The Return of Syphilis

MICAH DERBY, DO, AAHIVS

Objectives

- Understanding the etiology, symptoms, risk factors of syphilis, and test of syphilis
- Recognizing the varieties of syphilis
- Describing the complexities of syphilis treatment

Disclosures:

No Disclosures

Contact:

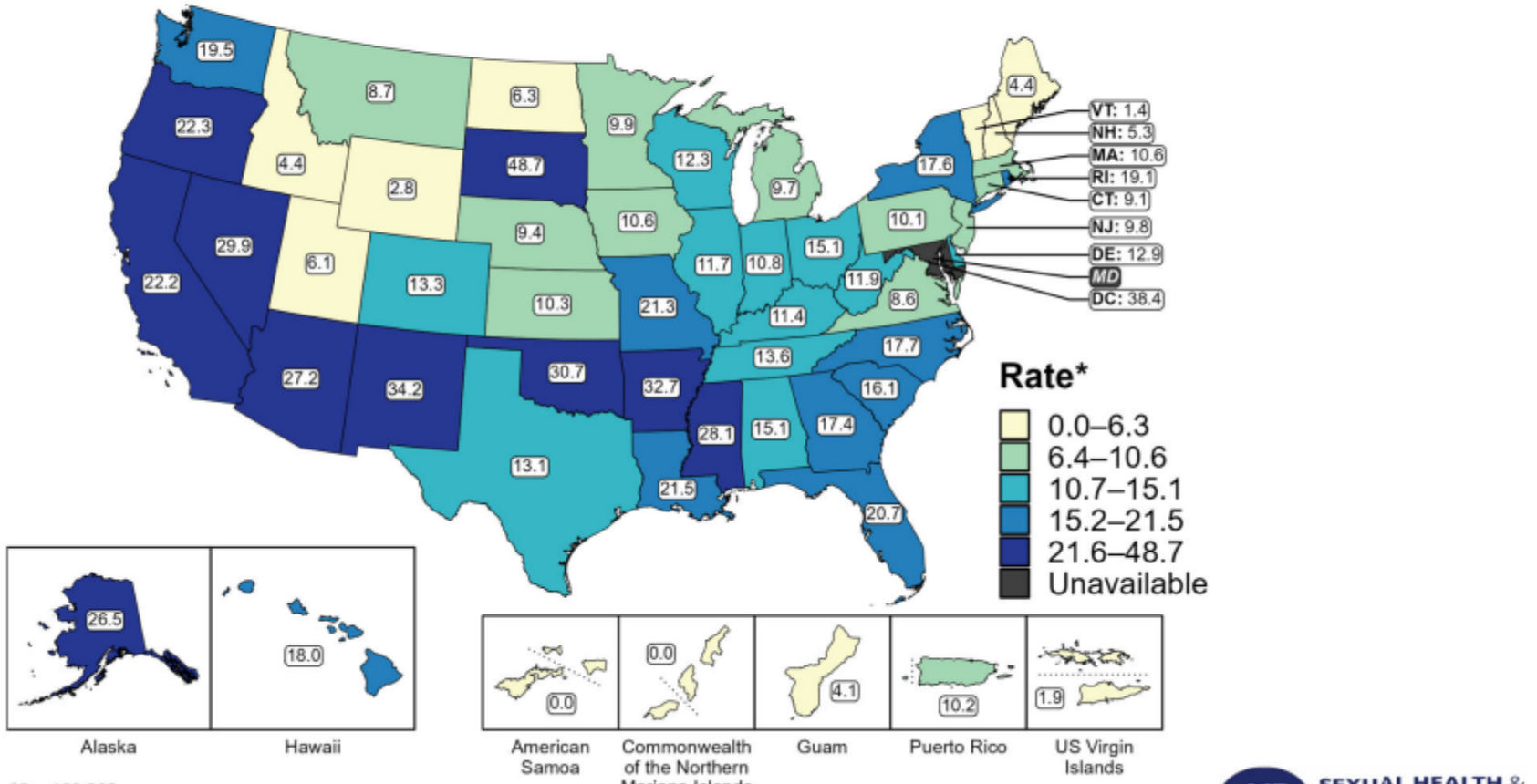
Micah.derby@okstate.edu

Syphilis and Oklahoma

- Oklahoma health department has noticed a "sharp increase" in cases within state
  - Rate has been increasing since 2000
- Oklahoma is the 4th highest rate in the nation for primary and secondary syphilis
  - New Mexico, Arkansas, and South Dakota
  - 30.2% rate increase from 2020 to 2021
- Increase in cases is largely believed to be due to "fallout from the pandemic and increase in methamphetamine use."
- Congenital syphilis
  - 3 cases in 2016
  - 53 cases in 2020
  - 80 cases in 2021
  - In 2020, Oklahoma was the 5th in the nation with a rate of 1 / 100,000 live births
  - In 2021, Oklahoma was the 6th in the nation
- 8-fold increase in cases among women from 2014 – 2018

