

Syphilis, doxy PEP, and mpox

Tim W Menza, MD, PhD

Associate Professor, Allergy & Infectious Disease, University of Washington School of Medicine
Co-Medical Director, Sexual Health Clinic, Public Health – Seattle & King County

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Disclaimer

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Today's agenda

- Explore the epidemiology of syphilis, including syphilis in pregnancy and congenital syphilis, in Washington State
- Review the staging, clinical manifestations, and treatment of syphilis
- Assess the data on doxycycline for post-exposure prophylaxis, particularly for syphilis
- Discuss the increased in cases of mpox, an endemic STI in the US

Epidemiology

POLL Question

- Compared to 5 years ago, syphilis cases are:

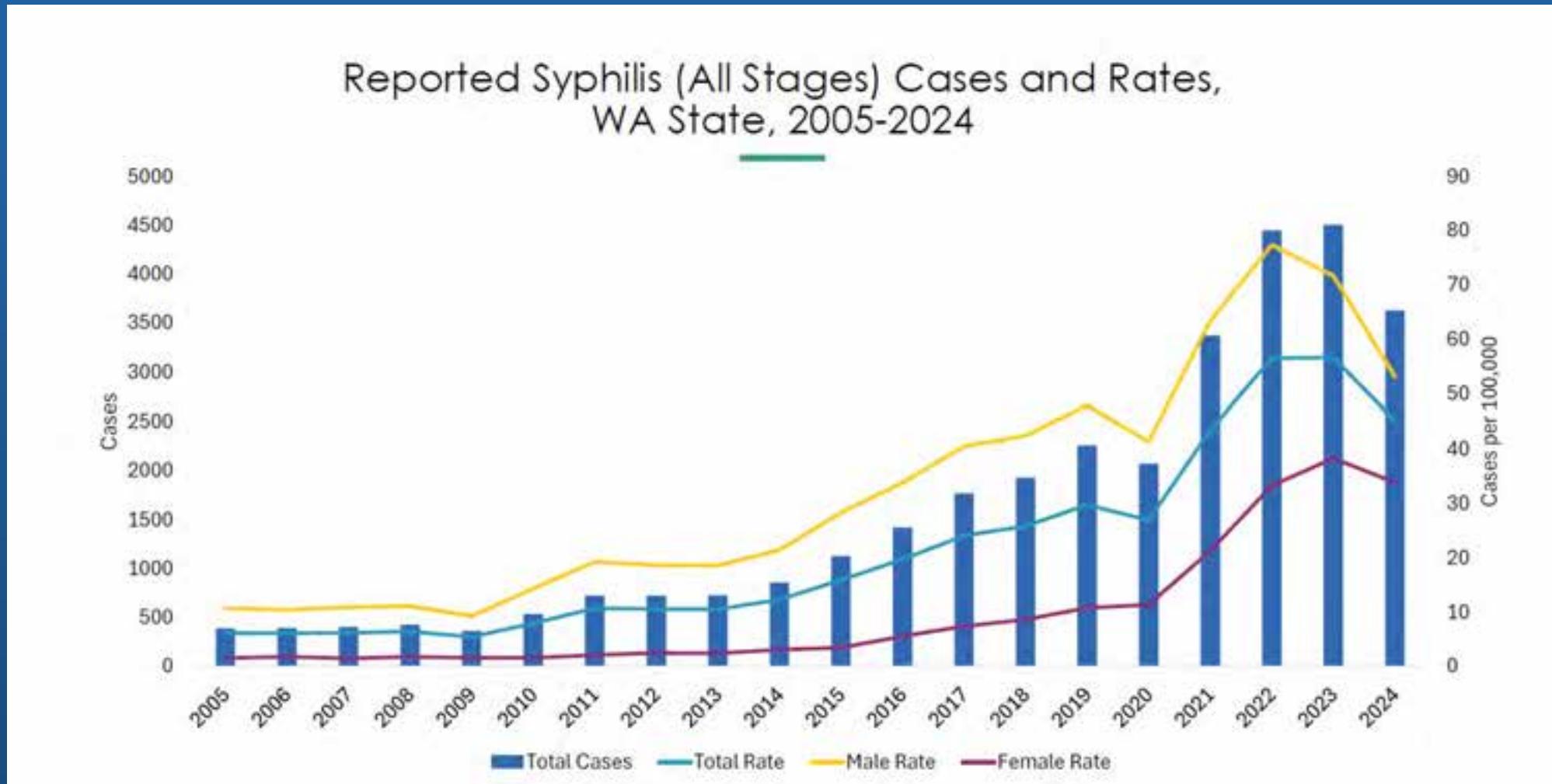
Lower

About the same

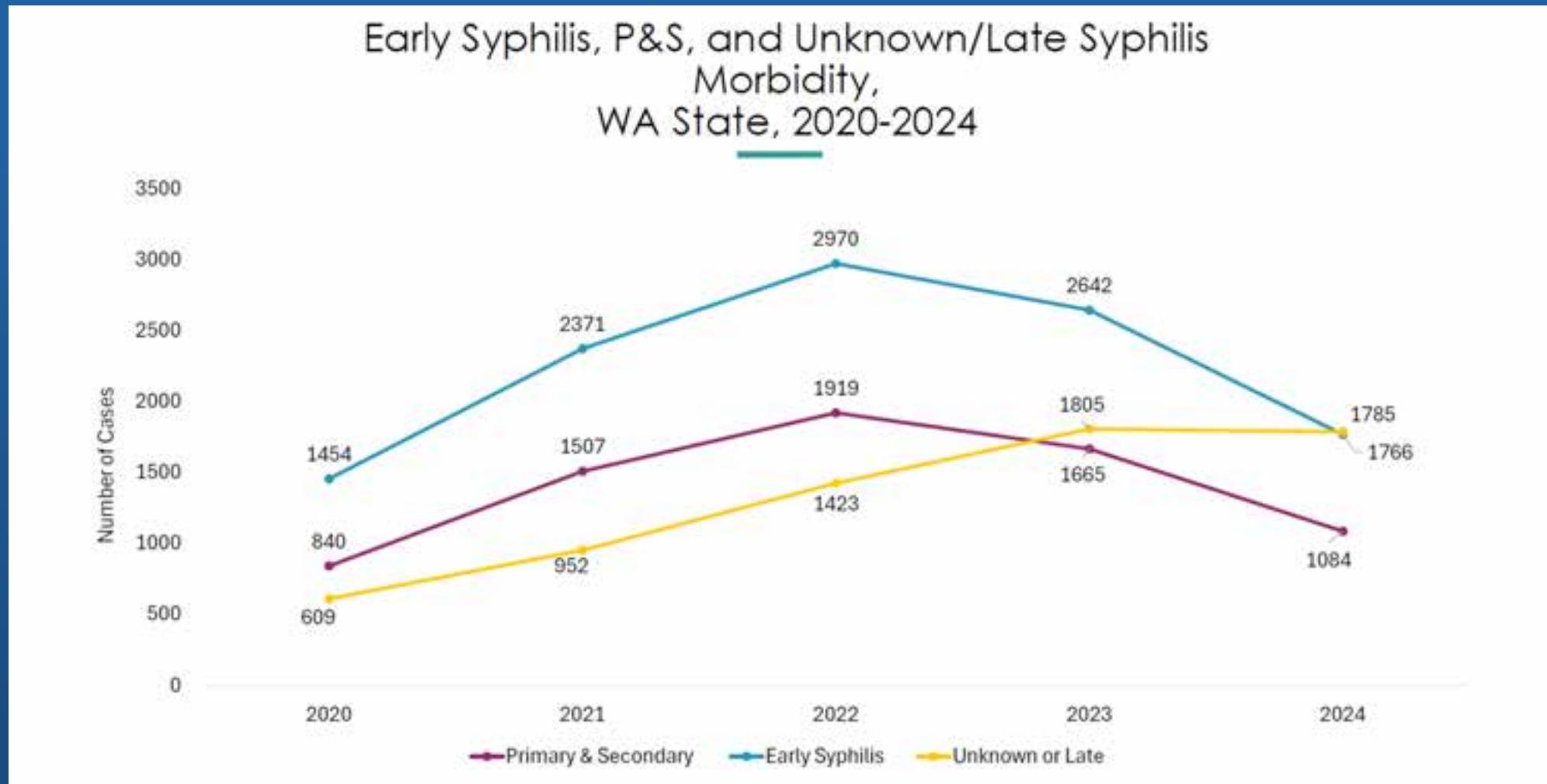
Higher

Dramatically higher

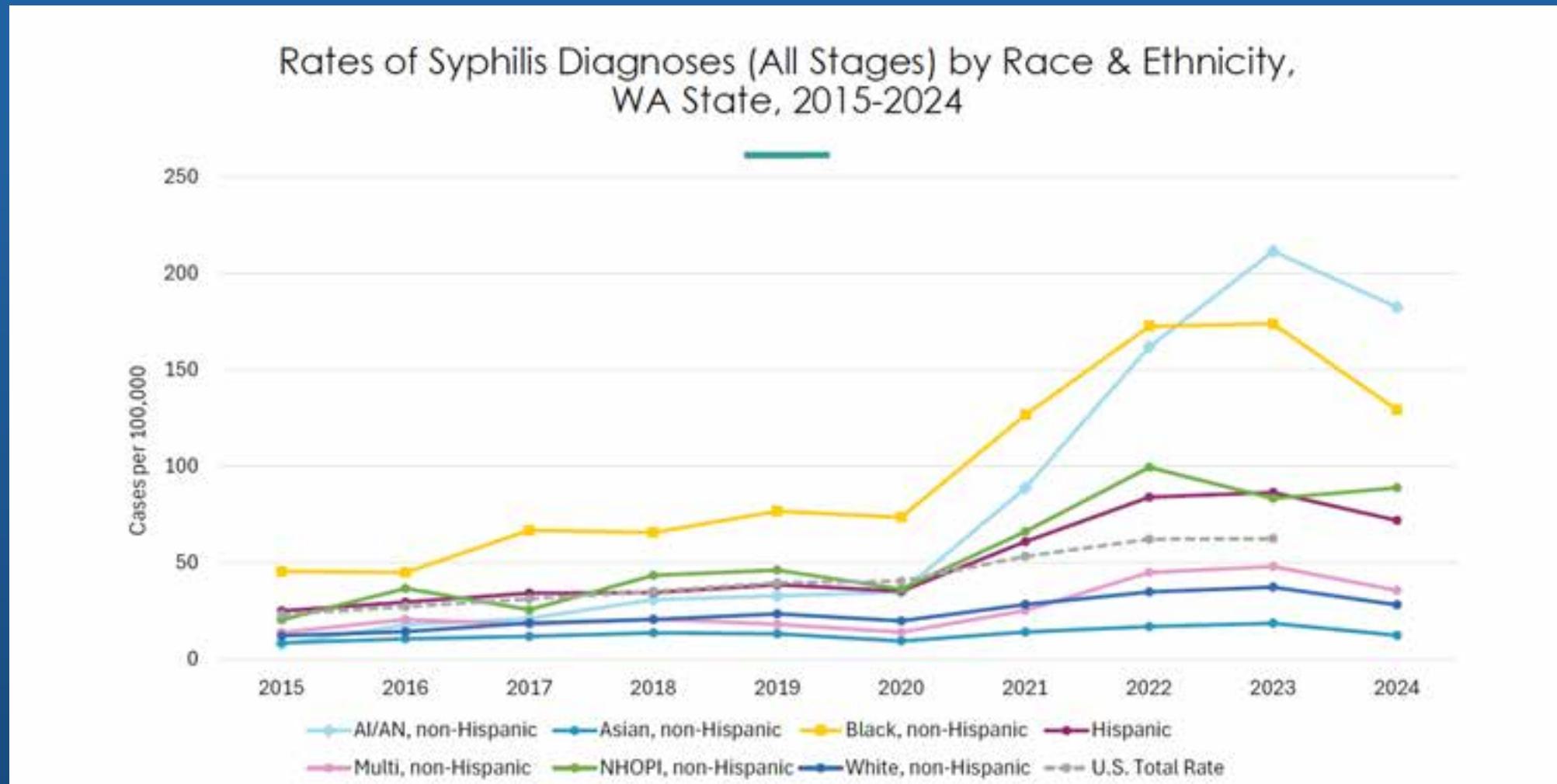
After year over year increases, the syphilis epidemic in Washington appears to be decelerating (but still high!)



