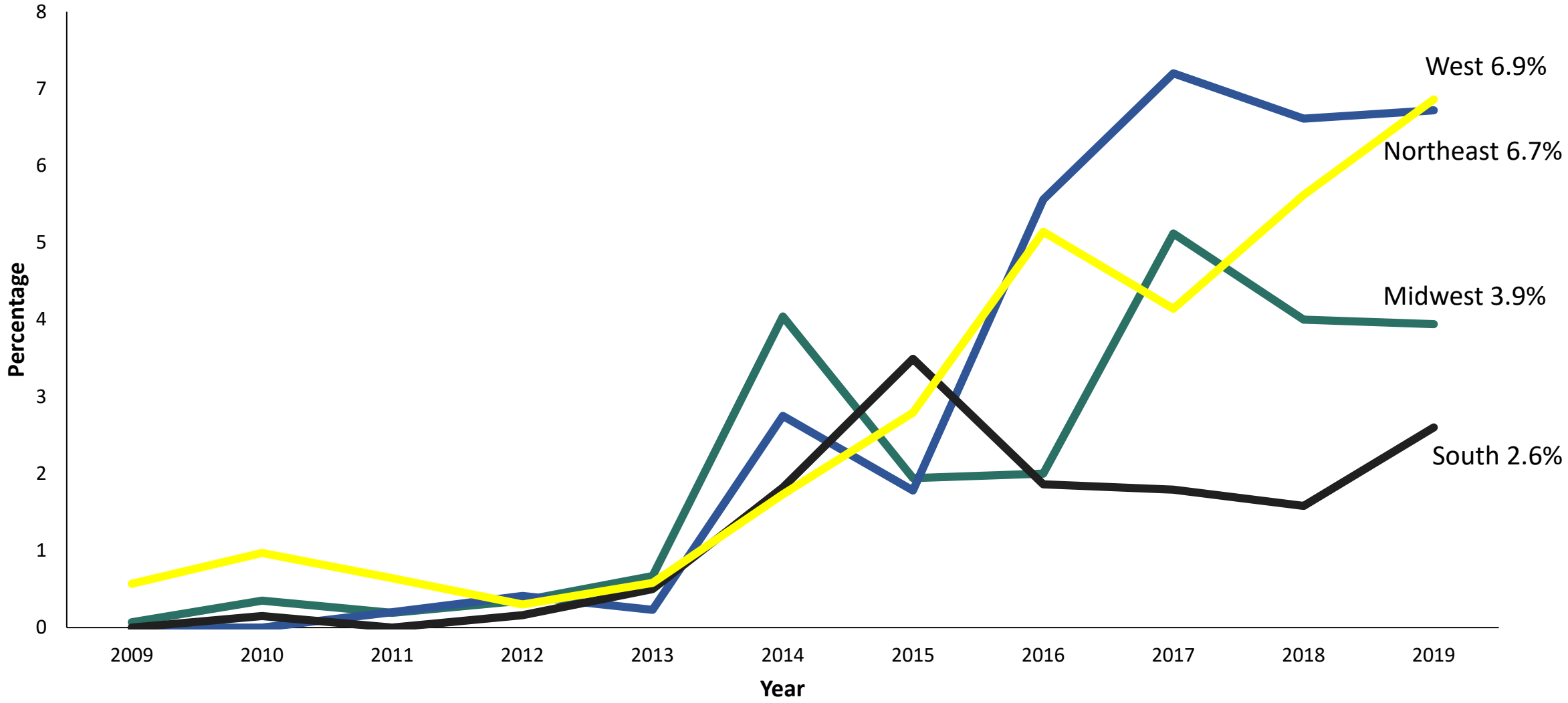


Neisseria gonorrhoeae — Percentage of Isolates with Elevated Minimum Inhibitory Concentrations (MICs) to Azithromycin, Cefixime, and Ceftriaxone, Gonococcal Isolate Surveillance Project (GISP), 2010–2019

