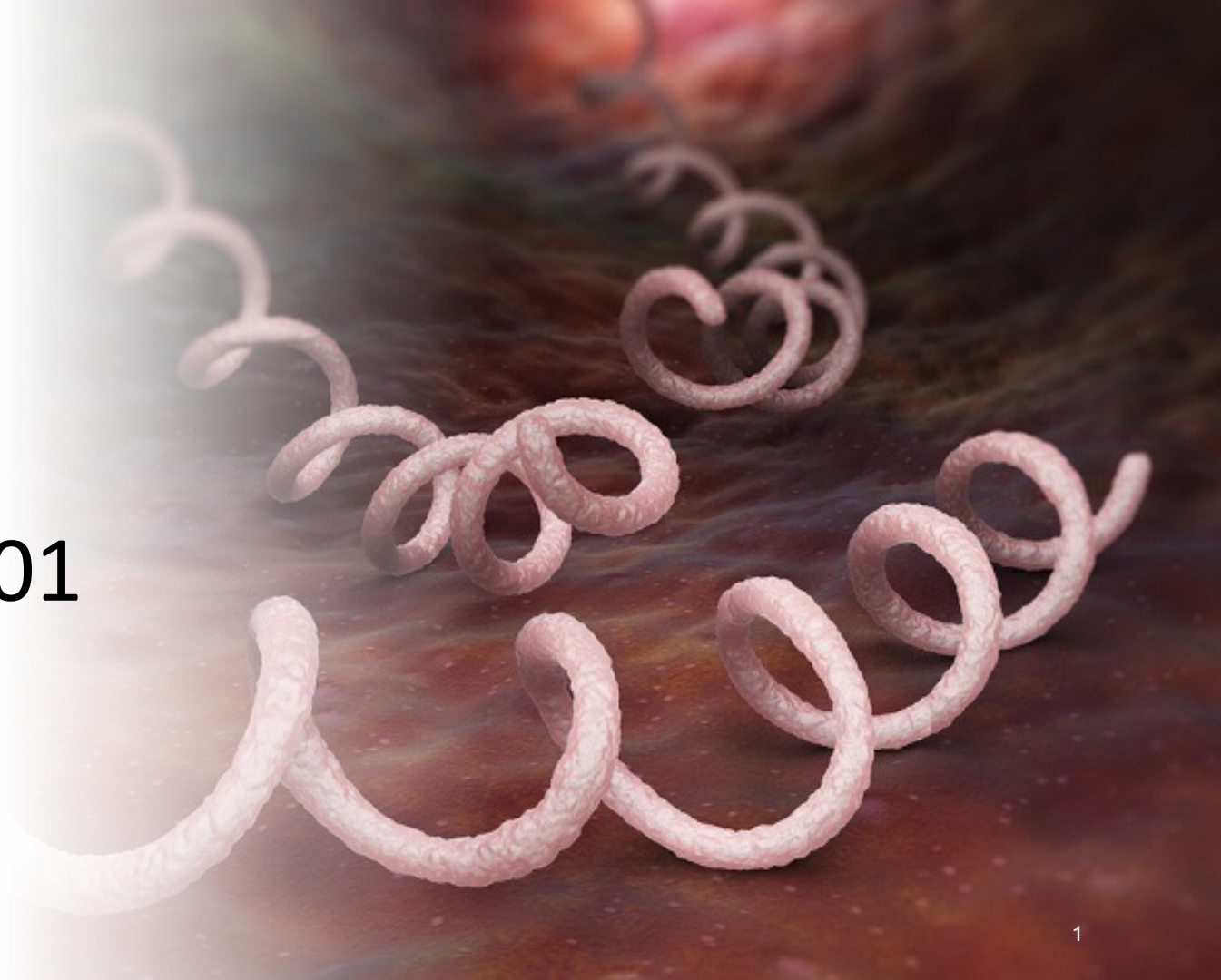


Syphilis 101

Jorge Mera, MD



Disclosure Slide

- Gilead Sciences - Advisor/Researcher
- Merck - Researcher
- Abbvie Pharmaceutical - Researcher/Speaker
- Roche - Advisor

Acknowledgment

- **Andrew Yu, MS, RN, ACRN**
- National HIV/HCV/STI Clinical Coordinator, HIS
- Melanie Taylor, MD