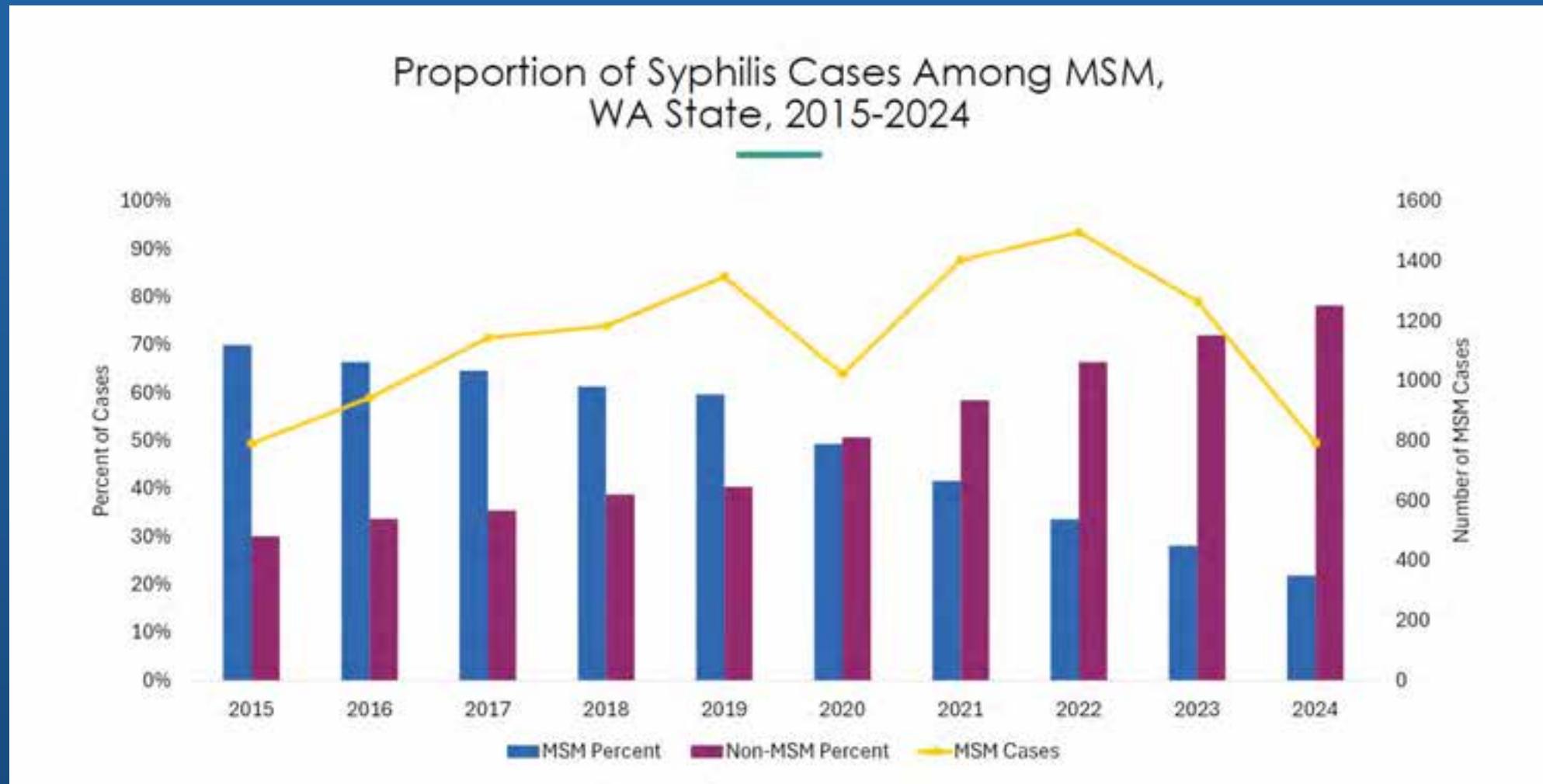
Early syphilis cases have declined, while late/unknown duration cases have stabilized



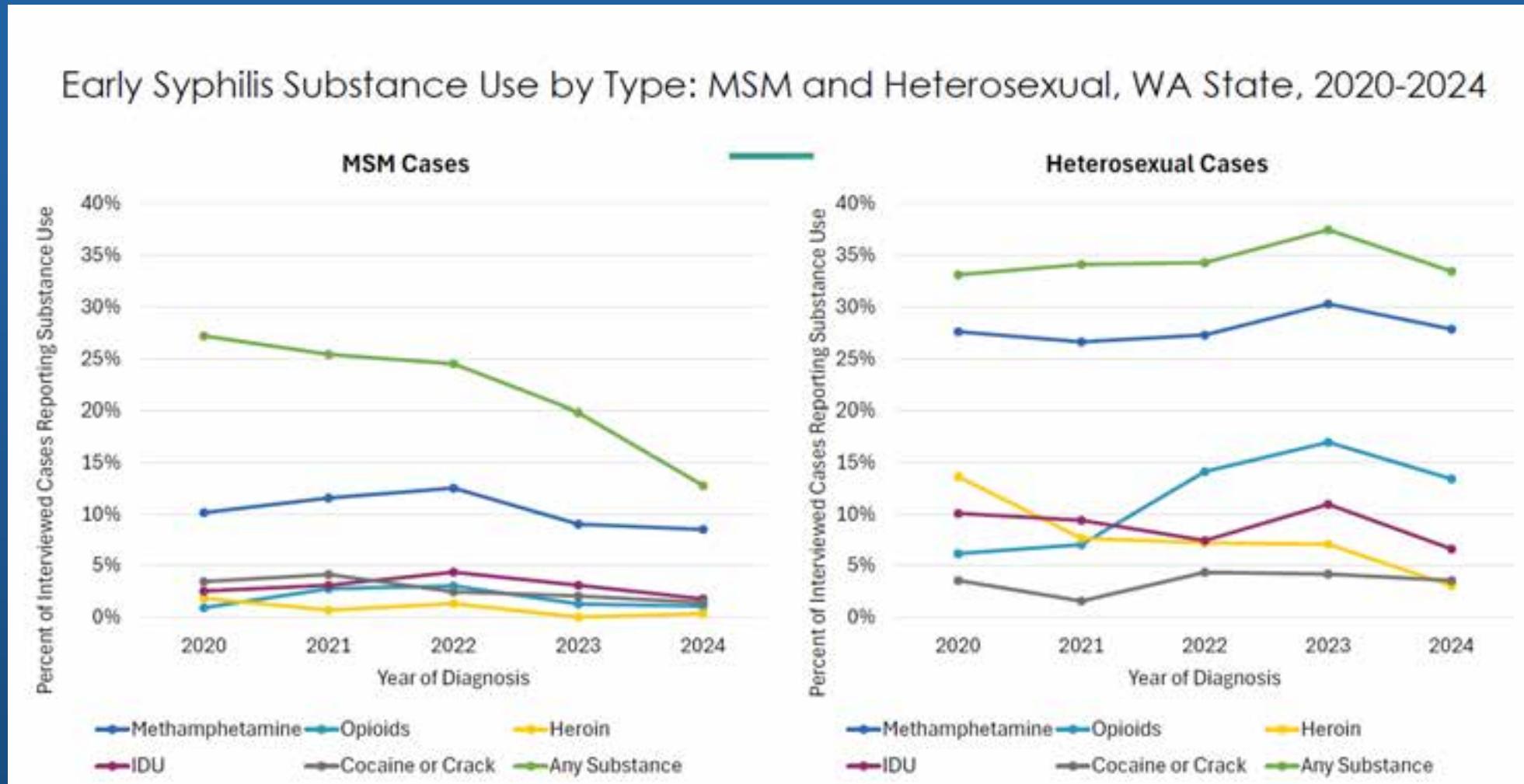
Indigenous and Black communities experience a disproportionate burden of syphilis



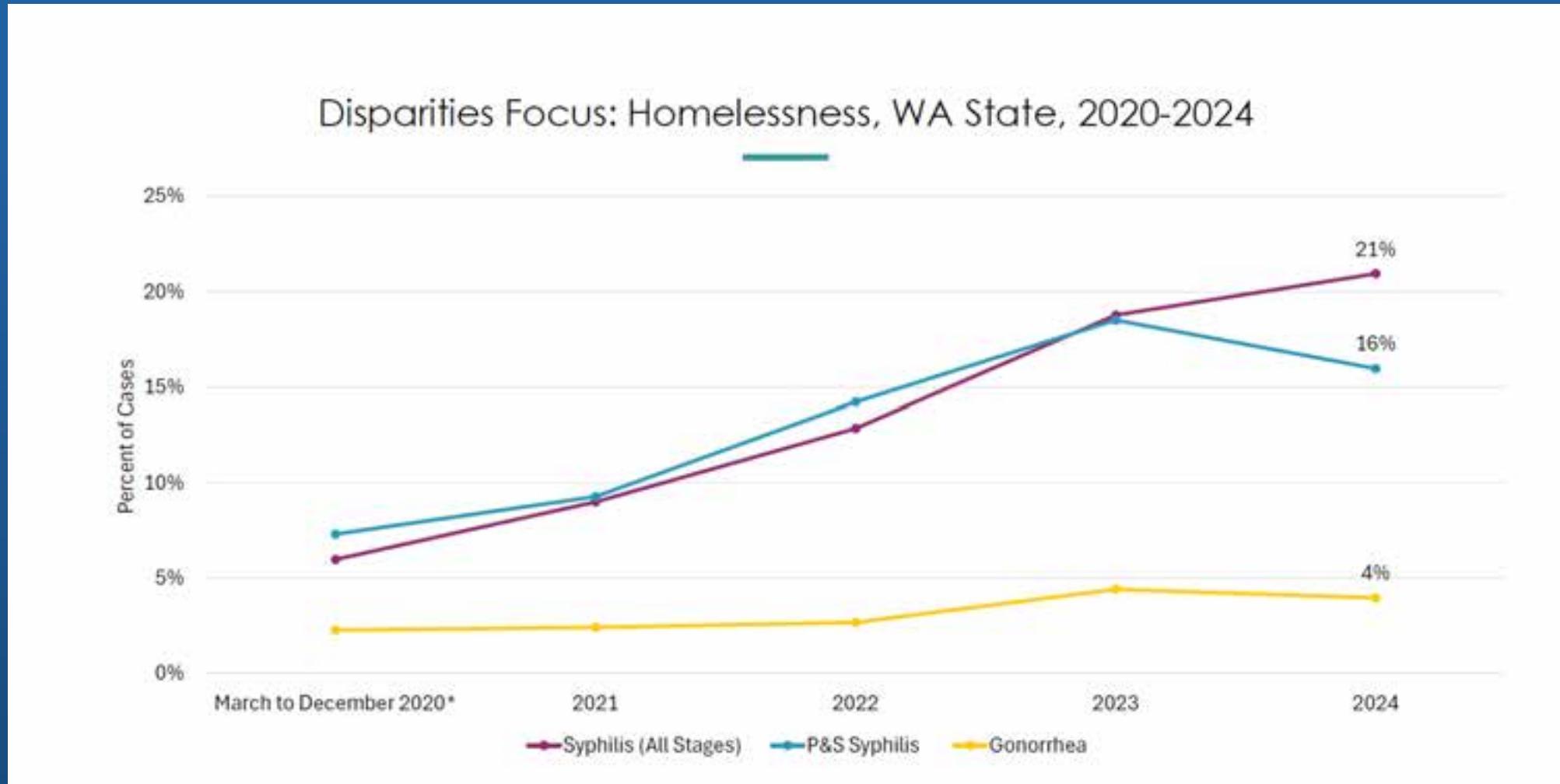
Syphilis in Washington is now a predominantly heterosexual epidemic



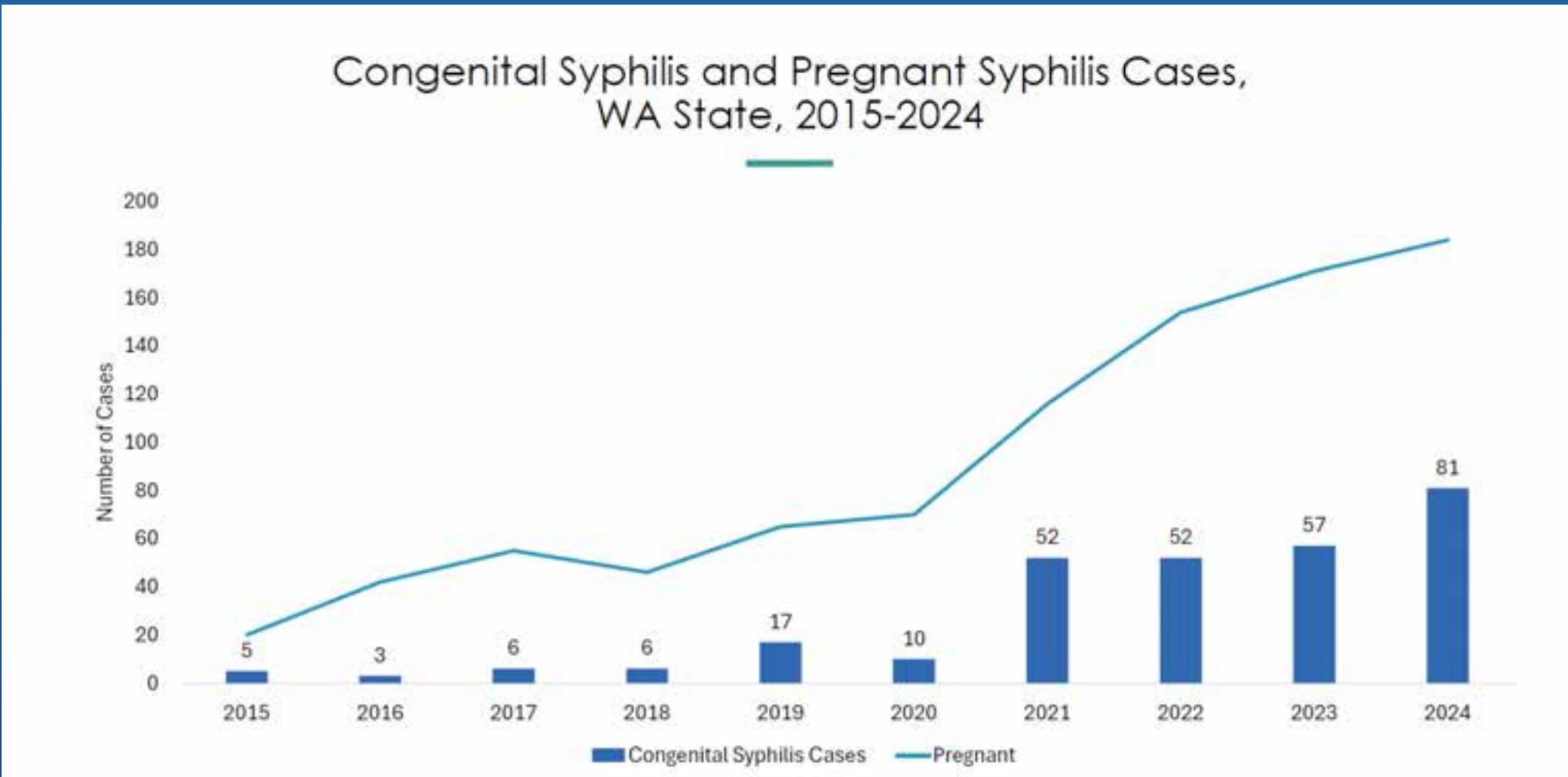
Methamphetamine is the most commonly reported drug among people diagnosed with early syphilis