Primary and Secondary Syphilis

Rates of Reported Cases by State and Territory, United States, 2021

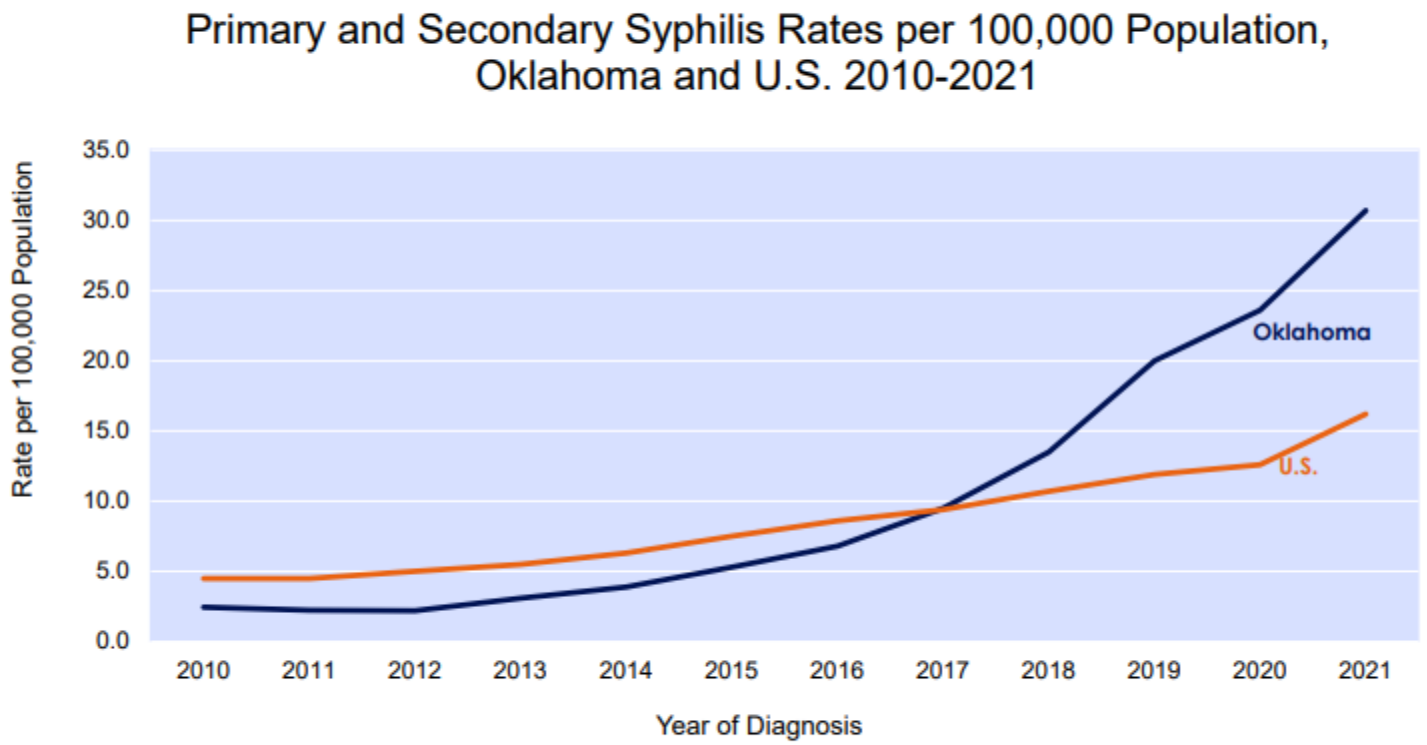


*Per 100,000.

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

SEXUAL HEALTH & HARM REDUCTION SERVICE

Primary and Secondary Syphilis

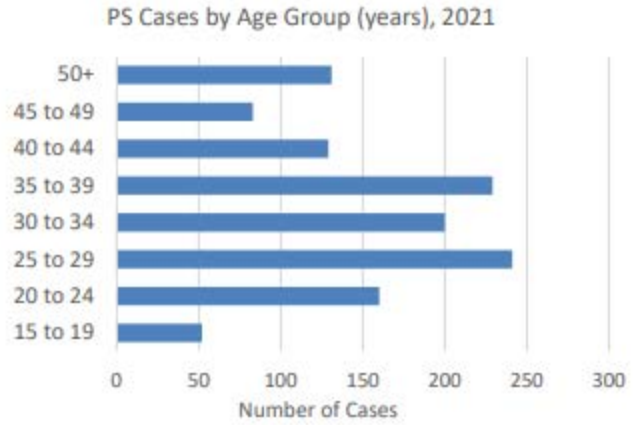


SEXUAL HEALTH & HARM REDUCTION SERVICE

Primary and Secondary Syphilis

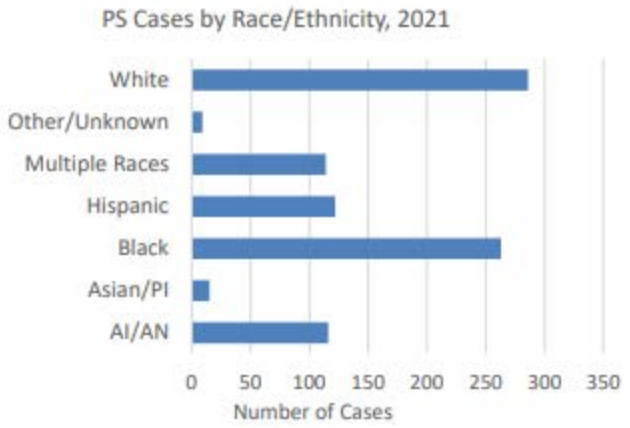
By Age Group

- 25-29 years age group had the highest rate: 90.3 per 100,000 (241 cases; 19.7%).
- 35-39 years age group had the second highest rate: 85.2 per 100,000 (229 cases; 18.7%).



