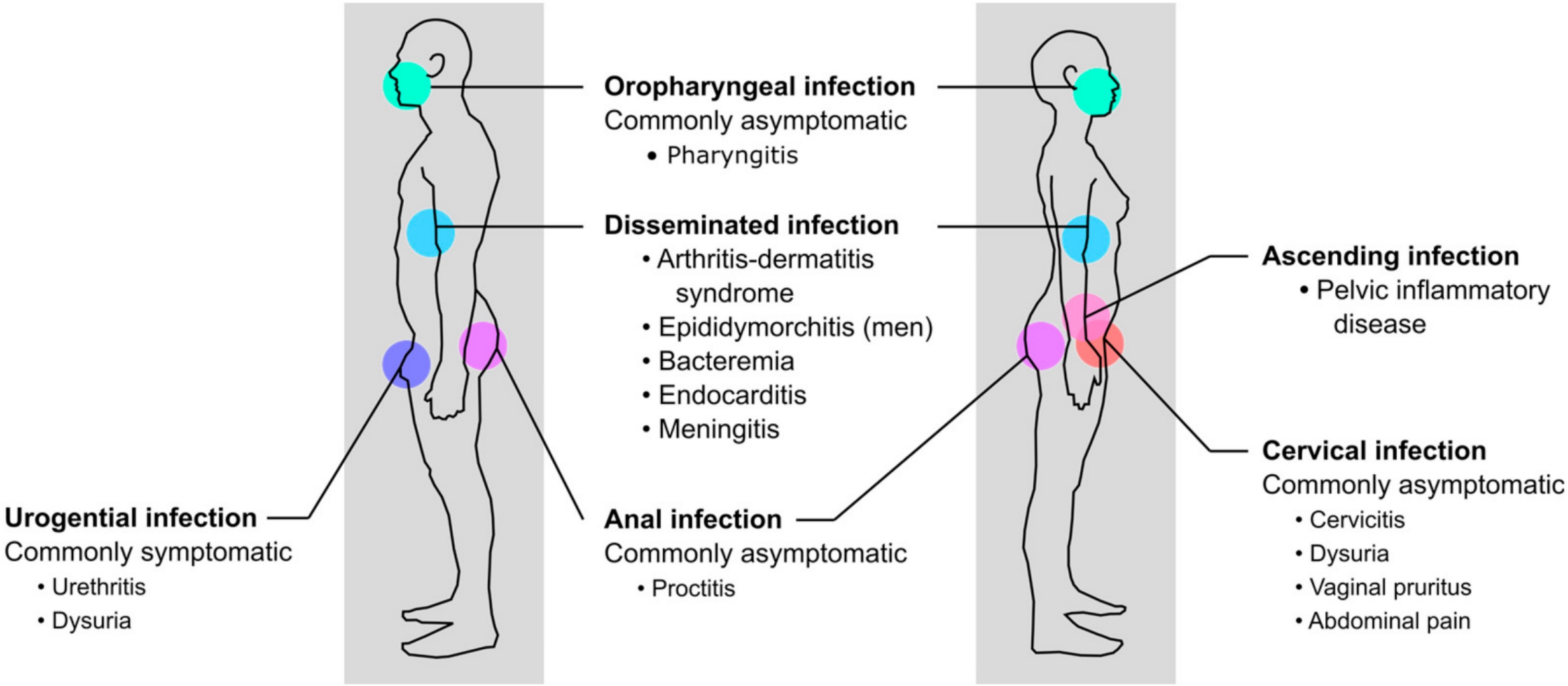
Antimicrobial resistance in *N. gonorrhoeae*

Yonatan Grad, MD, PhD

Intro to gonorrhea (’the clap’)

N. gonorrhoeae sites of infection and sequelae



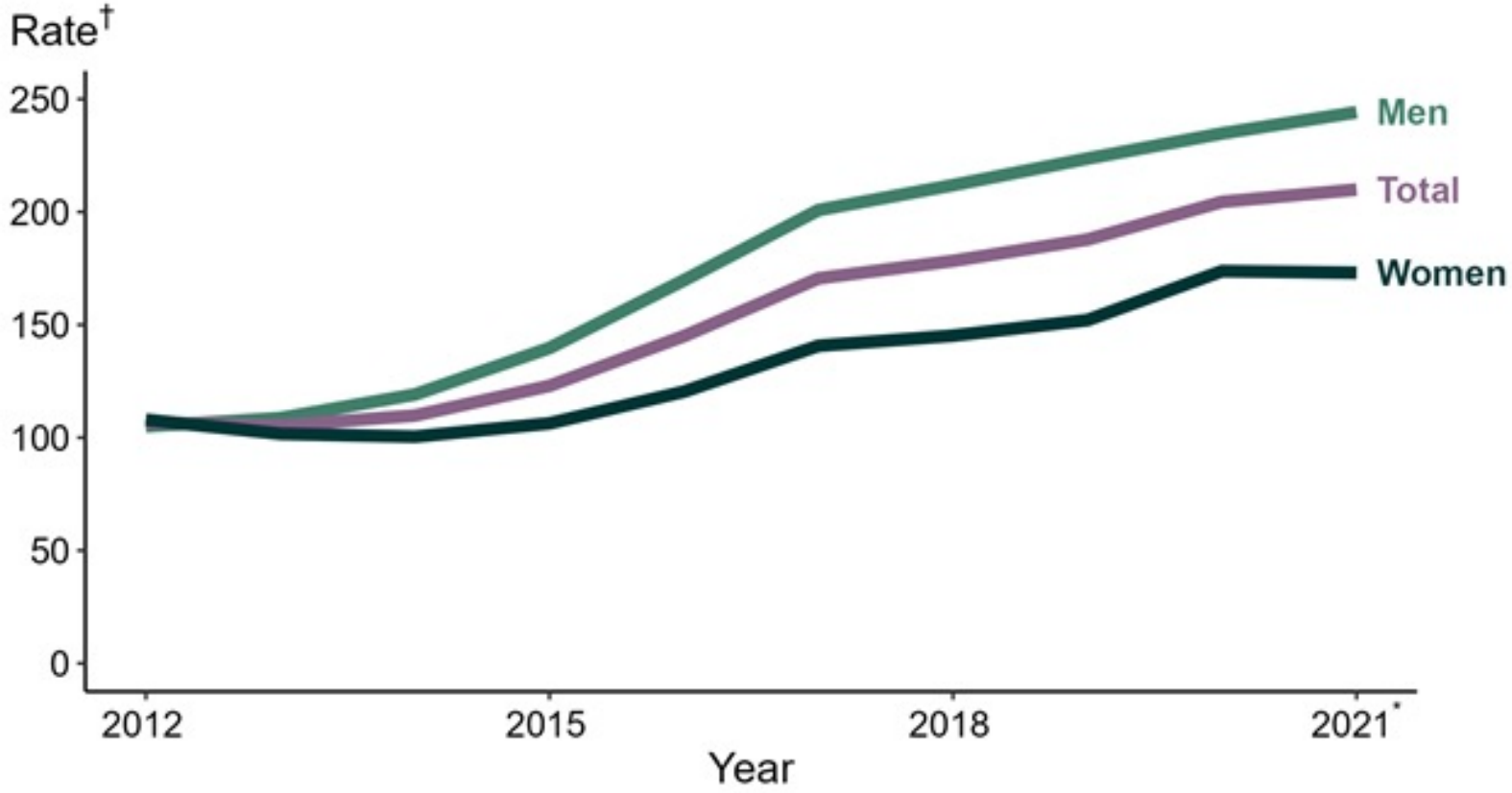
Haese, Thai, and Kahler *Vaccines* 2021

Clinical approach

- Diagnosis:
  - Most often made by nucleic acid amplification test: sensitive and specific, but no information on resistance.
  - Rarely made by culture: time and labor intensive, but gold standard for assessing resistance.

- Treatment:
  - Empiric, based on population AMR surveillance data.
  - Currently (US CDC guidelines): ceftriaxone 500mg IM x 1
  - Test of cure 7-14d after treatment for pharyngeal infections, “monitor vigilantly” for treatment failures at other sites.

