



National Network of
STD Clinical Prevention
Training Centers

Earthquakes in Management of Urethritis: Gonorrhea, Chlamydia, and Mycoplasma, Oh My!

May 16, 2024

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Faculty Disclosures

Consultant: Talis Biomedical Corporation

I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation:

- Off-label uses of antibiotics, for the purposes of *M. genitalium* treatment



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Objectives

- Discuss management of urethritis
- Distinguish relevant updates to STI epidemiology as they pertain to clinical care
- Provide clinical resources to access expert guidance on STD management at point-of care



Case

- 22-year-old cisgender man presents with 3 days of dysuria and penile discharge. He has sex with cisgender women and cisgender men.
- ***What evaluation (specimen types and tests) would you recommend, and how would you treat him?***

... Diagnostic stewardship is necessary to reduce unnecessary testing

OBJECTIVE EVIDENCE OF URETHRITIS



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Massachusetts Department of Public Health
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Objective Evidence of Urethritis

If microscopy is unavailable, urethritis can be documented by any of the following signs or laboratory tests:

- Mucoid, mucopurulent, or purulent discharge on exam
- Positive leukocyte esterase test on first-void urine
- Microscopic examination of sediment from a spun first-void urine demonstrating ≥ 10 WBCs/HPF

... we are headed into an era where you won't always be able to count on cephalosporins

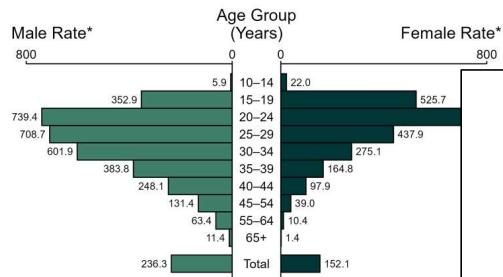
IF THIS WERE GONORRHEA ...



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Gonorrhea is concentrated in ...

Gonorrhea — Rates of Reported Cases by Age Group and Sex, United States, 2022

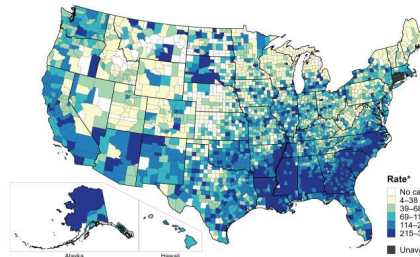


* Per 100,000

NOTE: Total includes cases of all ages, including those with unknown age.



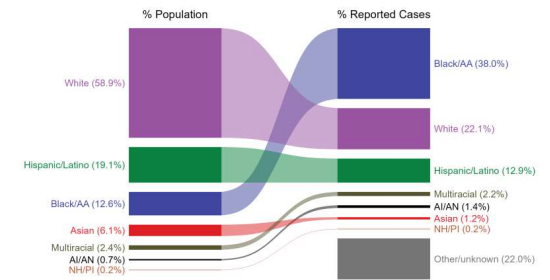
Gonorrhea — Rates of Reported Cases by County, United States, 2022



* Per 100,000



Gonorrhea — Total Population and Reported Cases by Race/Hispanic Ethnicity, United States, 2022



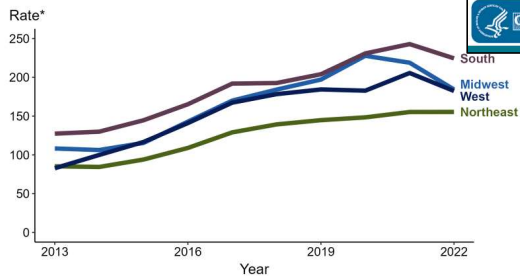
* Per 100,000

NOTE: In 2022, a total of 142,317 gonorrhea cases (22.0%) had missing, unknown, or other race and were not reported to be of Hispanic ethnicity. These cases are included in the "other/unknown" category.

ACRONYMS: AI/AN = American Indian or Alaska Native; Black/AA = Black or African American; NH/PI = Native Hawaiian or other Pacific Islander

32

Gonorrhea — Rates of Reported Cases by Region, United States, 2013–2022



* Per 100,000

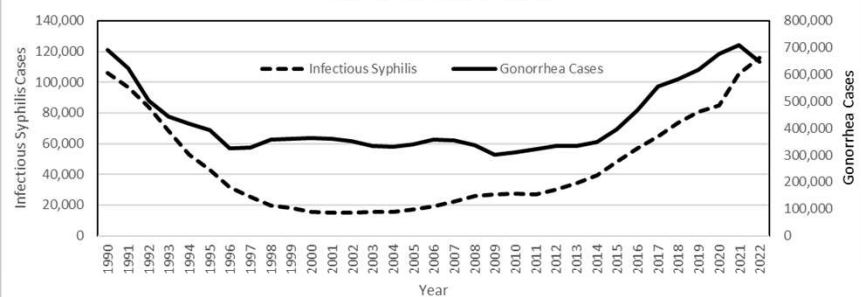


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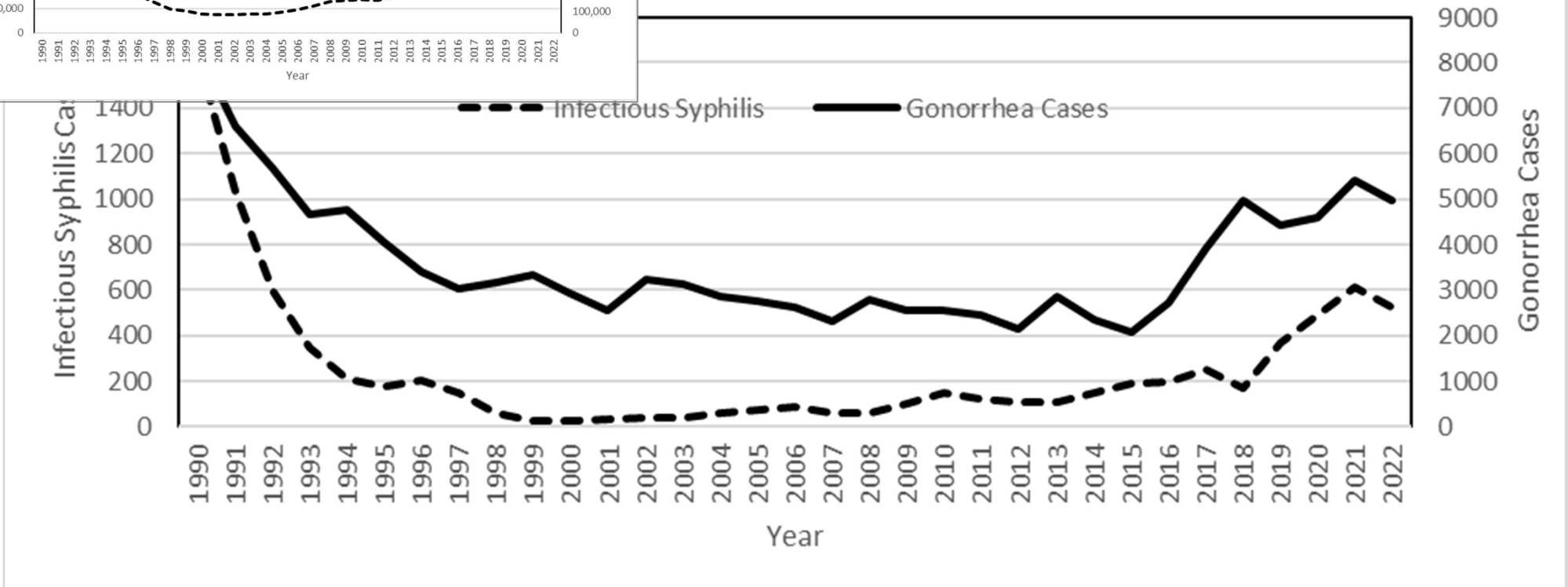
- Youth and young adults
- Southern U.S.
- Non-white populations
- ... but no one and nowhere is exempt

Connecticut: Base STI Case Report Numbers Have Almost to 1980s Levels

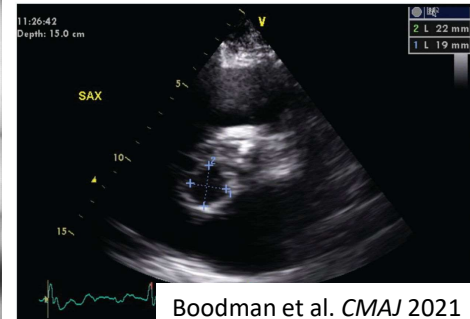
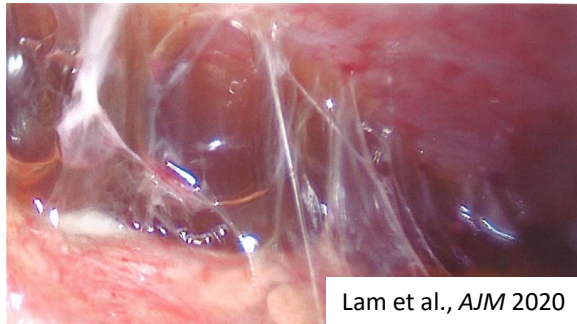
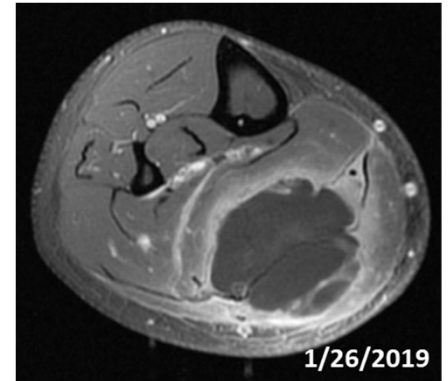
Infectious Syphilis and Gonorrhea Cases
United States 1990-2022



Infectious Syphilis and Gonorrhea Cases
Connecticut 1990-2022



Gonorrhea: Mucosal and Systemic Disease: Increase in Base Case Numbers Dictates Increase in Complex Disease



- CDC's list of antibiotic resistance threats, 2013 and 2019
- How NG evolves resistance
- Why we care more NOW

WHY MDR GONORRHEA IS AN URGENT THREAT



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CDC cares about gonorrhea ... so should we!

