Syphilis Resurgence: Clinical Challenges and Approach for Internists

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Disclosures

Mizzou
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- Financial research support Gilead, ViiV, NIH
- Speaker Gilead Sciences, ViiV healthcare

Syphilis

- Epidemiology in the US and in MO
- Review of transmission, micro
- Staging of syphilis
- Diagnostic testing
- Treatment
- Challenging cases

Syphilis on the rise

In 2023, there were **209,253 cases of syphilis** reported in the United States.

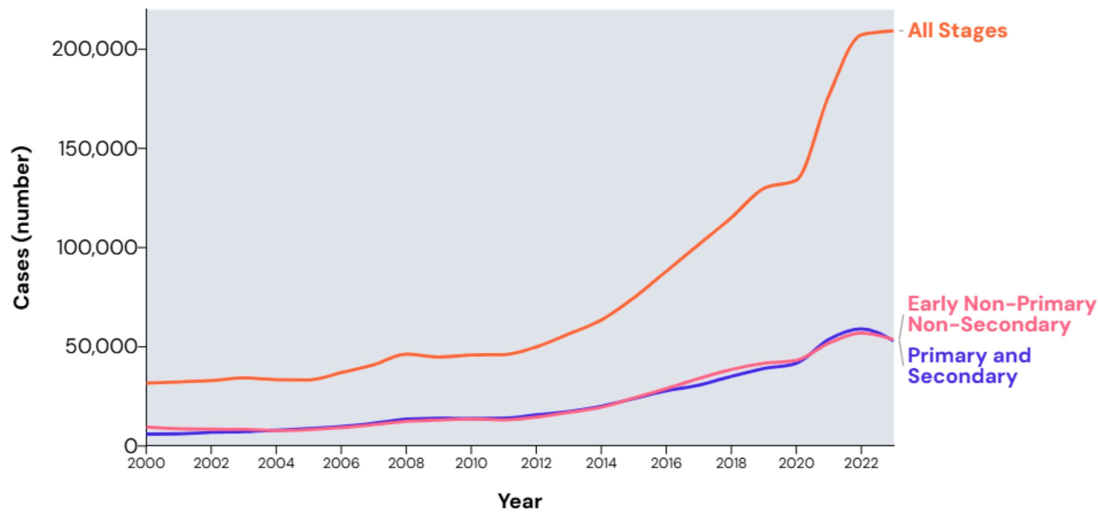
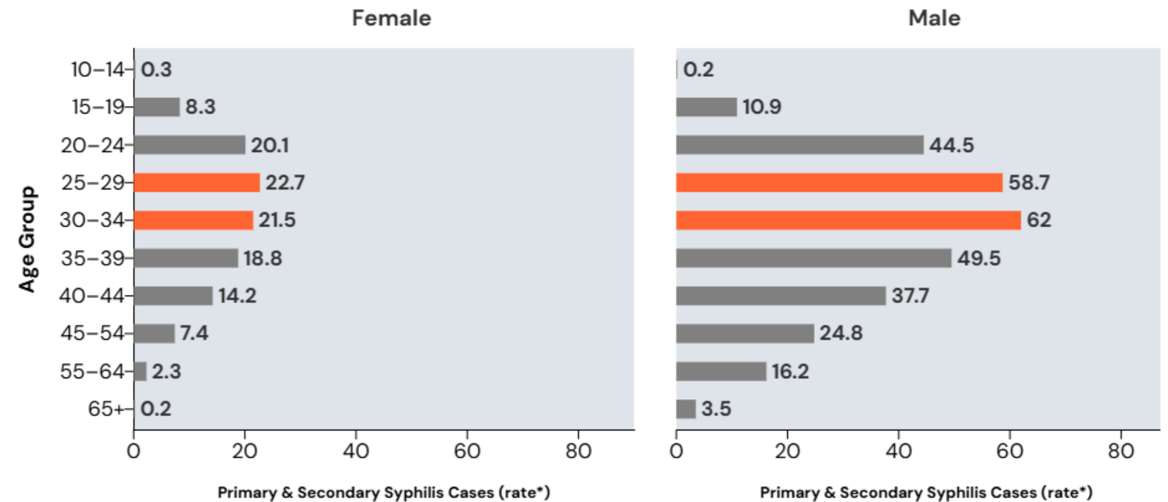


Figure 2 (Image Series). Syphilis Epidemiology in the United States

Source: Centers for Disease Control and Prevention. Sexually Transmitted Infections Surveillance, 2023. Atlanta: U.S. Department of Health and Human Services; November 2024.



