



# Syphilis

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Southeast AETC

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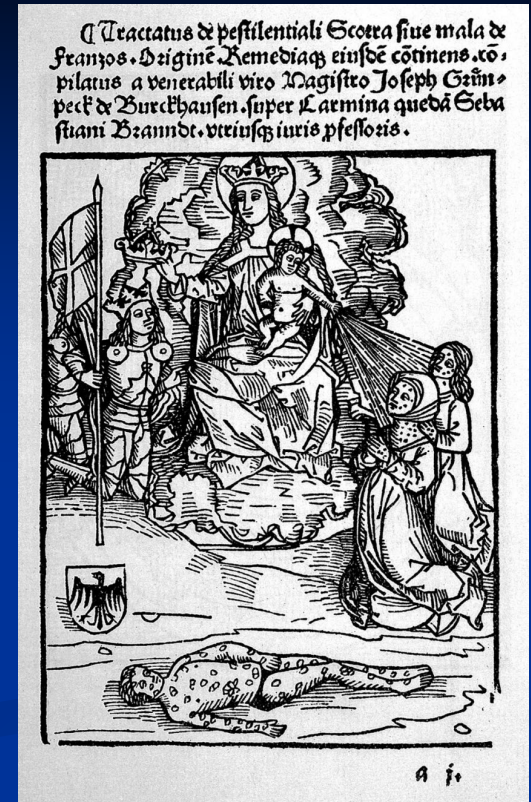


# Syphilis

- Understand marked increase in the incidence of Syphilis and significance.
- Identify the stages of syphilis and recommended treatment.
- Identify symptoms of Neurosyphilis.
- Manage patients after treatment for syphilis appropriately - including identifying patients that require re-treatment or neurologic evaluation.

# Syphilis

- 1500s “The Great Pox”
  - Spread from Italy & France throughout Europe
  - “*Syphilis, or the French Disease*”
    - Named from poem - shepherd named Syphilus who offended Apollo & was punished
  - The French called it “the Italian disease”
    - Dutch called it ... “the Spanish disease”
    - Russians called it “the Polish...”
    - Turks called it “the Christian...”
    - Japanese called it “the Portuguese disease”



Sebastian Brandt's 1496 woodcut

# Syphilis

- Rapid spread in 16th century
  - 1767 John Hunter self –inoculation
    - Urethral pus containing *Neisseria gonorrhoeae* and *T. pallidum*
    - 2 diseases were considered same for some time
  - Mid-19th century, cause, epidemiology, and clinical manifestations of syphilis were well known
- Leading cause of neurological & cardiovascular disease in middle-aged people turn of 20<sup>th</sup> century





# Syphilis

- Arsenic derivative “magic bullet”
  - Ehrlich in 1910
- Mercury and bismuth
- Induced-fever therapy (malaria, heat box, hot baths)
  - Julius von Jauregg
  - Nobel Prize in 1927
    - Malaria to treat “paralytica dementia” (neurosyphilis)
- Penicillin
  - 1928 - Alexander Fleming
    - Mold *Penicillium notatum*
  - Late 1940s available in sufficient quantities
  - 1943 - US Public Health Service – treated 1<sup>st</sup> patient with PCN



Brettman Collection. 1929.

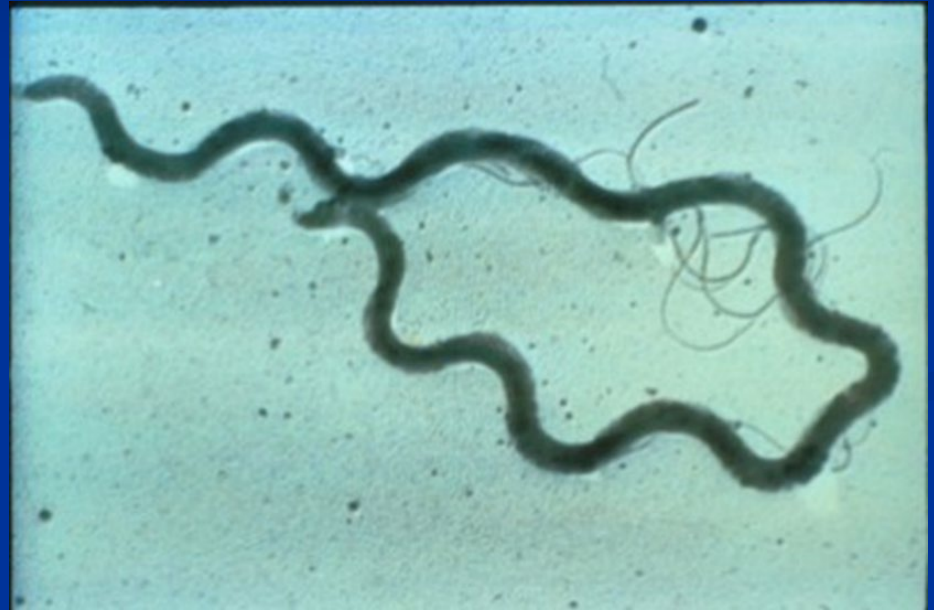
# Syphilis

- Tuskegee Syphilis Study
- 1932 until 1972 – FORTY years
- ~600 African American men prospectively followed
  - 412 WITH syphilis, 192 without
  - US Public Health Service – advised patients they were treating “for bad blood”– but NOT treated
  - Despite proven efficacy of penicillin by 1943
    - Participants offered transportation, hot meals, burial insurance
    - Advised the participants that multiple "back shots" (lumbar punctures) were “therapeutic”
    - 4 fold increase morbidity/mortality in untreated
    - Led to Belmont Report, establishment of National Human Investigational Board, and IRBs



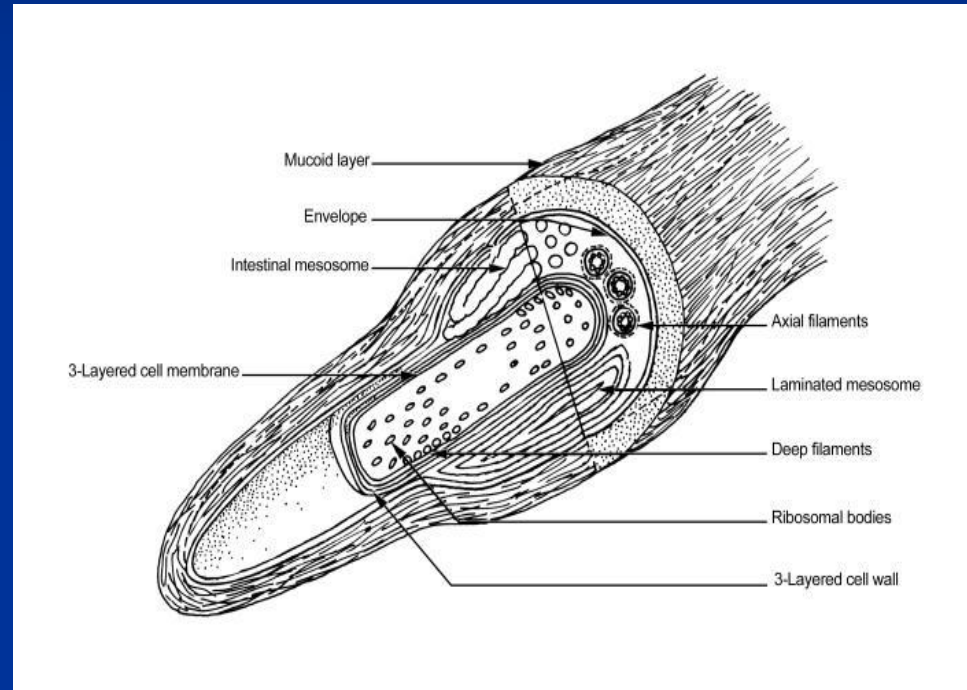
# Syphilis

- Order Spirochaetales
- *Treponema pallidum*
  - subsp. *pallidum*
- Slender, tightly coiled, unicellular, helical cells
  - 5 to 15  $\mu\text{m}$  long
  - 0.1 to 0.2  $\mu\text{m}$  wide
- Ends of cells are tapered



# Syphilis

- Outer membrane containing relatively few surface-exposed proteins
  - Hypothesis – “stealth” by minimizing number of surface membrane-bound targets
- Genome lacks transposable elements
  - Genome is conserved
  - Remains sensitive to penicillin



# Syphilis



- *T. pallidum* penetrates intact mucous membrane or gains access through abraded skin
  - Enters lymphatics or blood stream
  - Disseminates throughout body → w/in hours
    - Any organ in body can be invaded
      - CNS
    - Divides ~ every ~30+ hours
    - Incubation period directly proportional to size of inoculum
    - Median incubation period 3 weeks