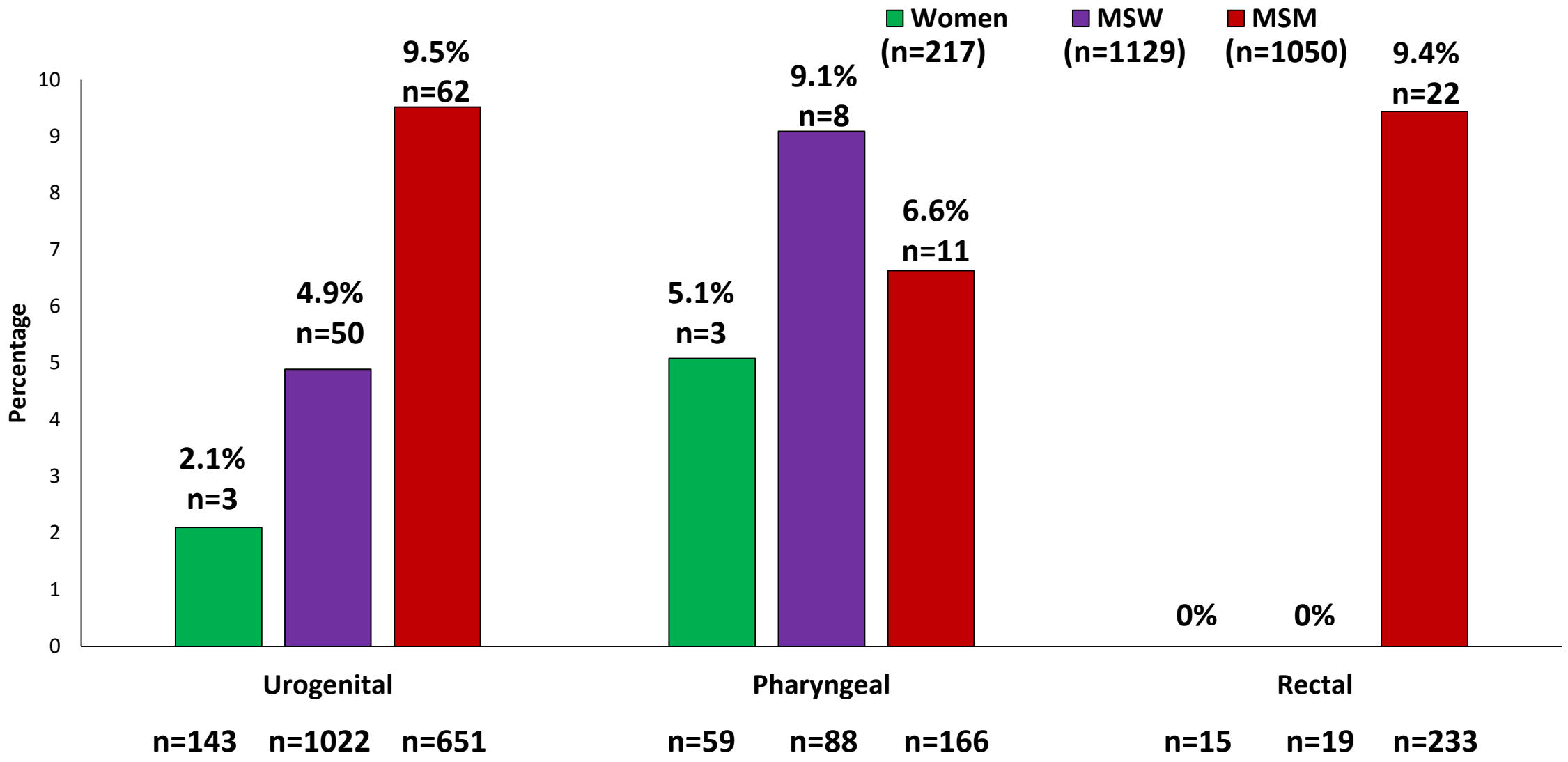


NOTE: Elevated MIC = Azithromycin: ≥ 2.0 µg/mL; Cefixime: ≥ 0.25 µg/mL; Ceftriaxone: ≥ 0.125 µg/mL

Prevalence of Isolates with Elevated Minimum Inhibitory Concentrations (MICs) to Azithromycin(MIC ≥ 2.00 µg/ml) by Region, GISP, 2009-2019