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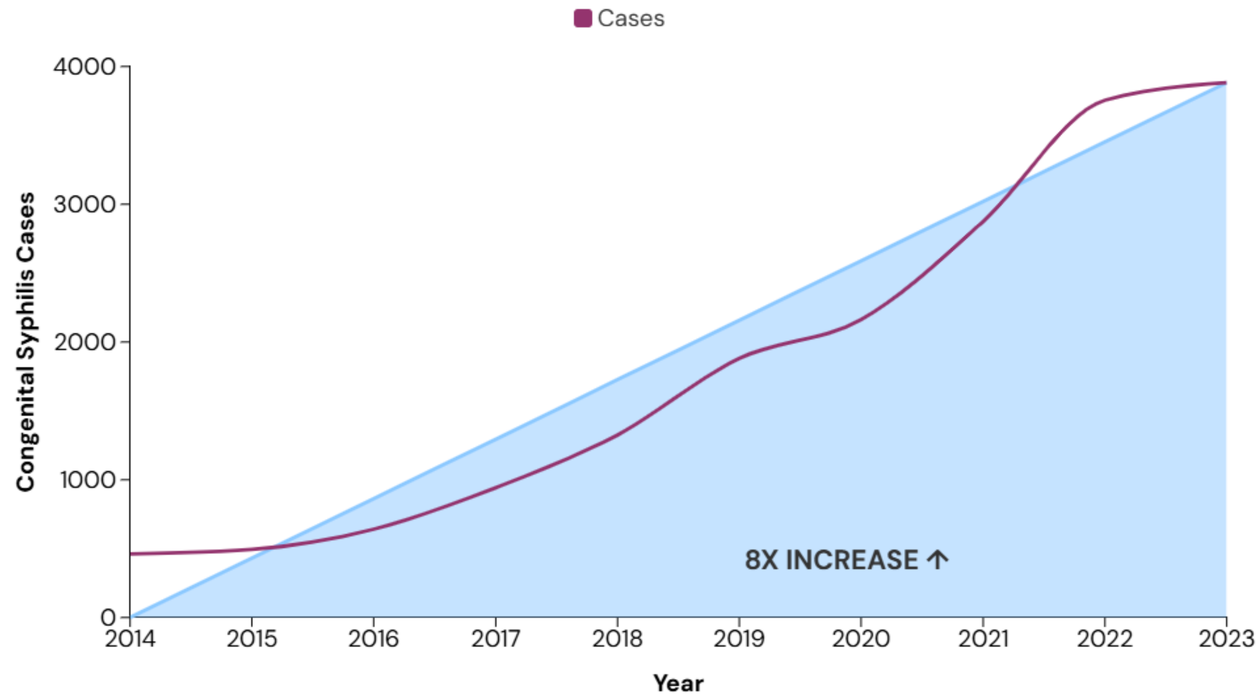
Source: Centers for Disease Control and Prevention. Sexually Transmitted Infections Surveillance, 2023. Atlanta: U.S. Department of Health and Human Services; November 2024.

Congenital syphilis

In 2023, there were
3,882 cases of congenital syphilis
reported in the United States.