SET EDITION: U.S. | INTERNATIONAL | MÉRICO | ARABIC
 TV: CNN | CNN | CNN en Español | RLN

CNN Health

Home TV & Video CNN Trends U.S. World Politics Justice Entertainment Tech Health Livn

CDC sets threat levels for drug-resistant 'superbugs'
 By Miriam Falck updated 5:48 PM

Antibiotic Resistance Threats in the U.S., 2013
 Microorganisms with the threat level of URGENT:

Neisseria gonorrhoeae -- the drug-resistant form of this bacteria causes gonorrhea, the second most commonly reported infection in the United States. Gonorrhea can cause a variety of illnesses in men and women, including infertility. The CDC estimates there are 820,000 infections each year. In nearly a third of the cases, treatment of the sexually-transmitted disease, is hampered by growing antibiotic resistance.

Sexually-transmitted superbug could be major crisis

the cabinet months and

none of

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES

2019



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

Revised Dec. 2019

In 2013, CDC assessed antibiotic resistance threats and categorized the threat level of each germ as urgent, serious, or concerning. Like the 2013 report, the 2019 report assesses threats according to seven factors:

- Clinical impact
- Economic impact (when available)
- Incidence
- 10-year projection of incidence (new infections over the next 10 years)
- Transmissibility (how easily a germ spreads or causes infections)
- Availability of effective antibiotics
- Barriers to prevention

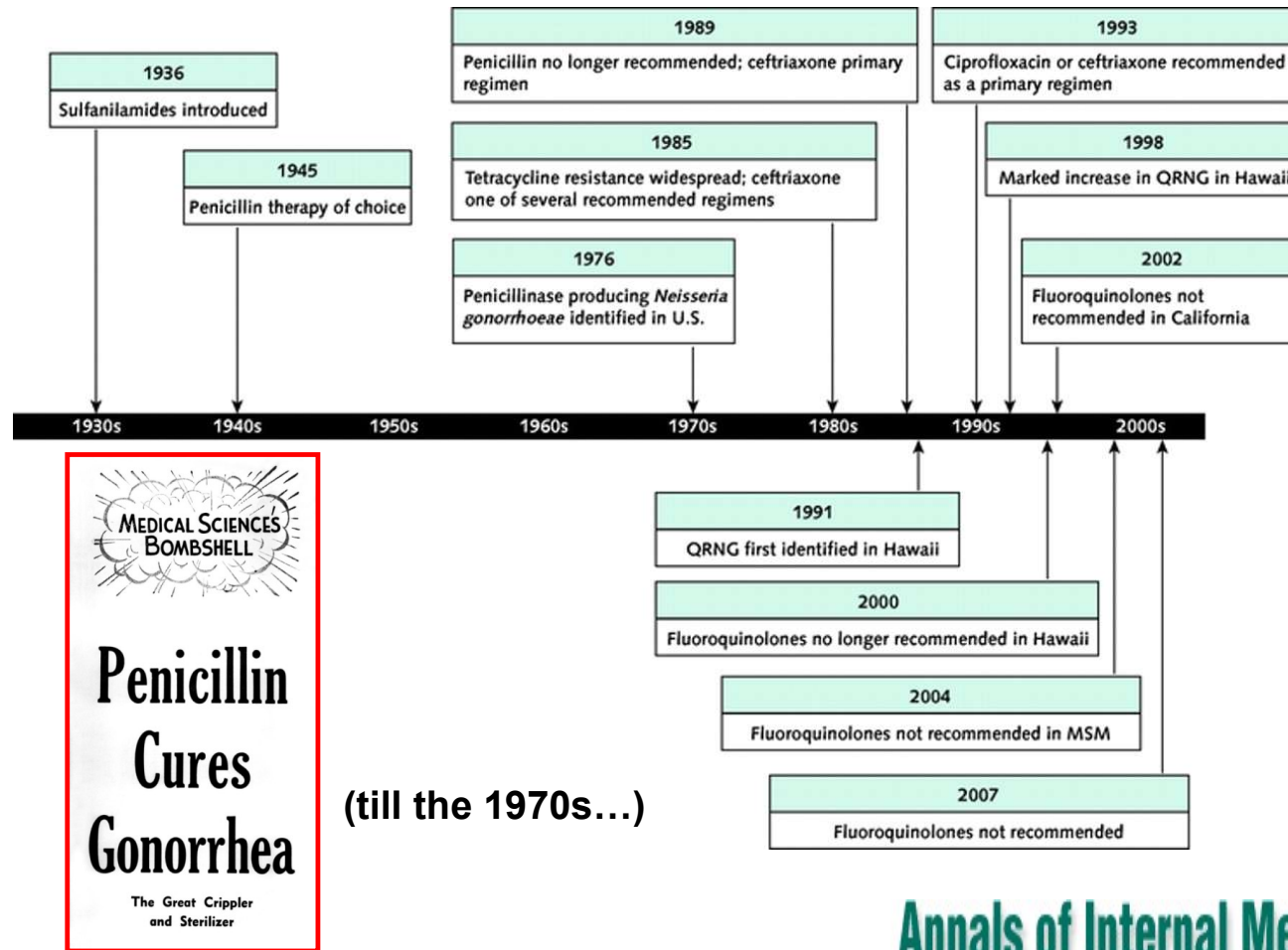
The assessment focused on domestic impact, but the international context of antibiotic resistance was taken into account in the 10-year incidence projection. Threats assigned to the urgent and serious categories require greater attention and action. Regardless of category, CDC efforts are tailored to address challenges associated with each germ.

Urgent Threats

These germs are public health threats that require urgent and aggressive action:

-  **CARBAPENEM-RESISTANT ACINETOBACTER**
-  **CANDIDA AURIS**
-  **CLOSTRIDIODES DIFFICILE**
-  **CARBAPENEM-RESISTANT ENTEROBACTERIACEAE**
-  **DRUG-RESISTANT NEISSERIA GONORRHOEAE**

Figure 126-2. Historical Perspective, Gonococcal Antimicrobial Resistance in United States



Annals of Internal Medicine

©2008 by American College of Physicians

Workowski KA et al. Ann Intern Med 2008;148:606-613

First Description of High-Level Cephalosporin Resistance

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3538–3545
0066-4804/11/\$12.00 doi:10.1128/AAC.00325-11
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Vol. 55, No. 7

Is *Neisseria gonorrhoeae* Initiating a Future Era of Untreatable Gonorrhea?: Detailed Characterization of the First Strain with High-Level Resistance to Ceftriaxone^{∇†}

Makoto Ohnishi,¹ Daniel Golparian,² Ken Shimuta,¹ Takeshi Saika,³ Shinji Hoshina,⁴
Kazuhiro Iwasaku,⁵ Shu-ichi Nakayama,¹ Jo Kitawaki,⁵ and Magnus Unemo^{2*}

National Institute of Infectious Diseases, Tokyo, Japan¹; Swedish Reference Laboratory for Pathogenic *Neisseria*, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden²; Mitsubishi Chemical Medicine Corporation, Tokyo, Japan³; Hoshina Clinic, Kyoto, Japan⁴; and the Kyoto Prefectural University of Medicine, Kyoto, Japan⁵

- Isolate came from pharynx of female CSW in Kyoto
- Cftx MIC 2 mcg/ml
 - (R) to cefixime (MIC 8 mcg/ml), β -lactams, fluoroquinolones, macrolides, tetracycline, TMP-SMX, chloramphenicol, nitrofurantoin
 - (S) to spectinomycin, rifampin, possibly aminoglycosides and tigecycline, possibly carbapenems
- Unique *penA* mosaic allele similar to that found in *N. meningitidis* and *N. flavescens* – encodes variant of PBP2
 - *mtrB*, *penB*, *ponA1* mutations also present

Decreased Cephalosporin Susceptibility



Hook, IDSA 2011

How does gonococcal resistance develop?

- Transformation plays the key role
 - *N. gonorrhoeae* highly competent for transformation throughout life cycle by its own DNA or via closely related bacteria such as other *Neisseria* commensals and *N. meningitidis*
 - **Pharyngeal gonorrhea** may act as a reservoir where asymptomatic co-colonization with other *Neisseria* species of this obligate human pathogen can occur
 - Example: Asp345A insertion in PBP2 resulting in decreased penicillin binding affinity, likely originates from commensal *Neisseria* species
 - Cross-species conjugal plasmid transfer also possible
 - *TetM* and B-lactamase-encoding plasmids relatively efficiently transferred intercellularly between *N. gonorrhoeae* strains, as well as *N. meningitidis*, *H. influenzae*, and *E. coli*