Percentage of Isolates with Elevated Minimum Inhibitory Concentrations (MICs) to Azithromycin by Anatomic Site and by Gender and Gender of Sex Partners, eGISP, 2018



In summary:

- Surveillance methods for gonorrhea resistance in the U.S. continue to expand
- Reduced susceptibility to cephalosporins among gonorrhea isolates in the U.S. remains low
- The percentage of isolates with elevated MICs to azithromycin detected through U.S. surveillance systems continues to increase

Antimicrobial Stewardship and Collateral Damage

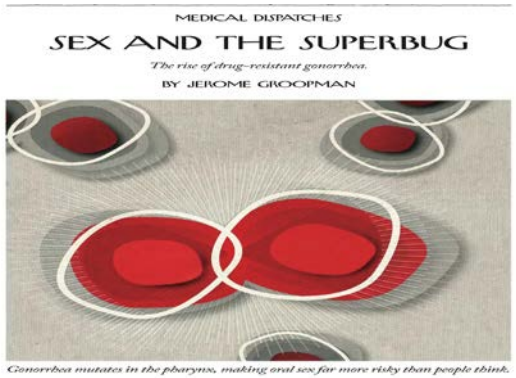
ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES

2019

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Role of Extra-genital sites

- **Well-documented that screening for GC and CT in asymptomatic MSM yield more infection than traditional genitourinary screening**
- **Understanding of the interaction between organisms and environment still poorly understood**
  - GC more difficult to eradicate in the pharynx
  - The pharynx may be a special place for the development of drug resistance (influence of resident flora that may exchange genetic material)
  - The asymptomatic nature of extra-genital infections may select for resistance at these sites
  - Concerns about rectal chlamydia and treatment response; ?autoinoculation of vagina/cervix
  - Understanding of drug penetration in these orifices limited