20% of people with syphilis report being houseless



The public health emergency that is syphilis in pregnancy and congenital syphilis continues unabated



Syphilis screening recommendations in pregnancy

- Screen at first presentation to prenatal care
- Screen in early third trimester (24-28 weeks)
 - Bundle with glucose tolerance testing
 - Can detect seroconversion during pregnancy or re-infection
 - Allows enough time to arrange for treatment if reactive
- Screen at delivery
- Screen in the event of a fetal demise > 20 weeks
- Consider screening at the 6-week post-partum visit



Additional screening recommendations in pregnancy

- **Every visit is a prenatal visit.** Screen pregnant patients with no/limited/unknown prenatal care when they present to:
 - Emergency departments or urgent care clinics
 - Carceral settings
 - Substance use disorder treatment or drug user health programs
 - OB triage
- Screen for infections that may co-occur with syphilis, including HIV, hepatitis B and hepatitis C

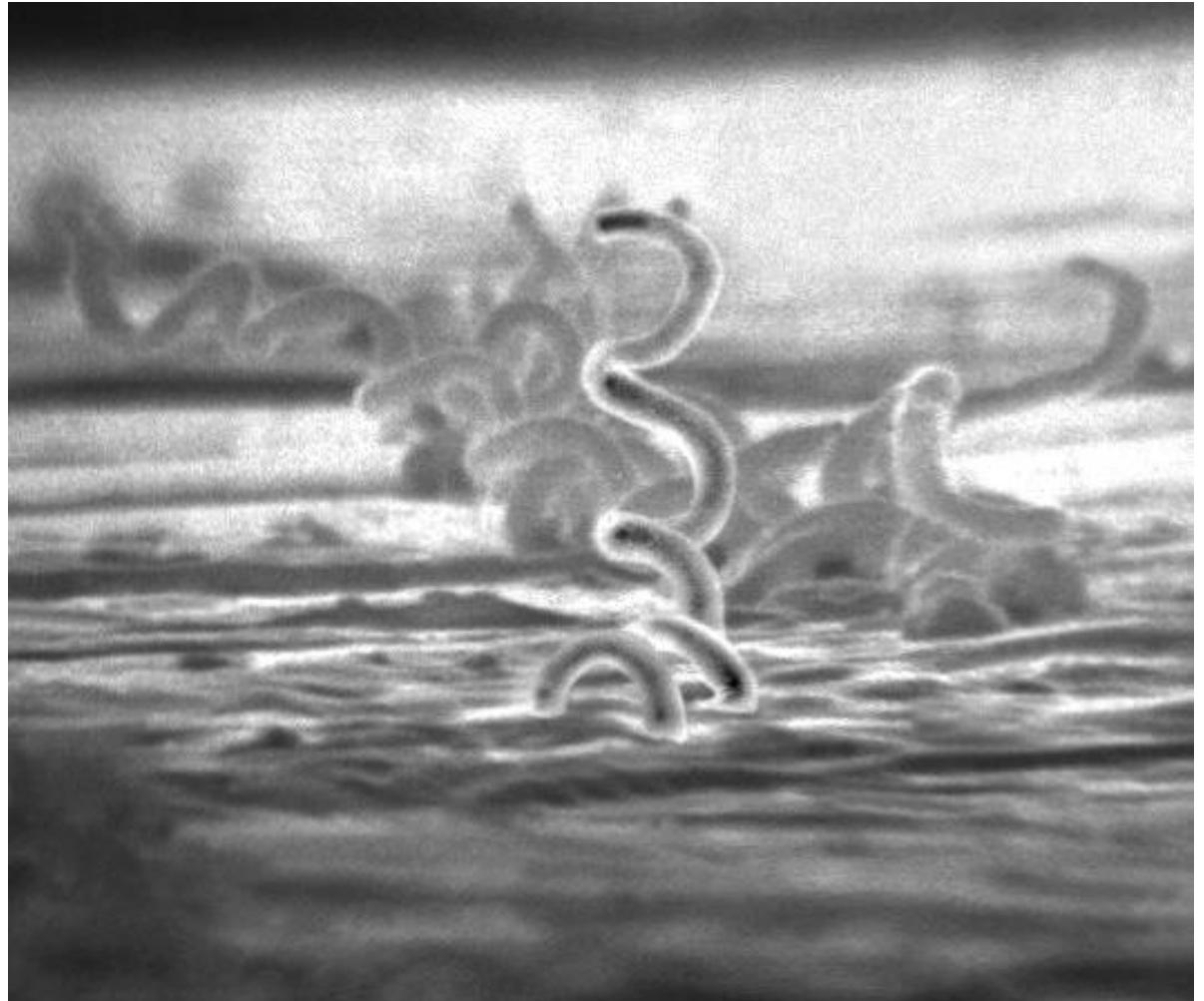
Clinical

POLL Question

- Have you treated a case of syphilis in the prior year?
 - Yes
 - No

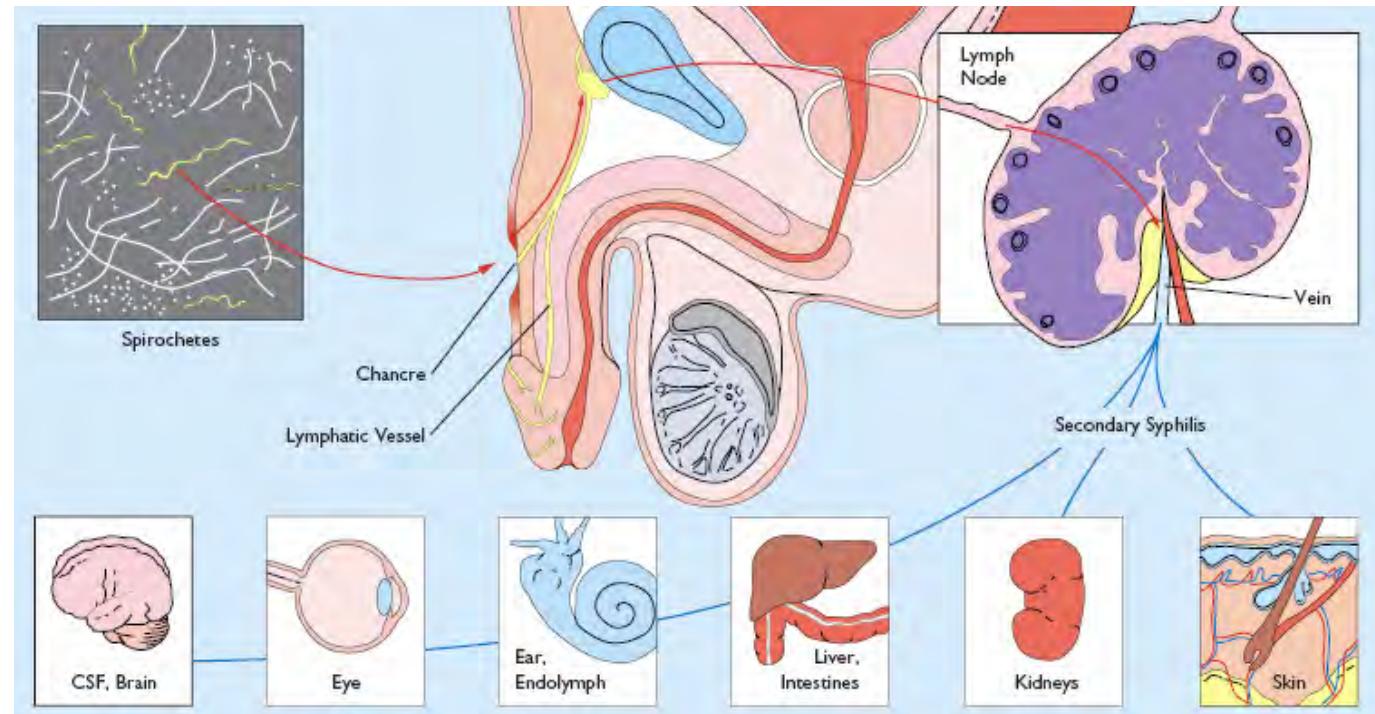
Syphilis

- Chronic sexually transmitted infection caused by *Treponema pallidum*
- Infection through small breaks in the skin or mucous membranes
- Risk of contracting syphilis per sexual contact = 10-60% (on average ~ 30%)
- Highest risk of transmission is during primary and secondary syphilis
- Lesions with treponemes transmit most efficiently/effectively
- Plausible but rare to contract *T pallidum* through blood-sharing activities