# Syphilis Transmission

- Acquired
  - Sexual contact
    - Most infectious early
      - Chancre, mucous patch, or condyloma latum
      - Decreased risk of infection w/ time
  - Passage through placenta (congenital syphilis)
  - Close contact with active lesion
    - Wet nurses
  - Transfusion of fresh human blood
    - Blood donors tested for nontreponemal blood test
    - *T. pallidum* not survive >24 - 48 hours in blood bank storage
  - Accidental direct inoculation

# Syphilis Transmission

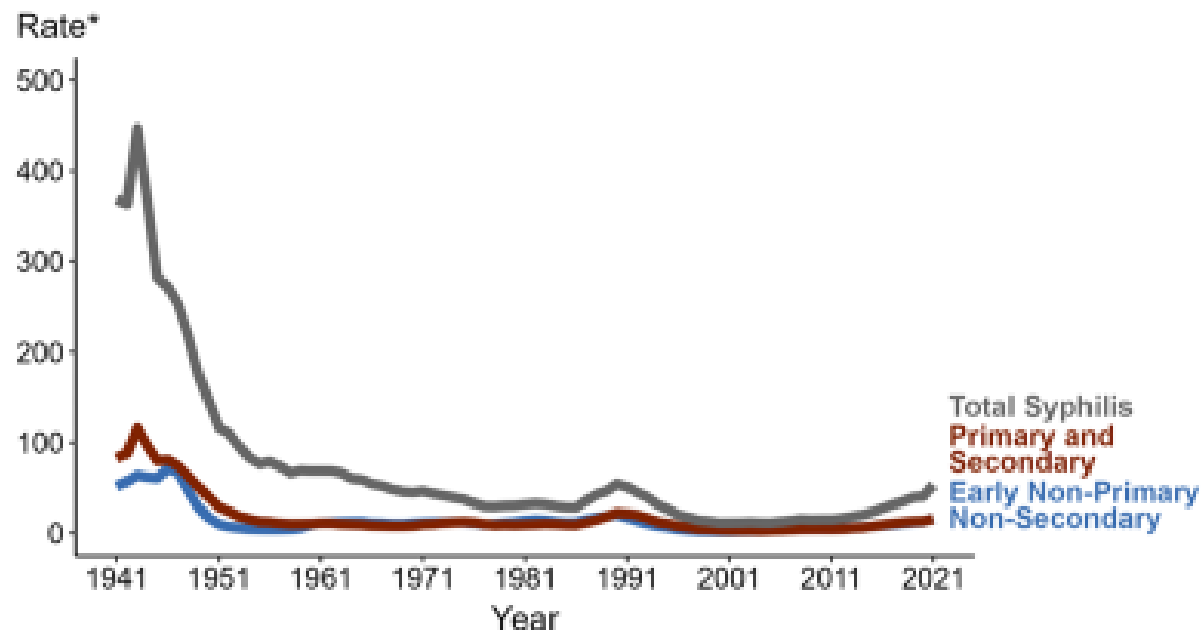
Risk of developing syphilis after sexual contact 10-60% (average about 30%)

Highest risk with contact to early syphilis



# Syphilis

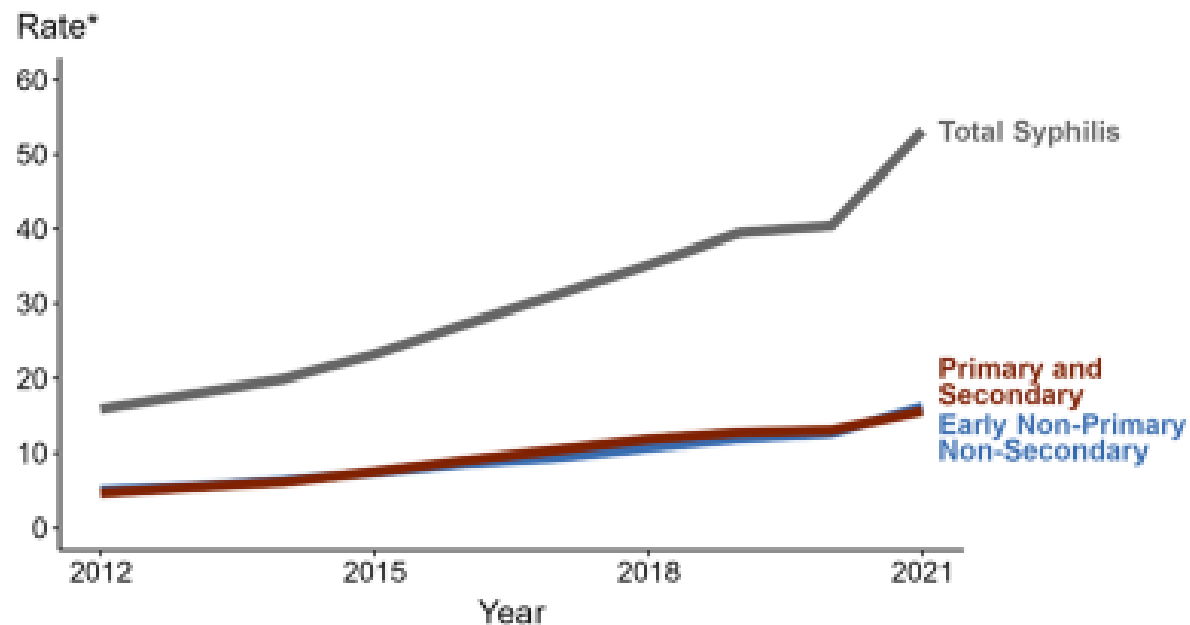
## Syphilis — Rates of Reported Cases by Stage of Infection, United States, 1941–2021



\* Per 100,000

# Syphilis

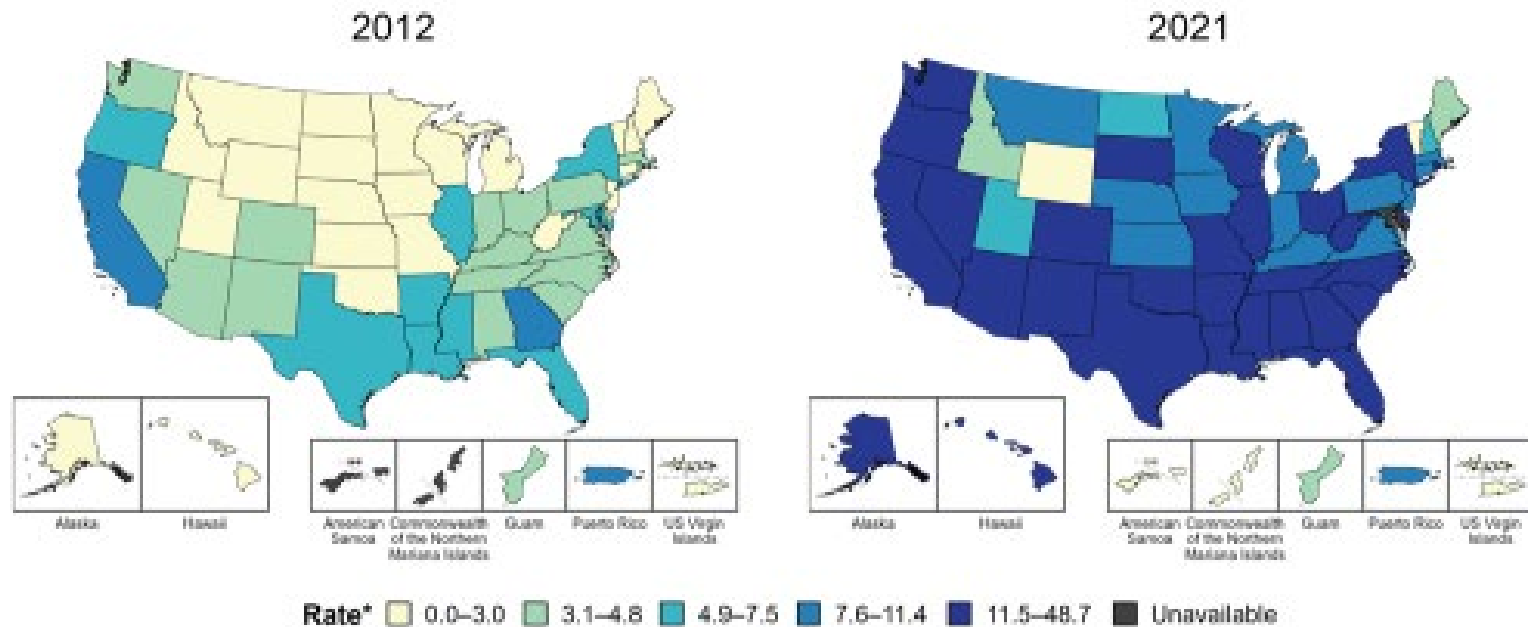
## Syphilis — Rates of Reported Cases by Stage of Infection, United States, 2012–2021