Gonorrhea is a highly prevalent infection—and on the rise

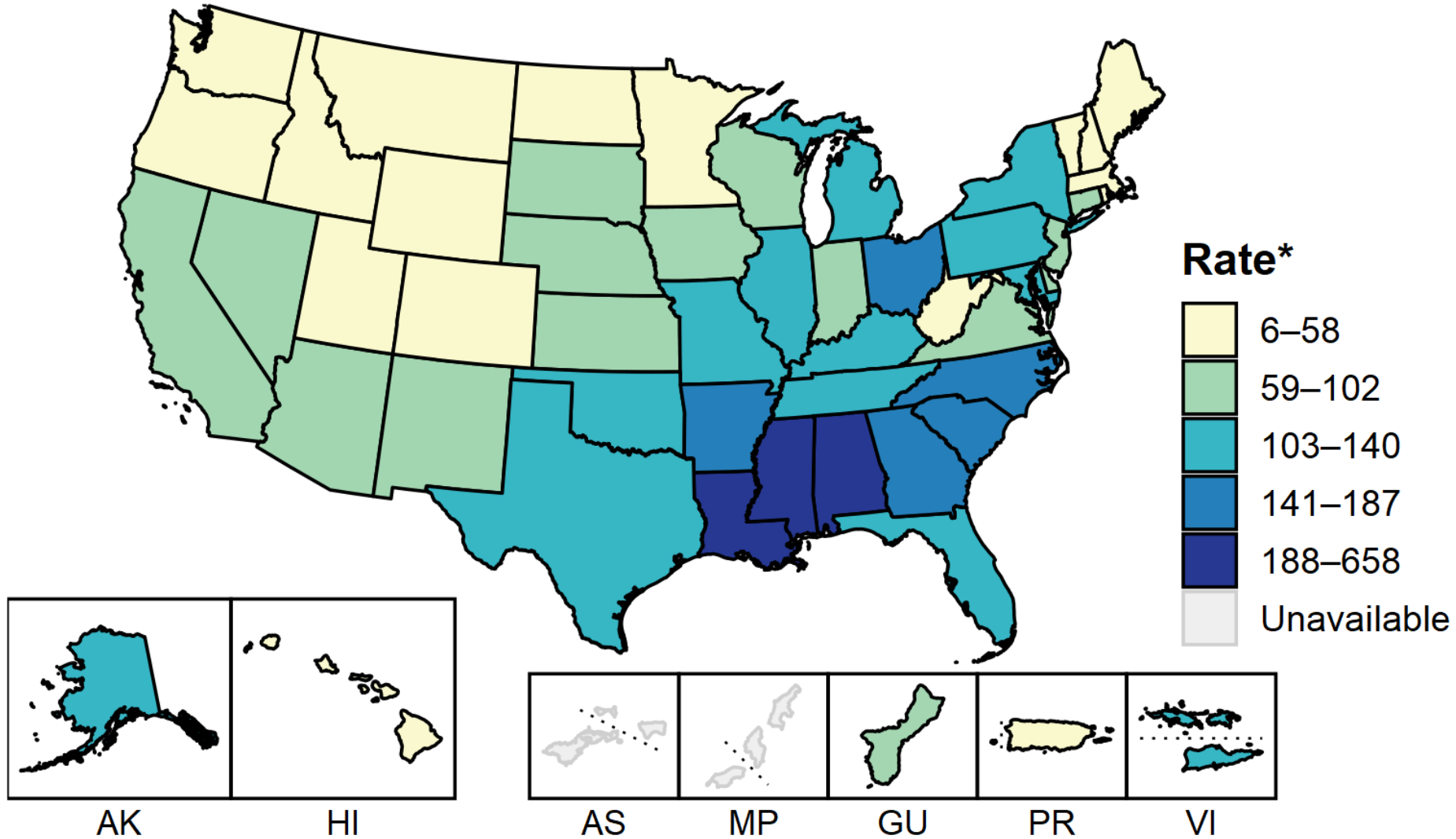


* Reported 2021 data are preliminary as of July 7, 2022

† Per 100,000

https://www.cdc.gov/std/statistics/2021/slides/13.png

2011



https://www.cdc.gov/std/statistics/2020/figures/GC-1.htm

N. gonorrhoeae is increasingly drug resistant, with XDR strains in circulation

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

FEBRUARY 9, 2012

The Emerging Threat of Untreatable Gonococcal Infection

Gail A. Bolan, M.D., P. Frederick Sparling, M.D., and Judith N. Wasserheit, M.D., M.P.H.

Resistance has emerged to each antibiotic used to treat gonococcal infections

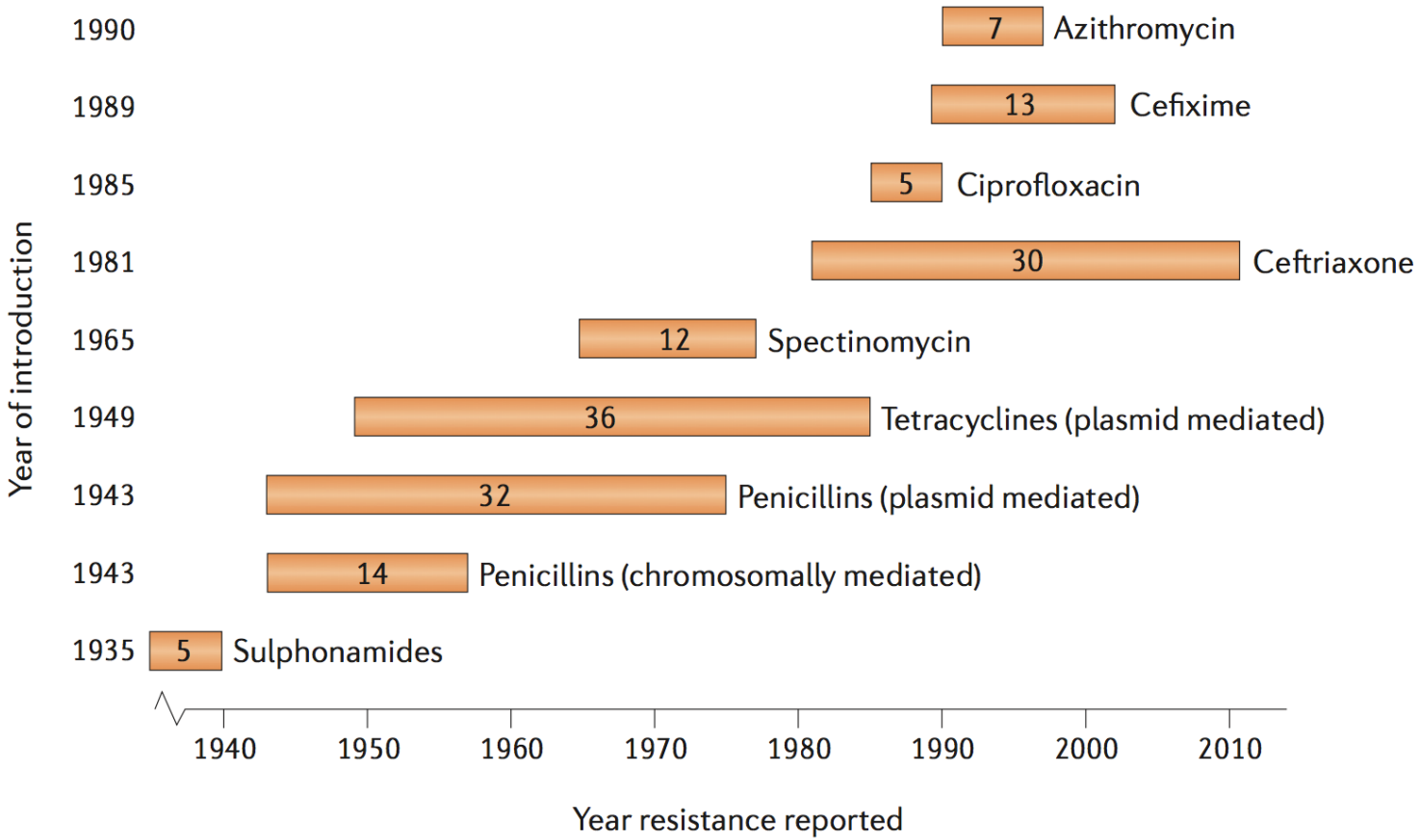


Figure 1 | **The history of *Neisseria gonorrhoeae* antimicrobial resistance.** Since 1935, a wide range of antibiotics have been used to treat gonorrhoea; the figure shows the date of introduction of each antibiotic into clinical use and the year in which resistance was first observed; the numbers on the bars reflect the number of years the antibiotic was in use before resistance was reported.

Goire et al., Nature Rev Gen 2014

Thunderclap comes to Boston

MAURA T. HEALEY
Governor

KIMBERLEY DRISCOLL
Lieutenant Governor

Division of STD Prevention
Tel: (617) 983-6940
Fax: (617) 887-8790
www.mass.gov/dph/cdc/std

MARY A. BECKMAN
Acting Secretary

MARGRET R. COOKE
Commissioner

Tel: 617-624-6000
www.mass.gov/dph

CLINICAL ALERT

January 19, 2023

MULTI-DRUG NON-SUSCEPTIBLE GONORRHEA IN MASSACHUSETTS

- A novel strain of multidrug-non-susceptible *Neisseria gonorrhoeae* with reduced susceptibility to ceftriaxone, cefixime, and azithromycin, and resistance to ciprofloxacin, penicillin, and tetracycline, has been identified in a Massachusetts resident. Although ceftriaxone 500 mg IM was effective at clearing infection for this case, this is the first isolate identified in the United States to demonstrate resistance or reduced susceptibility to all drugs that are recommended for treatment.

- Enhanced surveillance has identified a second isolate that, based on its genome, likely has similarly reduced susceptibility to ceftriaxone and cefixime.