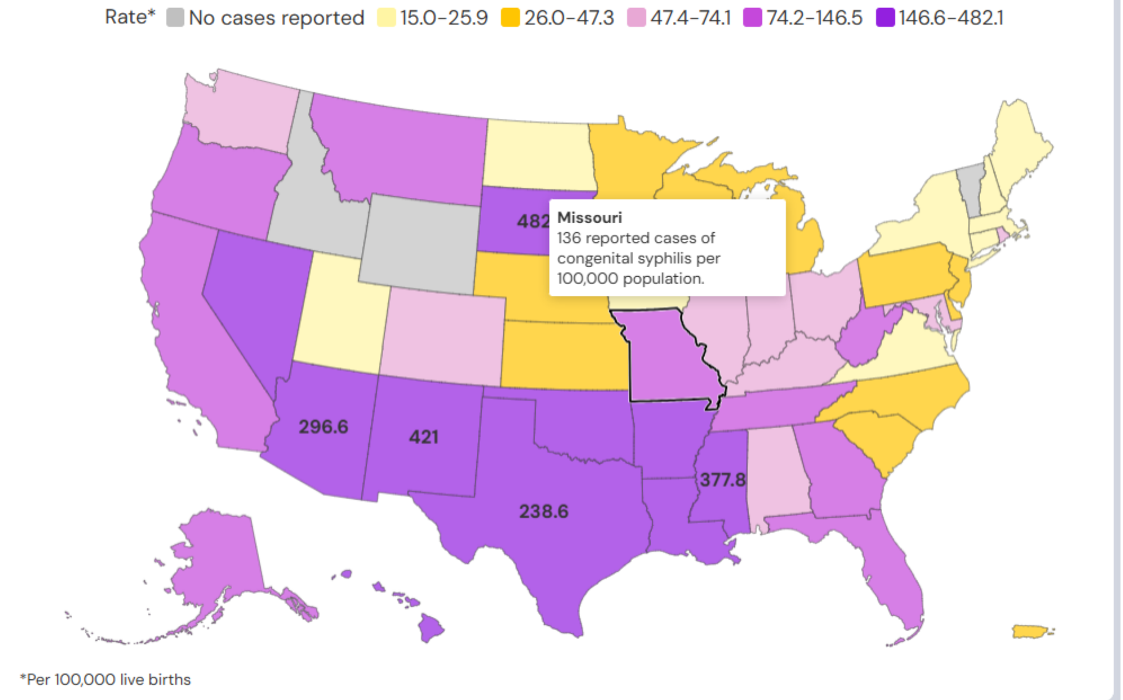


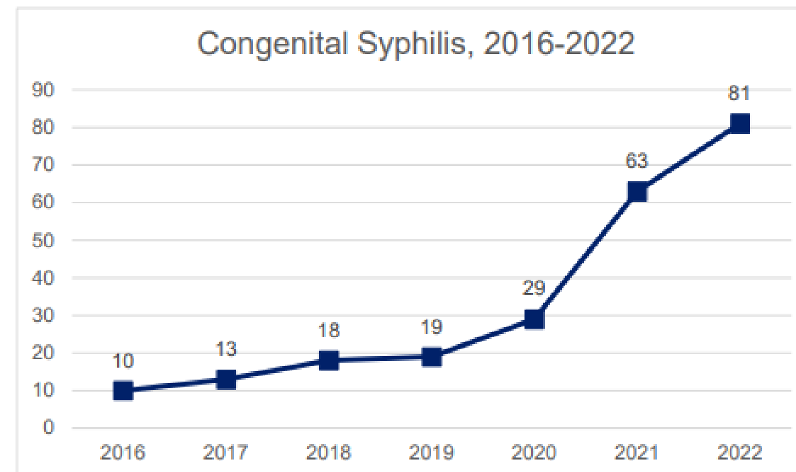
Figure 3 (Image Series). Congenital Syphilis in the United States

Source: Centers for Disease Control and Prevention. Sexually Transmitted Infections Surveillance, 2023. Atlanta: U.S. Department of Health and Human Services; November 2024.

Syphilis in Missouri

Syphilis cases have **increased by 230% from 2016 to 2022 in Missouri, ,** from 676 cases to 2,228 cases

In 2022, 81 congenital syphilis cases were reported in Missouri, compared to 10 cases in 2016. The number of cases in 2022 represent the highest reported in nearly 30 years



The basics…

Which one of the following statements is TRUE regarding the biology of Treponema pallidum?

A. Treponema pallidum can be cultured in most microbiology labs if special culture media is used

B. Treponema pallidum can be visualized via standard light microscopy with a modified Gram stain

C. Treponema pallidum is a motile spirochete bacterium that is approximately 6 to 20 micrometers in length

D. Treponema pallidum is an atypical gram-negative bacterium that lacks lipopolysaccharide and is approximately 0.1 to 0.3 micrometers in length

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Which one of the following statements is TRUE regarding transmission of Treponema pallidum?

A. Transmission most often occurs via airborne respiratory droplets during the secondary stage

B. Transmission is frequently transmitted through fomites (contaminated objects) and with gastrointestinal secretions

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Syphilis has often been called "the great imitator"

- Consider syphilis in your differential diagnosis
- Readily screen for syphilis, especially in your pregnant patients.

Stages of syphilis

- Early after infection, before any signs appear, T. pallidum spread to the circulatory system, lymphatic system, regional lymph nodes, and the CNS.
- **Primary syphilis** formation of a primary lesion or **"chancre"** at the site of inoculation
- Progress from a papule to an ulcer, which is typically painless
- Appear in 2 - 3 weeks
- Highly infectious and heal spontaneously in 3 - 8 weeks
- The most common sites where chancres develop include the oral region, penis, labia, or perianal region
- Regional firm lymphadenopathy often develops in proximity to primary syphilitic lesions

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Secondary syphilis reflect hematogenous dissemination of T. pallidum,

- 4 -10 weeks after the onset of the primary chancre
- Signs and symptoms of secondary syphilis are often the first observed manifestations
- A wide array of manifestations can occur with secondary syphilis, generalized body rash involving palms and soles, systemic symptoms, mucus patches, condyloma lata, alopecia, organ involvement (nephritis, hepatitis with high Alk phos).

Syphilis has often been called "the great imitator"

Latent syphilis persistence of infection **without signs or symptoms**

Early Latent Syphilis (< 1 Year)

- A documented seroconversion within the past year (had a negative test in < 1 year)
- Fourfold or greater increase in the titer in the past year
- Unequivocal symptoms of primary or secondary syphilis within the past year
- Contact in the past year with a sex partner who had untreated primary, secondary, or early latent syphilis

Late Latent or Latent Unknown Duration Syphilis (>1 Year)

Stages of syphilis summary

- Primary – chancre
- Secondary – all symptoms
- Latent – no symptoms
  - Early latent if infection happened in < 1 year
  - Late latent (> 1 year) or unknown
- Tertiary – rare, without treatment ~ 30% will progress to the tertiary 2 – 50 years after infection
- Neurosyphilis – occur at any stage; invades the CNS, Ocular, and Otic syphilis.

Ocular syphilis

What region of the eye is most often involved with ocular syphilis?

A. Cornea
B. Sclera
C. Uvea
D. Retina

Ocular syphilis

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A. Cornea
B. Sclera
C. Uvea
D. Retina

- Although ocular syphilis can involve any region of the eye, the uvea is the region most often involved.
- Reported symptoms may include blurred vision, pain, redness, light sensitivity, and floaters.
- CSF examination is normal in up to 40% of cases
- Referral to an ophthalmologist for an immediate evaluation
- Any new significant visual symptoms in a person diagnosed with syphilis is concerning for possible ocular syphilis

Oto-syphilis

- Persons with otosyphilis usually present with hearing loss, tinnitus, vertigo, or a combination of these manifestations
- Hearing loss is typically <u>sensorineural and can involve one or both ears</u>
- CSF examination is normal in at least 40% of cases
- Referral for an immediate auditory examination by an otolaryngologist or audiologist.

