Updates in STI Management: A discussion of CDC's 2021 Guidelines

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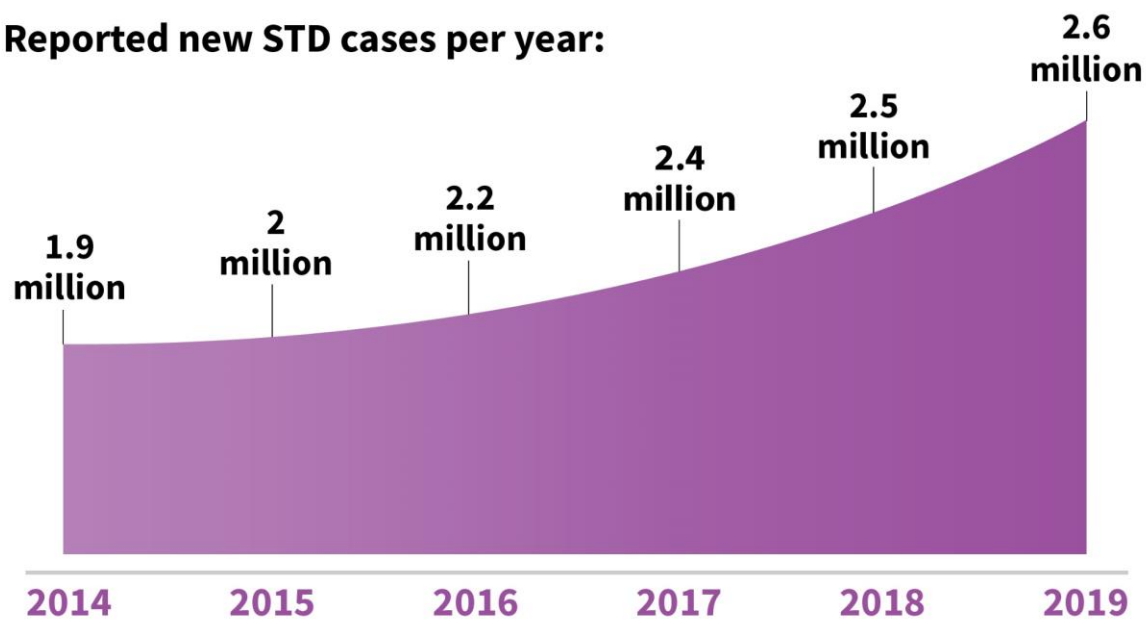
Learning objectives

1. Discuss the preferred treatments for common sexually transmitted infections (STIs)

2. Summarize the rationales for changes in STI management

6th consecutive year of RECORD-BREAKING STD cases

Reported new STD cases per year:



For more information visit ***www.cdc.gov/nchhstp/newsroom***

Disparities in STDs persist among racial & ethnic minority groups

While STDs are increasing across many groups, 2019 STD RATES WERE:

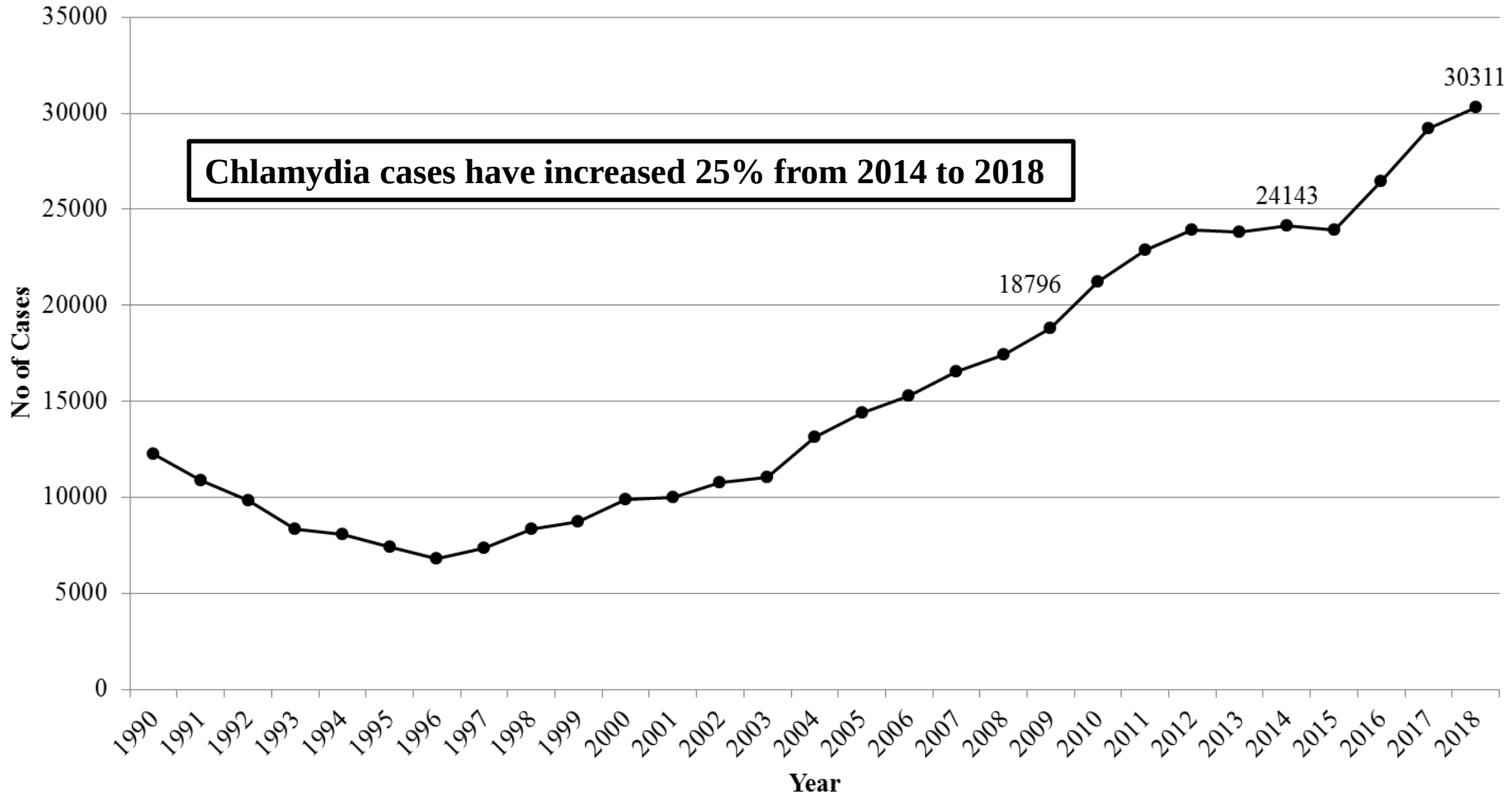
for Hispanic or Latino people

for American Indian or Alaska Native people and Native Hawaiian or Other Pacific Islander people