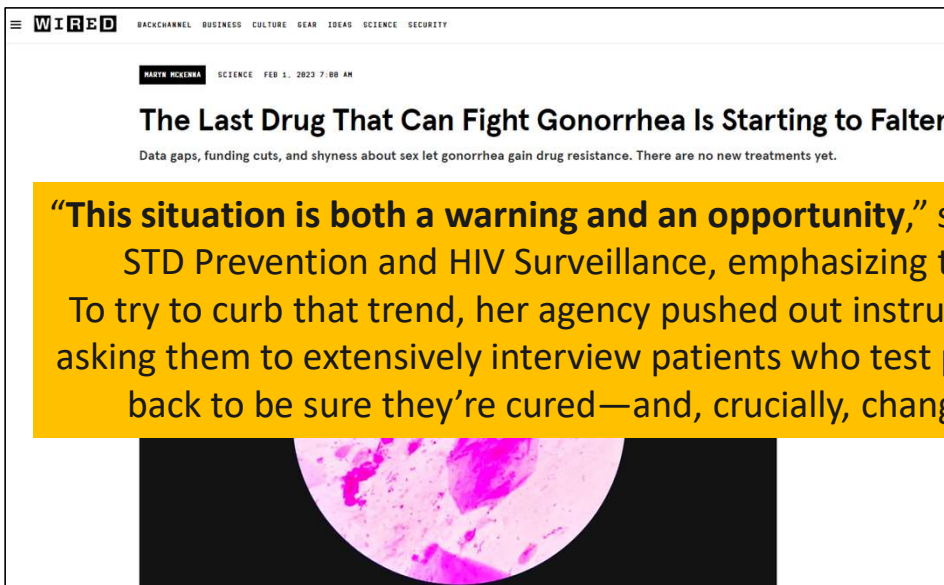
MDPH Clinical Alert: MDNS Gonorrhea

January 19, 2023

- **New guidance in Massachusetts (not nationally, nor regionally)**
 - Ensure compliance with recommended gonorrhea treatment
 - Staying at ceftriaxone 500 mg IM x 1 dose (higher if patient heavier) for now
 - Culture genital and extragenital sites of symptomatic individuals, in addition to doing NAAT
 - Discuss with your local clinical micro lab how to optimize, probably involves use of non-nutritive swab transport kits (e.g. Amies agar gel or liquid)
 - MDPH DSTDP Job Aid available
 - Test of cure with NAAT and/or culture (if sx) at all previously positive mucosal sites, 14 days after initial treatment
 - Test of reinfection with NAAT 3 months after treatment
 - Presumptive treatment of partners now limited to symptomatic partners or those who test positive
 - To spare ceftriaxone for those who need it
- **Expect disagreement between test results (NAAT more sensitive than culture) and need for increased counseling of patients**
- **Prepare for change (resisting resistance is futile, to some extent)**



Maryn McKenna, WIRED, February 1, 2023



TO AN UNFAMILIAR eye, the press release from the Massachusetts Department of Public Health two weeks ago looked pretty routine. Its language was a little unnerving, maybe, but phrased carefully: Analysts had discovered a resident with a strain of gonorrhea that showed “reduced response to multiple antibiotics,” but that person—and a second with a similar infection—had been cured.

To a civilian, the announcement may have felt like bumping over a little wave in a boat: a moment of being off-balance, then back to normal. To people in public health and medicine, it felt more like being on the *Titanic* and spotting the iceberg.

“This situation is both a warning and an opportunity,” says Kathleen Roosevelt, director of Massachusetts’ Division of STD Prevention and HIV Surveillance, emphasizing that rates of gonorrhea are at historic highs across the US. To try to curb that trend, her agency pushed out instructions to every frontline health care professional in the state, asking them to extensively interview patients who test positive, encourage those who’ve received treatment to come back to be sure they’re cured—and, crucially, change the way clinics test patients for infection to begin with.

Here is what the news actually said: A disease so old and basic that we barely think about it, even though it affects almost 700,000 Americans a year, is overcoming the last antibiotics now available to treat it. If it gains the ability to evade those drugs, our only options will be desperate searches for others that aren’t approved yet—or a return to a time when untreated gonorrhea caused crippling arthritis, blinded infants as they were born, and made men infertile through testicle damage and women via pelvic inflammatory disease.

The wearying thing, to professionals, is that they saw the iceberg coming. Gonorrhea is not like Covid, a new pathogen that took us by surprise and required heroic research

We have seen no further MDR GC

Table 1: Geographic distribution* of *N gonorrhoeae* isolates with AST collected from January 19, 2023 – January 18**, 2024 by Health Service Region*** (N=560)

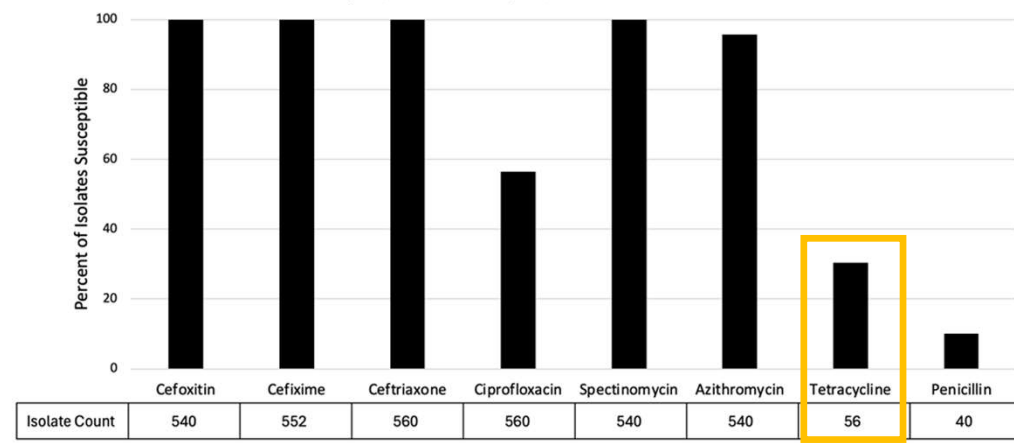
Health Service Region	Count	Percent
Western	20	3.6
Central	25	4.5
Northeast	116	20.7
Metro West	123	22.0
Boston	232	41.4
Southeast	41	7.3
Unknown	3	0.5
Total	560	100

* Based upon case residence at time of diagnosis

** When an individual patient had cultures positive from multiple anatomic sites on the same day, only one culture is represented

*** Definitions of Health Service Regions can be found at: [Health Services Regions.](#)

Figure 1: Antibiotic susceptibility results* for *N gonorrhoeae* isolates collected from January 19, 2023 - January 18, 2024 in Massachusetts**



* Antibiotic susceptibility testing was performed by e-test at the Massachusetts State Public Health Laboratory with additional testing performed at Mayo Clinic Laboratories, Massachusetts General Hospital, Lowell General Hospital, and Laboratory Corporation of America
 ** When an individual patient had cultures positive from multiple anatomic sites on the same day, only one culture is represented

<https://www.mass.gov/lists/data-and-reports-about-sexually-transmitted-infections-stis#data-from-massachusetts->

Improving interpretation and use of surveillance data for antimicrobial resistant *N. gonorrhoeae*

Kirstin Oliveira Roster

All PPML Meeting
February 29th, 2024

Roster et al., unpublished data

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC or other authors' affiliated institutions.



Project Aims

How deep is the iceberg?

Estimate the undetected disease burden upon discovery of a novel strain of gonorrhea.

Which surveillance signals indicate strain elimination?

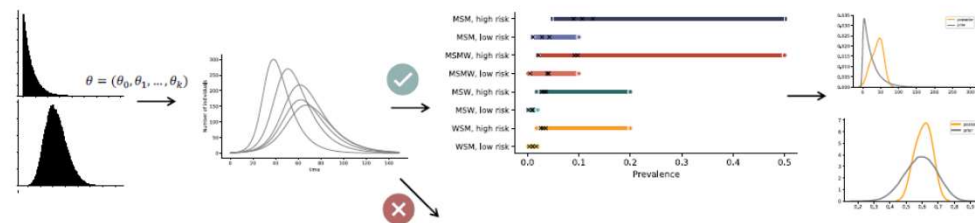
Assess the probability of strain elimination after increasing time without further detections.

Optimal strategies for resistance detection and monitoring?

Compare policies in their ability to quickly detect new strains and monitor the relative prevalence of resistant and susceptible strains.

Model calibration: Approximate Bayesian Computation

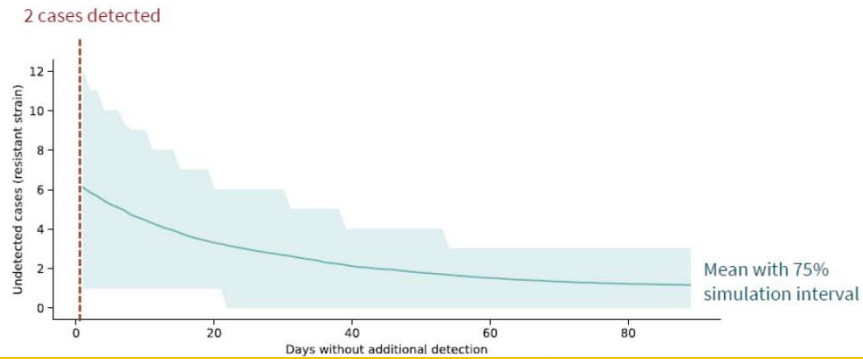
- 1 Sample parameters from prior distributions
- 2 Run simulations
- 3 Accept parameters that produce simulations with outputs within calibration target ranges
- 4 Estimate posterior distributions



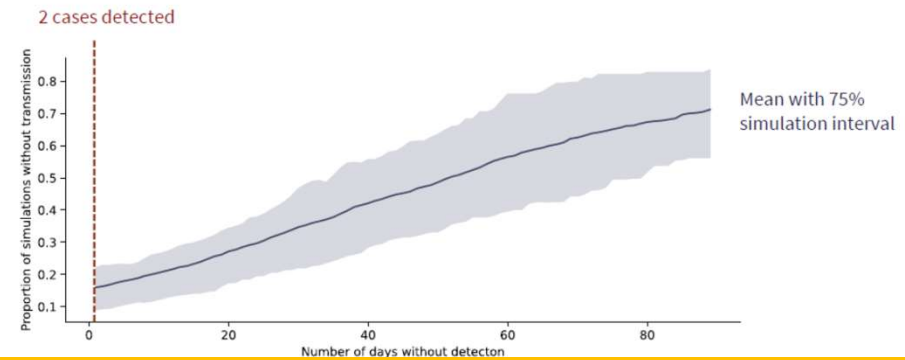
Simulations – Introducing the resistant strain



