

Biomedical Interventions to Control STIs

Jeffrey D. Klausner, MD, MPH

Professor of Medicine and Public Health

Attending Physician Ronald Reagan Medical Center

Division of Infectious Diseases: Global Health

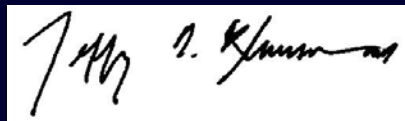
David Geffen School of Medicine

Department of Epidemiology

Karin and Jonathan Fielding School of Public Health

Disclosures

- Advisory fees from Visby Medical, Luminostics, BioFire, Shield Bio, SpeedX and Cepheid
- Donated research supplies from Hologic, Cepheid, and SpeedX
- Research grants from NIH, NSF, AIDS Healthcare Foundation, Gilead Sciences, Abbvie and Hologic

A handwritten signature in black ink on a white rectangular background. The signature appears to read "Jeffrey D. Klausner".

JDKlausner@mednet.ucla.edu

Outline

- Key theories
- Antibiotics
 - Novel antibiotics
 - Older ones for treatment and prevention
- Diagnostics
- Vaccines
- Condoms
- Male circumcision

Reproductive number

- β = transmission efficiency
- C = contact rate
- D = duration of infectiousness

Goal: Reproductive # $(\beta \times c \times d) < 1$

Core Group Theory

- Gonorrhea prevalence is $< 1\%$ overall
- $R_0 < 1$
- A core sub-population must exist to sustain endemicity

Dynamics and Control of the Transmission of Gonorrhea

JAMES A. YORKE, PhD, HERBERT W. HETHCOTE, PhD, AND ANNETT NOLD, PhD

Calculations revealed that approximately a third of the reported cases of gonorrhea in women during 1973-1975 were discoveries of the screening program. Theoretical models and epidemiologic data showed that the prevalence of gonorrhea adjusts rapidly to changes in social behavior, medical treatment, and control programs, that prevalence oscillates seasonally around an equilibrium state determined by the current social and medical conditions, and that this equilibrium moves as epidemiologic conditions change. The incidence of gonorrhea is theoretically limited by saturation in a sexually active core population, and this core causes gonorrhea to remain endemic.

GONORRHEA is a worldwide health problem. The U. S. Public Health Service estimates that there are about 2.6 million cases annually of infection with *Neisseria gonorrhoeae* in the United States.¹ This total represents an estimate of 1.3 million treated cases in men and takes into account under-reporting by private physicians; also included in the total are approximately 1.3 million treated and untreated cases in women.

Gonorrhea has distinct epidemiologic characteristics that must be considered in the development of a conceptual model. Only the sexually active individuals in a community who could be infected by their contacts need be considered. Since individuals do not recover spontaneously from gonorrhea for a long time after exposure, many infected persons remain infectious until they receive antibiotic treatment.² Since little immunity is

From the Institute for Physical Science and Technology, University of Maryland, College Park, Maryland, and the Department of Mathematics, The University of Iowa, Iowa City, Iowa

derived from having been infected, most treated individuals are susceptible again as soon as the antibiotics have left the body.

Since gonorrhea differs from frequently modeled infectious diseases, such as influenza and measles, where the infective levels are limited by the accumulation of immune individuals, new models for gonorrhea had to be developed. Cooke and Yorke³ analyzed a mathematical model for gonorrhea. Reynolds and Chan⁴ developed a model for gonorrhea in the United States, estimated the model parameters, and projected the prevalences for women and men, both without and with controls. Hethcote⁵ developed communicable disease models and used a host-vector model in a calculation for control of gonorrhea. Lajmanovich and Yorke⁶ presented a very general model for gonorrhea. The purpose of this paper is to develop useful theoretical concepts about the dynamics of transmission of gonorrhea and its control.

The Screening Program

In fiscal year 1972 a program was begun in the United States for bacteriologic culturing of cervical specimens from women to detect asymptomatic infection with *N. gonorrhoeae*.¹ In this report we estimate the number of women who are being discovered to have gonococcal infection but who would not be discovered without the screening program. We define a new case report as "diagnostic" when the (positive) culture test was administered to the woman because she had symptoms suggesting gonococcal infection or because she had had sexual contact with an individual thought to be infected. Screening program "discoveries" are those cases reported because of positive results of culture tests performed as

Partially supported by Center for Disease Control Contract 200-76-0613, and National Institute of Allergy and Infectious Diseases Grant AI 13233-01.

The authors thank the personnel of the Venereal Disease Control Division, Bureau of State Services, Center for Disease Control, Atlanta, Georgia, for valuable discussions and suggestions. Reprint requests: Herbert W. Hethcote, Ph.D., Department of Mathematics, The University of Iowa, Iowa City, Iowa 52242.

Received for publication on August 5, 1977, and in revised form on January 3, 1978.

The results in this paper are the responsibility of the authors and should not be taken as the policy of the Venereal Disease Control Division, Center for Disease Control, U. S. Public Health Service.

0148-5717-78-0400-0051 \$00.75 ©The American Venereal Disease Association

CDC Declares Gonorrhea Urgent Threat



40 years ago...

W.H.O. ACTS TO CURB A NEW STRAIN OF V.D.
By LAWRENCE K. ALTMAN Special to The New York Times
New York Times (1857-Current file); Jan 9, 1977; ProQuest Historical Newspapers
pg. 27

W.H.O. ACTS TO CURB A NEW STRAIN OF V.D.

Laboratories Asked to Begin Tests
To Detect a Type of Gonorrhea
That Resists Penicillin

By LAWRENCE K. ALTMAN
Special to The New York Times

GENEVA, Jan. 8—In an urgent step to prevent the development of a major international health problem, the World Health Organization has asked laboratories throughout the world to begin tests to detect a new penicillin-resistant strain of gonorrhea.

Already, the new type of venereal disease has infected Americans in at least 15 states and people in 10 other countries, and it threatens to become the dominant type among the millions of cases of gonorrhea that occur each year throughout the world.

"The volume of air travel throughout the world and the limited surveillance for this organism to date [means] every area of the world must view this as a real or potential problem," the World Health Organization said in a statement sent to health officials in 150 countries that are members of the organization, and to thousands of scientists.

Incurable new VD could strike, say feds

RESISTANT VD STRAIN ON RISE IN N.Y.

New gonorrhea fear

UNITED PRESS INTERNATIONAL

ATLANTA—A hard-to-kill gonorrhea strain is gaining a foothold in New York and in two other areas of the country, forcing doctors to abandon traditional penicillin therapy for more expensive antibiotics, federal health officials said yesterday.