for African American or Black people

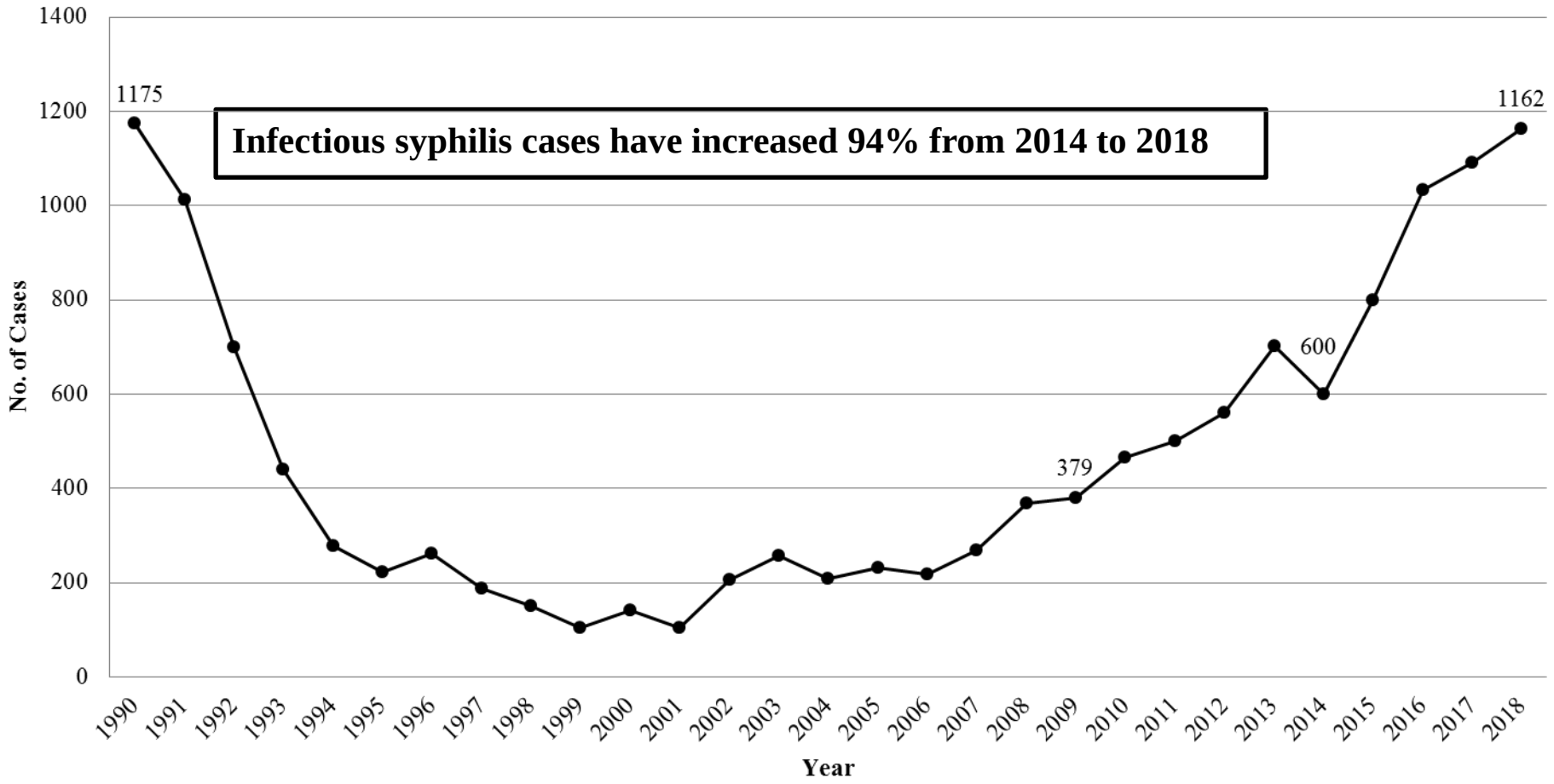
For more information visit ***www.cdc.gov/nchhstp/newsroom***

Confirmed Chlamydia Cases, Massachusetts, 1990 to 2018



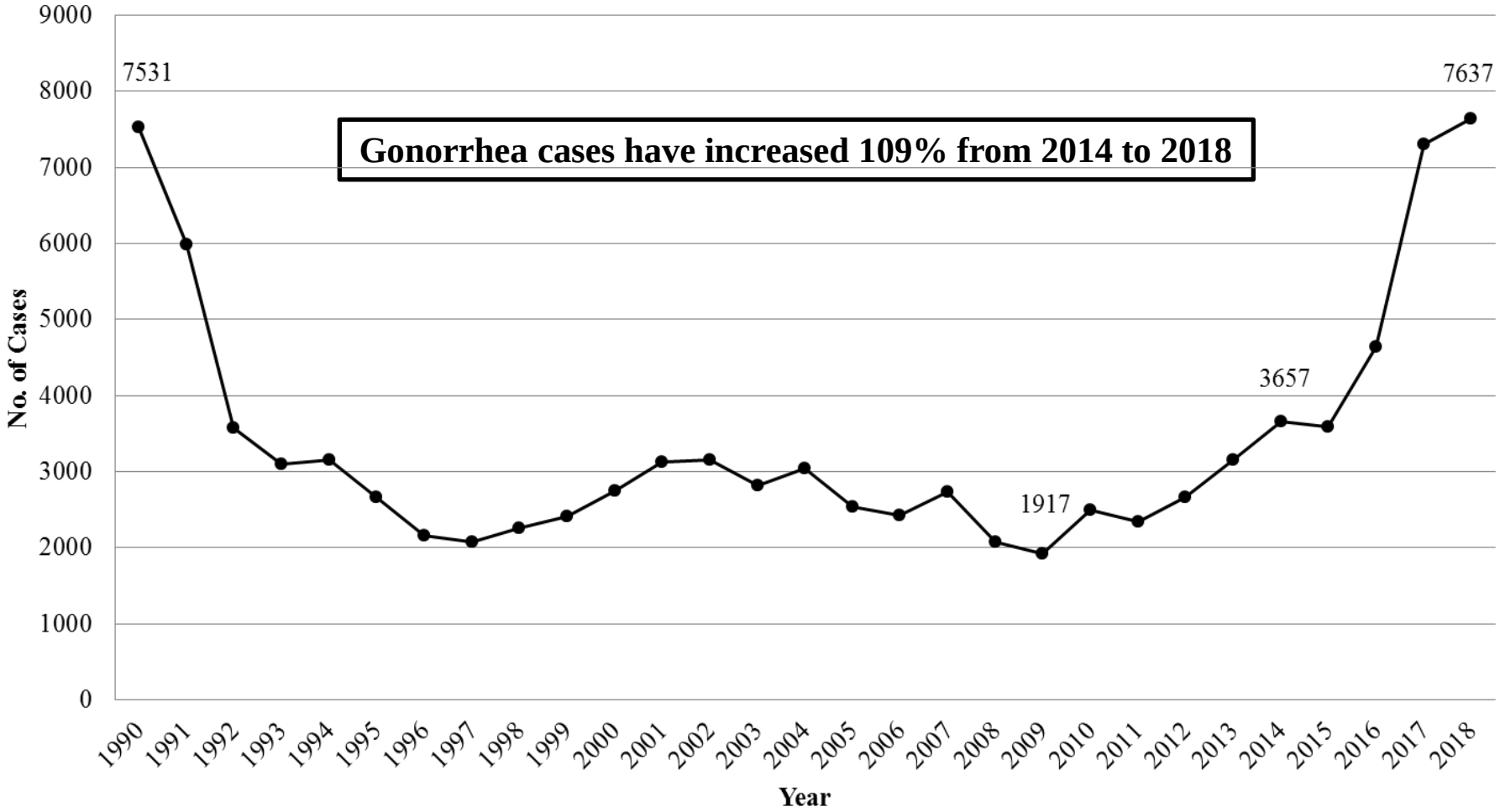
Data are current as of 3/26/2019 and are subject to change.
Data Source: Massachusetts Department of Public Health/Bureau of Infectious Disease and Laboratory Sciences/ Division STD Prevention

