AETC AIDS Education & Training Center Program
Southeast Regional Conference 2023

Evidence, Advances, and the Current State of STI Management in the U.S.

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Learning Objectives

- *Outline the current challenges related to management of STI*
- *Review current evidence-based guidance for the management of STI*
- *Discuss advances in STI prevention*
  - *DoxyPep*

Disclosures

- *Moderna – Research (HSV)*
- *Immunotherapeutix – Consultant (HSV)*
- *Wiley Press – Royalties*
- *My Sexual Health – Curriculum Development*

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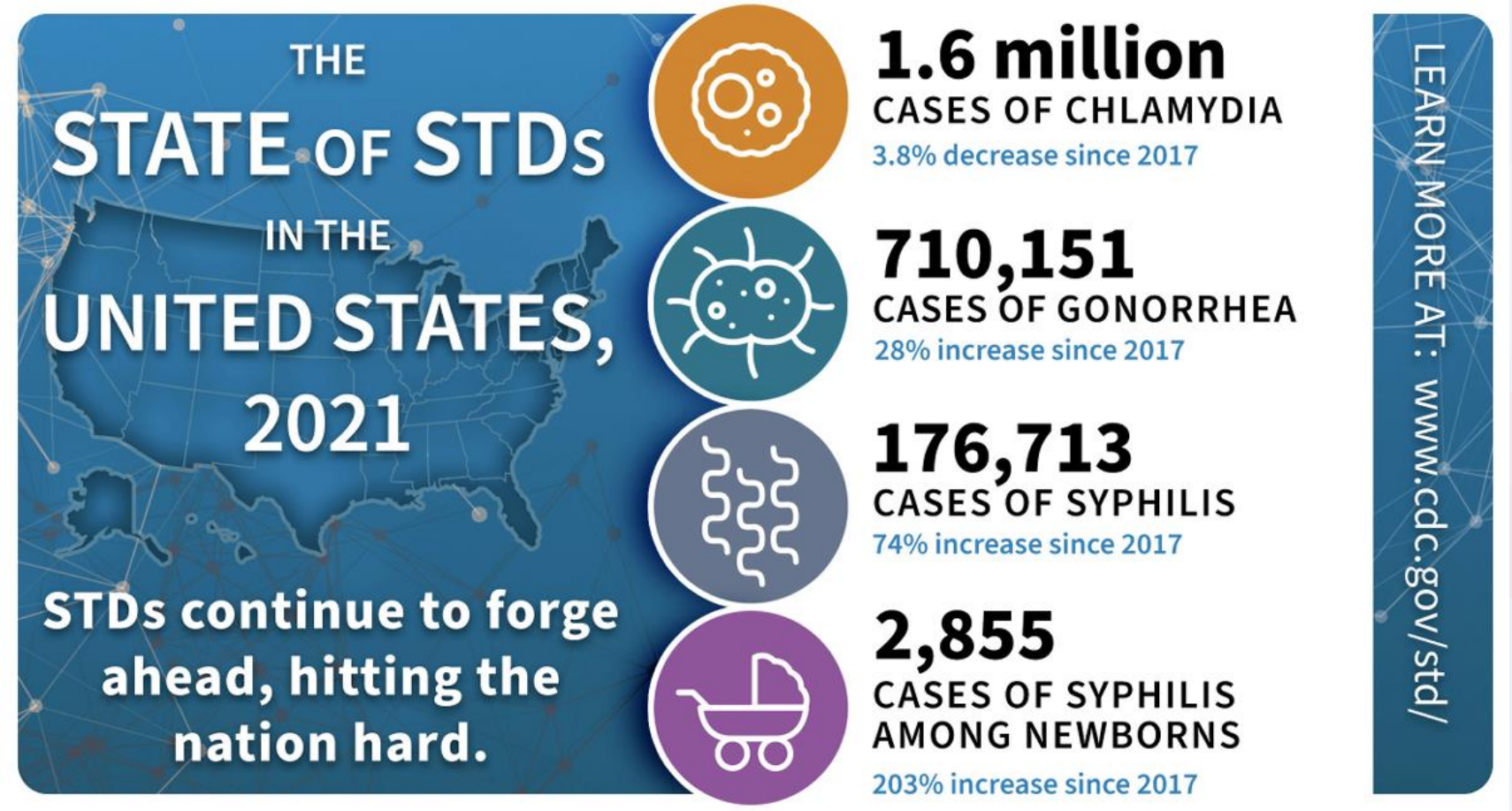
STI Now

- Incidence increasing, along with morbidity & mortality
- No new treatment
- Medication shortages
- Development of resistance
- Emergence of Mpox
- Stark disparities in incidence & adverse outcomes illustrate health inequity, legacy of structural racism, & biological sexism of STI
- Inextricable from epidemiology of incident & established HIV infection
- Limited prevention tools

Incidence increasing, along with morbidity & mortality



www.cdc.gov/std/statistics/national.pdf

No new treatments (yet) but studies continue

- Gonorrhea
  - Zoliflodacin
    - Phase 1: Safe with Good Bioavailability
    - Phase 2: Good cure rates
    - Phase 3: Ongoing (11/19 – 12/23)
  - Gepotidacin
    - Phase 1: Safe with Good Bioavailabilty
    - Phase 2: Good cure rates
    - Phase 3: Recruiting

Bradford PA, Miller AA, O'Donnell J, Mueller JP. Zoliflodacin: An Oral Spiropyrimidinetrione Antibiotic for the Treatment of *Neisseria gonorrheae*, Including Multi-Drug-Resistant Isolates. ACS Infect Dis. 2020 Jun 12;6(6):1332-1345. doi: 10.1021/acsinfecdis.0c00021. Epub 2020 May 12. PMID: 32329999.

Taylor SN, Morris DH, Avery AK, Workowski KA, Batteiger BE, Tiffany CA, Perry CR, Raychaudhuri A, Scangarella-Oman NE, Hossain M, Dumont EF. Gepotidacin for the Treatment of Uncomplicated Urogenital Gonorrhea: A Phase 2, Randomized, Dose-Ranging, Single-Oral Dose Evaluation. Clin Infect Dis. 2018 Aug 1;67(4):504-512. doi: 10.1093/cid/ciy145. PMID: 29617982; PMCID: PMC6070052.

Taylor SN, Marrazzo J, Batteiger BE, Hook EW 3rd, Seña AC, Long J, Wierzbicki MR, Kwak H, Johnson SM, Lawrence K, Mueller J. Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea. N Engl J Med. 2018 Nov 8;379(19):1835-1845. doi: 10.1056/NEJMoa1706988. PMID: 30403954.

https://clasic.clinicaltrials.gov/ct2/show/NCT03959527

Chen MY, Mobley V, Avery A, Whiley D, Tabrizi SN, Hardy D, Das AF, Nenninger A, Fairley CK, Hocking JS, Bradshaw CS, Donovan B, Howden BP, Oldach D; Solitaire-U Team. Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial. Lancet Infect Dis. 2019 Aug;19(8):833-842. doi: 10.1016/S1473-3099(19)30116-1. Epub 2019

Shortage
Penicillin G Benzathine Injectable Suspension

Result of Increased Demand

Estimated recovery Q2 2024

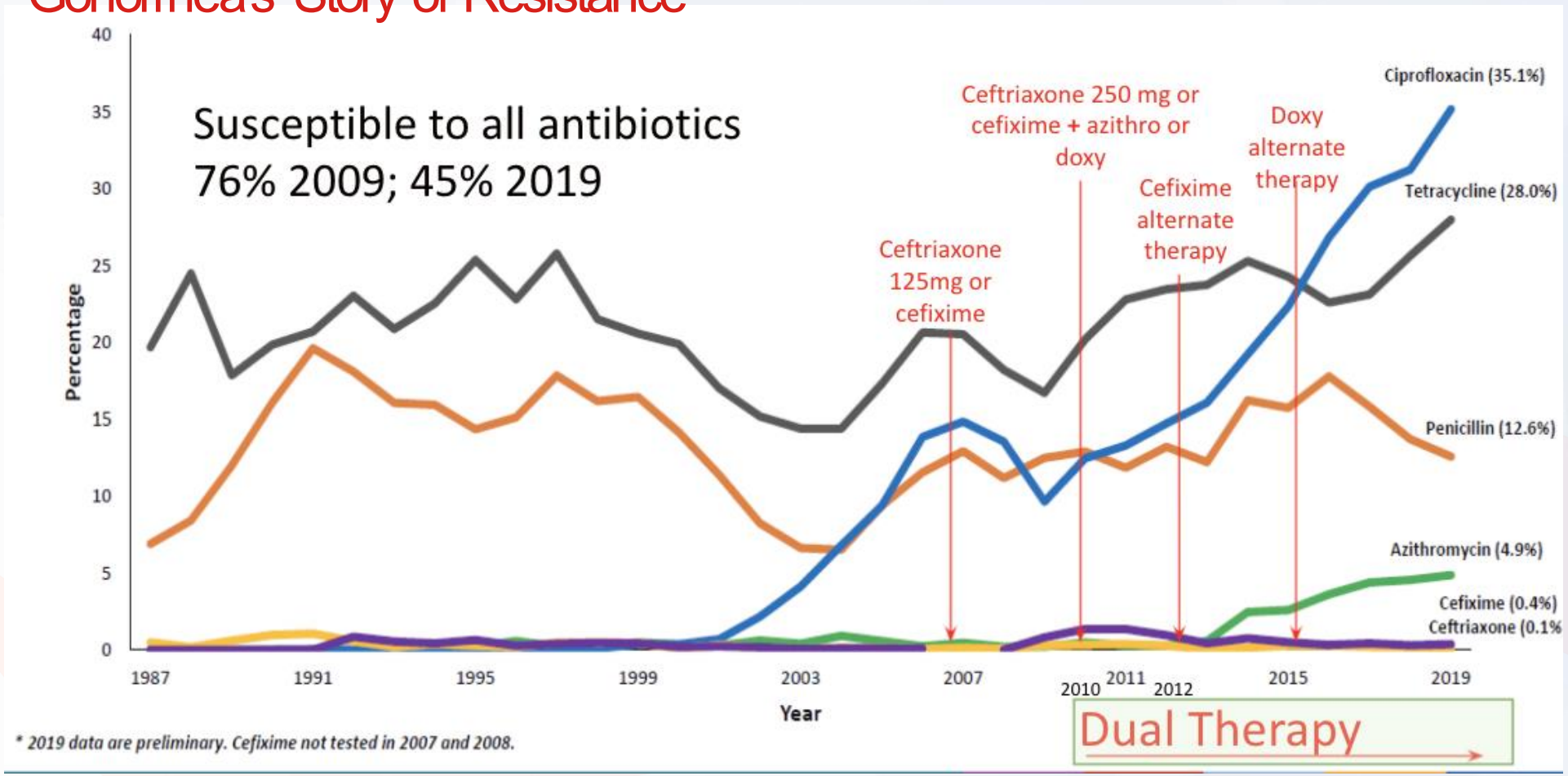
Shortage
Penicillin G Benzathine Injectable Suspension

- CDC Recommendations
  - Take inventory
  - Prioritize PCN G Benzathine Injectable to treat pregnant people with syphilis and babies with congenital syphilis – penicillin is the only recommended treatment for these populations
  - Appropriately stage syphilis cases to ensure appropriate use of antimicrobials
  - Communicate with healthcare providers and pharmacists
  - Notify DSTDP of shortages so CDC can continue to monitor this situation and provide situational awareness to FDA and Pfizer.

https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Penicillin%20G%20Benzathine%20Injectable%20Suspension&st=c&tab=tabs-1&ACSTrackingID=USCDCNPIN_122-DM109263&ACSTrackingLabel=Clinical%20Reminders%20during%20Bicillin%20L-A%C2%AE%20Shortage&deliveryName=USCDCNPIN_122-DM109263
https://www.cdc.gov/std/dstdp/dcl/2023-july-20-Mena-BicillinLA.htm

Development of Resistance

Gonorrhea's Story of Resistance

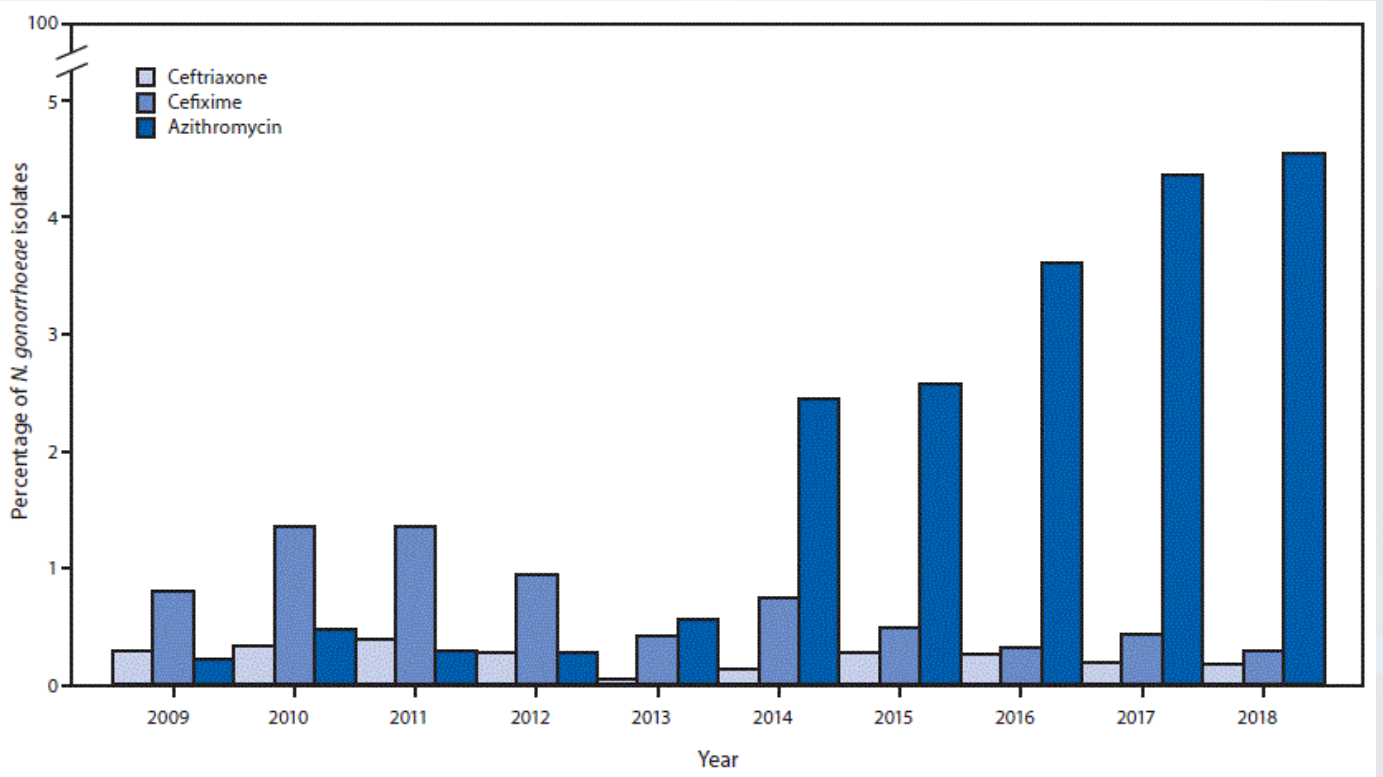


Sancta St. Cyr 2020 National STD Prevention Conference

Development of Resistance

- 2018, reduced azithromycin susceptibility (MIC >/= 2.0 microg/ml) increased almost 10-fold