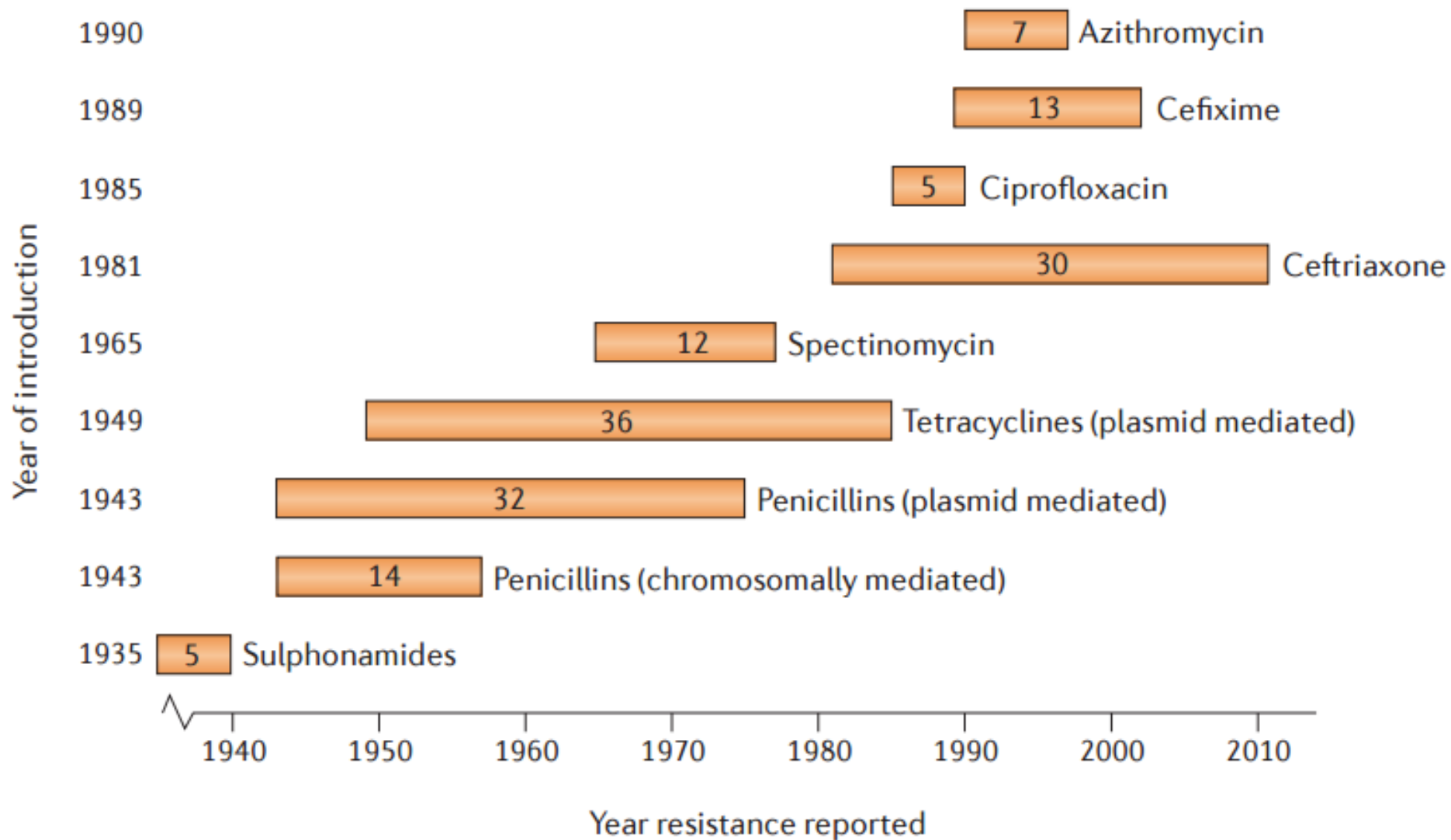
The resistant strain is also on the rise in South Florida

and Los Angeles, said Dr. Jonathan Zenilman, of the national Centers for Disease Control. "In certain parts of the country, penicillin as the drug of choice is becoming a thing of the past," he said.

The resistant strain, PPNG (for penicillinase-producing *Neisseria gonorrhea*), produces an enzyme that destroys the therapeutic effects of penicillin.

New York City reported 550 cases in the first six months of 1985. About one million cases of all strains are reported each year to the CDC.

Doctors are treating the new strain with the antibiotic spectinomycin and a newer drug, ceftriaxone, Zenilman said. But the new treatments are "eight times more expensive," he said.



New Drugs

- Solithromycin (halted)
- Gepotidacin (phase 3)
 - ClinicalTrials.gov Identifier: NCT04010539
- Zoliflodacin (phase 3)
 - ClinicalTrials.gov Identifier: NCT03959527