Confirmed and Probable Infectious Syphilis* Cases, Massachusetts, 1990 to 2018



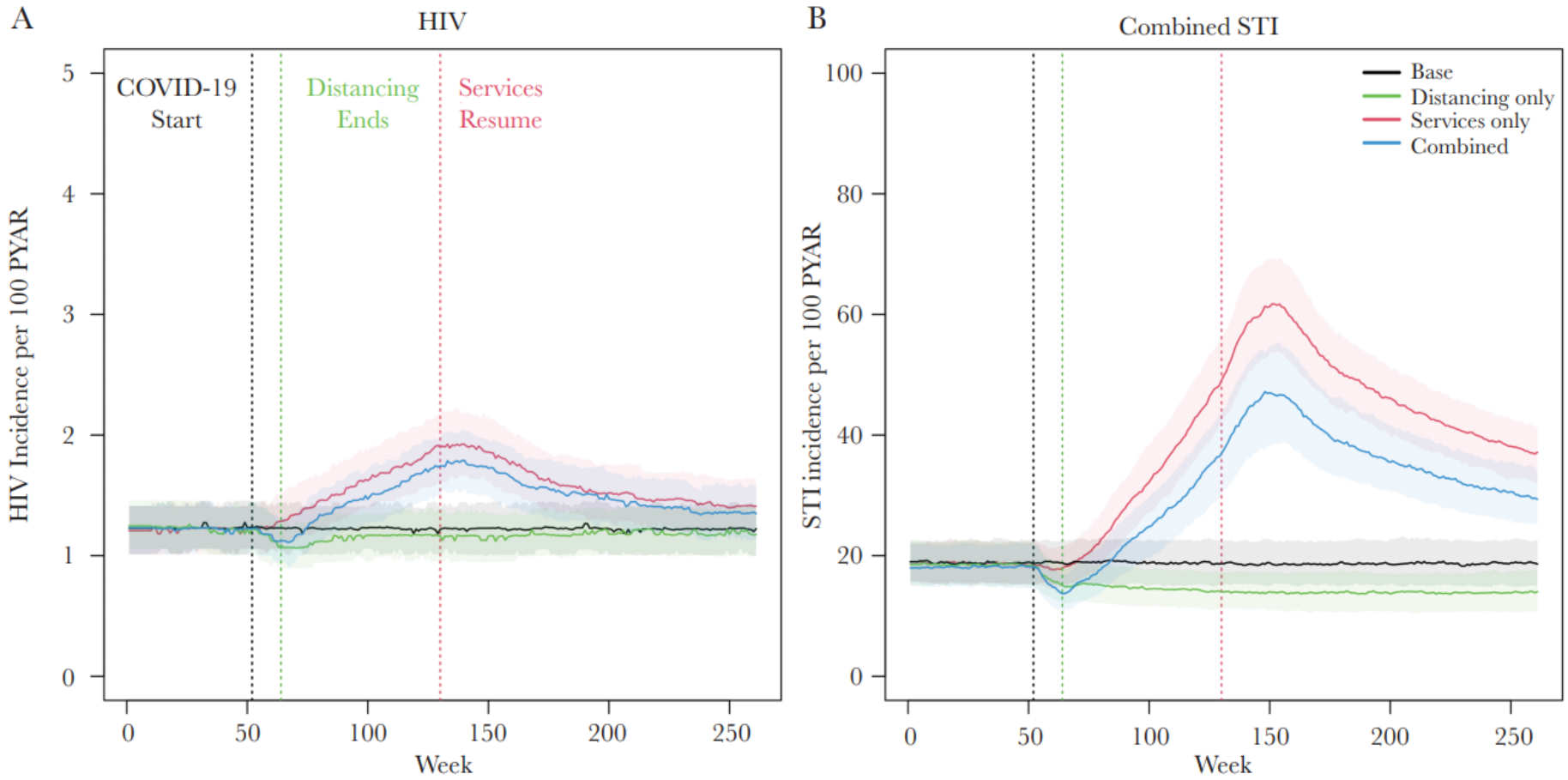
Data are current as of 4/5/2019 and are subject to change.
*Infectious syphilis is defined as primary, secondary and early latent stages of syphilis.
Data Source: Massachusetts Department of Public Health/Bureau of Infectious Disease and Laboratory Sciences/ Division STD Prevention

Confirmed Gonorrhea Cases, Massachusetts, 1990 to 2018



Data are current as of 3/29/2019 and are subject to change.
Data Source: Massachusetts Department of Public Health/Bureau of Infectious Disease and Laboratory Sciences/ Division STD Prevention

How will Covid-19 impact STIs?



Jeness SM, J Infect Dis, 2021

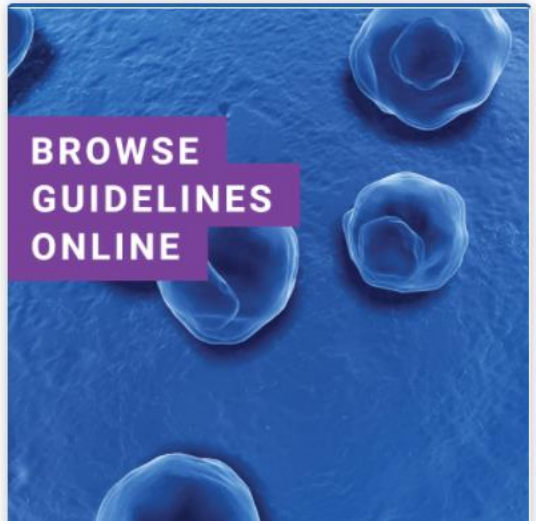
STI Treatment Guidelines

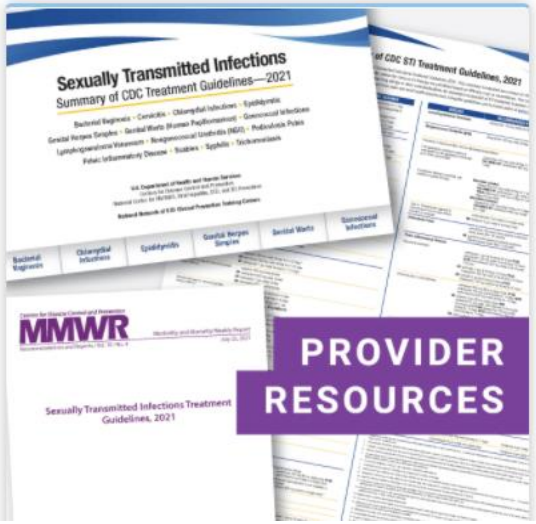
2021 RECOMMENDATIONS NOW AVAILABLE

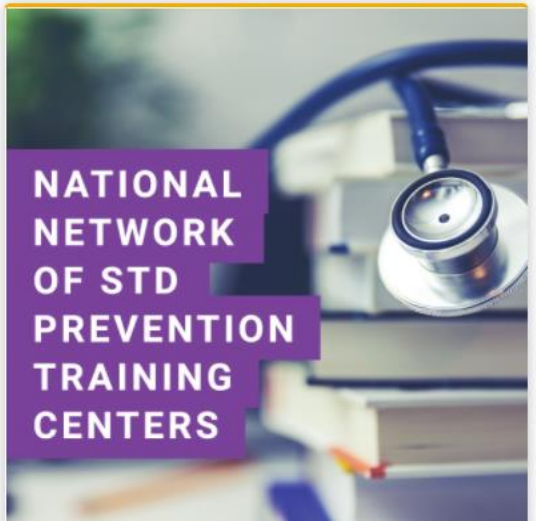
STI Treatment Guidelines Update

CDC's Sexually Transmitted Infections (STI) Treatment Guidelines, 2021 provides current evidence-based prevention, diagnostic and treatment recommendations that replace the 2015 guidance. The recommendations are intended to be a source for clinical guidance. Healthcare providers should always assess patients based on their clinical circumstances and local burden.

2021 Mobile App in Development
Learn how to use the interim, mobile-friendly solution.







www.cdc.gov/std/treatment-guidelines/default.htm

Case

- A 25-year-old woman presents for routine STI screening.
- She has no symptoms, is not pregnant, and has no known chronic medical problems.
- Laboratory test results show:
  - HIV antibody/antigen: **Negative**
  - Treponemal antibody: **Negative**
  - Vaginal gonorrhea/chlamydia NAAT: **Positive** for *Chlamydia trachomatis*, **negative** for *Neisseria gonorrhoeae*

What is the best treatment for her infection?

A. Azithromycin 1 gram by mouth once
B. Doxycycline 100 mg by mouth twice daily for 7 days
C. Ceftriaxone 500 mg by intramuscular injection once
D. Ciprofloxacin 250 mg by mouth twice daily for 3 days