Undetected infections

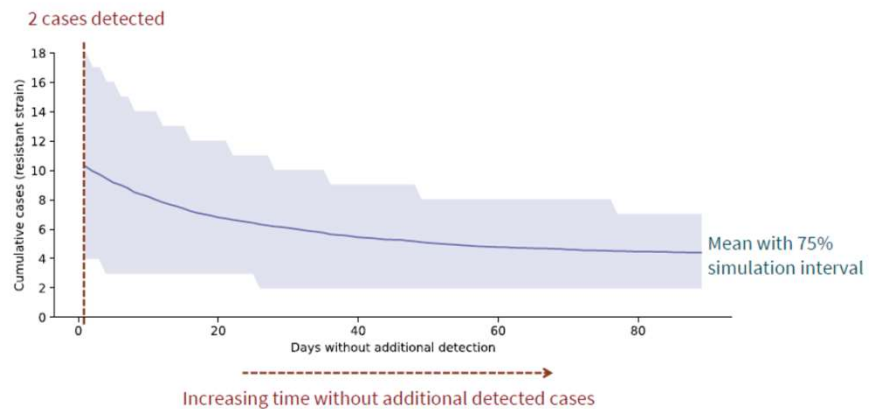


Likelihood of strain elimination

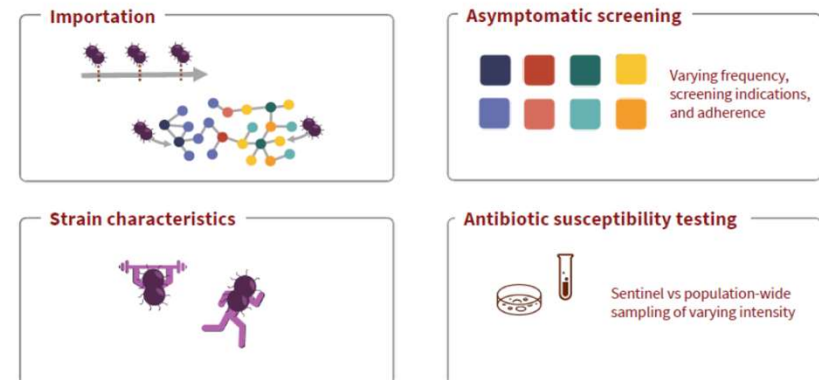


After 2 incident cases of interest, in a state with good health care access and electronic laboratory reporting, model simulations imply that if no further cases are detected at 90 days, further undetected infections are unlikely, cumulative disease burden decreases, and likelihood of strain elimination is high.

Cumulative disease burden



Next steps: Scenario analysis



Roster et al., unpublished data

1. New drugs or novel therapeutics for gonorrhea are coming
2. New strategies for antimicrobial stewardship using rapid molecular diagnostics
3. Vaccines under development

WAYS TO STEM THE TIDE OF MDR GC



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Funded by the CDC

Ways to Stem Tide of MDR GC:

1. Novel drugs and therapeutics

Solithromycin – oral fluoroketolide with activity against *N. gonorrhoeae*, *M. genitalium*, and *C. trachomatis*.

Solithromycin Versus Ceftriaxone Plus Azithromycin for the Treatment of Uncomplicated Genital Gonorrhoea (SOLITAIRE-U): A Randomised Phase 3 Non-Inferiority Trial. Chen et al. *Lancet Infect Dis*, 2019.

99 (80%) of 123 patients in the solithromycin group and 109 (84%) of 129 patients in the ceftriaxone plus azithromycin group had *N gonorrhoeae* eradication at test of cure (difference -4.0%, 95% CI -13.6 to 5.5), thus solithromycin did not meet the criterion for non-inferiority at the prespecified -10% margin. The frequency of adverse events was higher in the solithromycin....

A Phase 2 Trial of Oral Solithromycin 1200 Mg or 1000 Mg as Single-Dose Oral Therapy for Uncomplicated Gonorrhea. Hook et al. *Clin Infect Dis*, 2019.

59 participants were enrolled; 28 received 1200 mg of solithromycin and 31 received 1000 mg..

“100% effective for treatment of culture-proven gonorrhea at genital, oral, and rectal sites of infection and is a promising new agent for gonorrhea treatment”

Slide courtesy of Sanjay Ram

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.

Ways to Stem Tide of MDR GC: 1. Novel drugs and therapeutics

A spiropyrimidinetrione

Also active vs
chlamydia, ureaplasma,
M. genitalium

- 179 participants (167 men, and 12 women); 141 participants in the micro-ITT population could be evaluated
- Microbiologic cure at urogenital sites in 55 of 57 (96%) who received 2 g of zoliflodacin, 54 of 56 (96%) who received 3 g of zoliflodacin, and 28 of 28 (100%) who received ceftriaxone.
- Rectal infections cured in all 5 participants who received 2 g of zoliflodacin and all 7 who received 3 g, and in all 3 participants who received ceftriaxone.
- **Pharyngeal infections** were **cured in 4 of 8 participants (50%), 9 of 11 participants (82%), and 4 of 4 participants (100%)** in the groups that received **2 g of zoliflodacin, 3 g of zoliflodacin, and ceftriaxone, respectively.**
- 21 adverse events related to zoliflodacin, mostly GI.

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. Dumont⁶

¹Section of Infectious Disease, Louisiana State University Health Sciences Center, New Orleans; ²Desert AIDS Project, Palm Springs, California; ³Department of Medicine, Division of Infectious Diseases, MetroHealth Medical Center, Cleveland, Ohio; ⁴Department of Medicine, Division of Infectious Diseases, Emory University Department of Medicine, Atlanta, Georgia; ⁵Department of Medicine, Division of Infectious Diseases, Indiana University School of Medicine, Indianapolis; and ⁶Research & Development, GlaxoSmithKline, Collegeville, Pennsylvania

Gepotidacin (GSK) – another bacterial topoisomerase II inhibitor

- 69 participants (with microbiologically evaluable end-points), with *Ng* isolated from 69 (100%) urogenital, 2 (3%) pharyngeal, and 3 (4%) rectal specimens.
- 95% were male
- 1500-mg or 3000-mg single oral dose of gepotidacin
- At the **pharyngeal** and **rectal** sites, **1/2** and **3/3**, respectively, demonstrated microbiological cure.
- Overall, about 95% efficacy
- All 3 failures were isolates that demonstrated the highest observed gepotidacin MIC of 1 µg/mL and a common gene mutation

Ways to Stem Tide of MDR GC: 1. Novel drugs and therapeutics



[mBio](#). 2021 Mar-Apr; 12(2): e00242-21.

PMCID: PMC8092225

Published online 2021 Mar 16. doi: [10.1128/mBio.00242-21](https://doi.org/10.1128/mBio.00242-21)

PMID: [33727348](https://pubmed.ncbi.nlm.nih.gov/33727348/)

Synthetic DNA Delivery of an Optimized and Engineered Monoclonal Antibody Provides Rapid and Prolonged Protection against Experimental Gonococcal Infection

[Elizabeth M. Parzych](#),^a [Sunita Gulati](#),^b [Bo Zheng](#),^b [Mamadou A. Bah](#),^a [Sarah T. C. Elliott](#),^a [Jacqueline D. Chu](#),^a [Nancy Nowak](#),^b [George W. Reed](#),^b [Frank J. Beurskens](#),^c [Janine Schuurman](#),^b [Peter A. Rice](#),^b [David B. Weiner](#),^a and [Sanjay Ram](#)^{✉b}

Ways to Stem Tide of MDR GC:

2. New strategies for antimicrobial stewardship using rapid molecular diagnostics

- Rapid POC testing – same day diagnosis
 - Almost prime time
 - May include POC testing for resistance too
 - Will eliminate gap time to treatment for asymptomatic patients (therefore less carriage and transmission)
 - May provide information for more targeted antimicrobial treatment

Can molecular diagnostics help ‘repurpose’ drugs?



Clinical Infectious Diseases

MAJOR ARTICLE



Multiplex Real-Time PCR Assay for Simultaneous Identification of *Neisseria gonorrhoeae* and Its Ciprofloxacin Susceptibility Status

Sumudu R. Perera,^{a,b} Nurul H. Khan,^{a*} Irene Martin,^c Ali Taheri,^{a*} Rajinder P. Parti,^{a*} Paul N. Levett,^d Greg B. Horsman,^d Anthony Kusalik,^e Jo-Anne R. Dillon^{a,b}

Mutations in in GyrA highly predictive of Cipro resistance

Utility will depend on cost of testing (in turn depends on number of tests run), and prevalence of Cipro-R isolates

Allan-Blitz et al., *Sex Transm Dis* 2018

Resistance-Guided Treatment of Gonorrhoea: A Prospective Clinical Study

Jeffrey D. Klausner,¹ Claire C. Bristow,² Olusegun O. Soge,³ Akbar Shahkolahi,⁴ Toni Waymer,⁴ Robert K. Bolan,⁵ Susan S. Philip,⁶ Lenore E. Asbel,⁷ Stephanie N. Taylor,⁸ Leandro A. Mena,⁹ Deborah A. Goldstein,¹⁰ Jonathan A. Powell,¹¹ Michael R. Wierzbicki,¹¹ and Sheldon R. Morris²

CID, published online, Aug 2020

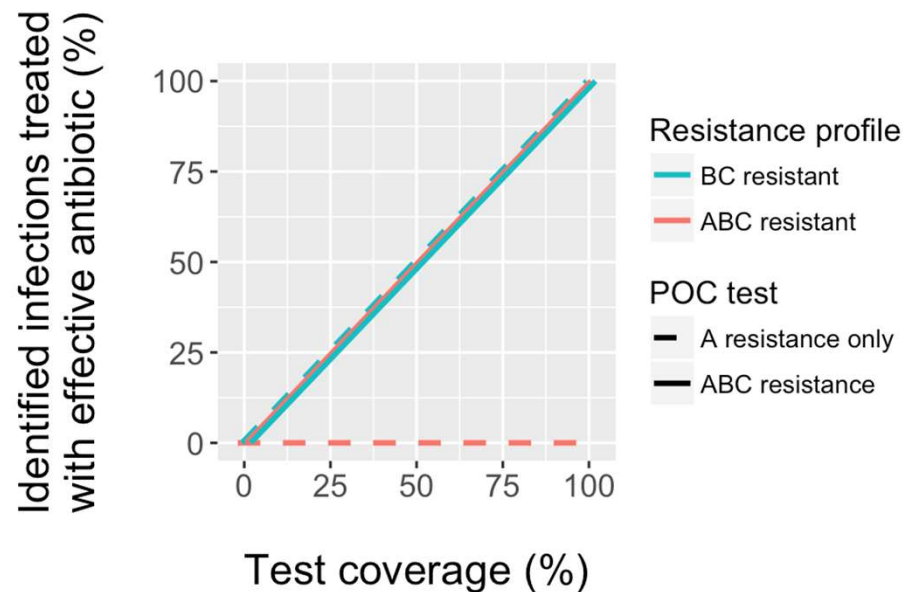
Samples used for NAAT tests evaluated for presence of serine 91 mutation in *gyrA* – ‘Wild-type’ Ser 91 predicts quinolone sensitivity

100% cure rate with quinolones when Ser 91 in GyrA present

Use restricted to asymptomatic persons – long turnaround time

Slide courtesy of Sanjay Ram

Single Antibiotic Test Does Not Improve Diagnosis of Triple-Resistant Gonococcal Infections



A Note of Caution:

“The failure of a single POC test to delay emergence of triply resistant isolates arises in part because all tested cases are treated appropriately except for triply-resistant infections, thereby reducing the burden of all other isolates and clearing the way for triply-resistant isolates.”