- Emergence of Azithromycin resistance is not limited to *N. gonorrhoeae*.
  - *Shigella*
  - *Campylobacter*
  - *M. genitalium*



St. Cyr S, Barbee L, Workowski KA, et al. Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1911–1916. DOI: http://dx.doi.org/10.15585/mmwr.mm6950a6

Bachmann LH, Kirkcaldy RD, Geisler WM, et al. Prevalence of Mycoplasma genitalium Infection, Antimicrobial Resistance Mutations, and Symptom Resolution Following Treatment of Urethritis. *Clin Infect Dis.* 2020;71(10):e624-e632. doi:10.1093/cid/ciaa293

Yousfi K, Gaudreau C, Pilon PA, et al. Genetic Mechanisms behind the Spread of Reduced Susceptibility to Azithromycin in *Shigella* Strains Isolated from Men Who Have Sex with Men in Quebec, Canada. *Antimicrob Agents Chemother.* 2019;63(2):e01679-18. Published 2019 Jan 29. doi:10.1128/AAC.01679-18

Gaudreau C, Pilon PA, Sylvestre JL, Boucher F, Bekal S. Multidrug-Resistant Campylobacter coli in Men Who Have Sex with Men, Quebec, Canada, 2015. *Emerg Infect Dis.* 2016;22(9):1661-1663. doi:10.3201/eid2209.151695

Development of Resistance

Mass.gov

Search Mass.gov SEARCH

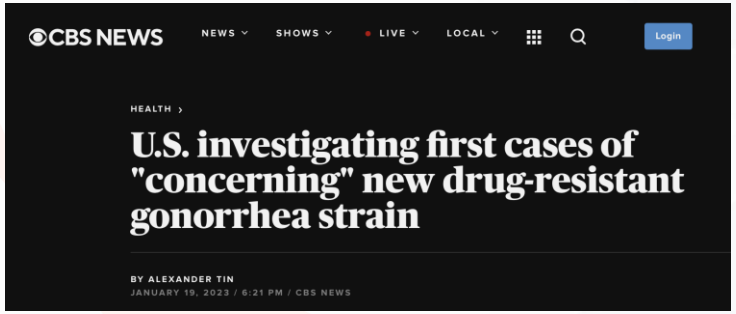
Executive Office of Health and Human Services > Department of Public Health

OFFERED BY Bureau of Infectious Disease and Laboratory Sciences

PRESS RELEASE

Department of Public Health announces first cases of concerning gonorrhea strain

FOR IMMEDIATE RELEASE:
1/19/2023 Department of Public Health



CBS NEWS NEWS SHOWS LIVE LOCAL Login

HEALTH >

U.S. investigating first cases of "concerning" new drug-resistant gonorrhea strain

BY ALEXANDER TIN
JANUARY 19, 2023 / 6:21 PM / CBS NEWS

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Centers for Disease Control and Prevention (CDC)
Atlanta GA 30333

Dear Colleagues,

We are writing to inform you of two gonococcal infections with concerning lab results identified in Massachusetts (see clinical alert). The first case had a cultured isolate which showed decreased susceptibility to ceftriaxone, cefixime and azithromycin, as well as resistance to ciprofloxacin, tetracycline, and penicillin. Molecular testing confirmed that the reduced susceptibility to ceftriaxone was caused by a mutation in the *penA60* allele and a second case was found to have the *penA60* allele through molecular surveillance. Although both cases were successfully clinically and microbiologically cured following treatment with ceftriaxone, these findings are concerning.

Background

A patient presented to a primary care clinic with symptoms of urethritis. *N. gonorrhoeae* was isolated from a clinical specimen. The Massachusetts State Laboratory identified a concerning susceptibility pattern through culture testing and sent isolates to CDC for further testing (see box).

Box 1: Minimum Inhibitory Concentrations (MIC) by Agar Dilution of the Massachusetts Gonococcal Isolate of Concern

Drug	MIC	Susceptible	Intermediate Resistance
Ceftriaxone	1.0 µg/mL	≤ 0.25 µg/mL	UD^
Cefixime	>1.0 µg/mL	≤ 0.25 µg/mL	UD^
Azithromycin	2.0 µg/mL	≤ 1.0 µg/mL	UD^
Ciprofloxacin	16.0 µg/mL	≤ 0.06 µg/mL	0.12–0.5 µg/mL
Tetracycline	2.0 µg/mL	≤ 0.25 µg/mL	0.5–1.0 µg/mL
Gentamicin	8 µg/mL	UD^	UD^
Penicillin	32.0 µg/mL	≤ 0.06 µg/mL	0.12–1.0 µg/mL

^UD: undefined

https://www.mass.gov/news/department-of-public-health-announces-first-cases-of-concerning-gonorrhea-strain

Follow-up testing performed by the Centers for Disease Control and Prevention's Sexually Transmitted Disease (STD) Laboratory identified the *penA60* allele, previously associated with ceftriaxone non-susceptible cases, as well as an additional case with the *penA60* allele as part of molecular surveillance.

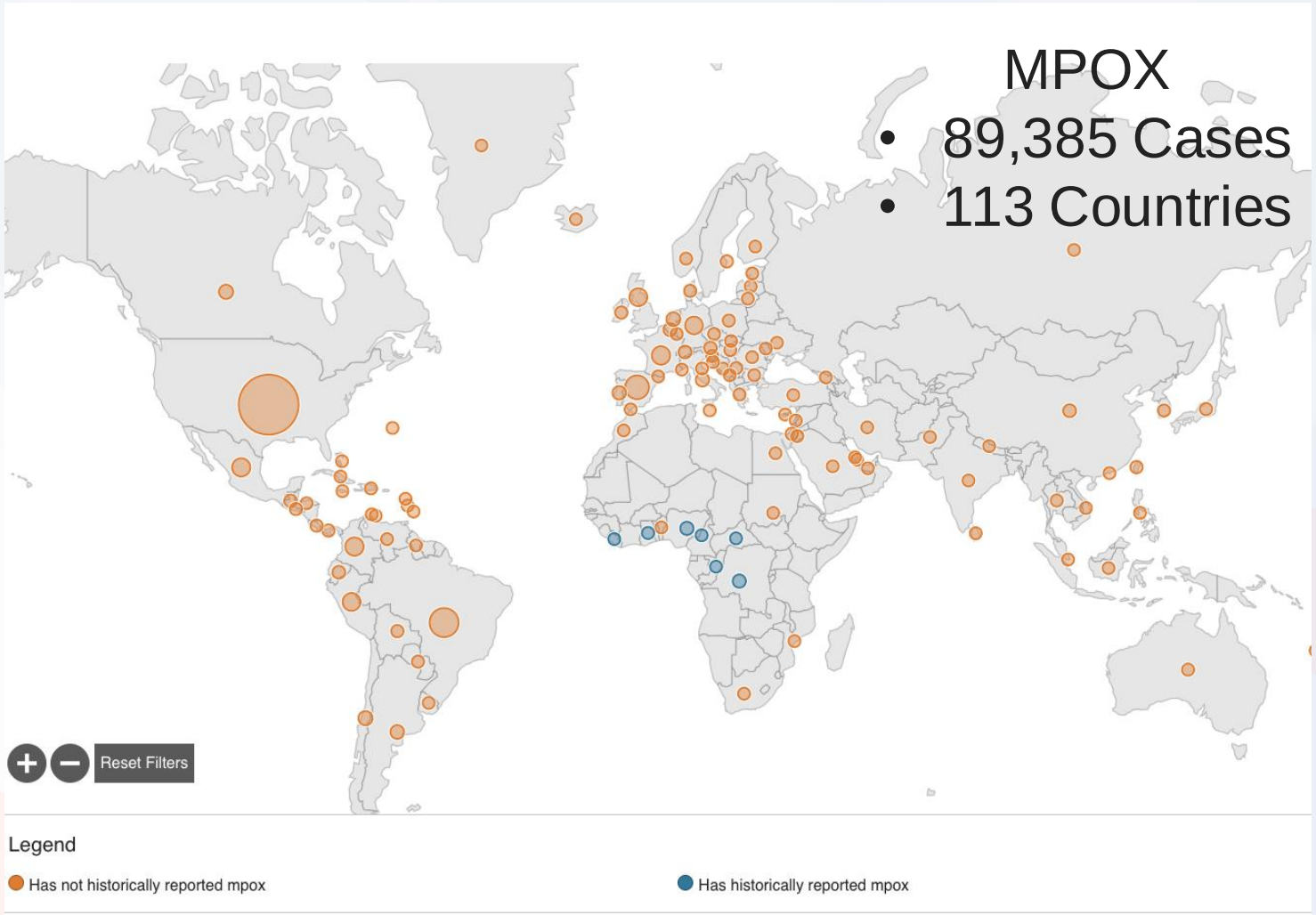
This is the first case of documented resistance to 6 of the 7 drugs tested on the standard GISP (Gonococcal Isolate Surveillance Project) panel, and these are the second and third identified gonococcal cases in the US with the *penA60* allele. The first *penA60* allele was identified in Las Vegas, Nevada in December 2019. The United Kingdom (UK) also recently published a case series of ten ceftriaxone-resistant cases, nine carrying the *penA60* allele. All isolates were identified in the first six months of 2022 and most reported travel to Asia. All were cured with UK's recommended gonorrhea treatment – a single injection of ceftriaxone 1g intramuscularly. In the United States, the recommended regimen is a single injection of ceftriaxone 500 mg intramuscularly. CDC also recommends routine test of cure for all known pharyngeal infections.

What to do if treatment failure is suspected

There are specific actions you can take if there is suspicion of a gonococcal treatment failure in any patient at any anatomic site:

- **Conduct a thorough sexual history to evaluate for possible reinfection.**
- **If reinfection has been ruled out, repeat NAAT testing at all exposed anatomic sites, along with collection of specimens for gonococcal culture and antimicrobial susceptibility testing (AST). Clinics that do not have access to culture and AST can reach out to two regional laboratories.**
- **Treating clinicians should consult a STD Clinical Prevention Training Center clinical expert or CDC for advice on obtaining cultures, antimicrobial susceptibility testing, and treatment.**
- **Presumptive treatment failures, where re-infection has been ruled out, should be reported to CDC through the local or state health department within 24 hours of diagnosis.**

Emerging STI



https://www.cdc.gov/poxvirus/mpox/response/2022/world-map.html

MPX virus in human samples and implications for transmission

Exposure source	Mpox virus DNA detected by PCR	Replication-competent virus detected/isolated	Epidemiologically supported source of infection
Skin	Yes	Yes	Yes
Oropharynx and saliva	Yes*	Yes	Yes
Anorectum	Yes	Yes	Yes†
Semen	Yes*	Yes	Insufficient data
Urine/urethra	Yes	Yes	Insufficient data
Conjunctivae or ocular fluid	Yes	Yes	Insufficient data
Blood/plasma/serum	Yes	Insufficient data	Insufficient data
Feces	Yes	Insufficient data	Insufficient data
Vagina	Yes	Insufficient data	Insufficient data†
Breastmilk	Insufficient data	Insufficient data	Insufficient data
Contaminated sharp‡	Insufficient data	Insufficient data	Yes

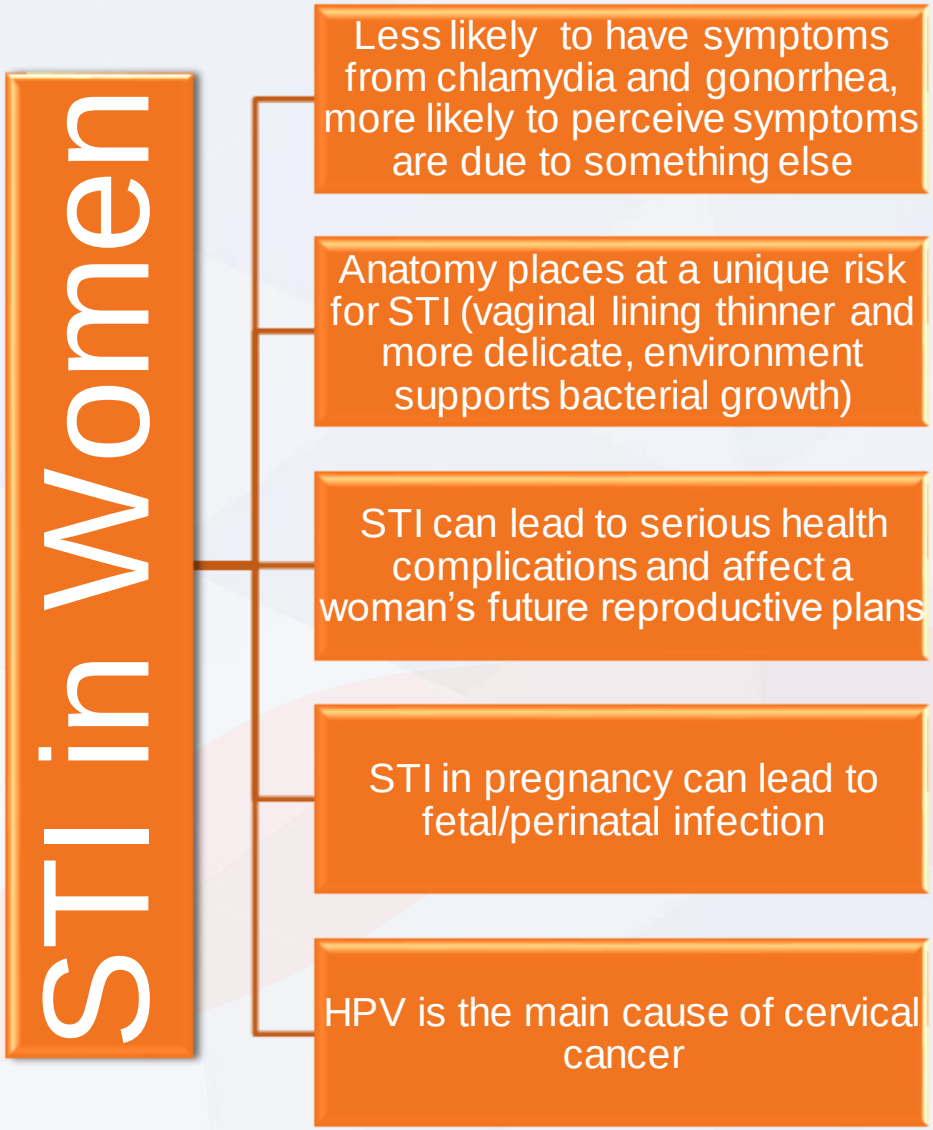
* DNA has been detected at Ct values <35 in recovered patients more than 30 days after illness onset in an upper respiratory tract swab, saliva, and semen.

† The preponderance of existing data support exposure to anorectal and vulvovaginal tissues and fluids as capable of transmitting infection; however, it is difficult with current evidence to definitively isolate these exposures from other concomitant exposures (see text).