2015

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

2021

Recommended Regimens for Chlamydial Infection Among Adolescents and Adults

Doxycycline 100 mg orally 2 times/day for 7 days

Alternative Regimens

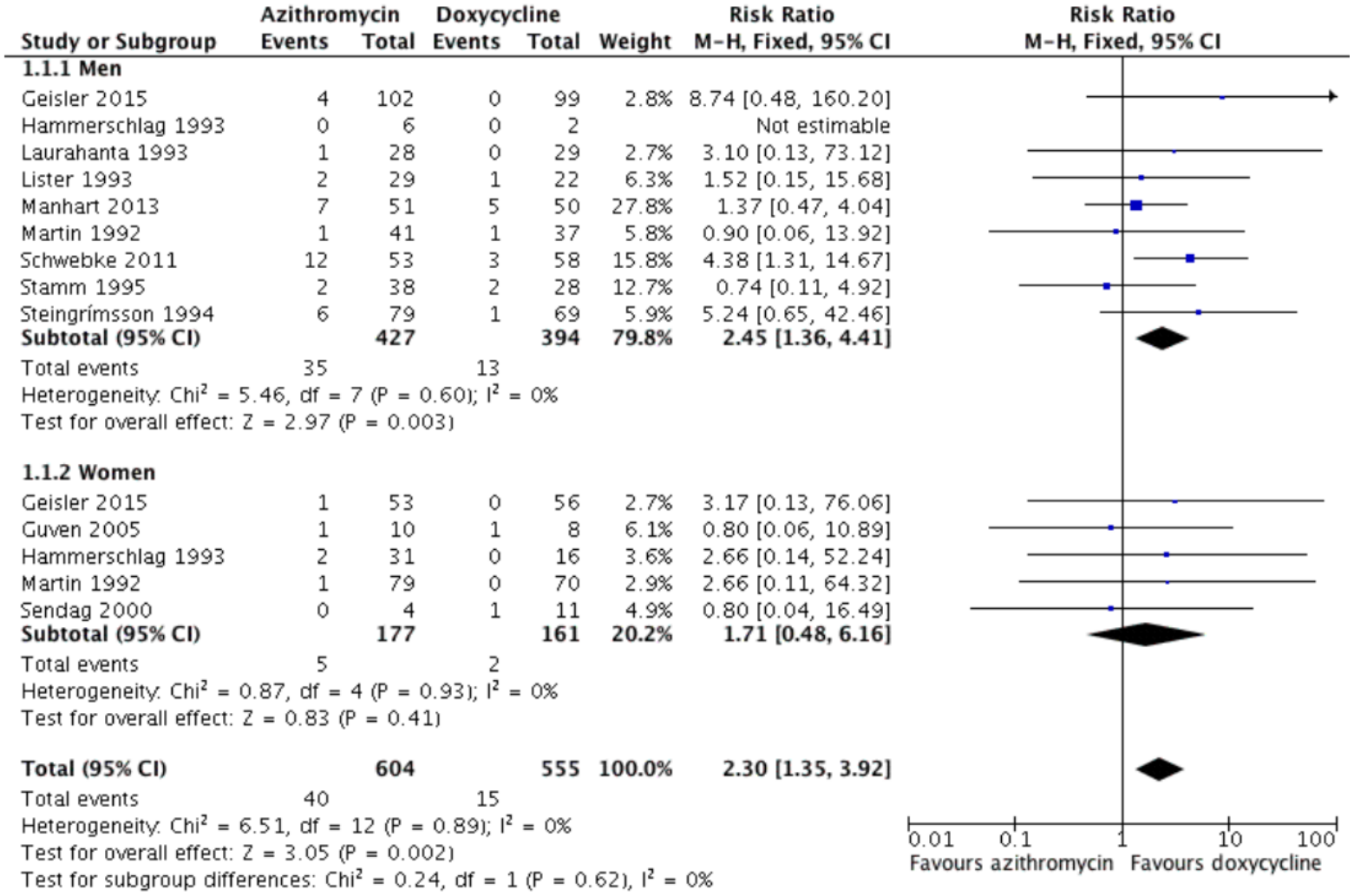
Azithromycin 1 g orally in a single dose

OR

Levofloxacin 500 mg orally once daily for 7 days

Why is doxycycline now preferred for chlamydia?

Azithromycin versus doxycycline for urogenital chlamydia, outcome = microbiologic cure

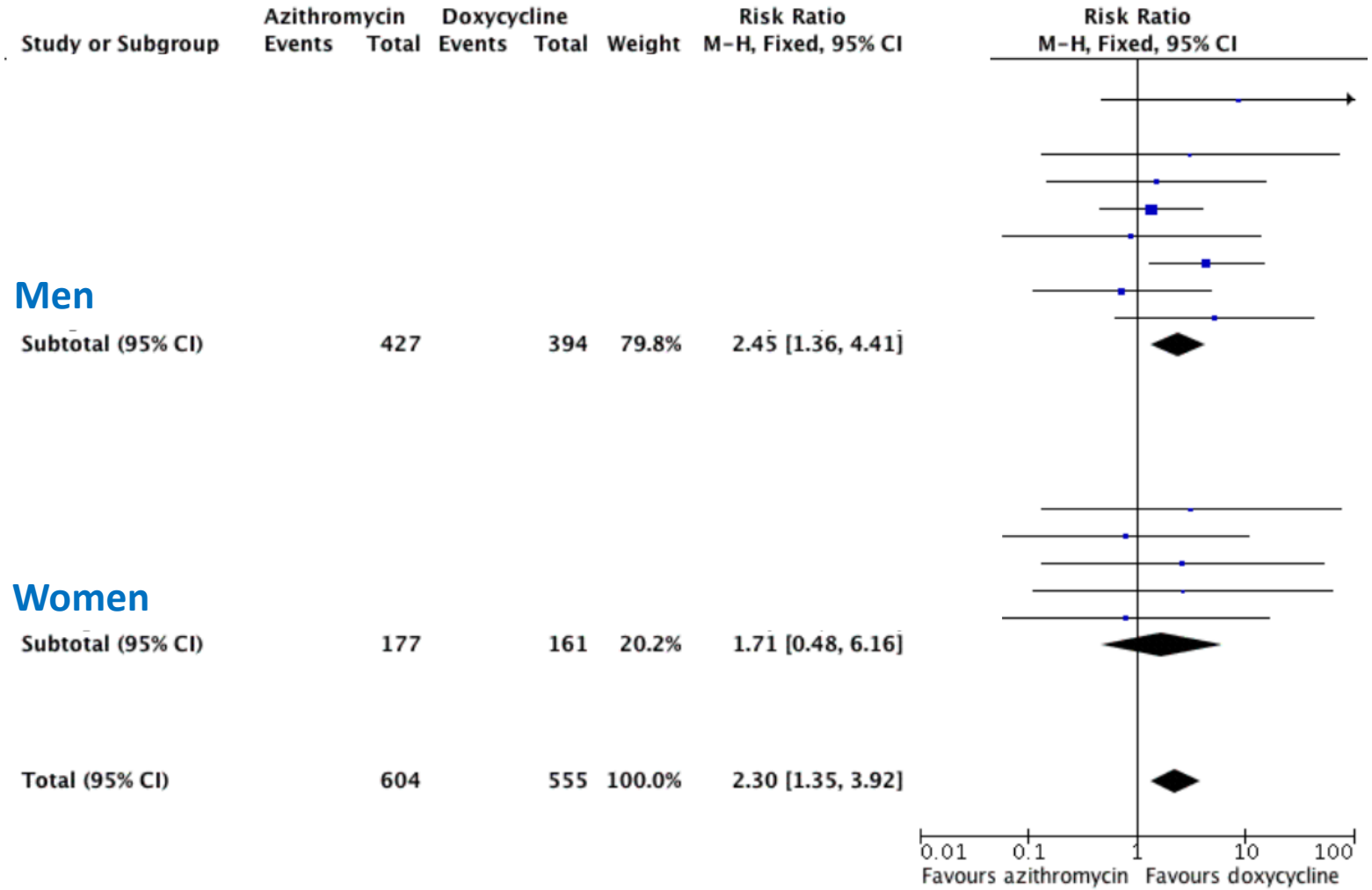


Study or Subgroup	Azithromycin Events	Azithromycin Total	Doxycycline Events	Doxycycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Men						
Geisler 2015	4	102	0	99	2.8%	8.74 [0.48, 160.20]
Hammerschlag 1993	0	6	0	2		Not estimable
Laurahanta 1993	1	28	0	29	2.7%	3.10 [0.13, 73.12]
Lister 1993	2	29	1	22	6.3%	1.52 [0.15, 15.68]
Manhart 2013	7	51	5	50	27.8%	1.37 [0.47, 4.04]
Martin 1992	1	41	1	37	5.8%	0.90 [0.06, 13.92]
Schwebke 2011	12	53	3	58	15.8%	4.38 [1.31, 14.67]
Stamm 1995	2	38	2	28	12.7%	0.74 [0.11, 4.92]
Steingrímsson 1994	6	79	1	69	5.9%	5.24 [0.65, 42.46]
Subtotal (95% CI)		**427**		**394**	**79.8%**	**2.45 [1.36, 4.41]**
Total events	35		13			
Heterogeneity: $Chi^2 = 5.46$, df = 7 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 2.97 (P = 0.003)						
1.1.2 Women						
Geisler 2015	1	53	0	56	2.7%	3.17 [0.13, 76.06]
Guven 2005	1	10	1	8	6.1%	0.80 [0.06, 10.89]
Hammerschlag 1993	2	31	0	16	3.6%	2.66 [0.14, 52.24]
Martin 1992	1	79	0	70	2.9%	2.66 [0.11, 64.32]
Sendag 2000	0	4	1	11	4.9%	0.80 [0.04, 16.49]
Subtotal (95% CI)		**177**		**161**	**20.2%**	**1.71 [0.48, 6.16]**
Total events	5		2			
Heterogeneity: $Chi^2 = 0.87$, df = 4 (P = 0.93); $I^2 = 0\%$						
Test for overall effect: Z = 0.83 (P = 0.41)						
Total (95% CI)		**604**		**555**	**100.0%**	**2.30 [1.35, 3.92]**
Total events	40		15			
Heterogeneity: $Chi^2 = 6.51$, df = 12 (P = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 3.05 (P = 0.002)						
Test for subgroup differences: $Chi^2 = 0.24$, df = 1 (P = 0.62), $I^2 = 0\%$						

Paez-Canro C, Cochrane Database Syst Rev, 2019

Why is doxycycline now preferred for chlamydia?

