Rapid Syphilis Review

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Overview

- Epidemiology
- Clinical Manifestations and Staging
- Congenital Syphilis (CS)
- Testing, Diagnosis, and Management
- Strategies to prevent CS
- Conclusions

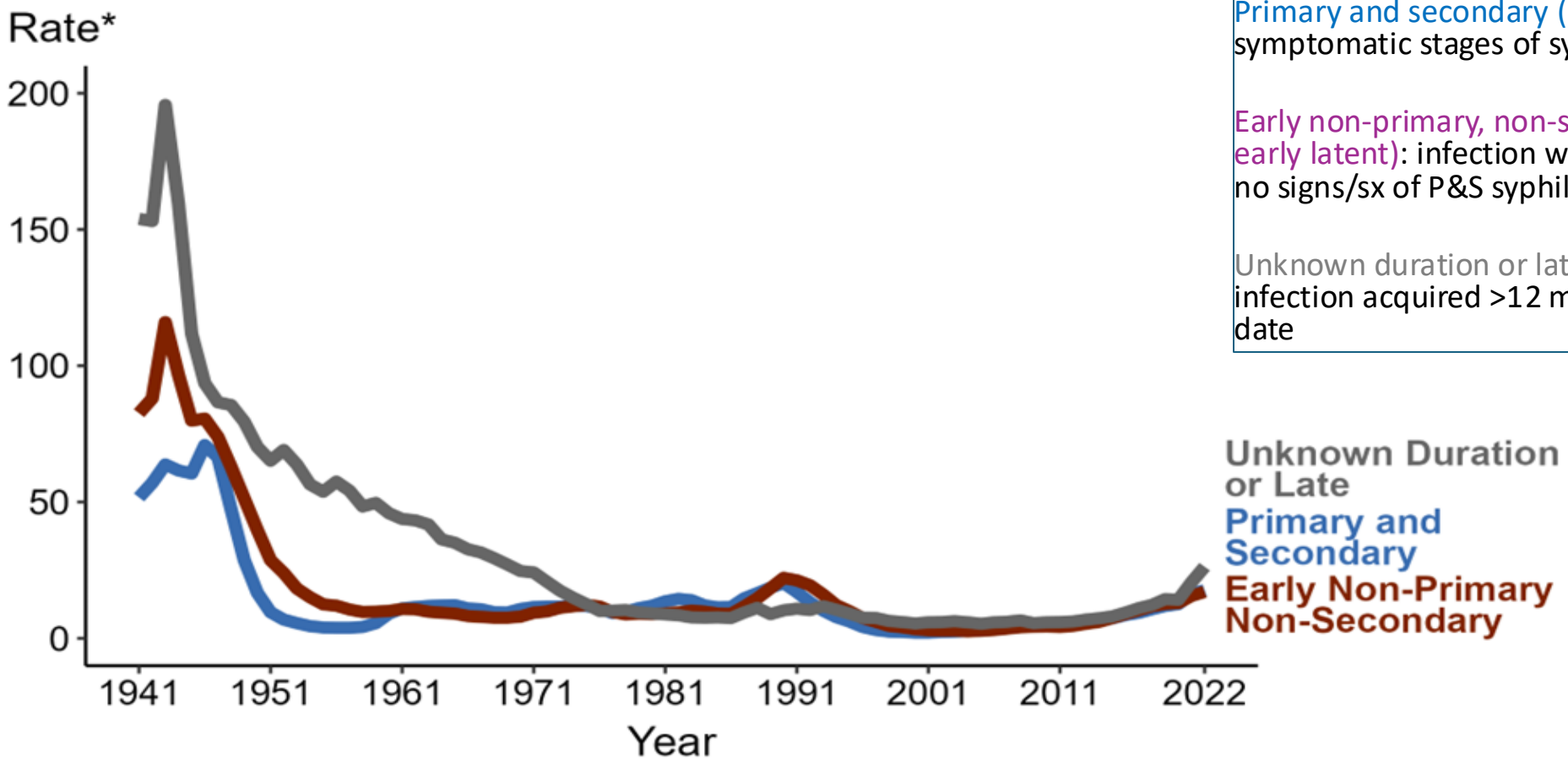
Disclaimers

- Slides largely credited to STD PTC and Dr. tim menza

Epidemiology

Syphilis is back.

Rates of Syphilis (per 100,000) by Stage, US 1941-2022



Primary and secondary (P&S) syphilis: early symptomatic stages of syphilis

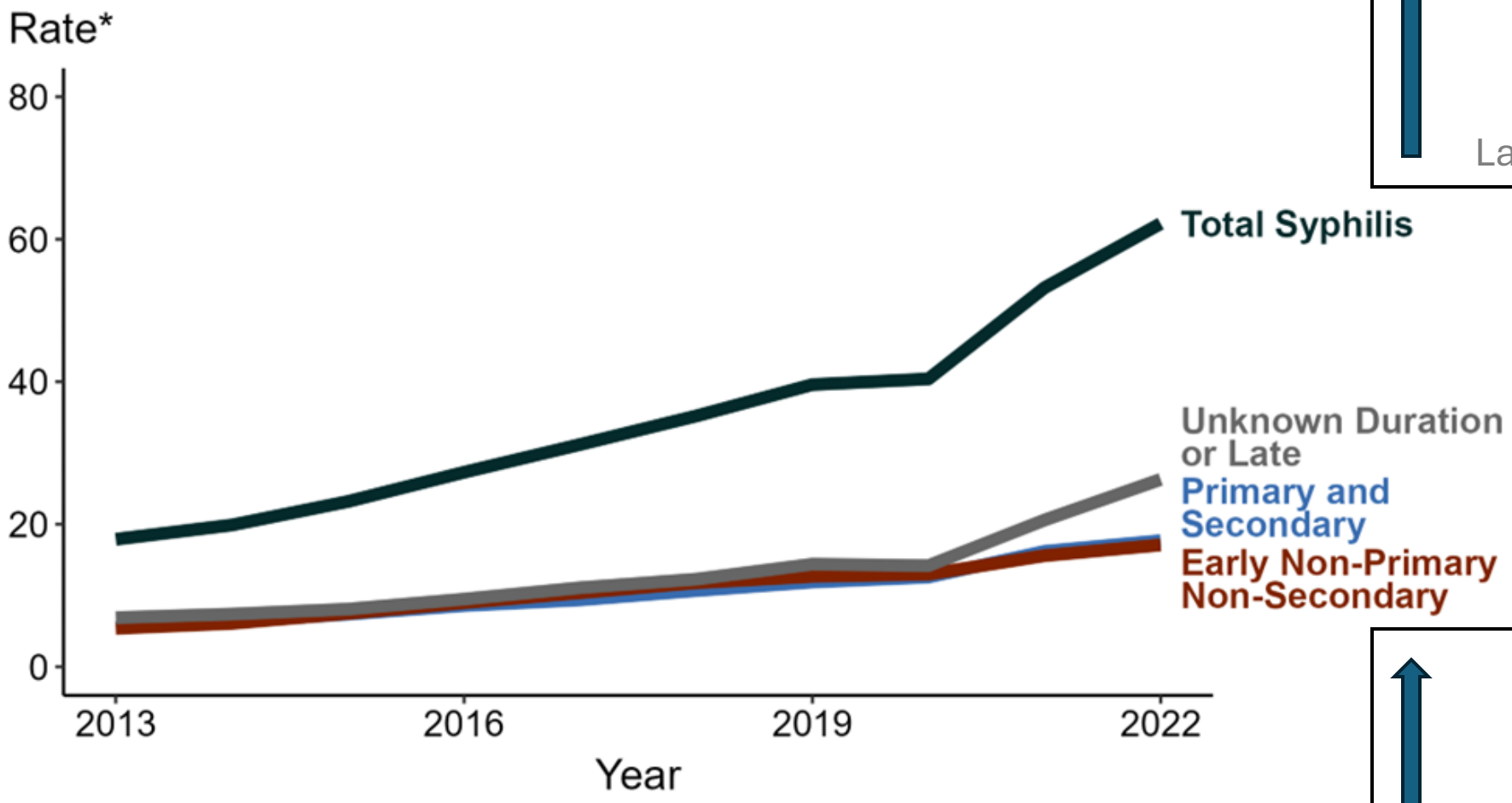
Early non-primary, non-secondary (formerly known as early latent): infection within the past 12 months with no signs/sx of P&S syphilis

Unknown duration or late (formerly late latent): infection acquired >12 mo ago or unable to determine date

Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention

A recent, rapid rise…

Rates of Syphilis (per 100,000) by Stage, US 2013-2022



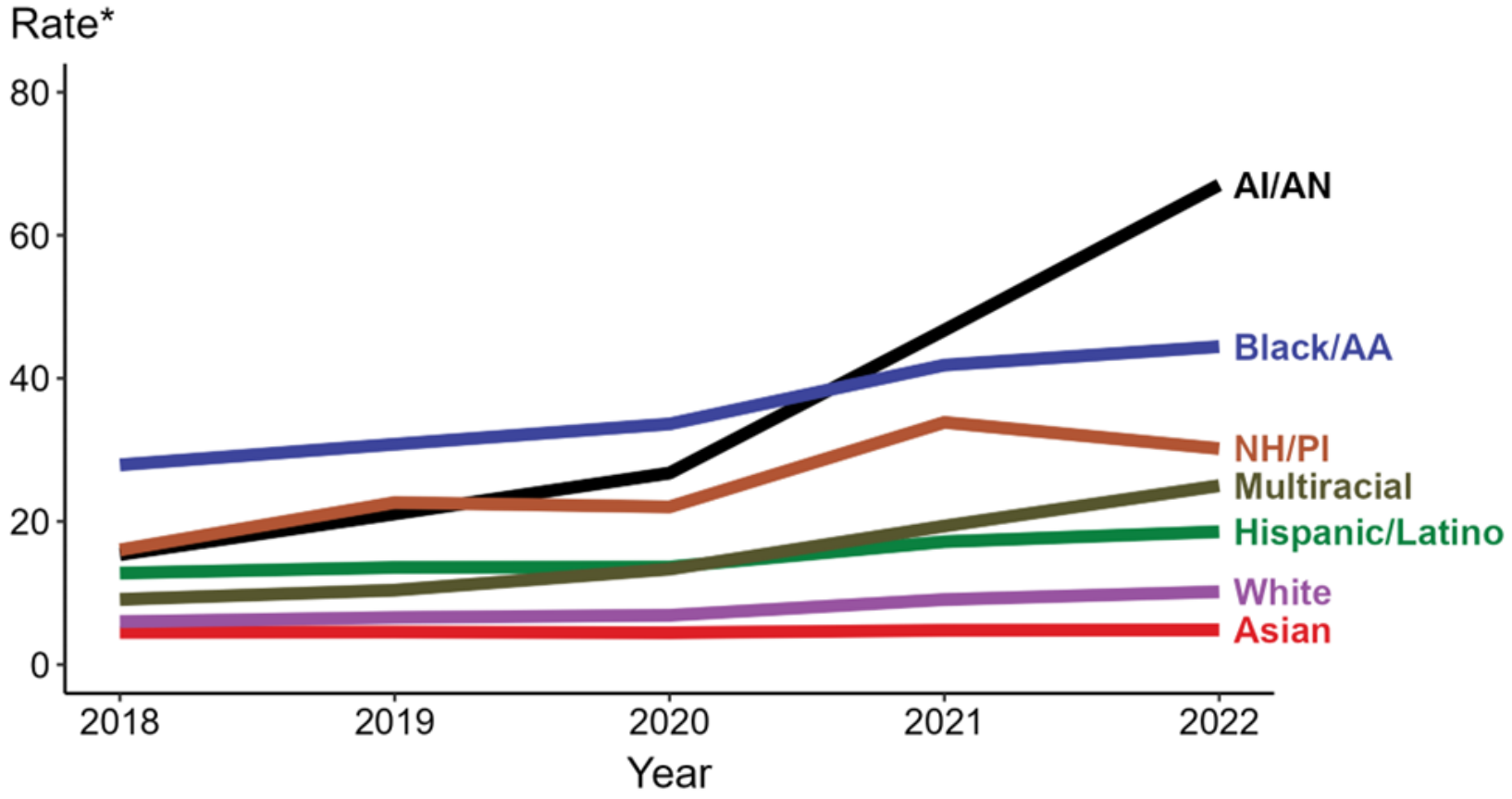
From 2021 to 2022:
All syphilis 17%
P/S syphilis 9%
ENPNS 10%
Late/unknown duration 28%

From 2018 to 2022:
All syphilis 77%
P/S syphilis 65%
ENPNS 45%
Late/unknown duration 114%

Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention

Racism drives inequities in rates of syphilis.

Rates of P/S Syphilis Cases by Race/Ethnicity, US, 2018-2022



AI/AN people experienced the greatest increase in the rate of primary and secondary syphilis.