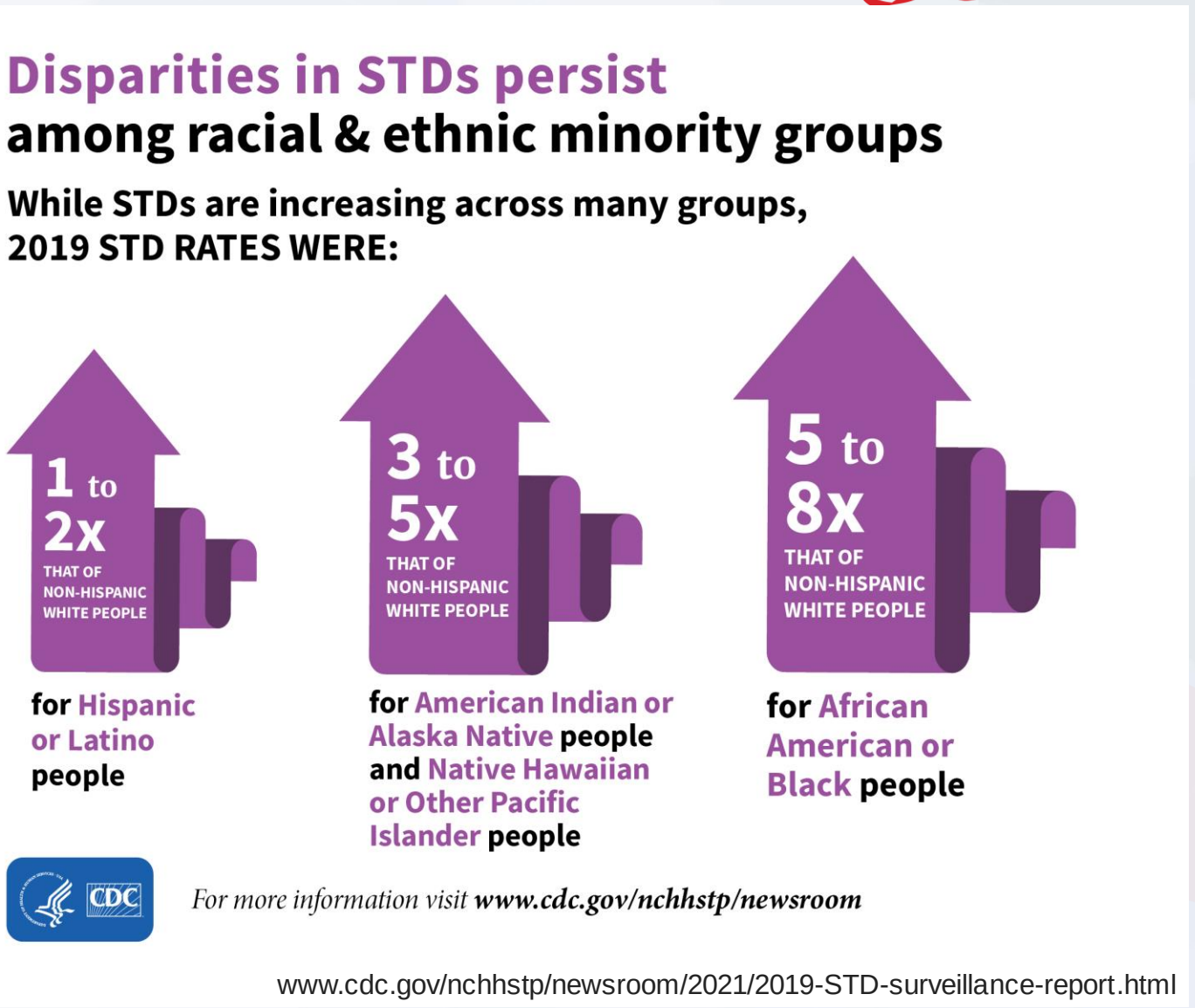
‡ Includes body modification with piercings and tattooing.

https://www.cdc.gov/poxvirus/monkeypox/about/science-behind-transmission.html

Disparities in incidence and adverse outcomes



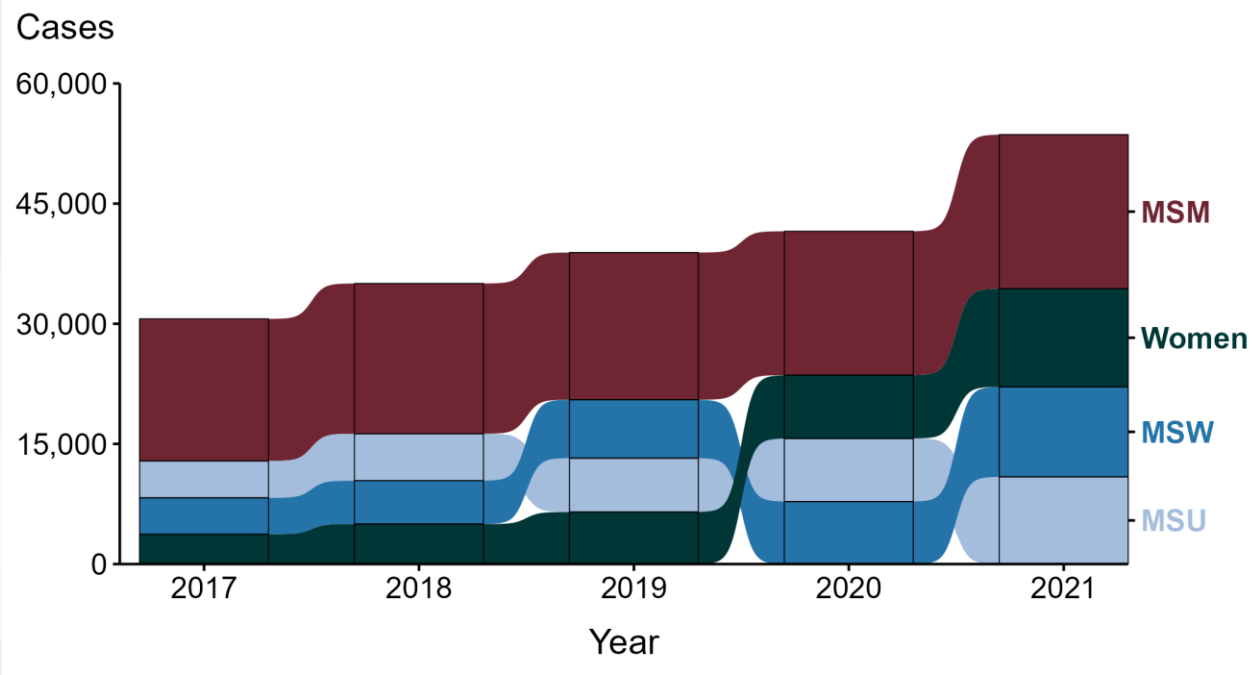
Disparities in incidence and adverse outcomes



www.cdc.gov/nchhstp/newsroom/2021/2019-STD-surveillance-report.html

Disparities in incidence and adverse outcomes

Primary and Secondary Syphilis — Reported Cases by Sex and Sex of Sex Partners, United States, 2017–2021

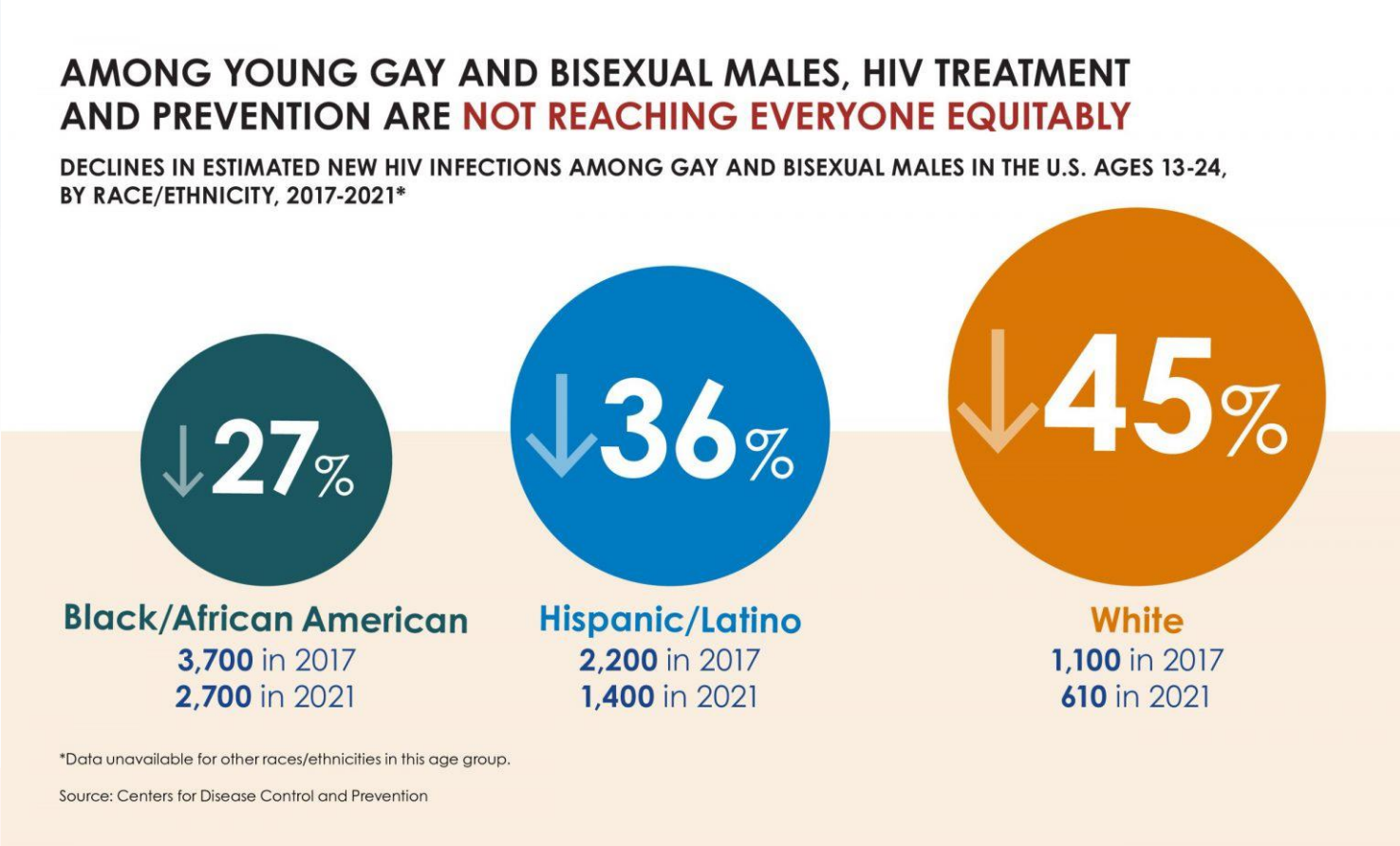


ACRONYMS: MSM = Gay, bisexual, and other men who have sex with men; MSU = Men with unknown sex of sex partners; MSW = Men who have sex with women only

NOTE: Over the five year period, 0.2% of cases were missing sex and were not included.

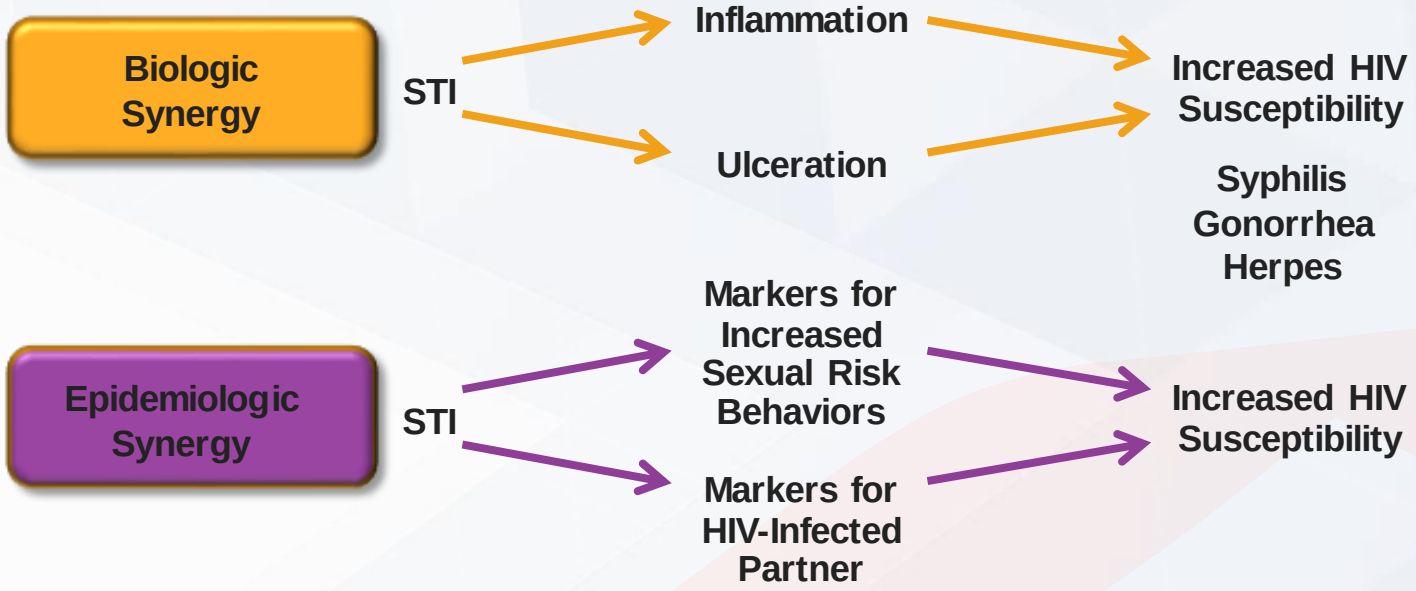
STI Surveillance 2021. CDC

Disparities in incidence and adverse outcomes



https://www.ashasexualhealth.org/young-men-who-have-sex-with-men-lead-progress-in-hiv-prevention-and-treatment-but-disparities-still-exist/

Inextricable link between STI and epidemiology of incident & established HIV infection



Mayer KH, et al. *Am J Reprod Immunol.* 2011;65:308-316.
Mayer KH, et al. *J Int AIDS Soc.* 2018;21(7):e25164.
https://www.cdc.gov/std/hiv/stdfact-std-hiv-detailed.htm

STI Prevention

Condoms

- 1,000 BC – Linen
- 1700 – Animal Intestine
- 1840 – Rubber
- 1920 – Latex
- 1990 – Advanced Latex

https://en.wikipedia.org/wiki/History_of_condoms

STI Prevention

- U=U
- PrEP

Increasing STI in Some Groups

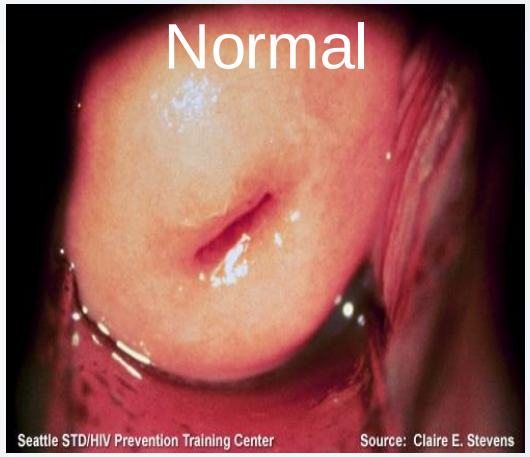
STI Now

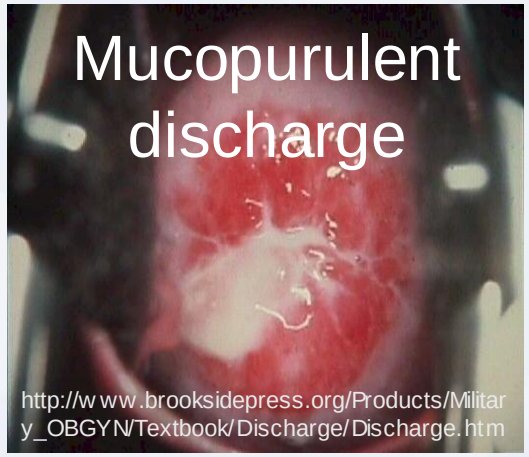
- Incidence increasing, along with morbidity & mortality
- No new treatment
- Medication shortages
- Development of resistance
- Emergence of Mpox
- Stark disparities in incidence & adverse outcomes illustrate health inequity, legacy of structural racism, & biological sexism of STI
- Inextricable from epidemiology of incident & established HIV infection
- Limited prevention tools