Tuite et al, JID, 2017

Ways to Stem Tide of MDR GC: 3. Vaccines

N. meningitidis serogroup B vaccine showed
~31% effectiveness against gonorrhea in
New Zealand

Thought to be due to outer membrane
protein similarities between *N. meningitidis*
and *N. gonorrhoeae*

NIH-sponsored study of meningococcal
group B vaccine rMenB+OMV NZ (Bexsero)
to prevent gonococcal infection now
underway

<https://clinicaltrials.gov/ct2/show/NCT0450138>



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Articles

Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black

Summary
Background Gonorrhoea is a major global public health problem that is exacerbated by drug resistance. Effective vaccine development has been unsuccessful, but surveillance data suggest that outer membrane vesicle meningococcal group B vaccines affect the incidence of gonorrhoea. We assessed vaccine effectiveness of the outer membrane vesicle meningococcal B vaccine (MeNZB) against gonorrhoea in young adults aged 15–30 years in New Zealand.

Methods We did a retrospective case-control study of patients at sexual health clinics aged 15–30 years who were born between Jan 1, 1984, and Dec 31, 1998, eligible to receive MeNZB, and diagnosed with gonorrhoea or chlamydia, or both. Demographic data, sexual health clinic data, and National Immunisation Register data were linked via patients' unique personal identifier. For primary analysis, cases were confirmed by laboratory isolation or detection of *Neisseria gonorrhoeae* only from a clinical specimen, and controls were individuals with a positive chlamydia test only. We estimated odds ratios (ORs) comparing disease outcomes in vaccinated versus unvaccinated participants via multivariable logistic regression. Vaccine effectiveness was calculated as $100 \times (1 - OR)$.

Findings 11 of 24 clinics nationally provided records. There were 14730 cases and controls for analyses: 1241 incidences of gonorrhoea, 12487 incidences of chlamydia, and 1002 incidences of co-infection. Vaccinated individuals were significantly less likely to be cases than controls (511 [41%] vs 6424 [51%]; adjusted OR 0.69 [95% CI 0.61–0.79]; $p < 0.0001$). Estimate vaccine effectiveness of MeNZB against gonorrhoea after adjustment for ethnicity, deprivation, geographical area, and sex was 31% (95% CI 21–39).

Interpretation Exposure to MeNZB was associated with reduced rates of gonorrhoea diagnosis, the first time a vaccine has shown any protection against gonorrhoea. These results provide a proof of principle that can inform prospective vaccine development not only for gonorrhoea but also for meningococcal vaccines.

Funding GSK Vaccines, Auckland UniServices.

Introduction
Gonorrhoea is associated with significant morbidity, including pelvic inflammatory disease, infertility, and chronic pain, and is a major global public health concern, with an estimated 78 million incident new cases each extent, Norway,^{1,2} suggesting that OMV vaccines could affect the incidence of gonorrhoea. OMV vaccines are generally only thought to be useful against epidemics dominated by strains belonging to the

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See Online Comment
[http://dx.doi.org/10.1016/S0140-6736\(17\)31605-7](http://dx.doi.org/10.1016/S0140-6736(17)31605-7)
Department of General Practice and Primary Health Care (H Petousis-Harris PhD), J Paynter PhD, Prof F Goodyear-Smith MD, School of Medicine (J Morgan MD), Department of Social and Community Health (P Saxton PhD), and Connect, Auckland UniServices (B McArdle MCh), University of Auckland, Auckland, New Zealand; Sexual Health Services, Waikato District Health Board, Hamilton, New Zealand (J Morgan); and Center for Global Health, Cincinnati Children's Hospital, Cincinnati, OH, USA (Prof S Black MD)
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h.petousis-harris@auckland.ac.nz

Petousis-Harris et al.
Lancet, 2017

Ways to Stem Tide of MDR GC:

3. Vaccine epitopes under development

The Journal of
Infectious Diseases

[J Infect Dis.](#) 2022 May 15; 225(10): 1861–1864.

PMCID: PMC9113499

Published online 2021 Dec 31. doi: [10.1093/infdis/jiab630](https://doi.org/10.1093/infdis/jiab630)

PMID: [34971376](https://pubmed.ncbi.nlm.nih.gov/34971376/)

Efficacy of an Experimental Gonococcal Lipooligosaccharide Mimitope Vaccine Requires Terminal Complement

[Lisa A Lewis](#),^{✉1} [Sunita Gulati](#),¹ [Wioleta M Zelek](#),² [B Paul Morgan](#),² [Wen-Chao Song](#),³ [Bo Zheng](#),¹ [Nancy Nowak](#),¹
[Rosane B DeOliveira](#),¹ [Bryan Sanchez](#),¹ [Leandro DeSouza Silva](#),¹ [Janine Schuurman](#),⁴ [Frank Beurskens](#),⁴
[Sanjay Ram](#),¹ and [Peter A Rice](#)¹



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A Project of the Division of STD Prevention
Massachusetts Department of Public Health
Funded by the CDC

Back to Our Case ...

- 22-year-old cisgender man presents with 3 days of dysuria and penile discharge. He has sex with cisgender women and cisgender men.
- ***What evaluation (specimen types and tests) would you recommend, and how would you treat him?***

Slide adapted from Jason Zucker, MD, MS



Etiologies of non-gonococcal urethritis

- *C. trachomatis* (15-40%)
- *M. genitalium* (15-25%)
- *T. vaginalis* (1-8%)
- Herpes simplex virus (3%)
- *N. meningitidis*
- Other bacteria (i.e. *H. influenzae*)
- Other viruses (i.e. adenovirus, Epstein-Barr virus)
- Unknown (~50%)

WHERE WE WERE WITH CHLAMYDIA TREATMENT ...



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First-Pass Answer: RCT: Chlamydia Treatment Azithromycin vs. Doxycycline for **Urogenital** Chlamydia infection

Antibiotic group	Treatment failures	Efficacy
Doxycycline	0	100%
Azithromycin	5 (3.2%; 95%CI 0.4-7.4%)	97%

- Captive audience: juvenile detention facilities
- Difference in failure rates was 3.2%
- The non-inferiority of azithromycin was not established
- Both medications are effective
- **Azithro had some treatment failures, but adherence is likely to be much greater with single-dose azithromycin**

You can't ignore extragenital sites

WHERE WE ARE NOW WITH CHLAMYDIA TREATMENT



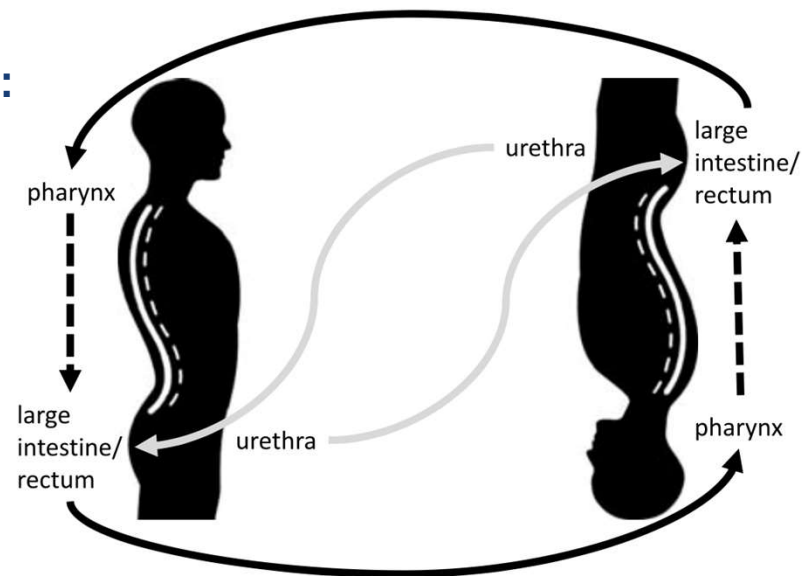
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Chlamydia Transmission