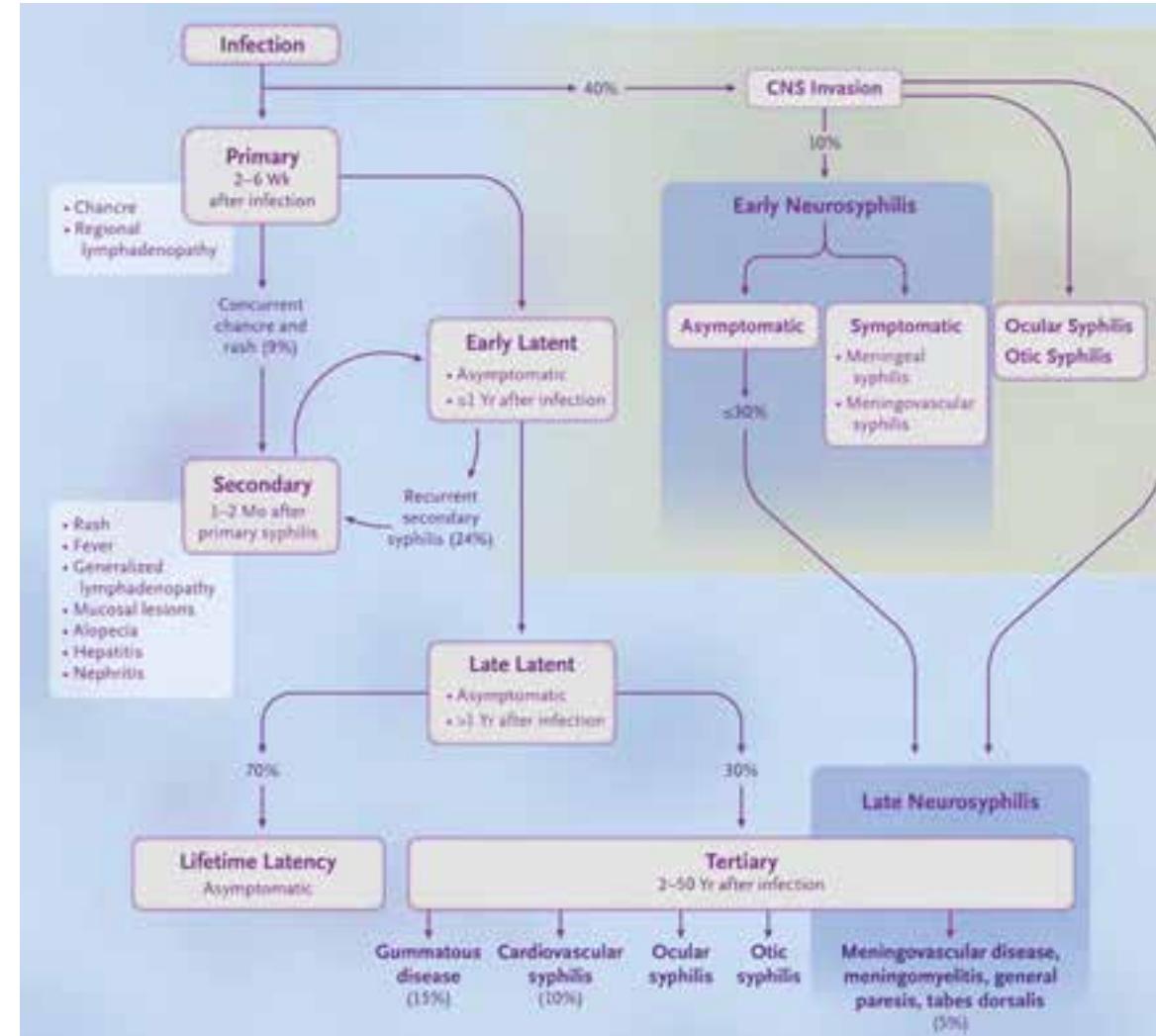


Syphilis is SYSTEMIC

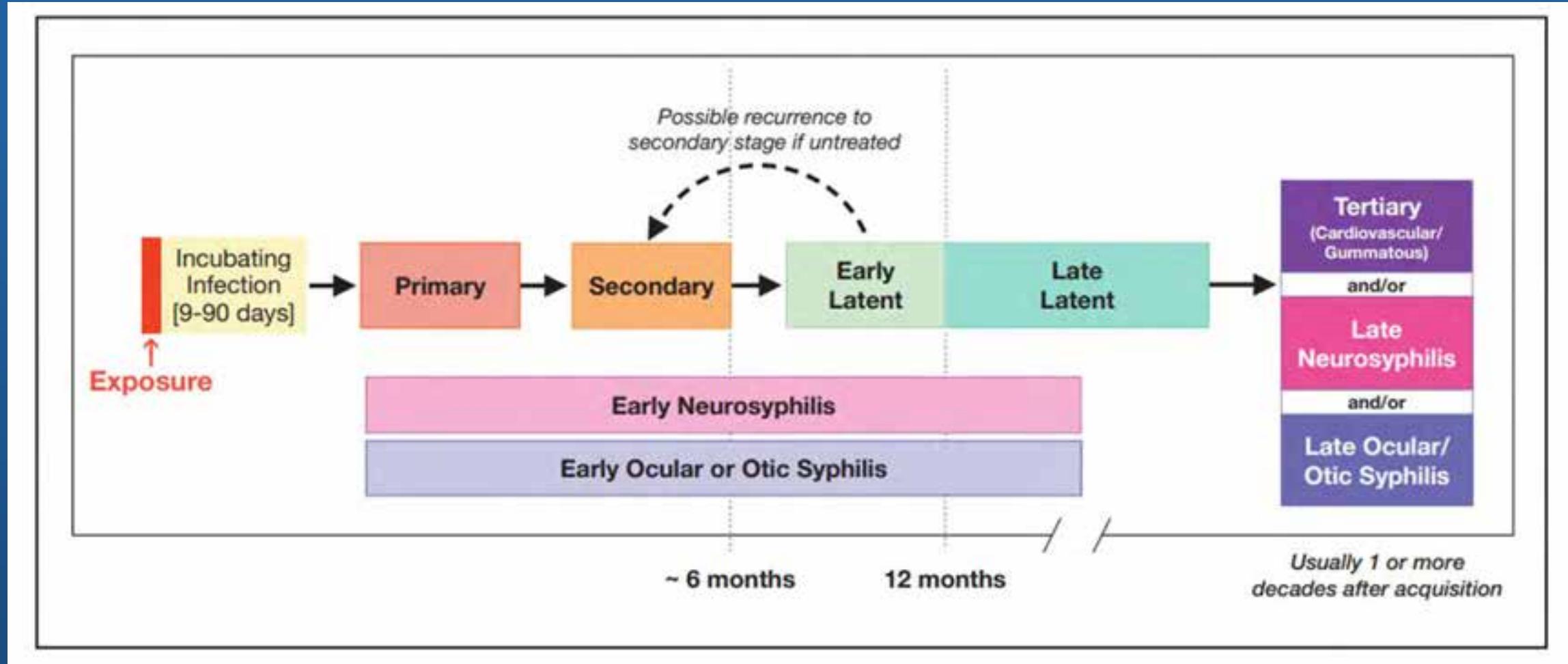
- Syphilis is a multisystem infection
- Progresses through stages with intervening periods of no disease activity
- Invades ALL parts of the body, including the central nervous system
- The incubation time is 10-90 days, on average 21 days



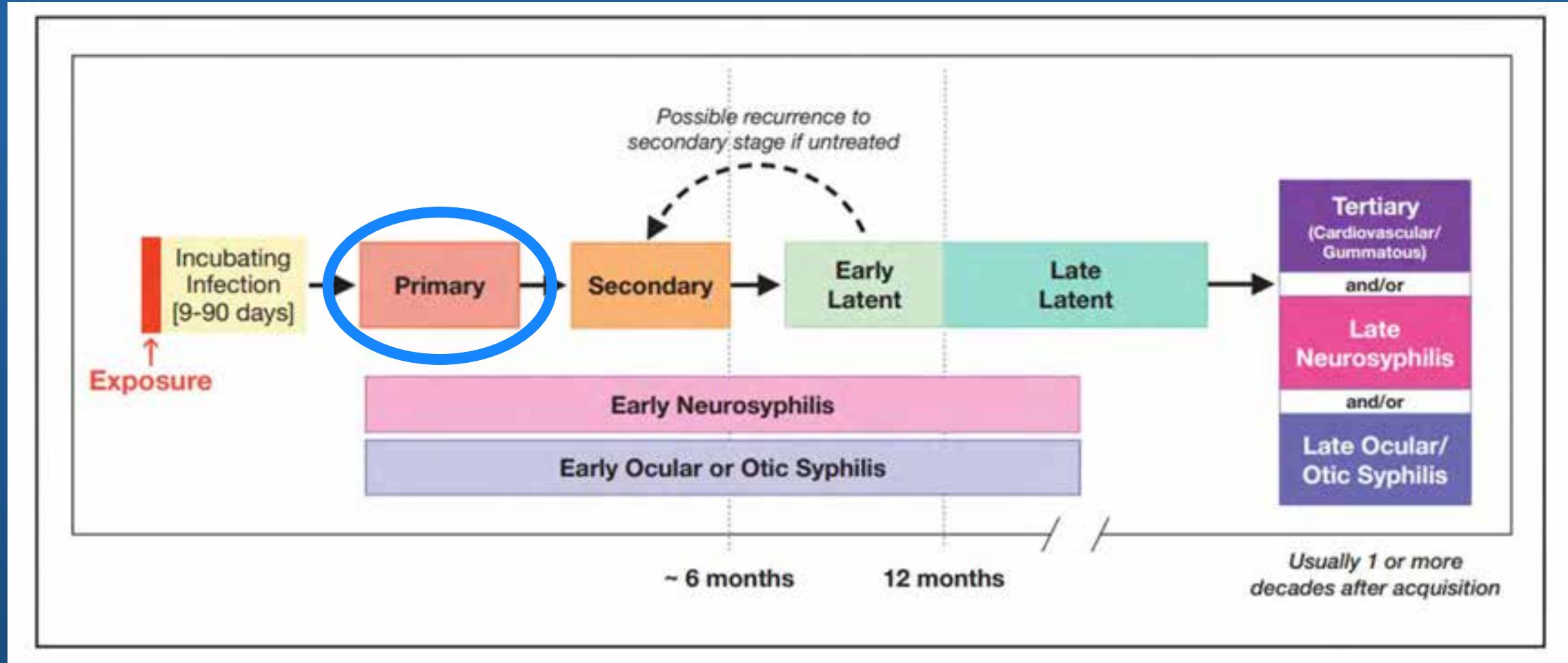
Syphilis presents in stages



Syphilis stages simplified



Syphilis stages simplified



Primary syphilis: presentation and pearls

- The **chancre** is pathognomeric for primary syphilis, appears 10-90 days after exposure
- Usually painless, singular; though atypical presentations (multiple, painful) are more common
- Occurs at the point of entry of *T pallidum* which can be any part of the body: fingers, mouth, lips, anus, vulva, vagina, penis
- Facilitates HIV acquisition (in the absence of PrEP)
 - The chancre attracts macrophages and activated T cells
- The RPR can be negative in 15-25% of cases of primary syphilis, so don't wait for labs to return



If you think it's syphilis, don't wait, just TREAT!

Loss to follow-up and risk of forward transmission is HIGH



Clinical images coming now

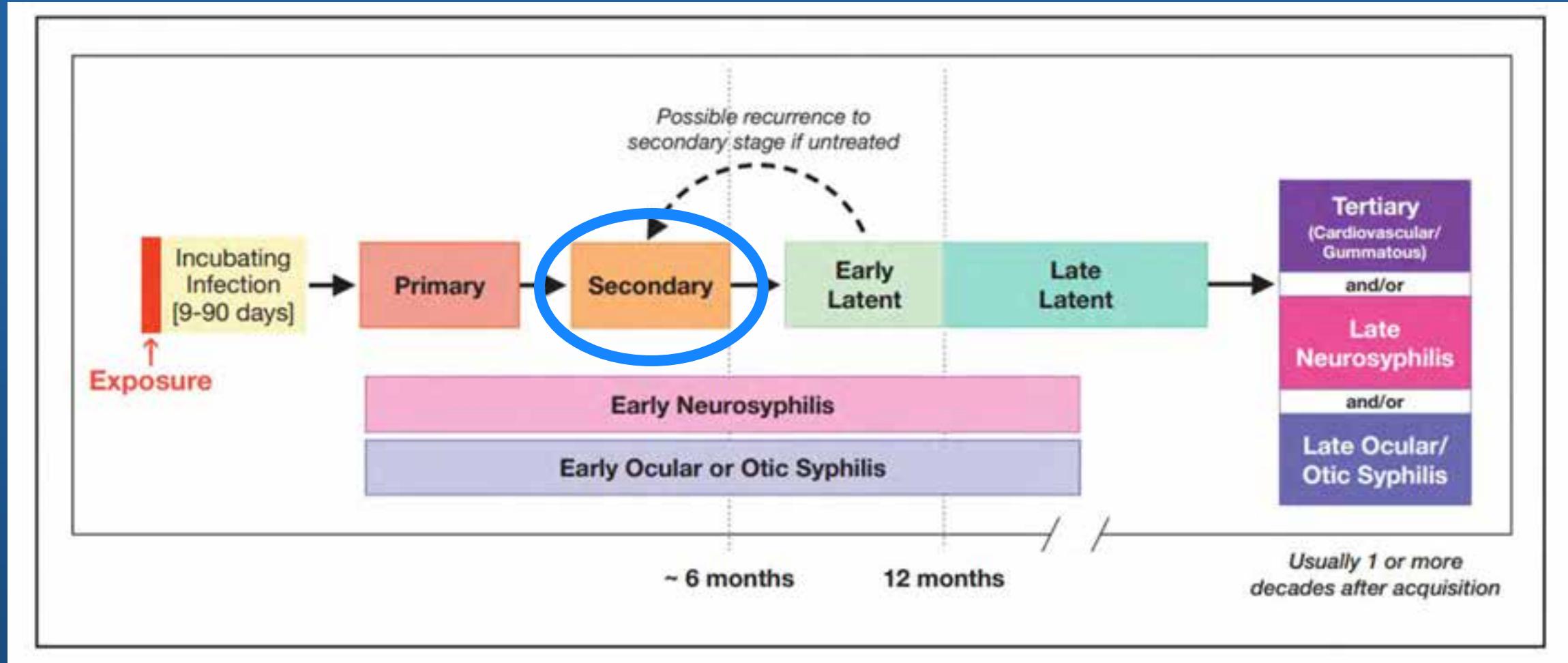
Genital, perianal, and cervical chancres



Oral chancres, and multiple, atypical chancres

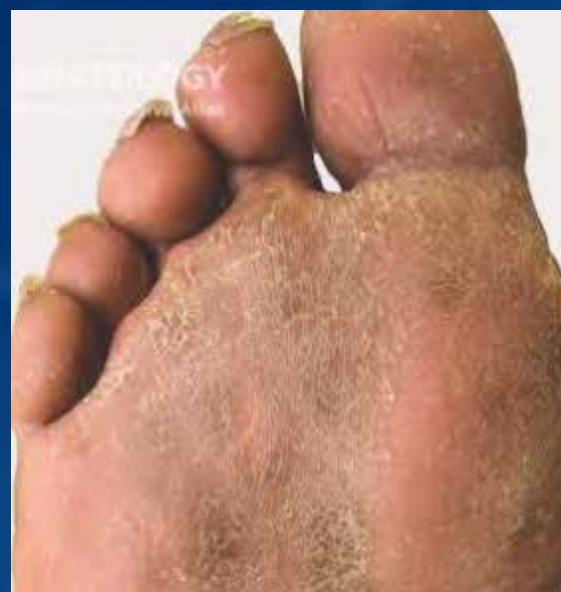
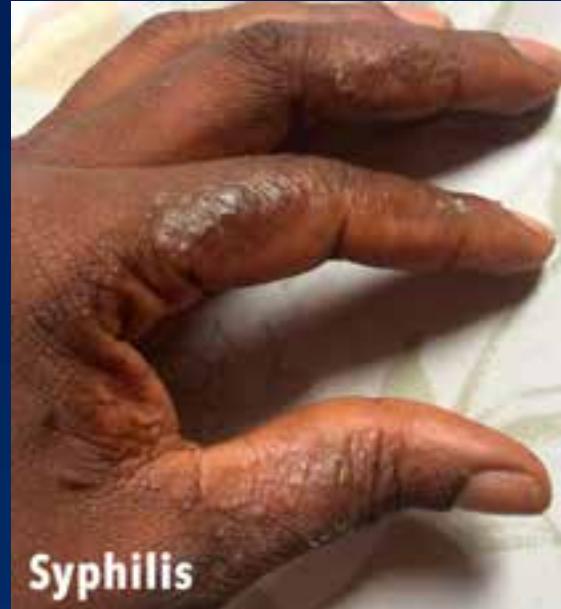