For sharing his knowledge, syphilis slides and cases

Outline

Trepanomatoses



A brief history of syphilis



Syphilis 101

Human Treponematoses

Syphilis: *T. pallidum* spp. *pallidum*

- Globally distributed
- Sexually transmitted
- Vertically transmitted

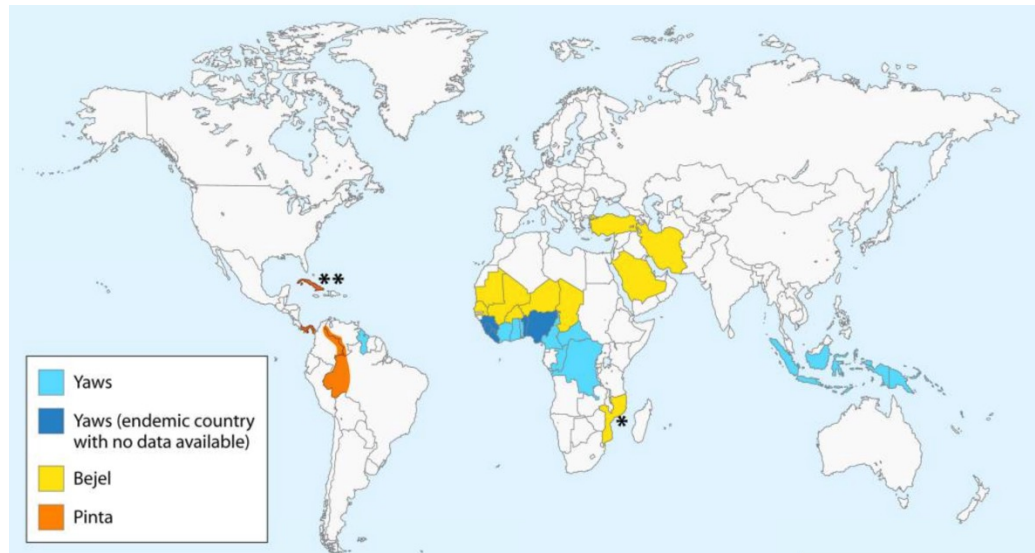
Endemic Treponematoses:

Yaws: *T. pallidum* spp. *Pertenue*

Bejel: *T. Pallidum* spp. *Endemicum*

Pinta: *T. Pallidum* spp. *carateum*

- Mainly cause disease of the skin, joints, soft tissue, oral cavity and bone
- No evidence of vertical transmission



Giacani L, Lukehart SA. The endemic treponematoses. Clin Microbiol Rev. 2014 Jan;27(1):89-115.

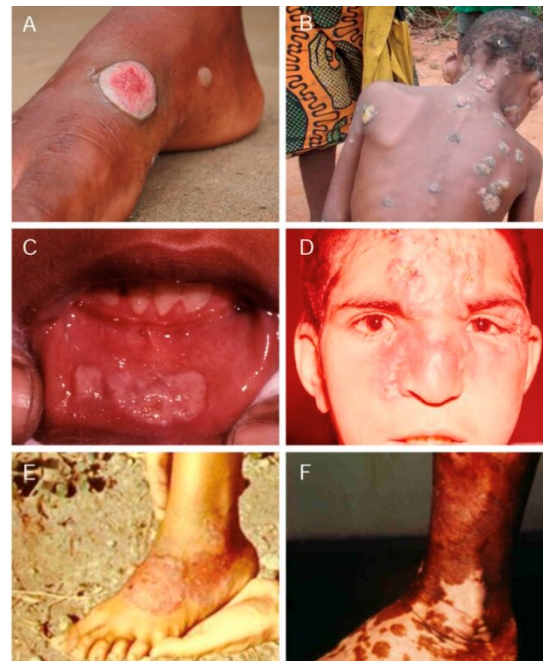
Human Treponematoses

Have a clonal origin with common ancestor

Genomically, morphologically, and serologically similar

Infection occurs following an exposure of mucosal surfaces or traumatized skin

The organisms multiply and disseminate hematogenously or via lymphatic systems.



- A: Papillomatous primary yaws lesion
- B: Disseminated papilloma of secondary yaws
- C: labial mucosal plaques of primary bejel
- D: Disfiguring infiltration of the nose, glabella, and forehead in a patient with secondary bejel
- E: Squamous plaque of primary pinta
- F: Late achromic pinta.

History of Syphilis

Origins of Syphilis: Columbian Hypothesis

- *T. pallidum* first arose in the Old World as a non-venereal infection and likely underwent genetic mutations giving rise to *T. pallidum* spp *pallidum*

Where does the name of Syphilis come from:

- A poem called "Syphilis, Sive Morbus Gallicus" ("Syphilis, or the French Disease"), written by Italian physician-poet Girolamo Fracastoro in 1530.

The "Great Imitator"

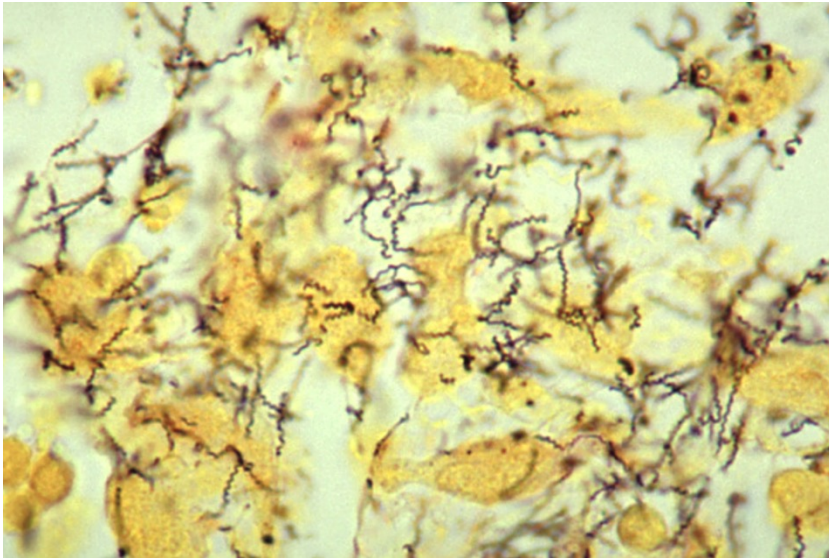
- Supposedly described by Sir William Osler

First reported outbreak:

- Among the French troops in Europe during the war of Naples in 1495

The Beginning of Laboratory Diagnosis of Syphilis: Direct Detection of Organisms using Microscopy