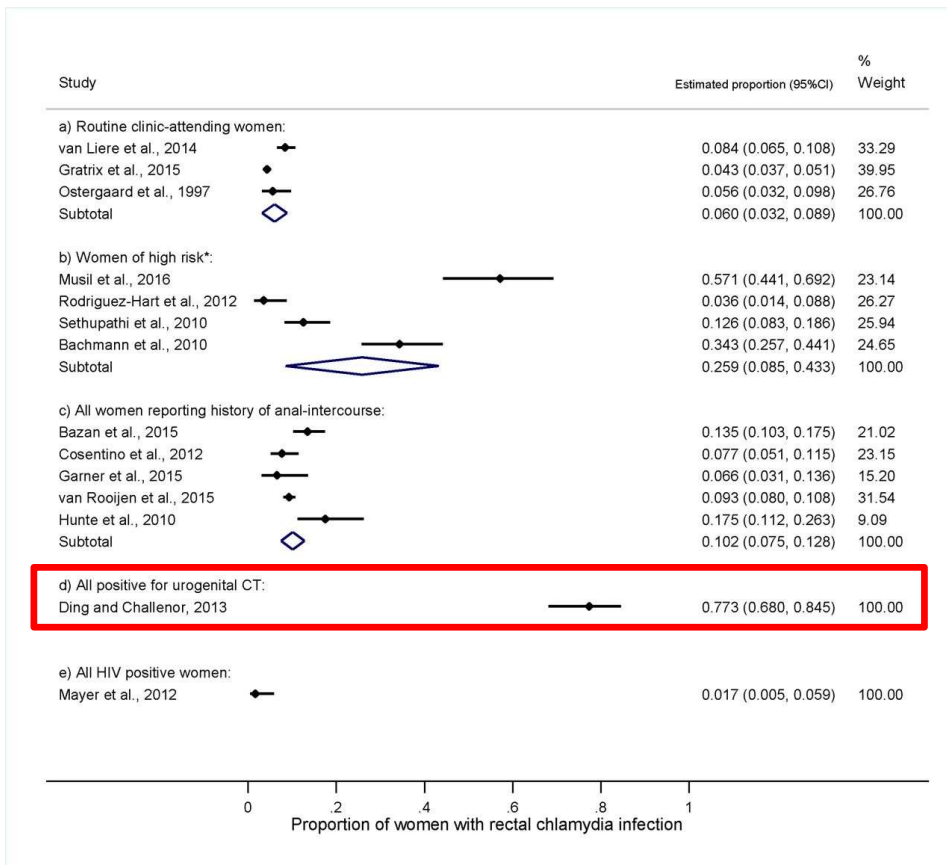
- Infectiousness / reservoir not been accurately defined
- Transmission has been attributed largely to asymptomatic carriers

Proposed transmission patterns:

- Genitoanal (grey)
- Ano-oral (black)
- Gastrointestinal transit to large intestine and rectum



Individual study and study subgroup summary estimates of rectal chlamydia positivity in women stratified by clinical subgroup/population type (n=14).



Chandra et al. *Sex Transm Infect* 2018;94:320-326

Rectal CT summary prevalence in women:

- Attending routine clinics: 6% (95% CI 3 – 9%)
- Among those positive for urogenital chlamydia: 68% (95% CI 57 – 80%)
- Using reported anal intercourse as an indicator for rectal testing leads to missed diagnoses

STI

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INCREASING EVIDENCE THAT DOXYCYCLINE X 1 WEEK IS SUPERIOR TO AZITHROMYCIN X 1 DOSE FOR RECTAL CHLAMYDIA



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Next Answer: **Rectal** Chlamydia: Microbiologic Cure is Better with Doxycycline

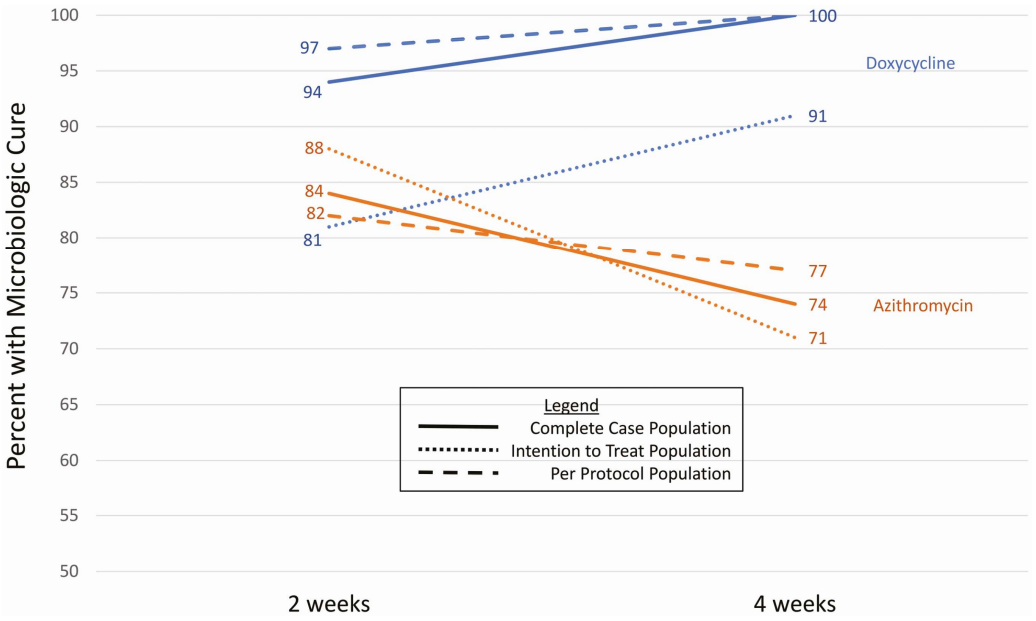
WOMEN

- **Dukers-Muijers et al., *CID* 2019**
 - Prospective multicenter cohort study (FemCure)
 - Women in Netherlands
 - Microbiologic cure in rectal infxns
 - azithromycin 78.5%
 - doxycycline 95.5%
- **Peuchant et al., *Lancet ID* 2022**
 - Multicentre, open-label, randomised, controlled, superiority trial (Clazidoxy)
 - Women in France
 - Microbiologic cure in concurrent rectal+vaginal infxns
 - azithromycin 85%
 - doxycycline 94%

MEN

- **Dombrowski et al., *CID* 2021**
 - Randomized, double-blind, placebo-controlled trial
 - MSM in Seattle and Boston
 - Microbiologic cure in rectal infxns across analysis groups
 - azithromycin 71 – 77%
 - doxycycline 91 – 100%
 - Trial stopped early due to interim analysis
- **Lau et al., *NEJM* 2021**
 - Randomized, double-blind, placebo-controlled trial
 - Australian men with asx rectal chlamydia
 - Microbiologic cure in rectal infxns
 - azithromycin 76.4%
 - doxycycline 96.9%

Figure 2. Comparison of 2-week and 4-week cure percentage by treatment group and analysis population.



“Azithromycin performed so poorly that even in the context of expected imperfect adherence in real-world use, doxycycline should be the recommended treatment for rectal CT in MSM.”

RESEARCH SUMMARY

Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis*

Lau A et al. DOI: 10.1056/NEJMoa2031631

CLINICAL PROBLEM

Chlamydia trachomatis is a common STI globally among men who have sex with men and is most often asymptomatic. Although guidelines have recommended treatment with either doxycycline or azithromycin, data from randomized trials are lacking.

CLINICAL TRIAL

Design: A double-blind, randomized trial in Australia involving men with asymptomatic rectal chlamydia to compare the efficacy of doxycycline with that of azithromycin.

Intervention: 625 men were assigned to receive either doxycycline or azithromycin. The primary outcome was a negative nucleic acid amplification test for rectal chlamydia (microbiologic cure) at 4 weeks.

RESULTS

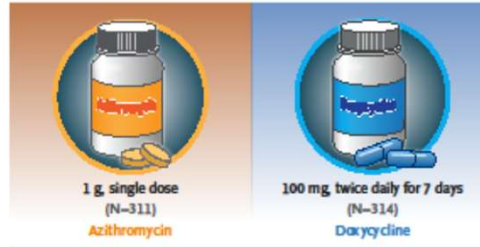
Efficacy: The doxycycline regimen was significantly more efficacious than the azithromycin regimen for the treatment of asymptomatic rectal chlamydia.

Safety: Adverse events including nausea, diarrhea, and vomiting were less common in the doxycycline group than in the azithromycin group.

LIMITATIONS AND REMAINING QUESTIONS

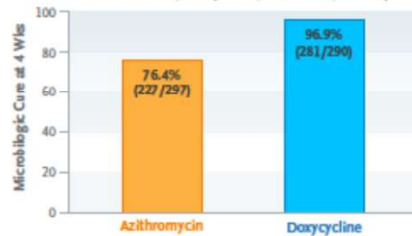
Further study is required to understand the following:

- Why azithromycin is less efficacious for rectal chlamydia, since other trials have shown it to be only slightly less effective than doxycycline for urogenital infection
- Whether larger azithromycin doses may be more effective for higher-load infections
- Whether azithromycin will cure rectal chlamydia in women



Microbiologic Cure in Modified Intention-to-Treat Population

Risk difference, 19.9 [95% CI, 14.6 to 25.3; P<0.001]



Adverse Events, including Nausea, Diarrhea, and Vomiting

Risk difference, -11.3 [95% CI, -19.5 to -3.2; P=0.006]



CONCLUSIONS

A 7-day course of doxycycline was superior to single-dose azithromycin in the treatment of rectal chlamydia infection among men who have sex with men.

“Adverse events including nausea, diarrhea, and vomiting were less common in the doxycycline group than in the azithromycin group.”