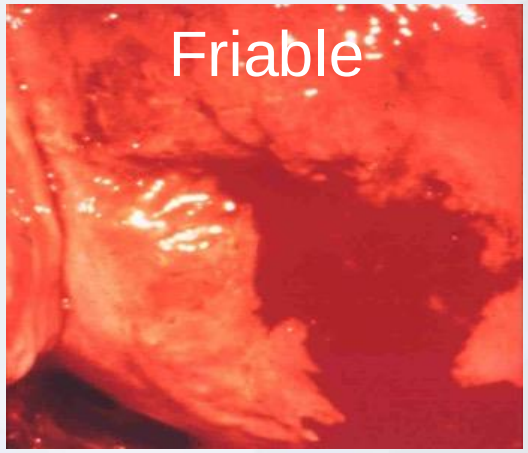
Current evidence-based guidance for the management of STI

Cervicitis: Causes and Presentation

- *C. trachomatis*
- *N. gonorrhoeae*
- *M. genitalium*
- Less Common Causes
  - HSV
  - Adenovirus
  - CMV
  - bacterial vaginosis
  - retained foreign body

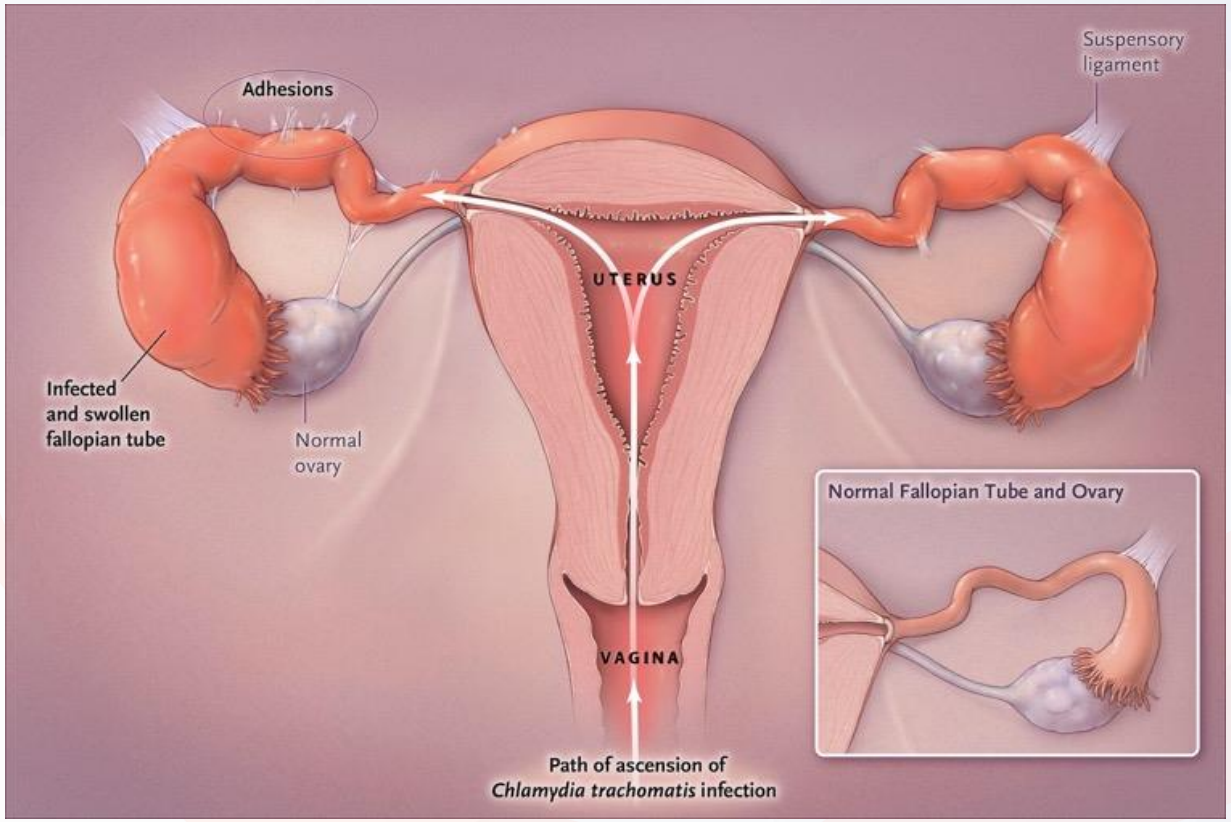






- Usually asymptomatic or present with non-specific symptoms
  - Intermenstrual bleeding
  - Mucopurulent vaginal discharge
  - Pain with intercourse
- Reservoir for sexual / prenatal transmission
- Usual source from which upper genital tract infections develop

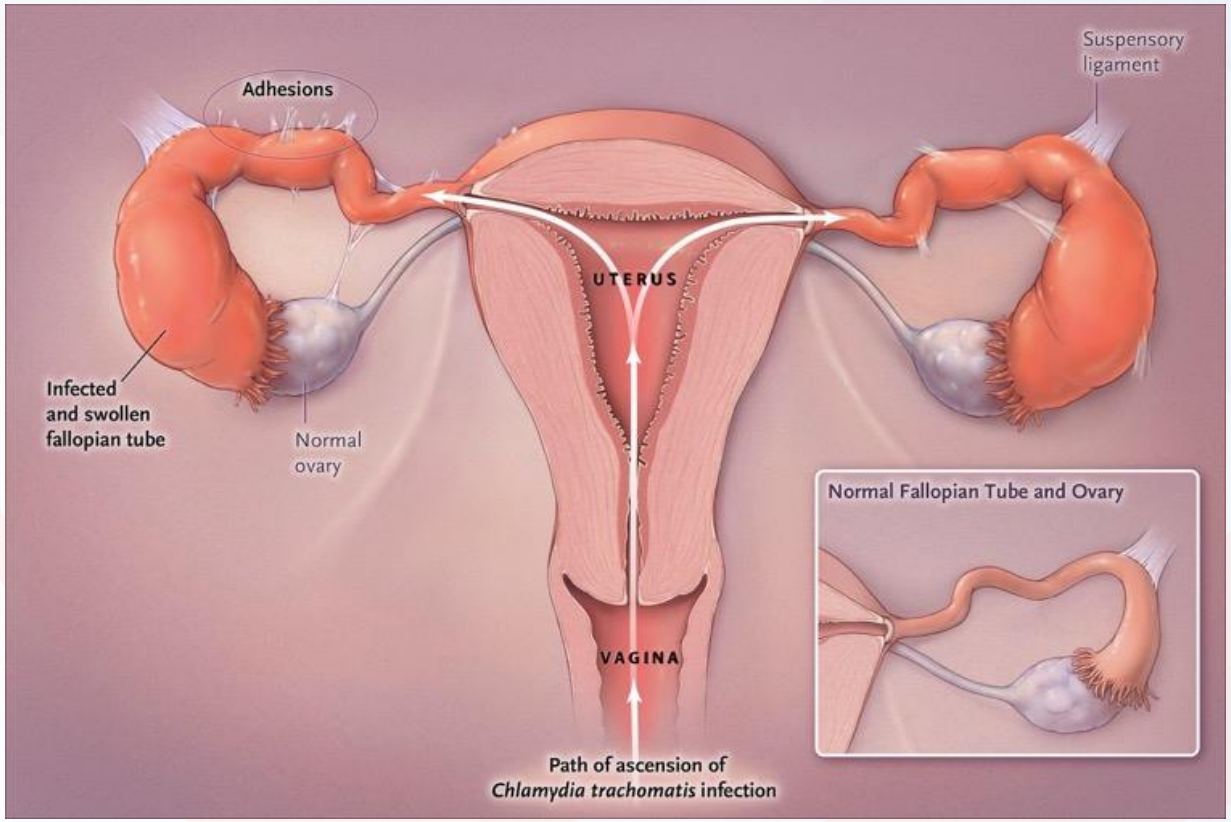
Pelvic Inflammatory Disease--Inflammatory process involving the upper genital tract



Source: Wiesenfeld HC. Screening for *Chlamydia trachomatis* infections in women. N Engl J Med. 2017;376:765-73.

- Endometritis
- Salpingitis
- Oophoritis
- Tubo-ovarian abscess
- Pelvic peritonitis
- Perihepatitis

Pelvic Inflammatory Disease--Inflammatory process involving the upper genital tract

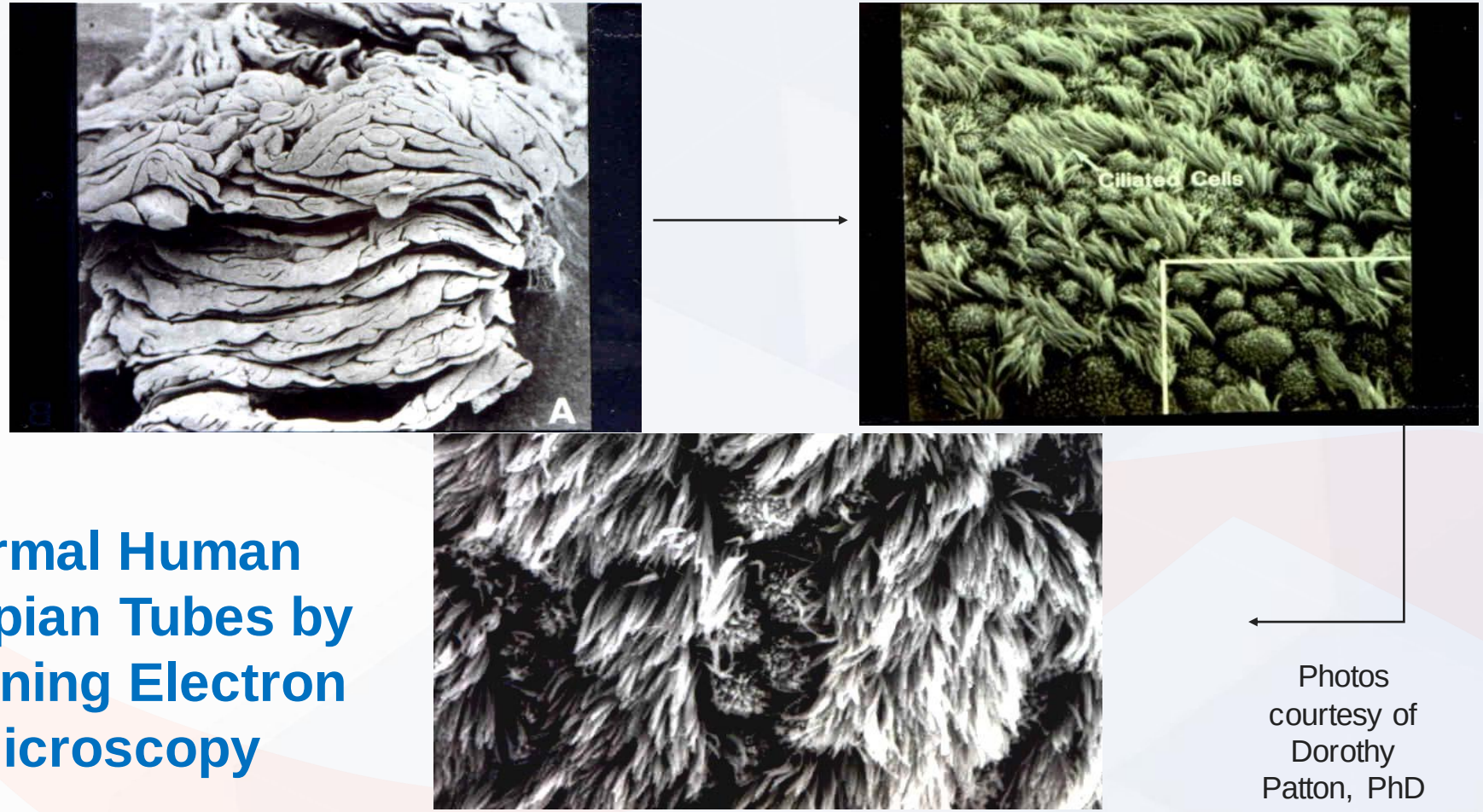


Source: Wiesenfeld HC. Screening for *Chlamydia trachomatis* infections in women. N Engl J Med. 2017;376:765-73.

Infectious Causes

- *C. trachomatis*
- *N. gonorrhoeae*
- Anaerobes (*Bacteroides, Fusobacterium spp)*
- Gram neg. facultative aerobes
- Streptococci (*S. agalactiae*)
- *M. genitalium*
- Less common but reported: S. pneumoniae; Haemophilus spp.

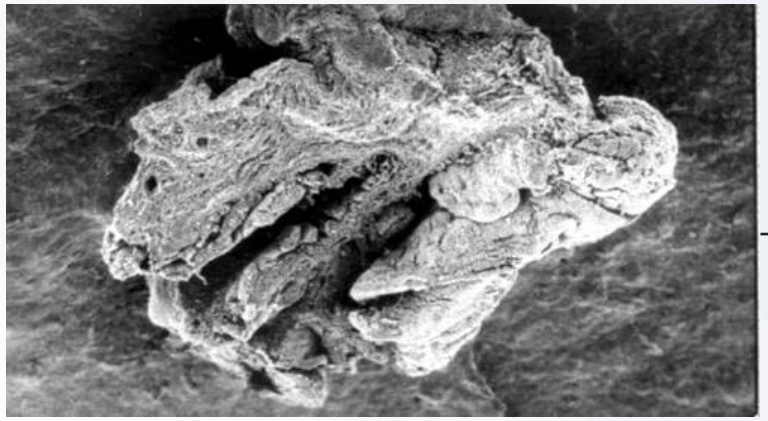
Pelvic Inflammatory Disease

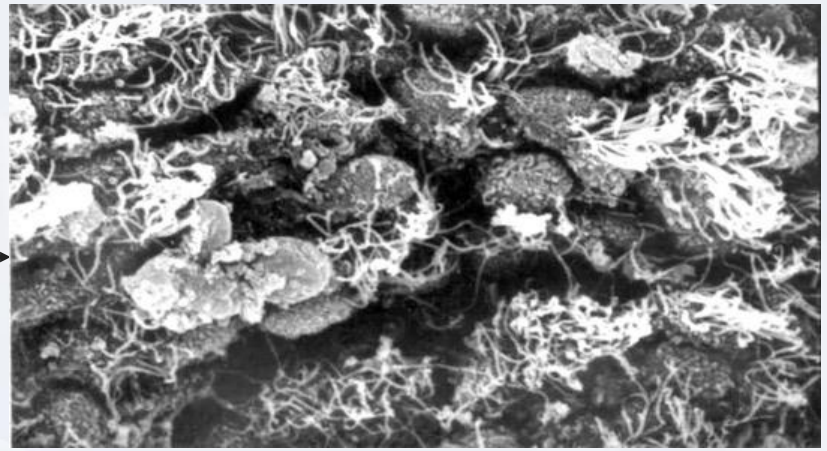


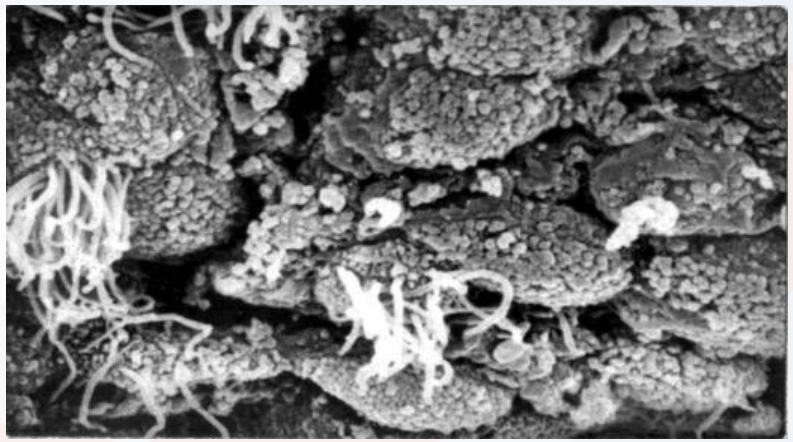
Normal Human Fallopian Tubes by Scanning Electron Microscopy