The New Yorker, October 2012

Macrolide and Nonmacrolide Resistance with Mass Azithromycin Distribution

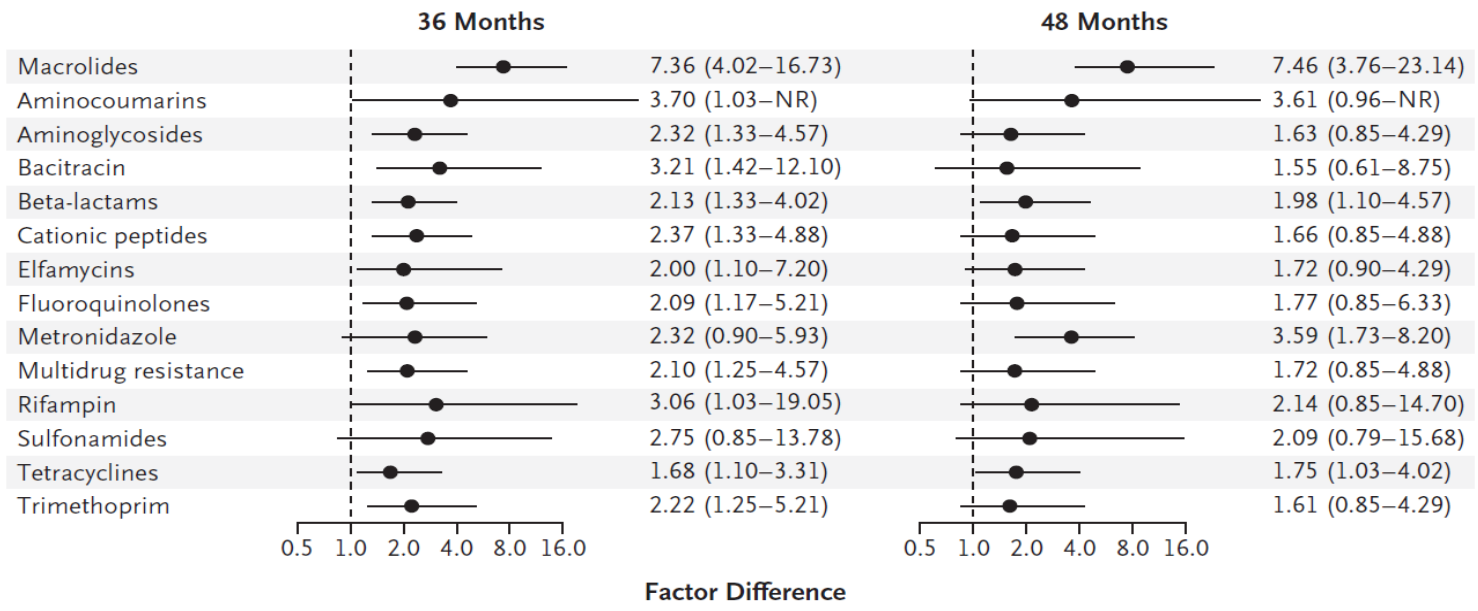


Figure 4. Antibiotic-Resistance Determinants in the Gut of Children at the 36-Month and 48-Month Samples.

The difference in antibiotic-resistance determinants in the azithromycin-treated group as compared with the group that received placebo is shown, with associated 95% confidence intervals. The 36-month samples were obtained 6 months after the sixth distribution, and the 48-month samples were obtained 6 months after the eighth distribution. NR denotes not reached.