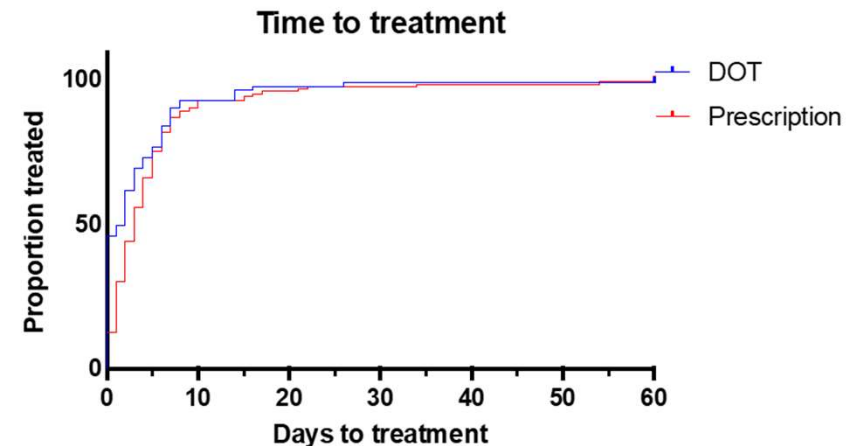
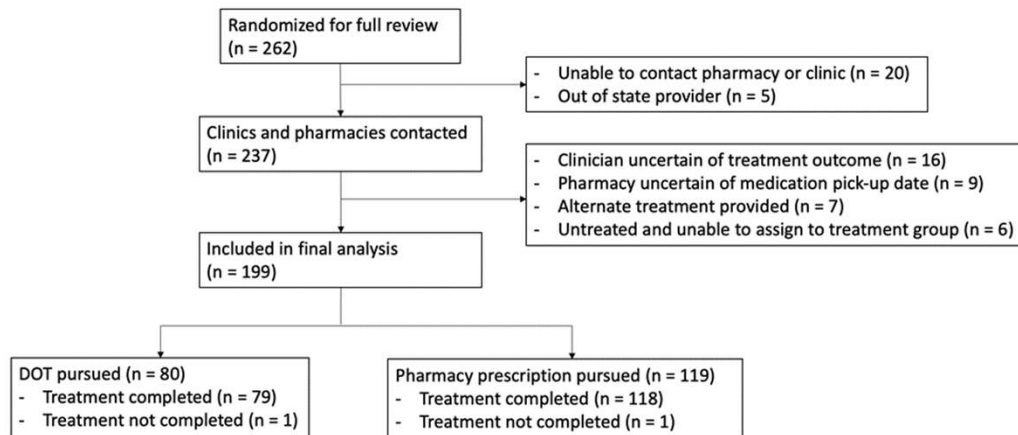
Links: [Full article](#) | [NEJM Quick Take](#)

Lau et al., *NEJM* 2021

Chlamydia Treatment in Massachusetts: DOT versus ‘Scripts’

- Fig. 1 Patient Flow Diagram

- Fig. 2 Time to Treatment



“Pharmacy prescriptions are frequently used for the treatment of chlamydia in Massachusetts. We did not observe a significant difference in time to treatment between directly observed therapy and pharmacy prescriptions.”

Platt LR et al., *J Prim Care Community Health* 2021

Data source: MDPH Bureau of Infectious Disease and Laboratory Sciences, Division STD Prevention



What about chlamydia in pregnancy?

First-line therapy is still single-dose azithromycin.



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Original Research

High rates of persistent and recurrent chlamydia in pregnant women after treatment with azithromycin



Jodie Dionne-Odom, MD, MSPH; Akila Subramaniam, MD, MPH; Kristal J. Aaron, DrPH, MPH; William M. Geisler, MD, MPH; Alan T. N. Tita, MD, PhD; Jeanne Marrazzo, MD, MPH

BACKGROUND: *Chlamydia trachomatis* is a common bacterial sexually transmitted infection that can persist or recur after antibiotic treatment. Universal screening for chlamydia in pregnancy is recommended to prevent adverse birth outcomes. Single-dose oral azithromycin has been the first-line therapy for chlamydia in pregnancy since 2006. **OBJECTIVE:** In the setting of limited data and rising sexually transmitted infection rates in the United States, our goal was to document rates and risk factors for persistent or recurrent chlamydia after azithromycin treatment in pregnancy. **STUDY DESIGN:** This retrospective cohort study included pregnancies with urogenital chlamydia and follow-up testing in women who delivered at an Alabama facility between November 2012 and December 2017. Pregnancies with prescribed azithromycin therapy and repeat chlamydia testing ≥ 21 days later were included. *Chlamydia trachomatis* nucleic acid amplification testing was performed on genital swab or urine samples. Descriptive characteristics and birth outcomes were compared for categories stratified by repeat test results: persistence (+ +), recurrence

(+ - +), or clearance (+ -). Logistic regression models were used to identify demographic and clinical risk factors for persistent or recurrent chlamydia in pregnancy. **RESULTS:** Among 810 women with 840 pregnancies with repeat chlamydia testing after azithromycin treatment, 114 (14%) had persistence and an additional 72 (9%) had recurrence later in pregnancy. The median time to repeat testing was 30 days (interquartile range, 24–49 days). Concomitant gonorrhea or syphilis in pregnancy was independently associated with persistent or recurrent chlamydia (adjusted odds ratio, 1.6; 95% confidence interval, 1.1–2.4). **CONCLUSION:** Persistent or recurrent chlamydia after azithromycin treatment was detected in nearly 1 in 4 pregnancies with repeat testing in our urban center, highlighting the importance of performing a test of cure and ensuring partner therapy to reduce recurrent chlamydia risk. **Key words:** azithromycin, *Chlamydia trachomatis*, infection in pregnancy, recurrent chlamydia

Introduction

Chlamydia trachomatis is an intracellular bacterium that causes cervical infection. More than 1.1 million cases of chlamydia in women were reported to the US Centers for Disease Control and Prevention (CDC) in 2018.¹ Women between the ages of 15 and 24 years and women who reside in the southeastern United States, where the case rate is 744 cases per 100,000 persons, are disproportionately affected by chlamydia.^{1–4} Untreated chlamydia in pregnancy has been associated with preterm delivery and low birthweight (LBW) infants.^{5–9} Infection in women is usually asymptomatic, and timely screening and treatment in pregnancy can prevent adverse outcomes.¹⁰ Despite rising

chlamydia rates in the US, few studies focus on chlamydia treatment outcomes after azithromycin therapy in pregnant women.^{1,11}

The American College of Obstetricians and Gynecologists (ACOG) has recommended universal screening for chlamydia in pregnancy since 2007.¹² CDC recommends performing a test of cure for pregnant women with chlamydia at least 21 days after treatment and repeat testing 12 weeks later to screen for reinfection.^{13,14} In an observational study from a commercial laboratory database in the United States (2005–2008), 59% of pregnant women had chlamydia testing and 3.5% had a positive result. Among women with chlamydia who underwent repeated testing, 6% had repeat positivity during pregnancy but treatment data were not available.¹² Recurrent chlamydia in nonpregnant women is well documented: a systematic review suggested a 14% recurrence rate during follow-up periods ranging from 2 months to 13 years.¹⁵ Younger age (<26 years) and bacterial sexually transmitted infection (STI) coinfection have been associated

with recurrent chlamydia in nonpregnant women.^{16–19}

Chlamydia infection that recurs after antibiotic treatment and clearance (defined by a negative test) usually represents reinfection from a sexual partner. The mechanism for repeatedly positive chlamydia testing is more varied. It may represent recurrent infection (after undocumented clearance), false-positive polymerase chain reaction test result owing to residual DNA/RNA, or treatment failure.¹⁶ Unlike gonococcal infection, antimicrobial resistant chlamydial infection is rare.^{20–22} Single-dose oral azithromycin (1 g) is the CDC-recommended treatment for chlamydia in pregnancy.²³ Azithromycin has a favorable safety profile in pregnancy, and it is one of the most commonly prescribed antibiotic agents worldwide.²⁴ Recent reports suggest that clinical treatment failure can occur with azithromycin treatment for rectal chlamydia and nonresponse to azithromycin for urogenital chlamydia in pregnancy has been reported.^{21,25–27}

Cite this article as: Dionne-Odom J, Subramaniam A, Aaron KJ, et al. High rates of persistent and recurrent chlamydia in pregnant women after treatment with azithromycin. *Am J Obstet Gynecol* MFM 2020;2:100216.

2589-0333
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<https://doi.org/10.1016/j.ajogmf.2020.100216>

“In this retrospective cohort study of 810 pregnant women with urogenital chlamydia treated with first-line azithromycin, nearly 1 in 4 pregnancies with repeat chlamydia testing had persistence or recurrence. STI coinfection with gonorrhea or syphilis during pregnancy was the only significant risk factor for persistent or recurrent chlamydia in a model that adjusted for age, race, and insurance status.”

