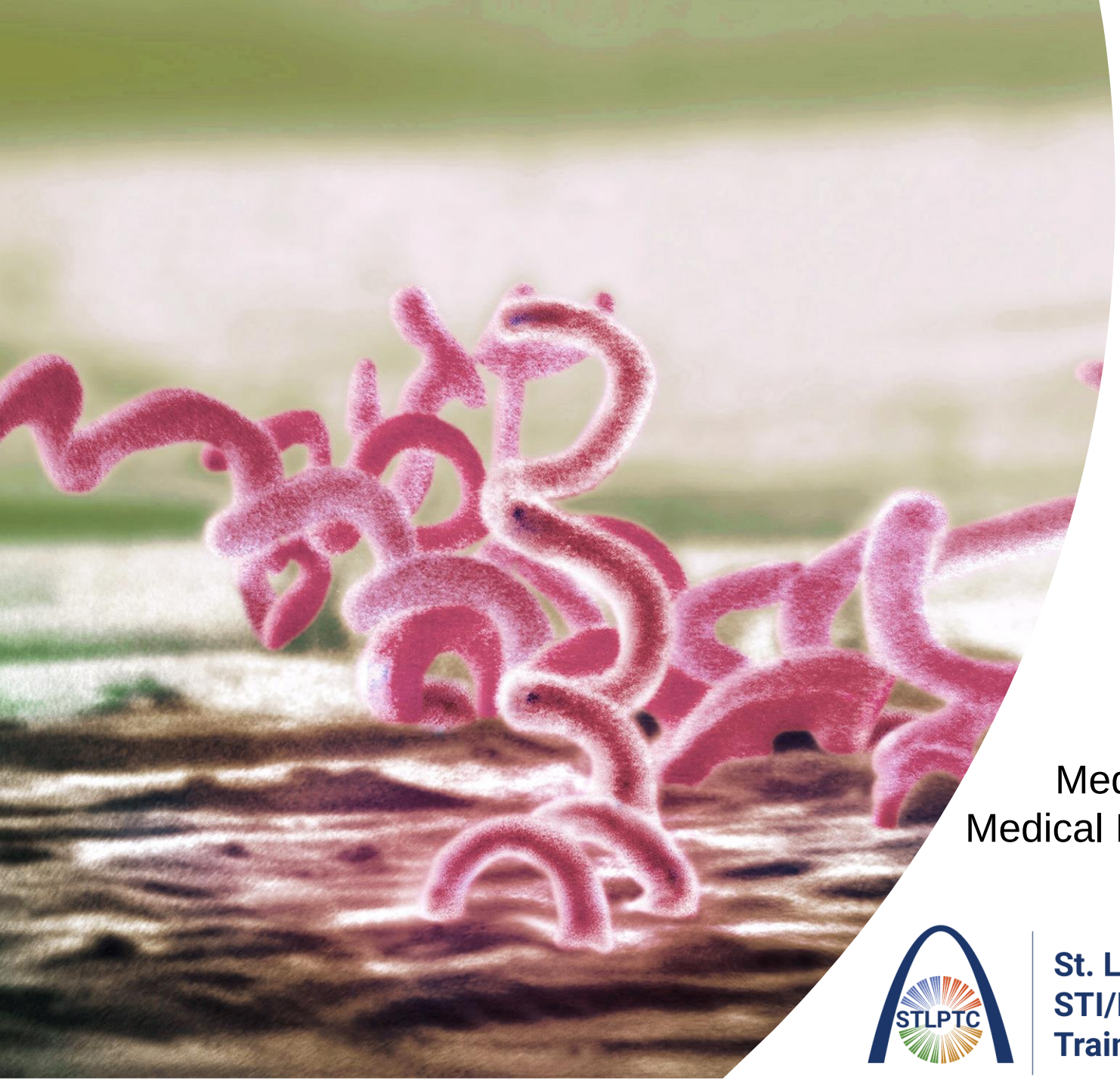

The Resurgence of Syphilis and Congenital Syphilis: What Do We Do Now?

Hilary Reno, MD, PhD, FIDSA
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St. Louis
STI/HIV Prevention
Training Center

UNIVERSITY OF WASHINGTON
STD Prevention
Training Center

Disclosures

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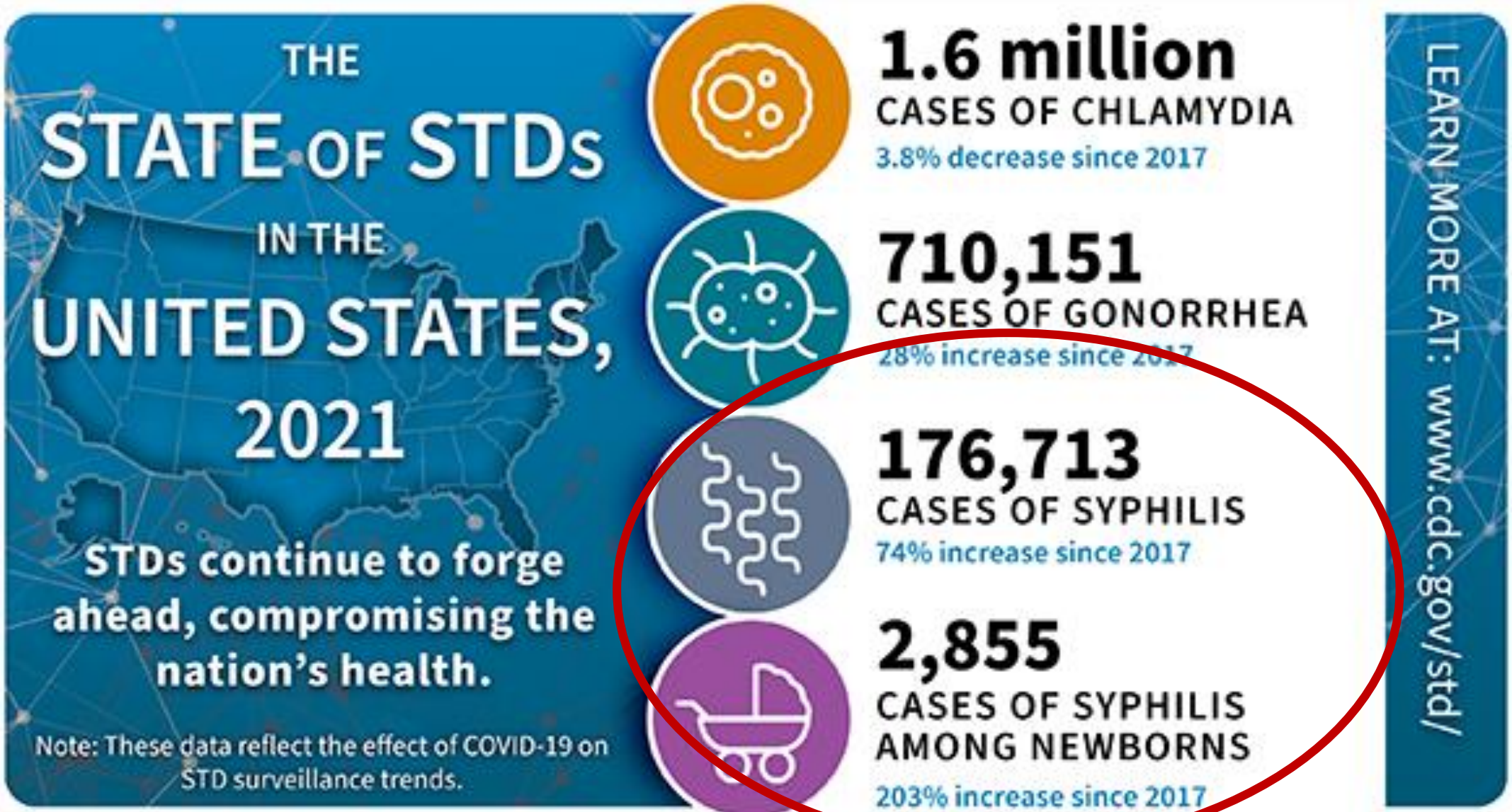
St. Louis STI/HIV Prevention Training Center