Old Drugs

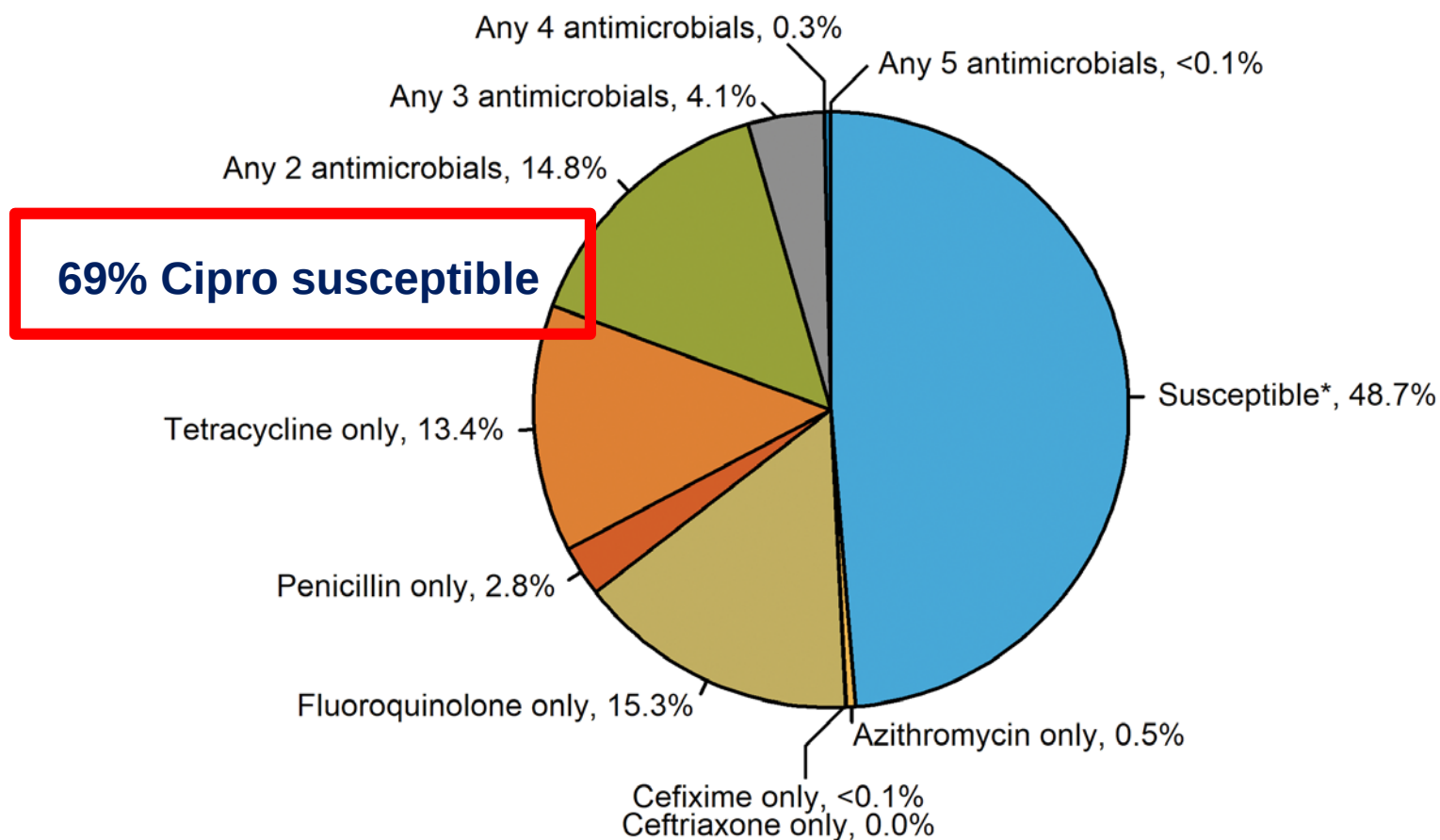
- Ertapenem IM/IV 1000 MG
- Fosfomycin Oral Suspension
 - ClinicalTrials.gov Identifier: NCT03294395
- Ciprofloxacin for NG treatment
 - ClinicalTrials.gov Identifier: NCT02961751
- Doxycycline for rectal CT treatment
 - ClinicalTrials.gov Identifier: NCT03608774
- Doxycycline for STI prevention
 - Seattle/San Francisco, Vancouver, Sydney/
Melbourne, Paris and Kenya

Old Drugs

- Ertapenem IM/IV 1000 MG
- Fosfomycin Oral Suspension
 - ClinicalTrials.gov Identifier: NCT03294395
- Ciprofloxacin for NG treatment
 - ClinicalTrials.gov Identifier: NCT02961751
- Doxycycline for rectal CT treatment
 - ClinicalTrials.gov Identifier: NCT03608774
- Doxycycline for STI prevention
 - Seattle/San Francisco, Vancouver, Sydney/
Melbourne, Paris and Kenya

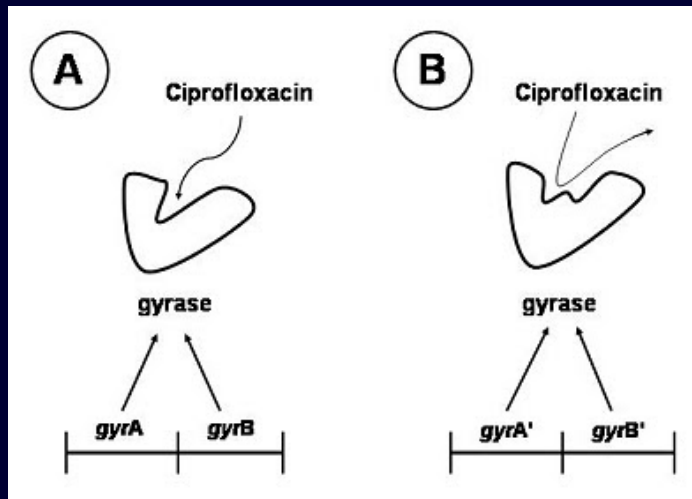
Figure 32. Resistance or Elevated MIC Patterns of *Neisseria gonorrhoeae* Isolates to Antimicrobials, Gonococcal Isolate Surveillance Project (GISP), 2018

A. By Number of Antimicrobials



Gyrase A Serine 91

Ciprofloxacin targets the DNA Gyrase subunit



Ser-91
-TCC-
↓
-TTC-
Phe-91

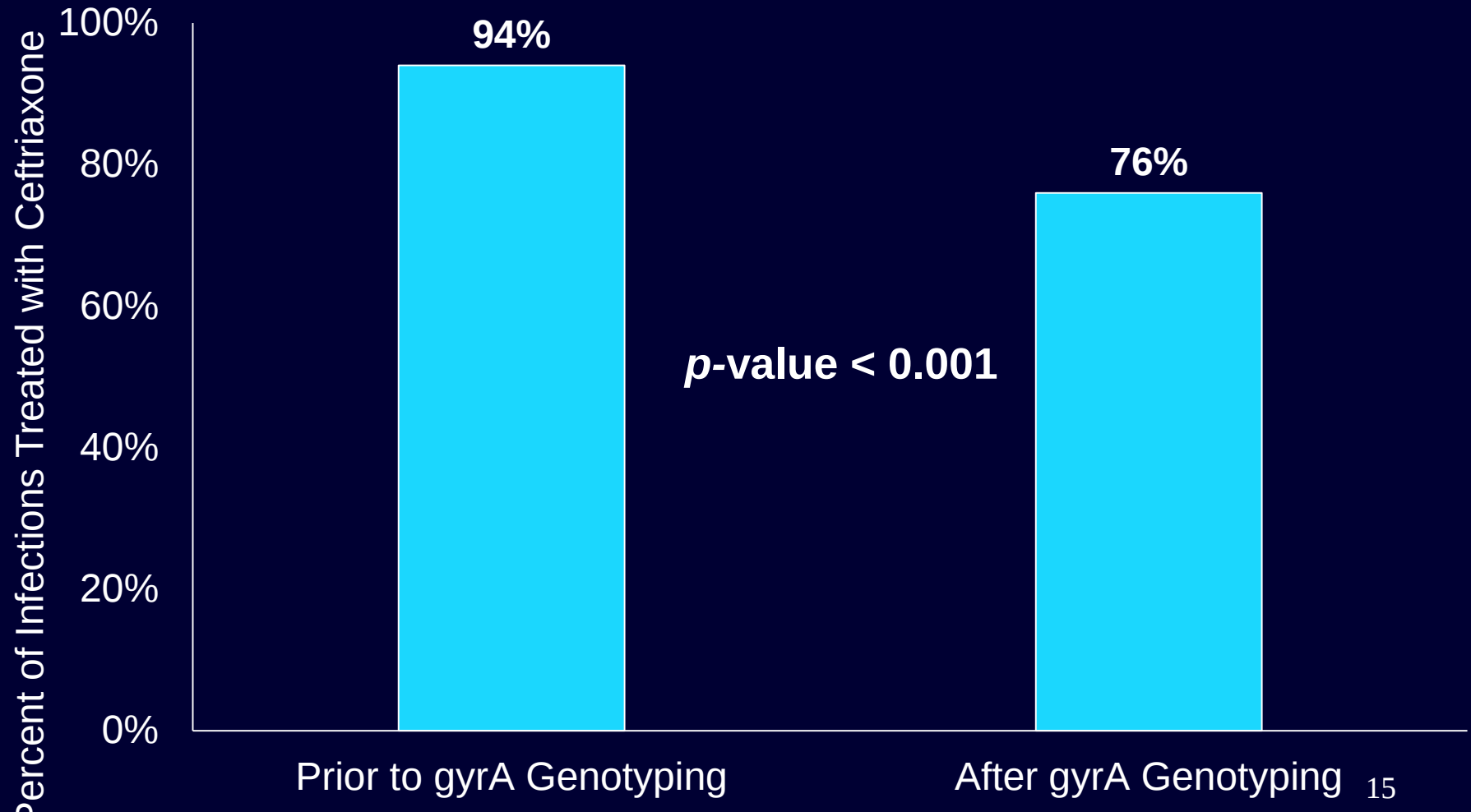
N > 5000 isolates, 1996-2006, 16 countries
Mutated Ser-91 (S91F) is necessary and sufficient
Detected resistance in 98.6% of infections