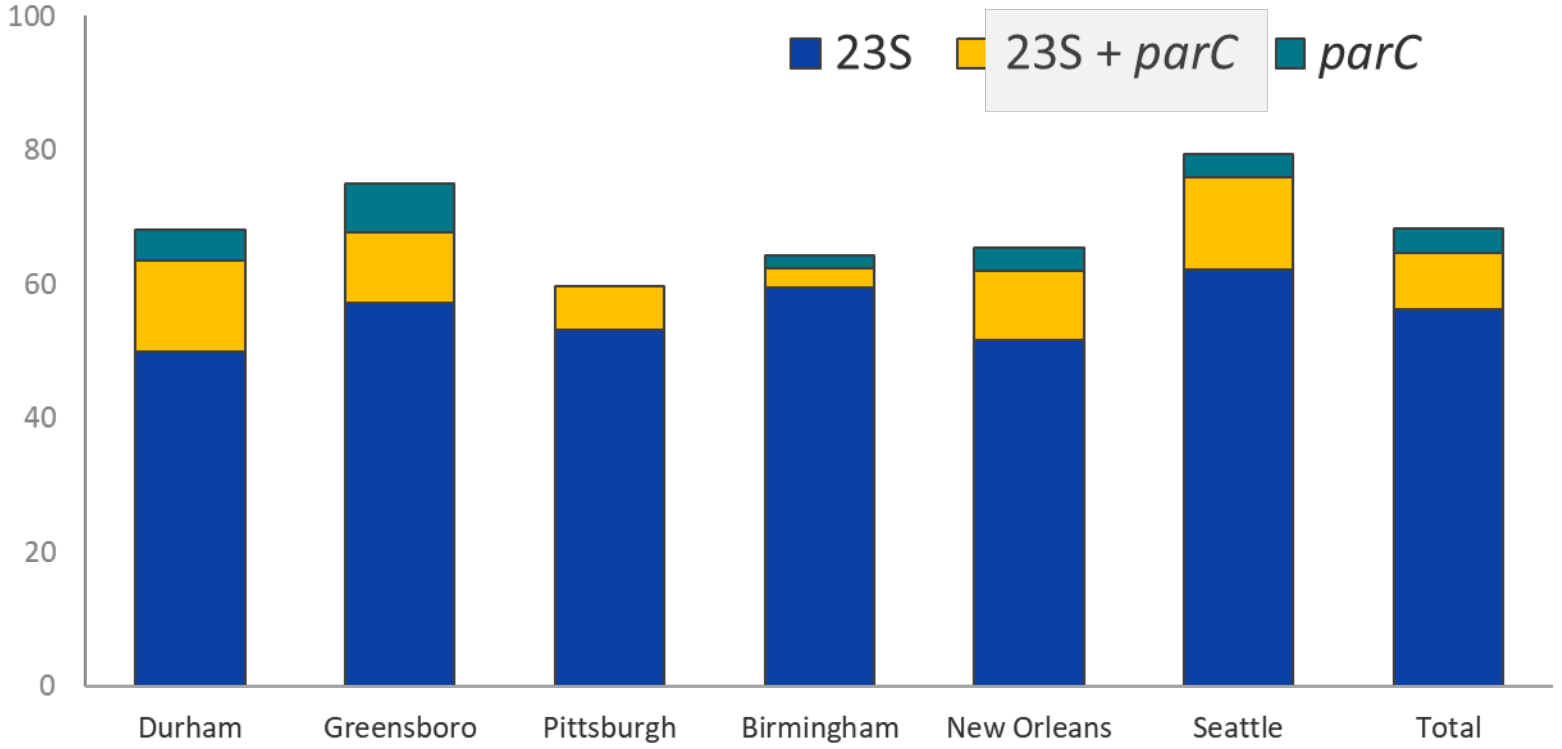
Doan T. NEJM
Nov 12, 2020

MAGNUM

Prevalence of 23S rRNA macrolide resistance mutations and *parC* fluoroquinolone resistance mutations by study site

Men with urethritis symptoms enrolled from 6 U.S. STD clinics 6/2017–8/2018

Total (n=914) MG prevalence = 28.7% (95% CI 23.8-33.6)



National Institutes of Health [HHSN2722013000121, HHSN272000010, DIMD16-0039]

Bachmann LH, Kirkcaldy RD, et al. CID 2020

Clinical Infectious Diseases

MAJOR ARTICLE

International Spread of Multidrug-Resistant *Campylobacter coli* in Men Who Have Sex With Men in Washington State and Québec, 2015–2018