1905 *T. pallidum*, was first observed in diseased tissues by German zoologist Fritz Schaudinn



1906 Karl Landsteiner, used dark-field microscopy to detect syphilitic treponemes in infected specimens



<https://asm.org/articles/2019/june/revisiting-the-great-imitator,-part-i-the-origin-a>

Non-Treponemal Testing

In 1906 the Wassermann, Neisser and Bruck

- Developed the first serologic test for the diagnosis of syphilis
- Complement Fixation

In 1907 Landsteiner elucidated the antibodies

- “Reagins” were directed against a cardiolipin found tissue

In 1922 a flocculation test was developed

- Led to development of RPR and VDRL

In 2018 A study found that *T. pallidum* contained a cardiolipin

- The increase in the anti cardiolipin antibody production are the combined effects of both the *T. pallidum* cardiolipin antigen and the damaged host-cell cardiolipin antigen during syphilis infection.

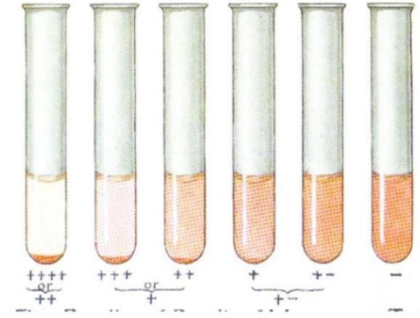
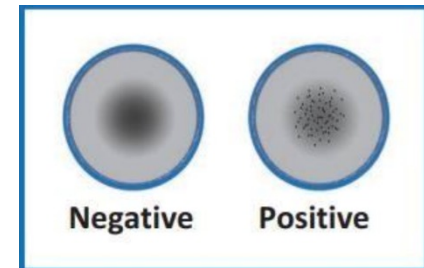


Figure 5. Wasserman test [19]



Non-Treponemal Testing

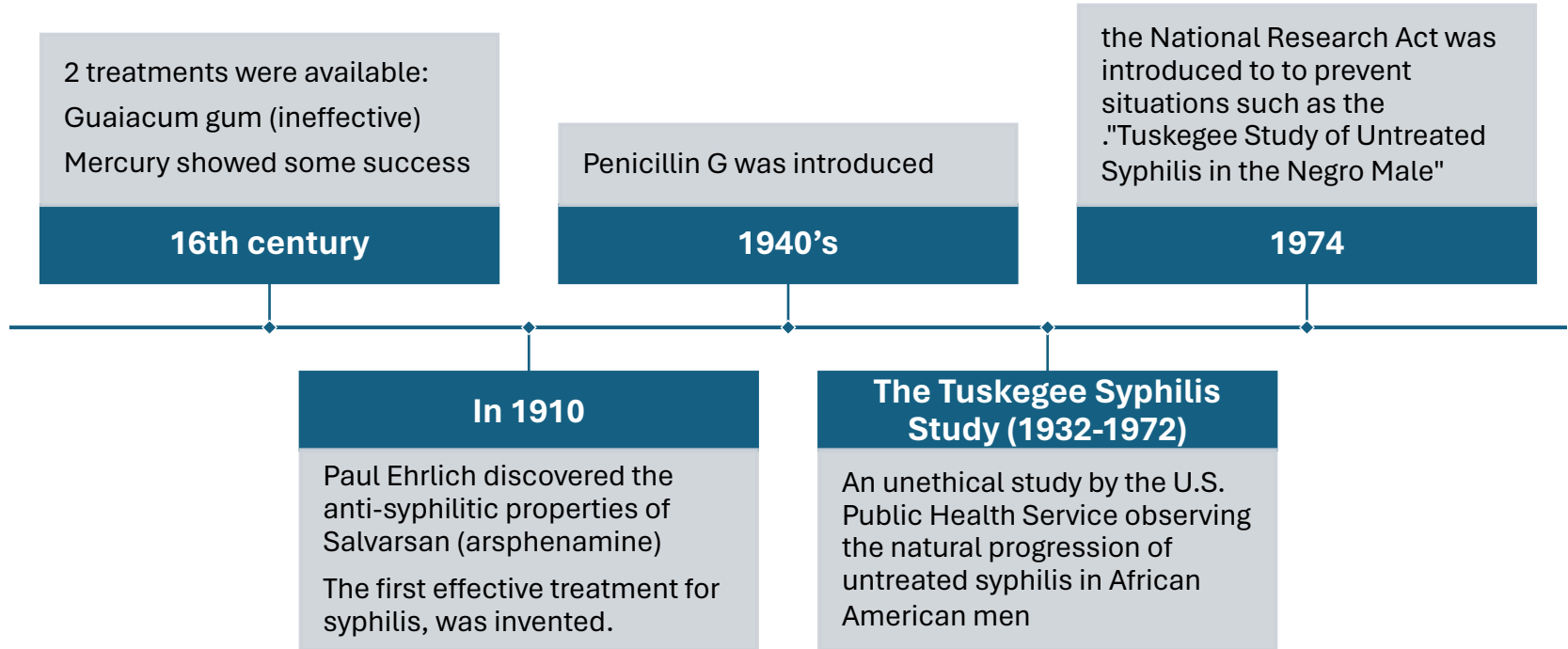
In 2018 A study found that *T. pallidum* contained a cardiolipin

- The increase in the Wasserman antibody (anti-phospholipid antibody) production was suggested to be a result of the combined effects of both the *T. pallidum* cardiolipin antigen and the damaged host-cell cardiolipin antigen during syphilis infection.