Photos courtesy of Dorothy Patton, PhD

Pelvic Inflammatory Disease





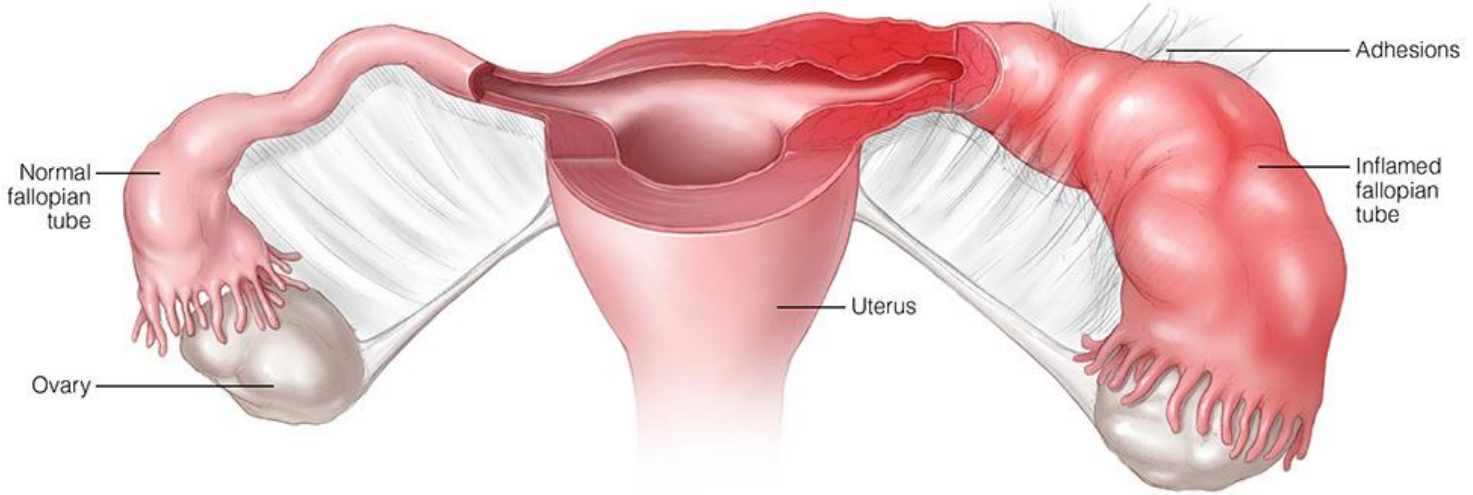


Fallopian Tubes SEM after *Chlamydia trachomatis* infection

Photos courtesy of Dorothy Patton, PhD

Pelvic Inflammatory Disease: Involuntary Infertility

- Accounts for 21% of cases
- Likelihood increases with number of episodes of PID

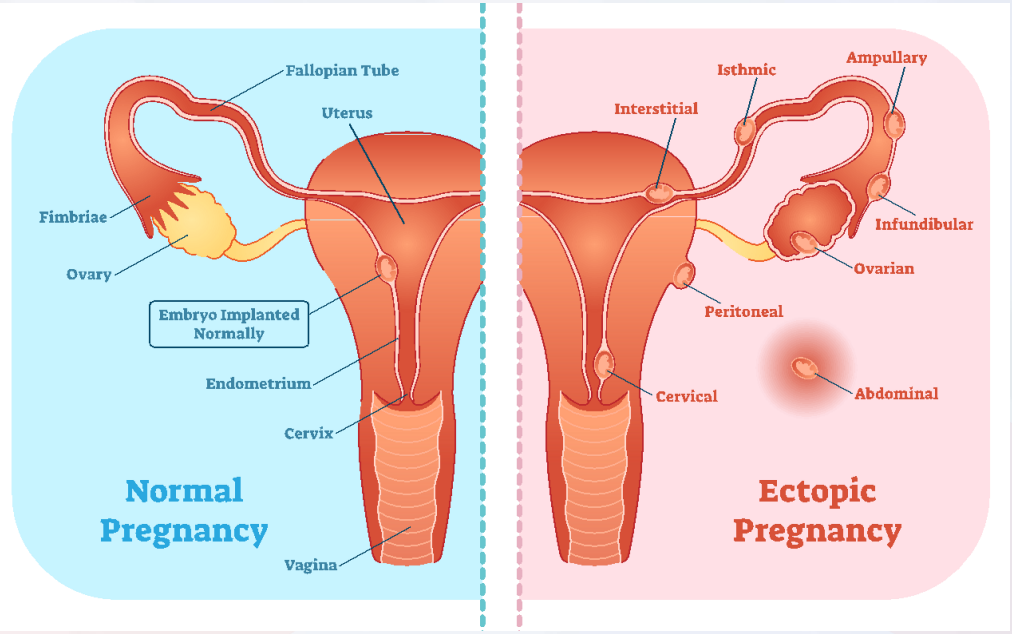


Inflammation and associated tissue repair from PID leads to tubal occlusion and tubal adhesion (intraluminal and extraluminal)

Westrom et al. Sex Transm Dis 1992;19
National STD Curriculum

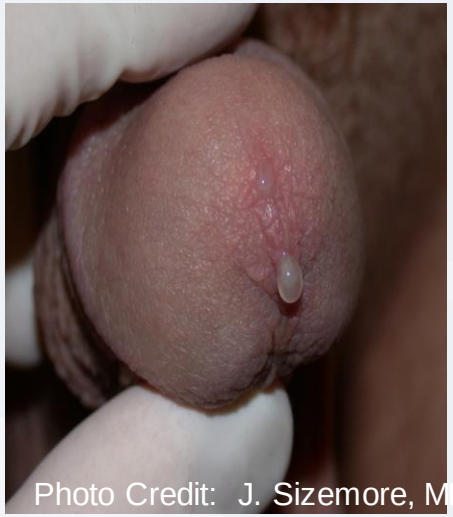
Pelvic Inflammatory Disease – Other Consequences

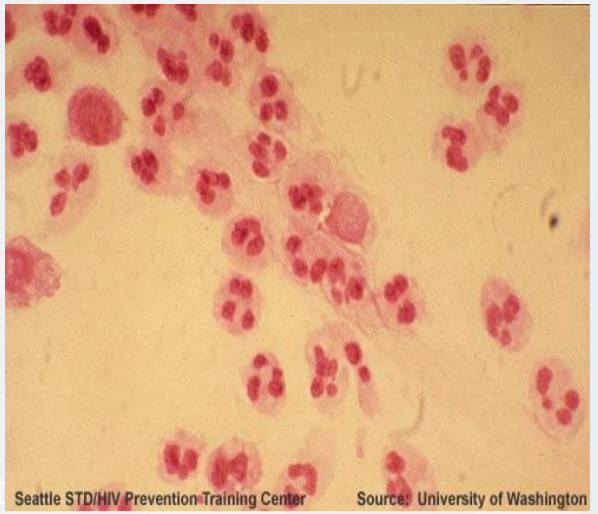
- Any sequelae: 25%
- Ectopic pregnancy: 6-10 times increased likelihood
  - Tubal location: 96%
- Chronic pelvic pain: 18%

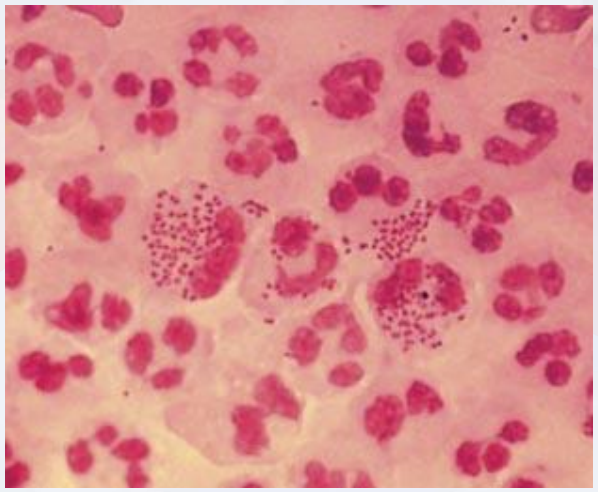


Urethritis: Causes and Presentation

- *C. trachomatis*
- *N. gonorrhoeae*
- *T. vaginalis*
- *M. genitalium*
- Less common Causes
  - Herpes simplex virus
  - Coliforms (E. coli, other rectal flora)







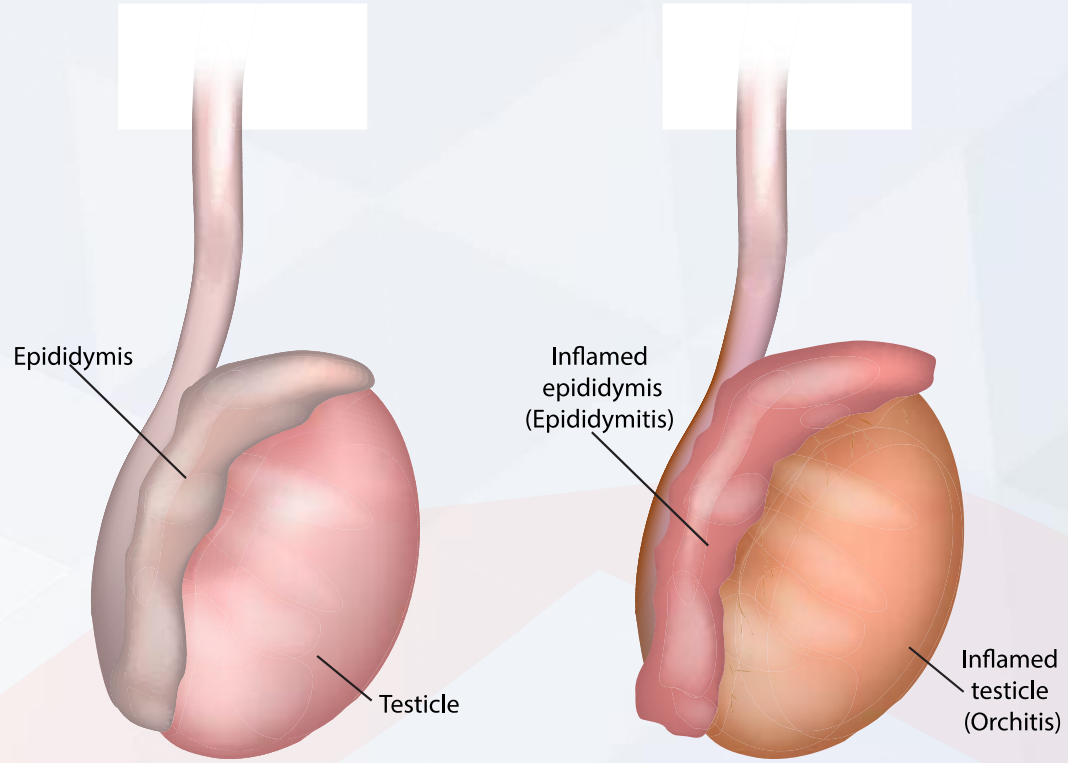
Epididymitis: Inflammation of epididymis usually due to infection

Symptoms

- Unilateral testicular pain and tenderness

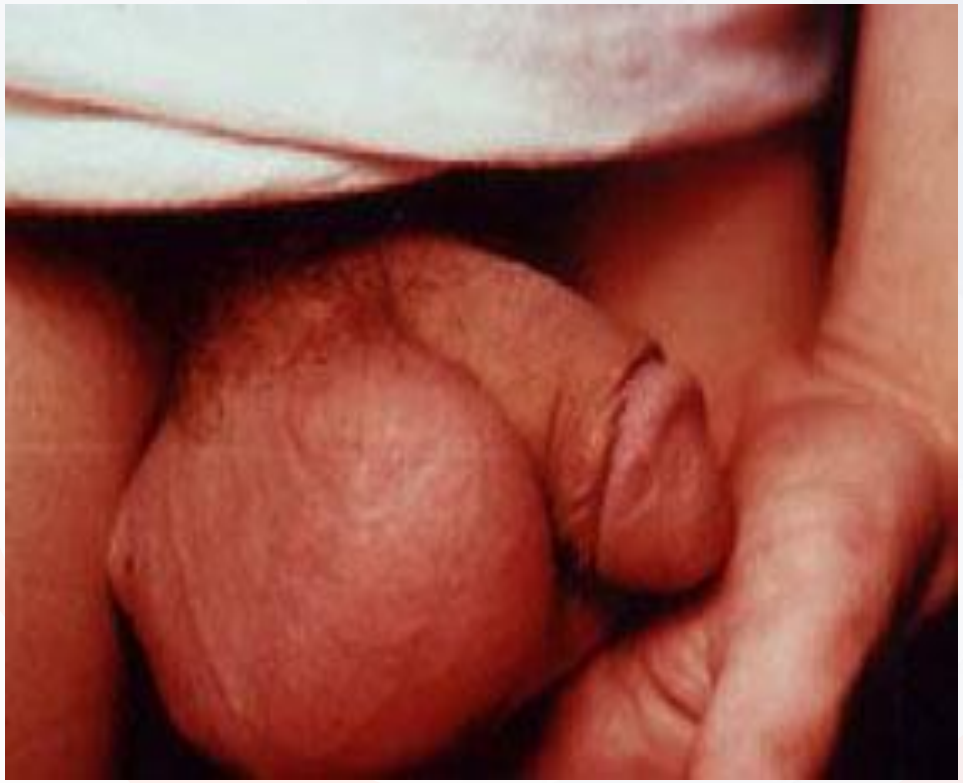
Signs

- Tender/swollen testicle and/or scrotum
- Palpable swelling and tenderness of the epididymis
- Urethral discharge
- Hydrocele may be present



Taylor, SN. CID 2015:61 (suppl 8)

Epididymitis: Inflammation of epididymis usually due to infection



http://www.siamhealth.net/Disease/infectious/std/Epidi.htm

Infectious Causes

- *C. trachomatis*
- *N. gonorrhoeae*
- Coliform bacteria
- M. tuberculosis
- MOTT
- Brucellosis
- H. influenzae
- Listeria
- Streptococcus
- Fungal
- Viral
- Parasitic

Taylor, SN. CID 2015:61 (suppl 8)