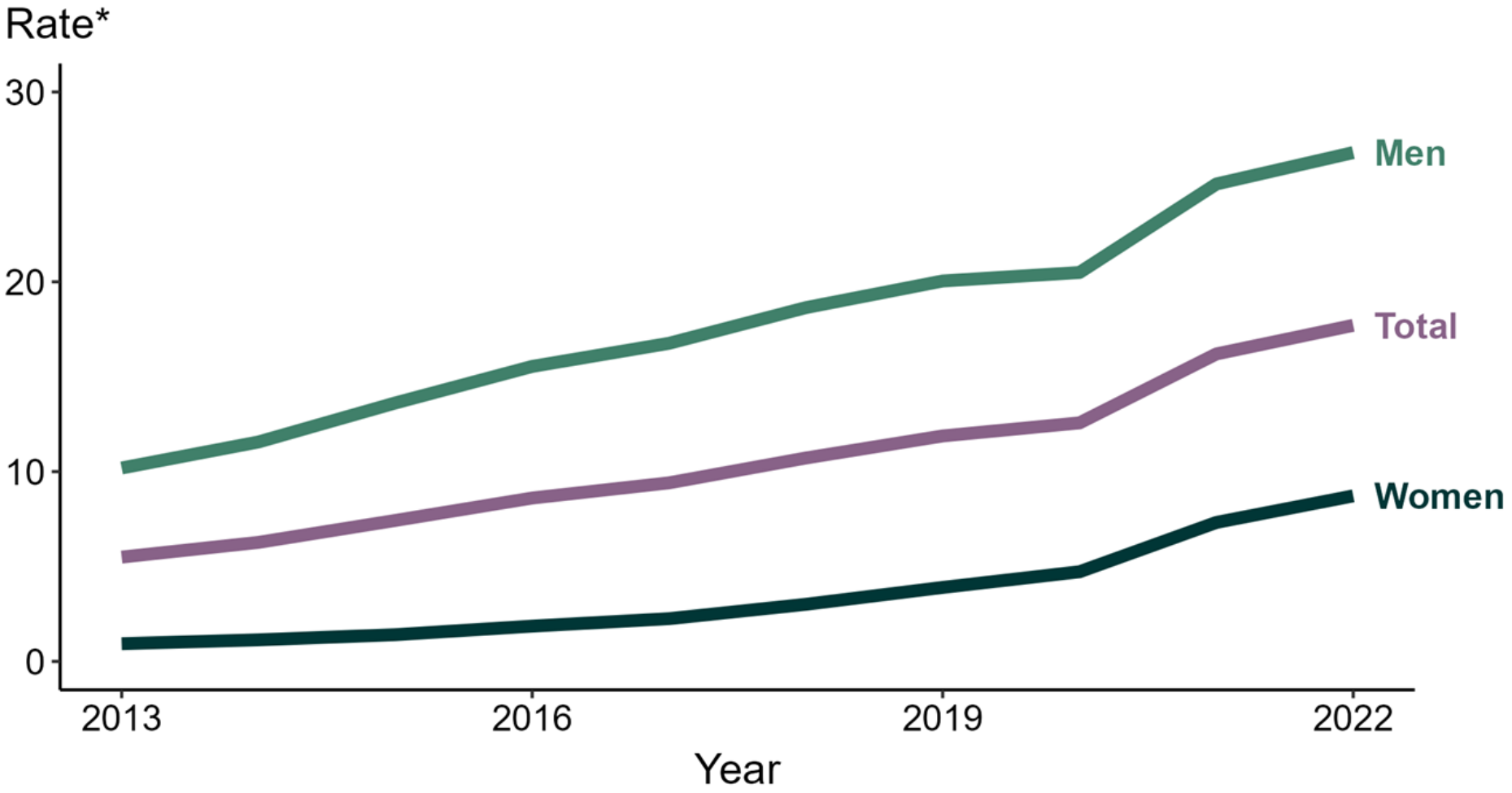
From 2021 to 2022: 44%
From 2018 to 2022: 335%

* Per 100,000

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

The increase in syphilis is affecting women more than men.

Rates of Reported Cases by Sex, United States, 2013–2022



From 2021 to 2022:
Women 19%
Men 6%

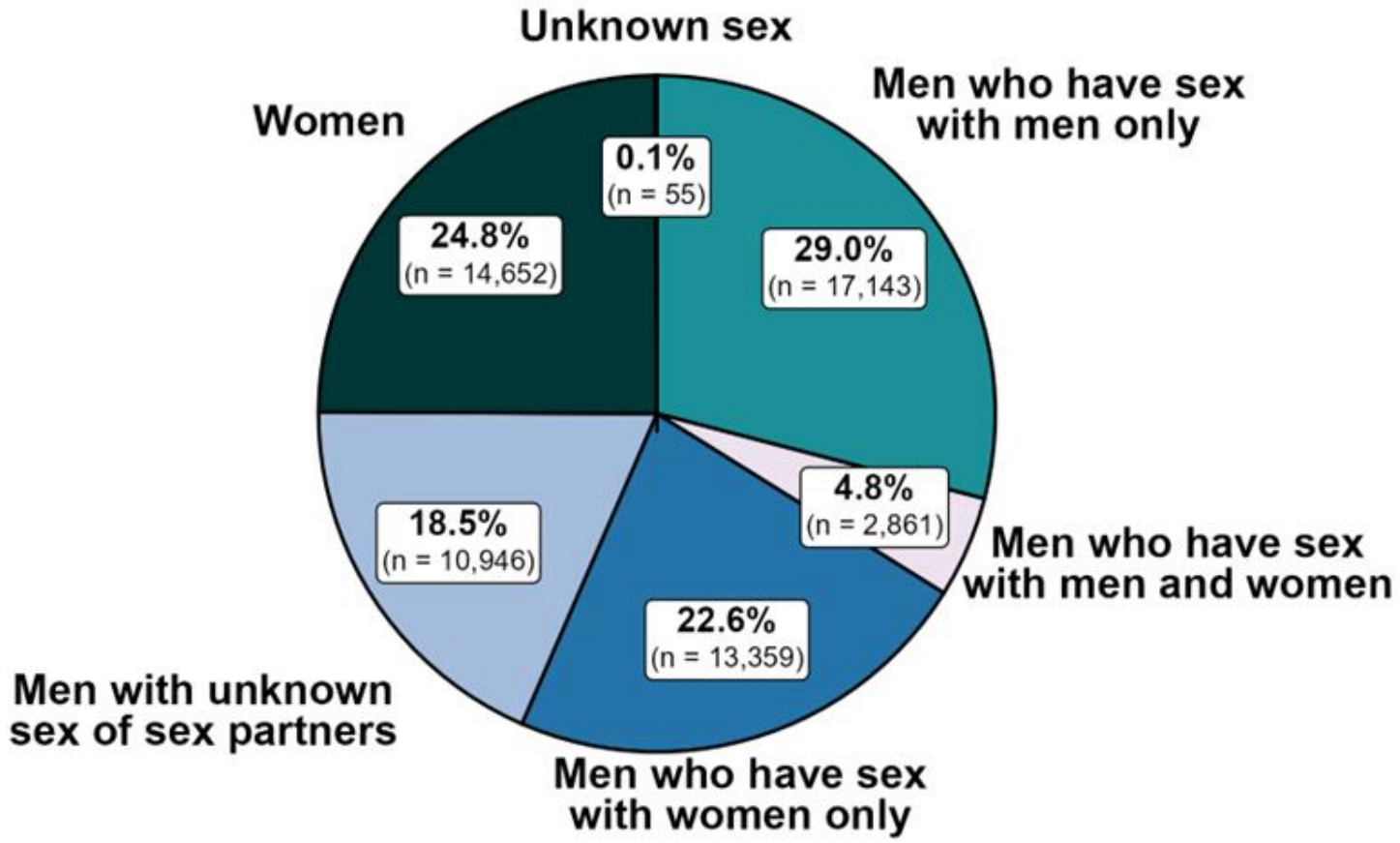
From 2018 to 2022:
Women 190%
Men 44%

From 2013 to 2022:
Women 867%
Men 163%

Women make up 25% of P/S syphilis cases...

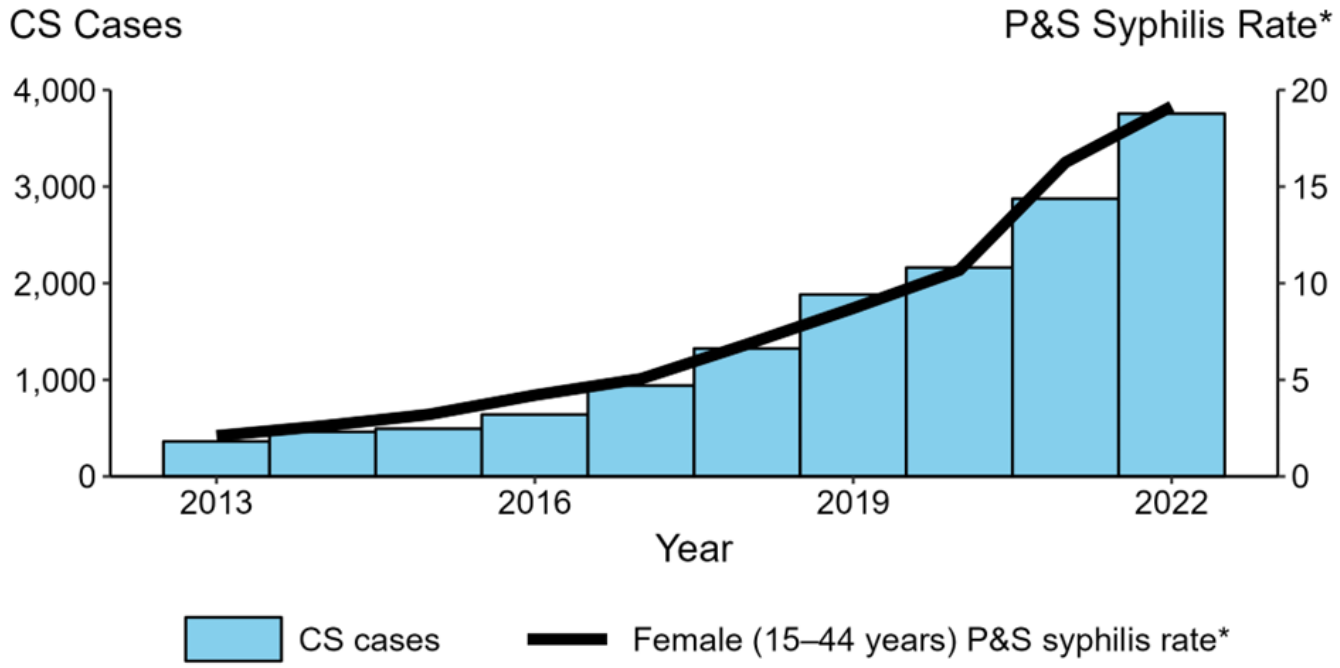
Distribution of Cases by Sex and Sex Behavior, US, 2022

Women +
MSW +
MSWM =
52.2% of cases



…resulting in an exponential rise in congenital syphilis.

Congenital Syphilis — Reported Cases by Year of Birth and Rates of Reported Cases of P/S Syphilis Among Women Aged 15–44 Years, US, 2013–2022

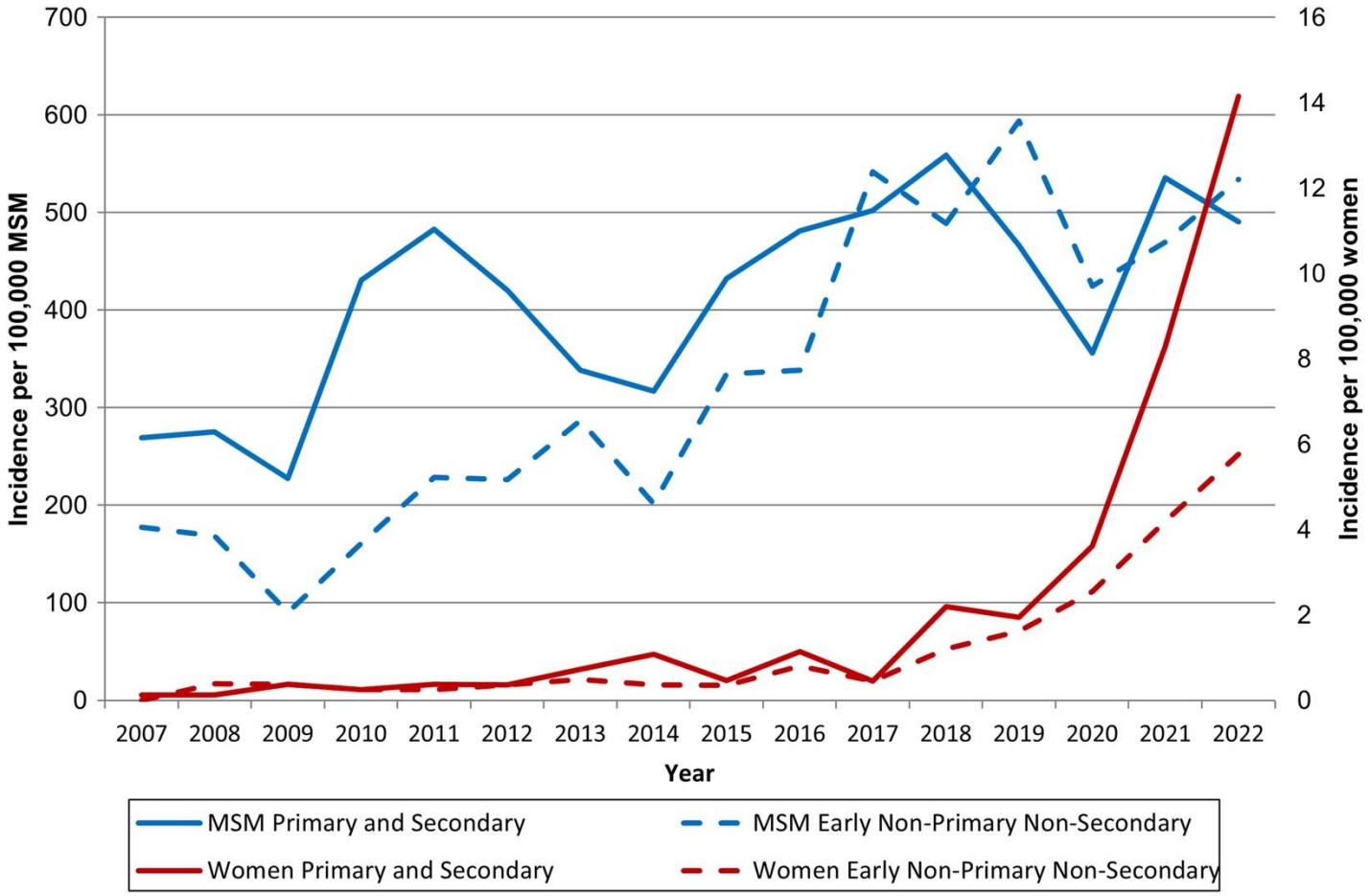


In 2022, there were 3755 cases of CS with 231 stillbirths and 51 neonatal deaths.