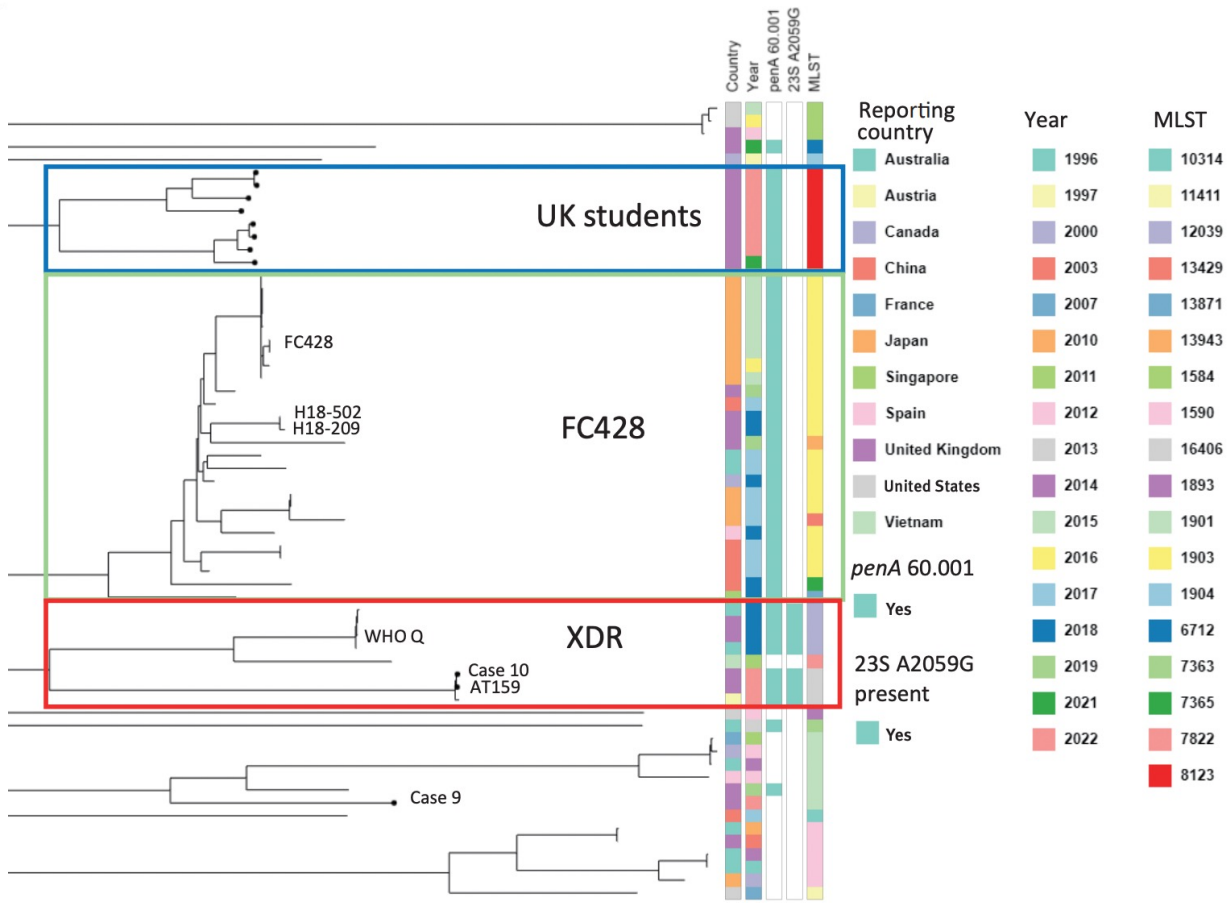
- Identification of this strain, the same as what was recently reported in the United Kingdom[1] and previously reported as circulating in Asia-Pacific countries, is a warning that *N. gonorrhoeae* is becoming less responsive to a limited arsenal of antibiotics.

Reimche et al., *Lancet Inf Dis* 2024

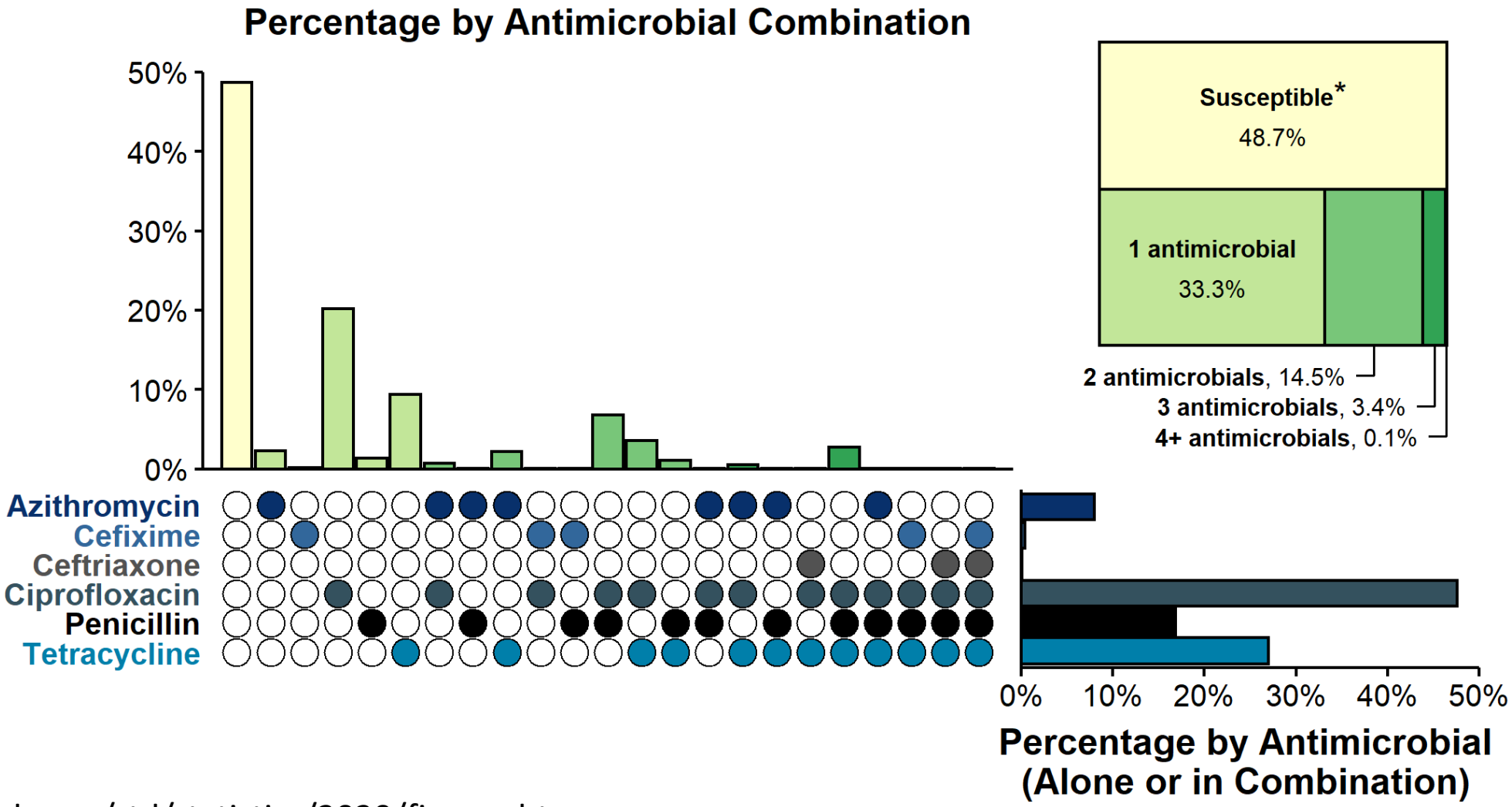
RAPID COMMUNICATION

Detection of 10 cases of ceftriaxone-resistant *Neisseria gonorrhoeae* in the United Kingdom, December 2021 to June 2022

Michaela Day[1], Rachel Pitt[1], Nisha Mody[1], John Saunders[1], Rupa Rai[1], Achyuta Nori[1], Hannah Church[1], Sarah Mensforth[1], Helen Corkin[1], Jacqueline Jones[2], Preneshni Naicker[3], Wazirzada M Khan[1], Rebecca Thomson Glover[1], Kalani Mortimer[1], Chloe Hylton[1], Elizabeth Moss[1], Thomas Joshua Pasvol[1], Ania Richardson[1], Suzy Sun[1], Neil Woodford[1], Hamish Mohammed[1], Katy Sinka[1], Helen Fifer[1]



Most strains in the US remain susceptible



https://www.cdc.gov/std/statistics/2020/figures.htm

To address the challenges posed by AMR gonorrhea, we need…

- More antibiotics
- Tools for prevention
- Better diagnostics: both for epidemiological purposes and to help with diversifying selection pressures
- Better global surveillance: by identifying where the problems originate, can we slow the emergence and spread of resistance?

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Drugs in the pipeline

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

Stephanie N. Taylor, M.D., Jeanne Marrazzo, M.D., M.P.H., Byron E. Batteiger, M.D., Edward W. Hook, III, M.D., Arlene C. Seña, M.D., M.P.H., Jill Long, M.D., M.P.H., Michael R. Wierzbicki, Ph.D., Hannah Kwak, M.H.S., Shacondra M. Johnson, B.S.P.H., Kenneth Lawrence, Pharm.D., and John Mueller, Ph.D.

Clinical Infectious Diseases

MAJOR ARTICLE

Gepotidacin for the Treatment of Uncomplicated Urogenital Gonorrhea: A Phase 2, Randomized, Dose-Ranging, Single-Oral Dose Evaluation

Stephanie N. Taylor,[1] David H. Morris,[2] Ann K. Avery,[3] Kimberly A. Workowski,[4] Byron E. Batteiger,[5] Courtney A. Tiffany,[6] Caroline R. Perry,[6] Aparna Raychaudhuri,[6] Nicole E. Scangarella-Oman,[6] Mohammad Hossain,[6] and Etienne F. Dumont[6]

What’s the best way to introduce a new antibiotic for gonorrhea?

What's the best way to introduce a new antibiotic for gonorrhea?