UNIVERSITY OF WASHINGTON STD Prevention Training Center

Objectives

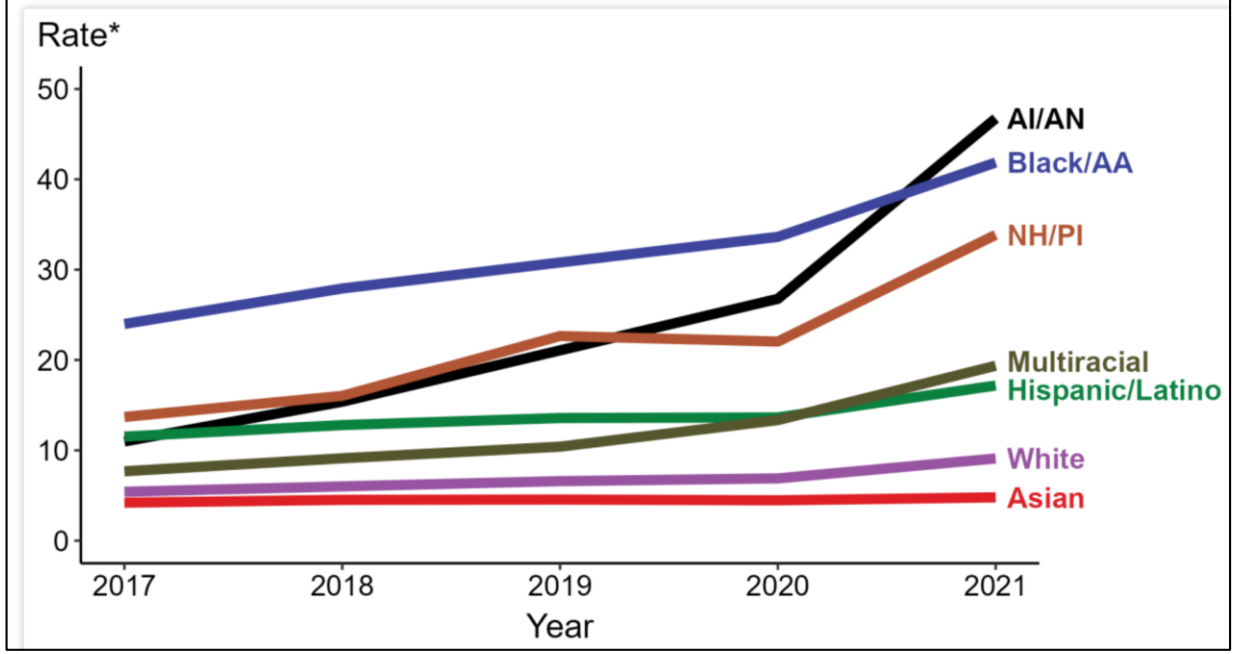
- Review current epidemiology of syphilis and then, congenital syphilis
- Understand the stages of syphilis and where diagnostic mistakes are made.
- Discuss treatment in the time of medication shortages.
- Describe a syndemic approach and why it may be essential to syphilis care.


THE
STATE OF STDs
IN THE
UNITED STATES,
2021
STDs continue to forge ahead, compromising the nation's health.
Note: These data reflect the effect of COVID-19 on STD surveillance trends.
1.6 million
CASES OF CHLAMYDIA
3.8% decrease since 2017
710,151
CASES OF GONORRHEA
28% increase since 2017
176,713
CASES OF SYPHILIS
74% increase since 2017
2,855
CASES OF SYPHILIS AMONG NEWBORNS
203% increase since 2017
LEARN MORE AT: www.cdc.gov/std/

Syphilis in 2021

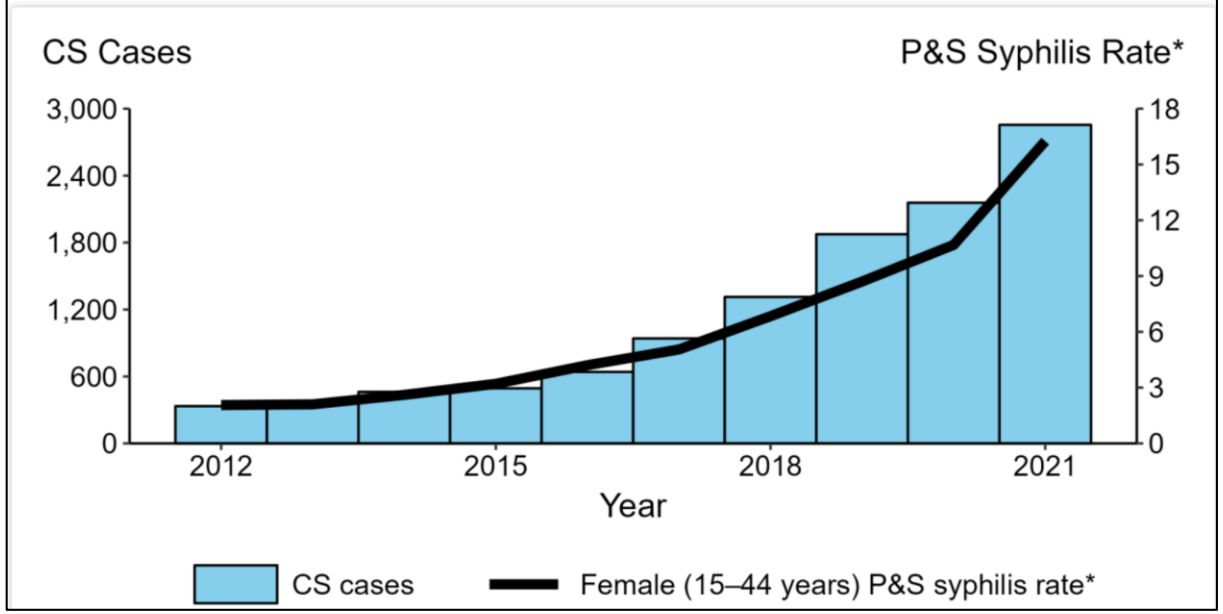
Primary and Secondary Syphilis — Rates of Reported Cases by Race/Hispanic Ethnicity, United States, 2017–2021

Print



Congenital Syphilis — Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis Among Women Aged 15–44 Years, United States, 2012–2021