In the 1940s structure of the antigen in the Wassermann test was identified

- It is a diphosphatidylglycerol called cardiolipin
- Commonly found in normal non-syphilitic tissues

History of Syphilis: Treatment



Case 1:

HPI:

- 20 yo cis-gender female who has sex with cis-gender males, presents for a pregnancy test only. She reports last had oral and vaginal sex without protective barrier 3 weeks ago and had 2 partners over the past 6 months. No current signs or symptoms, and doesn't recollect any in the past year
- Never tested for HIV; last gonorrhea/chlamydia (urine only) and RPR tests were 11 months ago, all negative

Social History:

- Denies drug use, reports unstable housing and transportation, no regular access to phone

Labs in Office

- Rapid pregnancy test: **negative**
- Agrees to rapid HIV/Syphilis test in office when offered incentive
- HIV: **non-reactive**; Syphilis (treponemal antibody): **reactive**

Case 1:

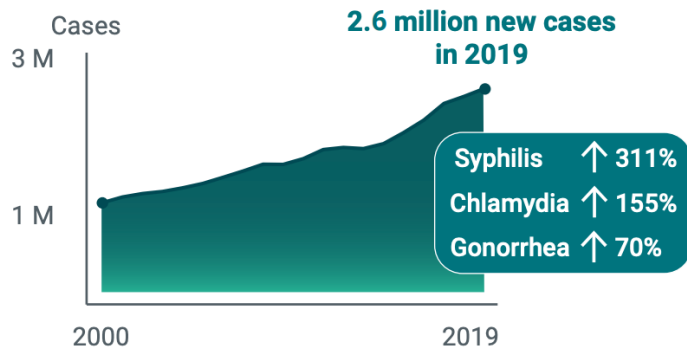
What are the recommended next steps? (Check all that apply)

- A. No further testing necessary, as initial reason for the visit (pregnancy testing) already completed
- B. Draw serum HIV, test for gonorrhea and chlamydia in the urine and throat
- C. Draw RPR, wait for results (~1 week) to determine treatment
- D. Draw RPR and immediately administer 2.4 MU IM injection of benzathine penicillin for early latent stage syphilis
- E. Draw RPR and immediately administer 2.4 MU IM injection of benzathine penicillin weekly x 3 weeks (total 7.2 MU) for late latent stage syphilis

Reversing the Rise in STIs: Integrating Services to Address the Syndemic of STIs, HIV, Substance Use, and Viral Hepatitis

STI Overview

Chlamydia, gonorrhea, and syphilis cases have been increasing for years.

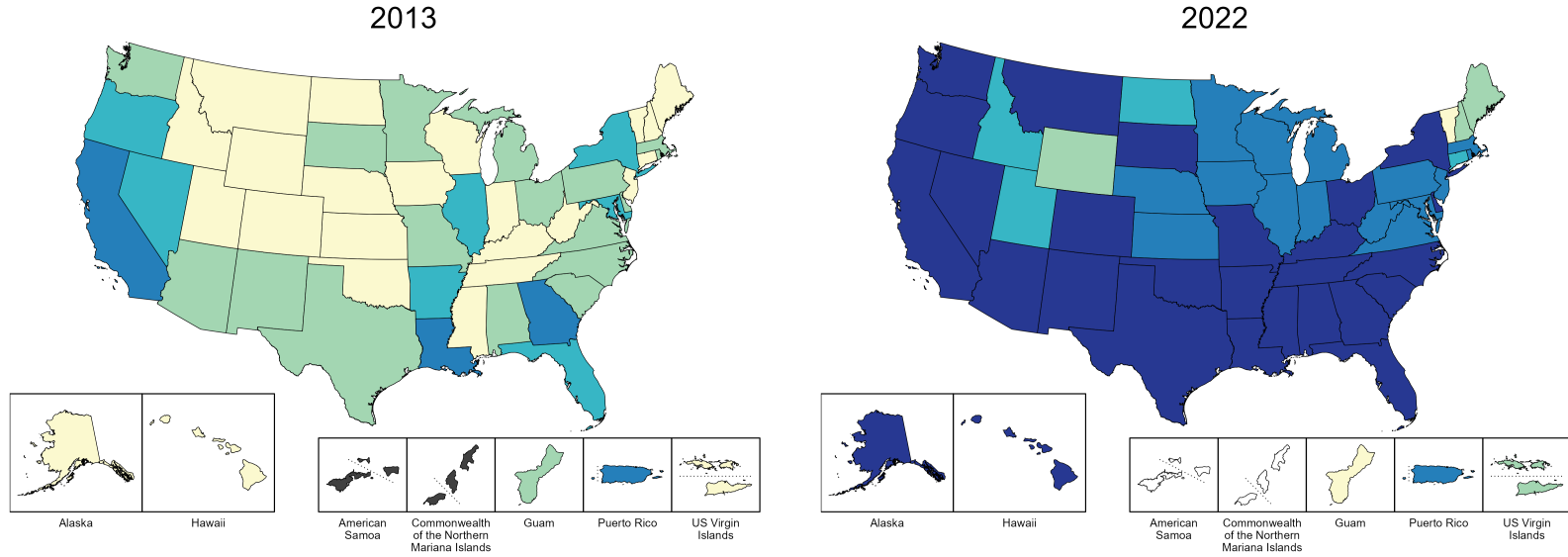


People most affected by STIs include:

- Adolescents and people aged 15-24 years
- Gay, bisexual, and other men who have sex with men
- Pregnant people
- People from some racial and ethnic minority groups

Reported cases of sexually transmitted infections (STIs) have increased dramatically in recent years. HIV, substance use, and viral hepatitis affect similar populations as STIs and each of these health concerns directly affects the others. A holistic, whole-of-society approach, including addressing social and economic barriers, is required to improve this syndemic and America's health.