GyrA Serine 91 Testing UCLA Health 2015-2017

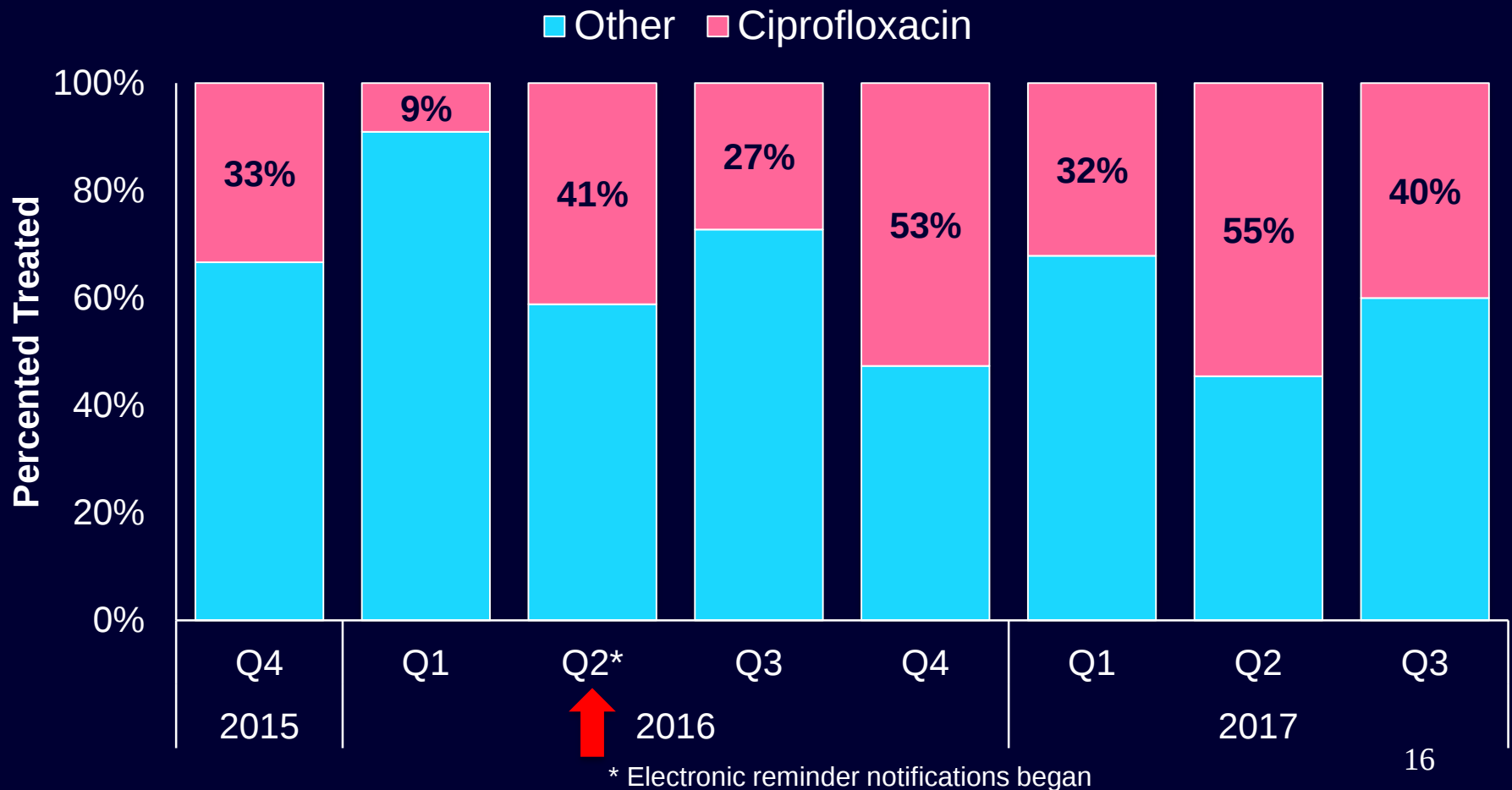
- November 2015, UCLA Health began reflex *gyrA* serine 91 genotyping all *Neisseria gonorrhoeae* nucleic acid positive clinical specimens
- UCLA Health serves > 500,000 lives



Decline in Ceftriaxone/Azithro Use for Treatment of *Neisseria gonorrhoeae* Infections with Implementation of *gyrA* Genotyping



Ciprofloxacin Use for *Neisseria gonorrhoeae* Infection November 2015 - September 2017 Among Non-Empirically Treated Wild Type *GyrA* Infections