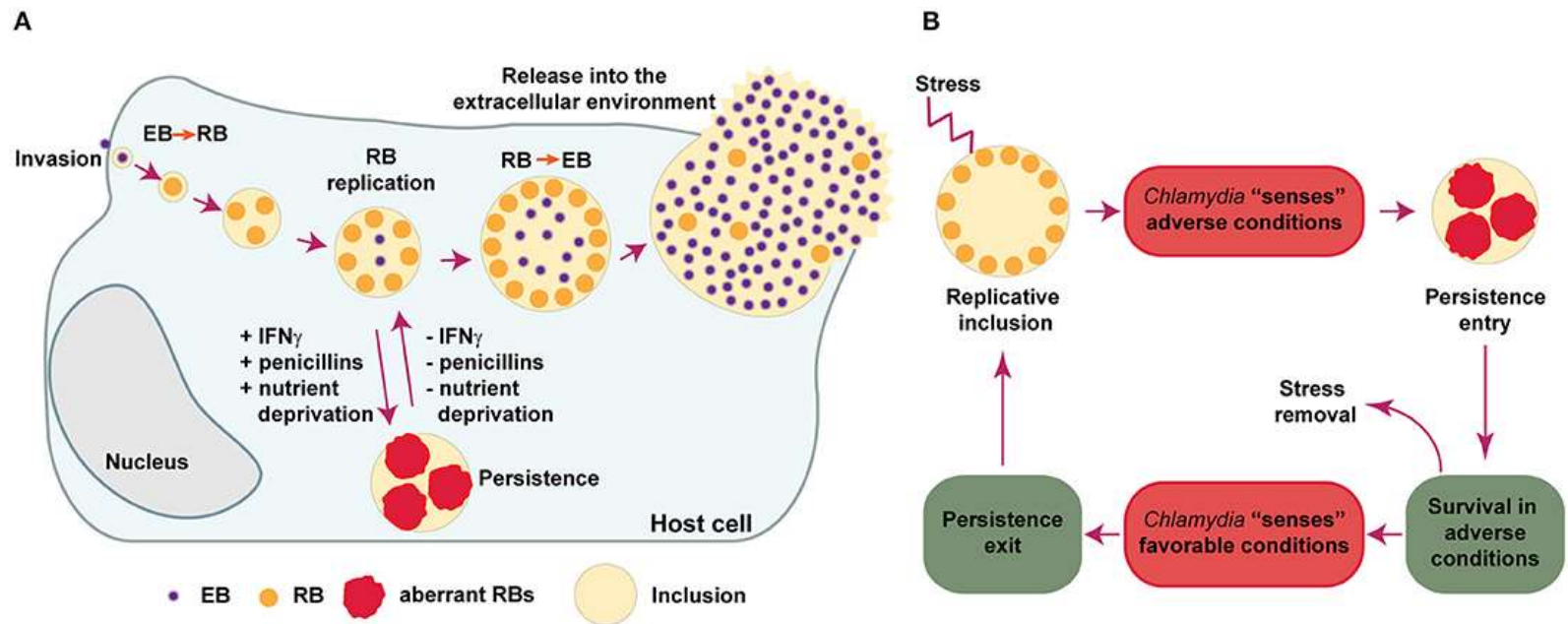
Dionne-Odom et al., *AJOG MFM* 2021

Unanswered Questions

- **What about alternative regimens – azithromycin daily or weekly?**
- **Mechanism of azithromycin failure unknown**
 - **Not likely:**
 - Mechanism of action (doxycycline and azithromycin both target bacterial protein synthesis and are considered bacteriostatic)
 - Antibiotic resistance (never (!) conclusively demonstrated *in vivo*)
 - Inadequate tissue penetration of drug in rectal environment (Fong et al. *PLoS One* 2017: azithromycin concentration above MIC for chlamydia for at least 14 days)
 - Prevalence of LGV biovars (uncommon in Dombrowski et al. study)
 - **Temporary suppression with single-dose azithromycin? (chlamydia persistence)**
 - **Different host-microbe interactions in rectal environment vs. genital tract?**



Chlamydia trachomatis is atypical ...



Back to Our Case ...

- 22-year-old cisgender man presents with 3 days of dysuria and penile discharge. He has sex with cisgender women and cisgender men.
- ***What evaluation (specimen types and tests) would you recommend, and how would you treat him?***

Slide adapted from Jason Zucker, MD, MS



Case 1, continued

- A nucleic acid amplification test returns negative for *Trichomonas vaginalis*, but one for *Mycoplasma genitalium* is positive.
- ***How would you treat him now? What would you recommend for his recent sex partners?***



Mycoplasma genitalium: Diagnostic Stewardship leads to Antimicrobial Stewardship

When to Test

- Recurrent NGU or cervicitis
- Consider testing in pelvic inflammatory disease
- Asymptomatic screening not recommended

How to Test

- FDA approved genital and urine NAAT

Emerging Drug Resistance

- In U.S., Canada, Europe, & Australia, macrolide resistance 44%-90%
- U.S. fluoroquinolone resistance 0-15%

Treatment

- Resistance guided therapy, if resistance testing is available
- Sex partners of symptomatic persons treated **only if positive**



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Mycoplasma genitalium

- Men with urethritis symptoms were enrolled from 6 U.S. STD clinics during 6/2017–8/2018
- More than 1 in 4 men with urethritis had *Mycoplasma genitalium*

Clinical Infectious Diseases

MAJOR ARTICLE



Prevalence of *Mycoplasma genitalium* Infection, Antimicrobial Resistance Mutations, and Symptom Resolution Following Treatment of Urethritis

Laura H. Bachmann,¹ Robert D. Kirkcaldy,¹ William M. Geisler,² Harold C. Wiesenfeld,³ Lisa E. Manhart,⁴ Stephanie N. Taylor,⁵ Arlene C. Seña,⁶ Candice J. McNeil,⁷ Lori Newman,⁸ Noelle Myler,⁹ Rachael Fuchs,⁹ and Katherine E. Bowden¹⁰; for the MAGNUM¹ Laboratory Working Group

¹Division of Sexually Transmitted Diseases Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA, ²Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA, ³Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, ⁴Department of Epidemiology, University of Washington, Seattle, Washington, USA, ⁵Department of Medicine, Louisiana State University Health Sciences, New Orleans, Louisiana, USA, ⁶Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, ⁷Department of Medicine, Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA, ⁸Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA, and ⁹FHI 360, Durham, North Carolina, USA

Bachmann LH, Kirkcaldy RD, Geisler WM, Wiesenfeld HC, Manhart LE, Taylor SN, Seña AC, McNeil CJ, Newman L, Myler N, Fuchs R, Bowden KE; MAGNUM Laboratory Working Group. Prevalence of *Mycoplasma genitalium* Infection, Antimicrobial Resistance Mutations, and Symptom Resolution Following Treatment of Urethritis. Clin Infect Dis. 2020 Dec 17;71(10):e624–e632. doi: 10.1093/cid/ciaa293. PMID: 32185385; PMCID: PMC7744987.

Study Site (n)	Prevalence of MG (95% CI)
Durham, NC (n=93)	24.7 (16.0–33.5)
Greensboro, NC (n=152)	38.8 (31.1–46.6)
Pittsburgh, PA (n=174)	27.6 (20.9–34.2)
Birmingham, AL (n=235)	29.8 (23.9–35.6)
New Orleans, LA (n=103)	29.1 (20.4–37.9)
Seattle, WA (n=157)	20.4 (14.1–26.7)
TOTAL (n=914)	28.7 (23.8–33.6)

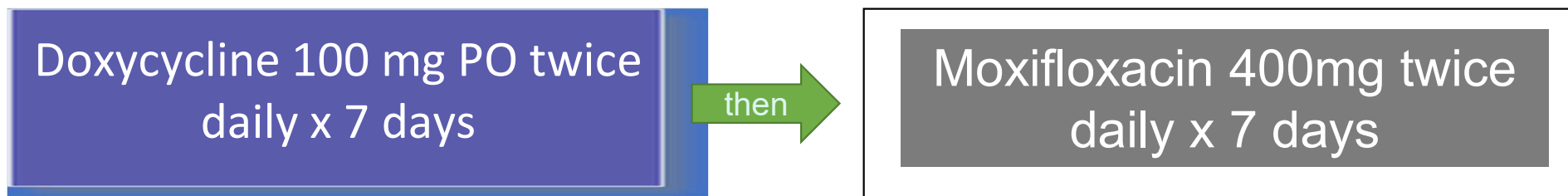
Slide courtesy of Jason Zucker, MD, MS

Mycoplasma genitalium

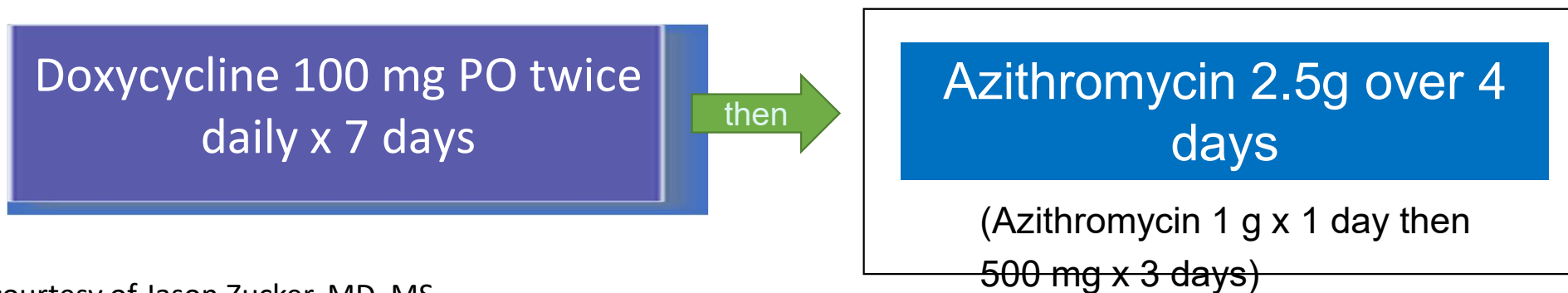


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- Start with doxycycline to reduce bacterial load



If macrolide sensitivity available and sensitive



Slide courtesy of Jason Zucker, MD, MS

It's **Friday** at 4:30pm. You are called about a male patient with **urethritis** who tested **positive** for **M. Genitalium** and has **persistent symptoms** despite treatment with multiple antibiotic regimens including doxycycline, azithromycin, and moxifloxacin. You suspect resistance. What do you do next?





Treatment Failure Considerations and Options

1. Minocycline for 2-4 weeks (There may be some increased activity compared to doxycycline);
2. Obtain pristinamycin (streptogramin) or sitafloxacin through an EUA (challenging);
3. If the person is going to Europe, send a prescriptions for this medication to that country (if available);
4. Lefamulin (not available).

*Before concluding resistance, **exclude re-infection** (partners should be tested and treated if positive)

Would only move to last-line(s) if **symptomatic (Only re-test if symptomatic)



Mycoplasma genitalium – Take homes

When to Test

- Recurrent NGU or cervicitis
- Consider testing in pelvic inflammatory disease
- Asymptomatic screening **not recommended**

How to Test

- FDA approved genital and urine NAAT

Treatment

- Doxycycline followed by Moxifloxacin
- Sex partners of symptomatic persons treated **only if positive**

RESOURCES



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Want to know more about STDs? *There's an app for that.*



CDC STD Treatment
Guidelines App for Apple
and Android

Available **NOW, FREE!**
(accept no competitors)

Search "STD Treatment"
in App store



National
STD Clin
Training C

STD Clinical Consultation Network

- Provides STI/STD clinical consultation services within 1-5 business days, depending on urgency, to clinicians nationally
- Consultation request is linked to your regional PTC's STI/STD expert faculty
- Just a click away: www.STDCCN.org
- Also embedded in Treatment Guidelines App!



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Brown/
Women&Infants



Dr. Katherine K. Hsu
Pedi ID, Boston Med
Ctr/MDPH



Dr. Devika Singh
ID, U of Vermont



Dr. Zoon Wangu
Pedi ID,
UMass/MDPH



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