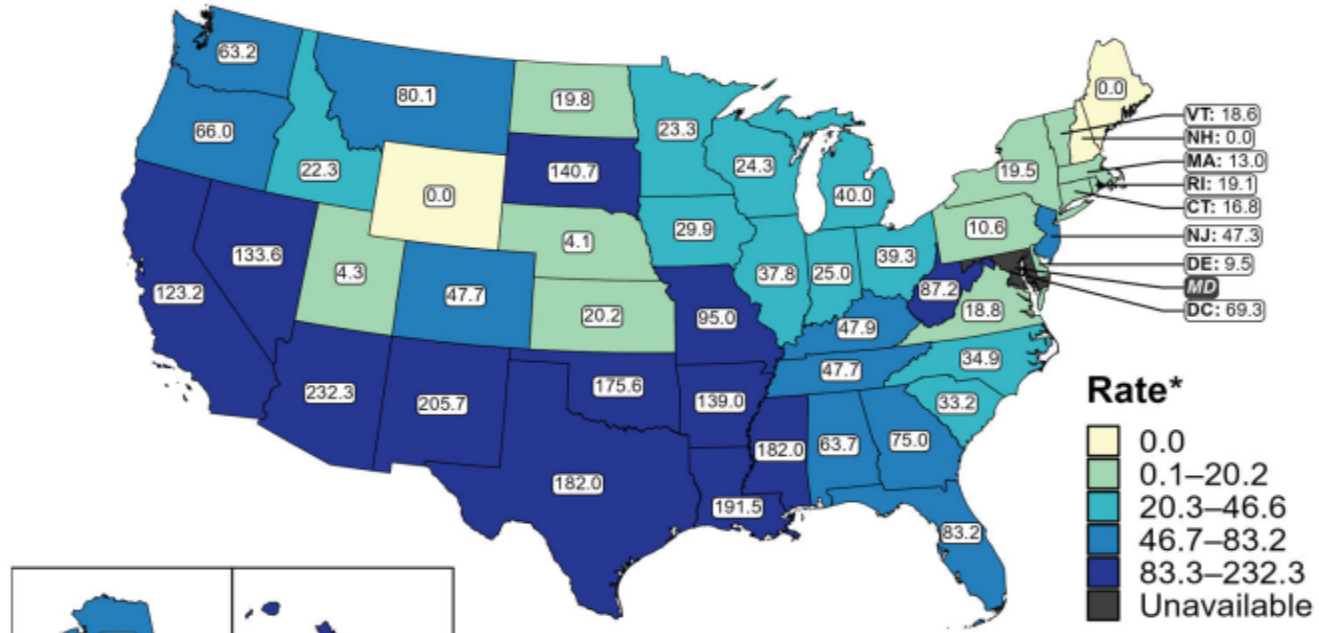
By Race/Ethnicity

- Blacks had highest rate: 88.8 per 100,000 (263 cases; 21.5%), nearly 4 times the rate of whites.
- Whites made up 47.8% of cases at a rate of 23.0 per 100,000.



Congenital Syphilis -

Rates of Reported Cases by Year of Birth and State and Territory, United States, 2021



*Per 100,000 live births

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

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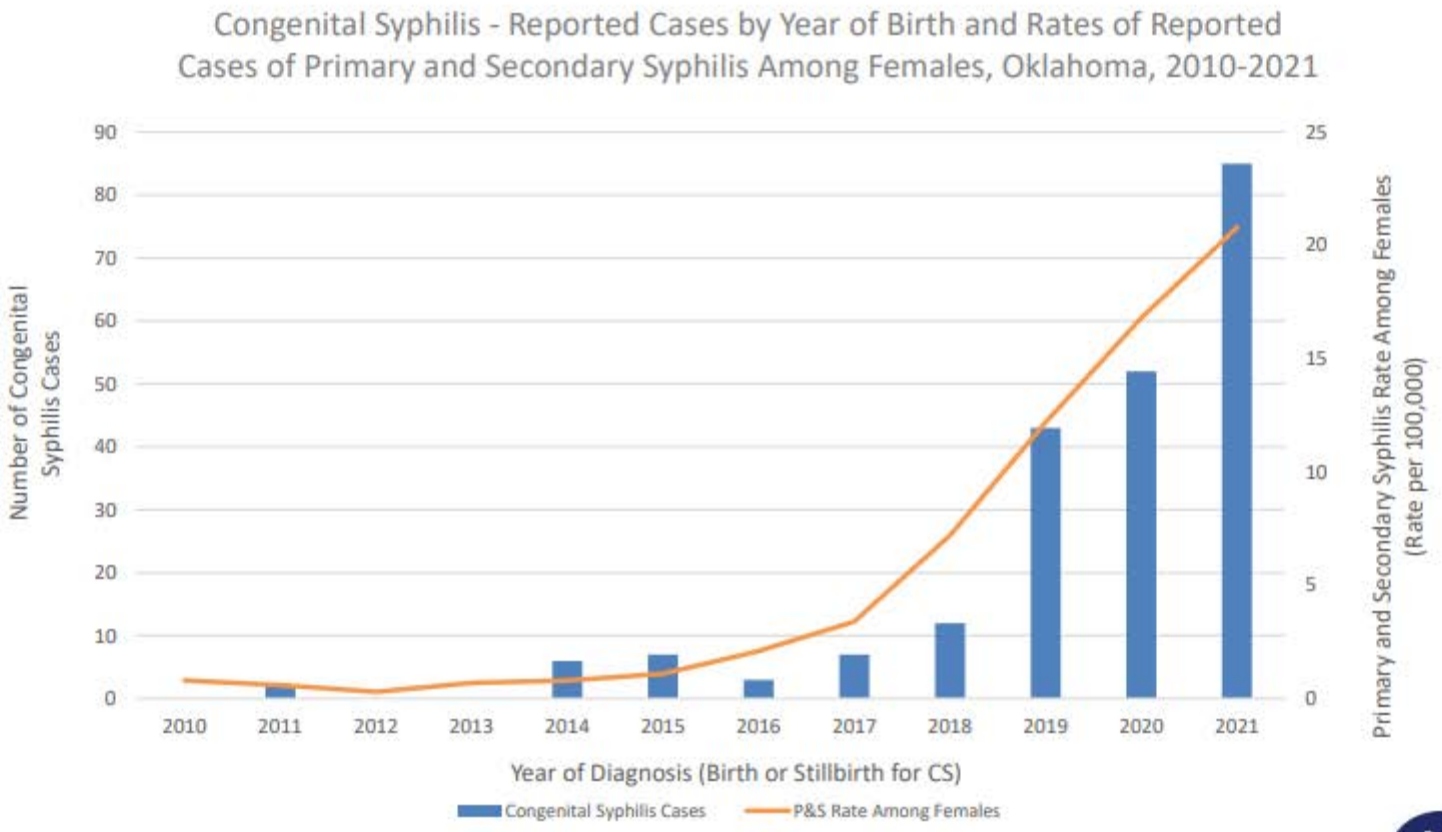
Congenital Syphilis in Oklahoma, 2010-2021