* Per 100,000

ACRONYMS: CS = Congenital syphilis; P&S Syphilis = Primary and secondary syphilis

Other distinct features of the recent epidemic



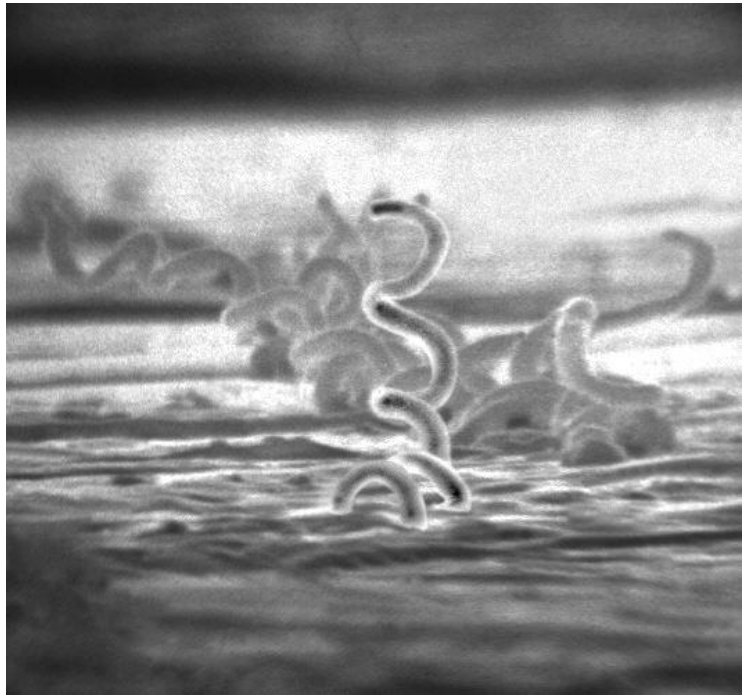
- Increasing rates among heterosexuals
  - Association with drug use, unstable housing, etc.
  - Compared to MSM, fewer heterosexuals have ever tested or test regularly
  - Implications on staging, longer treatment courses required, etc.
- Benzathine PCN (Bicillin) shortages
- Difficulty locating and managing persons who need to be treated

Berzkalns A, et al. OFID 2023

Clinical manifestations and staging

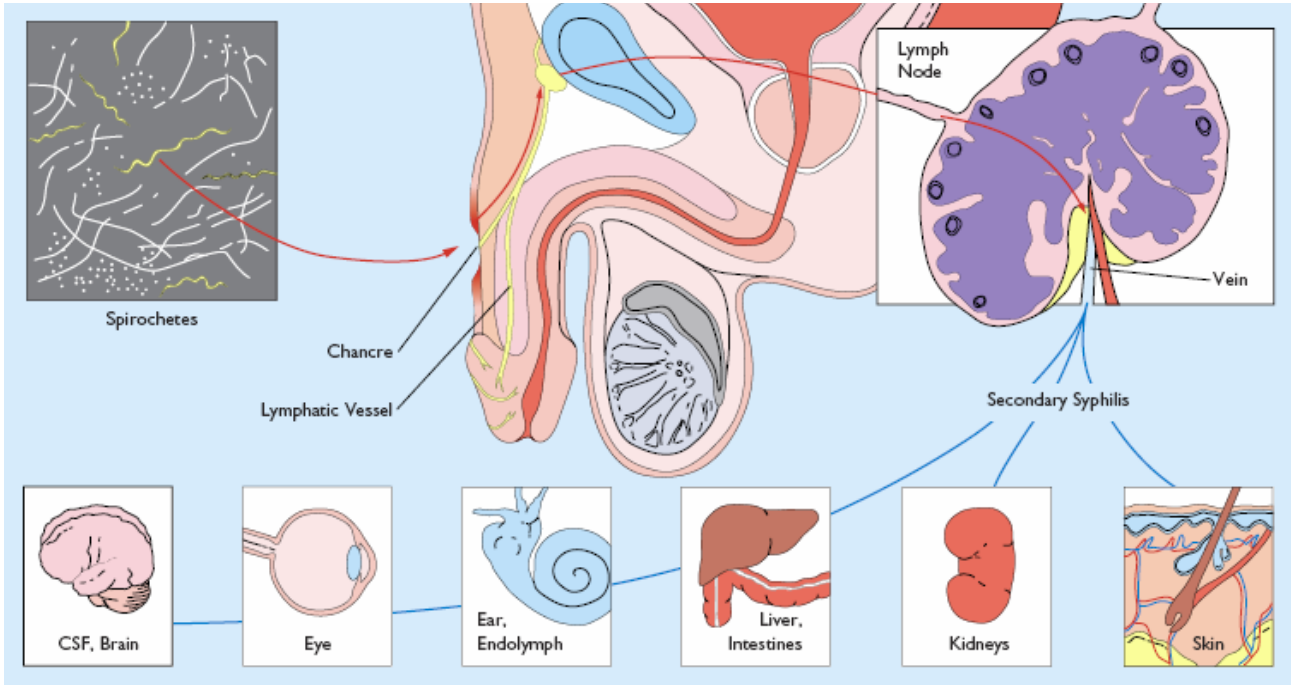
Syphilis: Disease transmission

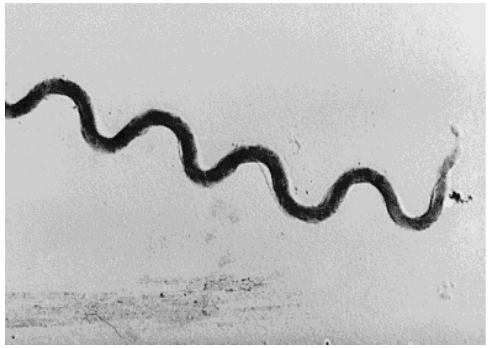
- Chronic sexually transmitted infection caused by *Treponema pallidum*
- Infection through small breaks in skin or mucous membranes
- Risk of contracting syphilis per sexual contact 10-60% (average about 30%)
- Highest risk with contact to early syphilis
- Lesions with many treponemes transmit most effectively
- Plausible but uncommon to contract via blood-sharing activities



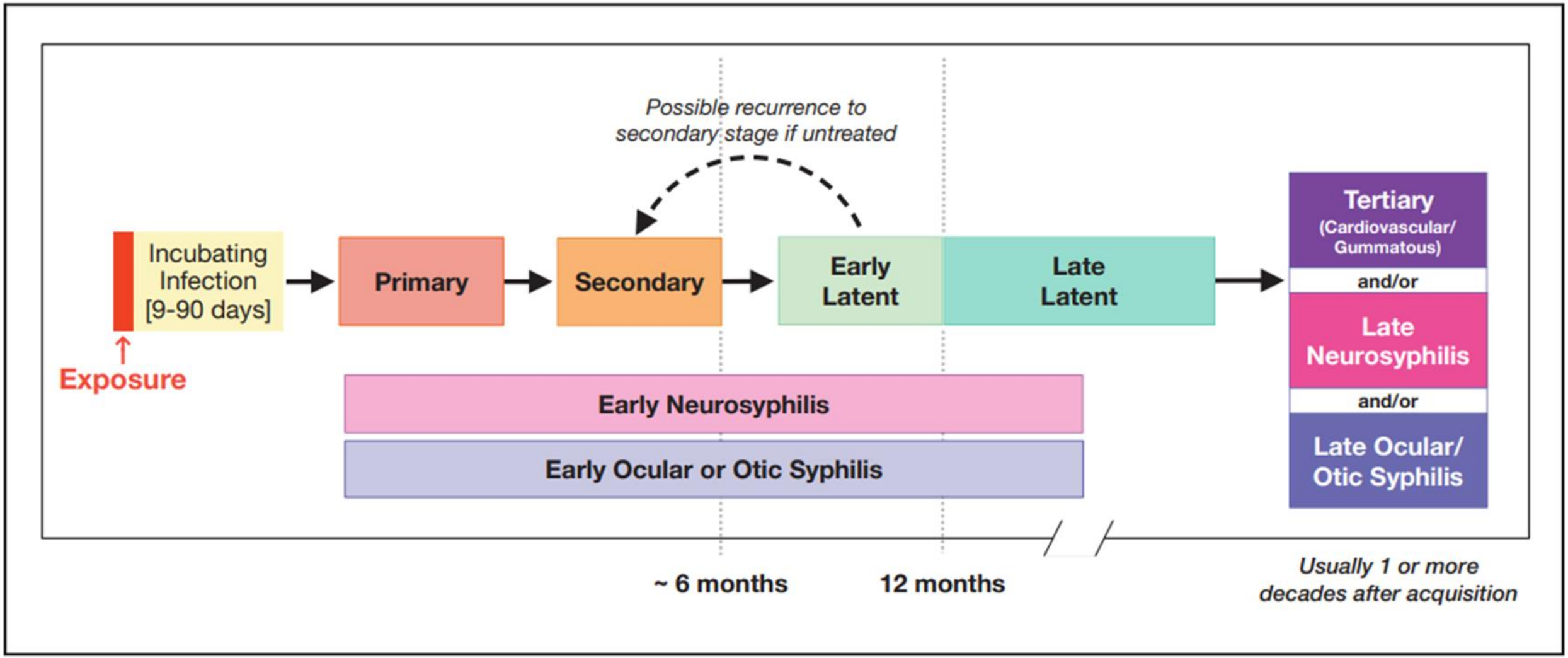
Syphilis is systemic

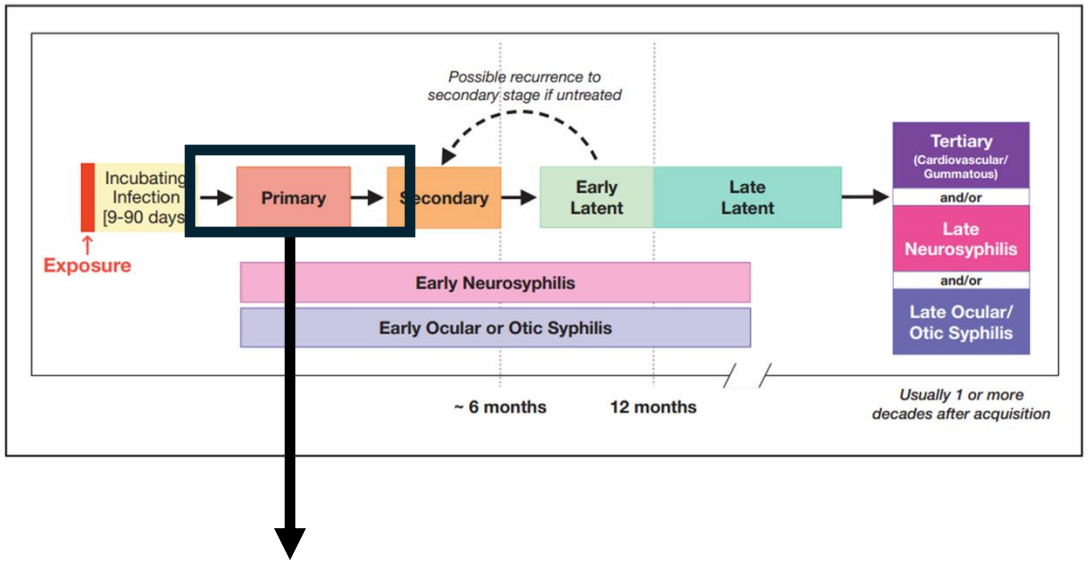
- Syphilis is a multisystem infection
- Progresses in stages with intervening periods of no disease activity
- Invades all parts of body, including central nervous system (CNS)
- Incubation time is 10 – 90 days, average ~ 3 weeks





Stages of syphilis

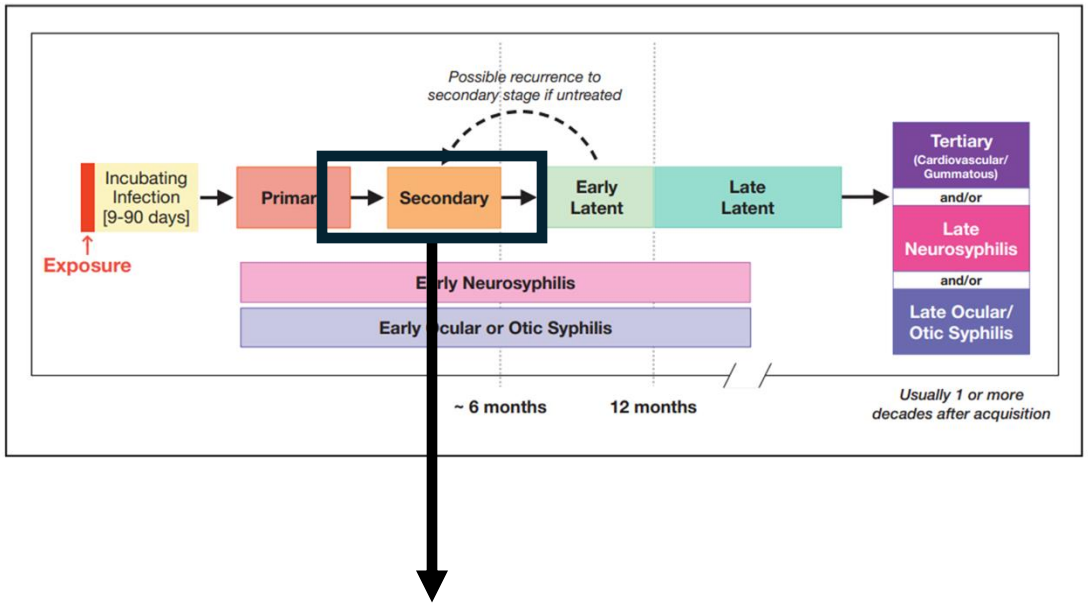




Chancre is the hallmark of primary infection.