Syphilis stages simplified

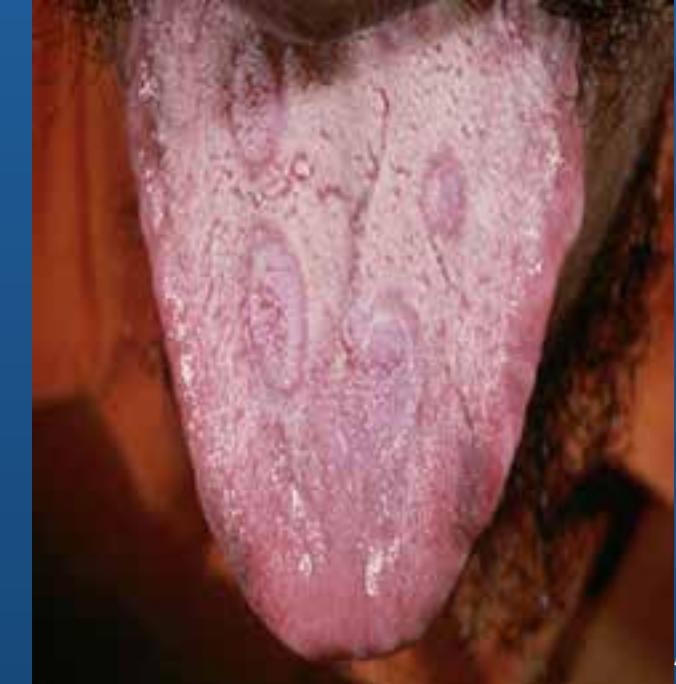


Secondary syphilis: presentation and pearls

- Systemic spread of *T pallidum* that lasts about 2-6 weeks
- Generalized non-pruritic rash in 90% of patients with secondary syphilis
 - Subtle, rough coalescent pink, red, reddish-brown, brown papules or plaques (trunk)
 - Macular, red, “copper penny” in color, annular (palms and soles)
 - Marginal collarette scale (Biett’s sign)
- Mucous patches (mouth), condylomata lata (groin, inner thighs, umbilicus, under the breasts), alopecia (scalp, beard, lateral eyebrows)
- Fever, malaise, lymphadenopathy, myalgia, arthralgia
- Nearly every diagnostic test is positive in this stage; if testing is negative, consider an alternative diagnosis



Alopecia and mucous patches



Condylomata lata

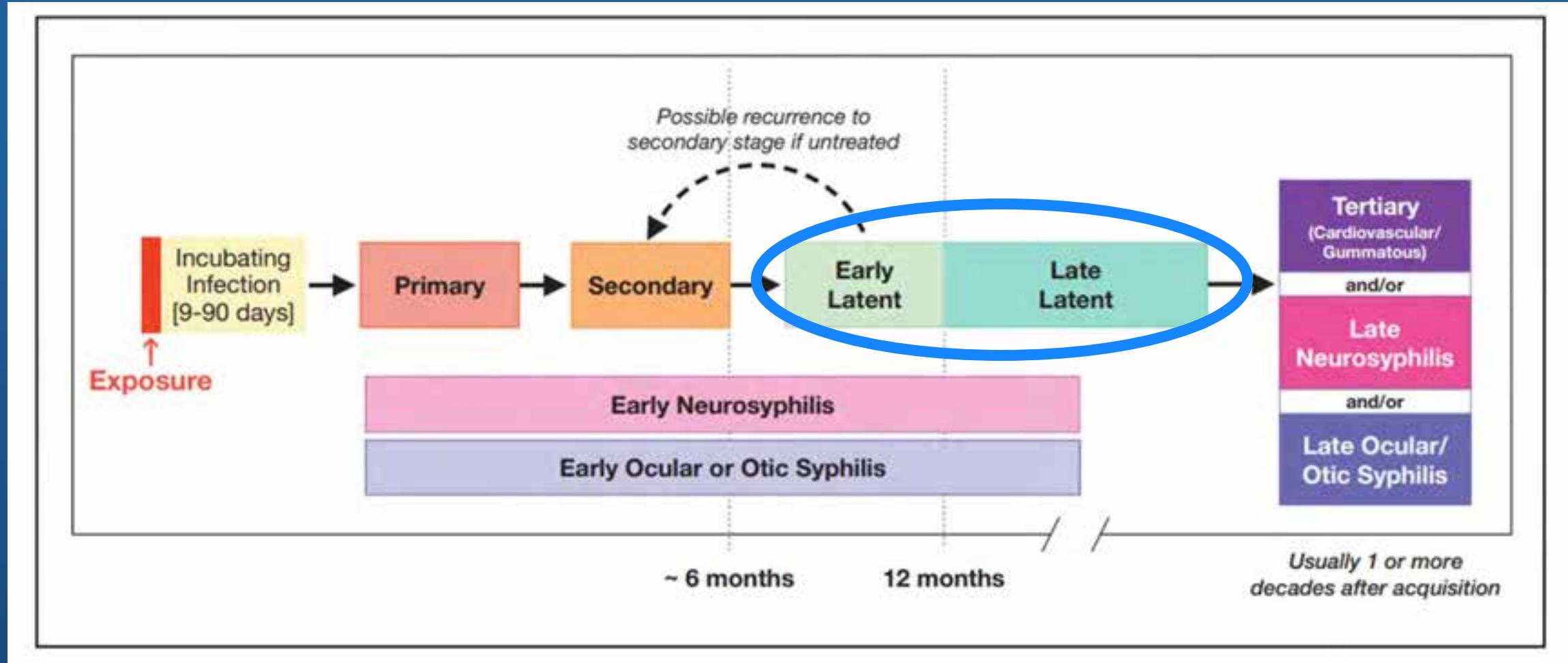
- Moist, grey-white or pinkish plaques, flat-topped nodules
- Groin, inner thighs, umbilicus, under the breasts
- Large numbers of treponemes = very contagious



Don't forget about syphilis mimics!



Syphilis stages simplified



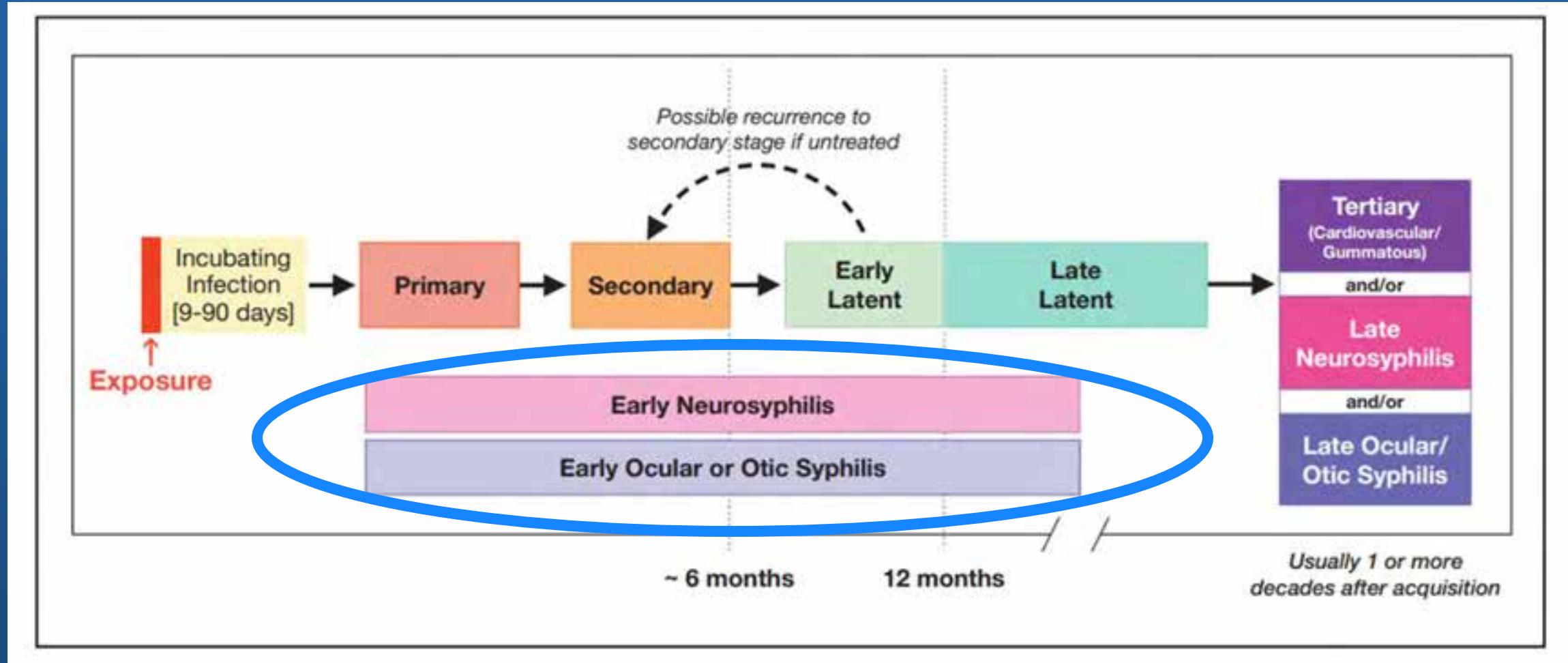
Asymptomatic [latent] stages of syphilis

	Early latent (early non primary non secondary syphilis)	Late latent/Unknown duration
Symptoms?	None	None
Timing of infection	Within the last year	Over one year ago (or at an unknown time)
Staging	<ul style="list-style-type: none">• A newly positive titer in the prior yr• A 4-fold increase in titer in the prior yr• History of signs/sx P or S syphilis in the prior 12 months• Known contact to someone with early syphilis• Sexual (re)-debut in the prior 12 months	<ul style="list-style-type: none">• Reactive syphilis testing without a negative serology in the past year or no prior history of syphilis• A 4-fold increase in titer comparing a current titer to one drawn more than a year ago• No signs/sx P or S in the prior year• No known contacts
Other features	Can recrudesce as secondary syphilis	Requires three weeks of treatment

Treatment

	Recommended Treatment	Alternative Treatment if Penicillin Allergic
Primary, secondary, early non-primary non-secondary	Long-acting BPG 2.4 million units IM in a single dose	Doxycycline 100 mg PO BID for 14 days (not for pregnant patients)
Unknown duration or late 	Long-acting BPG 7.2 million units as three doses of 2.4 million units each at 1-week intervals (7-9 days ideal, 10-14 may be okay, just not for pregnant people)	Doxycycline 100 mg PO BID for 28 days (not for pregnant patients) OR long-acting BPG 2.4 million units x 1 followed by doxycycline 100 mg PO BID for 28 days

Syphilis stages simplified



Neurologic, ocular and otic syphilis

Cluster	Symptoms and signs
Meningeal; acute syphilitic meningitis (12m post-infection)	Headache, photophobia, neck stiffness, confusion; cranial nerve palsies (3,6,7,8) with double or blurry vision, ptosis, facial droop, hearing loss, tinnitus; partial seizures with or without secondary generalization, myoclonus
Ocular (anytime)	Varied, vision loss, anterior and posterior uveitis , optic nerve dysfunction, optic nerve atrophy/neuropathy, chorioretinitis, retinal vasculitis
Otic (anytime)	Varied, sensorineural or conductive hearing loss, vertigo, balance issues, hearing loss, tinnitus
Cerebrovascular accident (5-12y post-infection)	Cerebral and spinal infarcts, acute, focal neurologic deficit (more likely in people living with HIV)
General paresis (15-20y post infection)	Chronic progressive meningoencephalitis, communicating hydrocephalus, cognitive impairment (includes dementia and delirium), behavior change, psychosis
Tabes dorsalis (20-25y post-infection)	Degeneration and demyelination of posterior roots and columns of the spinal cord, ataxia, paresthesias, lancinating pains, visceral crises
Gummas (2-40y post-infection)	Benign cerebral and spinal tumors

ROS for everyone with syphilis for complicated syphilis

- Eyes: new changes in vision, seeing black spots, flashing lights, floaters, blurring, double vision, photophobia, eye discomfort, redness, burning
- ENT: new changes in hearing (hearing loss, muffled hearing), tinnitus
- Neck: stiffness
- Neuro: headaches out of the ordinary, new confusion or memory problems, trouble concentrating, change in personality, changes in coordination, trouble walking, paresthesia or numbness in limbs, seizure

CSF examination may be negative in 30% of ocular and up to 90% of otic syphilis cases.

Emergent/urgent referrals to ophthalmology, ENT/audiology.

For otic syphilis, patients are often treated empirically.