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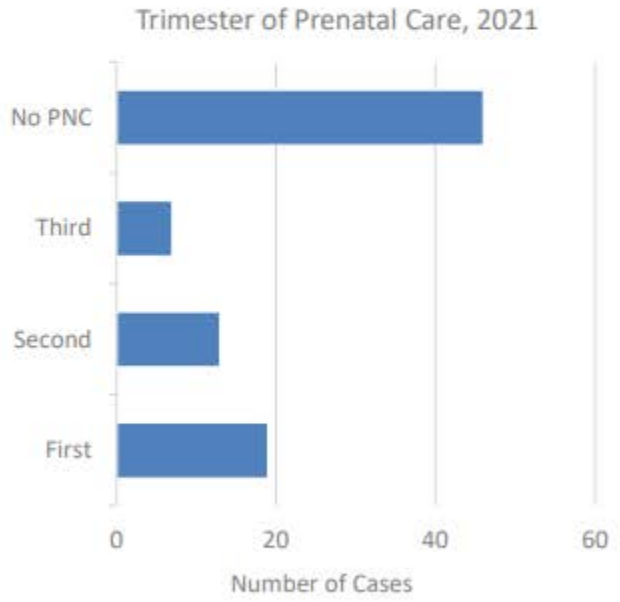
Congenital Syphilis Cases in 2021, by Prenatal Care and Screening

- **45.9%** (39/85) had prenatal care (PNC).
- Of those with PNC:
  - **64.1%** were tested for syphilis at their first appointment.
  - **59.0%** were tested at 28-32 weeks gestation
- **89.4%** (76/85) were tested for syphilis at delivery.



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Syphilis Basics

- Bacterium: *Treponema pallidum, spirochete*
- Transmitted by direct contact *with lesion:*
  - Vaginal lesion
  - Penial lesion
  - Anal lesion
  - Oral lesion (lips / mouth)
- Not transmitted by:
  - Toilet seats
  - Doorknobs
  - Swimming pools
  - Hot tubs
  - Bathtubs
  - Sharing eating utensils or clothing
- “The Great Pretender”

Who Do I Test?

- People who are high risk for contracting an STI:
  - Sexually active person
  - Patient with inconsistent condom usage
  - Previous history of STI
  - MSM or Bisexual
  - Commercial sex worker
  - HIV patient
  - Incarcerated patient
  - Patient with known history of exchanging sex for drugs or money
  - Patient taking PrEP
  - Patient whose partner tested positive for syphilis
  - Anyone who asks to be tested
  - Pregnant patient

Primary Syphilis

- Skin lesion: Chancre
- Number of lesions: Typically, one, multiple can be seen in HIV
- Features: Firm, raised, round, painless, nonexudative ulcer,
- Local lymphadenopathy present: Yes!
- Sites of infection: Penis, vagina, oral pharynx or anus (areas of inoculation)
- Incubation period: 3 days - 12 weeks
- Median incubation period: 21 days
- Resolution: Heals without treatment in 3 – 6 weeks
- Untreated: Progression to the next stage secondary syphilis

Primary Syphilis: Chancre

Secondary Syphilis

- Skin lesion: Symmetric macular or papular eruptions
- Number of lesions: Diffuse or local
- Features: Discrete copper, red or reddish brown, scaly but also may be smooth
- Itching: Typically no, until it does
- Painful lymphadenopathy present: Yes!
- Sites of infection: Trunk, extremities, palms and soles of feet
- Other features: Headache, malaise, anorexia, sore throat, myalgias, and weight loss
- Incubation period: Weeks to months after primary syphilis
- Resolution: Heals without treatment, can relapse up to 5 years later if left untreated

Secondary Syphilis: Macular / Papular Rash

Secondary Syphilis: Macular / Papular Rash

Secondary Syphilis: Pustular

- Skin lesion: Small pustular syphilide, large pustular syphilide, flat pustular syphiloderm, and pustular-ulcerative syphilide
- Number of lesions: Diffuse or local
- Itching: Typically no, until it does
- Painful lymphadenopathy present: Yes!
- Sites of infection: Anywhere
- Other features: Headache, malaise, anorexia, sore throat, myalgias, and weight loss
- Incubation period: Weeks to months after primary syphilis
- Resolution: Heals without treatment, can relapse up to 5 years later if left untreated

Secondary Syphilis: Pustular

Secondary Syphilis: Mucosal

- Skin lesion: Mucosal patches, whitish erosion, split papules, condylomata lata
- Sites of infection: Oral mucosa, tongue, oral commissures, moist areas of the mouth and perineum; typical eruptions are localized to where the primary lesion once erupted
- Features: Large, raised, grey or white lesions
- Painful lymphadenopathy present: Yes!
- Other features: Headache, malaise, anorexia, sore throat, myalgias, and weight loss
- Incubation period: Weeks to months after primary syphilis
- Resolution: Heals without treatment, can relapse up to 5 years later if left untreated