- Appears 10-90 days after exposure
- Painless (usually); may occur anywhere inoculated by direct contact (fingers, mouth, lips, anus, vulva, vagina)
- Atypical presentations more common (painful and/or multiple chancres*, etc.)
- Highly associated with concurrent or future HIV infection
- Nontreponemal tests (RPR, VDRL) negative in 15-25% cases of primary syphilis
- Don't need definitive diagnosis: if you think it's early syphilis – TREAT!
- Loss to follow up and risk for forward transmission is high

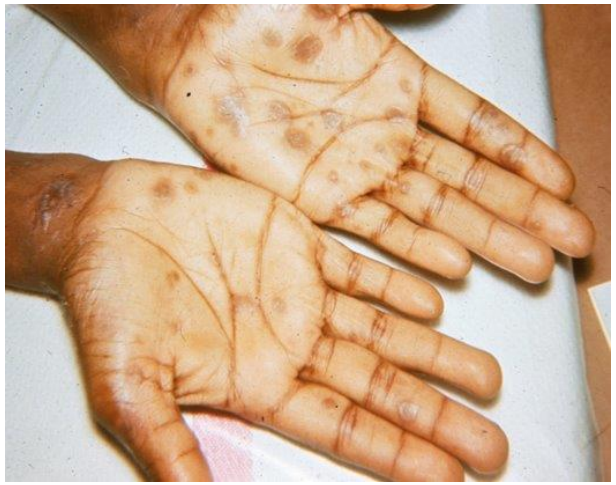
Pathela et al, CID 2015 // Partially adapted from Hilary Reno



Secondary infection is characterized by systemic spread of syphilis

- Lasts 2-6 weeks
- Generalized rash: evanescent, copper color, macular evolves to reddish, papular, affects palms and soles
- Condylomata lata, mucous patches, lateral loss of eyebrows and alopecia, fever (usually low grade), generalized lymphadenopathy
- Nearly every diagnostic test is positive in this stage. If negative, consider alternative diagnosis!

Secondary syphilis: rashes



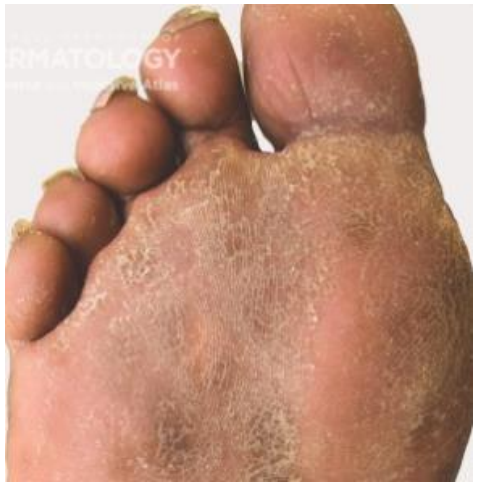
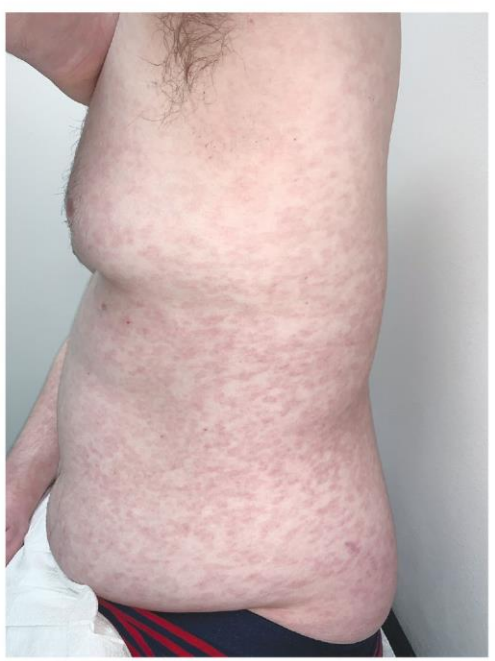
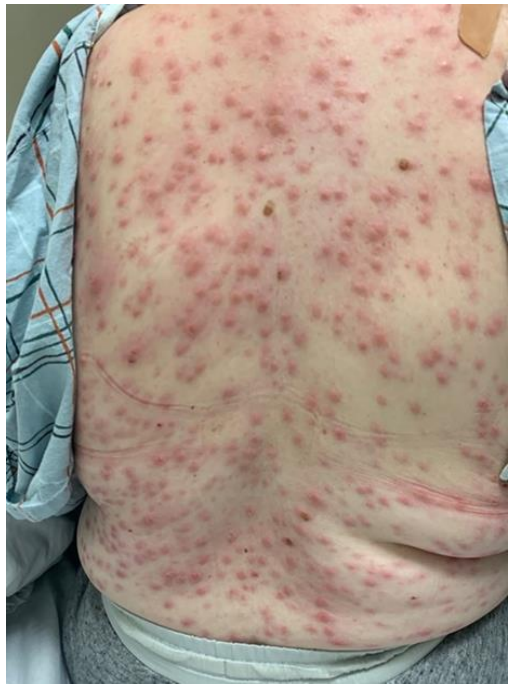
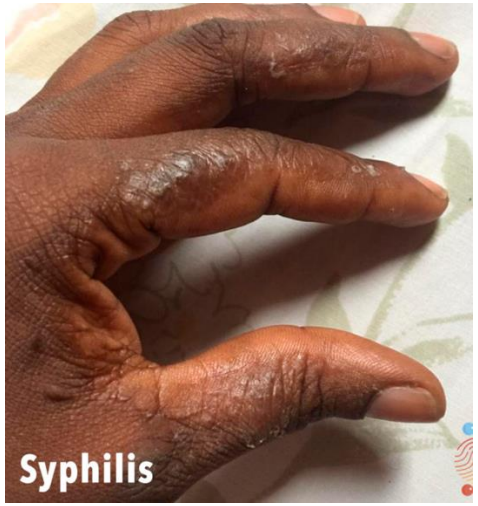
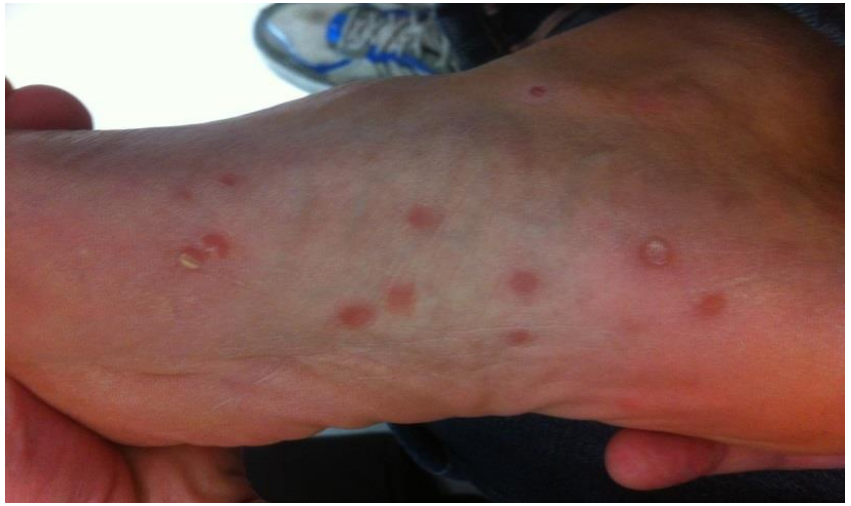


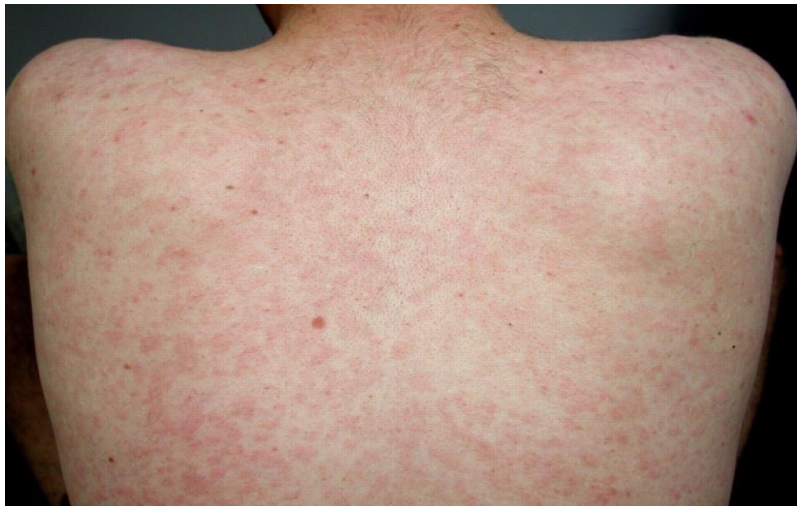
Figure 1. Full-body erythematous, nonscaling rash with substantial annular pattern on torso