Print



Ensure quality care

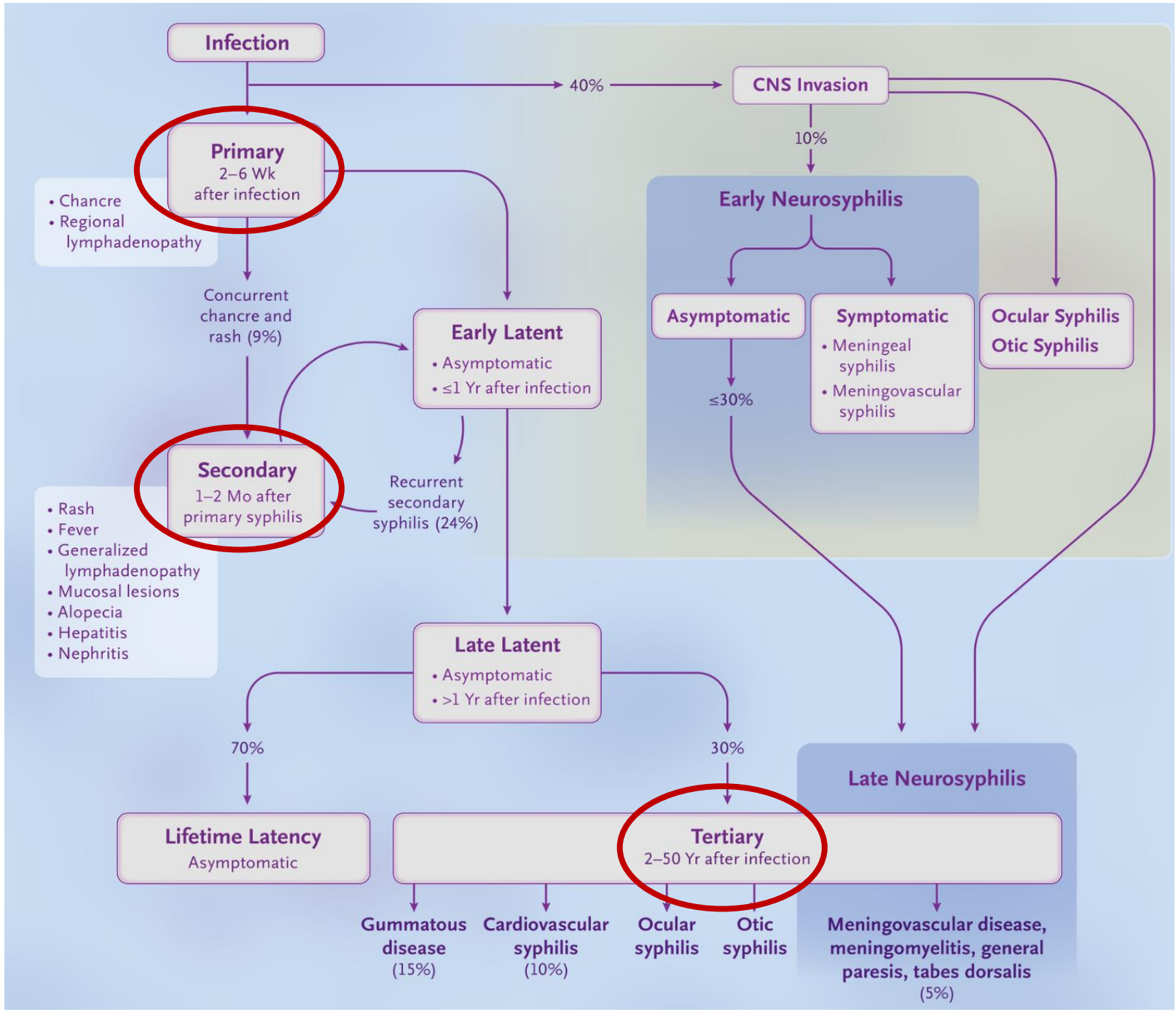
Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 70 / No. 4
July 23, 2021

Sexually Transmitted Infections Treatment Guidelines, 2021

Updates to CDC STI Screening Guidelines

Syphilis

Women	• Screen asymptomatic women at increased risk (history of incarceration or transactional sex work, geography, race/ethnicity) for syphilis infection[2,7]
Pregnant Women	• All pregnant women at the first prenatal visit[8] • Retest at 28 weeks gestation and at delivery if at high risk (lives in a community with high syphilis morbidity or is at risk for syphilis acquisition during pregnancy [drug misuse, STIs during pregnancy, multiple partners, a new partner, partner with STIs])[2]
Men Who Have Sex With Women	• Screen asymptomatic adults at increased risk (history of incarceration or transactional sex work, geography, race/ethnicity, and being a male younger than 29 years) for syphilis infection[2,7]
Men Who Have Sex With Men	• At least annually for sexually active MSM[2] • Every 3 to 6 months if at increased risk[2] • Screen asymptomatic adults at increased risk (history of incarceration or transactional sex work, geography, race/ethnicity, and being a male younger than 29 years) for syphilis infection[2,7]
Transgender and Gender Diverse People	• Consider screening at least annually based on reported sexual behaviors and exposure[2]
Persons with HIV	• For sexually active individuals, screen at first HIV evaluation, and at least annually thereafter[2,6] • More frequent screening might be appropriate depending on individual risk behaviors and the local epidemiology[2]



Stages of Syphilis

Key Points:

- Ocular and otic syphilis can present at any stage of syphilis
- Without treatment, secondary syphilis can be recurrent.
- Work with DIS/ health department to review patient's history
- Consult with DIS, ID, colleague to stage correctly.

Ghanem KG, Ram S, Rice PA. The Modern Epidemic of Syphilis. *N Engl J Med*. 2020;382(9):845-854. doi:10.1056/NEJMra1901593

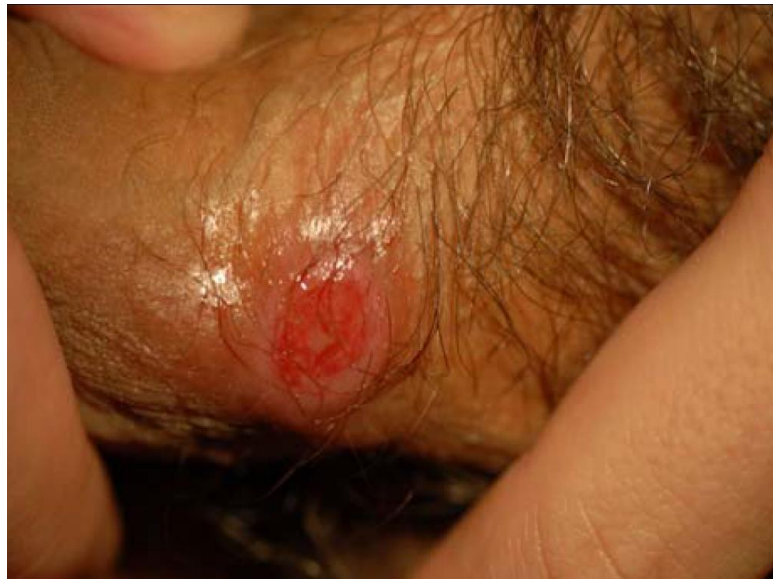
MUST KNOWS to understand syphilis

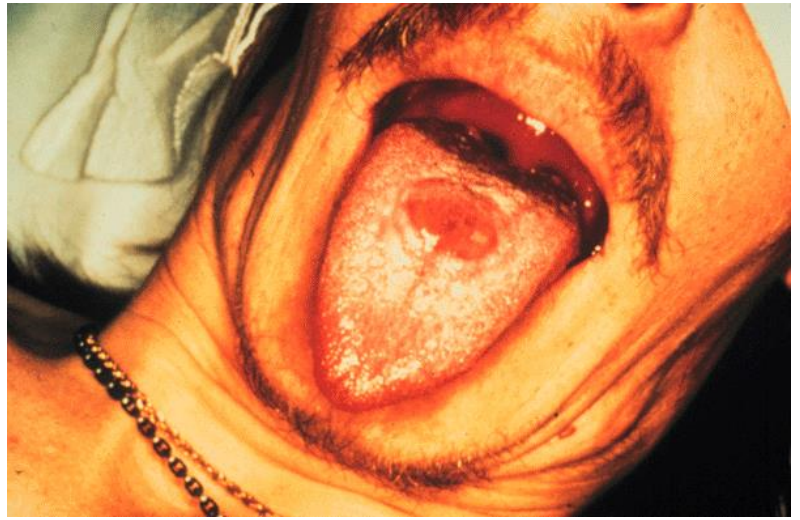
- Syphilis must be on the differential to be diagnosed
- Disseminates at every stage
- The more syphilis we see, the more unusual presentations we see.
- Recent rise in cases is somewhat due to an increase in association with drug use.
- Two things every patient with syphilis needs:
    - Neuro ROS→ if positive, continue with further assessment
    - Assessment of pregnancy status