Laboratory Diagnostic Tests

- **Primary syphilis** – chancre, absent or very low levels of antibodies early after infection, serologic tests will be negative. **Dark-Field Microscopy,** rarely used in clinical practice, no FDA-approved PCR for syphilis

- **Serologic testing** involves the use of **treponemal and nontreponemal**
- **Treponemal test,** antibodies against T. pallidum antigens; IgG only, or IgM and IgG.

- **Nontreponemal tests** (RPR and VDRL), which measure antibodies directed against lipoidal antigens, not specific for T. pallidum, reported as a quantitative titer.

How to interpret these tests?

Use of only one type of serologic test is not sufficient for making a diagnosis of syphilis, since each test used alone has major limitations

False-positive higher with nontreponemal tests in older age, autoimmune disorders, cardiovascular disease, pregnancy, malaria, and recent immunizations

False-negative: **early** primary syphilis

False-Negative with non-treponemal tests (RPR) due to Prozone Effect: < 2% of cases. When very high serum antibodies supersaturate the antigens used in the assay, interfering with the visualization of the reaction.

Persons with a prior history of syphilis **maintain a positive treponemal test** for life, even after adequate treatment (**syphilis antibodies once reactive, it will remain reactive** with or without Rx)

Non-treponemal, RPR may become non-reactive over time with or without Rx, , typically correlates with disease activity