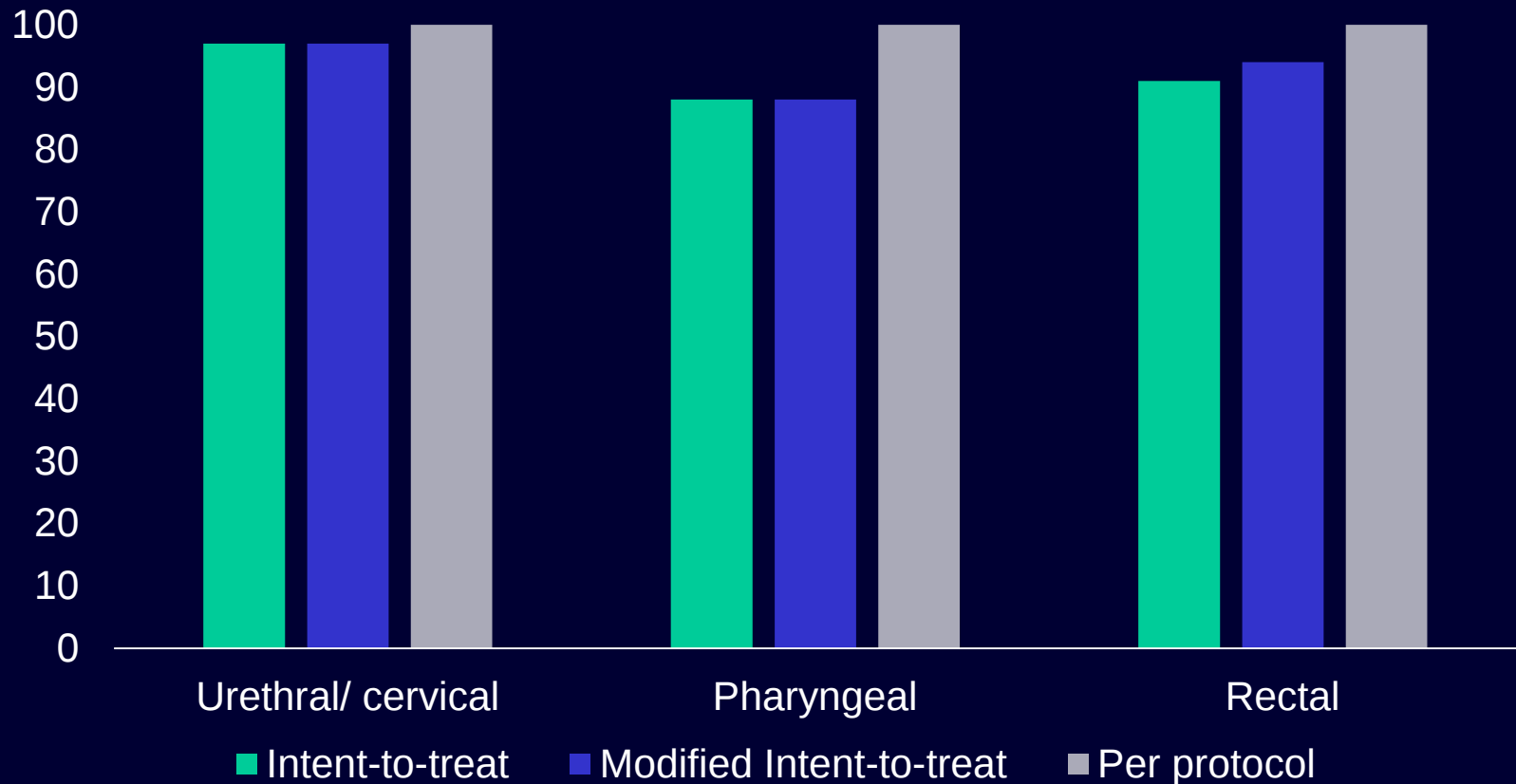
NIH Clinical Outcome Study

- Prospective clinical outcome study of Cipro 500 mg single dose oral therapy in *gyrA* wild type NG infections
- 8 clinics across the U.S.
- 117 culture-positive wild type infections at various anatomic sites
- Culture test of cure at 5-7 days

100% Cure Regardless of Anatomic Site

Analysis Population	Statistic	Cervical/ Urethral	Rectal	Pharyngeal	All anatomic sites
Intent-to-Treat	Number of Infections with Microbiological cure, n	38	81	35	154
	Number of infections, N	39	89	40	168
	Microbiological cure, %	97.4	91	87.5	91.7
	95% CI, %	90.4, 100.0	85.0, 100.0	77.0, 100.0	87.6, 100.0
Microbiological Intent-to-Treat	Number of Infections with Microbiological cure, n	33	74	14	121
	Number of infections, N	34	79	16	129
	Microbiological cure, %	97.1	93.7	87.5	93.8
	95% CI, %	89.1, 100.0	89.0, 100.0	69.5, 100.0	89.6, 100.0
Per-Protocol	Number of Infections with Microbiological cure, n	30	73	14	117
	Number of infections, N	30	73	14	117
	Microbiological cure, %	100	100	100	100
	95% CI, %	90.5, 100.0	96.0, 100.0	80.7, 100.0	97.5, 100.0