Clinical presentation

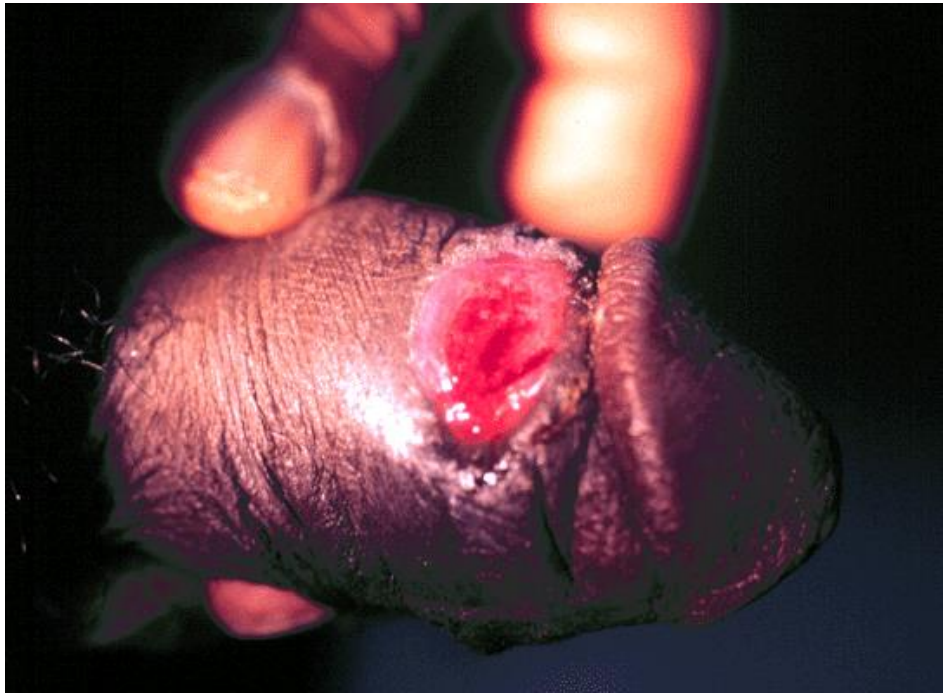
- Chancre is hallmark of primary infection: 10-90d after exposure
  - Painless (but not always*)
  - Can have more than one chancre.
  - Macrophages and activated T cells at chancre site—and highly associated with HIV acquisition
  - median time to HIV diagnosis is 1.6 years.**
  - New in 2021: Atypical presentations are more common (painful chancres, condyloma lata etc.)

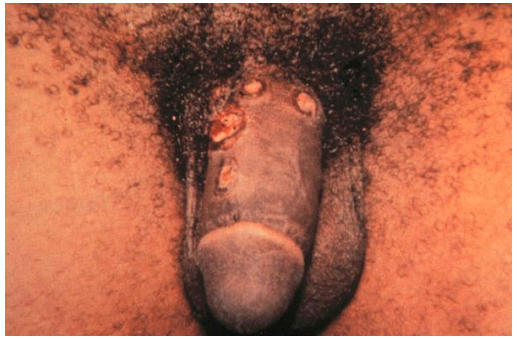
**Pathela et al CID 2015

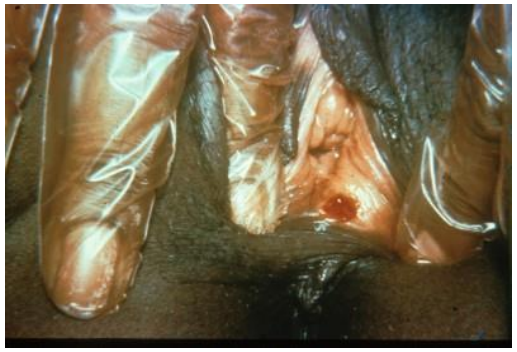


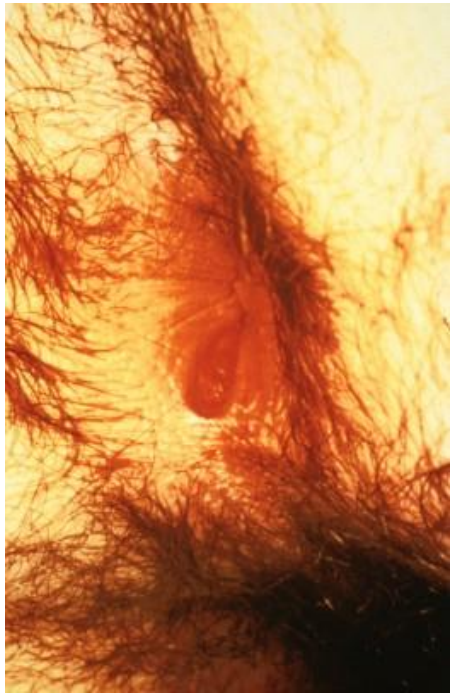


Primary syphilis - chancre





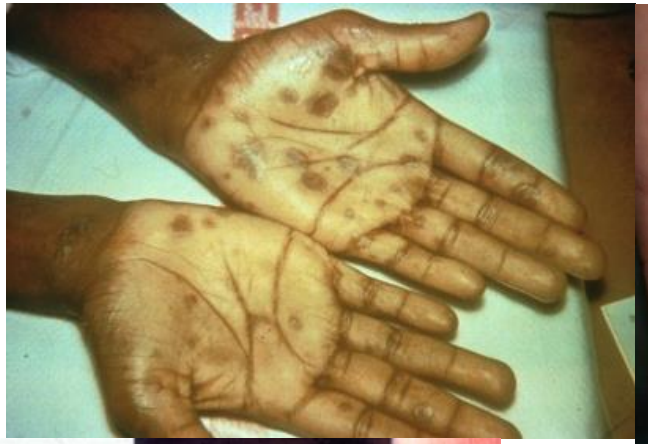


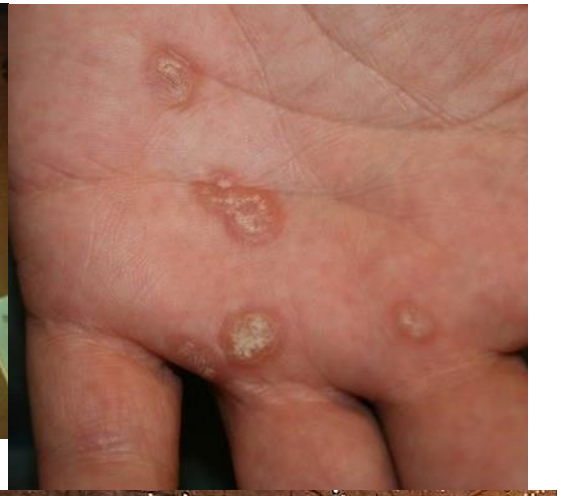


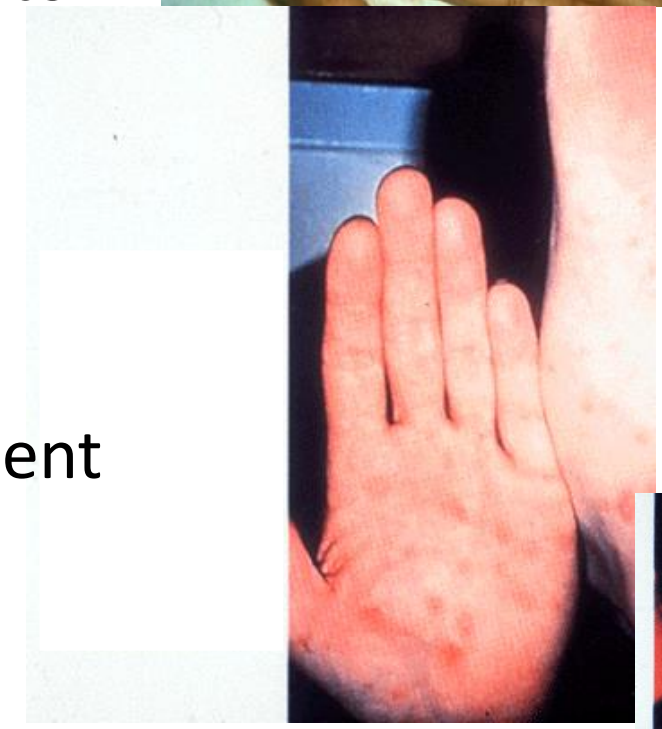
If HSV and mpox are on the differential, syphilis should be too.