Diagnosis of syphilis – screening

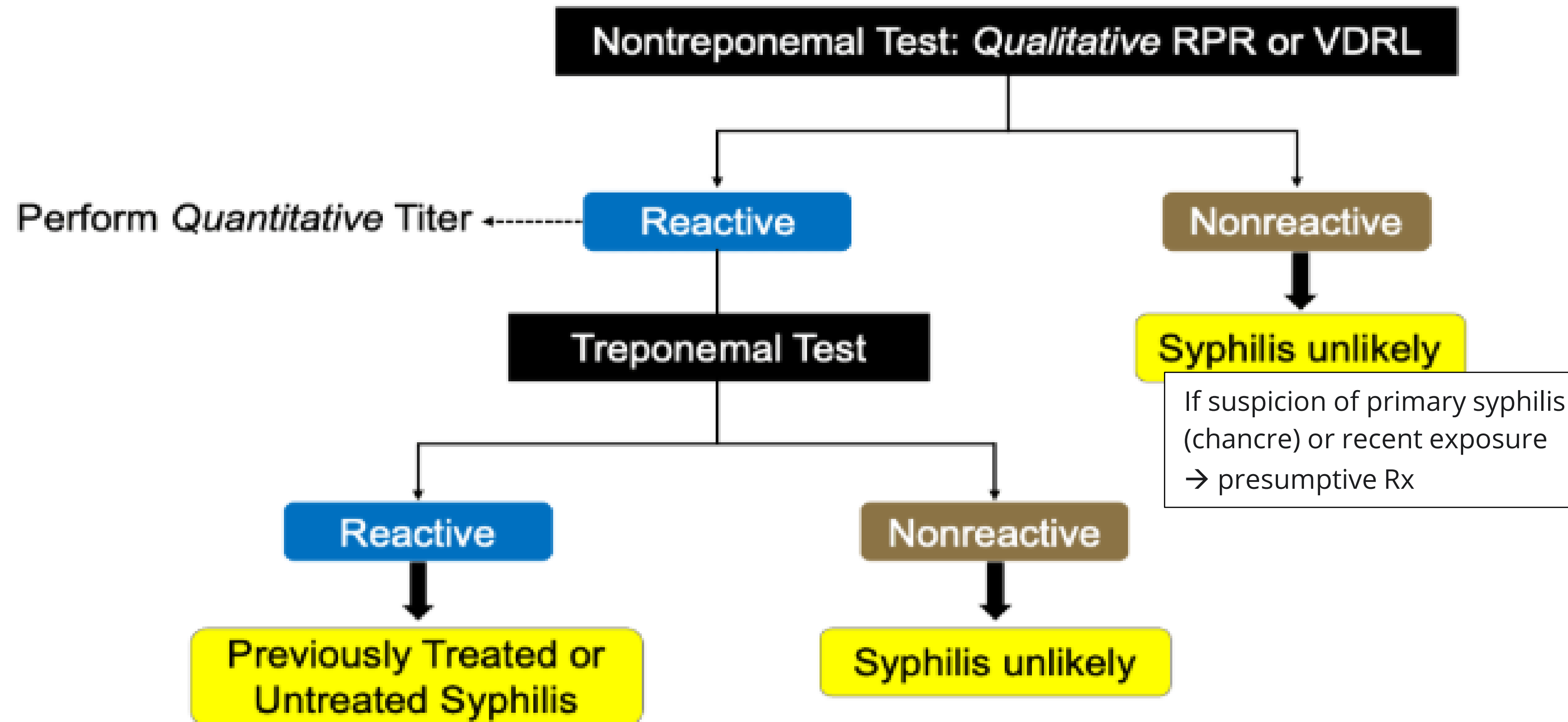

Figure 10. Syphilis Serologic Screening—Traditional Sequence Algorithm

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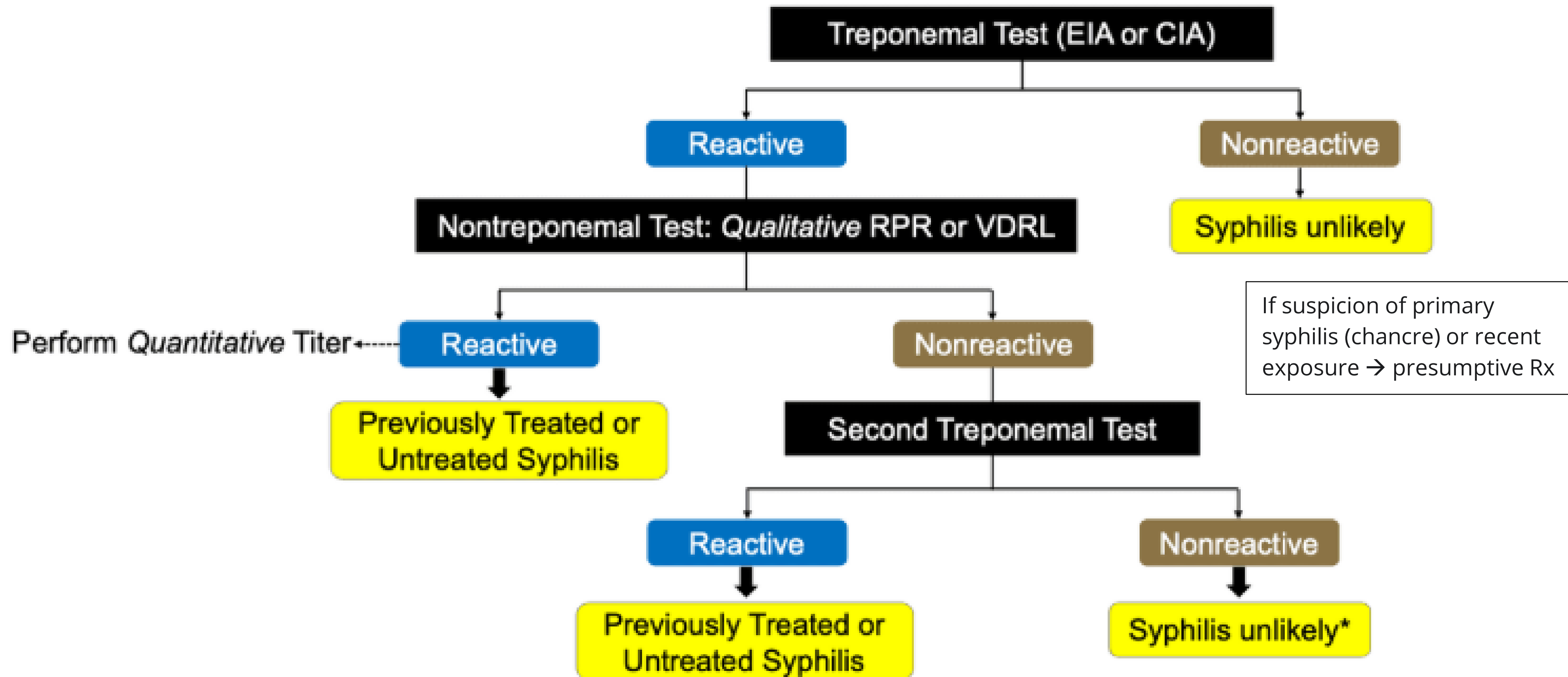
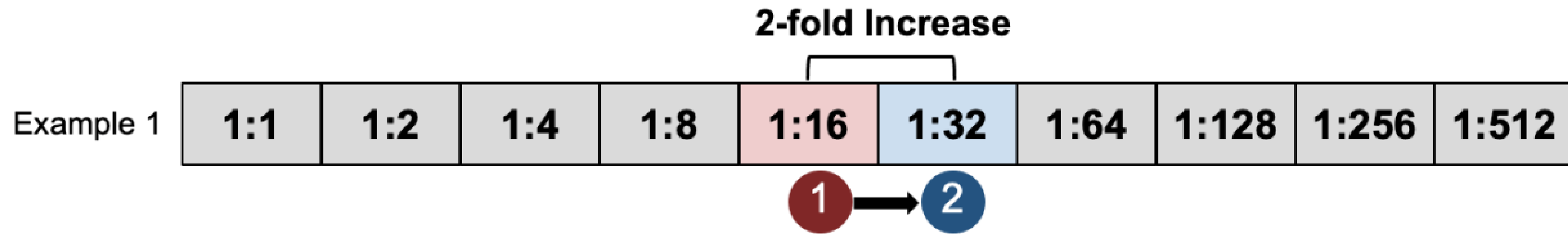
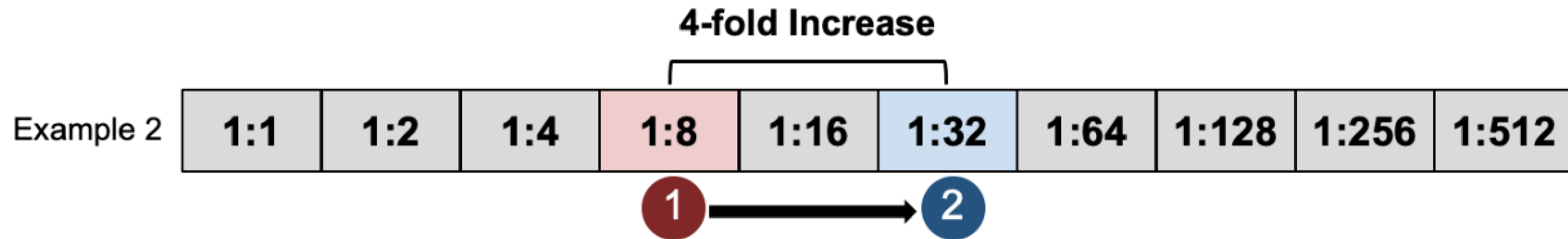