1. Hold the new antibiotic in reserve until the current therapy reaches a threshold prevalence of resistance
2. Use either drug immediately
3. Gradually introduce the new drug
4. Combination therapy

Reichert et al., *Lancet Microbe* 2023

What's the best way to introduce a new antibiotic for gonorrhea?

Across a range of fitness costs of resistance and likelihood of emergence of resistance on treatment….

1. Hold the new antibiotic in reserve until the current therapy reaches a threshold prevalence of resistance
2. Use either drug immediately
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4. Combination therapy

Reichert et al., *Lancet Microbe* 2023

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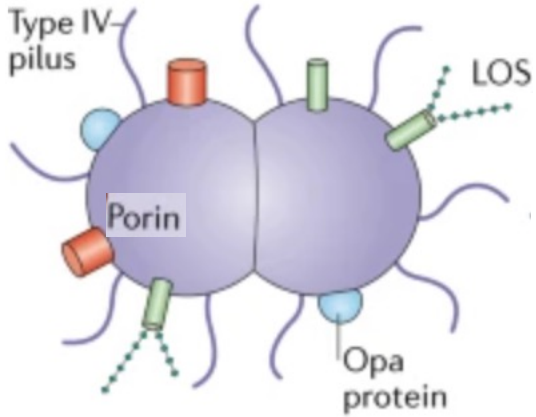
Vaccines

N. gonorrhoeae evades and inhibits the immune response

Phase and antigenic variation



Quillen and Seifert, Nature Reviews Micro, 2018

Immune inhibition

Antibody to Rmp (outer membrane protein 3) increases susceptibility to gonococcal infection.

F A Plummer, … , P Waiyaki, R C Brunham

J Clin Invest. 1993;91(1):339-343. https://doi.org/10.1172/JCI116190.

Antibody to Reduction Modifiable Protein Increases the Bacterial Burden and the Duration of Gonococcal Infection in a Mouse Model

Sunita Gulati ✉, Xin Mu, Bo Zheng, George W. Reed, Sanjay Ram, Peter A. Rice

The Journal of Infectious Diseases, Volume 212, Issue 2, 15 July 2015, Pages 311–315, https://doi.org/10.1093/infdis/jiv024

4CMenB seems to have some effectiveness?

Study	Estimated Vaccine Effectiveness % (95% CI)
Petousis-Harris et al., *Lancet* 2017	31% (21–39)
Abara et al., *Lancet Inf Dis* 2022	40% (23–53)
Bruxvoort et al., *Clin Inf Dis* 2022	46% (34-86)
Wang et al., *Lancet Inf Dis* 2022	32.7% (8.3–50.6)

Phase 3 trials underway

Doxycycline Post-Exposure Prophylaxis (Doxy-PEP)

Doxycycline to prevent bacterial STIs

Doxy-PEP = post-exposure prophylaxis using 200mg doxycycline, recommended within 72h of condomless sex

IPERGAY:	Molina et al., *Lancet Infect Dis* 2018
DoxyPEP:	Luetkemeyer et al., *NEJM* 2023
DOXYVAC:	Molina et al., CROI abstract 2023
dPEP:	Stewart et al., *NEJM* 2023

Background: Evidence for Doxy-PEP

DoxyPEP trial in U.S. showed significant reduction in quarterly incidence of gonorrhea in MSM/TGW for those using DoxyPEP

A PrEP Cohort

Analyses	Doxycycline	Standard Care	Relative Risk (95% CI)	P Value
	no. of quarterly visits with event /total no. of visits (%)			
Primary analysis				<0.001
Any STI	61/570 (10.7)	82/257 (31.9)	0.34 (0.24–0.46)	
Secondary analysis				
Any gonorrhea	52/570 (9.1)	52/257 (20.2)	0.45 (0.32–0.65)	
Urethral	5/570 (0.9)	12/257 (4.7)	0.19 (0.06–0.55)	
Pharyngeal	38/570 (6.7)	34/257 (13.2)	0.50 (0.32–0.78)	
Rectal	25/570 (4.4)	29/257 (11.3)	0.40 (0.23–0.69)	

B PLWH Cohort

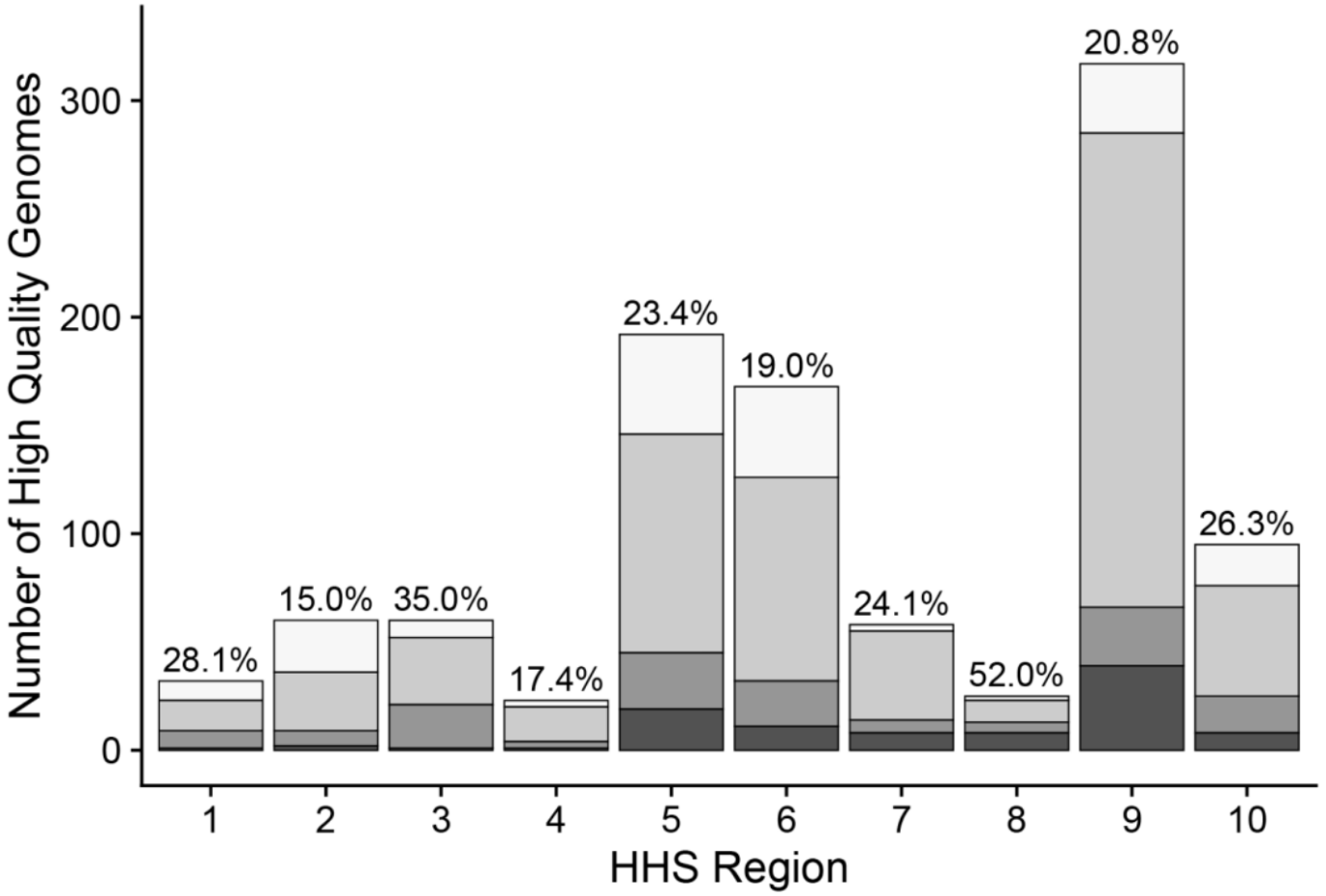
Analyses	Doxycycline	Standard Care	Relative Risk (95% CI)	P Value
	no. of quarterly visits with event /total no. of visits (%)			
Primary analysis				<0.001
Any STI	36/305 (11.8)	39/128 (30.5)	0.38 (0.24–0.60)	
Secondary analysis				
Any gonorrhea	27/305 (8.9)	26/128 (20.3)	0.43 (0.26–0.71)	
Urethral	3/305 (1.0)	5/128 (3.9)	0.23 (0.05–1.02)	
Pharyngeal	15/305 (4.9)	13/128 (10.2)	0.49 (0.23–1.03)	
Rectal	16/305 (5.2)	20/128 (15.6)	0.33 (0.17–0.63)	