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# Syphilis

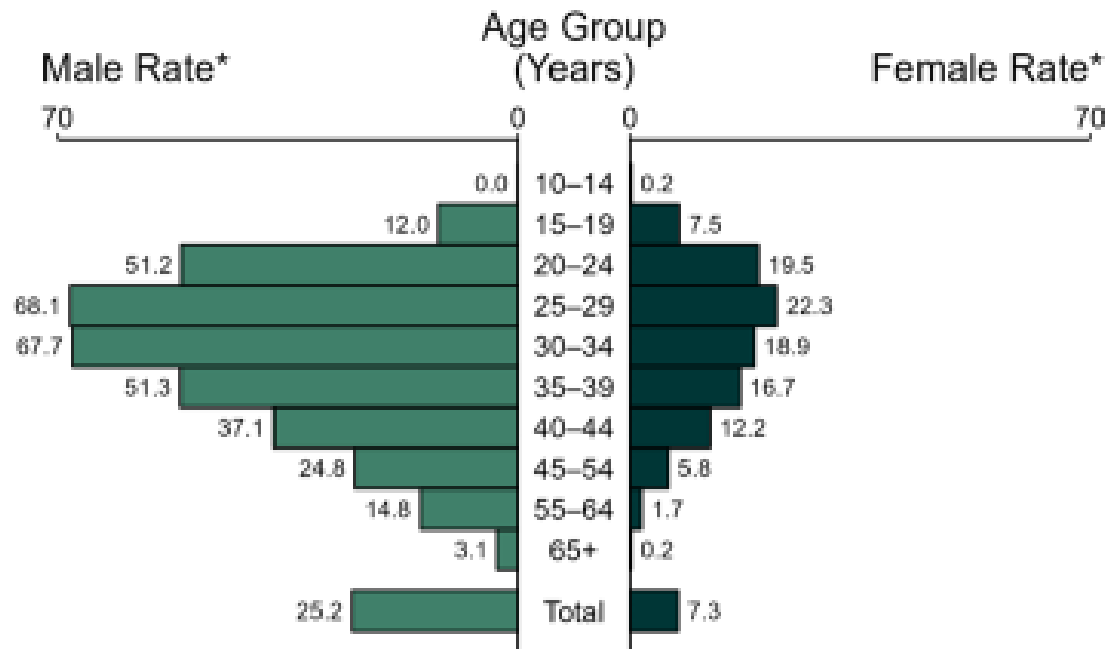
## Primary and Secondary Syphilis — Rates of Reported Cases by State, United States and Territories, 2012 and 2021





# Syphilis

## Primary and Secondary Syphilis — Rates of Reported Cases by Age Group and Sex, United States, 2021



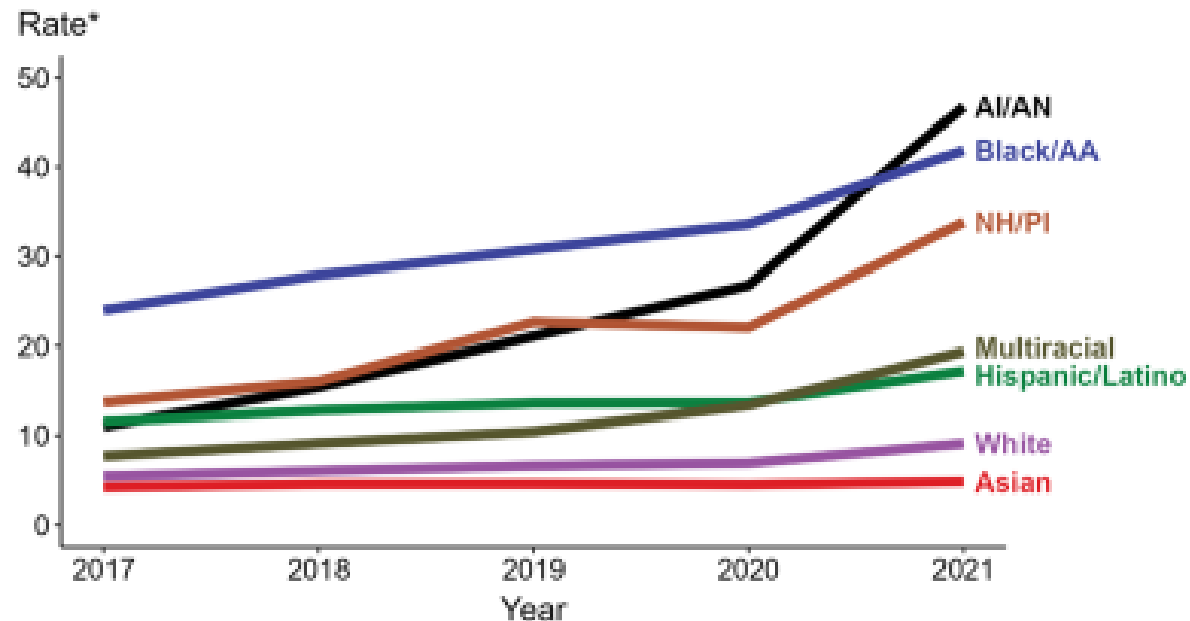
\* Per 100,000

NOTE: Total includes all ages.



# Syphilis

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



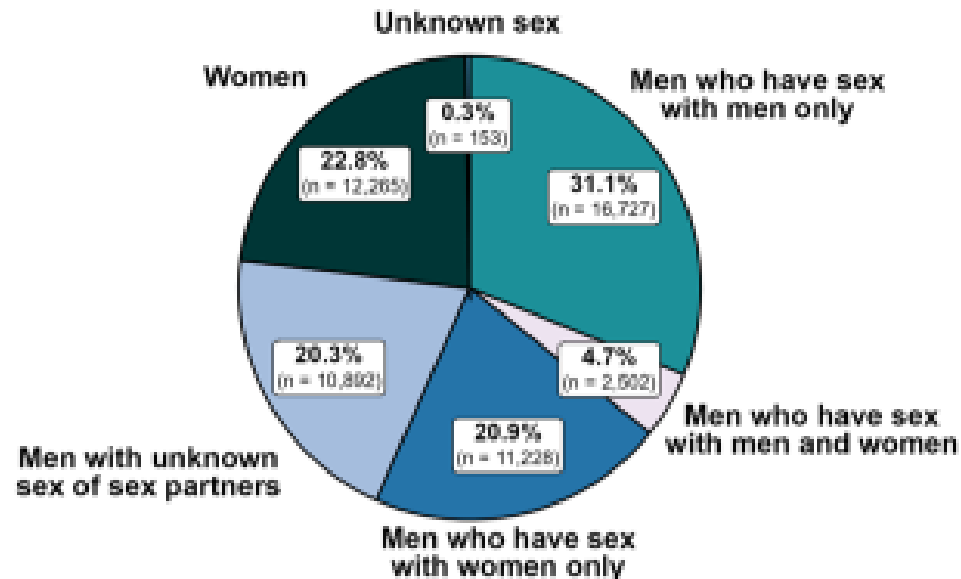
\* Per 100,000

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



# Syphilis

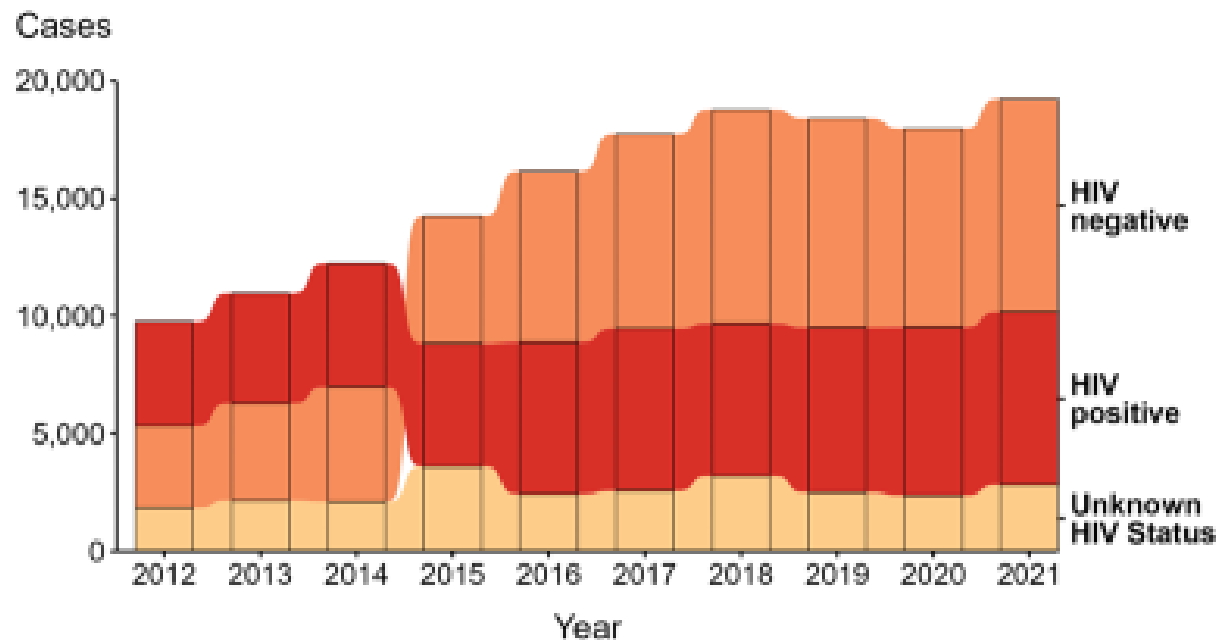
## Primary and Secondary Syphilis — Distribution of Cases by Sex and Sex of Sex Partners, United States, 2021