Alexander L. Greninger,[1,a] Amin Addetia,[1,a] Kimberly Starr,[1] Robert J. Cybulski,[2] Mary K. Stewart,[1] Stephen J. Salipante,[1] Andrew B. Bryan,[1] Brad Cookson,[1] Christiane Gaudreau,[3,4] Sadjia Bekal,[4,5] and Ferric C. Fang[1]

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

MECHANISMS OF RESISTANCE

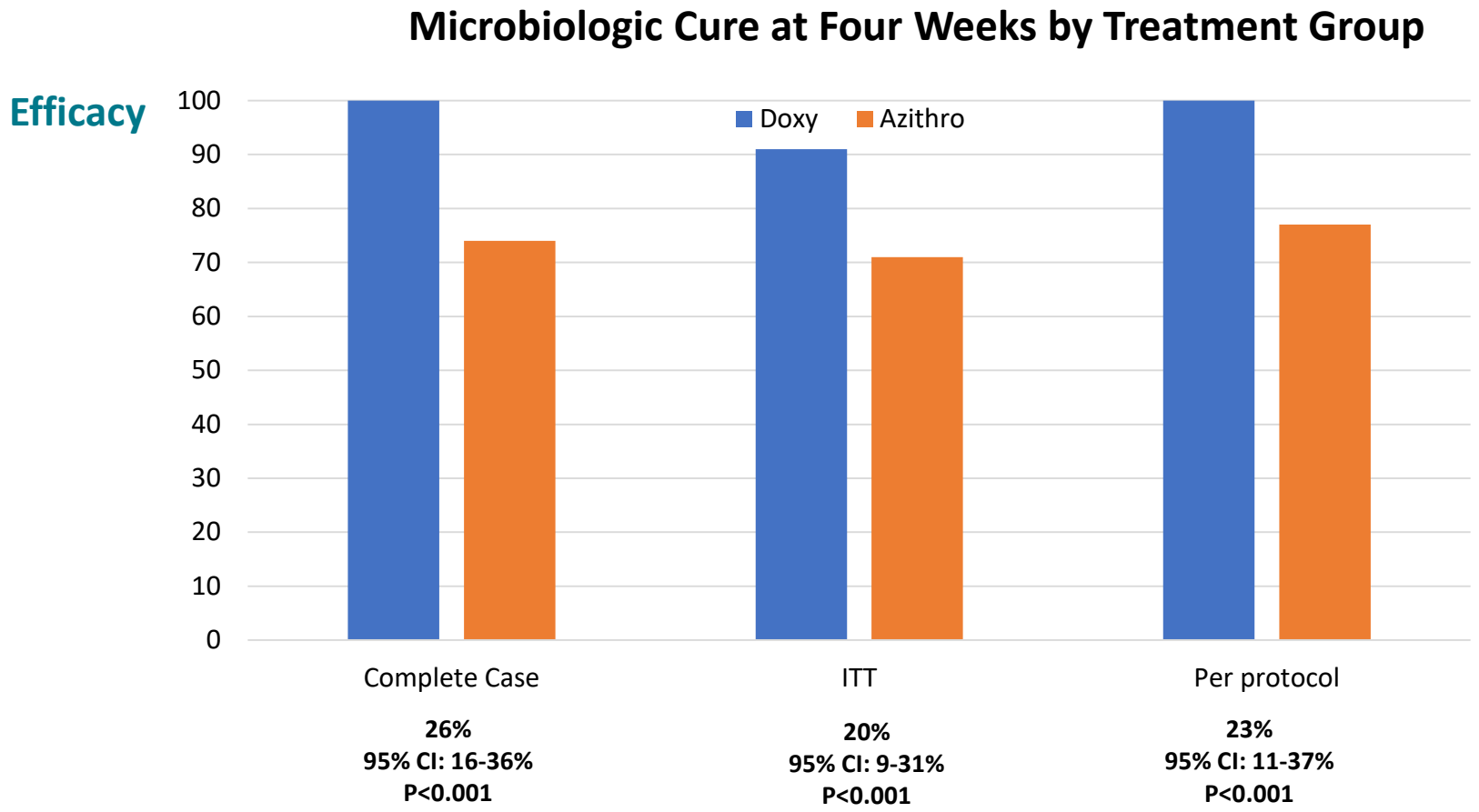
Genetic Mechanisms behind the Spread of Reduced Susceptibility to Azithromycin in *Shigella* Strains Isolated from Men Who Have Sex with Men in Québec, Canada