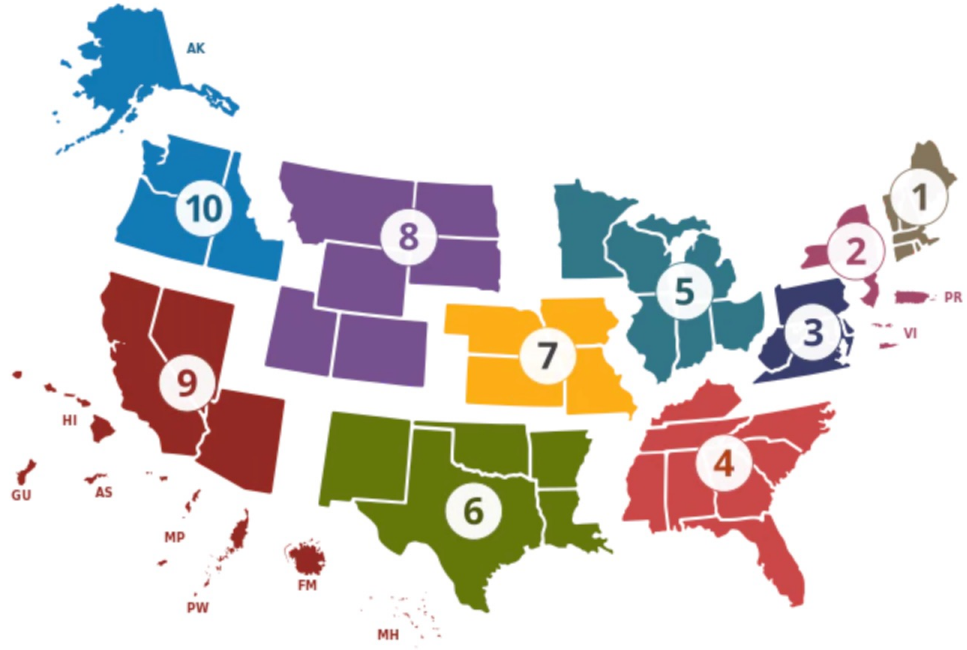
Luetkemeyer et al., *NEJM* 2023

Questions about Doxy-PEP

- How does doxy susceptibility vary across demographics/geography?
- Expect this will select for doxy resistant strains—what else are they resistant to, and how does this compare to the co-resistance in doxy susceptible strains?
- This might temporarily decrease the burden of gonorrhea—how long until resistant strains drive incidence back up?
- What about bystander selection in *S. aureus* and other bacteria?

Regional variation in *N. gonorrhoeae* tetracycline resistance (using genome sequencing data from the CDC; Reimche et al., 2021)





Mortimer and Grad, *Clinical Infectious Diseases* 2023

What’s going to happen with STI prevalence, antibiotic resistance, microbial ecology?

Potential increase in antibiotic consumption…

Given the DoxyPEP trial inclusion criteria, we estimate up to 0.89 million MSM may be eligible (0.53 million PLWH+0.36 million HIV PrEP users)

x

Assume 30% adoption among this population, similar to uptake of HIV PrEP among those eligible

x

Average doxyPEP: 4 doses per month

=

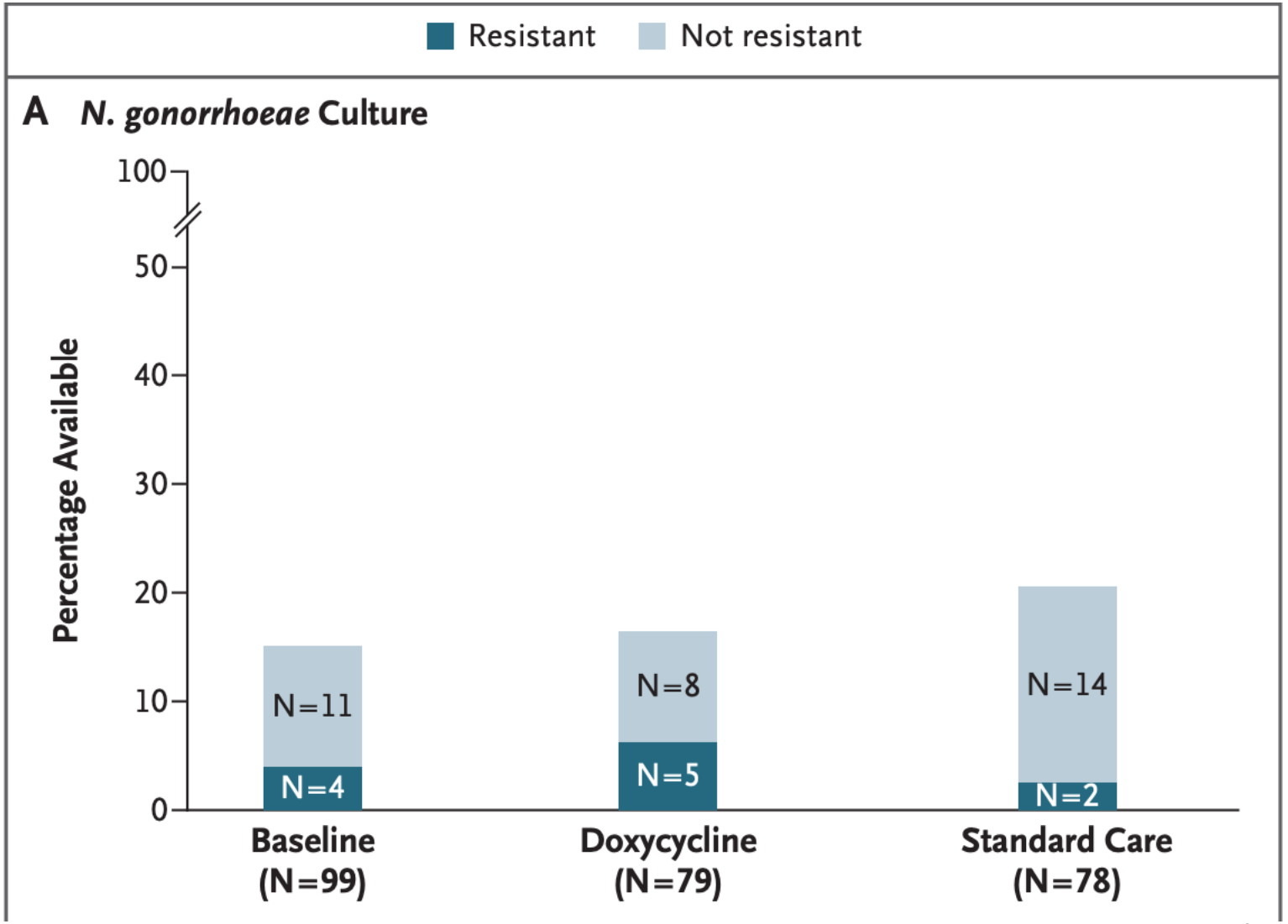
~1M doses of doxycycline per month

Cases of STIs averted:
monthly incidence of STIs among those on DoxyPEP*(1-RR)*DoxyPEP population

~27,000 doses of antibiotics per month

Roster and Grad, *Lancet Microbe* 2023

Too few data to make much of doxycycline resistance in the DoxyPEP trial…



Luetkemeyer et al., *NEJM* 2023

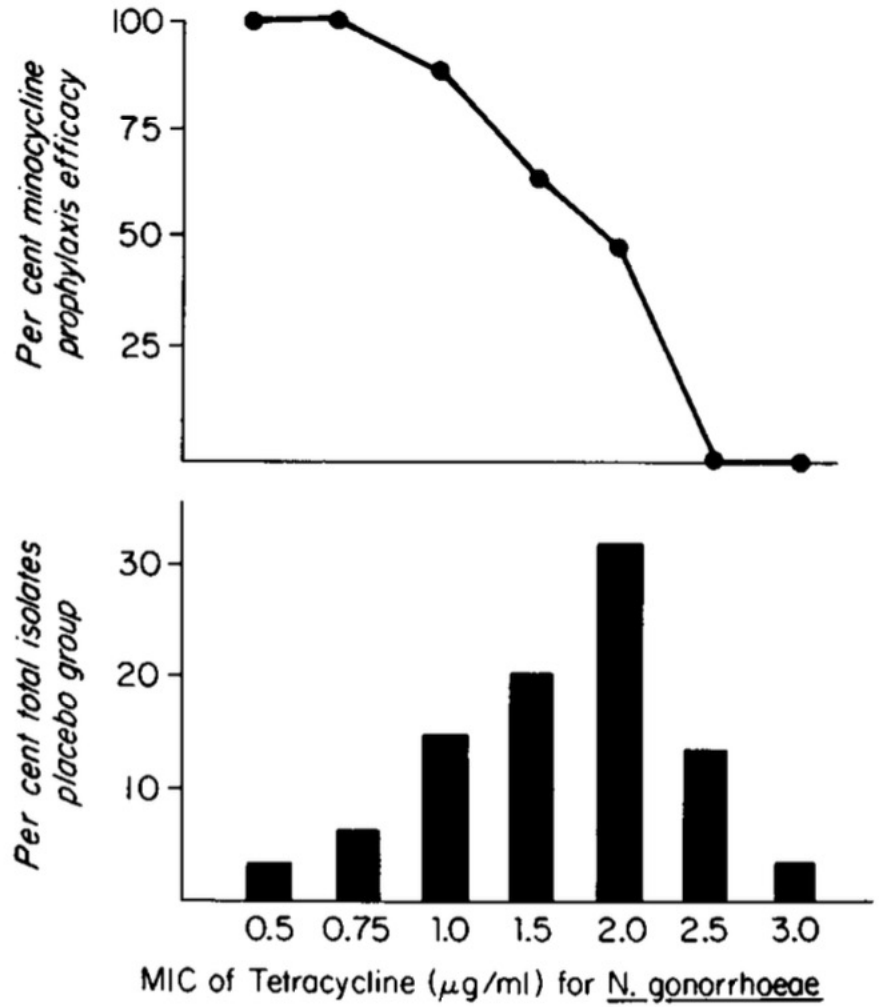
But a bit of history…

A TRIAL OF MINOCYCLINE GIVEN AFTER EXPOSURE TO PREVENT GONORRHEA

WILLIAM O. HARRISON, M.D., RICHARD R. HOOPER, M.D., PAUL J. WIESNER, M.D., AXEL F. CAMPBELL, M.D., WALTER W. KARNEY, M.D., GLADYS H. REYNOLDS, PH.D., OSCAR G. JONES, B.S., AND KING K. HOLMES, M.D., PH.D.