**Men 77%**

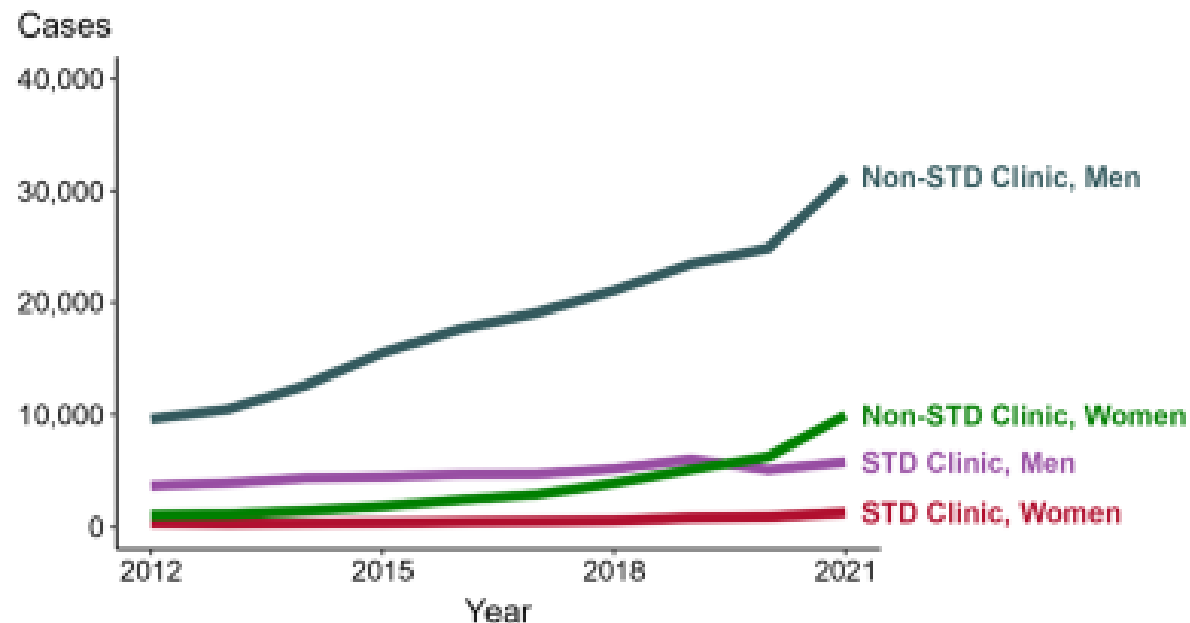
# Syphilis

**Primary and Secondary Syphilis — Reported Cases Among Men Who Have Sex with Men by HIV Status, United States, 2012–2021**



# Syphilis

## Primary and Secondary Syphilis — Reported Cases by Reporting Source and Sex, United States, 2012–2021

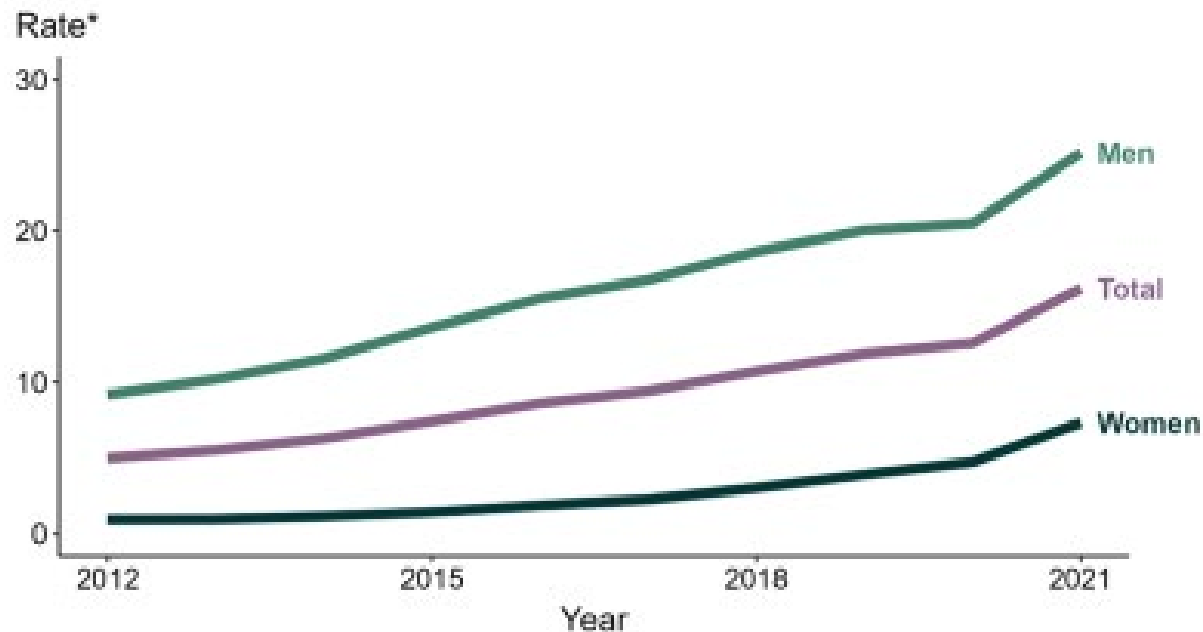


**NOTE:** During 2012 to 2021, the proportion of all male cases with unknown reporting source was 9.7%, from a low of 6.7% in 2014 to a high of 12.4% in 2018.



# Syphilis

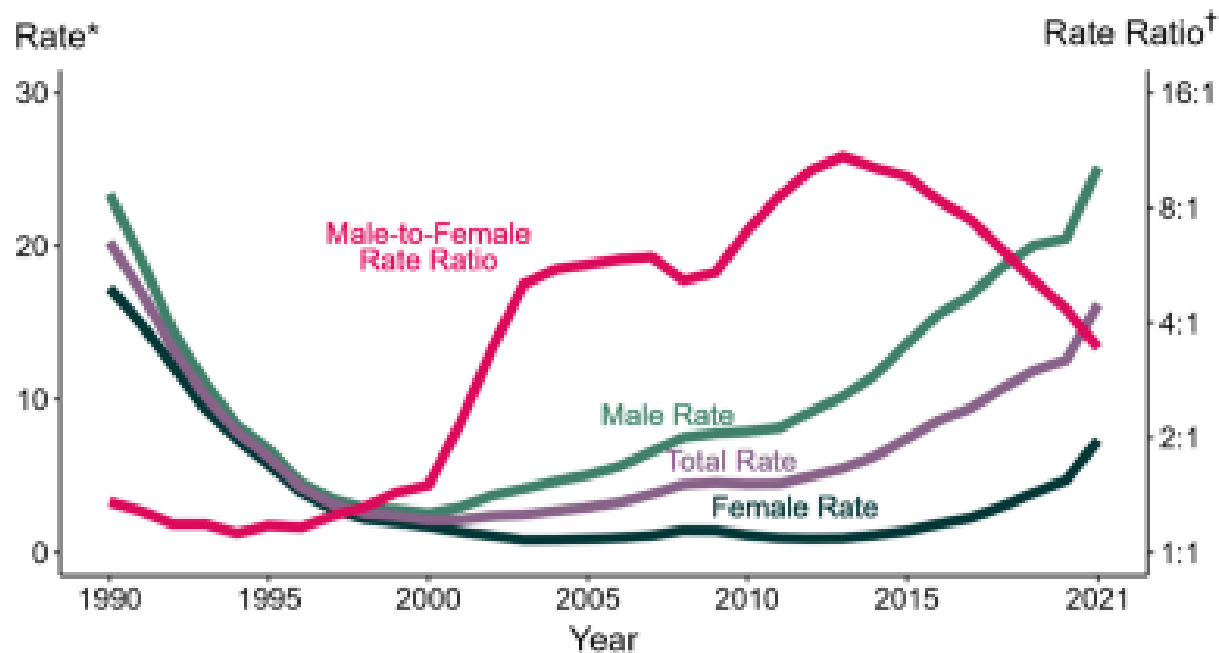
## Primary and Secondary Syphilis — Rates of Reported Cases by Sex, United States, 2012–2021