Proctitis - Causes

INFECTIOUS

- *N. gonorrhoeae*
- *C. trachomatis* (serovars D through K)
- Lymphogranuloma venereum
- *Treponema pallidum*
- *MPOX*
- Cytomegalovirus
- *M. tuberculosis*
- Human immunodeficiency virus
- Herpes simplex virus
- *H. ducreyi* (chancroid)
- *K. granulomatis* (granuloma inguinale)

NON-INFECTIOUS

Autoimmune conditions

- Crohn's disease
- Ulcerative colitis
- Lymphoid follicular proctitis
- Behçet's syndrome

Trauma

- Foreign bodies
- Chemical proctitis

Lymphoma

Ischemia

Amyloidosis

Idiopathic causes

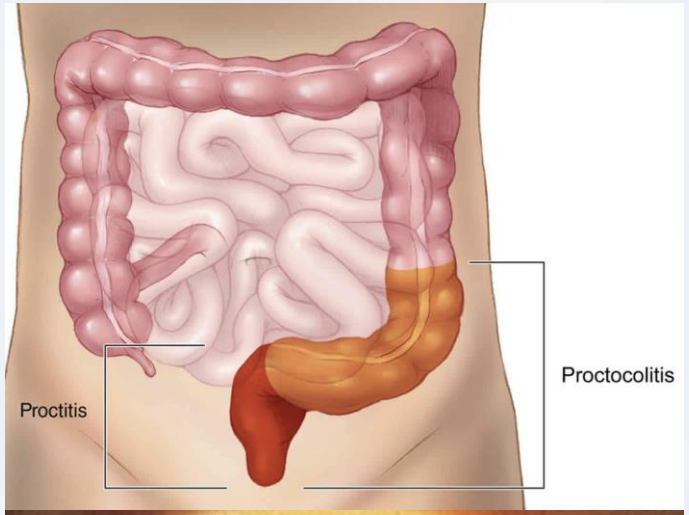
Proctitis – Inflammation of the Rectum

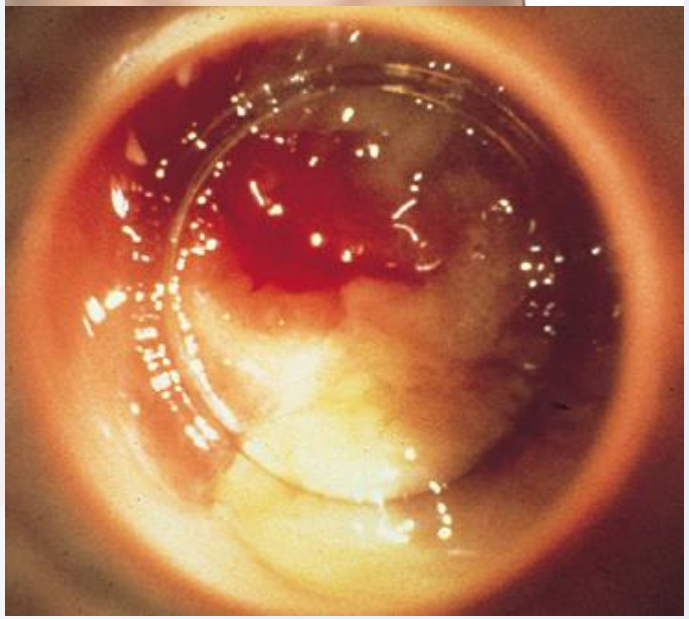
Symptoms

- Anorectal Pain
- Rectal Discharge
- Rectal Bleeding

Signs

- Mucopurulent discharge
- Spontaneous or easily induced bleeding
- Ulceration
- Rectal Gram stain >1 PMN/HPF





https://healthjade.net/proctocolitis/

Proctitis - Causes

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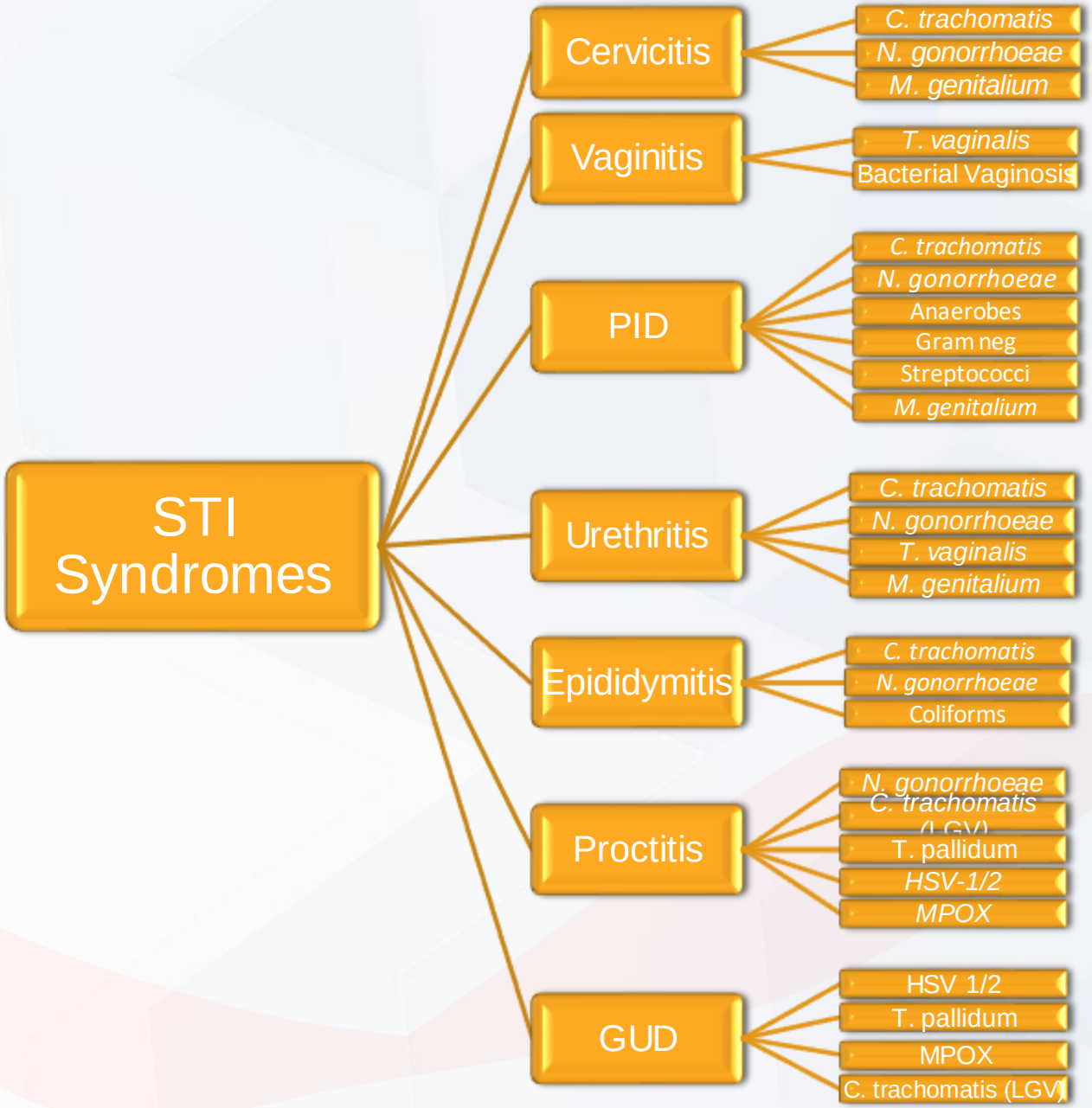
STI Syndromes
Cervicitis
C. trachomatis
N. gonorrhoeae
M. genitalium
Vaginitis
T. vaginalis
Bacterial Vaginosis
PID
C. trachomatis
N. gonorrhoeae
Anaerobes
Gram neg
Streptococci
M. genitalium
Urethritis
C. trachomatis
N. gonorrhoeae
T. vaginalis
M. genitalium
Epididymitis
C. trachomatis
N. gonorrhoeae
Coliforms
Proctitis
N. gonorrhoeae
C. trachomatis
T. pallidum
HSV-1/2
MPOX
GUD
HSV 1/2
T. pallidum
MPOX
C. trachomatis (LGV)

Gonorrhea Treatment - 2023

Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum

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

Alternative Regimens if Ceftriaxone Is Not Available
Gentamicin 240 mg IM in a single dose *plus* **Azithromycin** 2 g orally in a single dose *or* **Cefixime*** 800 mg orally in a single dose
* If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

Uncomplicated Gonococcal Infection of the Pharynx

Recommended Regimen for Uncomplicated Gonococcal Infection of the Pharynx Among Adolescents and Adults
Ceftriaxone 500 mg* IM in a single dose for persons weighing <150 kg
* For persons weighing ≥150 kg, 1 g ceftriaxone should be administered.

- No reliable alternative treatments are available for pharyngeal gonorrhea.
- For persons with a history of a beta-lactam allergy, a thorough assessment of the reaction is recommended.

Test of Cure for Pharyngeal Infections

- Perform TOC at 7-14 days after treatment
- Persistent nonviable organisms may cause a false positive NAAT
- Reinfection from re-exposure is a common cause of persistent positive GC tests

RNA NAAT

TOC Pharynx*	N	Persistent RNA NAAT N (%)	OR (95% CI)
0-7 days	309	27 (8.7)	1 -----
8-14 days	367	8 (2.2)	0.23 (0.1-0.52)
15-28 days	105	1 (1.0)	0.10 (0.01-0.75)

DNA NAAT

Pharyngeal GC persistence--DNA NAAT	% (95% CI)
7 days	13 (6.4-19.6)
14 days	8 (2.7-13.3)
All cultures negative	

- Hananta IPY, De Vries HJC, van Dam AP, van Rooijen MS, Soebono H, Schim van der Loeff MF. Persistence after treatment of pharyngeal gonococcal infections in patients of the STI clinic, Amsterdam, the Netherlands, 2012-2015: a retrospective cohort study. Sex Transm Infect. 2017 Nov;93(7):467-471. doi: 10.1136/sextrans-2017-053147. Epub 2017 Aug 19. PMID: 28822976; PMCID: PMC5739854.
- Bissessor M, Whiley DM, Fairley CK, Bradshaw CS, Lee DM, Snow AS, Lahra MM, Hocking JS, Chen MY. Persistence of Neisseria gonorrhoeae DNA following treatment for pharyngeal and rectal gonorrhea is influenced by antibiotic susceptibility and reinfection. Clin Infect Dis. 2015 Feb 15;60(4):557-63. doi: 10.1093/cid/ciu873. Epub 2014 Nov 3. PMID: 25371490.

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June 2022 Volume 60 Issue 6 e00399-22
https://doi.org/10.1128/jcm.00399-22

Time to Clearance of *Neisseria gonorrhoeae* RNA at the Pharynx following Treatment

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[b]Public Health Seattle and King County HIV/STD Program, Seattle, Washington, USA
[c]University of Washington, Department of Global Health, Seattle, Washington, USA
[d]University of Washington, Department of Epidemiology, Seattle, Washington, USA

ABSTRACT The number of days until pharyngeal *Neisseria gonorrhoeae* nucleic acid amplification test (NAAT) results become negative after treatment remains unknown. Between March 2019 and April 2021, we enrolled men who have sex with men (MSM) who had a clinical positive pharyngeal *N. gonorrhoeae* Aptima Combo 2 test result but had not yet been treated in a prospective longitudinal cohort study. MSM were enrolled on their day of treatment and self-collected daily pharyngeal specimens for 21 days at home. We used Kaplan-Meier estimates to determine the median time to clearance and the >95% time to clearance and the log rank test for equality to evaluate factors associated with time to clearance. Sixty-four men were enrolled in the study. Analyses excluded 8 men (12.5%) who were *N. gonorrhoeae* negative by NAAT at enrollment and 11 (17%) who failed to return any home-collected specimens. Among the 45 men included in the analysis, the median time to *N. gonorrhoeae* NAAT clearance was 3 days (95% confidence interval [CI], 2 to 5 days). Time to clearance for >95% of the cohort was 12 days (95% CI, 10 days to an undefined time). Men with a history of *N. gonorrhoeae* infection cleared faster than men without such history (8 days versus 17 days for >95% time to clearance; $P = 0.03$). In the absence of reexposure, positive *N. gonorrhoeae* Aptima Combo 2 assay results obtained prior to 12 days after treatment are likely false-positive results.

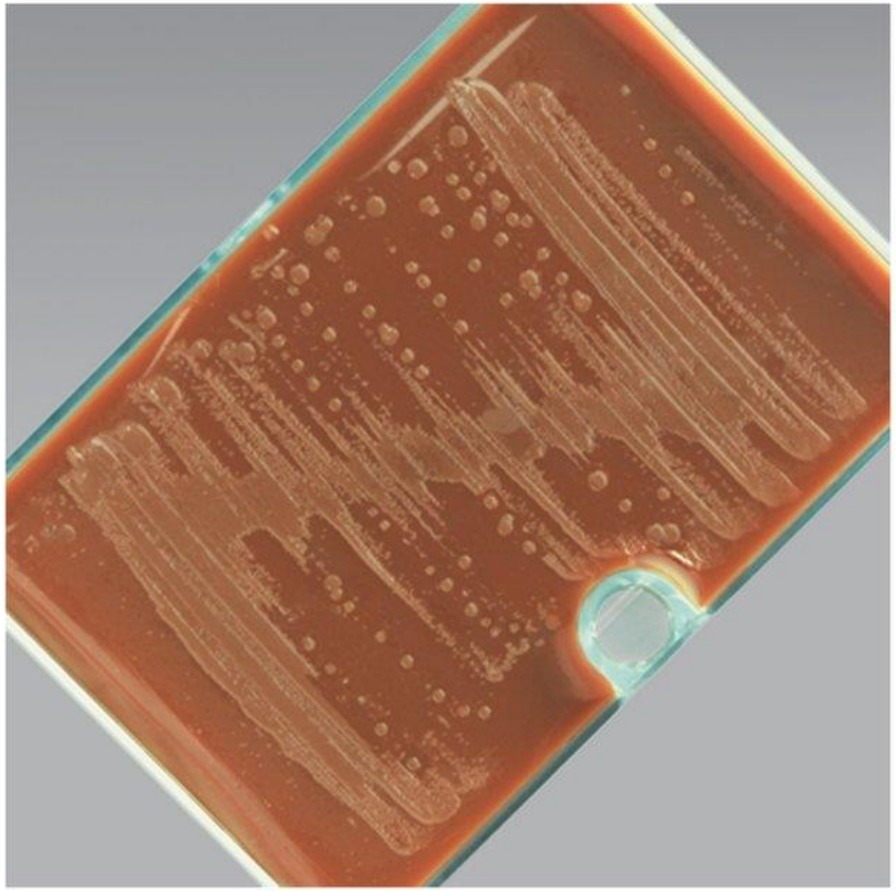
KEYWORDS NAAT, *Neisseria gonorrhoeae*, clearance

- Median time to NAAT clearance was 3 days
- >95% cleared in 12 days
- Men with ahistory of N. gonorrhoeae infection cleared more quickly than men without
  - 8 days versus 17 days

What if this patient's test of cure were positive?