Screening tool for complicated syphilis

Questions	
<u>Symptoms of Otosyphilis</u>	
1) Have you recently had new trouble hearing?	<input type="checkbox"/> Yes – refer to ENT <input type="checkbox"/> No
2) Do you have ringing in your ears?	<input type="checkbox"/> Yes – refer to ENT <input type="checkbox"/> No
<u>Symptoms of Ocular syphilis</u>	
3) Have you recently had a change in vision?	<input type="checkbox"/> Yes – refer to ophthalmology <input type="checkbox"/> No
4) Do you see flashing lights?	<input type="checkbox"/> Yes – refer to ophthalmology <input type="checkbox"/> No
5) Do you see spots that move or float by in your vision?	<input type="checkbox"/> Yes – refer to ophthalmology <input type="checkbox"/> No
6) Have you had any blurring of your vision?	
<u>Symptoms of neurosyphilis</u>	
7) Are you having headaches?	<input type="checkbox"/> Yes <input type="checkbox"/> No
8) Have you recently been confused?	<input type="checkbox"/> Yes <input type="checkbox"/> No
9) Has your memory recently gotten worse?	<input type="checkbox"/> Yes <input type="checkbox"/> No
10) Do you have trouble concentrating?	<input type="checkbox"/> Yes <input type="checkbox"/> No
11) Do you feel that your personality has recently changed?	<input type="checkbox"/> Yes <input type="checkbox"/> No
12) Are you having a new problem walking?	<input type="checkbox"/> Yes <input type="checkbox"/> No
13) Do you have weakness or numbness in your legs?	<input type="checkbox"/> Yes <input type="checkbox"/> No

Consider evaluation & treatment for neurosyphilis in patients with any of the following:

- 1) New persistent headache moderate or greater
- 2) New change in vision – loss, blurring, seeing spots or flashing lights
- 3) New change in hearing – loss, muffling or tinnitus
- 4) New and persistent change in personality, memory or judgement
- 5) New numbness of both legs or gait incoordination

Treatment for complicated syphilis

Recommended Regimen

Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion, for 10-14 days

Alternative Regimens

Procaine penicillin 2.4 million units IM + probenecid 500 mg PO QID for 14 days (Dunaway et al. CID, 2020)

Ceftriaxone 2 grams IV daily for 10-14 days (Marra et al. CID, 2000)

Doxycycline for STI prevention

POLL Question

- If you are a clinician, have you ever prescribed doxy PEP? If you are practice manager or administrator, does your clinic provide doxy PEP?
 - Yes
 - No

What is doxy PEP?

- **Doxycycline post-exposure prophylaxis (doxy-PEP):** strategy of taking 200mg of doxycycline PO within 24-72 hrs after condomless sex to prevent bacterial STI
- A user-controlled tool for persons who have a greater likelihood of acquiring a bacterial STI
- Safe, cheap, well tolerated, highly acceptable in RCT participants and real-world users



Who is doxy PEP for?

- People assigned male at birth who have sex with people with a penis AND
 - Who have had a bacterial STI in the prior year OR
 - Have condomless sex with multiple partners
- Prioritize people with a history of early syphilis or a history of more than one STI in the prior year
- In the absence of prior STI, consider episodic prescribing when patients anticipate increased sexual activity (travel, sex parties, group sex, trading sex, etc.)

Who is doxy PEP for?

- Consider prescribing doxy PEP for people assigned female at birth who have sex with people with a penis and who are at particularly high risk for syphilis.
- Some factors to consider:
 - Substance use (methamphetamine, fentanyl)
 - Unstable housing, houselessness
 - Exchange sex
 - History of syphilis
 - Exposure to a partner with syphilis

How is doxy PEP taken?

Doxy PEP – How to Take

Two 100mg pills of doxycycline ideally within 24 hours
but no later than 72 hours after condomless sex

 = sex without a condom,
including oral sex

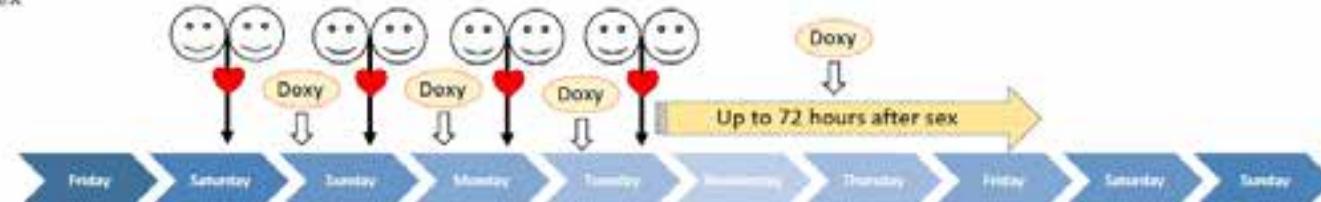
Example: Sex on Sat; take dose of doxy by Tues



Example: Sex on Thursday; take dose of doxy by Sunday



Example 2: Daily (or more) sex Sat-Tues; take daily dose of doxy and last dose within 24 hours *but not later than 72 hours* after last sex



No more than 200 mg every 24 hours

Doxy PEP is 47-65% effective in reducing overall STI incidence in clinical trials

Study (Location)	N	STI rate		Relative Risk Reduction	Absolute Risk Reduction
		Doxy-PEP	No Doxy-PEP		
IPERGAY (Paris, France)	232	38 per 100 p-y	70 per 100 p-y	47%	32 per 100 p-y
DoxyPEP (Seattle & San Francisco, US)	501	11% per quarter	32% per quarter	65%	140 per 100 p-y
DOXYVAC (Paris, France)	502	50 per 100 p-y	122 per 100 p-y	59%	72 per 100 p-y
dPEP Kenya (Kisumu, Kenya)	449	50 per year	59 per year	NS	9 per year

The number of people needed to use doxyPEP to prevent one STI in a 3-month period:

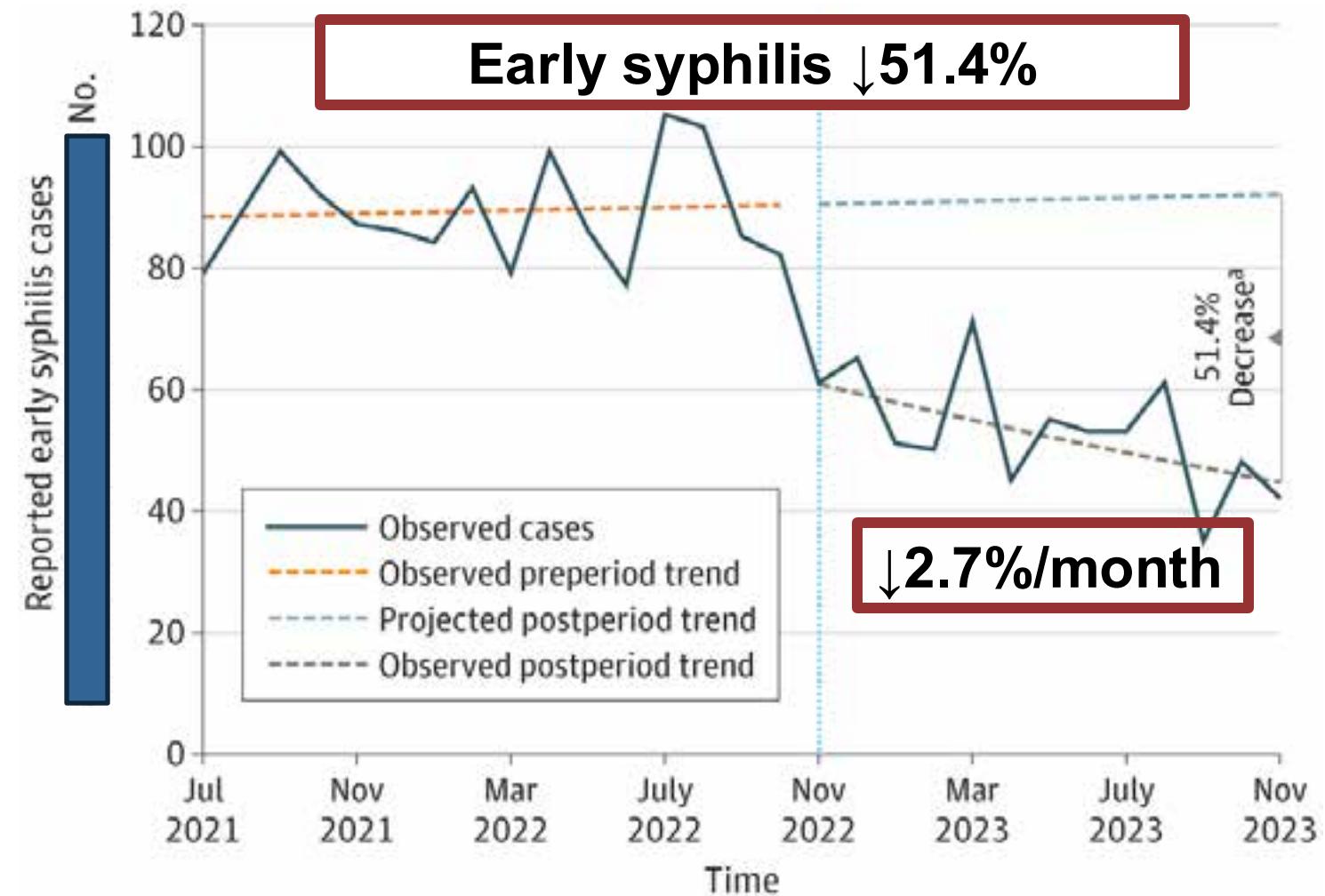
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Doxy PEP is 73-80% effective in reducing incident syphilis in clinical trials

Study (Location)	N	STI rate		Relative Risk Reduction	Absolute Risk Reduction	Syphilis Rate		Relative Risk Reduction	Absolute risk Reduction
		Doxy-PEP	No Doxy-PEP			Doxy-PEP	No Doxy-PEP		
IPERGAY (Paris, France)	232	38 per 100 p-y	70 per 100 p-y	47%	32 per 100 p-y	3.7 per 100 p-y	12.9 per 100 p-y	73%	9.2 per 100 p-y
DoxyPEP (Seattle & San Francisco, US)	501	11% per quarter	32% per quarter	65%	140 per 100 p-y	Not reported	Not reported	~80%	~8.6 per 100 p-y
DOXYVAC (Paris, France)	502	50 per 100 p-y	122 per 100 p-y	59%	72 per 100 p-y	2.8 per 100 p-y	13.0 per 100 p-y	78%	10.2 per 100 p-y
dPEP Kenya (Kisumu, Kenya)	449	50 per year	59 per year	NS	9 per year	NA	NA		

Population-level impact of doxy PEP: a 51% decrease in early syphilis

- In October 2022, SF was the first jurisdiction to develop and disseminate doxy PEP guidelines
- Ecologic analysis to assess the association of the release and implementation of doxy PEP guidelines and STI
- July 2021-November 2023



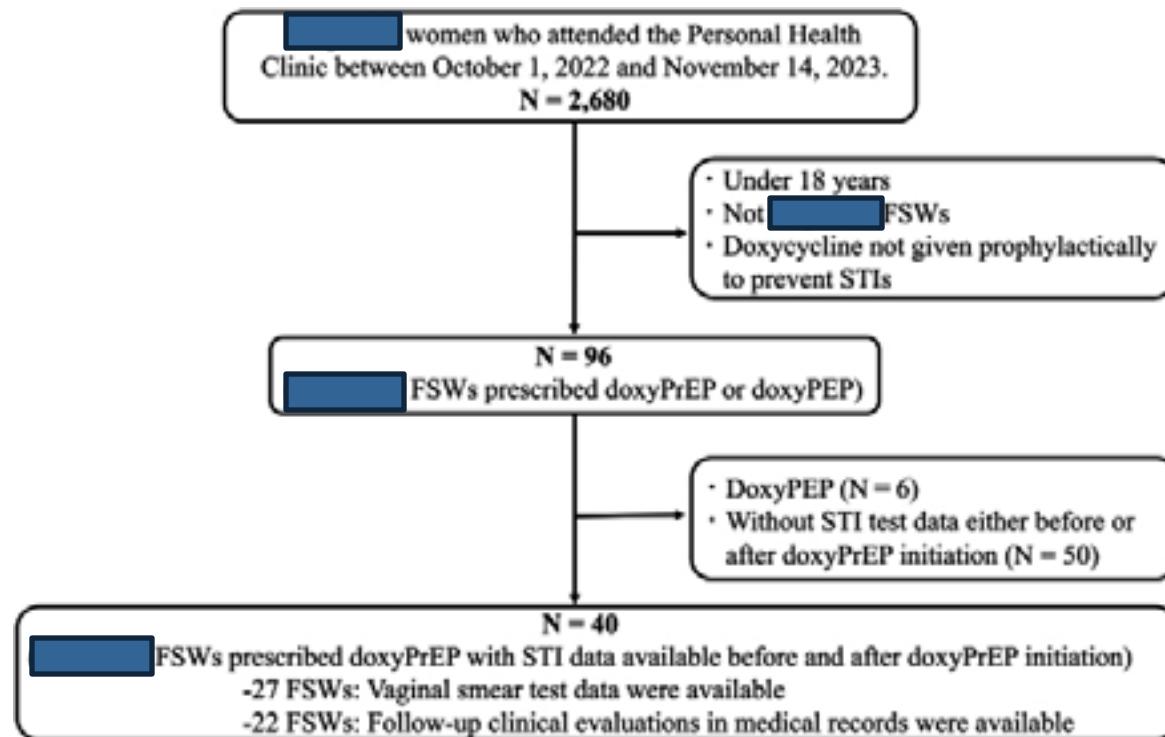
Weekly DOT doxy likely prevents chlamydia among women

Incident chlamydia rate with **weekly doxycycline**: 11.2 per 100 person years
Incident chlamydia rate in **dPEP Kenya SOC group**: 29.6 per 100 person years