\* Per 100,000

# Syphilis

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

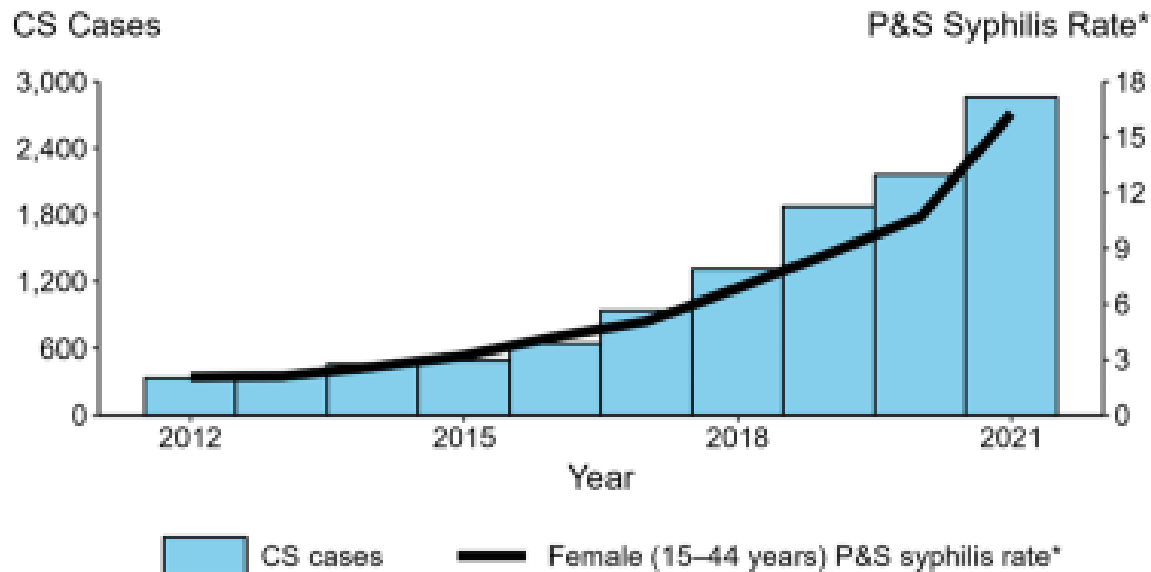


\* Per 100,000

† Log scale

# Congenital Syphilis

## 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



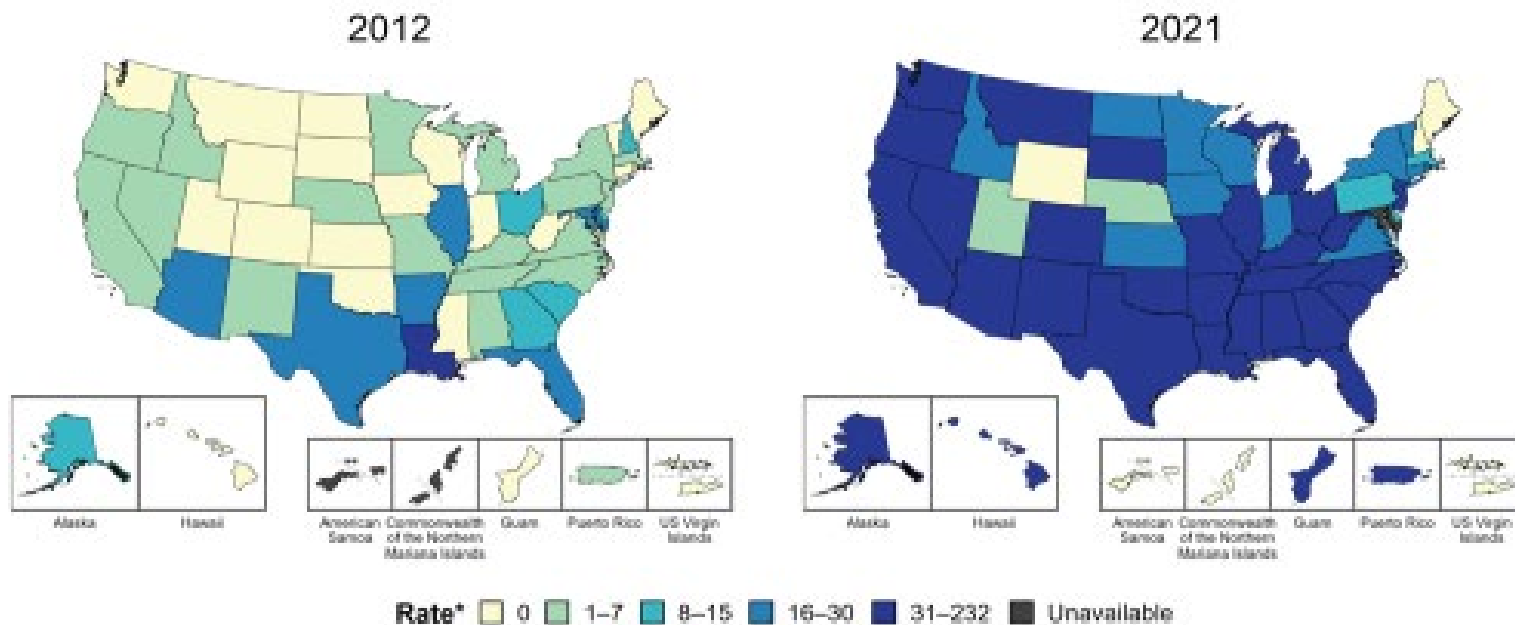
\* Per 100,000

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



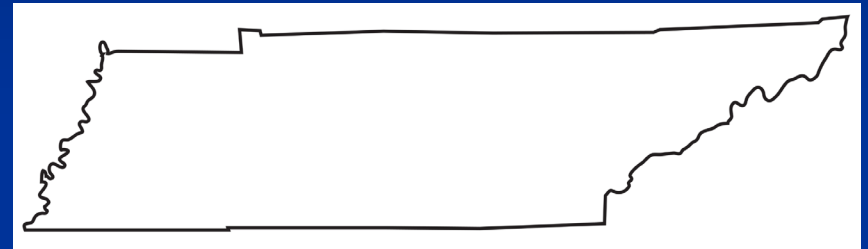
# Congenital Syphilis

## Congenital Syphilis — Rates of Reported Cases by Year of Birth and State, United States and Territories, 2012 and 2021



# Syphilis Rates

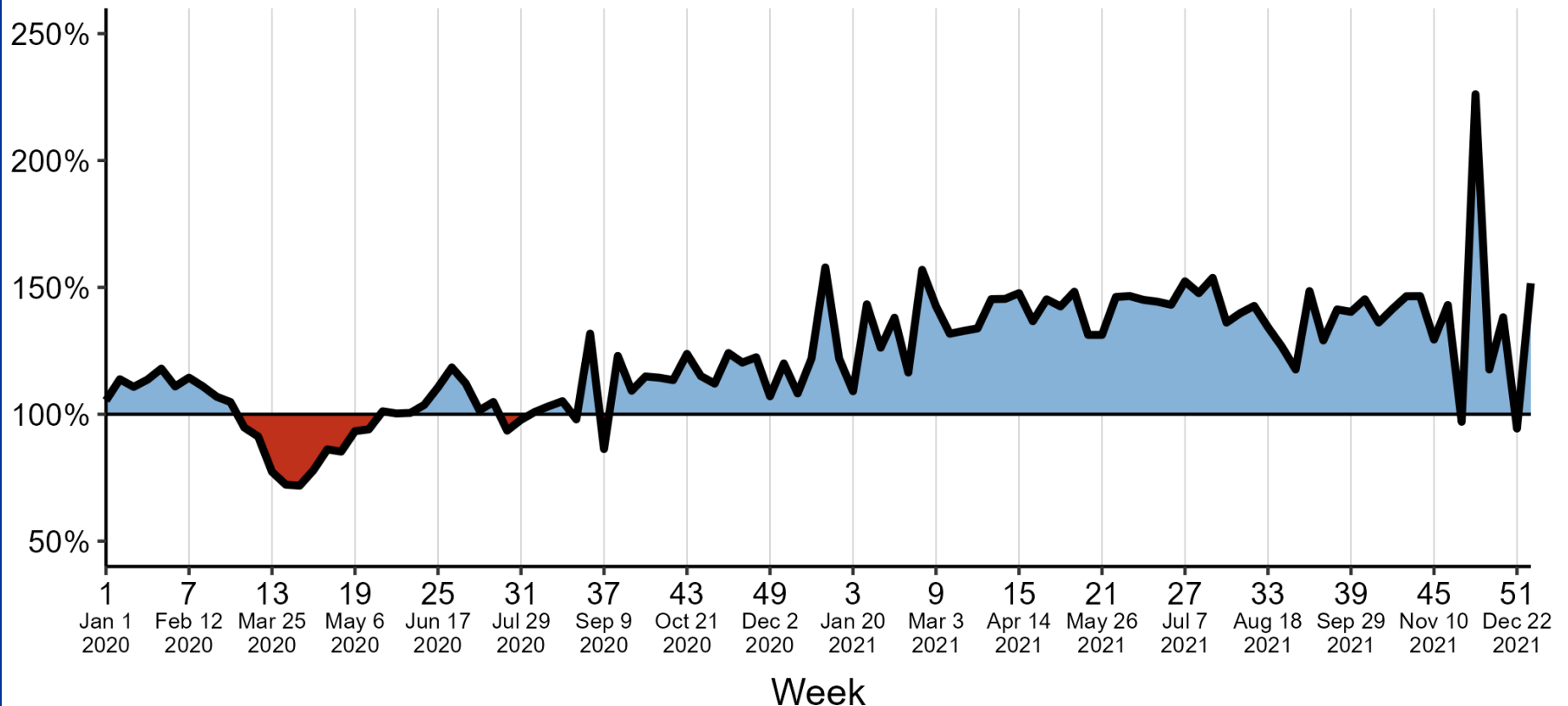
- 2017- 2021
  - Primary & Secondary syphilis
    - Rates up 72% US
    - Rates up 86% in Tennessee
  - Congenital Syphilis
    - Rates up 219% in US
    - Rates up 288% in TN