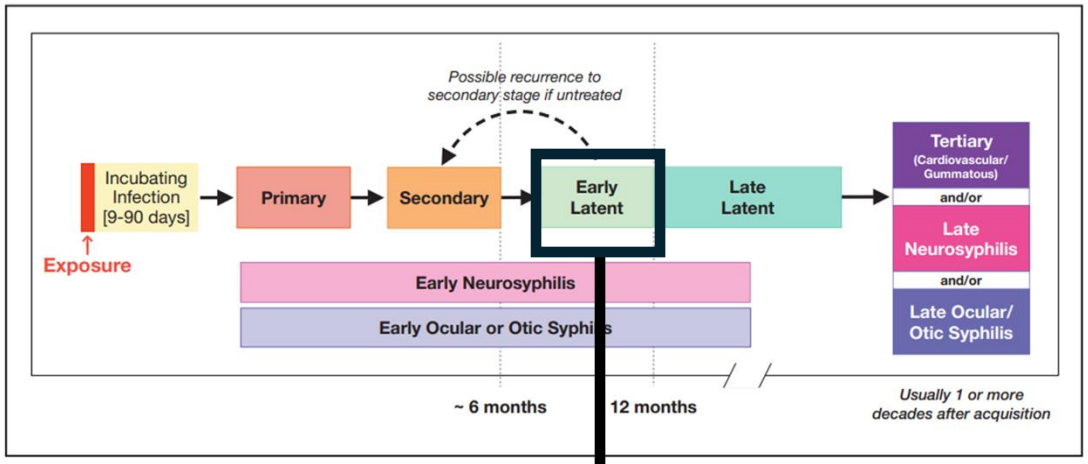






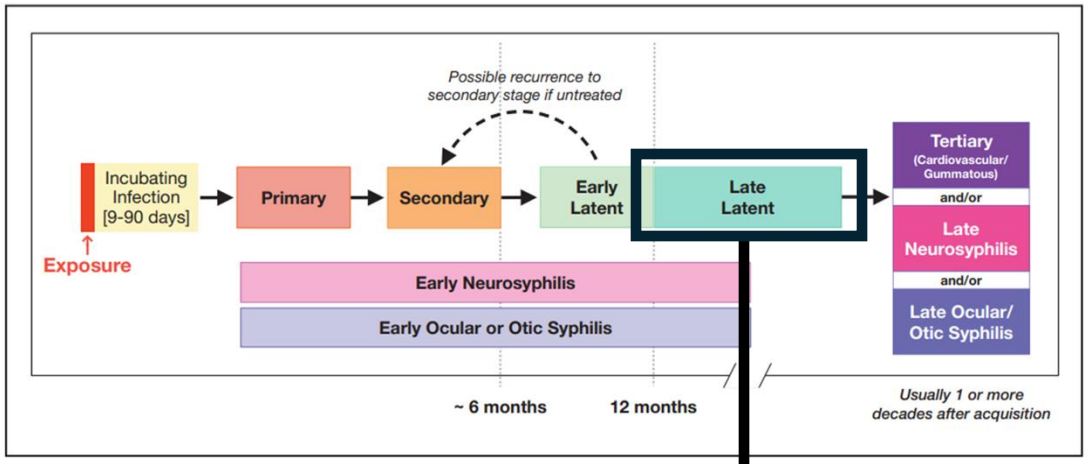






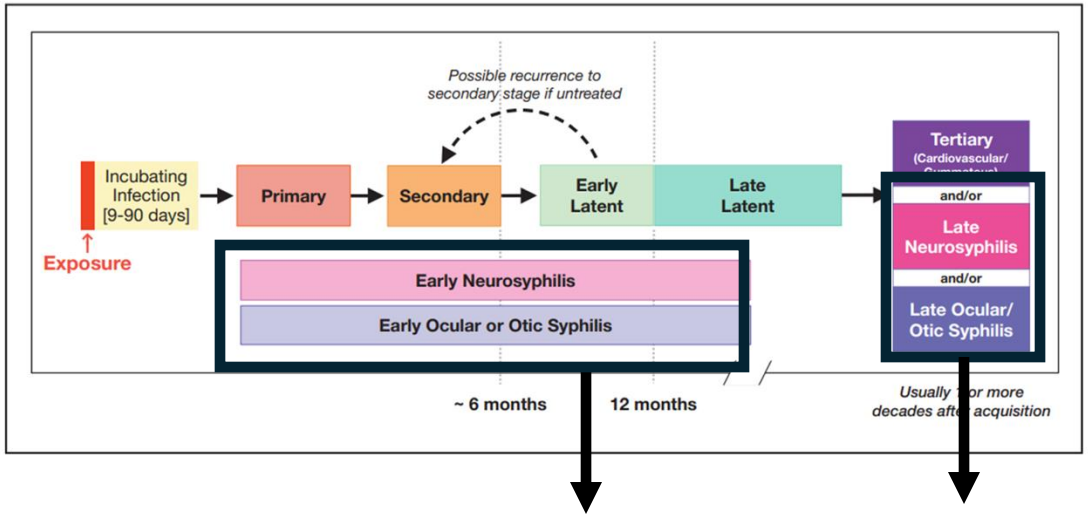
Early Non Primary Non Secondary Syphilis

- No signs/symptoms of primary or secondary syphilis at the time of initial examination/testing
- Evidence that infection with *Treponema pallidum* occurred within the previous 12 months
    - Documented seroconversion of a nontreponemal or treponemal test with tests a year or less apart
    - ≥ 4-fold increase in titer from one titer to the next with tests a year or less apart
    - History of symptoms of primary or secondary syphilis
    - Sex partners with and early (infectious) syphilis diagnosis
    - Sexual debut within last 12 months



Late (or unknown duration) infection occurred >1 year ago or unknown time

- Characterized by absence of signs/sx
- Evidence of infection
  - A current reactive RPR/VDRL and treponemal test without a negative serology in past year or no prior history of syphilis
  - A 4-fold increase in RPR/VDRL titer comparing a current titer to one drawn more than one year prior
- No history of signs/sx of primary or secondary syphilis in the past year
- Not a contact to a known case

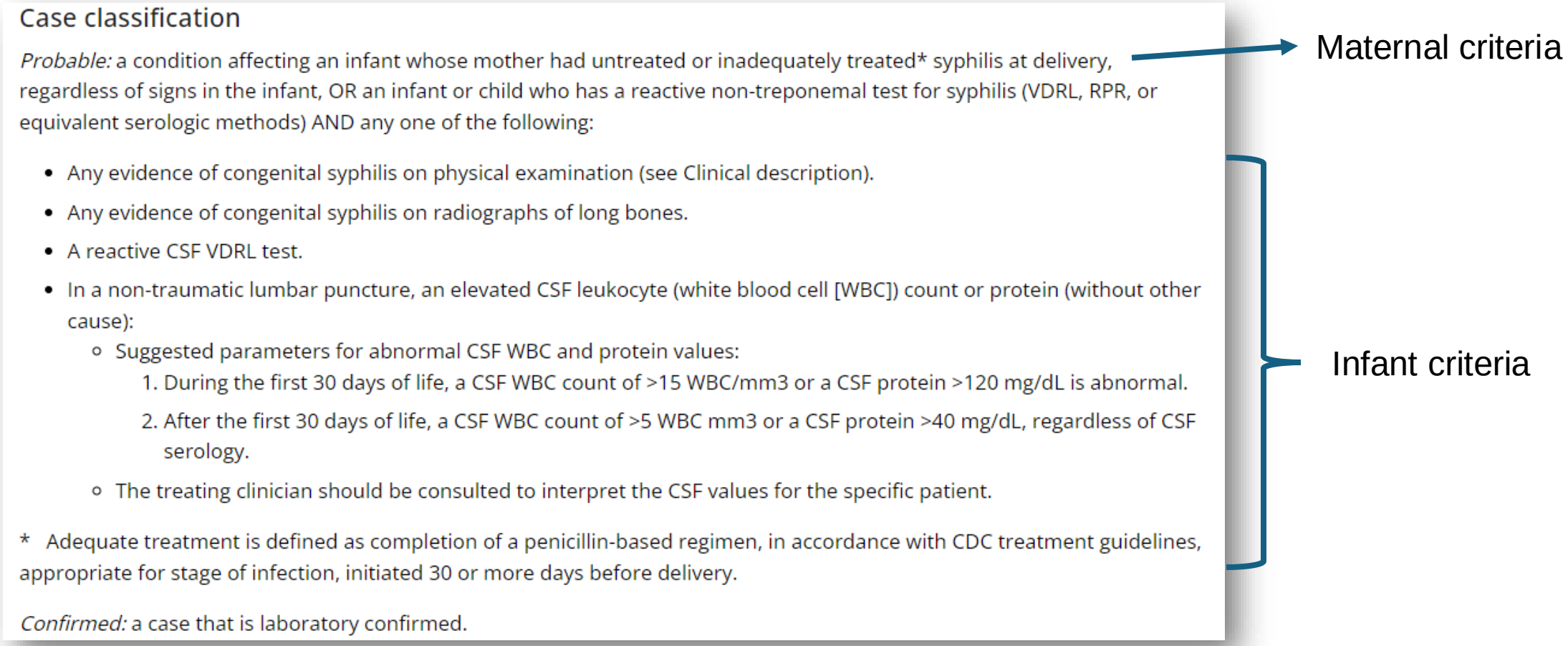


Conduct an ocular/otic/neuro review of systems for everyone who has a syphilis diagnosis

- 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

Congenital Syphilis

2018 CDC surveillance definitions



Case classification

Probable: a condition affecting an infant whose mother had untreated or inadequately treated* syphilis at delivery, regardless of signs in the infant, OR an infant or child who has a reactive non-treponemal test for syphilis (VDRL, RPR, or equivalent serologic methods) AND any one of the following:

- Any evidence of congenital syphilis on physical examination (see Clinical description).
- Any evidence of congenital syphilis on radiographs of long bones.
- A reactive CSF VDRL test.
- In a non-traumatic lumbar puncture, an elevated CSF leukocyte (white blood cell [WBC]) count or protein (without other cause):
  - Suggested parameters for abnormal CSF WBC and protein values:
    1. During the first 30 days of life, a CSF WBC count of >15 WBC/mm3 or a CSF protein >120 mg/dL is abnormal.
    2. After the first 30 days of life, a CSF WBC count of >5 WBC mm3 or a CSF protein >40 mg/dL, regardless of CSF serology.
  - The treating clinician should be consulted to interpret the CSF values for the specific patient.

* Adequate treatment is defined as completion of a penicillin-based regimen, in accordance with CDC treatment guidelines, appropriate for stage of infection, initiated 30 or more days before delivery.

Confirmed: a case that is laboratory confirmed.

Syphilis, stillbirth: fetal death after 20 weeks EGA or in which the fetus weighs >500 gm and [birth parent] had inadequately/untreated infection at delivery

Clinical manifestations in pregnancy

- Pregnancy does not alter clinical manifestations – presentation is similar to non-pregnant people (but much higher stakes)!

- Physical examination is critical – look for chancre, signs of secondary syphilis.

- Complicated (neuro, ocular, otic) is still possible; no data on whether this occurs more frequently among pregnant people

Clinical manifestations in the neonate

- Infection may result in **fetal loss (spontaneous abortion), stillbirth, neonatal death**, infant with active or latent syphilis
- Transplacental infection can occur during any stage of syphilis and at any time during gestation

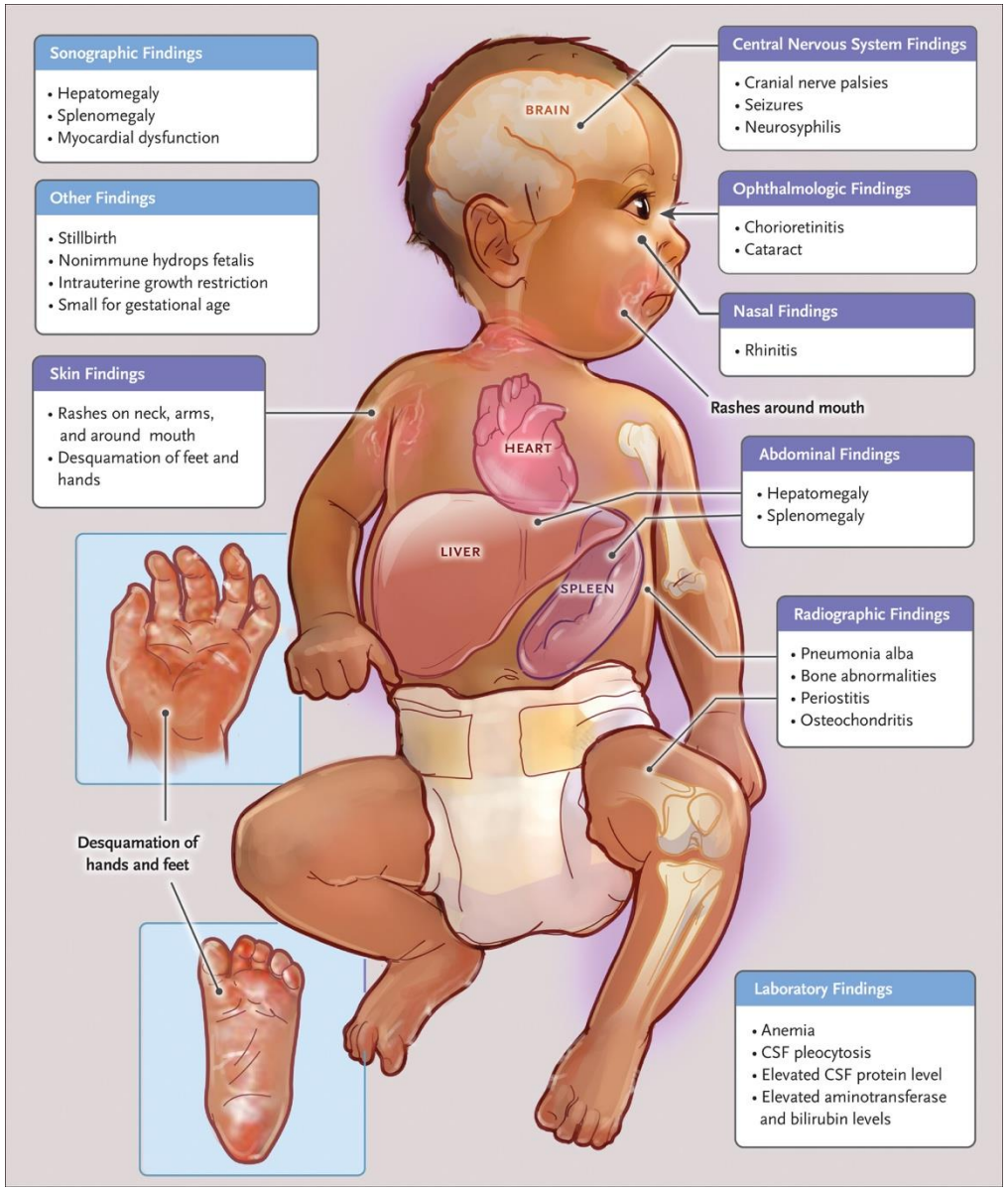
Early CS: detected before 2 years of age

- 30-40% asymptomatic at birth
- Manifestations: rhinitis (“snuffles”), HSM, skin rashes with desquamation, chorioretinitis, glaucoma, cataracts, optic neuritis, anemia, many others

Late CS: detected after 2 years of age

- Saddle nose deformity, frontal bossing, saber shins (tibial thickening), perforation of hard palate, tooth malformations (Hutchinson’s teeth, mulberry molars)
- CNS: Deafness, keratitis, neurosyphilis, optic atrophy, developmental delay