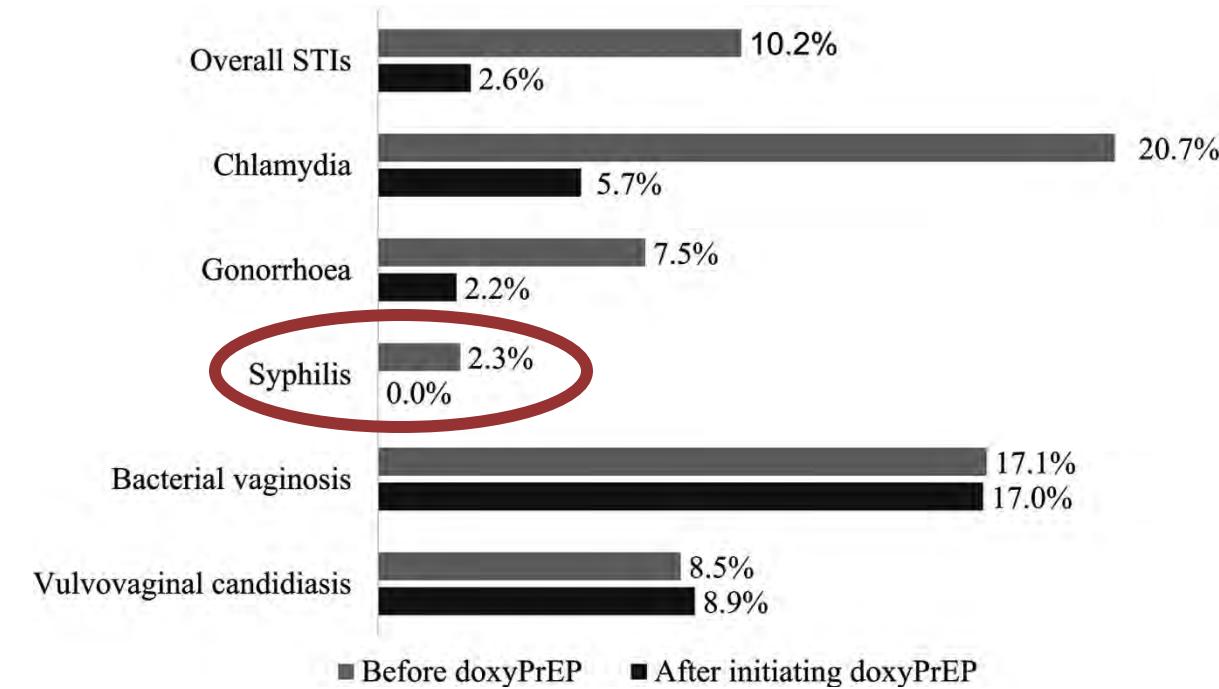
Analysis	Endpoint	Weekly DoxyDOT (N=60)	SOC dPEP Kenya (N=225)	RR	95% CI	P-value
GEE Censoring Clinical Hold Time	All STIs	6/57 (10.5%)	31/220 (14.1%)	0.73	0.28-1.91	0.52
	Chlamydia	3/57 (5.3%)	29/220 (13.2%)	0.39	0.12-1.25	0.11
	Gonorrhea	4/57 (7.0%)	5/220 (2.3%)	3.03	0.637-14.40	0.16

* Two additional cases of chlamydia and 3 additional gonorrhea cases among people on holds

Among women who trade sex, doxyPREP may reduce STI incidence



Daily doxy PREP: 73% took 100% of doses



STI incidence:
232.2/100 p-y → 79.2/100 p-y
67% reduction in STI

Benefits and risks of doxy PEP use

- Significant reductions in individual and population-level syphilis incidence
- Safe, well-tolerated, high adherence
- People want it, acceptable, cheap
- Low number needed to treat
- Improved piece of mind, pleasure, decreased stigma
- Most prevented STIs are asymptomatic
- Use of doxy PEP has led to/sustains tetracycline resistance in gonorrhea
- Increased tetracycline resistance in methicillin-sensitive *Staph aureus* and group A strep (though lower colonization with *Staph aureus* overall)
- Unclear impact on microbiome
- Goes against the trend of less rather than more antibiotics (antibiotic stewardship)

Counseling messages

At initiation

- Evidence of benefits
- Review known side effects and potential toxicities
- Potential but unknown risks to the microbiome and antibiotic resistance
- Not 100% effective
- No protection against viruses
- How to take it; expectations for monitoring
- Alternatives to doxy PEP
- Comprehensive sexual health services

On follow-up

- How/if doxy PEP Is being used?
- Number of doses in the prior month
- Timing of doses related to sex
- Side effects
- Not 100% effective
- New symptoms
- Engagement in comprehensive sexual health services (PrEP, HIV treatment, condoms, HIV/STI testing and treatment, vaccines)

Dosing and prescribing guidance

- 200 mg of doxy taken as soon as possible after and no later than 72 hours after condomless oral, anal or vaginal sex.
- Take up to daily, depending on frequency of sexual activity, but no more than 200 mg within a 24-hour period.
- Immediate release 100 mg is fine; hyclate or monohydrate*
- Take with fluids and remain upright for 30 minutes after the dose. Taking with food may increase tolerability.
- Suggested: #60 tabs with 0-1 refills; may vary depending on frequency of sex and mutual agreement about need for monitoring

Reference Links:

- Lexi-Comp

Product:

DOXYCYCLINE HYCLATE 100 MG CAPSULE

[View Available Strengths](#)

Sig Method:

[Specify Dose, Route, Frequency](#)

Taper/Ramp

Combination Dosage

[Use Free Text](#)

Dose:

200

mg

100 mg

Calculated dose: 2 capsule

Route:

oral

[Search](#) oral

Frequency:

Daily PRN

[Search](#)

Daily

BID

PRN is important as can distinguish doxy-PEP use from other doxycycline use

Duration:

[Calendar](#) [Doses](#) **Days** [30 days](#) [3 months](#) [1 year](#)

Starting: 10/17/2022 [Calendar](#) Ending: [Calendar](#) First fill: [Calendar](#)

Dispense:

Days/Fill: [Full \(0 Days\)](#) [30 Days](#) [90 Days](#)

Quantity 60 [capsule](#) Refill: [1](#) [0](#)

Dispense As Written

Consider 30 days with 0-1 refill for initial dispensing, then assess usage & tolerability

Mark long-term:

DOXYCYCLINE HYCLATE

⚠ Patient Sig:

Take 2 capsules (200 mg total) by mouth 1 time each day if needed (Take within 24 hours after condomless sexual contact, and no later than 72 hours after sex.). Not to exceed 200 mg in a 24 hour period. Take large glass of water, do not lie down for 30 minutes after.

[Edit the additional information appended to the patient sig](#)

[i](#) The sig contains both discrete and free text elements. Review the final sig above.

Class:

Normal

[Search](#)

Normal

[Print](#)