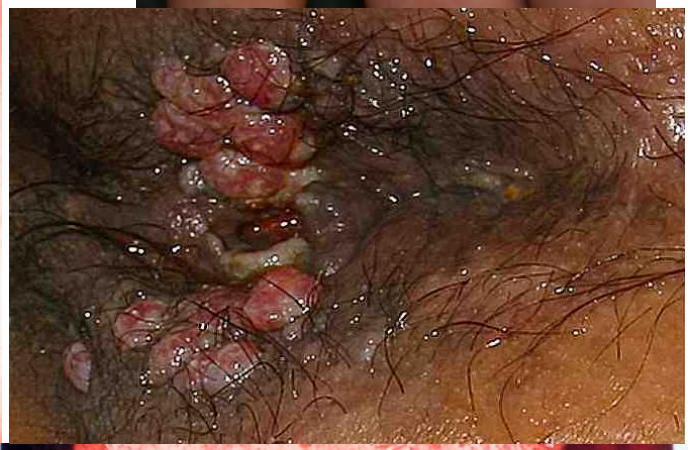
Secondary syphilis: It is not psoriasis

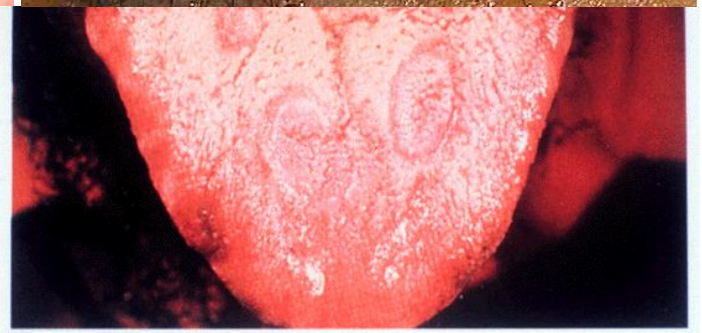
- Chancre heals spontaneously in 1 to 6 weeks
- Systematic symptoms (F, malaise, HA, LAN, etc) can occur
- Rash ultimately resolves, but infection is lifelong without treatment (latency)
- Condyloma lata!
- Don’t forget about Mpox.











31. Mucous patches on tongue in secondary syphilis

Case

25 year old cisgender woman who presents for STI workup with no complaints. She reports 2 cisgender male sexual partners in the last 3 months, uses condoms occasionally. Her exam is normal. Her RPR is reactive at 1:256, with reactive TP-PA, nonreactive HIV test, negative G/C NAAT.

You call the health department, and she has no previous RPRs on file.

What stage of syphilis does she have?

She returns to clinic for treatment?

A) 1 shot 2.4 million units Bicillin as outpatient
B) 3x weekly 2.4 million units Bicillin as outpatient
C) Admit for LP and IV Penicillin G for 2 weeks
D) Admit for IV Penicillin G for 2 weeks without LP

Case continued

With her return to clinic, she is not pregnant but with a complete review of neurological symptoms, she states that she has been having some vision changes which she describes as floaters and double vision at times. She also notes that she has had a headache more frequently within the last month. The rest of her neuro ROS is benign.

Now what should her treatment be?

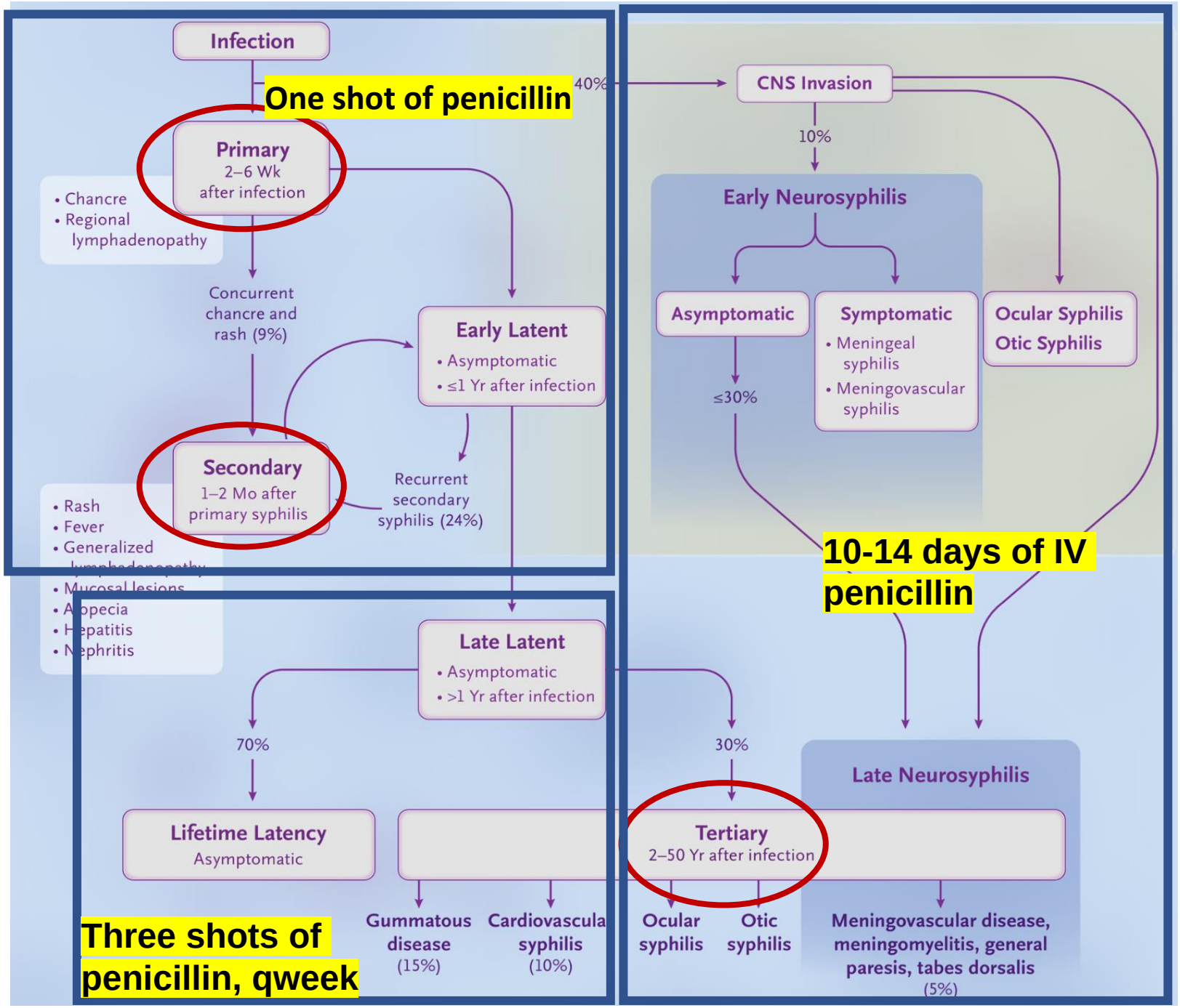
A) 1 shot 2.4 million units Bicillin as outpatient
B) 3x weekly 2.4 million units Bicillin as outpatient
C) Admit for LP and IV Penicillin G for 2 weeks
D) Admit for IV Penicillin G for 2 weeks without LP

Treatment of Syphilis

- IM Penicillin G benzathine should always be FIRST line therapy
- Doxycycline is alternative for TRUE penicillin allergies and for nonpregnant persons in setting of Bicillin shortage[1]
- IV penicillin for neuro/ ophtho/ otic syphilis
- Azithromycin should NOT be used; nearly all *T. pallidum* in US and globally is resistant[2]
- No new data to warrant a change in treatment recommendations.
- Reaffirmation that a lack of serological response should be followed out to:
  - 12 months after syphilis of < 1 year duration
  - 24 month in case of syphilis of unknown duration or late syphilis
  - And that it may not be seen if RPR titer is <1:4

1. https://www.cdc.gov/std/dstdp/dcl/2023-july-20-Mena-BicillinLA.htm
2. Beale et al, Nat Commun 2019

Treatment of Syphilis



- Who MUST be treated with Bicillin?
  - Pregnant people
  - Alternatives for treating neurosyphilis have little evidence of efficacy.

Ghanem KG, Ram S, Rice PA. The Modern Epidemic of Syphilis. *N Engl J Med*. 2020;382(9):845-854. doi:10.1056/NEJMra1901593

Bicillin shortage plan

Take inventory:

- Monitor local supply of Bicillin L-A® and determine the local pattern of use to forecast need.
- Continue to contact distributors to procure Bicillin L-A® as appropriate. Contact Pfizer (see "Dear Patient Letter" posted on the FDA website) if there is less than a 2-week supply, the distributor has no supply, and there is a risk that patients may not be treated.