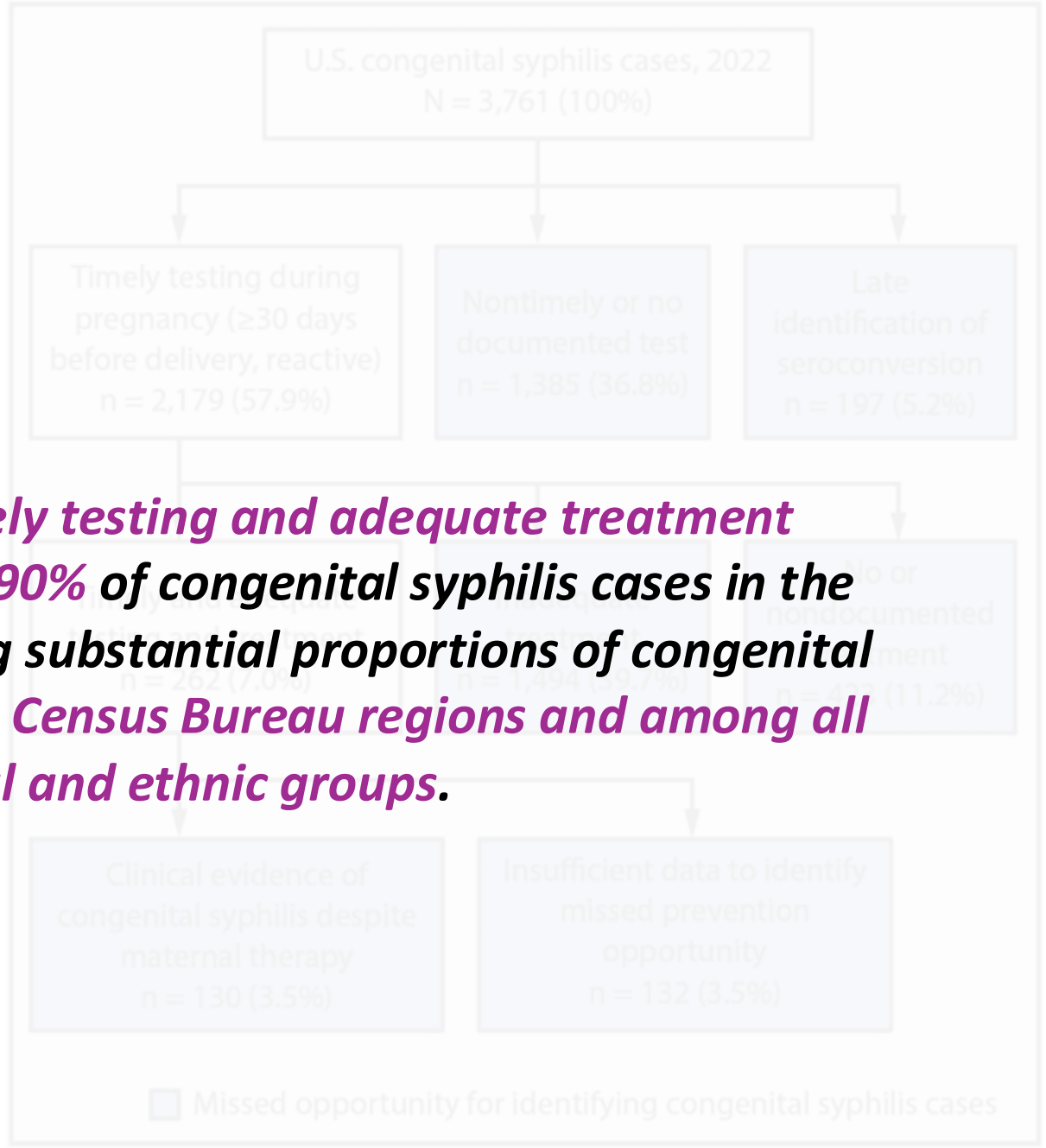
Congenital infection is a multisystem disease with high morbidity.
Get help from Pediatric ID! Call early if any questions



Stafford et al. NEJM 2024

Testing, diagnosis and management of syphilis in pregnant adults

Distribution of CS cases in US by missed prevention opportunities, 2022



In 2022, lack of timely testing and adequate treatment contributed to almost 90% of congenital syphilis cases in the United States, including substantial proportions of congenital syphilis cases in all U.S. Census Bureau regions and among all racial and ethnic groups.

McDonald et al, *MMWR* 2023

Non-treponemal (lipoidal) tests

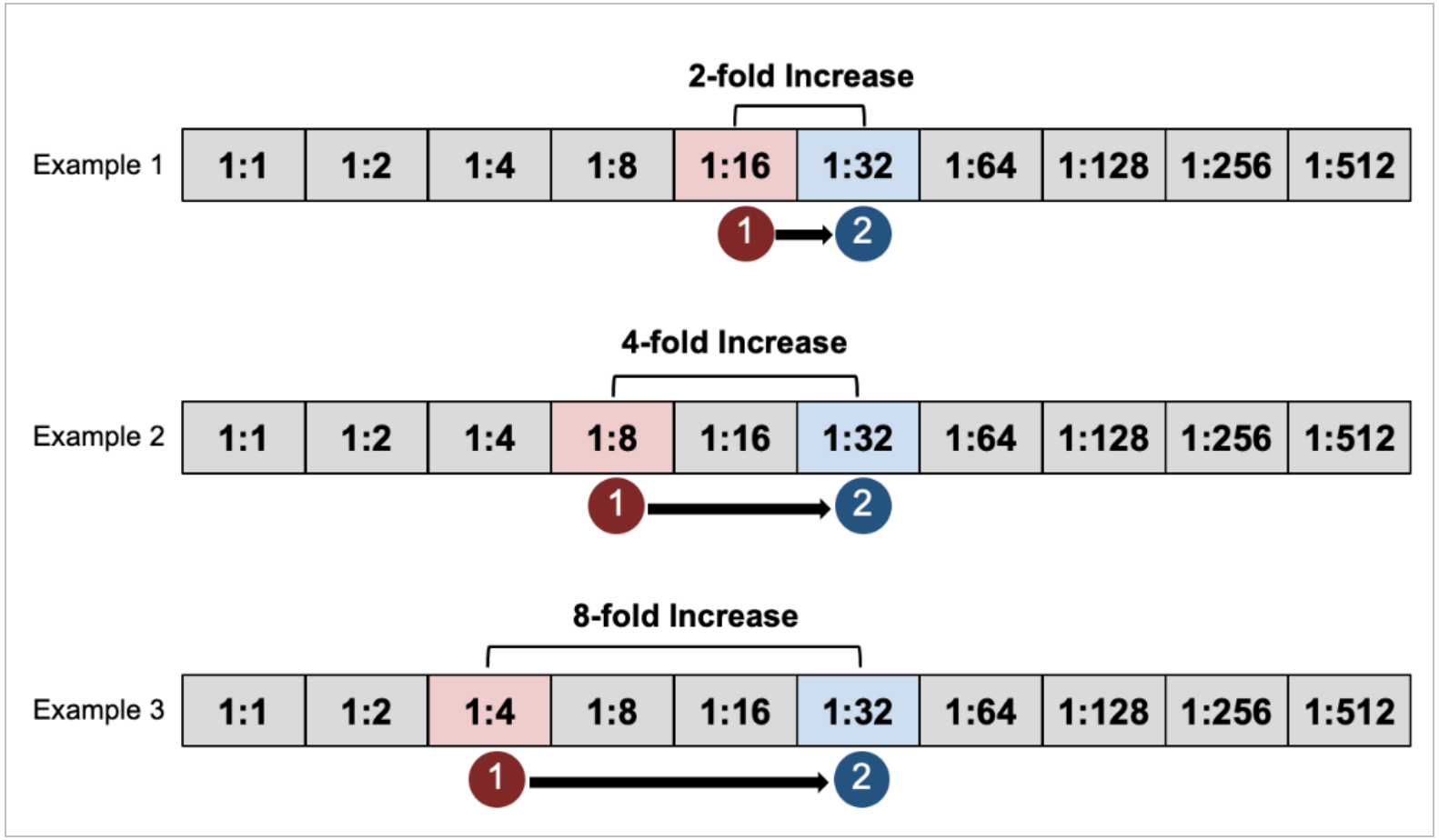
- RPR: most common
- VDRL: mostly used to test CSF in congenital syphilis or neurosyphilis cases
- Qualitative
- Quantitative titer (e.g.1:4, 1:32, 1:512)
- Detect antibodies to lecithin, cardiolipin, and antiphospholipid (crude measures of tissue damage)

Treponemal tests

- Detect antibodies (IgM and IgG) to *T. pallidum*
- Test types: Syph-TP, FTA, TPPA, EIA, CLIA, and more!
- Qualitative
- Quantitative (1+ to 4+)

Examples of increases in RPR titers

From the National STD Curriculum

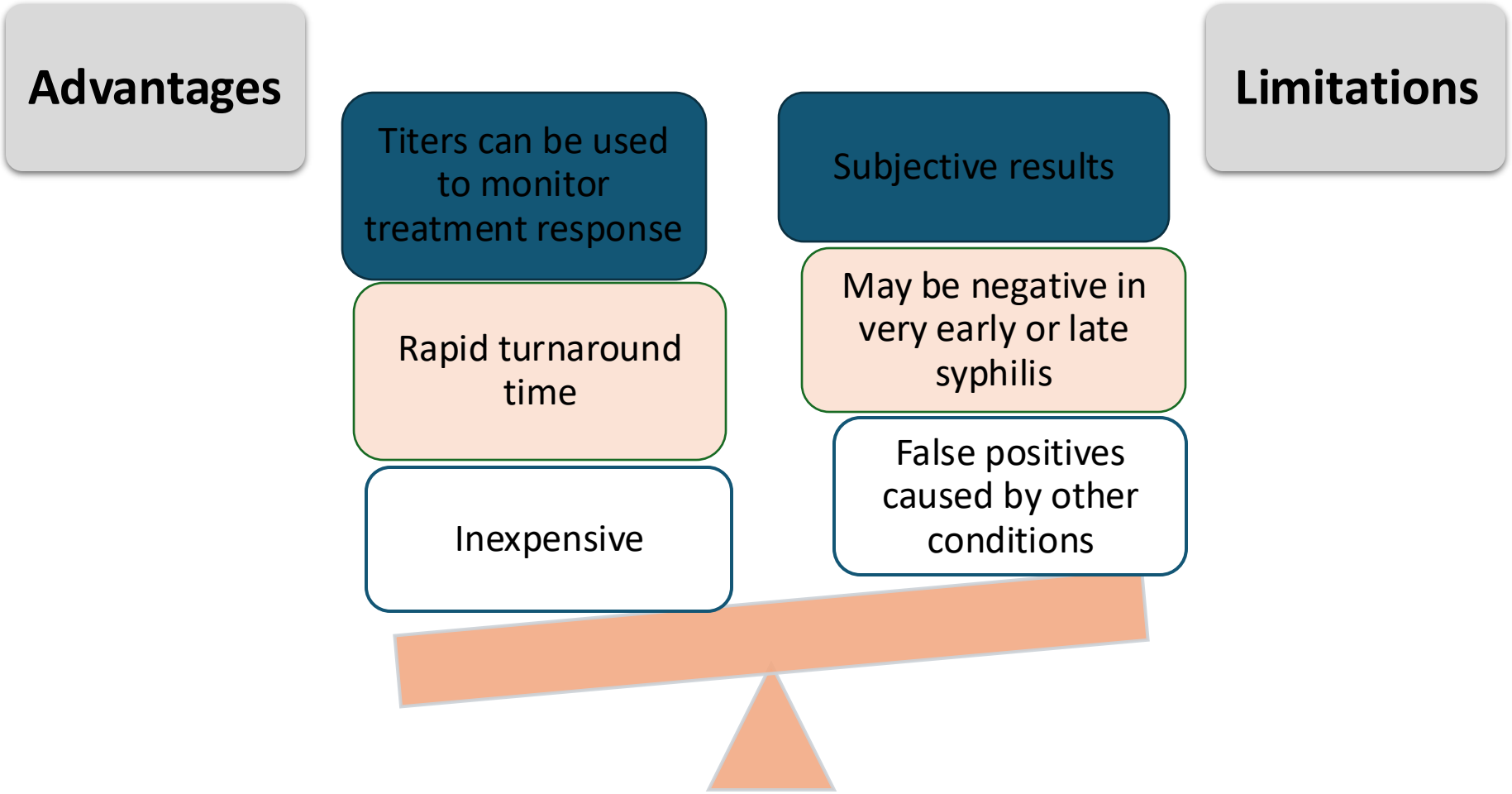


Clinically meaningful changes in RPR (or VDRL) titers are 4-fold or greater such that:

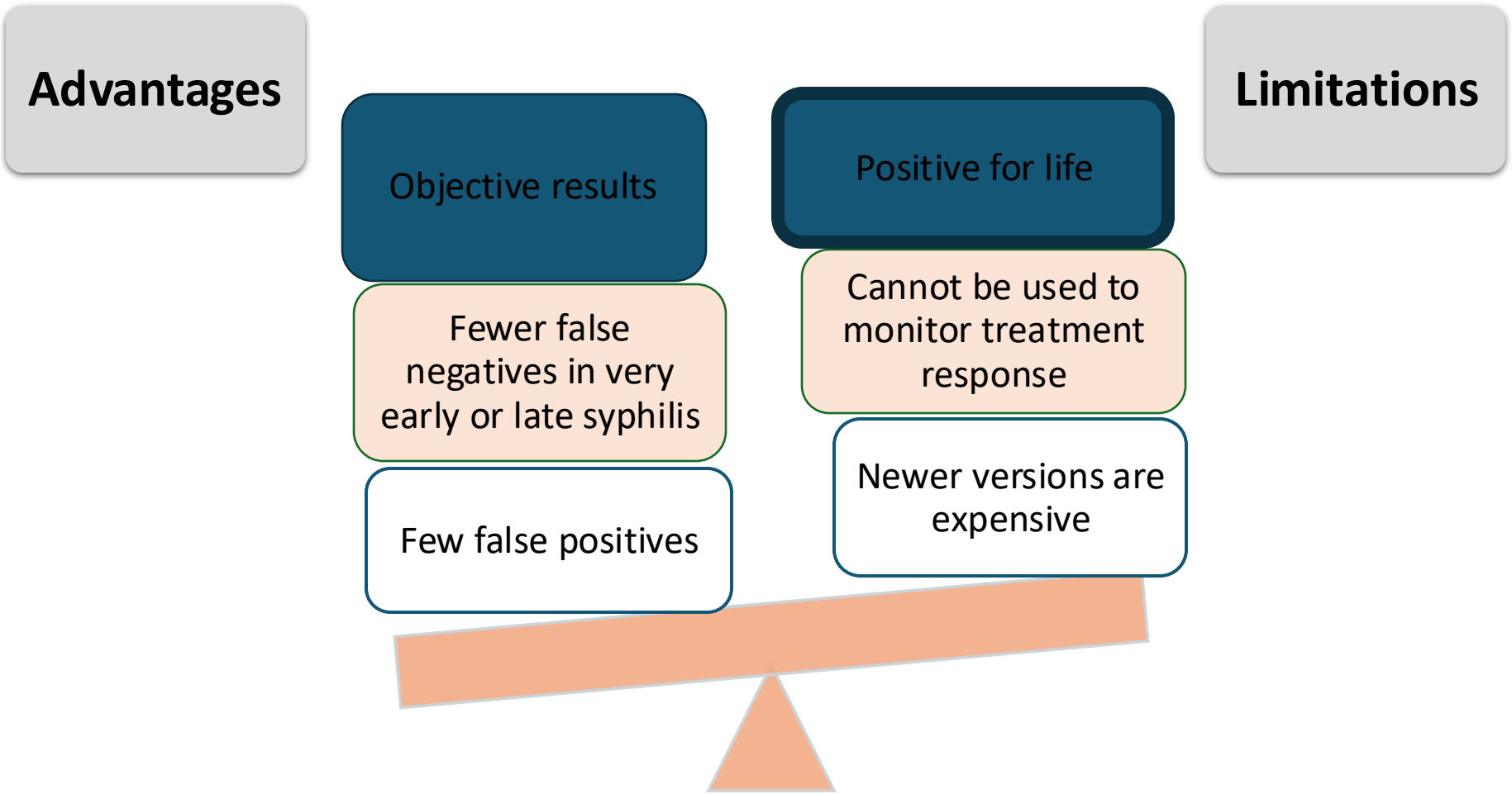
A 4-fold **increase** may indicate a new infection, re-infection, or treatment failure

A 4-fold **decrease** after treatment is consistent with treatment success

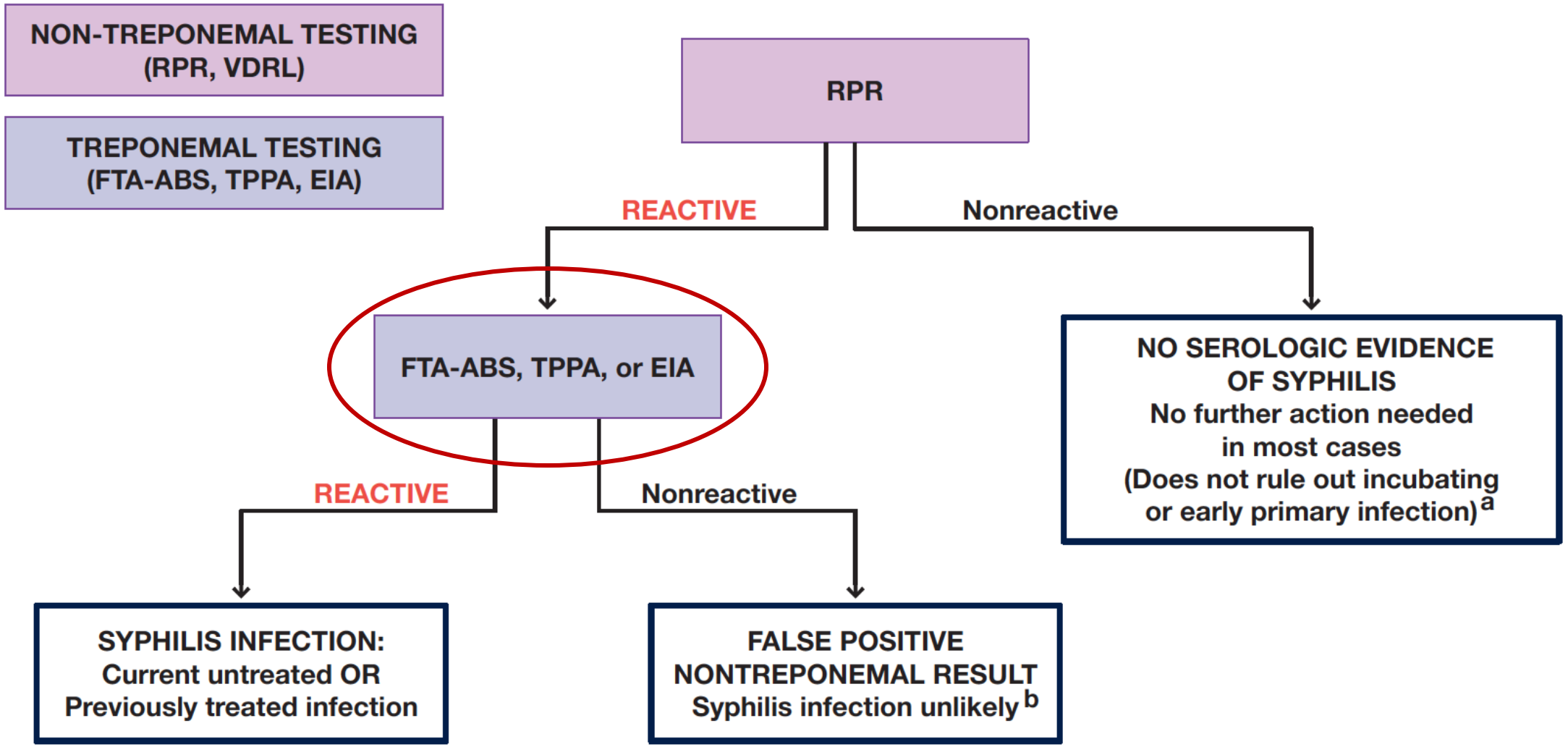
Non-treponemal test: RPR/VDRL



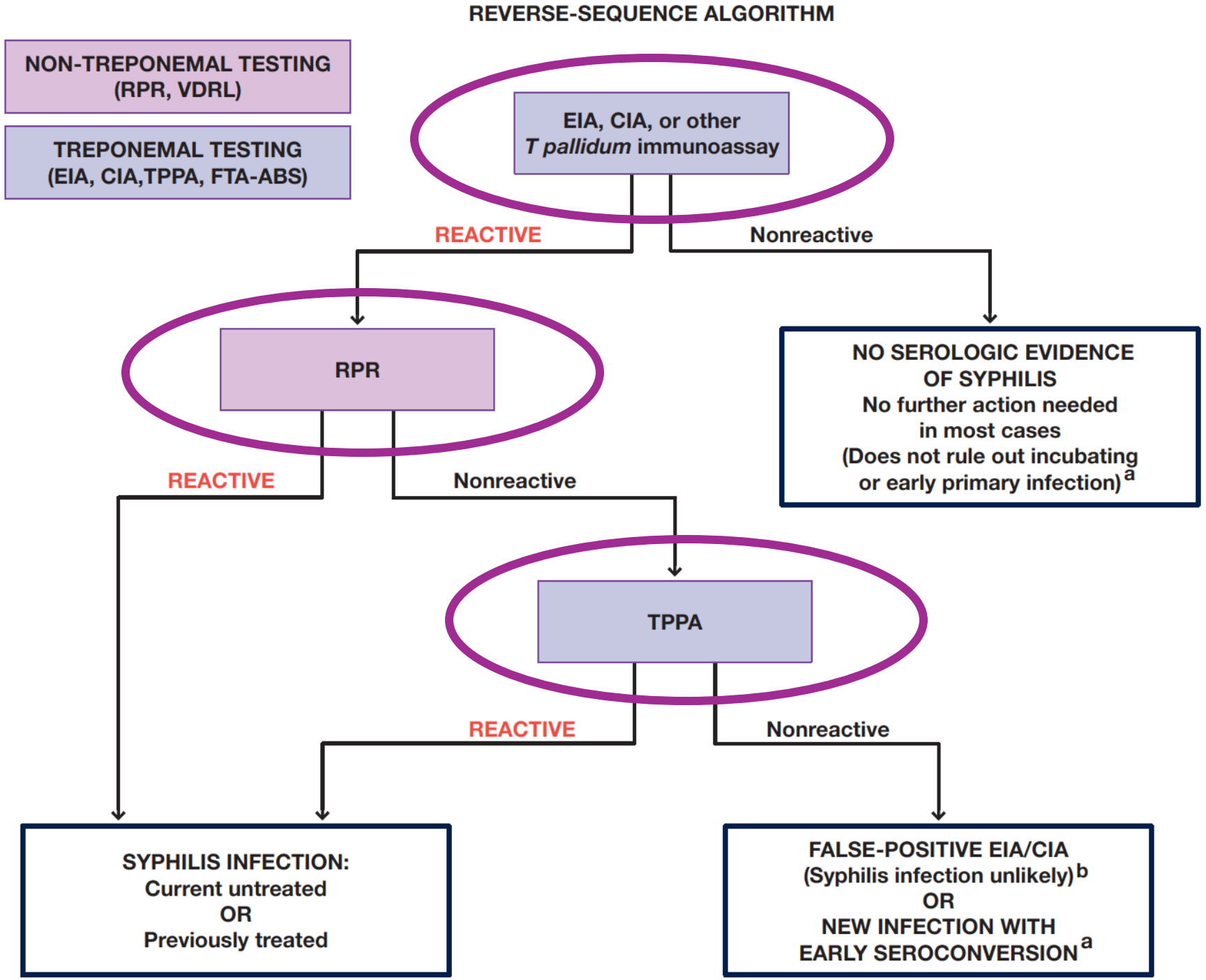
Treponemal tests



TRADITIONAL ALGORITHM



- NYC DOHMH, NYC STD PTC 2019



- NYC DOHMH, NYC STD PTC 2019

Treatment is 98% effective in preventing CS

		Recommended Treatment	Notes
EARLY	**Primary Secondary Early non-primary non-secondary**	Long-acting BPG* 2.4 million units IM in a single dose	Some experts recommend a second dose (success in secondary syphilis was 95%). May consider a second dose in pregnant people with HIV.
LATE	**Unknown duration or late**	Long-acting BPG as three doses of 2.4 million units IM each at 7-day intervals	Max interval between doses = 9 days before re-starting treatment
ANY TIME	**Neuro, ocular, otic syphilis**	Aqueous PCN G 4 million units IV every 4 hours or by continuous infusion for 10-14 days	Ceftriaxone 2 grams IV daily may be an alternative

*benzathine penicillin G

Alexander et al., Obstetrics & Gynecology, 1999.

Prenatal Syphilis Screening, Staging, and Management for Congenital Syphilis Prevention

Screen

Screen <u>all</u> patients at three points in pregnancy:

❶ First prenatal visit or time of pregnancy testing **❷ 28 weeks' gestation** **❸ Delivery**

Initial diagnosis requires both a non-treponemal test (RPR) and confirmatory treponemal test (TP-PA, FTA-ABS, EIA/CIA)

Stage

SYPHILIS DIAGNOSIS

Primary	+ Chancre	Late Latent or Unknown Duration	Neurosyphilis/ Ocular/ Otosyphilis[3]
Secondary	+ Rash and/or other signs[1]	<u>NO</u> symptoms, and infection does not meet criteria for early latent[2]	+ CNS signs or symptoms + CSF findings on lumbar puncture (LP)
Early Latent	<u>NO</u> symptoms, and infection occurred within the past year[2]		

RISK FACTORS FOR SYPHILIS IN PREGNANCY

If there is no record of syphilis screening in pregnancy or screening history is unknown, screen patients with any of these risks (particularly those who attend ED, urgent care, detention/correctional, and/or substance use treatment settings):

- Limited or no prenatal care
- Injection drug use (or partner who uses injection drugs)
- Methamphetamine or heroin use (any method)
- Houselessness or unstably housed
- Criminal justice involvement within previous 12 months (or partner with criminal justice involvement)
- Living with HIV or hepatitis C
- Other STI diagnosed within previous 12 months
- Multiple sex partners, a new partner, or partner with other partners

Treat

Primary, Secondary, Early Latent	Late Latent or Unknown Duration	Neurosyphilis/ Ocular/ Otosyphilis[3]
Benzathine penicillin G 2.4 Million Units Intramuscularly (IM) <u>Once</u> *Certain evidence indicates that additional therapy is beneficial for early syphilis in pregnancy. A second dose of benzathine penicillin G 2.4 million units IM can be given 7 days after the initial dose.*	**Benzathine penicillin G** 2.4 Million Units IM <u>every 7 days</u>, for 3 doses (7.2 Million Units total) *A 6-9 day interval between doses is acceptable. If any doses are late or missed, re-start the entire 3-dose series.*	**Aqueous 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. See 2021 CDC STI Treatment Guidelines for non-intravenous alternative regimen.