Phone In

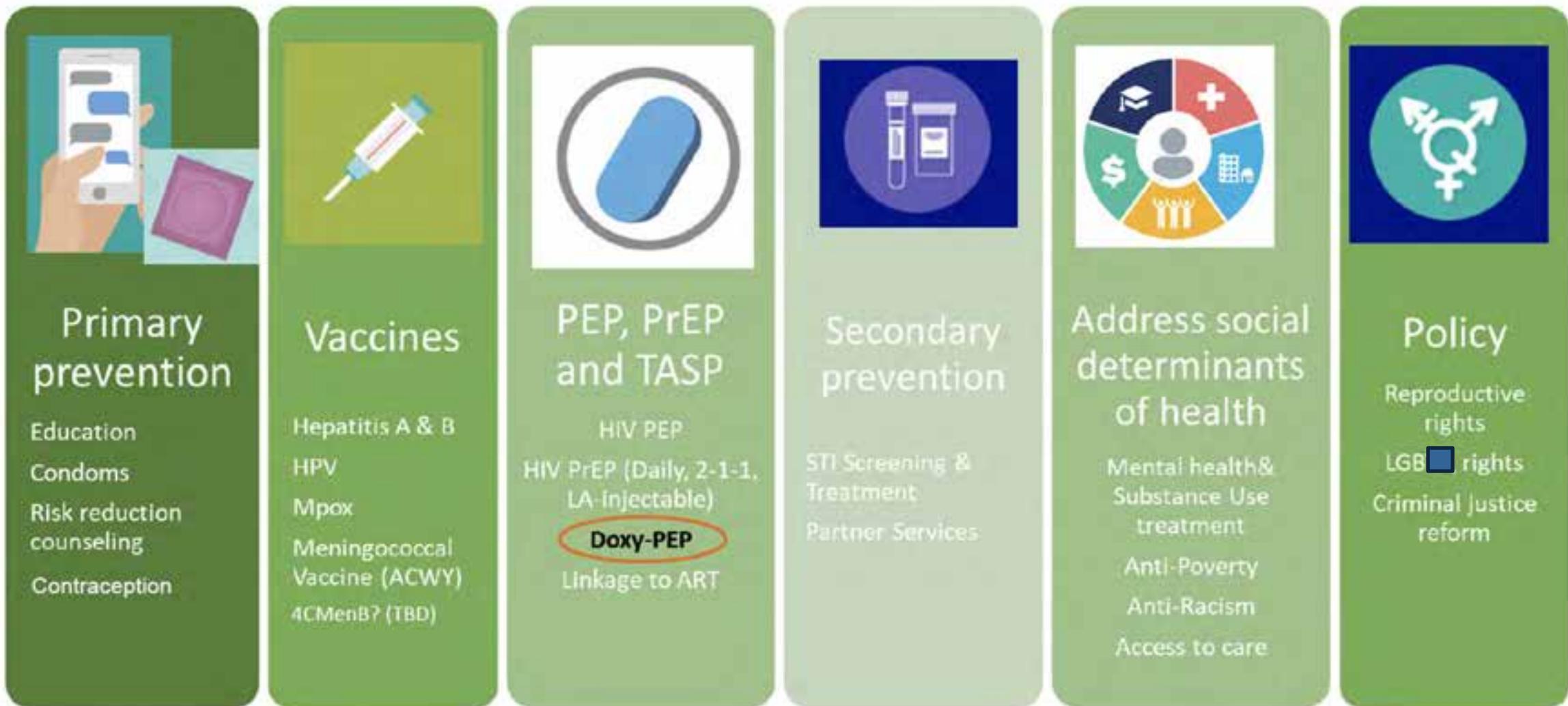
No Print

Sample

Doxy-PEP specific instructions

[i](#) This medication will not be e-prescribed. Invalid items: Pharmacy

Doxy PEP should be a part of comprehensive sexual health services

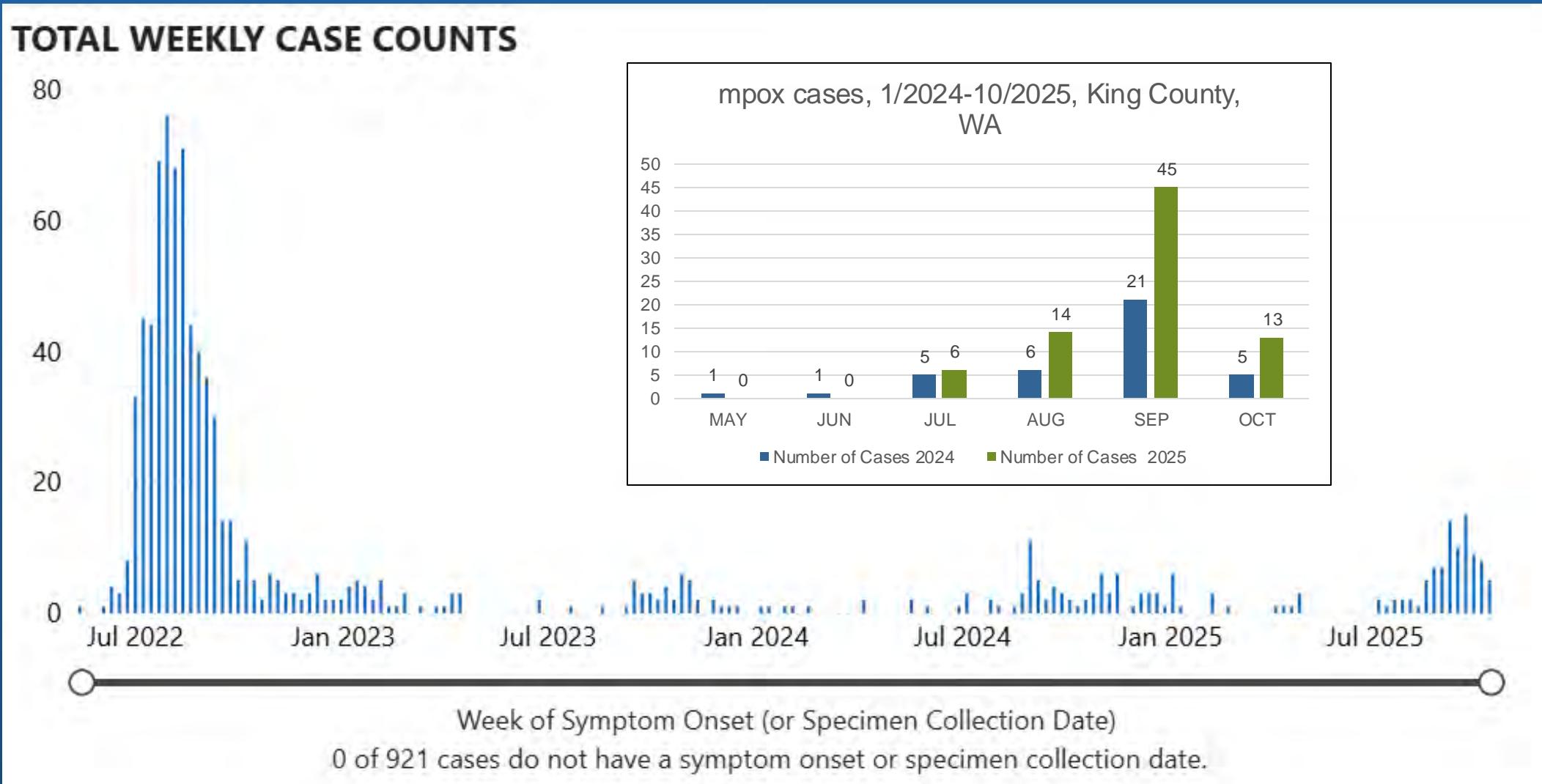


mpox

POLL Question

- Have you seen a case of mpox since the global outbreak in 2022?
 - Yes
 - No

mpox is an endemic, seasonal infection in Washington State and nationally

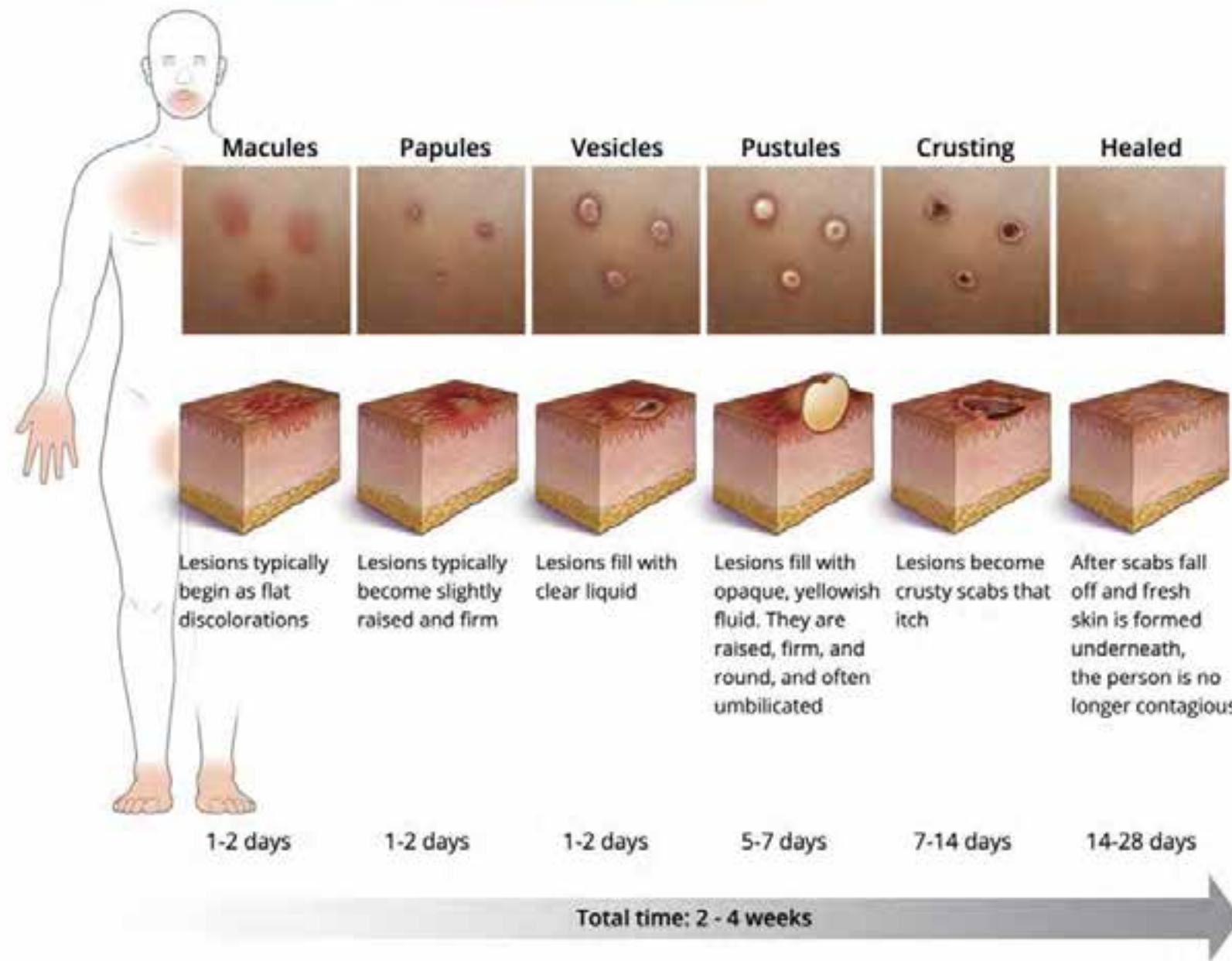


Clade 1 mpox is circulating in the United States

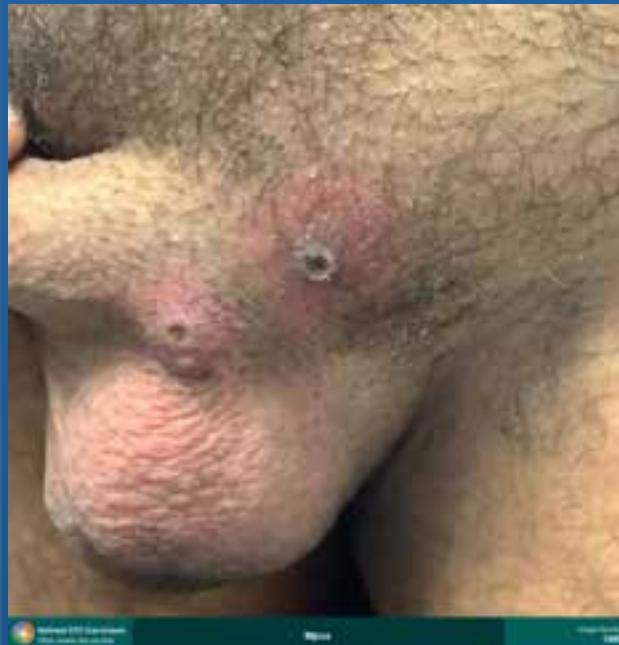
Three Cases of Mpoxy Tied to Severe Illness Worry Health Experts

None of the patients, all California residents, had traveled abroad, suggesting the Clade 1 form was transmitted locally.

MPOX LESION PROGRESSION DESCRIPTION AND TIMELINE



Exemplary mpox rash



The most effective mpox prevention tool is vaccination

Two doses 0.5 mL SQ 28 days apart

Persons Seeking Health Care	Case Patients	Control Patients	Vaccine Effectiveness (95% CI)	
			Unadjusted	Adjusted†
			number	percent
Unvaccinated, reference population	2022	6984		
Partially vaccinated, 1 dose	146	1000	52.0 (42.3–60.1)	35.8 (22.1–47.1)
Fully vaccinated, 2 doses	25	335	77.2 (65.0–85.1)	66.0 (47.4–78.1)

* CI denotes confidence interval.
† Adjustment was for age group (18 to 35, 36 to 49, and ≥ 50 years), race or ethnic group (non-Hispanic White, non-Hispanic Black, and other non-Hispanic), Social Vulnerability Index quartile (quartile 1 to 4, or unknown), and the presence or absence of an immunocompromising condition.

Many people can still benefit from vaccination

- As of August 1, 2023, only **42% of eligible Washingtonians received 2 doses of JYNNEOS and 26% received 1 dose**
- People who were not sexually active during the outbreak may now be sexually active without the protection of the vaccine (perhaps greater among young people)
- People who chose to change behavior over vaccination as a prevention strategy may have resumed their usual sexual activity
- Vaccine messaging has been less robust since the outbreak

Think mpox

- Report all cases of mpox to PHSKC
- Maintain a high index of suspicion for mpox for any patients with signs and symptoms of mpox even if:
 - Syphilis or HSV are considered more likely (co-infections are common)
 - The patient has been vaccinated (less severe, subtle proctitis, constitutional symptoms may be absent)
- Consider clade I if travel to Central or East Africa, areas of the US with community transmission of clade I, or contact with a case of clade I
- Test for mpox (PCR)
- Continue to vaccinate eligible individuals
- Provide PEP for people with recent exposure

Summary

- The syphilis epidemic is dynamic; overall, we are seeing a deceleration in cases but case numbers are still higher than they were 5 years ago
- Syphilis in pregnancy and congenital syphilis continue to be an unabated public health crisis
- Syphilis is a complicated, systemic, and treatable infection
- Doxy PEP is very effective at preventing syphilis and, perhaps, should/can be used primarily as a syphilis prevention tool
- Mpox cases in the late summer and early fall are the highest they've been since the global outbreak though substantially fewer than in 2022. Vaccination is still very relevant especially for people who were not sexually active in 2022

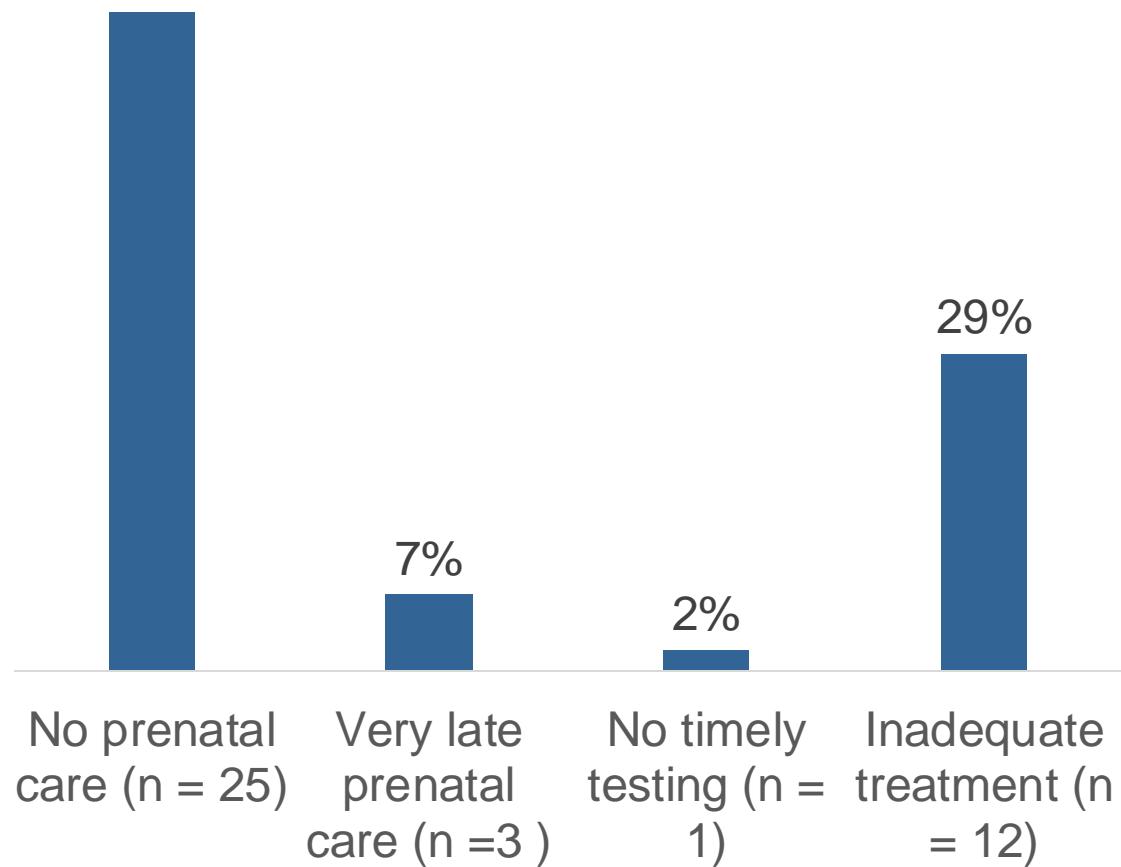
Thank you!
menza@uw.edu

Congenital syphilis is a symptom of systemic failure

- Syphilis in pregnancy and congenital syphilis is part of the **larger crisis of morbidity and mortality among birthing people and infants in the United States**, especially in Black and Indigenous communities
- Congenital syphilis is a **symptom of an under-resourced public health infrastructure and workforce**.
- Congenital syphilis occurs at the nexus of **misogyny, poverty, houselessness, structural racism, trauma, substance use, and mass incarceration**.
- A response that only focuses on congenital syphilis will not end congenital syphilis (**all policy is health policy**).

The threat of CPS/criminalization prevents access to prenatal care among pregnant patients with syphilis

Missed opportunities for CS prevention, King County, 2021-2023



Carceral system involvement among pregnant patients with syphilis associated with a case of congenital syphilis

Location	Period	Proportion
Ever involved in carceral system		
King County	2021-2023	23%
<u>Missouri</u>	2019-2022	32%
<u>Oregon</u>	2013-2021	57%
<u>Indiana</u>	2014-2016	17%
In custody in the prior year		
<u>California</u>	2017-2018	20%
<u>United States</u> (among all pregnant patients with syphilis)	2012-2016	7%
<u>Georgia</u>	2008-2015	9%

Congenital syphilis is a public health emergency

- The increase in syphilis in pregnant patients and congenital syphilis is a **public health emergency**
- Not one case of congenital syphilis is acceptable in a modern healthcare system

Infant deaths and stillbirths due to syphilis, United States, 2014-2023