Percent Cure by Anatomic Site and Study Population

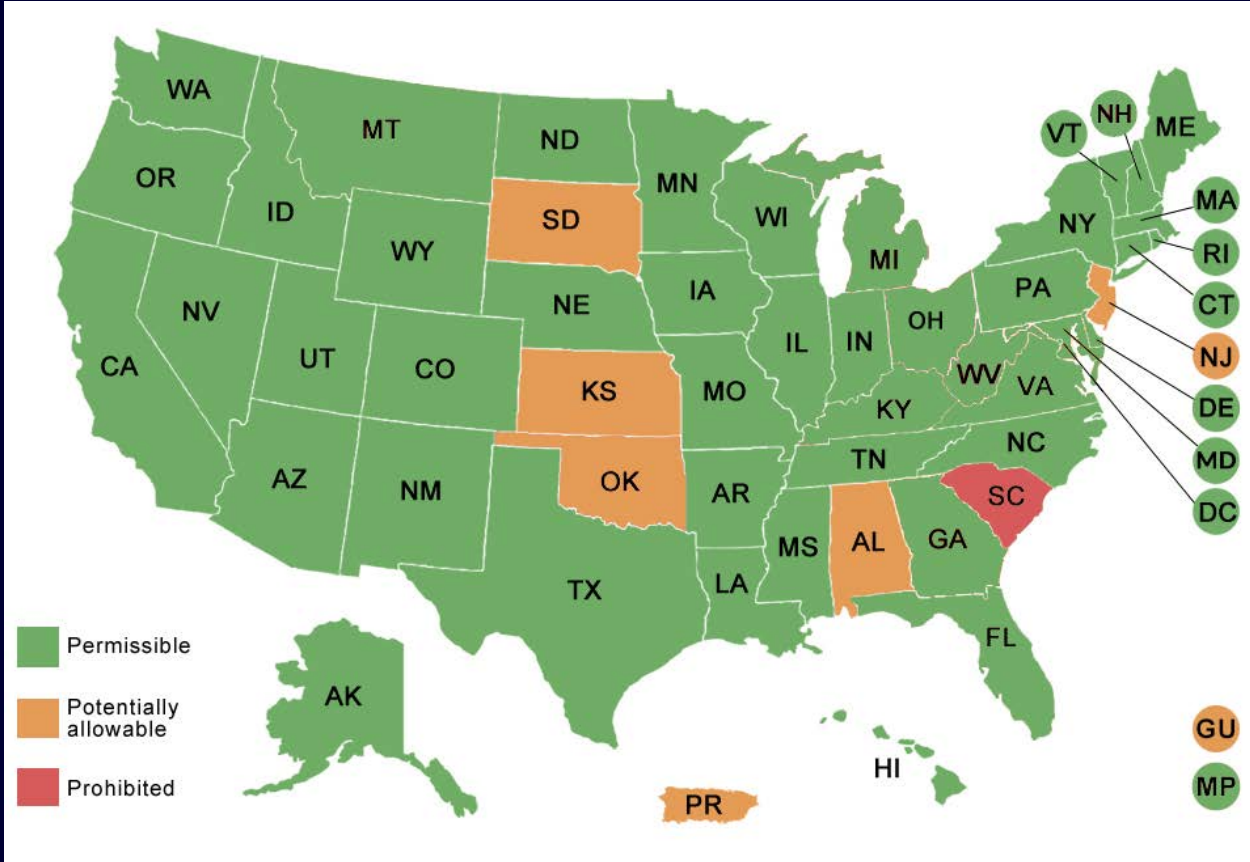


Advantages to Resistance-Guided Therapy with Ciprofloxacin

- Inexpensive
- Oral therapy
- Easy to use for partner treatment
- Safe for partner treatment
- Highly efficacious at ALL anatomic sites of infection
- Might reduce selection pressure and “save” ceftriaxone

...new companies bringing NG/ NG-resistance assays

Expedited Partner Therapy



CDC: EPT is a “useful option” to further partner treatment, particularly for male partners of women with chlamydia or gonorrhea

Doxycycline prophylaxis

- Traveler's diarrhea (Stack, Gastroenterology, 1979)
 - Doxy 100 mg daily = 85% efficacy
- Scrub typhus (Twartz, JID, 1982)
 - Doxy 200 mg weekly = 89% efficacy
- Leptospirosis (Takafuji, NEJM, 1984)
 - Doxy 200 mg weekly = 95% efficacy
- Lyme disease (Nadelman, NEJM, 2001)
 - Doxy 200 mg x 1 = 87% efficacy

Doxycycline Prophylaxis to Reduce Incident Syphilis among HIV-Infected Men Who Have Sex With Men Who Continue to Engage in High-Risk Sex: A Randomized, Controlled Pilot Study

Robert K. Bolan, MD, Matthew R. Beymer, MPH,*† Robert E. Weiss, PhD,‡ Risa P. Flynn,*
Arleen A. Leibowitz, PhD,§ and Jeffrey D. Klausner, MD, MPH¶*

- Daily 100 mg dose vs. behavioral intervention
- N = 30 men
- 48 week total follow-up



73% reduction in any STD

TABLE 3. Results of GLMMs for STDs (n = 30)*

Outcome	No. Visits With Outcome		Follow-Up Analysis (Through 48 wk)		On-Drug Analysis (Through 36 wk)	
	Doxy Arm	CM Arm	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)
STI contraction						
Gonorrhea or chlamydia only	4	8	0.18	0.36 (0.08–1.56)	0.25	0.42 (0.09–1.89)
Syphilis only	2	7	0.10	0.24 (0.04–1.33)	0.16	0.27 (0.04–1.73)
Any STD (gonorrhea, chlamydia, syphilis, or any combination thereof)	6	15	0.02	0.27 (0.09–0.83)	0.07	0.30 (0.08–1.09)

*ORs or rate ratios below 1 indicate the decreased odds/rates in the doxycycline arm compared with CM arm; OR or rate ratios above 1 indicate increased odds/rates in the doxy arm compared with the CM arm.

Trend toward 73% reduction in syphilis



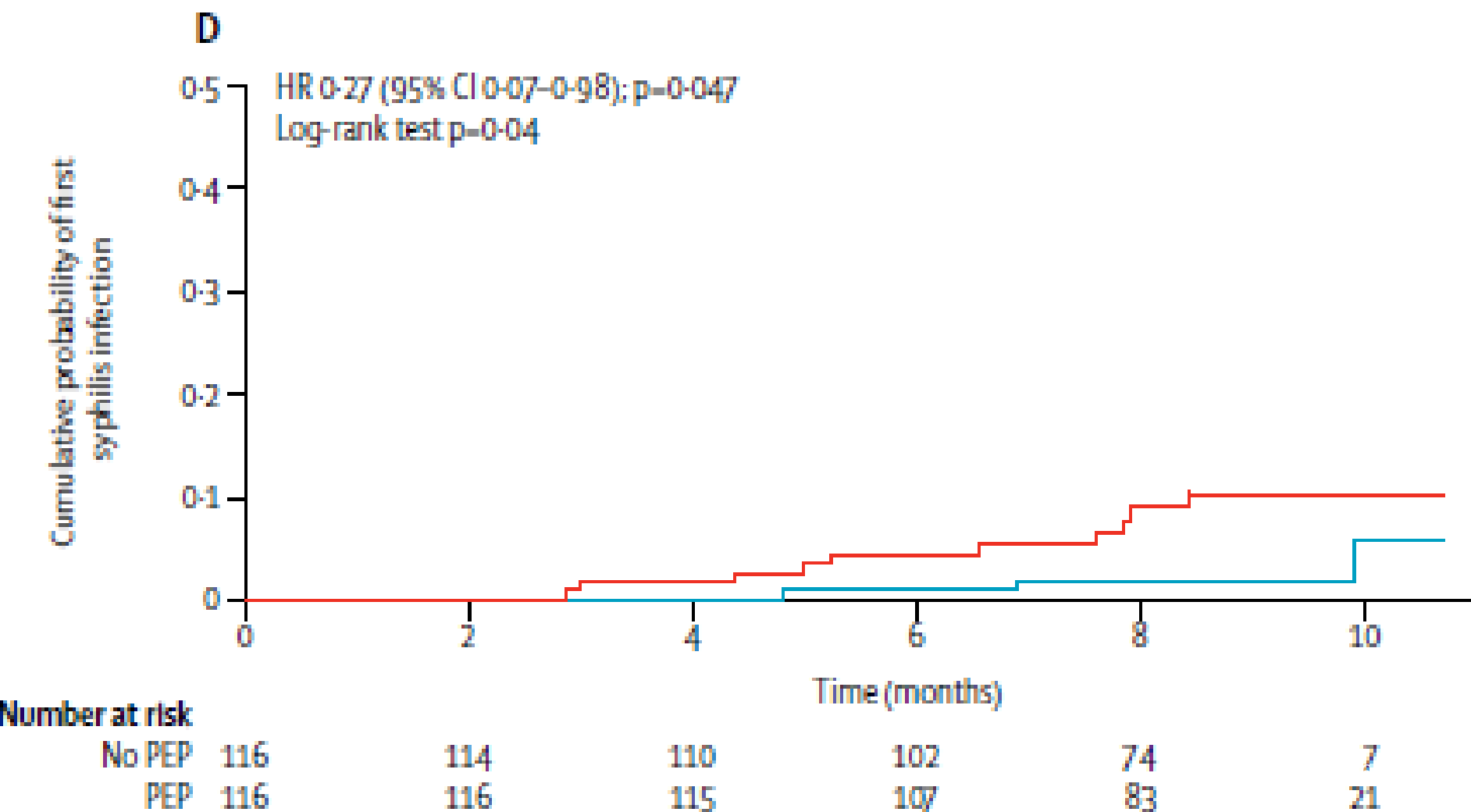
Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial

*Jean-Michel Molina, Isabelle Charreau, Christian Chidiac, Gilles Pialoux, Eric Cua, Constance Delaugerre, Catherine Capitant, Daniela Rojas-Castro, Julien Fonsart, Béatrice Bercot, Cécile Bébear, Laurent Cotte, Olivier Robineau, François Raffi, Pierre Charbonneau, Alexandre Aslan, Julie Chas, Laurence Niedbalski, Bruno Spire, Luis Sagaon-Teyssier, Diane Carette, Soizic Le Mestre, Veronique Doré, Laurence Meyer, for the ANRS IPERGAY Study Group**

**On Demand PEP with Doxycycline
(200 mg ~ 24h after sex, up to 72h)***

PEP with doxycycline reduced the overall incidence of bacterial STIs by 47% in MSM on PrEP (8.7 months of FU)

73% reduction in syphilis incidence



84% U.S. social media app users interested in doxy for STI prevention, 2019

High Interest in Doxycycline for Sexually Transmitted Infection Postexposure Prophylaxis in a Multicity Survey of Men Who Have Sex With Men Using a Social Networking Application.

Spinelli MA, Scott HM¹, Vittinghoff E², Liu AY¹, Coleman K¹, Buchbinder SP¹.

Author information

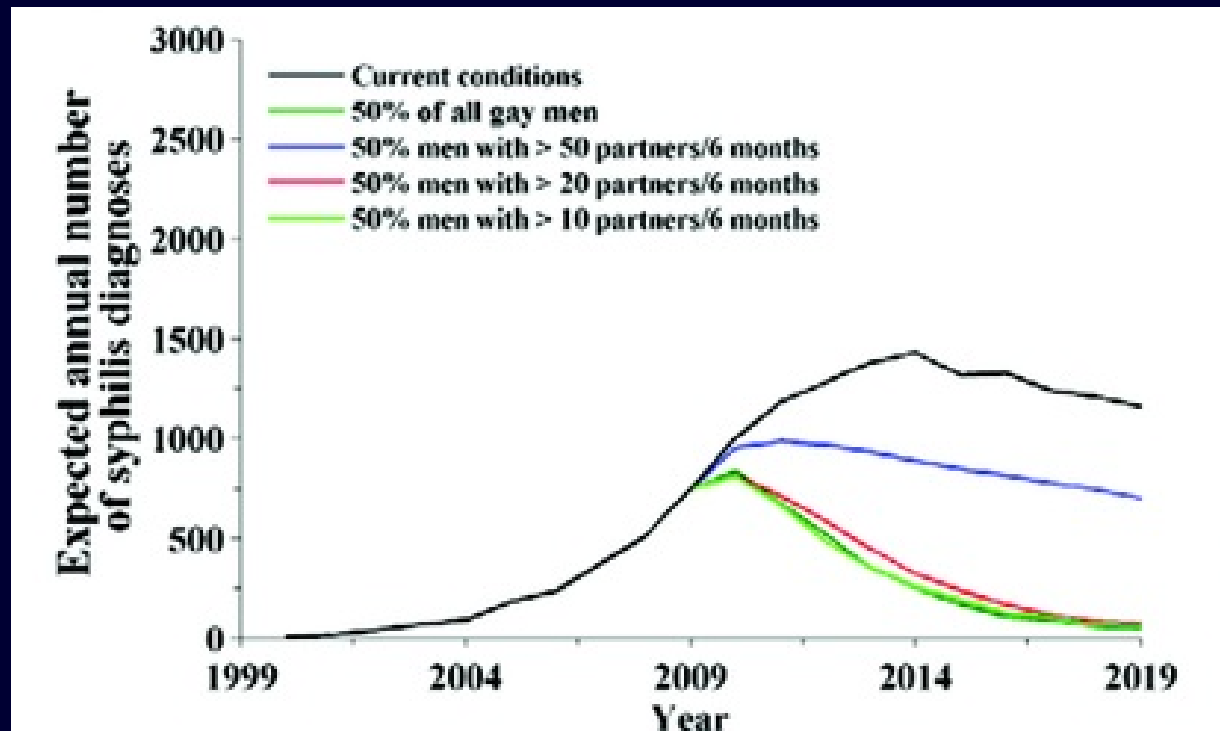
1 Bridge HIV, San Francisco Department of Public Health.

2 Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA.

Abstract

Current strategies to prevent sexually transmitted infections (STIs) are not controlling the epidemic. The efficacy of doxycycline STI postexposure prophylaxis shows promise in pilot studies, but wider acceptability is unknown. A majority (84%) of diverse individuals using a gay social networking application were interested in doxycycline STI postexposure prophylaxis. Doxycycline STI postexposure prophylaxis should be examined in larger trials.

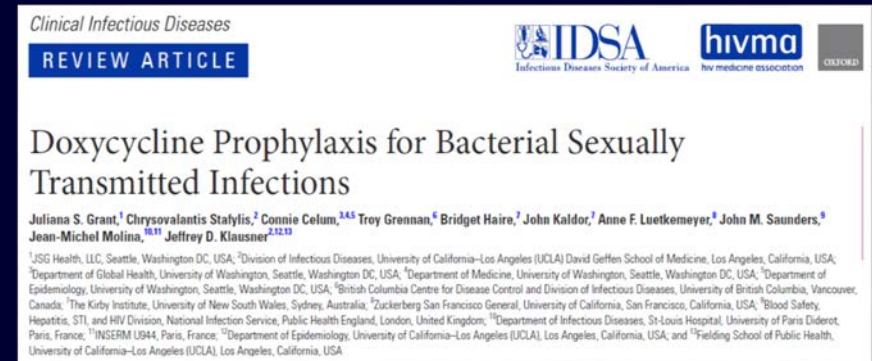
**70% use-effectiveness by 50% of gay men
predicted to reduce syphilis cases by
~50% after 12 months and 85% after 10 years**



**More prevention efforts gained targeting men
with higher sexual activity**

Doxy Concerns

- Resistance—other pathogens like *Staphylococcal aureus* (MRSA), Gram-negative enteric infections
 - No resistance in syphilis or chlamydia
- Long-term safety, microbiome
- Golden and Handsfield raised issues of risk vs. benefit: preventing a preventable disease vs. complications; cost-effectiveness