# Syphilis & COVID

Weekly Percentage of Cases Reported Compared to 2019



# Syphilis

- Protean clinical manifestations
  - “The great imitator” or “the great impostor”
- Stages
  - Incubating
  - Primary
  - Secondary
  - Latent
    - Early latent  $\leq 1$  year
    - Late latent – less infectious
  - Late or tertiary
- Most patients control infection & do not progress to late disease
  - Host develops intense immune response
    - Resulting inflammation responsible for clinical manifestations



# Syphilis

- Incubating Syphilis
  - Median incubation period **before** clinical manifestations is 21 days
    - Range 3 to 90 days
  - Early spirochetemia develops
    - Secondary invasion of virtually every organ



# Primary Syphilis

- Primary lesion or chancre
  - 2- 6 weeks after exposure
  - Occurs at site of inoculation
    - Usually external genitalia
      - Cervix, mouth, perianal area, anal canal
  - Single painless ulcer
  - Multiple chancres can occur
    - HIV
- Regional lymphadenopathy
- Spirochetes easily demonstrated
- Heals spontaneously 2 - 8 weeks
  - May persist for longer periods
    - HIV-infected persons
- Manifestations of 2<sup>0</sup> with chancre
  - Especially in HIV+ patients





# Secondary Syphilis

- 2 to 12 weeks after contact
  - Generalized condition
  - Manifestations- widespread and protean
    - Parenchymal
    - Constitutional
    - Mucocutaneous
- Rash – Non-pruritic macular, maculopapular, papular, or pustular lesions
  - Vesicular lesions absent
    - Except congenital syphilis
  - Trunk & proximal extremities
  - Persist few days to 8 weeks
    - **Palms and soles**
  - Patchy alopecia
  - Thinning/loss of eyebrows/beard



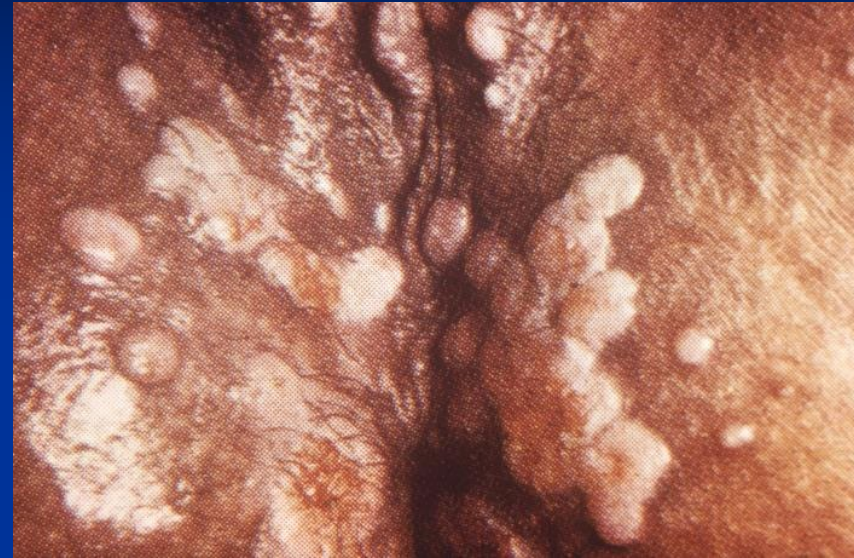
# Secondary Syphilis

## ■ Condylomata lata

- Painless, broad, moist, gray-white to erythematous, plaques
- Warm, moist intertriginous areas
- Highly infectious

## ■ Mucous patches

- Painless lesion on mucous membranes
- Silvery gray, superficial erosion with red periphery
- Highly infectious
- Not painful
  - Unless superinfected



Education &  
Center Program

# Secondary Syphilis

- Constitutional symptoms
  - Low-grade fever & Malaise
  - Pharyngitis/Laryngitis
  - Anorexia/weight loss
  - Arthralgias
  - Generalized painless LAD
    - Enlarged epitrochlear LN
- CNS
  - 40% involved
  - Headache and meningismus
  - Increased CSF protein & lymphs
    - Spirochetes isolated from CSF with no CSF abnormalities
  - CN involvement
- Syphilitic paraplegia (Erb's/brachial plexus)
- Amyotrophic meningomyelitis
- Renal involvement
  - Immune-complex glomerulonephritis
  - Proteinuria
  - Acute nephrotic syndrome
- Gastrointestinal tract
  - Infiltrated and/or ulcerated lesions
  - Syphilitic hepatitis
- Anterior or pan-uveitis
  - Worse with steroids
- Synovitis, osteitis, and periosteitis



# Latent Syphilis

- Latent period
  - Secondary stage subsides – no symptoms
  - Diagnosis only by obtaining positive serologic test
  - Early latent
    - Relapses possible
    - 90% of relapses occur within 1<sup>st</sup> year
      - Usually consequence of dysfunction in cellular immunity
  - Late latent
    - Relapses very unlikely



# Late Syphilis/Tertiary Syphilis

- Slow progressive, inflammatory disease - over years
  - Neurosyphilis
  - Cardiovascular syphilis
    - Aortitis with a saccular aneurysm
      - Aortic regurgitation and coronary artery stenosis
  - Gummatous syphilis
    - Nonspecific, granulomatous-like lesion
    - Skeletal, skin, and mucocutaneous
      - Single or multiple, variable size
    - PCN- rapid and dramatic response
  - Leuetic osteitis
    - Moth eaten appearance on X-ray

# Congenital Syphilis

- Infection of the fetus in utero can occur at any stage of infection
  - Early syphilis most common
- Late abortion
- Stillbirth
- Neonatal death
- Neonatal disease
- Latent infection

# Congenital Syphilis

- Normal exam
- Rhinitis (snuffles) - Earliest sign
- Diffuse, maculopapular, desquamative rash
  - Palms & soles
    - Vesicular rash/bullae
- Splenomegaly, anemia, thrombocytopenia, and jaundice
- Osteochondritis and perichondritis or periostitis
  - Saddle nose
  - Anterior bowing or “saber shin”
- Eighth-nerve deafness
- **Necrotizing funisitis**
  - Inflammatory process involving umbilical cord
- Hutchinson’s teeth



# Neurosyphilis

- Can occur at any stage
- Asymptomatic neurosyphilis
- Syphilitic Meningitis
- Meningovascular Syphilis
  - Thrombosis, Ischemia, infarction
  - Stroke in young person
  - Middle Cerebral Art most common – 66%
- Parenchymatous - Late
  - General paresis, Tabes dorsalis
- Ocular
- Otic, Vestibular



# Neurosyphilis

## Ocular

- Can occur at any stage
- Anterior uveitis, iritis
- Posterior uveitis,  
chorioretinitis
- Panuveitis
  - Worse with steroids
- Interstitial Keratitis
- Retinal vasculitis
- Optic neuropathy

### ■ Late

- Argyll Robertson pupil
  - Small bilateral pupils
    - Do not react to light
    - Constrict with accommodation
- Optic atrophy
  - Peripheral proceeds to central
    - “Gun barrel” sight

# Neurosyphilis

## Otosyphilis

- Sensorineural hearing loss
  - Unilateral or bilateral
    - May have sudden onset, progress rapidly
- Tinnitus
- Vertigo
- Need to evaluate for ocular, CNS involvement
  - CN VIII (Vestibulocochlear nerve)

# Neurosyphilis

- Clinical Suspicion
  - Screen all patients with syphilis
  - Perform neurologic exam
- Spinal Fluid Examination – Lumbar Puncture
  - Neurologic, ophthalmologic, otic symptoms
  - Evidence of tertiary syphilis
  - Treatment failure
  - HIV infection
    - Higher risk of Neurosyphilis
      - RPR  $\geq$  1:32
      - CD4  $\leq$  350
      - Detectable HIV RNA or not on antiretrovirals