Secondary Syphilis: Mucosal

Secondary Syphilis: Condylomata lata

Secondary Syphilis: HIV

- Skin lesion: Severe ulcerations / lues maligna
- Sites of infection: Anywhere
- Features: Large, multiple ulcerations
- HIV: Severely immunocompromised state with non-resolving skin lesions
- Painful lymphadenopathy present: Yes!
- Other features: Headache, malaise, anorexia, sore throat, myalgias, and weight loss
- Incubation period: Weeks to months after primary syphilis
- Resolution: Heals without treatment, can relapse up to 5 years later if left untreated

Secondary Syphilis: Lues Maligna

Secondary Syphilis: Alopecia

Secondary Syphilis: Other Sites of Infection

- Hepatitis: High AST with normal to slightly abnormal ALT
- Gastro: GI tract with extensive infiltrative or ulcerated mucosa; can be misdiagnosed as lymphoma
- MSK: Synovitis, osteitis, periostitis
- Renal: Mild transient albuminuria, nephrotic syndrome or acute nephritis with HTN and AKI

Tertiary Syphilis

- Late syphilis that has become symptomatic:
  - Cardiovascular system (especially aortitis)
  - Gummatous syphilis
  - CNS
- All tertiary syphilis *requires* CSF studies to rule out neurosyphilis

Tertiary Syphilis

- Approximately 25 – 40% of untreated syphilis patients develop tertiary syphilis
- Incubation period: 1 – 30 years after primary syphilis
- Patient may have had asymptomatic primary and secondary syphilis
- Can manifest in a wide variety of tissues
- Confirmatory late syphilis testing of lesions: Warthin-Starry silver and immunofluorescent staining or PCR along with a reactive treponemal serological test

Tertiary Syphilis: Cardiovascular

- Area affected: Ascending thoracic aorta resulting in dilated aorta with aortic valve regurgitation
- Vasculitis in the vasa vasorum
- Typically, asymptomatic murmur or systolic heart failure
- Timeframe: 15 – 30 years after initial infection from untreated syphilis
- Dissection rarely occurs from syphilis

Tertiary Syphilis: Gummatous

- Rare: Typically reported in individuals with HIV / Immunocompromised patients
- Area affected: Within any tissue: skin, bone, or internal organs
- Skin symptoms: small or large ulceration or granulomatous lesions with a round, irregular, or serpiginous shape
- Visceral gummas: mass lesion, biopsy may result as granuloma

Tertiary Syphilis: Gummatous

Neurosyphilis

- Incubation period: Typically, 25 years after initial infection; however, can happen at any stage of syphilis
- Symptoms: General paresis, headache, meningitis, cranial nerve deficits, stroke, AMS, imbalance, dysphagia
- Physical exam findings: Tabes dorsalis, Argyle Robertson pupils, dysmetria, gait disturbances, debility
- Symptomatic neurosyphilis requires hospitalization

Neurosyphilis: Ocular Syphilis

- Incubation period: Typically, 25 years after initial infection; however, can happen at any stage of syphilis. Most commonly identified in early stages with co-infection with HIV
- Symptoms: Vision loss, painful eye movements, photophobia, floaters, redness
- HIV: Very common in immunocompromised patients
- Ophthalmology: Anterior uveitis, posterior uveitis, or panuveitis
- Emergent evaluation by ophthalmology
- Can result in permanent vision field loss

Neurosyphilis: OtoSyphilis

- Incubation period: Typically, 25 years after initial infection; however, can happen at any stage of syphilis
- Symptoms: Tinnitus, vertigo, sensorineural hearing loss (sudden, unilateral or bilateral)
- Less diagnosed as compared to ocular syphilis
- Emergent evaluation by ENT
- Can result in permanent hearing loss

Neurosyphilis: HIV

- More likely and more rapidly to progress to neurosyphilis
- Greatest risk with CD4 ≤ 350 and / or in combination with RPR ≥ 1:32
- If patient has a positive serologic evidence of syphilis infection and a compatible neurologic abnormality on examination and any 1 of the following:
  - Elevated protein, WBC > 20 cells, reactive CSF – VDRL
  - Treat the patient

Latent Syphilis

- Latent syphilis diagnosis are time dependent
- Patient is asymptomatic
- Based strictly upon serological testing
- Two types of latent syphilis: early, latent syphilis; late, latent syphilis

Early, Latent VS Late, Latent Syphilis

- Keyword: *Asymptomatic*
- Early, latent syphilis definition: Initial infection occurred within the previous 12 months
- Late, latent syphilis definition: Initial infection occurred greater than 12 months ago
  - Patient without known syphilis breakout
  - Previously infected with syphilis, and RPR has increased by four-fold
  - Patient having symptoms of primary or secondary syphilis without seeking treatment
  - Known sexual exposure to someone with syphilis

If the timing is not known: Late, latent syphilis is assumed

Facts about Latent Syphilis

- Patient with late, latent syphilis, are they infectious? No, they do not have a lesion present that can transmit disease
- Patient with early, latent syphilis, are they infectious? Yes, patient may have transmitted to his current sexual partner, and provider may have missed a small, painless lesion on physical exam
- Pregnant women with late, latent syphilis can transmit to their fetus up to 4 years after inoculation

Why do we need to know the facts about which latent syphilis we are treating? Stay tuned

Pregnancy and Syphilis Treatment

- Treatment does not change in pregnancy, but if Penicillin allergic, desensitize. Do not use alternative treatments
- Screen during 1st appointment, 3rd trimester, and at birth in high-risk patient
- Screening during 1st appointment and birth in patient that are not high risk
- Congenital syphilis complications:
  - Blindness
  - Deafness
  - Seizures
  - Low birth weight
  - Bone growth irregularities
  - Stillborn