Prioritize using Bicillin L-A® to treat pregnant people with syphilis and babies with congenital syphilis – penicillin is the only recommended treatment for these populations.

- Choose doxycycline for non-pregnant people to help preserve Bicillin L-A® supplies. See CDC's treatment recommendations for more.
- Consider involving antimicrobial stewardship leaders to help institute systems-level approaches to limit the use of Bicillin L-A® and encourage the use of alternative effective antimicrobials for treatment of other infectious diseases.

Obtaining Bicillin for treatment in pregnancy

- **Providers can call Pfizer Supply Continuity Team to request Bicillin to treat pregnant persons**
  - Hours: 7 a.m. and 5 p.m. (CT)
  - Number: 1-844-646-4398 (select option 1 [Customer], then option 3
  - Or send an email to stdshortages@cdc.gov with a specific request to connect with Pfizer
- Contact CDC directly if unable to find a solution with Pfizer

Current and Resolved Drug Shortages and Discontinuations Reported to FDA

Report a Drug Shortage | Contact Us | FAQ | Background Info | Get Email Alerts | Download Current Drug Shortages

Search by Generic Name or Active Ingredient: Enter at least three characters Submit

Start Over | **Back to Search Results**

Penicillin G Benzathine Injection
Status: Currently in Shortage
»**Date first posted:** 04/26/2023
»**Therapeutic Categories:** Anti-Infective

https://www.cdc.gov/std/dstdp/dcl/2023-july-20-Mena-BicillinLA.htm

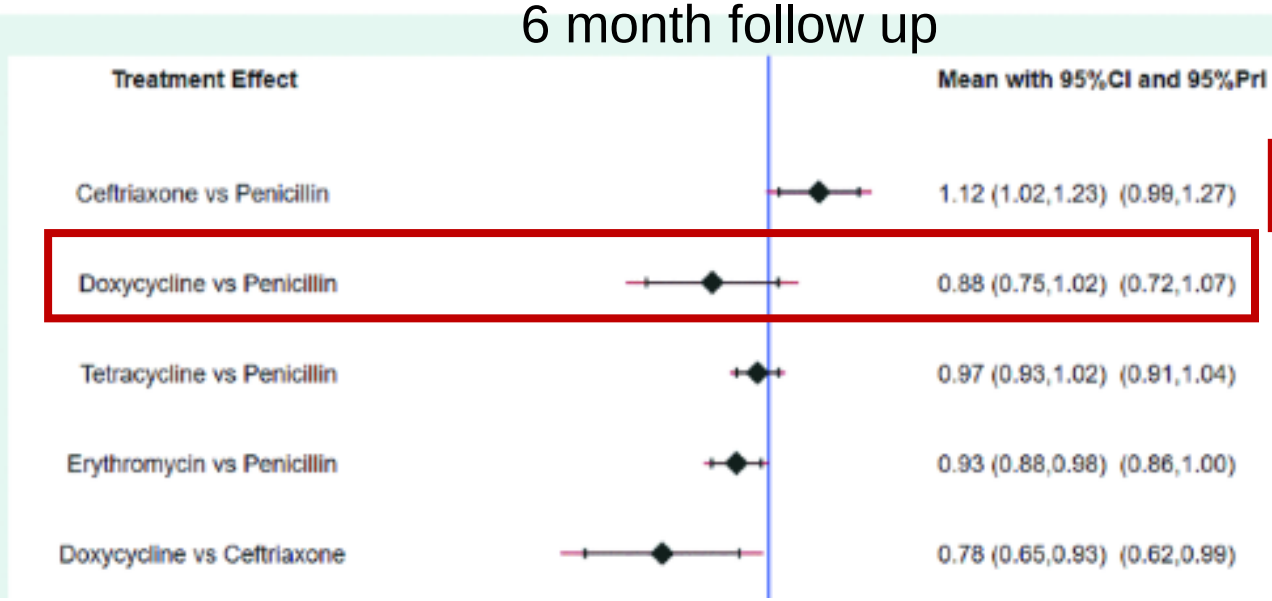
AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

RESEARCH ARTICLE
November/December 2022 Volume 10 Issue 6 e02977-22
https://doi-org.beckerproxy.wustl.edu/10.1128/spectrum.02977-22

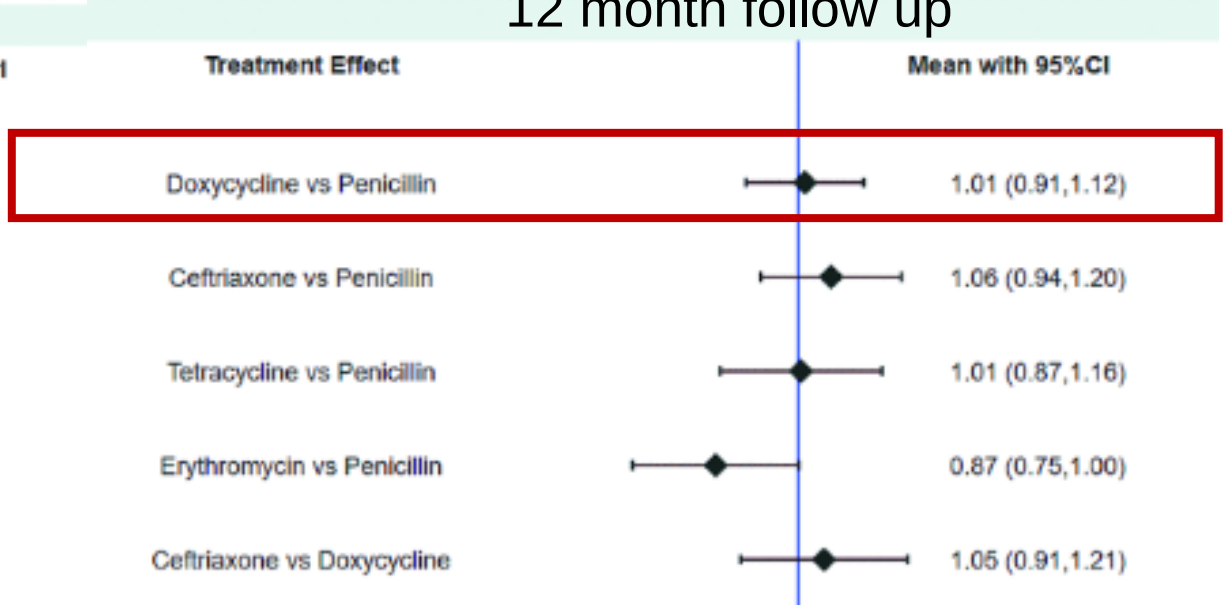
Efficacy and Safety of Treatments for Different Stages of Syphilis: a Systematic Review and Network Meta-Analysis of Randomized Controlled Trials and Observational Studies

Meixiao Liu[a], Yuxin Fan[a], Jingjing Chen[a], Jiaru Yang[a], Li Gao[a], Xinya Wu[a], Xin Xu[a], Yu Zhang[a], Peng Yue[a], Wenjing Cao[a], Zhenhua Ji[a], Xuan Su[a], Shiyuan Wen[a], Jing Kong[a], Guozhong Zhou[a], Bingxue Li[a], Yan Dong[a], Aihua Liu[a,b], Fukai Bao [a,b]