# Neurosypphilis

- Study evaluated patients with risk for NS
  - RRP > 1:32 or
  - CD4  $\leq$  350
  - No neuro symptoms
  - Randomized to LP vs no LP
  - 2/3 Cognitively impaired @ baseline
  - Cognitive impairment 3.8x w/ CSF pleocytosis
  - Patients treated - less cognitive decline vs non-treated





# Syphilis

## Who should be tested? (“Everyone”)

### ■ Men

- $\geq$  annually, sexually active\*  
MSM
- Every 3 - 6 months if at increased risk
- Male younger than 29 years
- Increase risk

### ■ Women

- Screen asymptomatic women at increased risk
- Pregnant women at 1st prenatal visit, retest at 28 wks & delivery if increased risk

### ■ People living with HIV

- Sexually active, screen at 1<sup>st</sup> visit, and at least annually

### ■ Increased Risk (CDC)

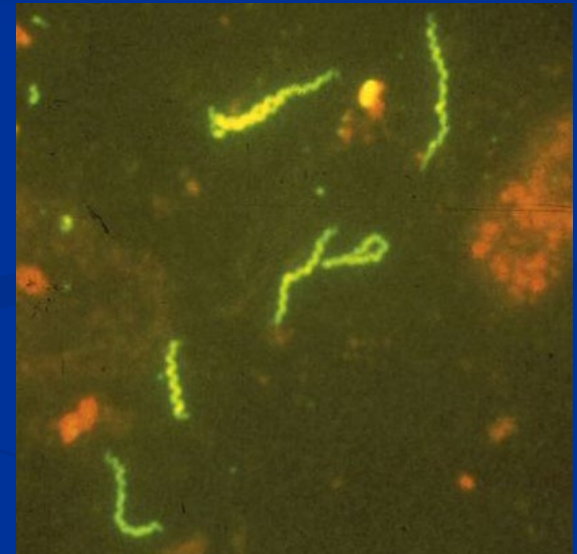
- H/o incarceration
- Transactional sex work
- Geography
- Race/ethnicity
- Male < 29 yo
- MSM

\* **sexual hx**

# Syphilis Diagnosis

## Direct examination

- Not cultivable
  - Rabbits – not develop 2<sup>0</sup>, Neuro
- Darkfield microscopy
  - Moves with drifting rotary motion
    - Characteristic undulating movement about center - Corkscrew motility
    - Not on oral specimen - not able to distinguish *T. pallidum* from other nonpathogenic treponemes



# Syphilis Diagnosis

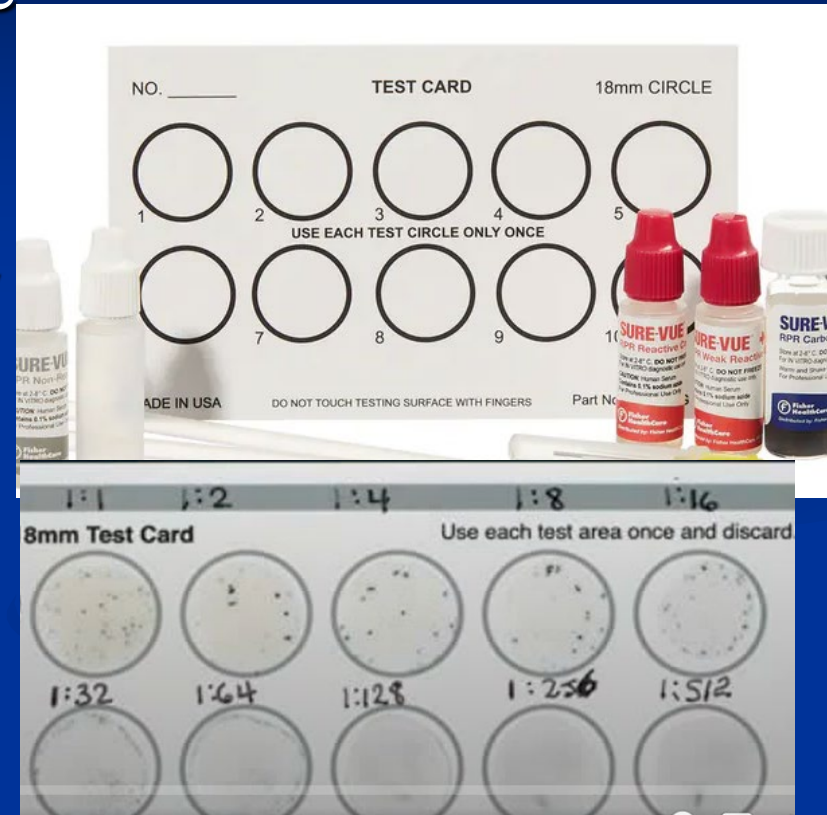
## ■ Serologic Tests

- *Nonspecific* nontreponemal reagenic antibody
- *Specific* anti-treponemal antibody
- To establish a diagnosis of **syphilis**, the two types of serologic tests are used together

# Syphilis Diagnosis

## ■ Nontreponemal Reaginic Tests

- IgG/IgM antibodies
  - Interaction of host tissues w/ *T. pallidum*
- RPR
- VDRL – used CSF
- Prozone phenomenon
  - Ab excess – High titer
    - Prevents agglutination
    - False negative
- False positives



# Syphilis False Positive Non-treponemal Test

- Parenteral drug use
- Autoimmune or connective tissue diseases
  - Lupus
- Aging
- Hypergammaglobulinemic states
- HIV co-infection
- Pregnancy
- *Mycoplasma pneumoniae*
- Lyme disease
- Measles
- Leptospirosis
- Chickenpox (Varicella)
- Relapsing fever
- Lymphogranuloma venereum
- Ratbite fever (*Spirillum minor*)
- Hepatitis (especially Hepatitis C)
- Leprosy
- Infectious mononucleosis
- Tuberculosis
- Pneumococcal pneumonia
- Blood transfusions (multiple)
- Malaria
- Trypanosomiasis

# Syphilis Diagnosis

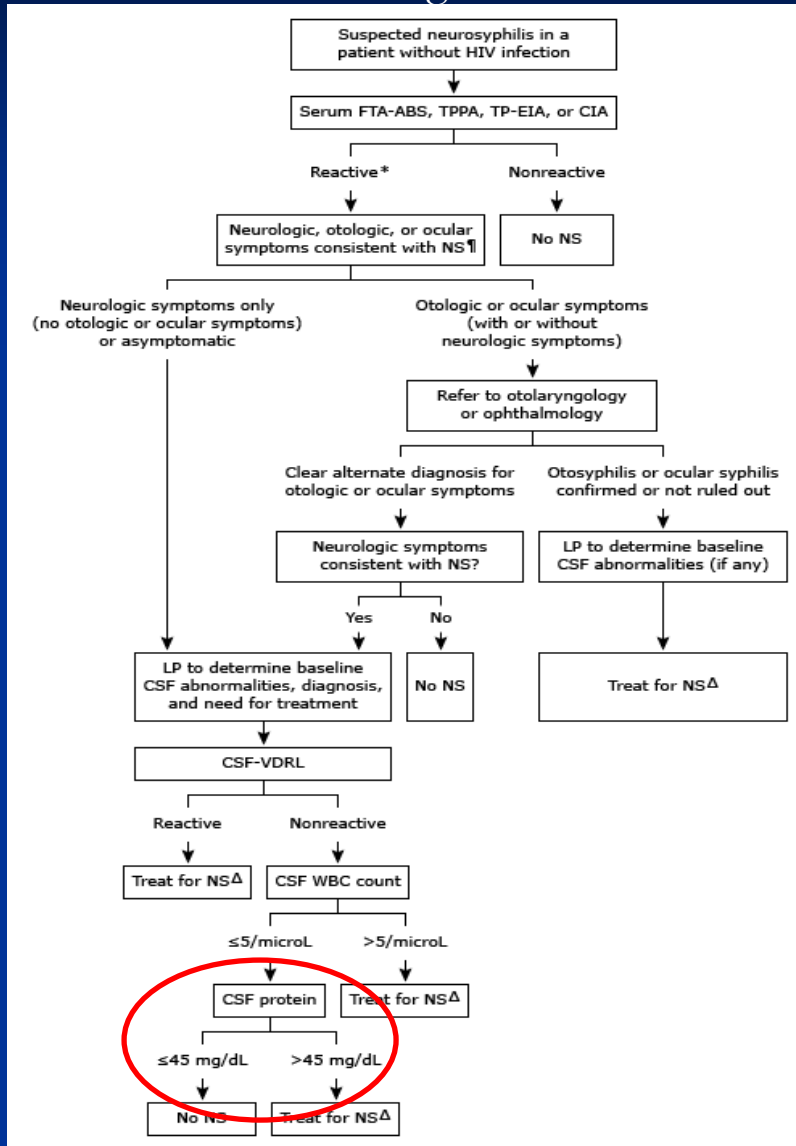
## ■ Specific Treponemal Tests

- Antibodies against specific *T. pallidum* antigens
- FTA-abs
- *T. pallidum* agglutination tests
  - TPHA and MHA-TP
- TP- EIA
- Once positive, patient positive for life
  - Rare primary diagnosis may revert after 2-3+ years.