Azithromycin versus doxycycline for urogenital chlamydia, outcome = microbiologic cure



Paez-Canro C, Cochrane Database Syst Rev, 2019

Doxycycline is more effective for rectal chlamydia.

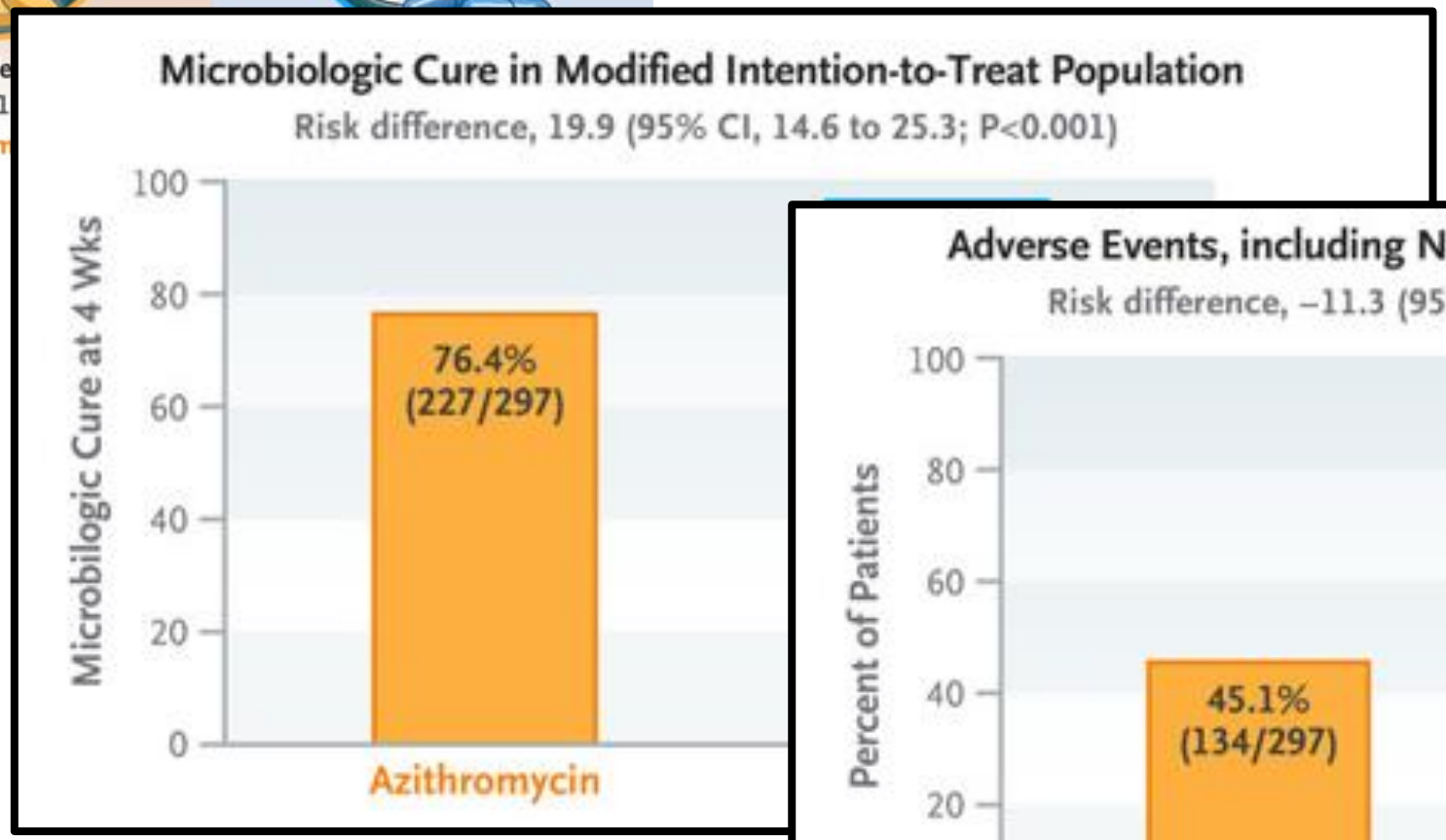
Randomized controlled trial of 177 MSM with rectal chlamydia

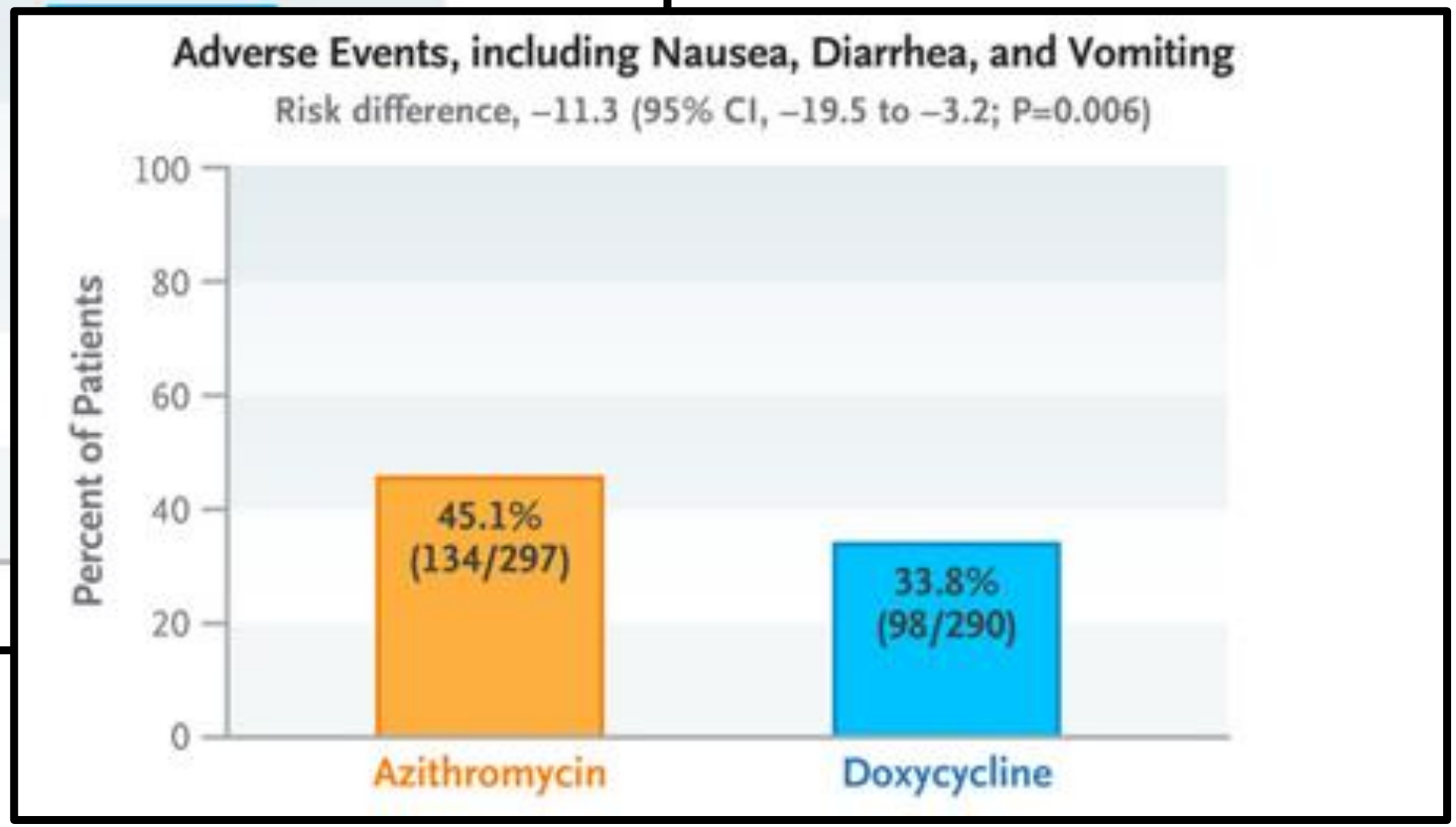
- Doxycycline versus azithromycin
- Outcome: Microbiologic cure
- Results: Cure 100% with doxycycline versus 74% with azithromycin ($p<0.001$)

"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"

Dombrowski JC, Clin Infect Dis, 2021

1 g, single
(N=31
Azithrom





Lau A, et al. N Engl J Med. 2021.

Why favor doxycycline over azithromycin for women with urogenital chlamydia?