6 month follow up



12 month follow up



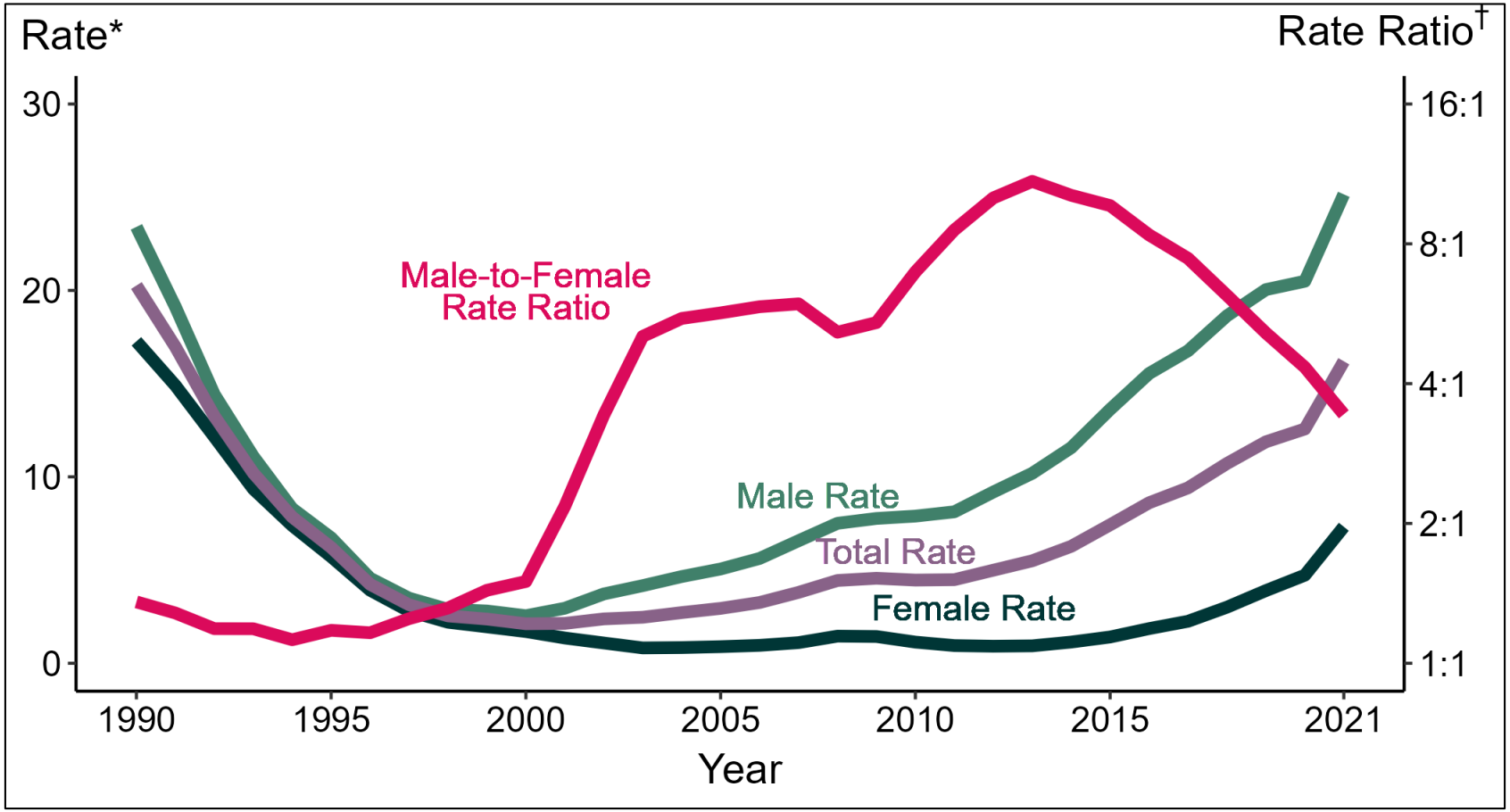
Congenital Syphilis

An example case

- Mom has adequate prenatal care with RPR NR at 8 wks gestation
- She presents with vaginal lesions at 35 weeks gestation
- HSV testing is negative.
- No other STI testing.
- Treated with valacyclovir.

- Presents in labor at 37 weeks.
- No RPR at delivery.
- Baby has work up at 5 months for slow weight gain and developmental delay.
- Hip xrays indicate periosteal abnormalities and CS is diagnosed.

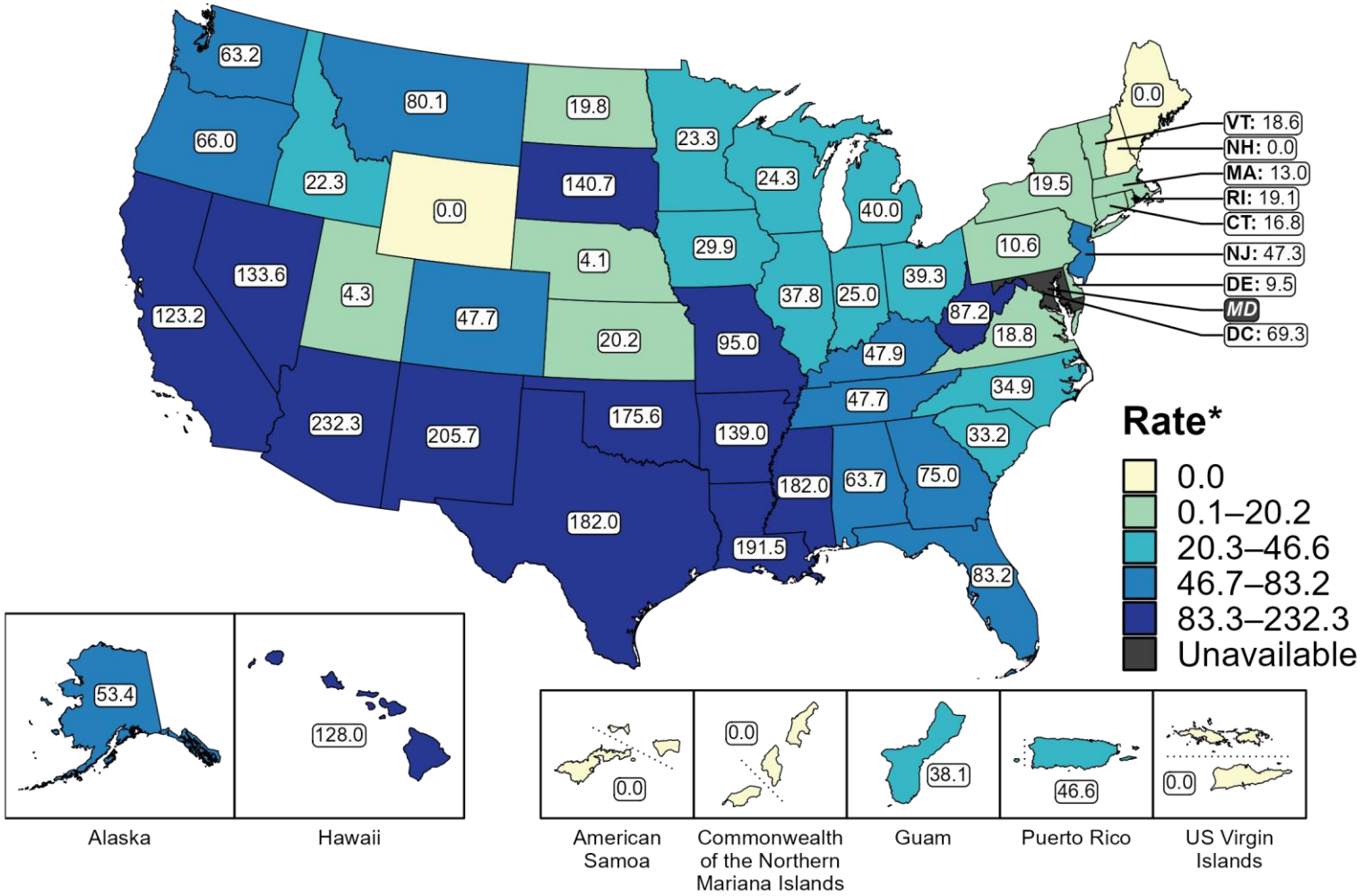
Primary and Secondary Syphilis — Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2021



* Per 100,000

† Log scale

Congenital Syphilis — Rates of Reported Cases by State, United States and Territories, 2021



Congenital syphilis prevention: screening

- Screen all women in early pregnancy
- Screen again twice in third trimester “for communities and populations in which the prevalence of syphilis is high, and for women at high risk of infection”
    - Screen at 28 weeks
    - Screen again at delivery

Sexually Transmitted Diseases Treatment Guidelines 2021

Congenital syphilis prevention: Quality Care

- Access to packaged STI testing for people of childbearing potential.
- Counseling pregnant people on STI prevention
  - Especially in the later half of pregnancy: Consider HSV and syphilis
- Do not forget syphilis can occur in pregnancy
- Go to the CDC STI guidelines for diagnosis and classifying CS

Scenario 1: Confirmed Proven or Highly Probable Congenital Syphilis

Any neonate with

- an abnormal physical examination that is consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold[§] (or greater) higher than the mother's titer at delivery (e.g., maternal titer = 1:2, neonatal titer ≥1:8 or maternal titer = 1:8, neonatal titer ≥1:32)[¶]; or
- a positive darkfield test or PCR of placenta, cord, lesions, or body fluids or a positive silver stain of the placenta or cord.