Monitor

If syphilis treated at/before 24 weeks' gestation, wait at least 8 weeks to repeat titer and repeat again at delivery. Repeat sooner if reinfection or treatment failure is suspected. If treated after 24 weeks' gestation, repeat titer at delivery. Consider more frequent monitoring if at high risk for reinfection in pregnancy (see risks at right).

If syphilis diagnosed after 20 weeks' gestation, management should include a fetal ultrasound to look for congenital syphilis.

Post-treatment serologic response during pregnancy varies widely. Many women do not experience a fourfold decline by delivery. If sustained (>2 weeks) fourfold increase occurs after treatment completion, evaluate for reinfection and neurosyphilis.

1. Signs of secondary syphilis also include condyloma lata, patchy alopecia, and mucous patches.
2. Persons can receive a diagnosis of early latent if, during the prior 12 months, they had a) seroconversion or sustained fourfold titer rise (RPR); b) unequivocal symptoms of primary or secondary syphilis; or c) a sex partner with primary, secondary, or early latent syphilis.
3. Neurosyphilis, ocular, and otic syphilis can occur at any stage. Patients need a full neurologic exam including ophthalmic and otic; If clinical evidence of neurologic involvement is observed (e.g. cognitive dysfunction, motor or sensory deficits, cranial nerve palsies, or symptoms or signs of meningitis or stroke), a CSF examination should be performed before treatment. If only ocular/otic manifestations without other abnormalities on neuro exam, CSF evaluation not necessary before starting treatment for neurosyphilis.

Adapted with permission from CDPH/CAPTC

Last Updated: 3/31/22

Important Considerations for Syphilis Treatment in Pregnancy

Screen early, treat as soon as possible
Treatment failure, and subsequent congenital syphilis, has been associated with treatment later in the pregnancy

Treatment is safe and highly effective for both the pregnant person and fetus

Benzathine Penicillin G (Bicillin L-A) is the ONLY recommended therapy for syphilis during pregnancy

Someone with signs, symptoms, or exposure to syphilis should receive treatment for early disease regardless of whether serology results are available

ADDITIONAL RESOURCES

- **For detailed treatment guidelines,** including penicillin allergy recommendations, see the CDC 2021 STI Treatment Guidelines: www.cdc.gov/std/treatment-guidelines
- **For clinical questions:**
  - Contact Dr. Tim Menza at the Oregon Health Authority (TIMOTHY.W.MENZA@dhsoha.state.or.us), or
  - Enter your consult online at the STD Clinical Consultation Network: stdccn.org

What if my patient is allergic to penicillin?

- **Verify the nature of the allergy.** Approximately 10% of the population reports a penicillin allergy, but less than 1% of the whole population has a true IgE-mediated allergy.
- **Symptoms of an IgE-mediated (type 1) allergy include:** Hives, angioedema, wheezing and shortness of breath, and anaphylaxis. Reactions typically occur within 1 hour of exposure.
- **Refer for penicillin skin testing** if the nature of the allergy is uncertain or cannot be determined.
- **Refer for desensitization with penicillin** if the skin test is positive or the patient has a true penicillin allergy.
- **Desensitization should be performed.** Serious allergic reactions can occur. Consult an allergist.
- **Treat the patient with benzathine penicillin G.** Treat according to appropriate stage of syphilis (see opposite page for treatment regimen).

FOR MORE INFORMATION ABOUT IgE-MEDIATED PENICILLIN ALLERGY:
www.cdc.gov/antibiotic-use/community/pdfs/penicillin-factsheet.pdf
www.cdc.gov/std/treatment-guidelines/penicillin-allergy.htm

Resources for Penicillin Allergy

Assessment of PCN/Cephalosporin Allergy at UW

WA DOH Penicillin Allergy Resources

BC Provincial Antimicrobial Clinical Expert Group

Sources
Workowski KA, Bachmann LH, Chan P et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep 2021;70 (No.4); Assessment, U. Screening for syphilis infection in pregnancy: US Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med, 2009. 150: p. 705-709; Alexander JM, Sheffield JS, Sanchez PJ, et al. Efficacy of treatment for syphilis in pregnancy. Obstetrics & Gynecology 1999;93(1):5-8; Plotzker RE, Murphy RD, Stoltey, JE. "Congenital Syphilis Prevention: Strategies, Evidence, and Future Directions." Sexually Transmitted Diseases (2018); Wendel GO, Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin Allergy and Desensitization in Serious Infections During Pregnancy. N Engl J Med 1985;312:1229–32.

Oregon Health Authority

AETC AIDS Education & Training Center Oregon AETC

END HIV

CONGENITAL SYPHILIS (CS)

Evaluation and treatment of infants (<30 days old) exposed to syphilis in utero*

Start

INFANTS AND BIRTHING PARENT (e.g., mother) SHOULD HAVE SERUM RPR TITER DRAWN AT DELIVERY

Infant and Maternal Criteria

Infant Criteria:
- CS findings on physical exam
- Infant titer ≥fourfold higher than mother's titer
- + darkfield or PCR of placenta, cord, lesions, or body fluid
- + silver stain of placenta or cord

No to all

Maternal Criteria:
- Not treated
- Inadequately treated§
- Treatment undocumented
- Treated with a non-penicillin G regimen
- Initiated treatment <30 days before delivery

No to all

Additional Maternal Criteria:
- Adequately treated with penicillin G regimen appropriate for stage, initiated ≥30 days before delivery

AND

- No concern for reinfection or treatment failure

Yes to any

Scenario 1: Proven or Highly Probable CS

Yes to any

Scenario 2: Possible CS‖

Yes to both

Scenario 3: Less Likely CS

Infant Evaluation

- **CSF analysis†** VDRL, cell count, and protein
- **Complete blood count (CBC),** differential, and platelet count
- **Long-bone radiographs**
- **Tests as clinically indicated by signs on physical exam**

- **CSF analysis†** VDRL, cell count, and protein
- **CBC,** differential, and platelet count
- **Long-bone radiographs**

No additional infant evaluation

Review Maternal Titers & Stage:
- ≥4 fold decrease in titer after treatment for early syphilis

OR

- Stable titer for low-titer, latent syphilis (RPR < 1:4)

Any abnormalities, results not available, *OR* follow-up¶ uncertain

No abnormalities *AND* follow-up¶ certain

No to both *OR* follow-up¶ uncertain

Yes to either *AND* follow-up¶ certain

Infant Treatment

Aqueous crystalline penicillin G‡
100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days

Benzathine penicillin G
50,000 units/kg/dose IM in a single dose

No treatment indicated
with close serologic follow-up of infant every 2-3 months for 6 months

So what can we do?

The bad news: Treating syphilis in pregnancy is hard

- ❑ Provider confusion over appropriate treatment for different syphilis stages
- ❑ Difficulty facilitating three weekly doses for late latent syphilis
- ❑ Difficulty managing penicillin allergies

Slide credit: Hilary Reno

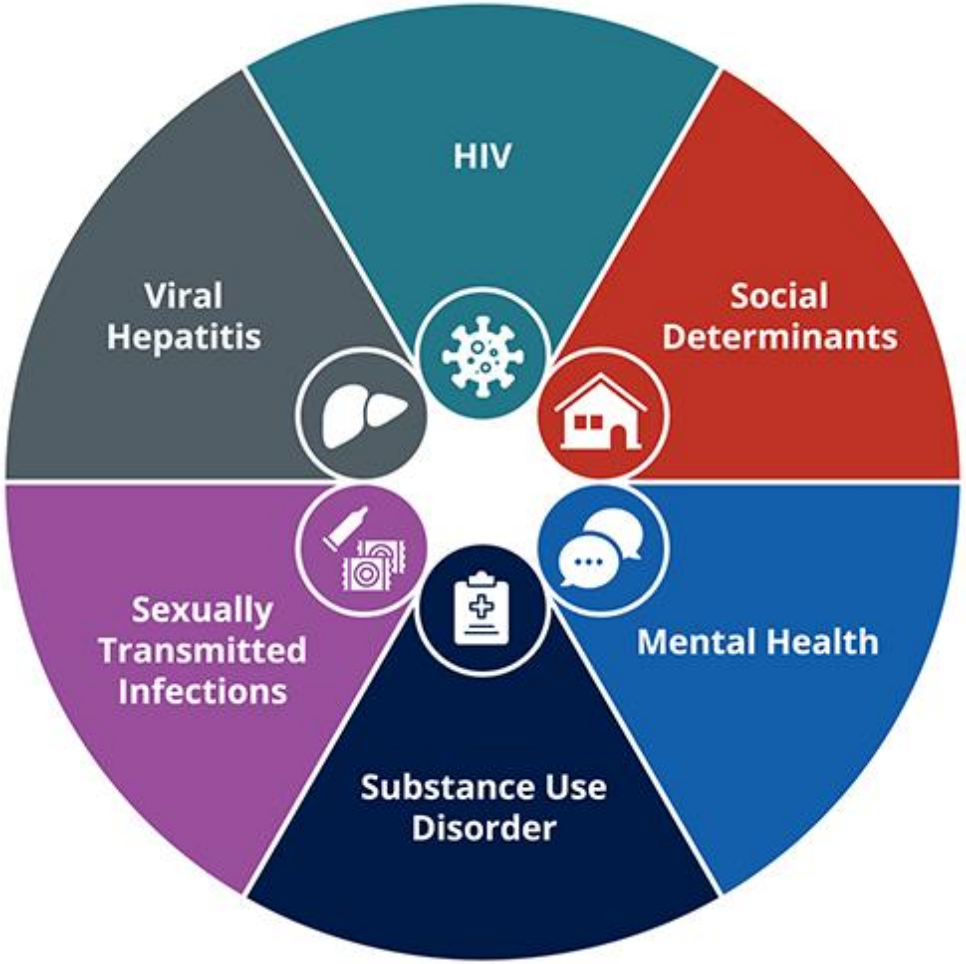
Congenital syphilis is **preventable**, but requires…

- ❑ Timely prenatal care
- ❑ Timely syphilis testing
- ❑ Timely, stage-appropriate parental treatment
- ❑ Timely identification of treatment failure, relapse, and seroconversion during pregnancy

Deadline to start treatment:
30 days prior to delivery!

Slide credit: Hilary Reno

A syndemic approach to congenital syphilis



- Ensure quality care
- Team management: DIS, clinician, community health worker, etc.
- Assess for social vulnerabilities
- Learn from programs that are doing work in adjacent areas
- Collaborate
- Involve community
- Always address prevention and stigma

Slide adapted from Hilary Reno
Photo: cdc.gov

Summary and key take-home points

- Rates of syphilis are increasing – both CS and in adults, in part due to changing and rising prevalence of sociobehavioral factors (drug use, unstable housing, etc.)
- Syphilis must be on differential to be diagnosed!
- If in doubt, always ok to treat (and test)!
- Every patient with syphilis needs: assessment of pregnancy status, neuro review
- Screening for syphilis and appropriate treatment are imperative in pregnancy
  - PCN is the **only** option for treatment
  - Treat index patients and all contacts
- Congenital syphilis *can be prevented*! Public health can provide support for diagnosis and treatment

Additional resources

National Network of STD Clinical Prevention Training Centers

University of WA STD Prevention Training Center

- www.uwptc.org

National Network of STD/HIV Prevention Training Centers

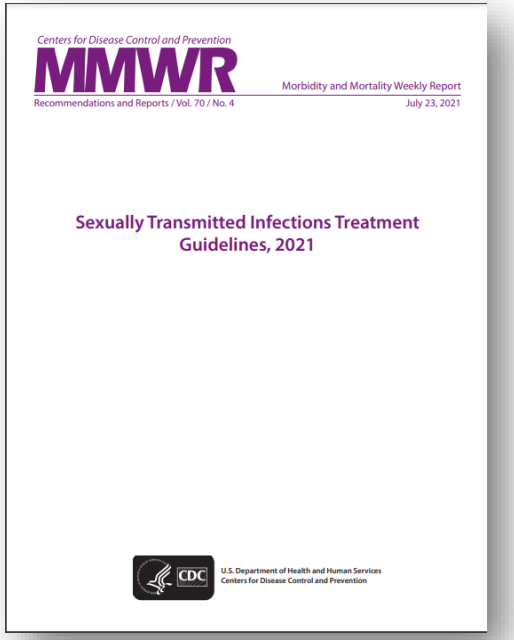
- www.nnptc.org

CDC Treatment Guidelines

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

American Sexual Health Association (ASHA) booklets, books, handouts, consultations, etc.

- https://www.ashasexualhealth.org/syphilis/
- (919) 361-8400



Thank you!

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