Figure 9. Syphilis Serologic Screening—Reverse Sequence Algorithm

If suspicion of primary syphilis (chancre) or recent exposure → presumptive Rx





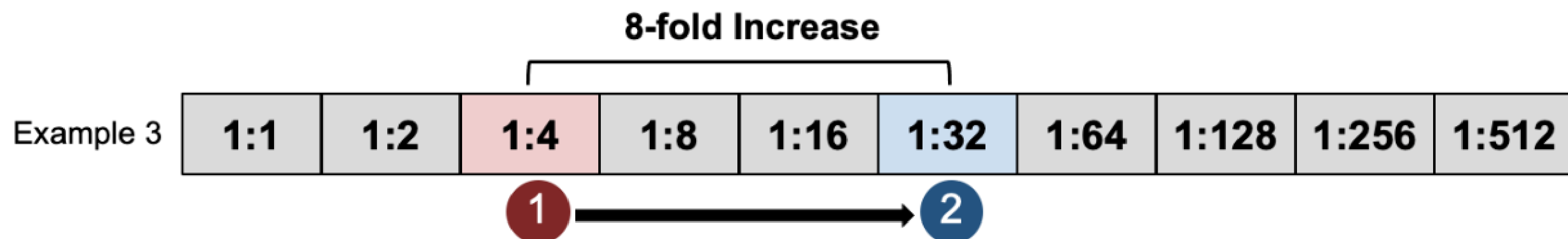


Figure 25 - Examples of Increases in Nontreponemal Titers

This graphic shows three examples of increases in nontreponemal titers when comparing two tests. Test number 1 is represented as red and test number 2 as blue.

Illustration by David H. Spach, MD

Screening Syphilis Ab positive → Reflex to RPR

→ if RPR is negative → TP-PA

→ if RPR is positive it will provide the titer

Questions to ask

1. Symptoms: primary vs. Secondary vs. non-symptoms (latent) vs. Neuro-syphilis (eyes, ears, meninges)
2. Exposure to someone with primary, secondary, or early latent and when
3. History of syphilis
4. Prior testing (when, results) date and results of the most recent serologic test for syphilis, 4x increase or decrease
5. History of Rx (when, what)

- LPHD may be able to provide information on whether the person has syphilis in the past, including serologic test results and treatment history. Information from other jurisdictions (or states) may also be available.

1. **Pregnancy**
2. **Allergies** (PCN, doxycycline)

Presentation	Criteria	Stage	Treatment
Symptoms of primary or secondary syphilis			No PCN allergy Benzathine PCN 2.4 M U IM x 1 TRUE PCN allergy Doxycycline 100 mg PO bid for 14 days
Asymptomatic	• No hx of syphilis/Neg. test < 1 yr • Prior Rx, RPR ≥ 4-fold increase < 1 year	Early latent	
	• No hx of syphilis/Neg. test > 1 yr • Never been tested • No Rx/incomplete Rx/spacing between doses > 10 days • Prior Rx, RPR ≥ 4-fold increase > 1 year	Late Latent	No PCN allergy Benzathine PCN 2.4 M U IM weekly x 3 TRUE PCN allergy Doxycycline 100 mg PO bid for 28 days
	• Prior Rx, RPR < 4-fold increase		No treatment indicated
Neurosyphilis, Ocular, Oto-syphilis			Aqueous crystalline penicillin G 3–4 million U IV Q4 hours or continuous infusion, for 10 days
			TRUE PCN allergy: IM or IV ceftriaxone 1–2 g/day for 10 days can be used as an alternative treatment

***Except if Pregnant, allergic to PCN, Desensitize

Resuming Sexual Activity:

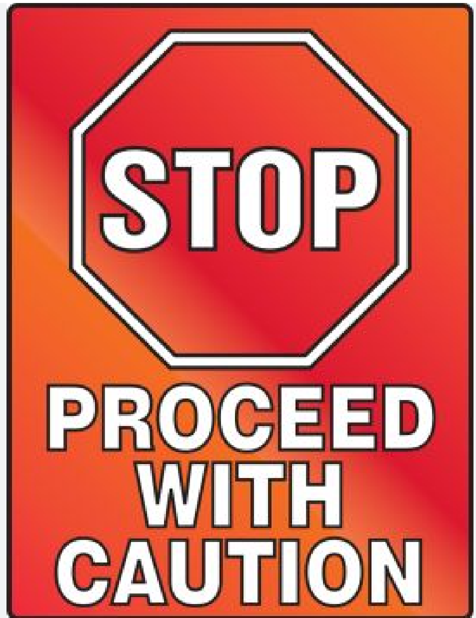
They should abstain from sexual activity until the following criteria are met:

(1) At least 7 days have elapsed since completing syphilis treatment

(2) All mucosal and skin lesions have resolved, and

(3) Sex partners have been treated for syphilis.

Comprehensive sexual health



- **Counseling** on how to reduce STI in the future
- **Partner notification** for all sex partners in the prior 90 days
- **Expedited partner therapy** not recommended for the sexual contacts of persons with syphilis.
- **Other STI testing** Chlamydia/gonorrhea NAAT oral, rectal, urine), trichomonas, HCV/HBV
- **HIV testing, HIV PrEP** indication history of bacterial STI in the last 6 M, discuss and offer
- **Doxycycline PEP** 200-mg single dose within 72 hrs after a condomless sexual encounter, prevent chlamydia, syphilis, and gonorrhea. Doxy PEP has been shown to be effective **for MSM** in several randomized trials.
- **Immunization** routine immunization, MPOX, Hep B, HPV, etc.
- **Follow – up testing** schedule appointment, repeat testing to document **adequate response to Rx, fourfold decrease in titers.**

A 53-year-old man is diagnosed with primary syphilis based on a non-painful genital ulcer. He reports one new male and one female sex partner in the past year. Both sex partners are contacted and instructed to come to the public health department for evaluation.

The female sex partner reported sexual contact with the man about 3 weeks ago. She has no symptoms and says she had negative testing for STIs and HIV about 6 months ago. No antibiotic allergies. **Which one of the following options should be recommended for the female sex partner regarding her management as a syphilis contact?**

- A. She does not need further evaluation or treatment at this time since she is asymptomatic
- B. Order serologic tests for syphilis and treat only if the syphilis test is positive
- C. Order serologic tests for syphilis and treat with a single dose of intramuscular benzathine penicillin G 2.4 million units before results return
- D. Defer serologic testing for syphilis for 3 weeks and treat only if the syphilis test is positive

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Post-treatment follow up

Extremely important to document response to therapy and to reevaluate for reinfection, **clinically** and **serologically by repeating RPR**

Primary and Secondary Syphilis

- **Persons without HIV,** re-examine clinically and serologically **at 6 and 12 months post-Rx**. Allow 1 year to see if the titers have declined appropriately (4-fold decrease)
- **PWH**: post-Rx follow-up at 3, 6, 9, 12, and 24 months; allow up to 2 years for response

Latent Syphilis

- **Persons without HIV** follow-up at 6, 12, and 24 months.
- **PWH** follow-up should occur at 6, 12, 18, and 24 months.

Allow up to 2 years to determine if the titers have declined appropriately

Case 1

- A 33 year old female patient with HIV well controlled with CD4 of 550, presents to urgent care with diffuse maculopapular rash involving palms and soles. Her LMP was 3 months earlier.

- Tests revealed Syphilis Ab +, RPR 1:64, urine pregnancy test positive

Screening Syphilis Ab positive → Reflex to RPR

→ if RPR is negative → TP-PA

→ if RPR is positive it will provide the titer

Questions to ask

1. Symptoms: primary vs. Secondary vs. non-symptoms (latent) vs. Neuro-syphilis (eyes, ears, meninges) → **Secondary syphilis**
2. Exposure to someone with primary, secondary, or early latent and when → **she had a new boyfriend 4 months ago**
3. History of syphilis → **No**
4. Prior testing (when, results) date and results of the most recent serologic test for syphilis, 4x increase or decrease → **Not previously tested**
5. History of Rx (when, what)
6. **Pregnancy**
7. **Allergies** (PCN, doxycycline) → **no allergies**

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- Tests revealed Syphilis Ab +, **RPR 1:64,** urine pregnancy test positive
- **Benzathine PCN 2.4 M U IM x 1**
- **6 months later, she delivers a healthy boy**
- **RPR repeated 6 months after Rx is RPR:1:32 (not gone 4X decline), RPR 1:16**
- What do you do?