Recommended Evaluation

- CSF analysis for VDRL, cell count, and protein**
- Complete blood count (CBC) and differential and platelet count
- Long-bone radiographs
- Other tests as clinically indicated (e.g., chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brain stem response)

Recommended Regimens, Confirmed or Highly Probable Congenital Syphilis

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

OR

Procaine penicillin G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days

If >1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding use of other antimicrobial agents (e.g., ampicillin). When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis (*648–650*). Using agents other than penicillin requires close serologic follow-up for assessing therapy adequacy.

Scenario 2: Possible Congenital Syphilis

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold of the maternal titer at delivery (e.g., maternal titer = 1:8, neonatal titer ≤1:16) and one of the following:

- The mother was not treated, was inadequately treated, or has no documentation of having received treatment.
- The mother was treated with erythromycin or a regimen other than those recommended in these guidelines (i.e., a nonpenicillin G regimen).††
- The mother received the recommended regimen but treatment was initiated <30 days before delivery.

Recommended Evaluation

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

This evaluation is not necessary if a 10-day course of parenteral therapy is administered, although such evaluations might be useful. For instance, a lumbar puncture might document CSF abnormalities that would prompt close follow-up. Other tests (e.g., CBC, platelet count, and long-bone radiographs) can be performed to further support a diagnosis of congenital syphilis.

Recommended Regimens, Possible Congenital Syphilis

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

ne penicillin G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days

hine penicillin G 50,000 units/kg body weight/dose IM in a single dose

www.cdc.gov/std

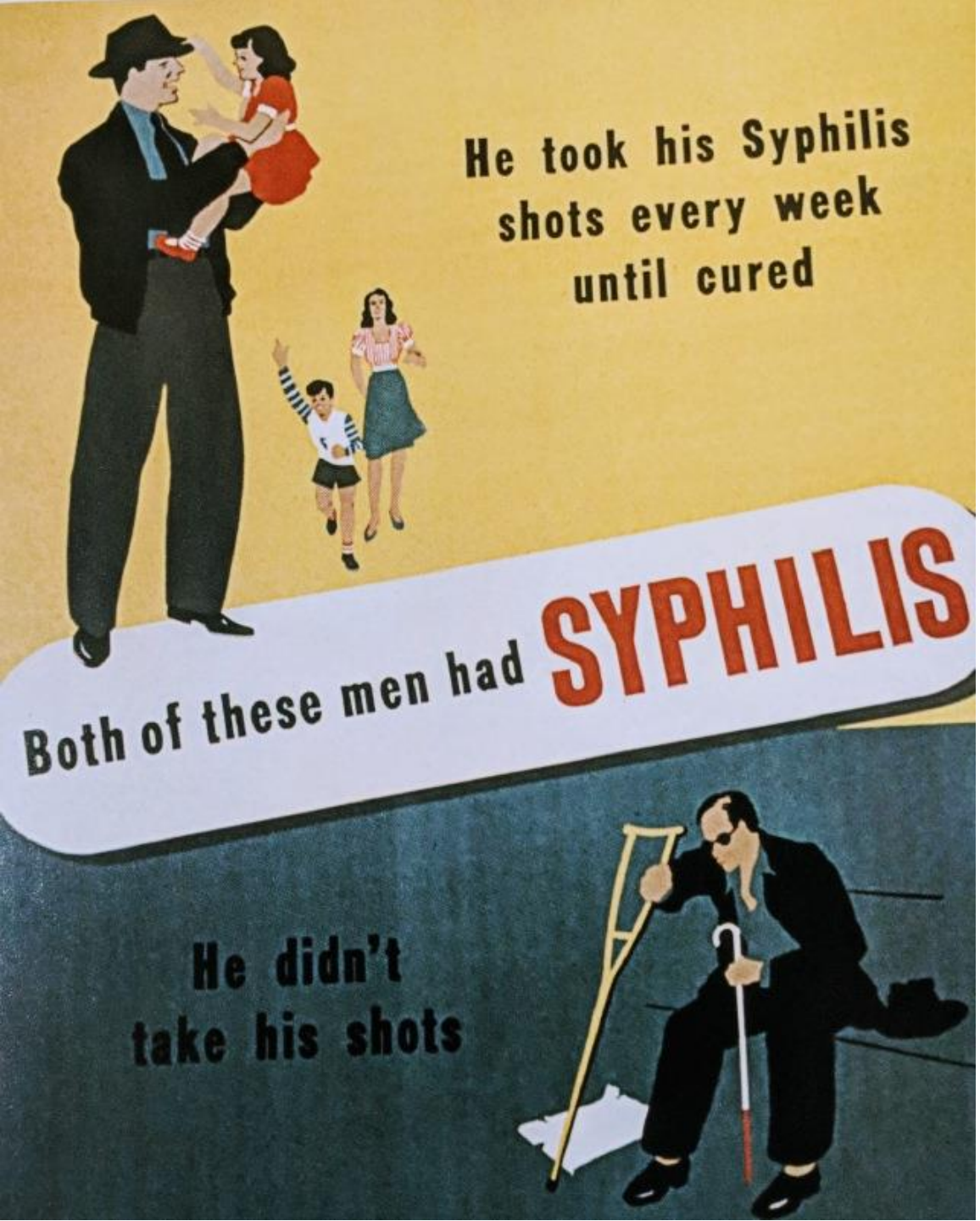
Case

26-year-old pregnant, cisgender female presents for a walk-in STI clinic visit. She is unhoused and does not have insurance.

She is 8 weeks gestation by dates, found to have RPR of 1:64, has never had syphilis testing in the past and currently has no symptoms and a normal physical exam. She states she is allergic to penicillin with history of rash and shortness of breath with amoxicillin, how would you proceed?

Management of syphilis in pregnancy

- Obtain previous treatment history to help management.
- Management is the same as non-pregnant people.
- There are **NO alternatives to IM Bicillin** – if penicillin allergy, must desensitize to use
- For P+S, ES, some give an additional IM dose 1 week after treatment.
- Goal is 7 days between doses of IM bicillin but if a person misses a dose, effort should be focused on getting the dose within 2 days.
  - Doses more than 9 days apart means restarting treatment.
- Ultrasound is used to monitor in second half of pregnancy but should not delay treatment.
- For patients with early syphilis or high titers, Jarisch-Herxheimer reaction counseling is advised.
- Recheck RPR 8 weeks after treatment.



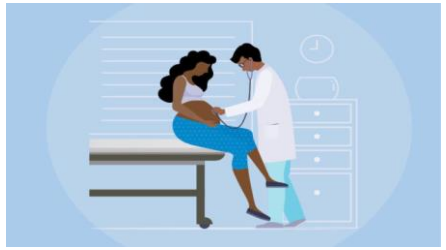
The bad news: Treating maternal syphilis is hard

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

Left: Unknown, 1941-1945

Slide: E. Daniels

Beyond demographics, some themes emerge:



Limited Prenatal Care

Interactions with the Prison System

Housing instability

Intimate Partner Violence

Unemployment

Substance Use

Sex Work/Trafficking

DCFS Involvement

E. Daniels et al.

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**

No-cost online clinical consultation on the prevention, diagnosis, and treatment of STDs by your Regional PTC Clinical Faculty

www.STDCCN.org

St. Louis STI/HIV Prevention Training Center

UNIVERSITY OF WASHINGTON STD Prevention Training Center