Population	Rectal prevalence of *Chlamydia trachomatis*, % (95% CI)
Women attending routine clinics	6% (3-9%)
Women at high risk	26% (9-43%)
Women reporting anal sex	10% (8-13%)
Women with urogenital chlamydia	77% (68-85%)

Chandra NL, et al. Sex Transm Infect. 2018.

Why is doxycycline more effective for rectal chlamydia?

- Not antimicrobial resistance to azithromycin
- Not due to inadequate drug penetration
- Not due to rectal lymphogranuloma venereum (LGV)

- Perhaps due to temporary suppression with single-dose azithromycin (ie, would a longer course of azithromycin work just as well as doxycycline)?
- Perhaps due to different host response to rectal versus genital infection?

Lau A, et al. N Engl J Med. 2021. Slide adapted from Dr. Katherine Hsu.

Choosing a treatment for chlamydia

Doxycycline

- Effectiveness
- Fewer side effects?

Azithromycin

- Ease
- Adherence
- Confidentiality
- Available at the point of care
- Pregnancy

Slide adapted from Jason Zucker

Case, continued

- She’s had sex with one man in the past 60 days.
- You’d like to provide expedited partner therapy for chlamydia, and she agrees to deliver it.

Image from https://health.maryland.gov/phpa/oidpcs/cstip/pages/expedited%20partner%20therapy.aspx

What's the best drug for EPT for chlamydia?

A. Azithromycin 1 gram by mouth once
B. Doxycycline 100 mg by mouth twice daily for 7 days

EPT is now more permissible for MSM.

2015:

Expedited partner therapy (EPT) "should not be used routinely in MSM."

2021:

For MSM, "shared clinical decision-making regarding EPT is recommended."

Schillinger J, 2019:

- Retrospective cohort study of 4,390 visits by MSM presenting as contacts to chlamydia or gonorrhea.
- Among those with chlamydia contact, HIV diagnosed at 8 visits (0.2%)

Other changes…

- Extragenital gonorrhea/chlamydia testing can be offered to all MSM regardless of reported sexual behaviors.
- Consider extragenital testing for women through “shared decision-making.”
- Extragenital gonorrhea/chlamydia testing is recommended annually for transgender women.
- Gonorrhea/chlamydia testing among transgender and gender diverse people should be based on anatomy, though the optimal screening strategy for surgically constructed genitalia is not known.

Case

- A 22-year-old man presents for STI screening.
- He has had oral and insertive/receptive anal sex with 3 men in the past 6 months.
- He has no symptoms.
- Laboratory testing shows:
  - HIV antibody/antigen: **Negative**
  - Treponemal antibody: **Negative**
  - 3-site gonorrhea/chlamydia NAAT: **Positive** for *Neisseria gonorrhoeae* in the throat; otherwise negative

Besides recommending PrEP, what are the next best steps in treatment?

A. Ceftriaxone 250 mg IM once
B. Ceftriaxone 500 mg IM once
C. Ceftriaxone 250 mg IM once with azithromycin 1 gram by mouth once
D. Ceftriaxone 500 mg IM once with doxycycline 100 mg by mouth twice daily for 7 days

2015

Recommended Regimen
Ceftriaxone 250 mg IM in a single dose
PLUS
Azithromycin 1 g orally in a single dose

2021

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.

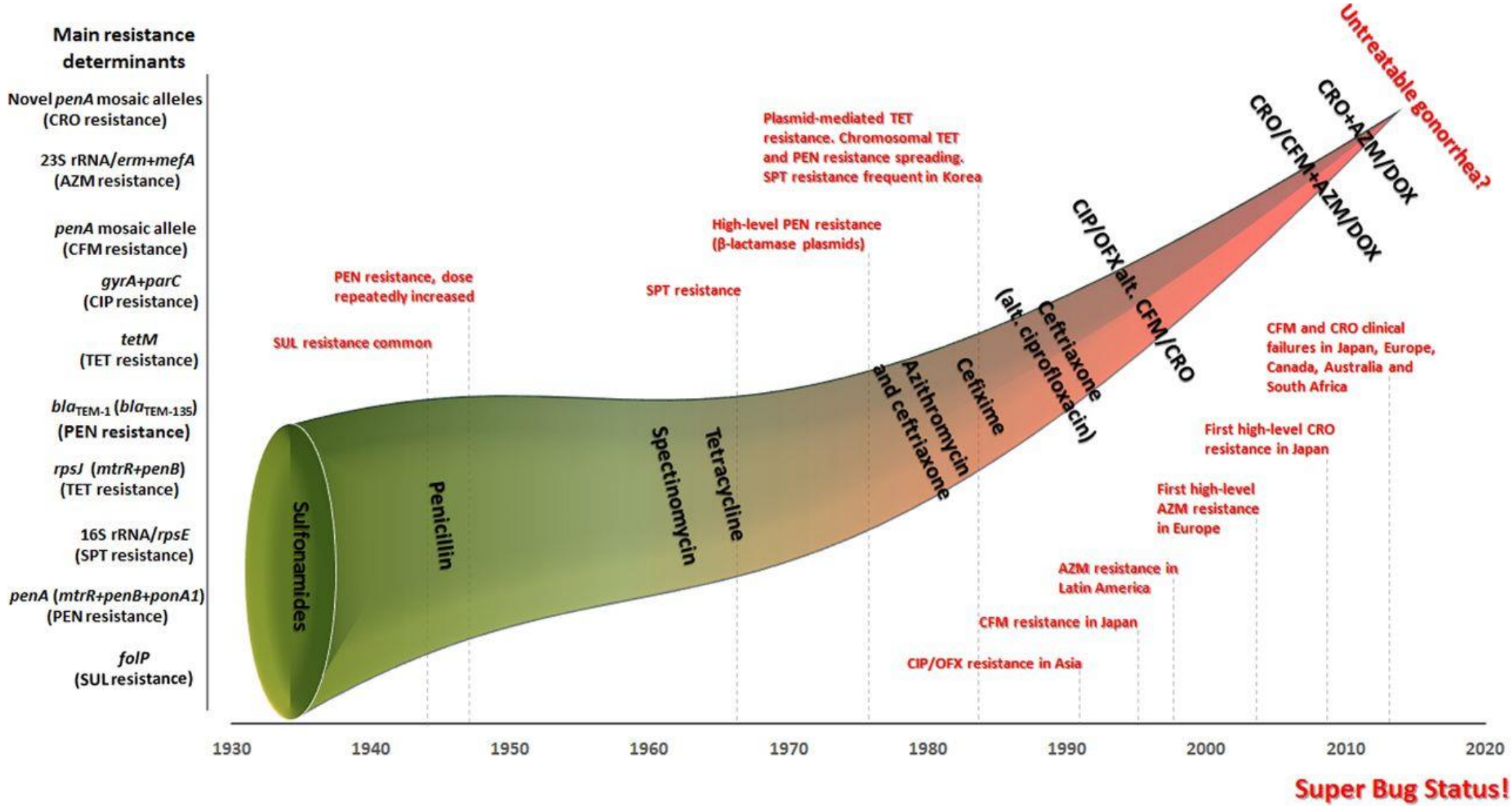
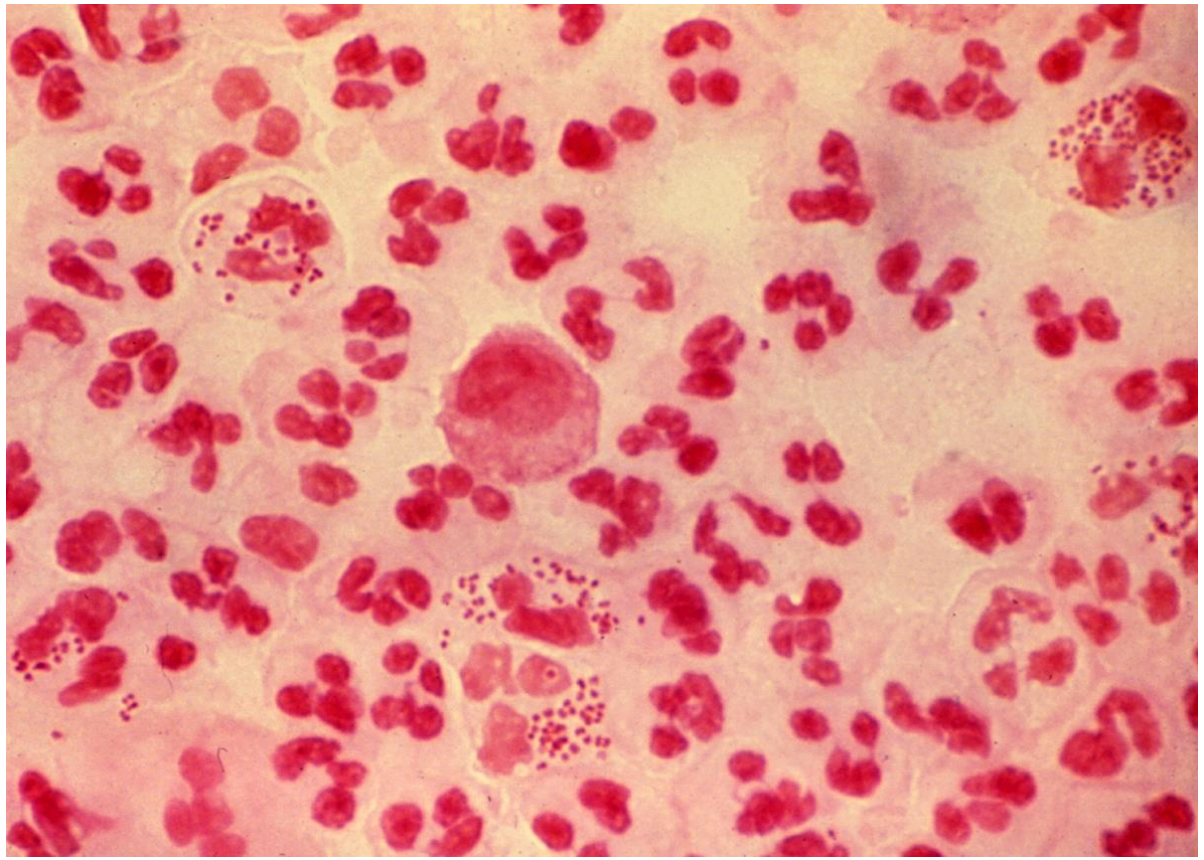