Primary and Secondary Syphilis — Rates of Reported Cases by Jurisdiction, United States and Territories, 2013 and 2022

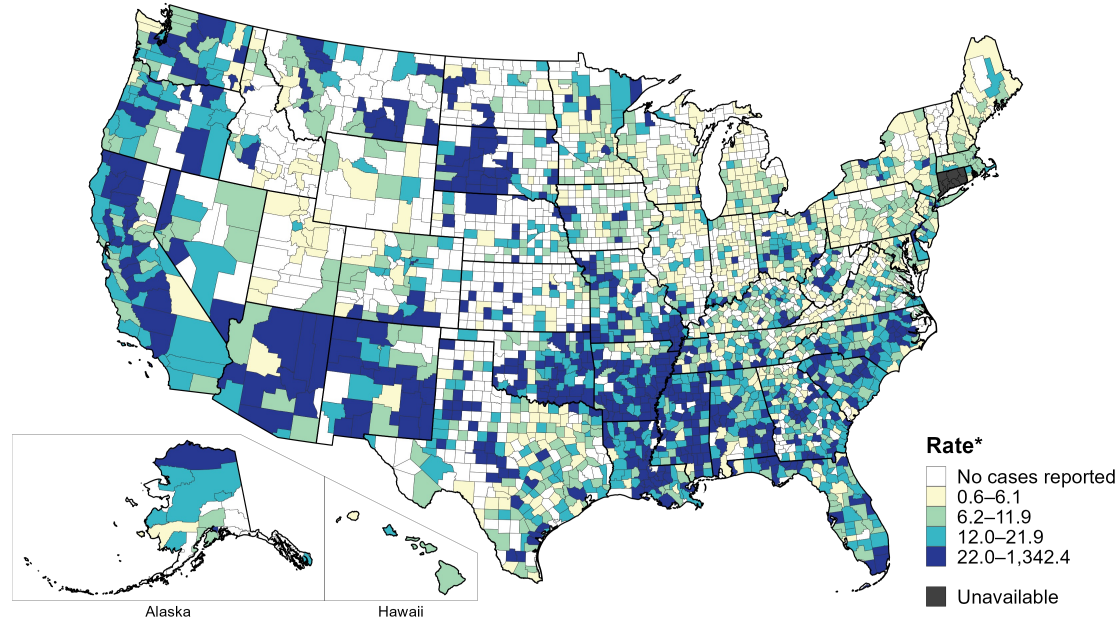


Rate* □ No cases reported □ 0.2–3.5 □ 3.6–5.9 □ 6.0–8.7 □ 8.8–13.5 □ 13.6–84.3 □ Unavailable

* Per 100,000



Primary and Secondary Syphilis — Rates of Reported Cases by County, United States, 2022



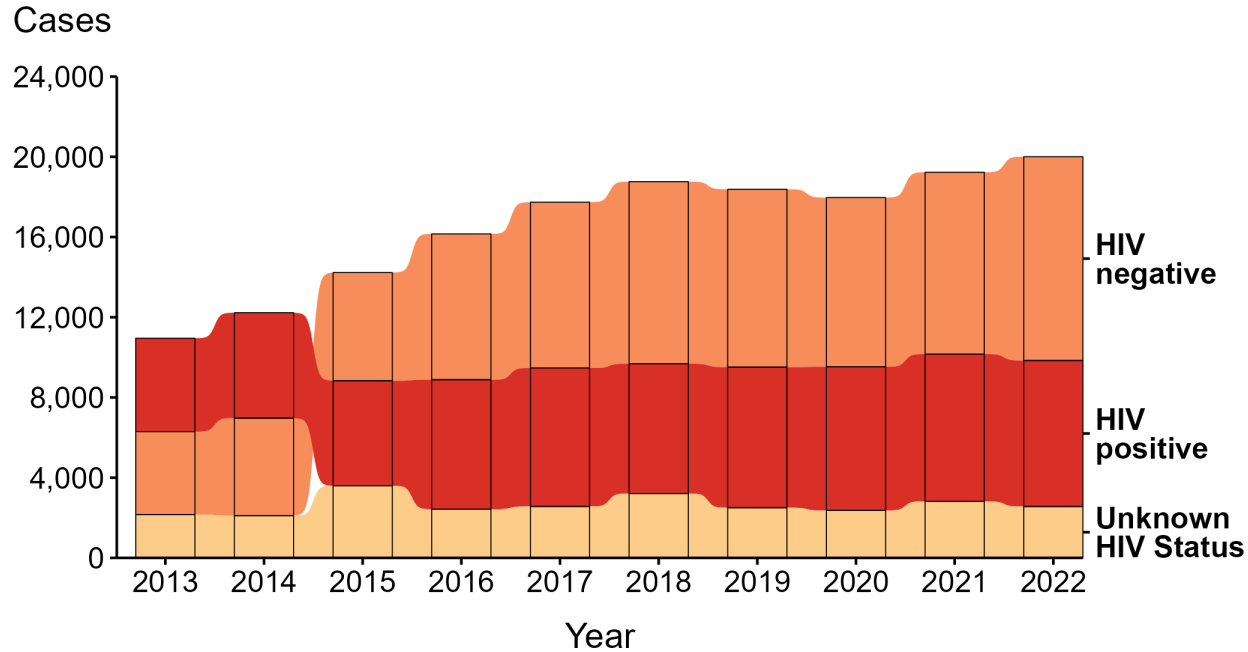
* Per 100,000

Primary and Secondary Syphilis — Reported Cases and Rates by State, United States, 2022