Serological Testing

- **Non-treponemal tests:**
  - Rapid plasma reagin (RPR)
  - Venereal disease research laboratory (VDRL)
  - Toluidine red unheated serum test (TRUST)
- **Treponemal tests** :
  - Fluorescent treponemal antibody absorption (FTA-ABS)
  - Microhemagglutination test for antibodies to T. pallidum (MHA-TP)
  - T. *pallidum* particle agglutination assay (TPPA)
  - T. *pallidum* enzyme immunoassay (TP-EIA)
  - Chemiluminescence immunoassay (CIA)

Nontreponemal Tests

- Nonspecific and not definitive
- Reported with a titer value (eg. 1:64)
- Titers wane over time even without treatment
- Therapy accelerates the decline of the antibody
- More cost effective than treponemal testing

Nontreponemal Tests

- Causing a false positive:
  - IV drug use
  - Lyme disease
  - Acute infections
  - Malaria
  - Pregnancy
  - Systemic lupus erythematosus and some other autoimmune disorders
  - Tuberculosis
  - HIV
  - Recent immunization

RPR Sensitivity:

- Primary syphilis 86%
- Secondary syphilis 100%
- Latent syphilis 73%

Treponemal Tests

- More specific than nontreponemal test
- Results as reactive or nonreactive
- Remain positive for life (usually)
  - If treated during primary syphilis, may become seronegative within 2-3 years
- More complex and expensive compared to nontreponemal tests
- Traditionally used as a confirmatory test
- New tests have been developed resulting in simple use

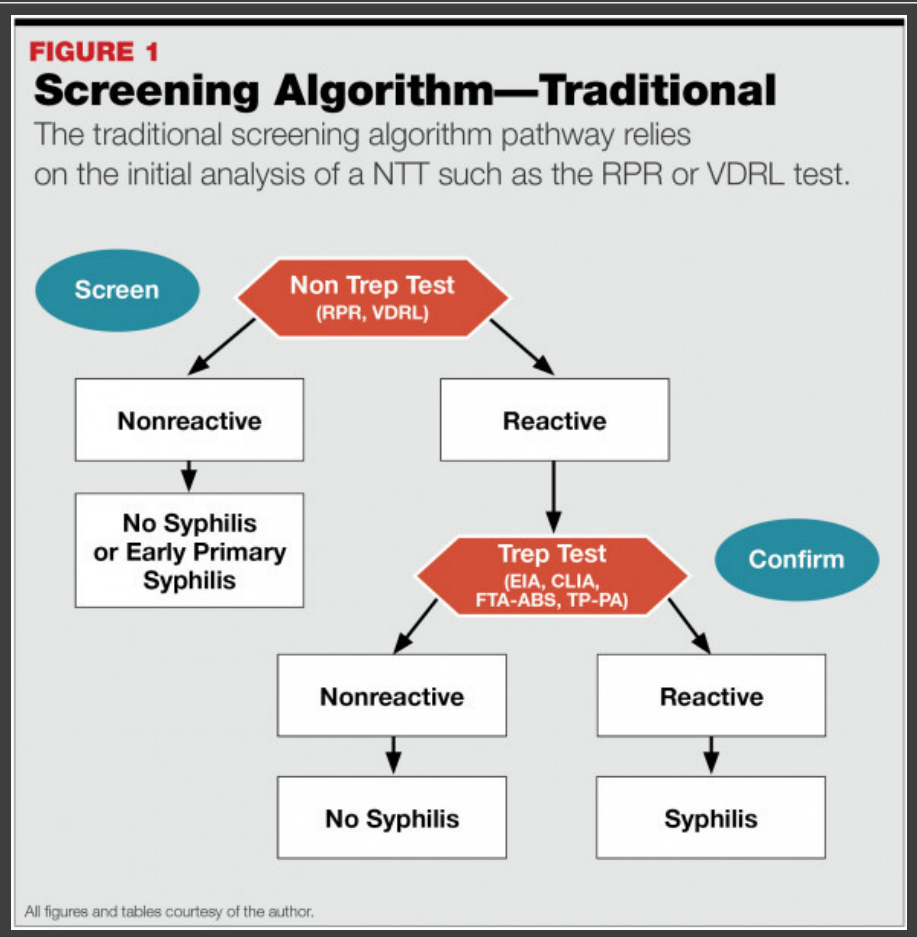
Lab Facts about Neurosyphilis

- CSF-VDRL highly specific, poor sensitivity
  - May be falsely negative 70% of the time
  - If CSF – VDRL is negative: Neurosyphilis is not ruled out.
    - Patient with HIV CSF cell count > 20 cells/microL; elevated protein
    - Patient without HIV CSF WBC>5 and CSF protein >45
- If CSF-VDRL is negative, but highly suspect neurosyphilis, obtain a CSF FTA-ABS or TP-PA
  - These test are less specific but very sensitive
  - CSF FTA-ABS test, less specific, highly sensitive for neurosyphilis; if negative, neurosyphilis unlikely