Khadidja Yousfi,[a] Christiane Gaudreau,[b,c] Pierre A. Pilon,[a,e] Brigitte Lefebvre,[a] Matthew Walker,[d] Éric Fournier,[a] Florence Doualla Bell,[a] Christine Martineau,[a,b] Jean Longtin,[a] Sadjia Bekal[a,b]

Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study

Kate S Baker, Timothy J Dallman, Philip M Ashton, Martin Day, Gwenda Hughes, Paul D Crook, Victoria L Gilbart, Sandra Zittermann, Vanessa G Allen, Benjamin P Howden, Takehiro Tomita, Mary Valcanis, Simon R Harris, Thomas R Connor, Vitali Sintchenko, Peter Howard, Jeremy D Brown, Nicola K Petty, Malika Gouali, Duy Pham Thanh, Karen H Keddy, Anthony M Smith, Kaisar A Talukder, Shah M Faruque, Julian Parkhill, Stephen Baker, François-Xavier Weill, Claire Jenkins, Nicholas R Thomson

Randomized Controlled Trial of Doxycycline vs Azithromycin for Rectal CT Infection in MSM



Dombrowski et al. 2020 STD Prevention Conference

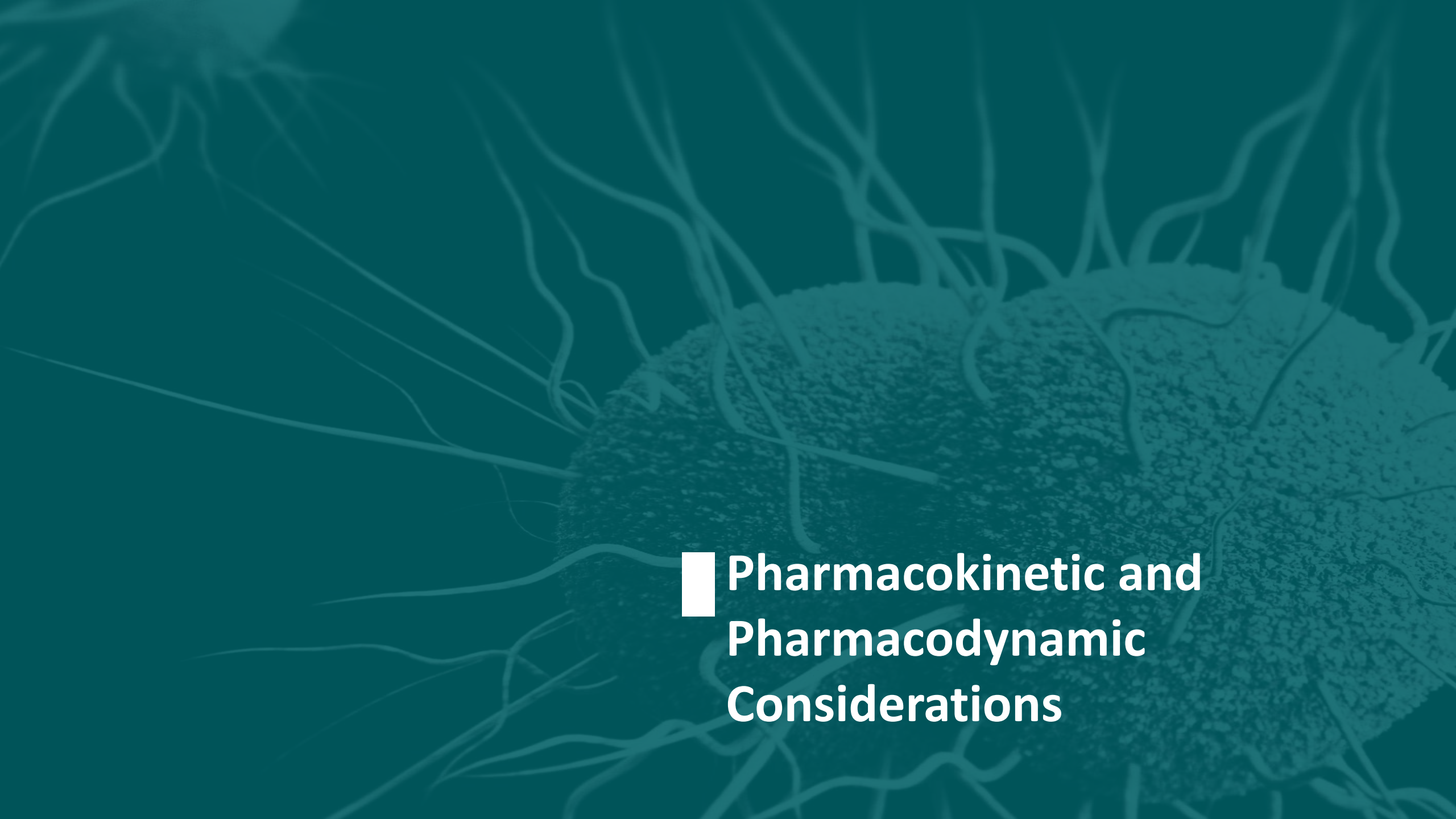
Rectal CT in Women

- **Rectal infection not uncommon in women with CT**
  - Rectum positive in 68.5% - 89%
- **History of anal sex not predictive of infection**
  - Auto-inoculation of the rectal site from an infected genital site
- **Can the rectal site serve as a reservoir for persistent chlamydial infection and a source of auto-inoculation from the GI to the GU tract?**

Van Liere GAFS STI 2014;
Workowski KA JAMA 1993;
Ding A Int J STD AIDS 2014;
van Liere GA BMC Infect Dis 2014;
Gratrix J CID 2014

In Summary

- **Evidence of:**
  - Microbiome impact from (relatively little) azithromycin
  - Increasing azithromycin resistance in potentially co-occurring pathogens
    - *M. genitalium*
    - *Shigella sp.*
    - *Campylobacter sp.*
  - Superior efficacy of doxycycline, most markedly for rectal CT
    - Despite concerns for difference in adherence
  - Increased concern related to (often undetected) rectal infections in women



Pharmacokinetic and Pharmacodynamic Considerations

Summary of Pharmacokinetic/Pharmacodynamic Parameters

PARAMETER	Ceftriaxone	Azithromycin
Activity	Bactericidal	Bacteriostatic
Bioavailability	100% IM/IV	37% (PO)
Tmax	2-3 hours	2-3 hours
Half-life	~8 hours	68 hours
Volume of Distribution	0.19	31.1
% Protein Binding	~95%	Concentration dependent: 51% at 0.02 mcg/mL to 7% at 2 mcg/mL
Saliva:plasma Ratio	<0.004	6
Excretion	Urine (active drug) & bile (byproduct)	Bile/feces
PK/PD Predictor	fT>MIC	AUC/MIC
Minimal Time or Ratio to predict Cure	20 - 24 hours	>40