Image from Unemo M, Shafer WM. Clin Microbiol Rev. 2020. Slide adapted from Dr. Katherine Hsu.

Recommended treatment for gonorrhea: Ceftriaxone 500 mg IM once



Rationale for the higher dose of ceftriaxone:

- A higher dose may be required to cure infections with decreased susceptibility
- A higher dose may be required to cure pharyngeal infections

Rational for no companion drug if chlamydia has been excluded:

- Increasing azithromycin resistance in N. gonorrhoeae and other pathogens
- Ceftriaxone alone cures gonorrhea

CDC 2021 STI Treatment Guidelines

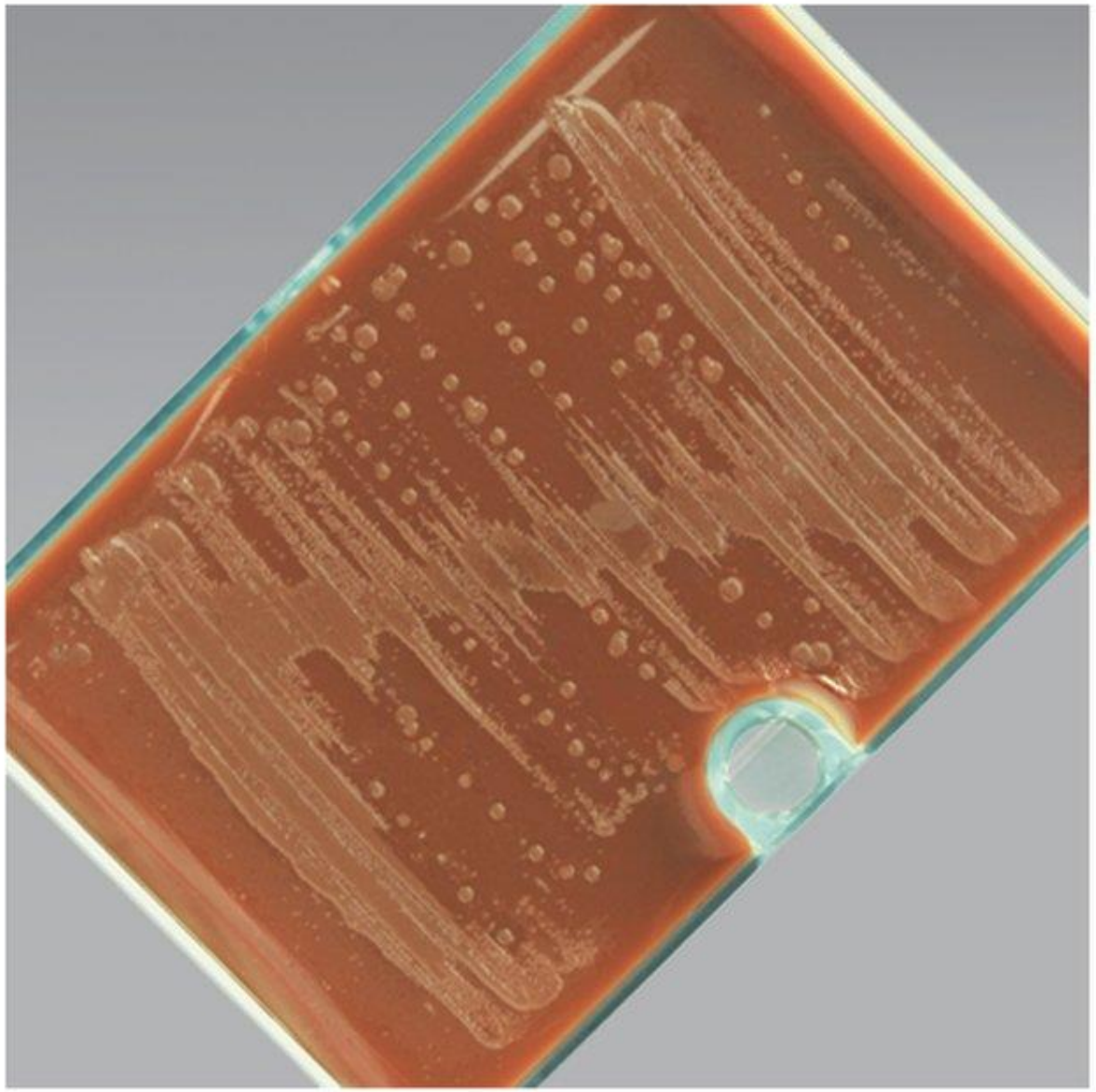
Tips about gonorrhea

- For people weighing ≥ 150 kg, treat with 1 gram of ceftriaxone once.
- Pharyngeal gonorrhea: Test of cure 7-14 days after treatment (I favor ≥ 14 days.)
- Retest all other people with gonorrhea at 3 months.
- For concurrent chlamydia, or if chlamydia has not been excluded, add doxycycline 100 mg by mouth twice daily for 7 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



https://www.thermofisher.com/order/catalog/product/R10320

Case

- A 23-year-old man taking TDF/FTC for PrEP presents for an urgent care visit due to rash and fever.
- The rash involves his chest, back, palms, and soles.
- He also has had left eye blurry vision for 1 day.
- He has no headache or other symptoms.

Image from https://www.cdc.gov/std/syphilis/images/palmar-1.jpg

Case, continued

- An urgent ophthalmologic examination shows panuveitis.
- A detailed neurological examination is otherwise normal.
- Laboratory testing shows:
  - HIV antibody/antigen: **Negative**
  - Treponemal antibody: **Positive**
  - Rapid plasma reagin (RPR): **1:256**
  - Gonorrhea/chlamydia NAAT: **Negative** from the throat, urine, and rectum

What is the next best step in management?

A. Treat with long-acting benzathine penicillin by intramuscular injection once
B. Treat with intravenous penicillin G for 10-14 days
C. Perform a lumbar puncture to assess for neurosyphilis
D. Send to ophthalmology for intravitreal injection of penicillin

Ocular syphilis

- Panuveitis and posterior uveitis are the most common manifestations.
- Can occur during any stage of syphilis
- Treated as a form of neurosyphilis
- CSF abnormalities are present in ~60%.
- Ask about visual symptoms in any patient with a new diagnosis of syphilis.

Clinical advisory: Ocular syphilis in the United States. CDC. 2016. Available at: https://www.cdc.gov/std/syphilis/clinicaladvisoryos2015.htm.
Image from radiopaedia.org

Neuro/ocular syphilis, RPRs, and CSF examinations

- Prior guidelines called for lumbar puncture in all patients with ocular syphilis, and every 6 months until normalization for people with neurosyphilis who had CSF pleocytosis at baseline.

- But, RPR response predicts normalization of CSF parameters (less so in people with untreated HIV).