Rank*	State	Cases	Rate per 100,000 Population
1	South Dakota	767	84.3
2	New Mexico	761	36.0
3	Arkansas	1,001	32.9
4	Oklahoma	1,278	31.8
5	Mississippi	913	31.1
6	Arizona	2,151	29.2
7	Montana	325	28.9
8	Nevada	902	28.4
9	Louisiana	1,225	26.7
10	Oregon	1,117	26.3
11	Washington	1,920	24.7
12	Missouri	1,454	23.5
13	Alabama	1,190	23.5
14	Delaware	238	23.4
15	North Carolina	2,473	23.1
16	Alaska	160	21.8
17	Florida	4,618	20.8
18	Ohio	2,402	20.4
19	California	7,849	20.1
20	Georgia	2,182	20.0
21	South Carolina	1,033	19.6
22	New York	3,603	18.3
	US TOTAL†	59,016	17.7

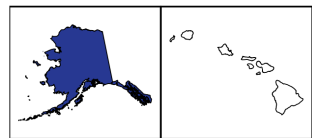
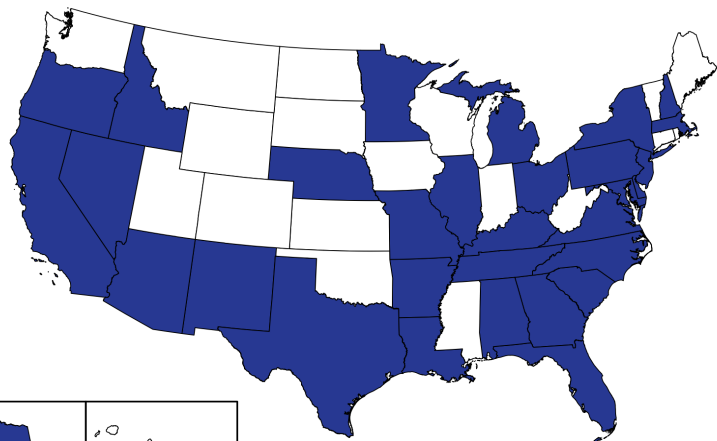
<https://www.cdc.gov/std/statistics/2022/table/21.htm>

Primary and Secondary Syphilis — Reported Cases Among Men Who Have Sex with Men by HIV Status, United States, 2013–2022



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

2012



Alaska

Hawaii



American Samoa

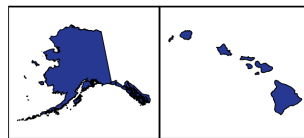
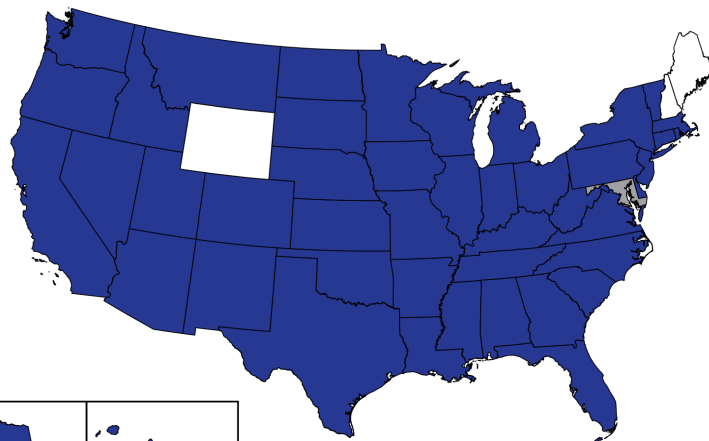
Commonwealth of the Northern Mariana Islands