Abstract In a prospective evaluation of antibiotic prophylaxis against gonorrhea, 1080 men were given 200 mg of oral minocycline or placebo after sexual intercourse with prostitutes in a Far Eastern port. Later, at sea, gonococcal infection was detected in 57 of 565 men given placebo and 24 of 515 men given minocycline ($P<0.001$). Minocycline prophylaxis completely prevented infection by gonococci susceptible to 0.75 μg or less of tetracycline per milliliter, reduced the risk of infection or prolonged the incubation period in men exposed to gonococci susceptible to 1.0 to 2.0 μg per milliliter, but did not prevent infection or prolong incubation in men exposed to gonococci resistant to 2.0 μg. Minocycline did not increase the proportion of asymptomatic infections. Minocycline prophylaxis would probably have limited effectiveness as a public-health measure because of the tendency to select resistant gonococci. (N Engl J Med 300:1074-1078, 1979)

But a bit of history…



10 GLAND JOURNAL OF MEDICINE May 10, 1979

N AFTER EXPOSURE TO PREVENT GONORRHEA

HARD R. HOOPER, M.D., PAUL J. WIESNER, M.D.,
W. KARNEY, M.D., GLADYS H. REYNOLDS, PH.D.,
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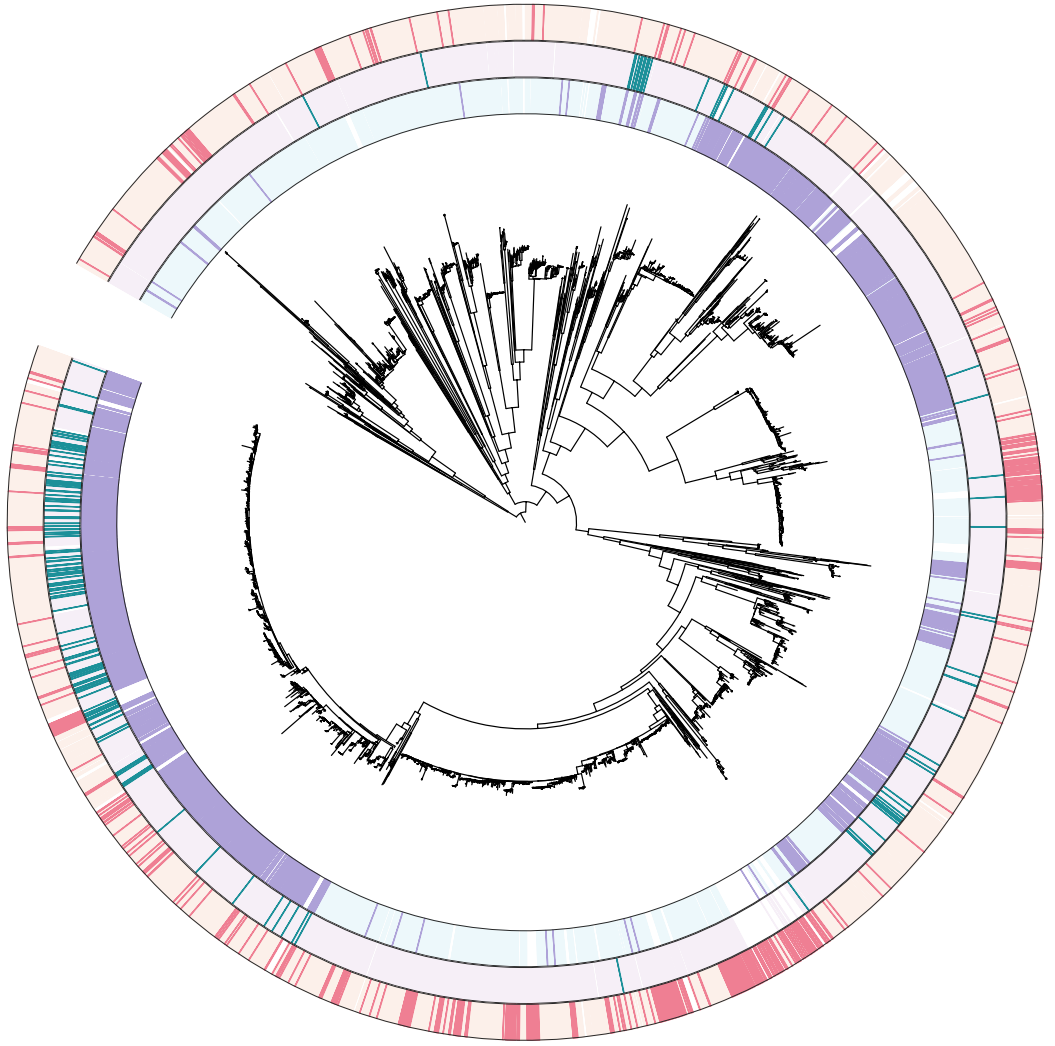
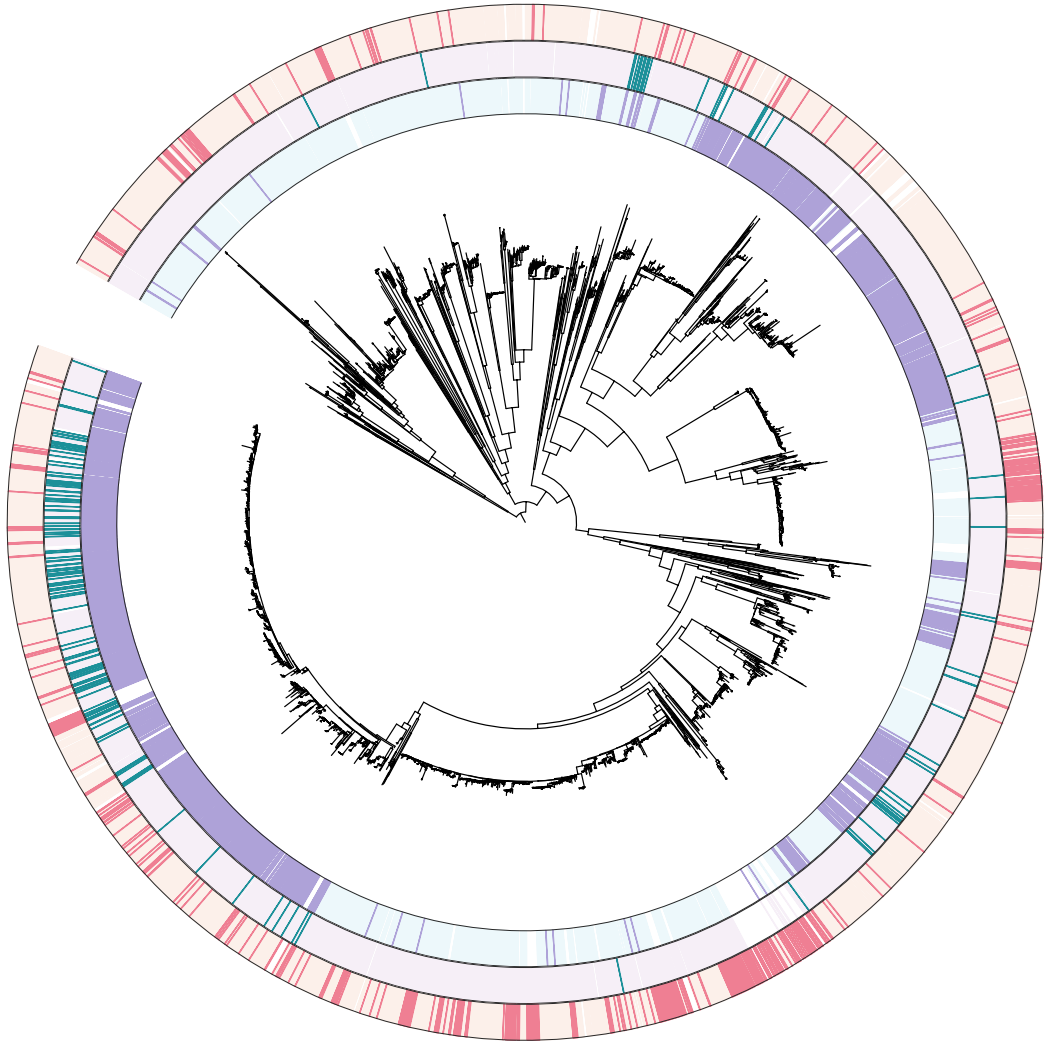
If most diagnoses are made by nucleic acid amplification tests already, what about rapid sequence-based prediction of AMR?

How well can we predict AMR phenotype from genotype?



Ma, Mortimer, et al.,
Nature Communications
2020

How well can we predict AMR phenotype from genotype?



CIP R^2: 0.94

Ma, Mortimer, et al.,
Nature Communications
2020

ResistancePlus® GC

Detect *Neisseria gonorrhoeae* and ciprofloxacin susceptibility markers
Dual *N. gonorrhoeae* targets (*opa* & *porA*), *gyrA* S91F mutant, & *gyrA* S91 wildtype
in a single-well multiplex qPCR test

Why use *ResistancePlus*® GC?

Antibiotic resistance in gonorrhoea infections is a global concern. There are limited effective treatment options and novel antibiotics are not readily available. Smarter and more directed use of antibiotics can be achieved through Resistance Guided Therapy.