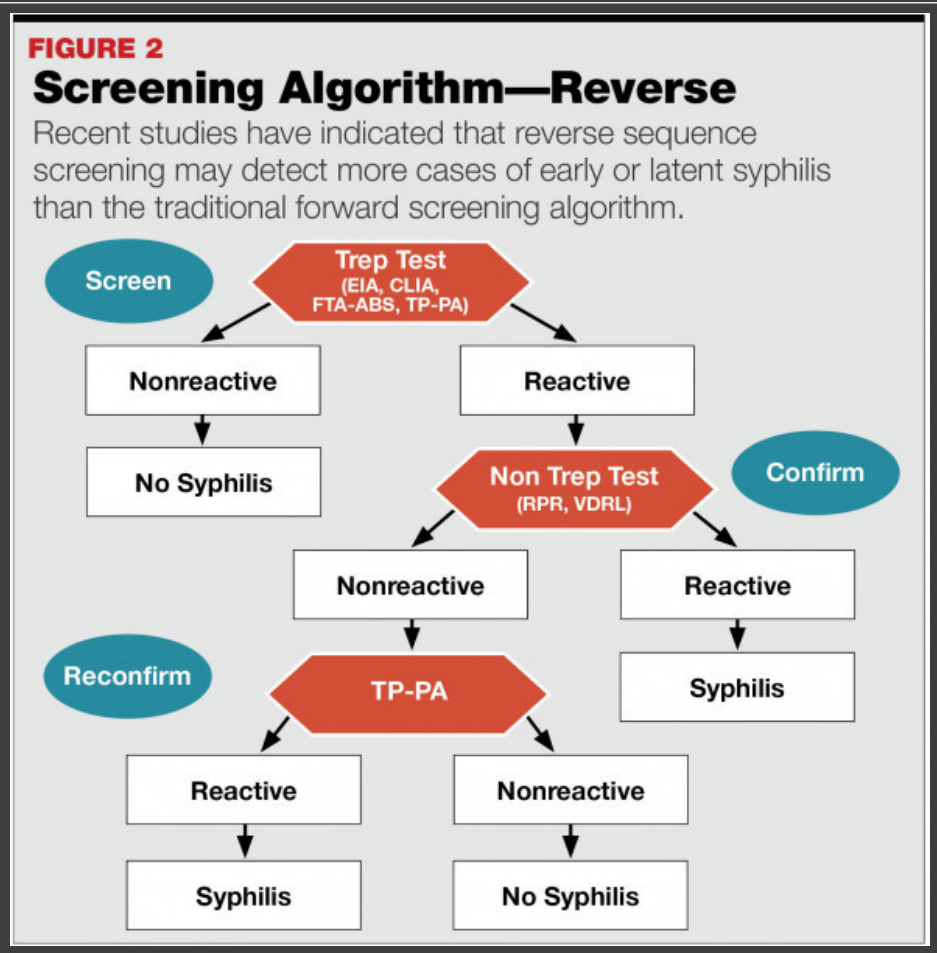
Honorable Mentions

- Rapid serologic testing
- Dark field microscopy
- Point of care serologic test
- Direct fluorescent antibody testing
- Polymerase chain reaction

Syphilis Screening: Traditional



Syphilis Screening: Reverse



Treatment

- Primary/Secondary/Early Latent:
  - 2.4 million units benzathine Penicillin G IM x 1
- Late Latent/Tertiary:
  - 2.4 million units benzathine Penicillin G IM weekly x 3
- Oto/Optic/Neurosyphilis:
  - Desensitize if PCN-allergic
    - IV Penicillin G 18-24 million units daily x 10-14 days
      - Post IV treatment: 1 – 3 weeks of Penicillin G IM 2.4 million units can be considered
    - Procaine Penicillin 2.4 million units IM daily + probenecid 500 mg QID X 10-14 days
      - Considered in those with IV drug history