Point-of-Care Diagnostics

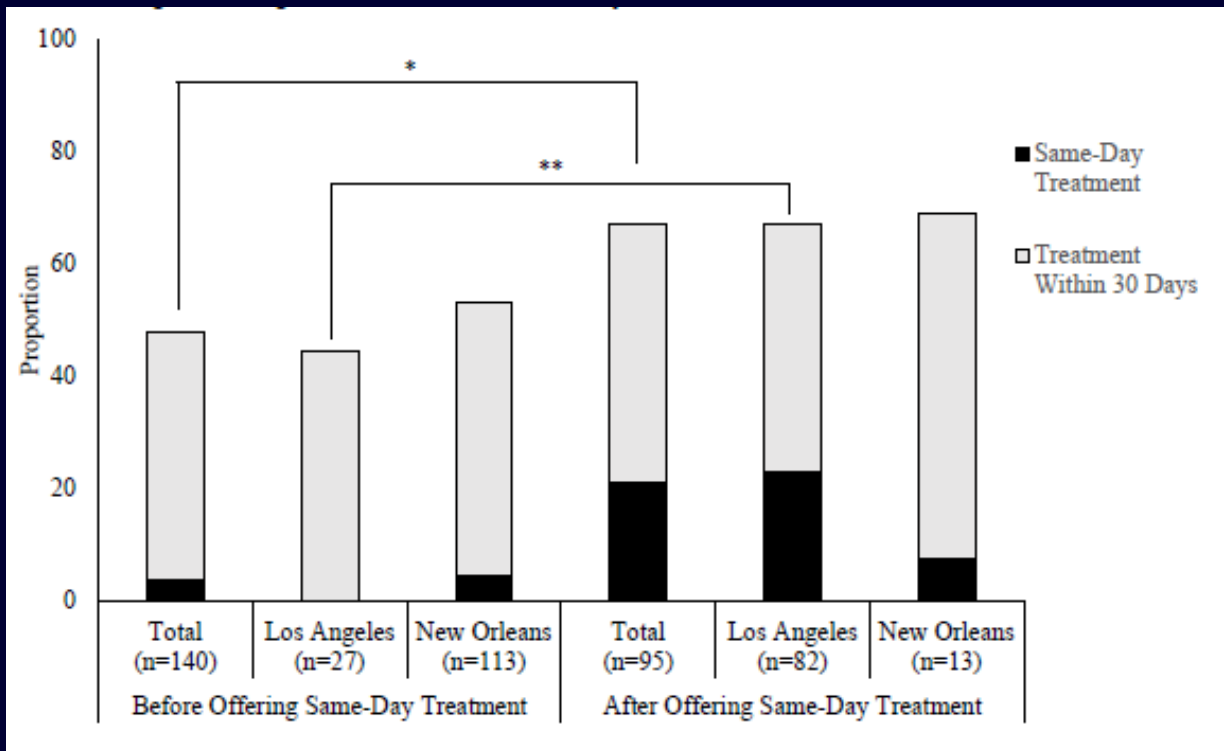


Ft. Lauderdale, New York City, Los Angeles, Boston, Mississippi

Same-day testing = same-day treatment

Safety and Effectiveness of Same-Day *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Screening and Treatment among Gay, Bisexual, Transgender, and Homeless Youth in Los Angeles, California and New Orleans, Louisiana

Erin Keizur;Cameron Goldbeck;Gabriella Vavala;Adriana Romero;Manuel Ocasio;Jasmine Fournier;Sung-Jae Lee;Sue-Ellen Abdalian;Mary Rotheram;Jeffrey Klausner;



Rapid 25-minute point-of-care

Binx



510K cleared August 13, 2019

Visby Medical



Clin Trials NCT03852316

Point-of-Care Rapid Treponemal Test



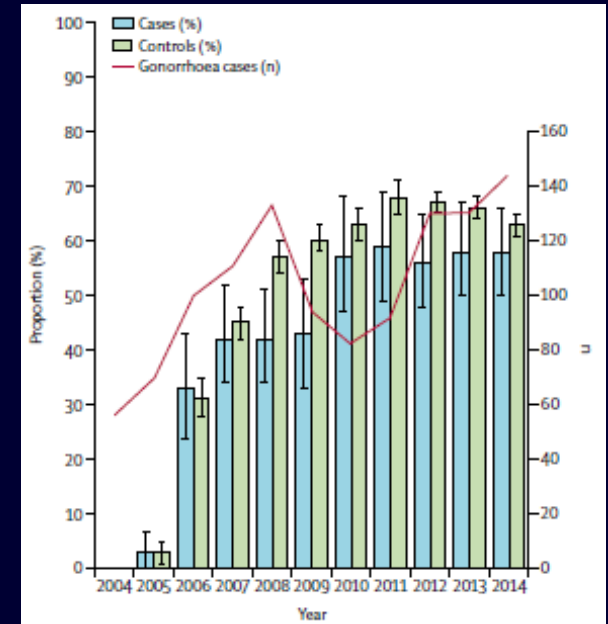
FDA-cleared Syphilis Health Check

Can testing decrease STIs at population level?

- Some evidence from San Francisco, Australia for syphilis
- Additional evidence from Paris for syphilis (14% decline 2017→ 2018)
- Evidence chlamydia screening reduces sequelae but not prevalence (Hocking et al, 63 clinic RCT)
- NG screening → drive resistance, labelling, cost

Vaccines

- MenB vaccine for gonorrhea
 - 30-40% protection 4 epi studies
 - NZ, Alberta, Norway, Cuba
 - NIH July 2020 and Australia
- NG peptide mimic vaccine (Rice)
- Phase 1 *C. trachomatis* vaccine (Abraham, Lancet Inf Dis, 2019)
- Immunogenicity *T. pallidum*-0751 adhesion (Cameron)



Condoms



Male Circumcision

Association between male circumcision and incidence of syphilis in men and women: a prospective study in HIV-1 serodiscordant heterosexual African couples

*Jillian Pintye, Jared M Baeten, Lisa E Manhart, Connie Celum, Allan Ronald, Nelly Mugo, Andrew Mujugira, Craig Cohen, Edwin Were, Elizabeth Bukusi, James Kiarie, Renee Heffron, for the Partners PrEP Study Team**

42% reduction in syphilis incidence

Summary

- Antibiotics
 - New antibiotics forthcoming
 - Smarter use of older antibiotics
 - Resistance-guided treatment of gonorrhea
 - Syphilis prophylaxis

Summary

- Diagnostics
 - Point-of-care diagnostics, rapid tests
- Vaccines
 - Promising vaccines ... but a long way off
- Condoms and male circumcision

Paradigm shift

From personal responsibility ...
to public health accountability

Thank you