- Global surveillance data indicate 50-70% of gonorrhoea infections remain susceptible to ciprofloxacin.
- Guidelines for gonorrhoea management call to preserve ceftriaxone and recommend use of ciprofloxacin when susceptibility information is available.
- Azithromycin resistance is rising, compromising dual-therapy options.

Tested on hundreds of clinical samples, ***Resistance****Plus*® GC demonstrates excellent sensitivity and specificity.

https://plexpcr.com/products/sexually-transmitted-infections/resistanceplus-gc/

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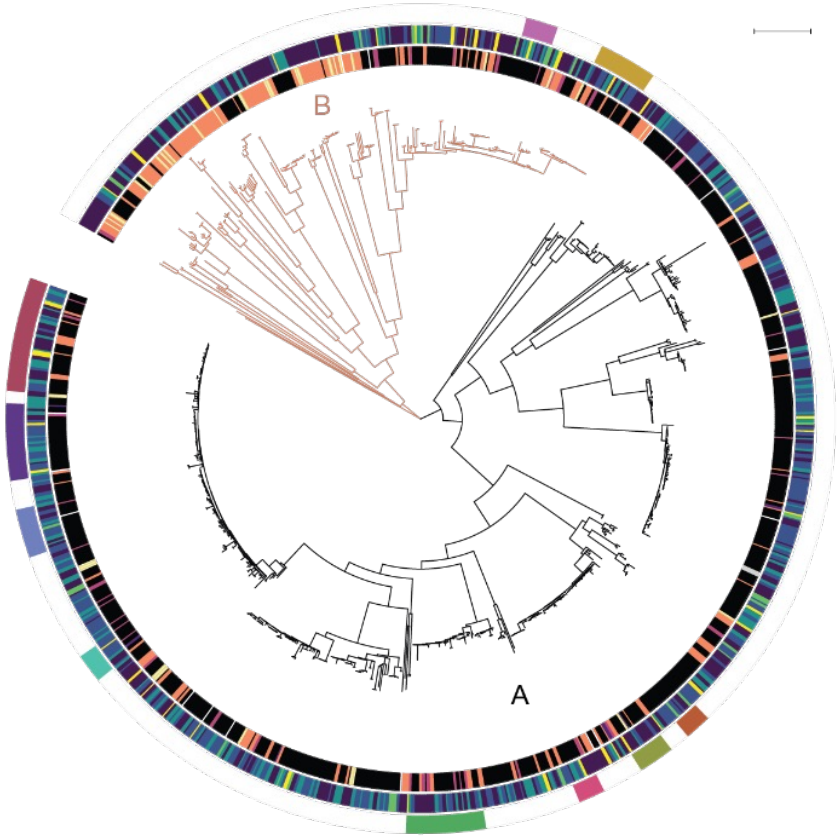
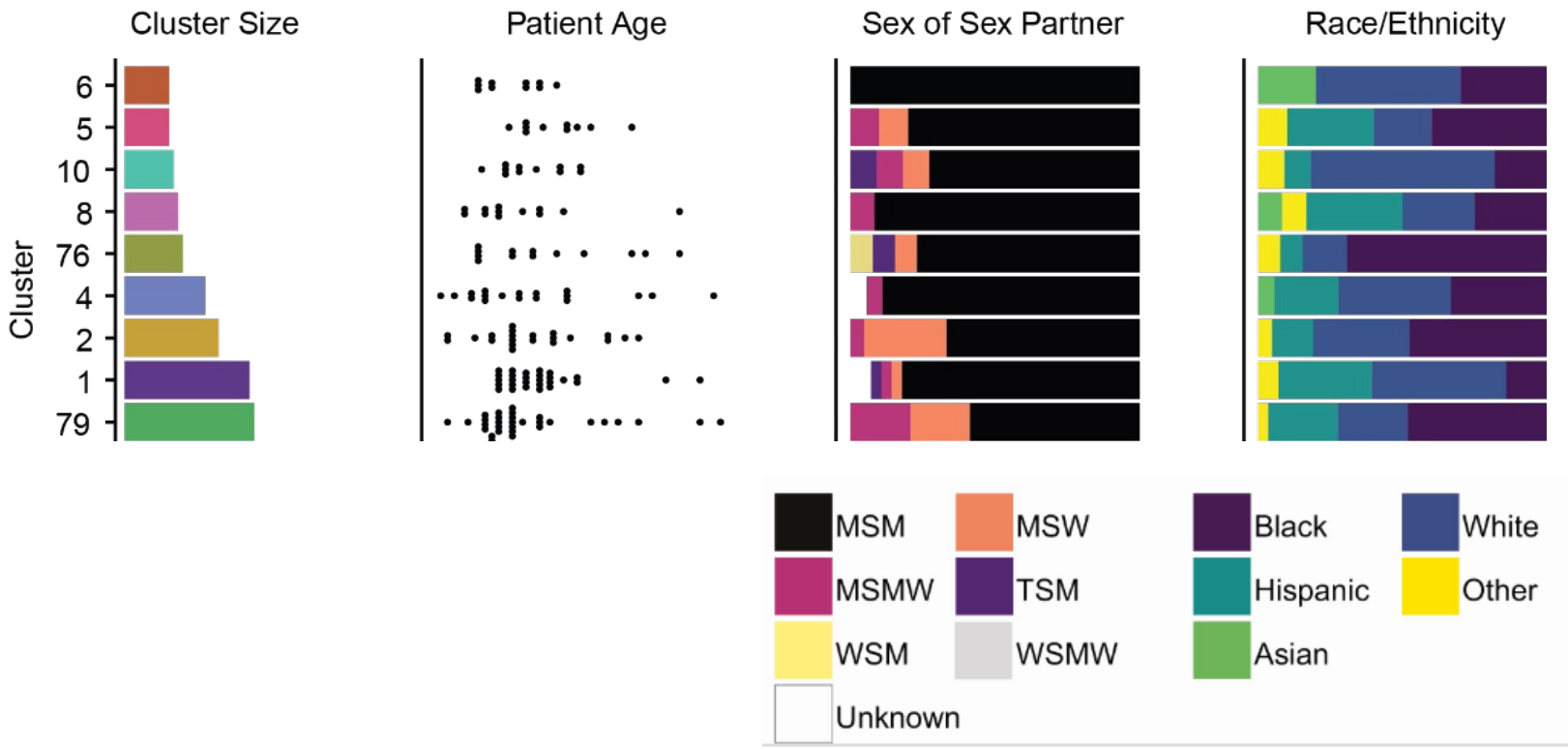
How does AMR influence the spread of *N. gonorrhoeae*?

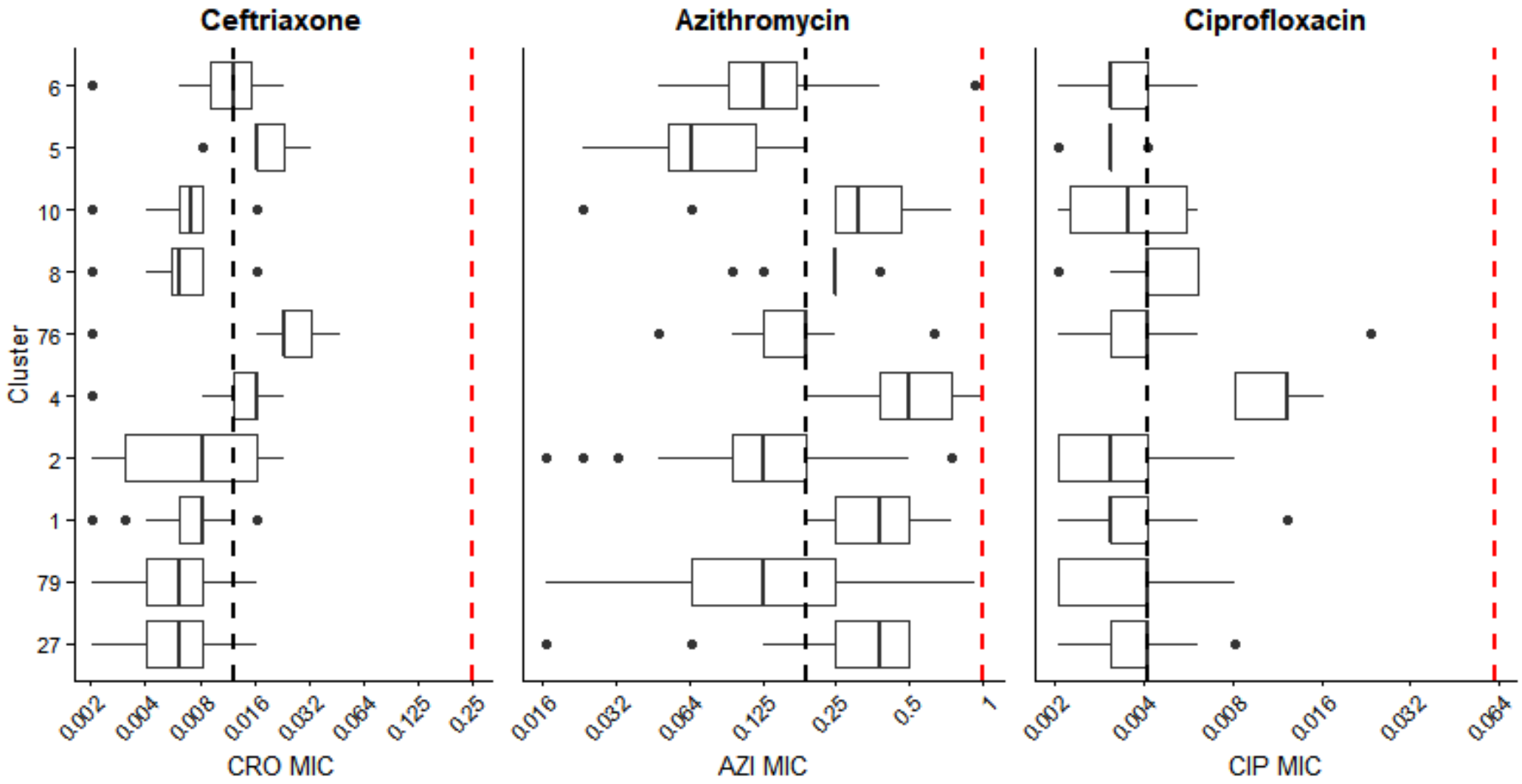
Genomic epidemiology of >1000 cases of gonorrhea in NYC