Guam

Puerto Rico

US Virgin Islands

2021



Alaska

Hawaii



American Samoa

Commonwealth of the Northern Mariana Islands

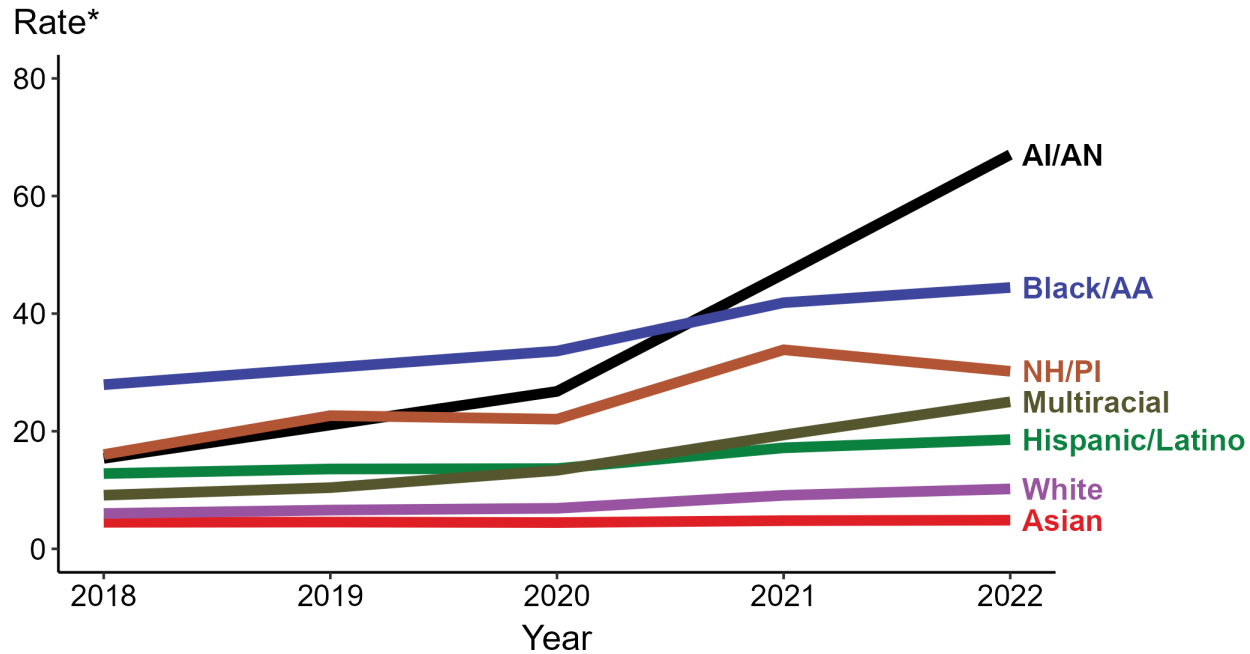
Guam

Puerto Rico

US Virgin Islands

Reported Cases ■ ≥1 case No cases Unavailable

Primary and Secondary Syphilis — Rates of Reported Cases by Race/Hispanic Ethnicity, United States, 2018–2022

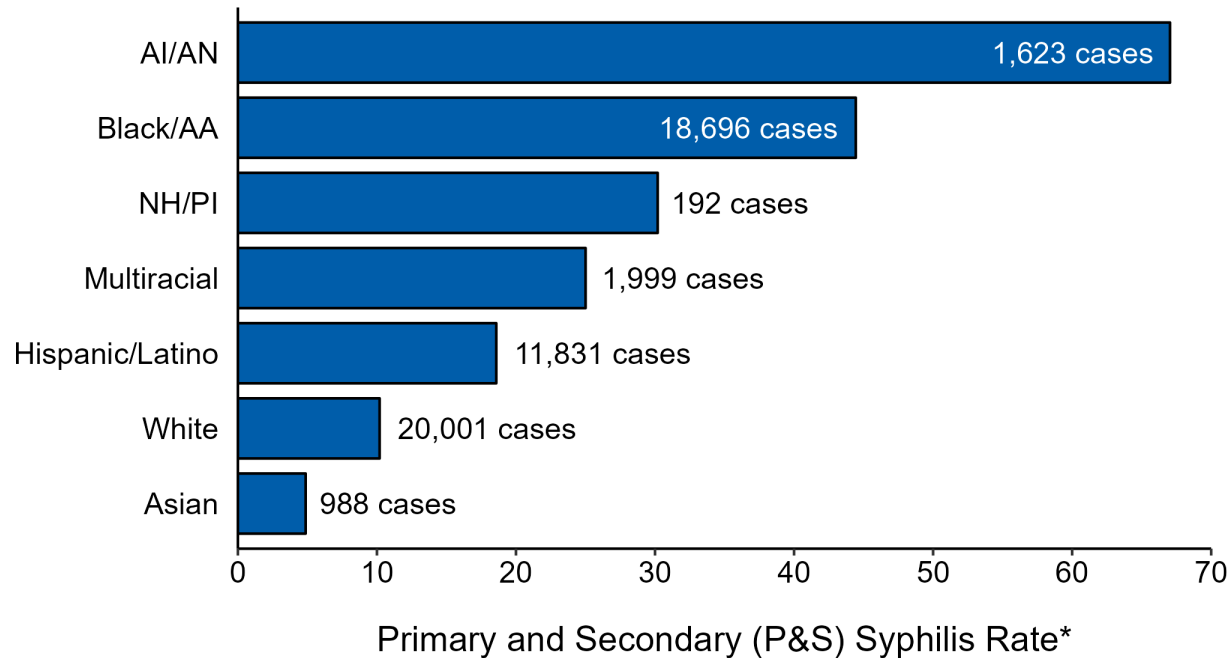


* Per 100,000

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



Primary and Secondary Syphilis — Case Counts and Rates of Reported Cases by Race/Hispanic Ethnicity, United States, 2022



* Per 100,000 population

NOTE: In 2022, a total of 3,686 P&S syphilis cases (6.2%) had missing, unknown, or other race and were not reported to be of Hispanic ethnicity. These cases are not shown in this plot.