Serological non-response management

No

- **Are there any neurologic, ocular, otic neurologic symptoms?**
- Rx accordingly

No

- **Did you wait long enough for the titers to decline?**
- Keep following

No

- **Did the patient get reinfected or is the patient pregnant?**
- Re-treat

No

- **Is the titer > = 1:64?**
- Consider CSF exam

No

- Keep followingthe titers or Rxwith PCN x 1 IM

Case 2

- A 47-year-old man with a **positive RPR test (titer of 1:64)** is referred from the PHD for further evaluation and treatment of syphilis.
- He reports having a total body rash and low-grade fever that resolved approximately 3 weeks ago.
- He reports new severe headaches in the past week, associated with nausea, vomiting, and mild photophobia. The headaches have not resolved with over-the-counter medications.
- He has not had prior testing or treatment for syphilis.
- A recent HIV-1/2 antigen-antibody test is negative.

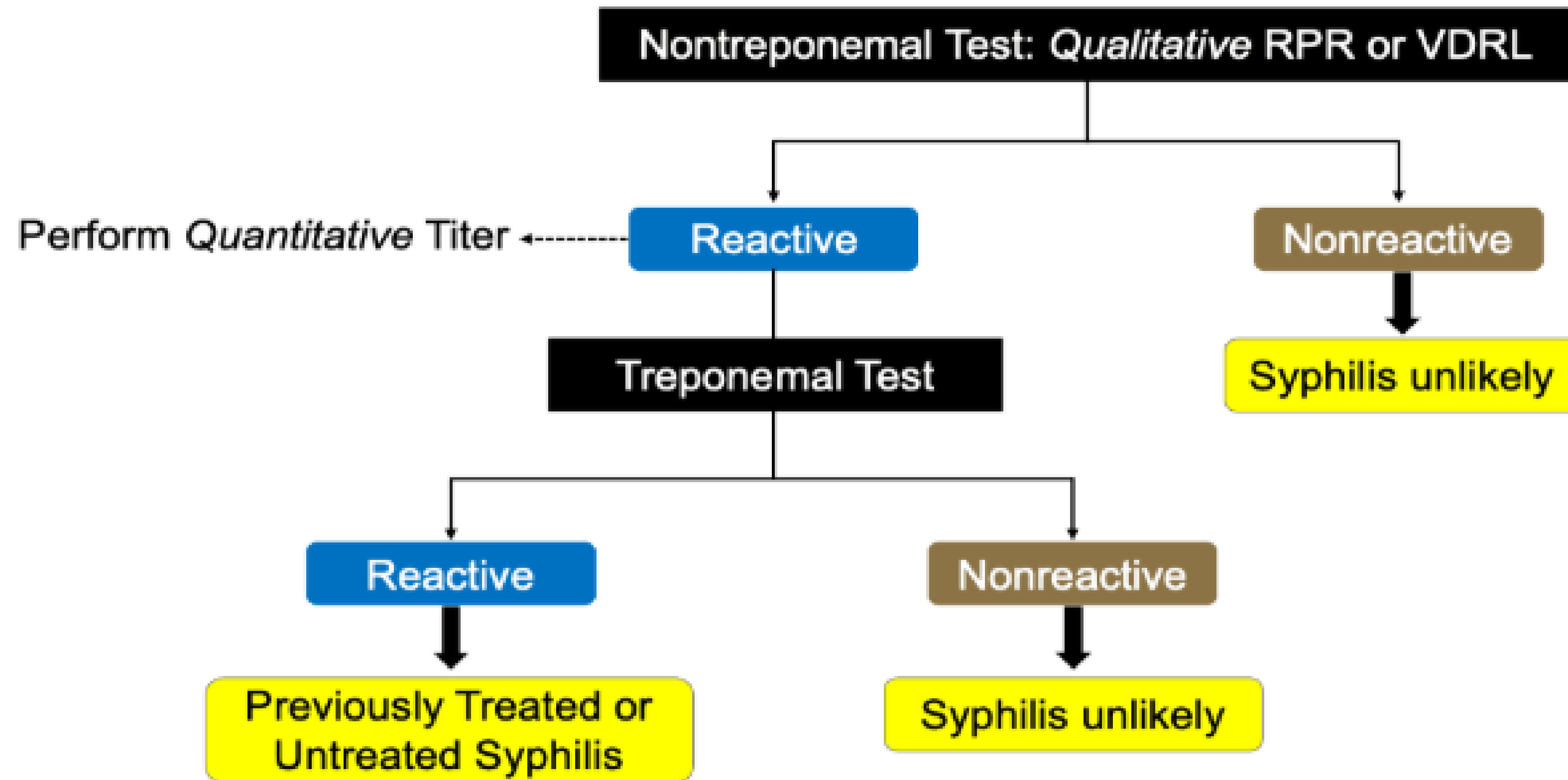
Does the patient have syphilis?

- Confirmation with treponemal test, positive

What stage?

Secondary syphilis, possibly neurosyphilis

Diagnosis of syphilis – screening



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How to diagnose neurosyphilis?

No
- **CSF VDRL + in the absence of gross blood contamination**
- Definite neurosyphliis

No
- **CSF > 5 WBC in absence of another plausible Dx**
- Presumptive neurosyphlis

YES
- **Elevated CSF protein**
- No --> neurosyphilis ruled out

YES
- **CSF treponemal antibodies (FTA-ABS)**
- No -> neurosyphilis ruled out

YES
- Presumptive neurosyphilis because of the elevated CSF protein

Thank you

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