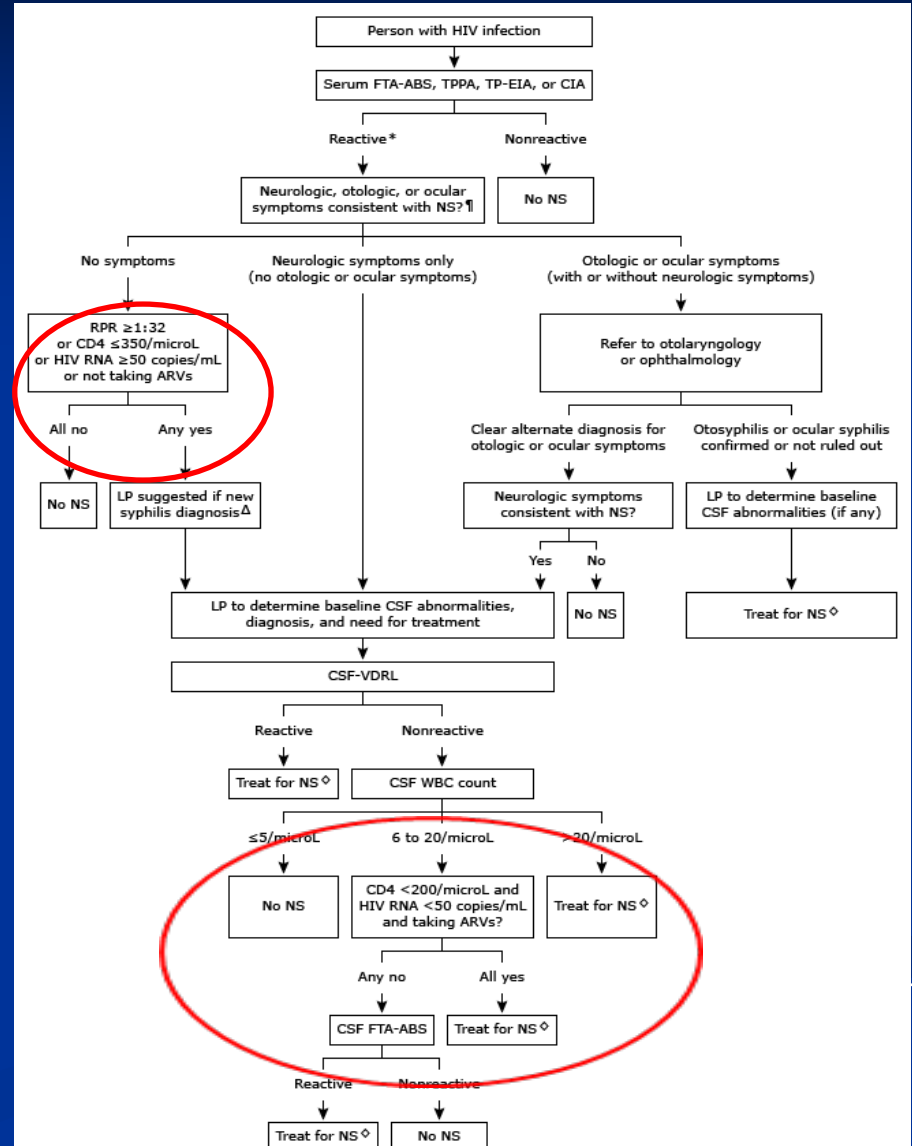


# Neurosyphilis

## HIV negative



## PLWH



# Syphilis

- Early (primary, secondary, or early latent)
  - Penicillin G benzathine 2.4 mu IM once
  - Doxycycline 100 mg po BID x 14 days
- Late
  - Penicillin G benzathine 2.4 mu IM q wk x 3
  - Doxycycline 100 mg po BID x 4 weeks
- Neurosyphilis
  - Penicillin G 24 million units/day x 10 - 14 days
  - (Penicillin G procaine 2.4 mu IM daily plus probenecid 500 mg QID x 10 - 14 days )
  - Ceftriaxone 2 g IV QD x 10 -14 days





# Drug Shortage

- Benzathine Penicillin - Bicillin
  - Shortages
  - Increased demand due to syphilis
  - Shortages in amoxicillin
  
- Procaine penicillin
  - Not being manufactured

# Syphilis

- Monitoring response to therapy
  - RPR should fall by 4 fold (2 levels i.e. from 1:16->1:8 -> 1:4)
    - 6 and 12 months for early syphilis
  - Rise of 4 fold
    - Indicate new infection
    - Lack of response
      - Neurosyphilis
- Neurosyphilis
  - Repeat LP @ 3, 6, 12 months
    - CSF WBC should normalize @ 6 months
    - CSF VDRL decline 4 fold or NR by 2 years after tx

# Syphilis



- Jarisch-Herxheimer Reaction
  - Systemic reaction resembling gram-negative sepsis
  - 2+ hours after initial treatment of **syphilis**
    - Fever, chills, myalgias, headache, tachycardia, hyperventilation, vasodilation with flushing, and mild hypotension.
    - Duration - 12 to 24 hours
    - Reaction is self limited
    - Prevent/treat with anti-inflammatory

# Syphilis

- Rates increasing – men, women, babies
  - Need to increase screening
    - Prevent infections
  - Better access to care
  - Ensure screening for neurosyphilis
    - Lumbar punctures, ophthalmologic, ENT
    - Treatment
- Treatment
  - Need to ensure PCN therapies available

# Syphilis

- Understand marked increase in the incidence of Syphilis and significance.
- Identify the stages of syphilis and recommended treatment.
- Identify symptoms of Neurosyphilis.
- Manage patients after treatment for syphilis appropriately - including identifying patients that require re-treatment or neurologic evaluation.



# Questions?

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Thank you



# Case 1

- New patient - 24 yo man presents w/ complaints of mild headache x 2 wks, feeling “like in a brain fog”, has some flashes of light in peripheral vision, and tinnitus. No travel, no known sick contacts, no pets. 3 new male sexual partners in past 6 mos. and reports a lesion on his penis that self-resolved without treatment ~ 2 mos prior.
- Best option for management at this time?
  - A. Admit to the hospital for IV PCN.
  - B. Draw Trep pallidum IgG/RPR and treat based on lab results.
  - C. Give doxycycline 100 mg BID x 4 weeks.
  - D. Draw serology labs and refer for LP, ophtho and ENT eval.

# Case 1

## ■ Best Answer D:

- With neurologic symptoms and likely syphilis diagnosis, would refer for LP, Ophtho, and ENT evaluation.
- With high suspicion – treat with benzathine.
- Draw treponemal antibody/RPR. Need to know prior lab testing/treatment.
  - If prior lab testing not available, can contact Health Dept.



# Case 2

- 56 yo man new to clinic. Screening labs drawn, positive TP Ab and neg RPR.
- Call patient to discuss – no history of prior syphilis diagnosis, symptoms, treatment.
- Repeat labs, TPPA +
  - A. Treat for primary syphilis
  - B. Likely false positive and no treatment indicated.
  - C. Treat for late latent syphilis.
  - D. Schedule LP due to symptoms and no prior treatment.

# Case 2

## ■ C.

- Treat for late latent syphilis (if reliable can wait).
- Treponemal antibody specific for syphilis
- Likely prior infection – RPR titer has waned over time.
- Treat for late latent – due to unknown duration.
  - Get more history.
  - If patient had prior testing, should be available through Health Dept.
- RPR NR, so do not need (can't) follow lab response.

# Case 3

22 yo man for routine f/u.  
He requests STD screening  
“just to be sure”. No new  
partners. No lesions, rashes,  
headaches, urethral d/c,  
rectal pain, ocular or auditory  
symptoms. PE normal.

Labs: TP Ab +.

H/o syphilis 2 yrs prior w/  
+ TP Ab & RPR =1:256

Tx'd w/ benzathine PCN 2.4  
mu IM q wk x 3 (no prior  
testing, late latent syphilis).

Date	RPR titer
06/2022	1:256 Tx'd w/ Benzathine PCN
12/2022	1:32
06/2023	1:4
12/2023	1:2
06/2024	1:4

# Case 3

- A. Treat with benzathine PCN 2.4 mu IM x 1
- B. Refer for neurosyphilis eval due to persistent RPR titer
- C. Advise patient he still has syphilis and should contact his partners
- D. Advise patient he has been treated and no further evaluation is indicated.

# Case 3

## ■ D. No treatment

### ■ Persistent RPR titer – serofast.

#### ■ Up to 1/3 in HIV

### ■ < 4x decline in titers

#### ■ Treatment failure

##### ■ Poor adherence with treatment

##### ■ Treatment with an alternative agent

##### ■ Immunocompromised status

##### ■ Undiagnosed central nervous system disease

#### ■ Re-infection

#### ■ Antibody titers <1:8 less likely to have fourfold decline