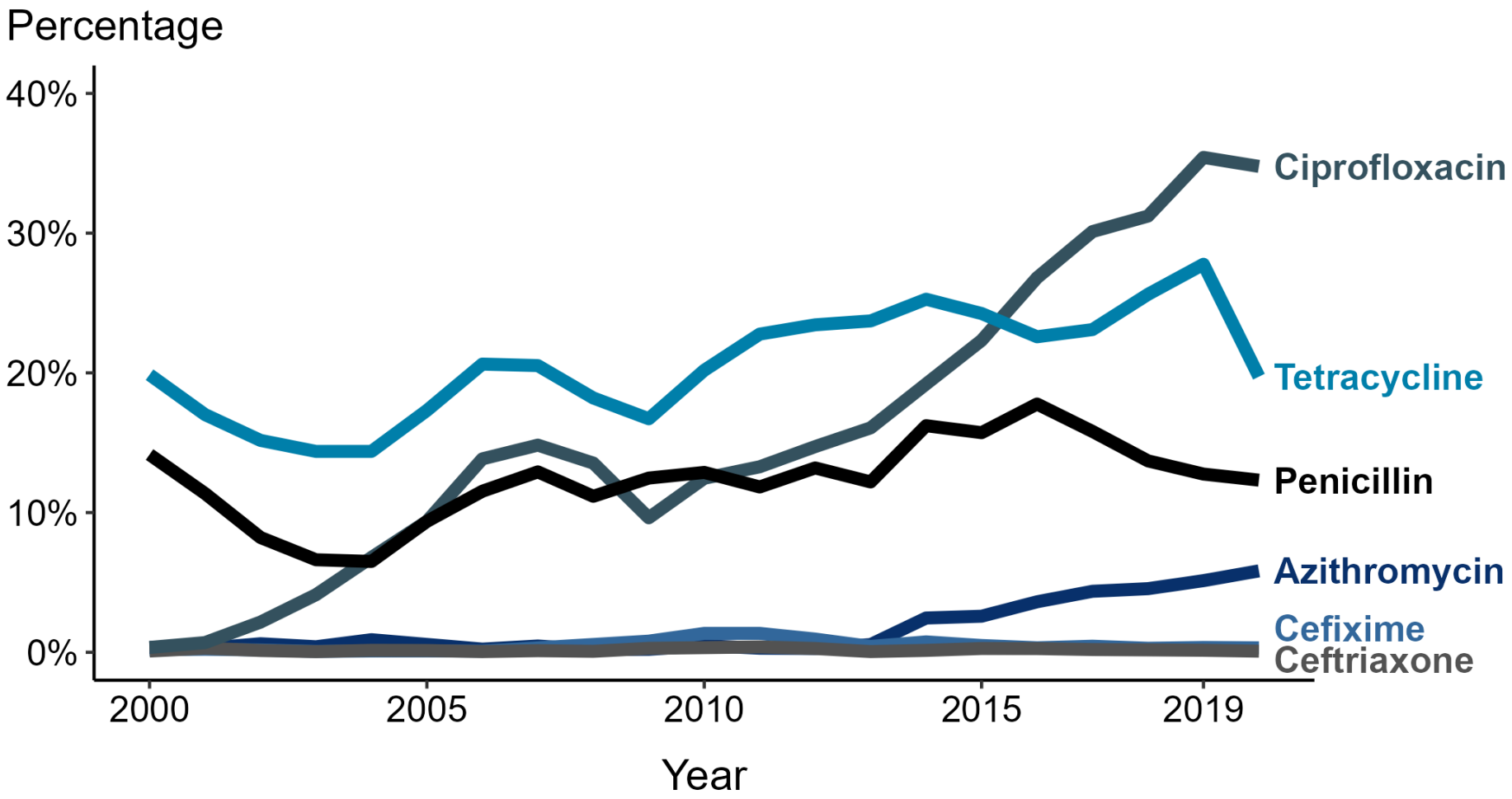
Mortimer et al., *CID* 2020

The largest clusters are drug susceptible



Mortimer et al., *CID* 2020

What is the relationship between resistance and prevalence?



https://www.cdc.gov/std/statistics/2020/figures.htm

Gonorrhea and AMR are global…

RAPID COMMUNICATION

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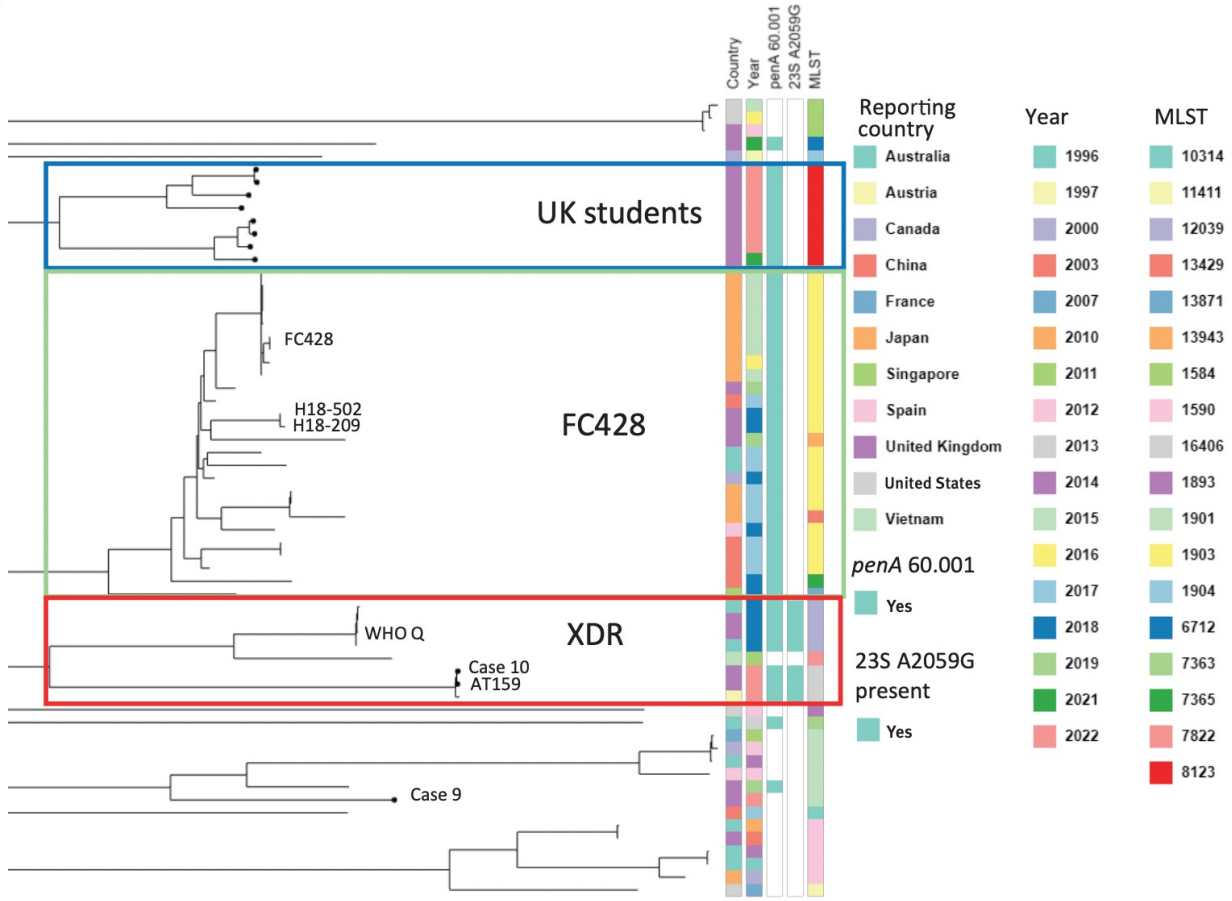

Conclusions

- Need more antibiotic development—and thinking about how best to introduce and use them
- Need more tools for prevention
  - DoxyPEP: short term benefit? Long term costs?
- Better diagnostics
  - Rapid AMR diagnostics based on phenotype?
- Better surveillance: by identifying where the problems originate, can we slow the emergence and global spread of resistance?

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Thank you!

NIH National Institute of Allergy and Infectious Diseases

CDC Centers for Disease Control and Prevention

wellcome

DORIS DUKE CHARITABLE FOUNDATION

RICHARD AND SUSAN Smith Family Foundation

BROADIGNITE