- New recommendations: A CSF examination is unnecessary
  - At diagnosis for **isolated** ocular or otic syphilis
  - For follow-up of immunocompetent people with confirmed neurosyphilis who have an **appropriate RPR and clinical response**

Workowski KA, 2015 STD Treatment Guidelines, 2015

What to do with titers that don't respond appropriately…

- **Lack of a fourfold decline in titers** after waiting a **full 12m** following therapy for early syphilis and a **full 24m** following therapy for late syphilis:
  - Any neurological signs/symptoms? **If yes, perform immediate LP**
  - Could the patient have been reinfected? **If yes, treat**
  - If both of the above are negative, you can either follow the patient carefully or you can give additional antibiotics. Several observational studies suggest that there are **NO short/intermediate-term benefits to additional antibiotics**
- A **four-fold increase in titers** after appropriate therapy:
  - Any neurological signs/symptoms? **If yes, perform immediate LP**
  - Could the patient have been reinfected? **If yes, treat**
  - If the patient denies the possibility of reinfection, and the titer continues to be elevated when repeated two weeks later, **consider performing a LP**

From Dr. Khalil Ghanem, 2021 STI Treatment Guidelines Update

Case

- A 37-year-old man with HIV on TAF/FTC/BIC presents with 3 days of dysuria and urethral discharge.
- In the past 3 months, he has had insertive and receptive anal sex with 3 men, using condoms about half the time.
- Physical examination shows scant, mucoid urethral discharge.
- Gonorrhea/chlamydia NAAT from the urine is **negative**.
- He is treated with doxycycline 100 mg by mouth twice daily for 7 days.
- His symptoms improve but increase 5 days after stopping doxycycline.
- A urine NAAT for *Mycoplasma genitalium* is **positive**.

How should he be treated?

A. Doxycycline 100 mg by mouth twice daily for 7 days, then moxifloxacin 400 mg by mouth twice daily for 7 days.
B. Doxycycline 100 mg by mouth twice daily for 7 days, then azithromycin 1 gram by mouth once, then azithromycin 500 mg by mouth daily for 3 days.
C. Moxifloxacin 400 mg by mouth daily for 7 days.
D. He does not require antibiotic treatment.

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 once 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

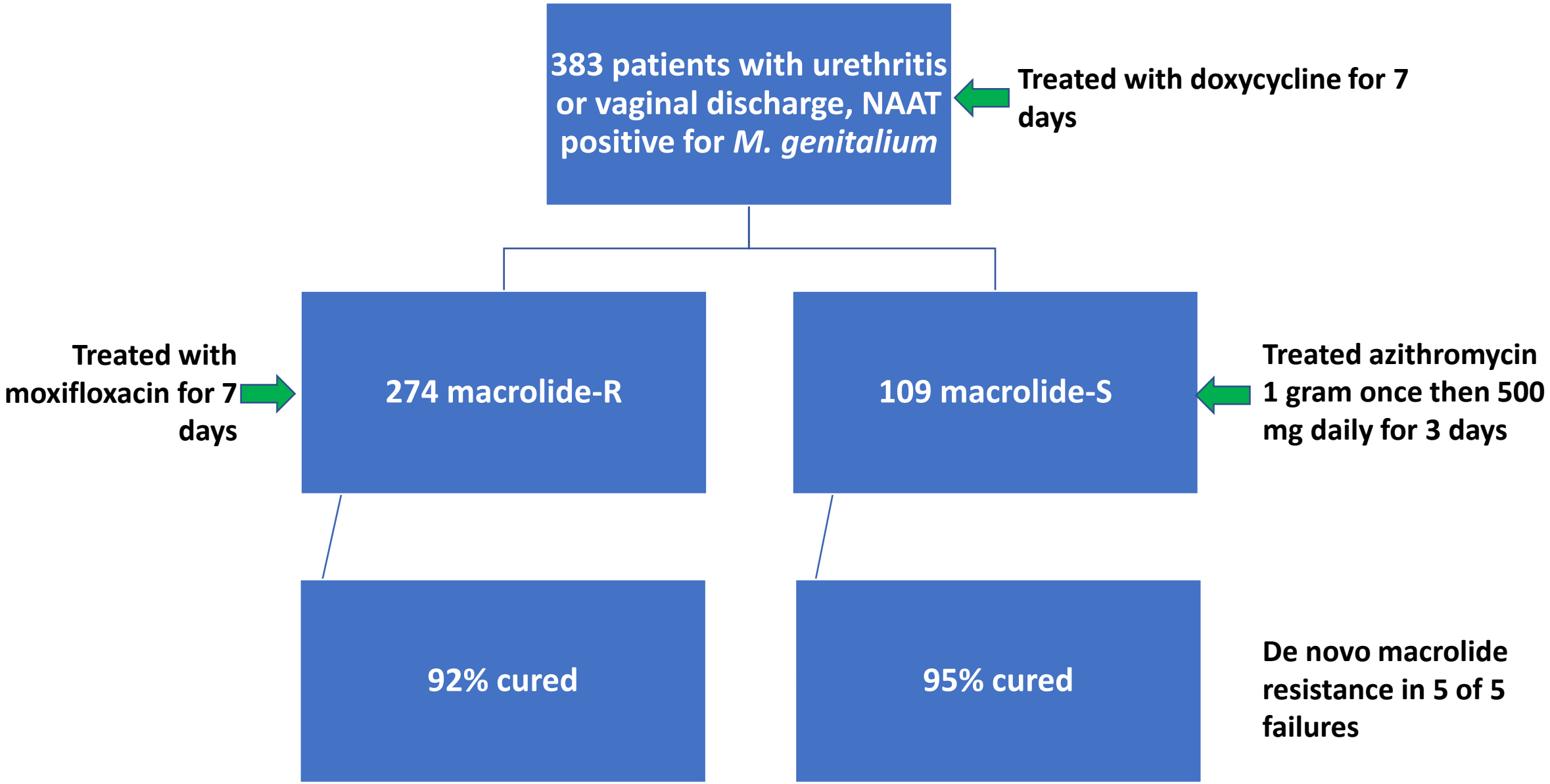
Recommended Regimens if *M. genitalium* Resistance Testing is Not Available

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

Mycoplasma genitalium is an important cause of urethritis in men.

- Accounts for 40% of cases of persistent urethritis among men
- Extremely difficult to culture (may take 6 months)
- Role in women is unclear, but may cause cervicitis and PID
- Antibiotic resistance is a worsening problem:
  - Cure rate for 7 days of doxycycline is ~30%
  - Macrolide resistance > 50% in many areas (> 80% among MSM)
  - Fluoroquinolone resistance mutations identified in up to 15% of isolates in the US

2021 STI Treatment Guidelines. CDC.
Durukan D, et al. Clin Infect Dis. 2020
Image available at https://www.infectiousdiseaseadvisor.com/home/topics/sexually-transmitted-diseases/mycoplasma-genitalium-challenges-in-diagnosis-and-treatment/



Durukan D, Clin Infect Dis, 2020

Questions about *Mycoplasma genitalium*

- Is sequential therapy the best strategy?
- Why not give doxycycline and moxifloxacin concurrently?
- If sequential therapy is needed, how much “lag” between doxycycline and moxifloxacin is permissible?
- What is the optimal strategy if the diagnosis can’t be confirmed?

Trichomonas

What hasn't changed:

- NAATs are the most sensitive test.
- Treatment for men = metronidazole 2 grams by mouth once

What has changed:

- Treatment for women = metronidazole 500 mg by mouth twice daily for 7 days
- Refraining from alcohol use while on metronidazole is unnecessary.
- For persistent infection not due to re-exposure, request a kit from CDC to perform drug resistance testing.

Image from: en.vircell.com

Evidence for week-long treatment for women

Randomized trial of metronidazole 2 grams once versus 500 mg twice daily for 7 days for Trichomonas among women.

- **Outcome:** *T. vaginalis* infection 4 weeks after treatment
- **Population:** 623 woman with *T. vaginalis* infection
- **Results:**
  - *T. vaginalis* infection at 4 weeks in 19% of single dose versus 11% of 7-day-dosing participants (p=0.001)
  - No difference by bacterial vaginosis status
  - Self-reported adherence > 95% in both arms

Kissinger P, Lancet Infect Dis, 2018

Summary

- Preferred treatment for chlamydia is doxycycline.
- Preferred treatment for gonorrhea (without concurrent chlamydia) is ceftriaxone 500 mg IM once.
- Lumbar puncture is unnecessary for isolated ocular or otic syphilis.
- Treat *Mycoplasma genitalium* with sequential therapy.
- Treat trichomoniasis among women with 7 days of metronidazole.