Slide credit: Lindley Barbee, MD

Calculated ceftriaxone doses for various human weights extrapolated from the Murine Model

Weight	3 mg/kg	5 mg/kg^	10 mg/kg	15 mg/kg	30 mg/kg	120 mg/kg
50 kg	150 mg	250 mg	500 mg	750 mg	1500 mg	6000 mg
80 kg*	240 mg	400 mg	800 mg	1200 mg	2400 mg	9600 mg
100 kg	300 mg	500 mg	1000mg	1500 mg	3000 mg	12,000 mg
150 kg	450 mg	750 mg	1500mg	2250 mg	4500 mg	18,000 mg

*Average U.S. Adult is 80kg (176lb)
^ Connolly et al murine model required 5 mg/kg for MIC of 0.008 (GISP MIC50)

Slide credit: Dr. Lindley Barbee & Dr. Sancta St. Cyr

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Slide credit: Dr. Lindley Barbee & Dr. Sancta St. Cyr

In summary:

- **Pharmacokinetic properties of ceftriaxone and azithromycin are very different**
  - Unclear if PK/PD for pharynx is the same as anogenital
  - Differences in antimicrobial properties by anatomic site may contribute to potential for resistance selection
  - Long tail for azithromycin; Enhance selection for resistance?
- **Ceftriaxone with highly variable individual pharmacokinetics**
- **Calculated doses based on weight suggest need to increase dose to achieve requisite time that serum free (unbound) drug concentration remains higher than the organism's MIC**

Treatment Recommendations

"A gonorrhea begins and God alone knows when it will end"
Phillipe Ricord, French venereologist

2015 CDC STD Treatment Guidelines

Ceftriaxone 250mg IM x 1

Plus

Azithromycin 1gm orally x 1*

(even if chlamydia ruled out)

*Azithromycin used as a strategy to protect ceftriaxone

Morbidity and Mortality Weekly Report

December 18, 2021

Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020

Sancta St. Cyr, MD[1]; Lindley Barbee, MD[1,2]; Kimberly A. Workowski, MD[1,3]; Laura H. Bachmann, MD[1]; Cau Pham, PhD[1]; Karen Schlanger, PhD[1]; Elizabeth Torrone, PhD[1]; Hillard Weinstock, MD[1]; Ellen N. Kersh, PhD[1]; Phoebe Thorpe, MD[1]

Uncomplicated Gonococcal Infections of the Cervix, Urethra, or Rectum **Recommended Regimen for Persons Weighing < 150 kg**
Ceftriaxone 500* mg IM in a single dose ***For persons weighing ≥150 kg, 1 gm ceftriaxone should be administered.**
If chlamydial infection has not been excluded, treat for chlamydia with Doxycycline 100 mg orally 2 times/day for 7 days.

Test of cure for pharyngeal infection 7-14 days after treatment

In Summary:

- **Gonorrhea Treatment Continues to Evolve**
  - Emerging antimicrobial resistance and the importance of antimicrobial stewardship affected gonorrhea treatment recommendations
  - Azithromycin resistance continues to increase with impacts across multiple organisms
  - New data on azithromycin efficacy for chlamydia (particularly rectal infection) factored into decision-making process in addition to the science of pharmacokinetics/pharmacology
- **Monitoring for the emergence of ceftriaxone resistance through surveillance and health care providers' reporting of treatment failures will be essential**
- **New gonorrhea preventive and therapeutic agents are needed**

Acknowledgements

- Sancta St. Cyr, MD, MPH
- Lindley Barbee, MD, MPH
- Kim Workowski, MD
- Cau Pham, PhD
- Karen Schlanger, PhD
- Lizzi Torrone PhD
- Hillard Weinstock, MD
- Ellen Kersh, PhD
- Phoebe Thorpe, MD, MPH
- Gail Bolan, MD
- Kim Gernert, PhD
- Kristen Kreisel, PhD