- Most suspected treatment failures are reinfections

- If re-infection is unlikely:
  - Obtain simultaneous NAAT and gonorrhea culture
  - Alert public health authorities
  - Treat with either ceftriaxone or gentamicin/azithromycin



Chlamydia Treatment - 2022

Recommended Regimens

Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days
OR
Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
OR
Levofloxacin 500 mg orally once daily for 7 days
OR
Ofloxacin 300 mg orally twice a day for 7 days

2015 Recommendation

Recommended Regimen for Chlamydial Infection Among Adolescents and Adults

Doxycycline 100 mg orally 2 times/day for 7 days

Alternative Regimens

Azithromycin 1 g orally in a single dose
or
Levofloxacin 500 mg orally once daily for 7 days

2021 Recommendation

Weighing the Data: Chlamydia Treatment

Doxycycline (better efficacy)

1. Urogenital RCT of DOT, Txt Efficacy
   Doxy 100% vs Azithro 97%

2. Meta-analysis; 8 observational studies rectal CT, Txt Efficacy
   Doxy 99.6% vs Azithro 82.9%

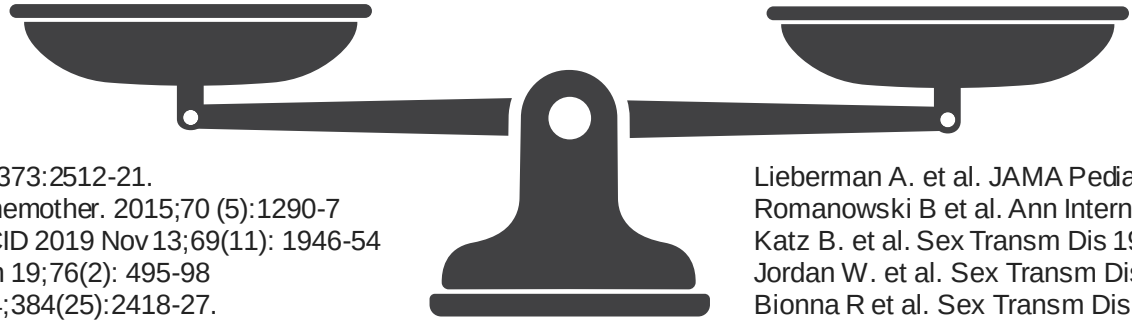
3. Rectal CT RCT in MSM, Txt Efficacy
   Doxy superior (20-26% difference)

Azithromycin (lower efficacy)

1. Medication access: Retrospective cohort 13-19 year olds with STI, 57.7% of prescriptions filled

2. Adherence: Doxycycline self-reported adherence 60-90%. Medication monitoring—strict adherence 16-40%

3. Confidentiality



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M. genitalium

- When to test
  - Persistent/recurrent NGU or cervicitis
  - Persistent epididymitis or proctitis
  - Consider testing in PID
  - **Asymptomatic screening in not recommended**
    - Natural history is not defined
- How to test
  - FDA approved NAAT (urine, urethral, penile, meatal, endocervical, and vaginal specimens)
- How to treat (must account for resistance)
  - Macrolide resistance: 44-90% (U.S., Canada, Europe, Australia)
    - Treatment with azithromcycin 1 gm in macrolide susceptible strains results in selection of resistant strains in 10-12% of cases
  - Fluoroquinolone resistance: 0-15% (U.S.)

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Li Y, Su X, Le W, et al. Mycoplasma genitalium in symptomatic male urethritis: macrolide use is associated with increased resistance. Clin Infect Dis. 2020;70(5):805–10.
Gesink D, Racey CS, Seah C, et al. Mycoplasma genitalium in Toronto, Ont: estimates of prevalence and macrolide resistance. Can Fam Physician. 2016;62(2):e96–101.
Bissessor M, Tabrizi SN, Twin J, et al. Macrolide resistance and azithromycin failure in a Mycoplasma genitalium-infected cohort and response of azithromycin failures to alternative antibiotic regimens. Clin Infect Dis. 2015;60(8):1228–36.

M. genitalium: Treatment - 2022

Recommended Regimens if *M. genitalium* Resistance Testing Is Available

If macrolide sensitive: **Doxycycline** 100 mg orally 2 times/day for 7 days, followed by **azithromycin** 1 g orally initial dose, followed by 500 mg orally daily for 3 additional days (2.5 g total)

If macrolide resistant: **Doxycycline** 100 mg orally 2 times/day for 7 days followed by **moxifloxacin** 400 mg orally once daily for 7 days

Recommended Regimen if *M. genitalium* Resistance Testing Is Not Available

If *M. genitalium* is detected by an FDA-cleared NAAT: **Doxycycline** 100 mg orally 2 times/day for 7 days, followed by **moxifloxacin** 400 mg orally once daily for 7 days

Indiscriminate screening for M. genitalium

- Routine screening for M. genitalium is not recommended by CDC in asymptomatic women (whether pregnant or not) or men.
- When screening for STI, use a screening test that does not include M. gent.
- No guidance about whether to treat asymptomatic M. gent.
- What to do when the test is positive in an asymptomatic patient?
  - We don't know
  - Consider a shared-decision making approach
- What do we do in pregnancy?
  - Azithromycin is the only safe agent.

Pelvic Inflammatory Disease - 2023

RCT of CTX & Doxycycline +/- MTZ for Acute PID

- Compared ceftriaxone 250 mg IM single dose and doxycycline for 14 days, with or without 14 days of MTZ

- Primary outcome:
  - Clinical improvement 3 days following enrollment.
  - Additional outcomes at 30 days
    - Presence of anaerobic organisms in endometrium
    - Clinical cure (absence of fever and reduction in tenderness)
    - adherence and tolerability

- 233 women (116 to MTZ and 117 to placebo)

Wiesenfeld HC et al. Clin Inf Dis 2021;72(7):1181-9

Pelvic Inflammatory Disease - 2023

RCT of CTX & Doxycycline +/- MTZ for Acute PID

- Clinical improvement at 3 days similar.

- At 30 days following treatment (MTZ vs. Placebo)
  - Anaerobic organisms less frequently recovered (8% vs 21%, $p<0.05$)
  - Cervical *M. genitalium* reduced (4% vs. 14%, $p<0.05$).
  - Pelvic tenderness less common (9% vs 20%, $p<0.01$).
  - Adverse events and adherence similar

- **Metronidazole should be routinely added to ceftriaxone and doxycycline for the treatment of acute PID**

Wiesenfeld HC et al. Clin Inf Dis 2021;72(7):1181-9

Pelvic Inflammatory Disease - 2023

Recommended Parenteral Regimens for Pelvic Inflammatory Disease

Ceftriaxone 1 g IV every 24 hours

PLUS

Doxycycline 100 mg orally or IV every 12 hours

PLUS

Metronidazole 500 mg orally or IV every 12 hours

OR

Cefotetan 2 g IV every 12 hours

PLUS

Doxycycline 100 mg orally or IV every 12 hours

OR

Cefoxitin 2 g IV every 6 hours

PLUS

Doxycycline 100 mg orally or IV every 12 hours

Recommended Intramuscular or Oral Regimens for Pelvic Inflammatory Disease

Ceftriaxone 500 mg IM in a single dose*

PLUS

Doxycycline 100 mg orally 2 times/day for 14 days

WITH

Metronidazole 500 mg orally 2 times/day for 14 days

OR

Cefoxitin 2 g IM in a single dose and **Probenecid** 1 g orally administered concurrently in a single dose

PLUS

Doxycycline 100 mg orally 2 times/day for 14 days

WITH

Metronidazole 500 mg orally 2 times/day for 14 days

OR

Other parenteral third-generation **cephalosporin** (e.g., ceftizoxime or cefotaxime)

PLUS

Doxycycline 100 mg orally 2 times/day for 14 days

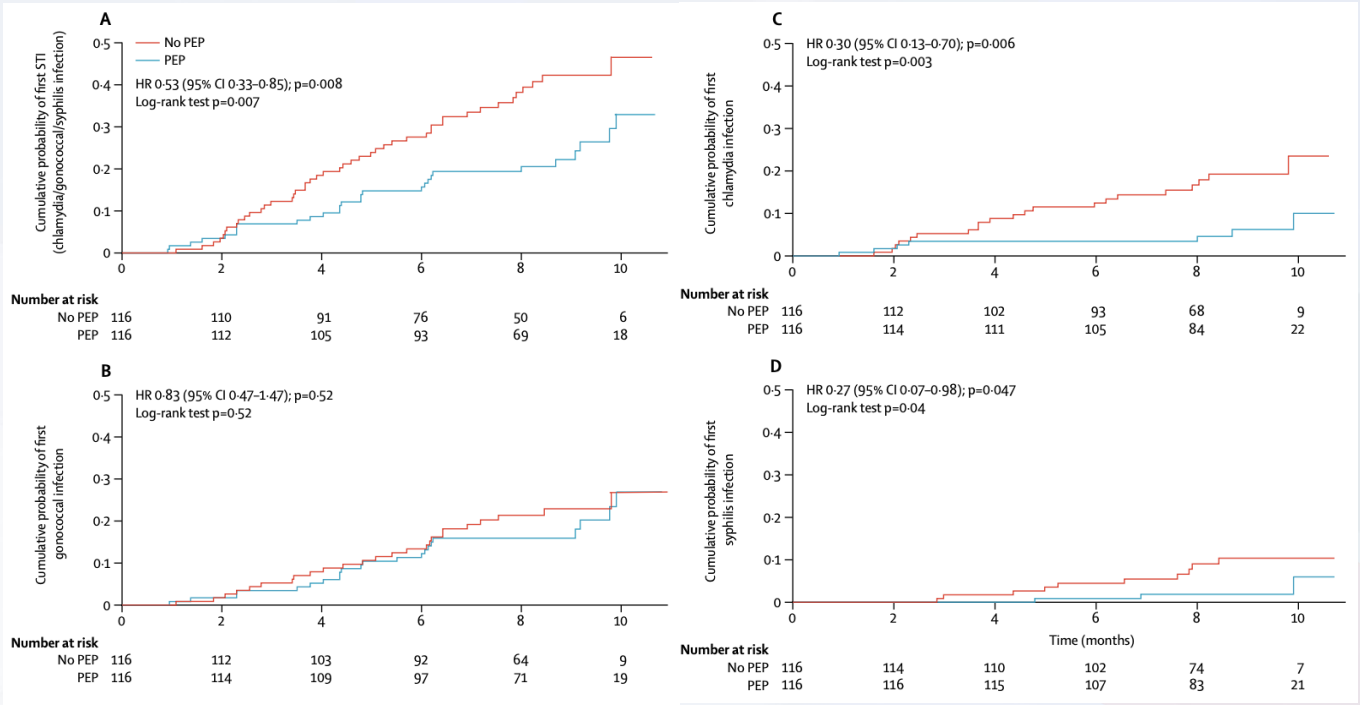
WITH

Metronidazole 500 mg orally 2 times/day for 14 days

*For persons weighing >150 kg (~300 lbs.) with documented gonococcal infection, 1 g of ceftriaxone should be administered.

Advances in STI Prevention

- 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
  - No PEP
  - Doxy PEP: 200 mg within 24 hours of sex and no later than 72 hours after sex



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Doxycycline as STI Pep

Doxycycline post-exposure prophylaxis for STI prevention among MSM and transgender women on HIV PrEP or living with HIV: high efficacy to reduce incident STI's in a randomized trial

- Methods
  - Open label RCT
  - Seattle and San Francisco MSM/TGW living with HIV or on PrEP
  - Diagnosed with *N. gonorroheae, C. trachomatis*, or early syphilis in past 12 months
  - 2:1 randomization to 200 mg doxycycline hyclate within 72 hours of condomless sex or no doxycycline with STI testing at enrollment, quarterly, and when symptomatic

https://www.cdc.gov/std/treatment-guidelines/clinical-primary.htm#CautionsForDoxyPEP

A. Luetkemeyer. **Doxycycline post-exposure prophylaxis for STI prevention among MSM and transgender women on HIV PrEP or living with HIV: high efficacy to reduce incident STI's in a randomized trial. AIDS 2022. https://programme.aids2022.org/Abstract/Abstract/?abstractid=13231**

Doxycycline as STI Pep

Table: Quarterly STI incidence by HIV status and by randomization to doxyPEP & control arms

	HIV uninfected MSM/TGW on PrEP		MSM/TGW living with HIV		Total	
	Doxy arm N=240	Control arm N=120	Doxy arm N=134	Control arm N=60	Doxy Arm N=374	Control arm N=180
Follow up quarters	491	220	266	108	757	328
Participants with an incident STI (GC, CT or syphilis)	41	42	24	18	65	60
Primary STI endpoints	47 (9.6%)	65 (29.5%)	31 (11.7%)	30 (27.8%)	78 (10.3%)	95 (29.0%)
Gonorrhea	40 (8.1%)	45 (20.5%)	21 (7.9%)	20 (18.5%)	61 (8.1%)	65 (19.8%)
Chlamydia	7 (1.4%)	23 (10.5%)	12 (4.5%)	16 (14.8%)	19 (2.5%)	39 (11.9%)
Syphillis	1 (0.2%)	5 (2.3%)	3 (1.1%)	2 (1.9%)	4 (0.5%)	7 (2.1%)

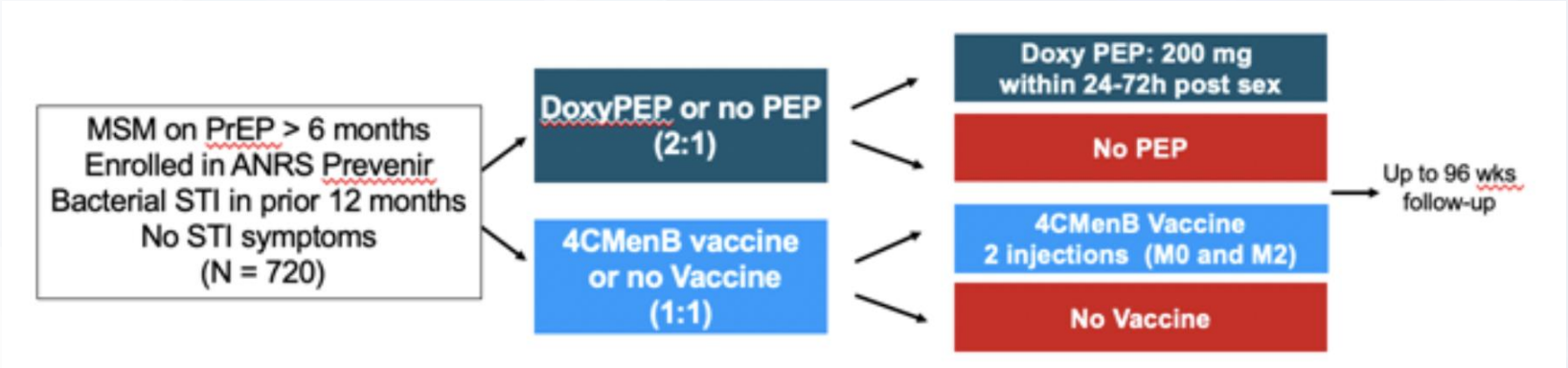
A single interim analysis at ~50% of follow-up time occurred May 2022; the DSMB recommended stopping the control arm based on prespecified efficacy thresholds measured independently in PLWH and PrEP cohorts.

https://www.cdc.gov/std/treatment-guidelines/clinical-primary.htm#CautionsForDoxyPEP

A. Luetkemeyer. **Doxycycline post-exposure prophylaxis for STI prevention among MSM and transgender women on HIV PrEP or living with HIV: high efficacy to reduce incident STI's in a randomized trial. AIDS 2022. https://programme.aids2022.org/Abstract/Abstract/?abstractid=13231**

Doxycycline as STI Pep

DOXYVAC: An open label randomized controlled trial to prevent STI in MSM on PrEP



Primary Efficacy endpoint:

- Time to first episode CT and Syphilis (DoxyPEP)
- Time to first episode GC (4CMenB)

Results

- DoxyPep: 65% reduction in STI (~80% for CT and Syphilis; ~55% GC)
- 4CMenB Vaccine: Adjusted incidence rate (0.66 CI 0.43-1.00, p 0.052)

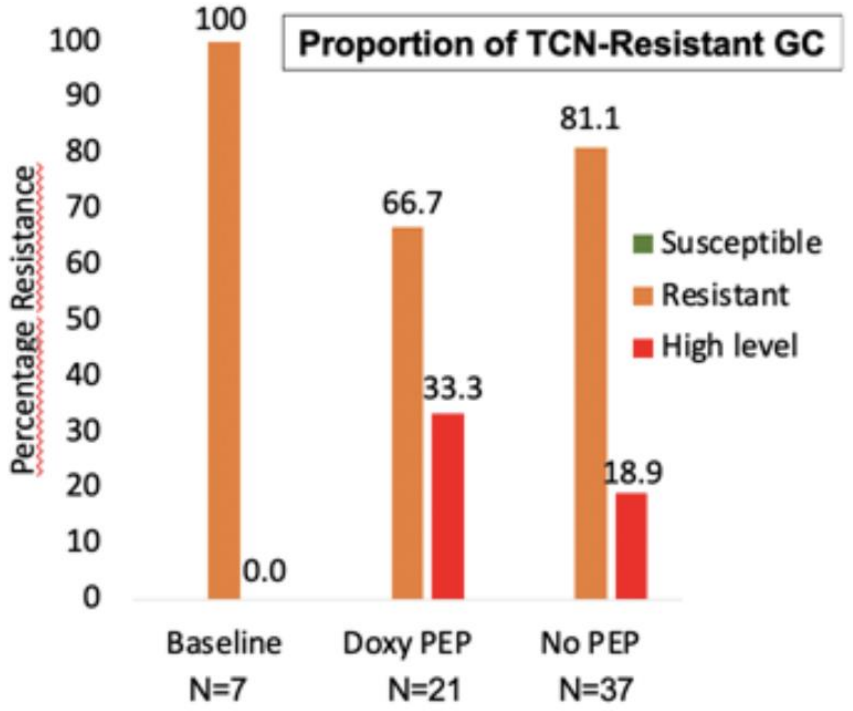
Molina et al. CROI, 2023

Doxycycline as STI Pep

DOXYVAC: An open label randomized controlled trial to prevent STI in MSM on PrEP

Tetracycline (TCN) Resistance for GC and CT

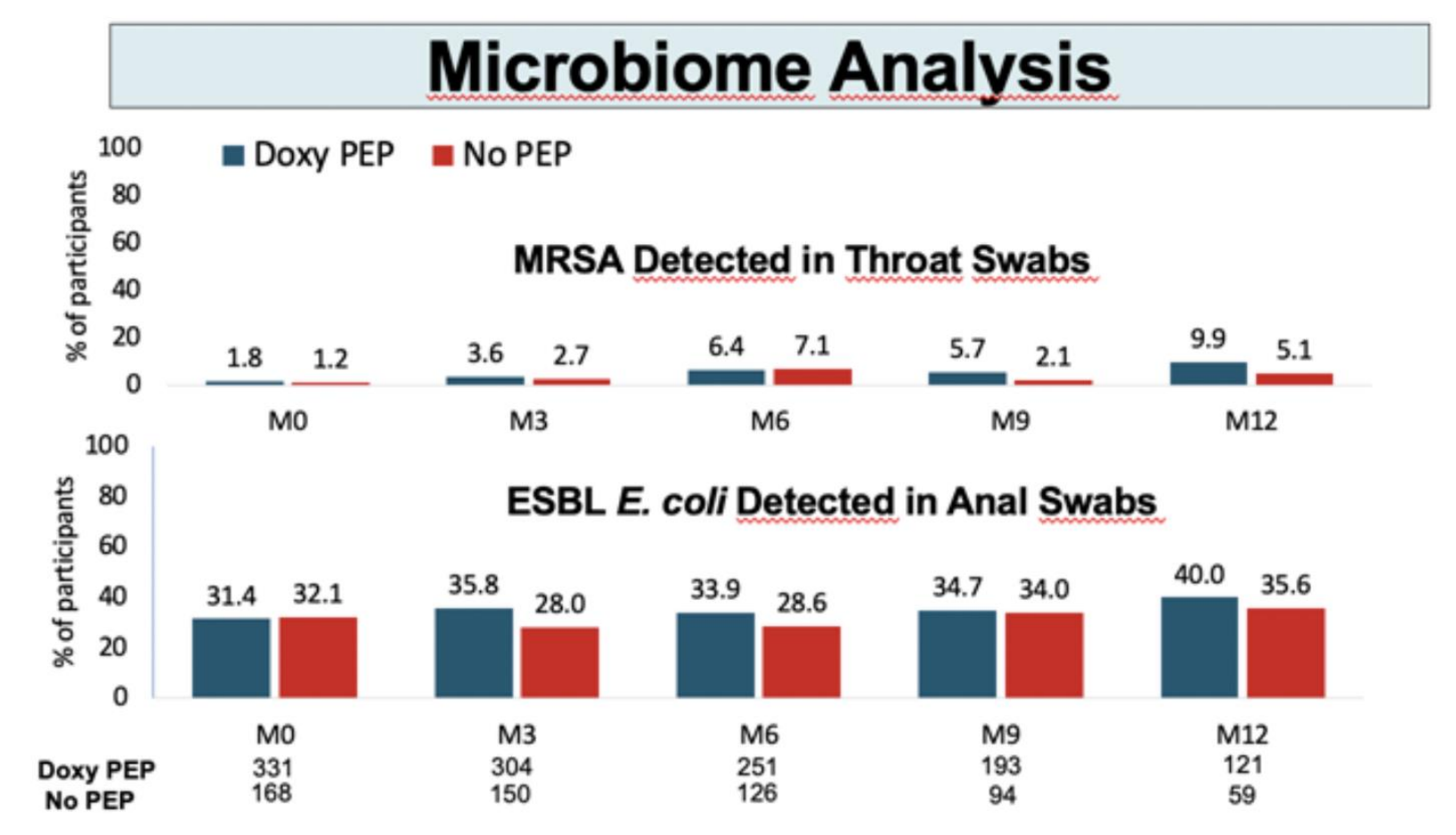
- **GC:**
  - 65 cultures available for resistance testing (15% of PCR positive samples)
  - Tetracycline MICs determined by Etest
  - Resistance using EUCAST 2023 breakpoints
    - Resistance: MIC > 0.5 mg/L
    - High level resistance: MIC > 8 mg/L
- **CT:**
  - 4/23 strains tested for TCN-R in culture: no resistance (but none from PEP arm)
  - 53/65 PCR+ swabs with16S rRNA sequenced: no TCN-R mutation (only 3 from PEP arm)



Molina et al. CROI, 2023

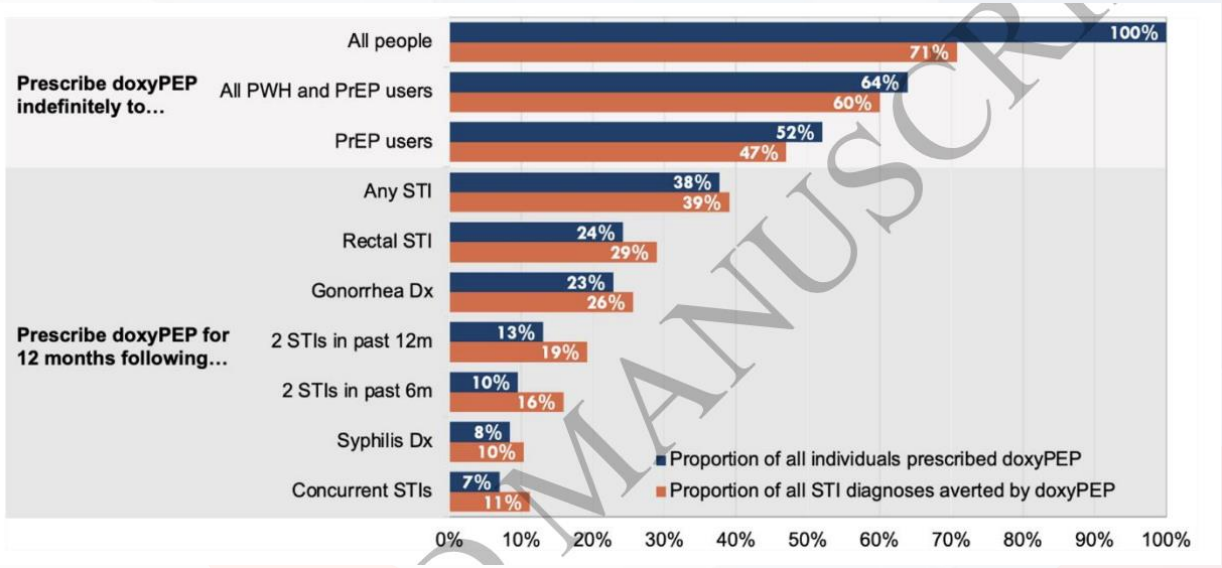
Doxycycline as STI Pep

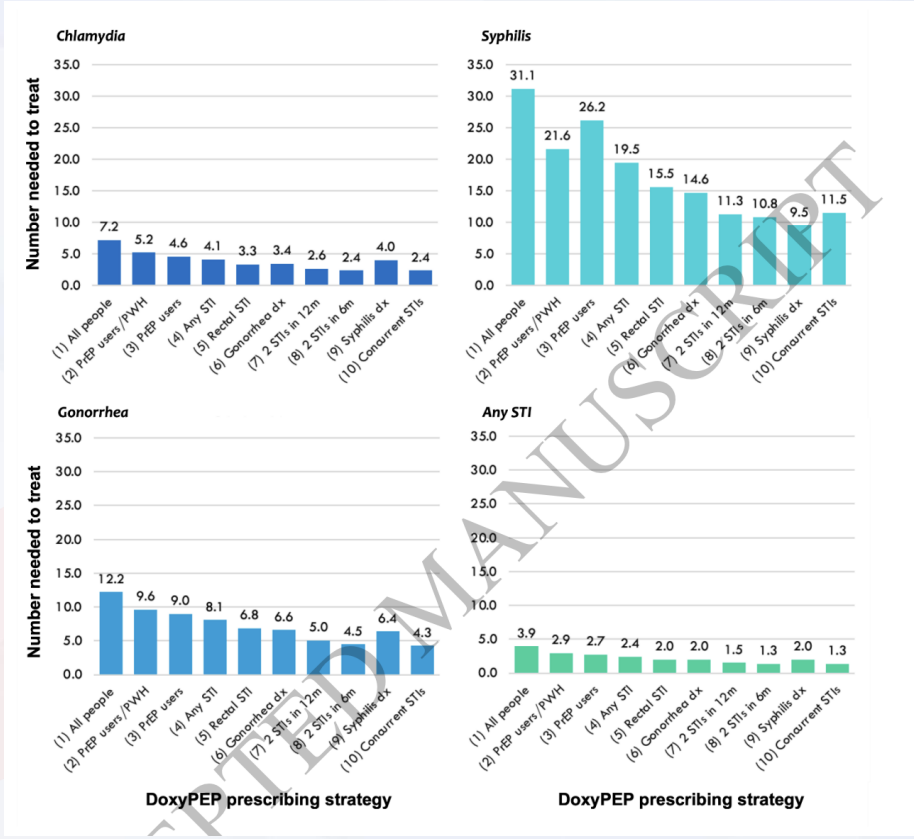
DOXYVAC: An open label randomized controlled trial to prevent STI in MSM on PrEP



Molina et al. CROI, 2023

Potential impact of doxycycline post-exposure prophylaxis prescribing strategies on incidence of bacterial sexually transmitted infections – Modeling Study (GBM)





Traeger MW, Mayer KH, Krakower DS, Gitin S, Jenness SM, Marcus JL. Potential impact of doxycycline post-exposure prophylaxis prescribing strategies on incidence of bacterial sexually transmitted infections. Clin Infect Dis. 2023 Aug 18:ciad488. doi: 10.1093/cid/ciad488. Epub ahead of print. PMID: 37595139.

Doxycycline as STI Pep

Doxycycline does not prevent STIs among cisgender women

- Kisumu, Kenya
- 449 cisgender women on PrEP
  - Annual STI Incidence was 27%
- Randomized to receive doxy versus standard or care
- 12-month follow-up
- 109 new STI
  - DoxyPep: 50
  - Standard of Care: 59
  - 78% were CT
    - DoxyPEP: 35
    - Standard of Care: 50
- Why didn't it work
  - Difference in anatomy
  - Antibiotic resistance
  - Adherence

Stewart J et al. *Doxycycline postexposure prophylaxis for prevention of STIs among cisgender women*. 30th Conference on Retroviruses and Opportunistic Infections, Seattle, abstract 121, 2023.

DoxyPep: Areas that need further Exploration

Clarifying	Understanding	Weighing	Determining
Clarifying frequency/population with which desired efficacy is reached	Understanding the individual health risks vs. benefits	Weighing the public health risks vs. benefits	Determining optimal groups for this targeted intervention

Cdc.gov

CDC Guidance

Doxycycline as STI PEP: Considerations for Individuals and Healthcare Providers of Gay or Bisexual Men or Transgender Women

As CDC and others work quickly to evaluate data to inform clinical guidance on the safe and effective use of post-exposure prophylaxis with doxycycline (also called doxy as PEP) to prevent gonorrhea, chlamydia, and syphilis, we acknowledge there are individuals and clinicians who are already engaged in the off-label use of doxycycline as bacterial STI post-exposure prophylaxis or considering it. As such, we are providing the following considerations to inform those decisions:

- Current efficacy data only applies to gay and bisexual men and transgender women. Studies among heterosexual cis-gender women are ongoing.
- Doxycycline 200 mg administered within 24-72 hours of condomless sex was the regimen evaluated in this study. Other antibiotics should not be considered for PEP.
- In addition to informing patients about the potential STI prevention benefits of doxy as PEP, providers should also counsel patients about potential adverse side effects of doxycycline including phototoxicity, gastrointestinal symptoms, and more rarely esophageal ulceration.
- Providers should continue to screen, test, and treat for bacterial STIs in accordance with CDC's STI Treatment Guidelines and CDC's PrEP for the Prevention of HIV guidelines, even among people who may be using doxycycline as PEP or PrEP.

https://www.cdc.gov/std/treatment-guidelines/clinical-primary.htm#CautionsForDoxyPEP

Thank you!

- *Outline the current challenges related to management of STI*
- *Review current evidence-based guidance for the management of STI*
- *Discuss advances in STI prevention*
  - *DoxyPep*

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AETC Program National Centers and HIV Curriculum

- **National Coordinating Resource Center –** serves as the central web –based repository for AETC Program training and capacity building resources; its website includes a free virtual library with training and technical assistance materials, a program directory, and a calendar of trainings and other events. Learn more: https://aidsetc.org/
- **National Clinical Consultation Center –** provides free, peer-to-peer, expert advice for health professionals on HIV prevention, care, and treatment and related topics. Learn more: https://nccc/ucsf.edu
- **National HIV Curriculum –** provides ongoing, up –to-date HIV training and information for health professionals through a free, web –based curriculum; also provides free CME credits, CNE contact hours, CE contact hours, and maintenance of certification credits. Learn more: www.hiv.uw.edu