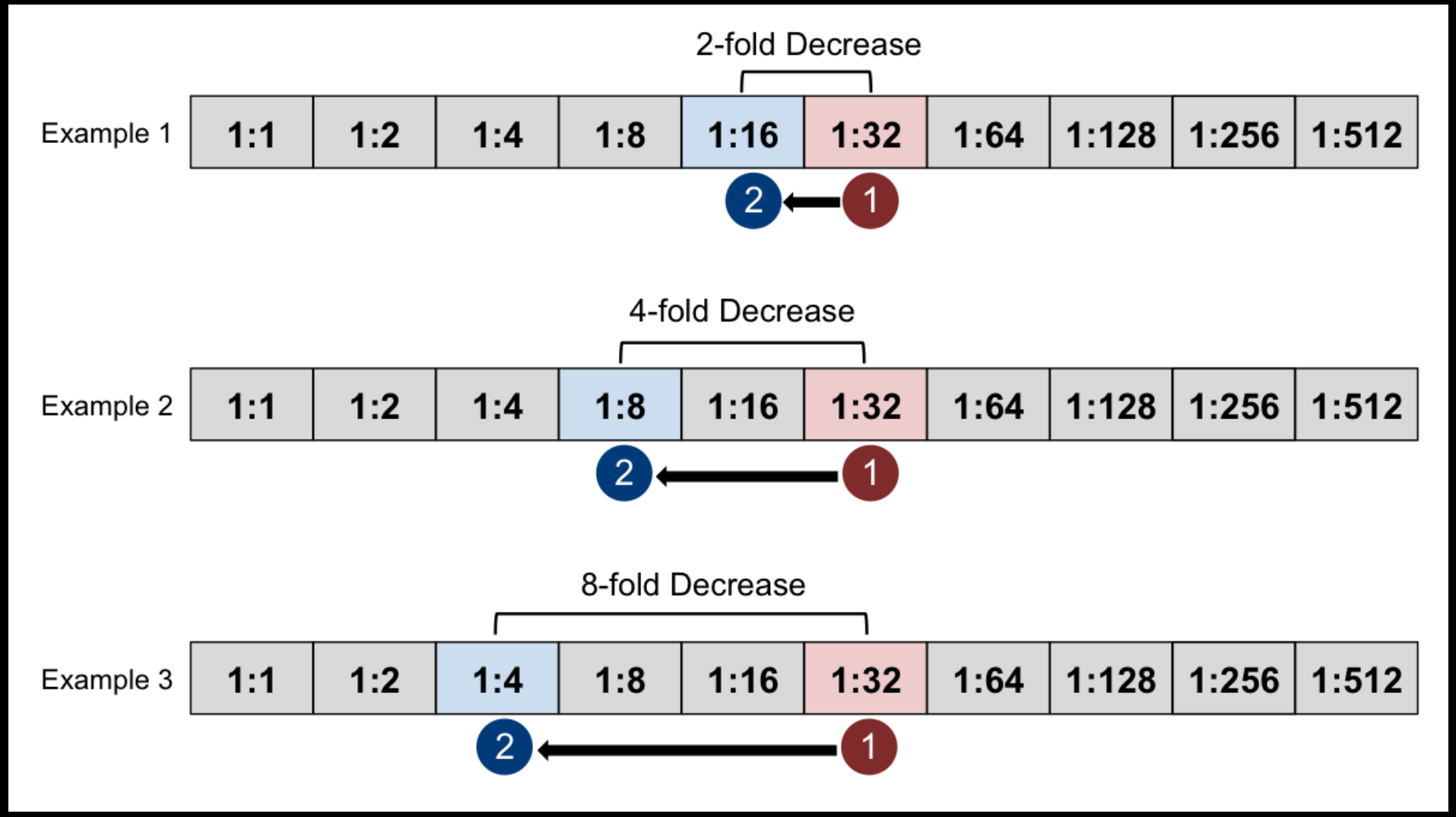
Nonpenicillin Treatment Alternative

- Not first line therapy
  - Primary, secondary, and early, latent syphilis
    - Doxycycline 100 mg PO BID X 14 days
    - Ceftriaxone 1 – 2 grams daily either IM or IV for 10 – 14 days
  - Tertiary and late, latent syphilis
    - Doxycycline 100 mg PO BID X 28 days
    - Ceftriaxone 2 grams daily either IM or IV for 10 – 14 days
  - Neurosyphilis
    - Ceftriaxone 2 grams daily either IM or IV for 10 – 14 days

Post Treatment Monitoring

Monitor RPR:

- Primary, secondary, tertiary, early, latent syphilis, and neurosyphilis
  - Follow RPR at 6 and 12 months
- Late, latent syphilis
  - Follow RPR at 6, 12, and 24 months
  - If RPR does not decrease by four-fold in these time periods, patient is either infected again or did not respond to initial treatment
- Neurosyphilis post treatment:
  - Serum RPR drops by 4-fold, assumptions can be made that the CSF has returned to normal. No follow-up CSF studies required


2-fold Decrease
Example 1
1:1
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
2
1
4-fold Decrease
Example 2
1:1
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
2
1
8-fold Decrease
Example 3
1:1
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
2
1

Treatment Failure

- Signs or symptoms that persist or recur
- Four-fold increase or greater in titer sustained for more than 2 weeks
- Nontreponemal titers do not decrease four-fold 12-24 months after therapy
- All treatment failures requires CSF exam
- Retreatment with benzathine Penicillin G 2.4 million units IM weekly x 3 weeks

References

Syphilis | NIH (hiv.gov)
Syphilis cases increasing in Oklahoma. Here's what to know about it (oklahoman.com)
Table 20. Congenital Syphilis — Reported Cases and Rates of Reported Cases by State, Ranked by Rates, United States, 2020 (cdc.gov)
RPR test (ucsfhealth.org)
Syphilis Statistics - STD information from CDC
FTA-ABS test Information | Mount Sinai - New York
Part 1 of a 2-part series: Navigating Syphilis Diagnostic Changes : April 2020 - MedicalLab Management Magazine (medlabmag.com)
Question 4 - Question Bank - National STD Curriculum (uw.edu)
Pictures: Courtesy of Charles Hicks, MD.
Pictures: Courtesy of visualdx.com

Quiz Time!

Patient #1

Asymptomatic

Date 01/01/22	Date 10/01/22
RPR – Negative	RPR – Positive
	Titer 1:32

What is the DX?

- Early, Latent syphilis

What is the TX?

- 2.4 million units of Bicillin X1 dose

Patient #2

Patient has a penial chancre

Date 01/01/21	Date 04/01/22
RPR – Negative	RPR – Positive
	Titer 1:32

What is the DX?

- Primary Syphilis

What is the TX?

- 2.4 million units of Bicillin X1 dose

Patient #3

Patient with ulceration on their knees that has been present for several weeks and continues to grow.
Biopsy consistent with spirochete

Date 01/01/1995	Date 04/01/22
RPR – Negative	RPR – Positive
	Titer 1:32
	Syphilis IgG is positive

What is the DX?

- Tertiary Syphilis

What is the TX?

- 2.4 million units of Bicillin X3 dose 1 week apart

Patient #4

Asymptomatic

Date 01/01/2020	Date 04/01/22
RPR – Negative	RPR – Positive
	Titer 1:32
	Syphilis IgG is positive

What is the DX?

- Late, latent syphilis

What is the TX?

- 2.4 million units of Bicillin X3 dose 1 week apart

Patient #5

Sexually active MSM; asymptomatic but with numbness in his feet

Date 01/01/2020	Date 04/01/22
RPR – Negative	RPR – Positive
	Titer 1:32
	Syphilis IgG is positive

What is the DX?

- Late, latent syphilis

What is the TX?

- 2.4 million units of Bicillin X3 dose 1 week apart

What else is required?

- Lumbar Puncture

Patient #6

Symptomatic with oral lesion – Sexually active MSM

Date 12/01/2021	Date 04/01/22
RPR – Negative	RPR – Negative
	Syphilis IgG is positive

What is the DX?

- Suspect Early syphilis (oral chancre)

What is the TX?

- 2.4 million units of Bicillin X1

Patient #7

Asymptomatic patient with HIV; CD4 count is 150

Date 01/01/22	Date 10/01/22
RPR – Negative	RPR – Positive
	Titer 1:32

What is the DX?

- Early, latent syphilis

What is the TX?

- 2.4 million units of Bicillin X1

What else is required?

- Lumbar Puncture

CSF studies, elevated Protein, elevate WBC, CSF VDRL 1:8

What is the DX?

- Neurosyphilis

What is the TX?

- 24 million units IV Penicillin G q24 hours X 14 days