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

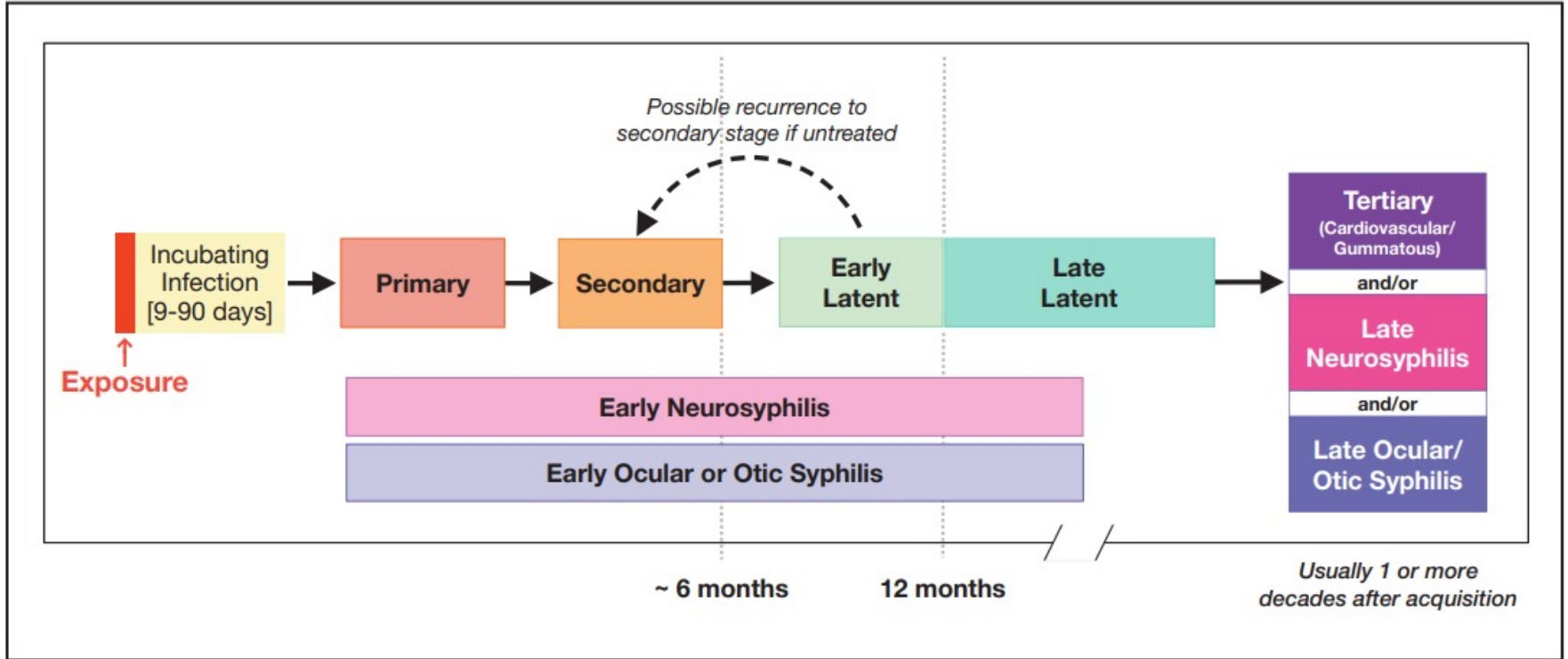


Syphilis

- **Sexual** (horizontal) and vertical transmission
- Average incubation period is **21 days** (can range from 10-90 days)
- **Four stages**
 - Primary
 - Secondary
 - Early (non-primary, non-secondary)
 - Unknown duration or late



The Natural History of Untreated Syphilis



Primary Syphilis

- **A single chancre** marks the onset of primary syphilis (can be multiple)
- **Usually firm, round, and painless**
Located where syphilis enters the body
- Can appear in **difficult to notice** locations (anus, vagina)
- **Lasts 3 to 6 weeks** and heals regardless of whether a person receives treatment
- If untreated, **will progress** to the secondary stage



40 % present with multiple painful ulcers

Secondary Syphilis

- **Skin rashes**

- Usually does not itch, may appear as rough, red, brown spots

- **Mucous membrane lesions**

- Sores in the mouth, vagina or anus mark the second stage of symptoms

- **Other symptoms:**

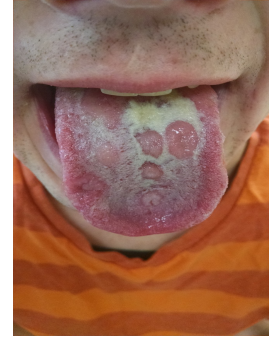
- Fever, swollen lymph nodes, sore throat, hair loss, aches and pains

- **Resolves** regardless of whether a person receives treatment

- If untreated, **will progress** to the latent and possible tertiary stages



Torso rash



Mucous patches



Alopecia



Palmar rash



Plantar rash



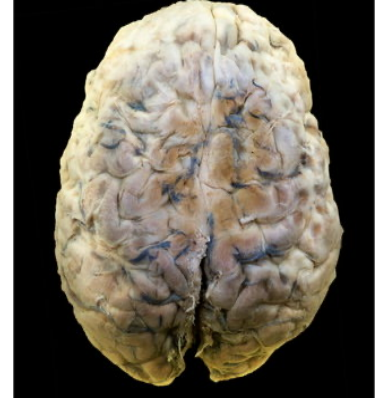
Condyloma lata

Latent Syphilis

- Latent (hidden) stage of syphilis is when there are no visible signs or symptoms of syphilis
- Early latent syphilis is where infection occurs **within the past 12 months**
- Late latent syphilis is where infection occurs **more than 12 months ago**
- Latent syphilis of unknown duration is when there is **not enough evidence** to confirm initial infection was within the previous 12 months

Tertiary Syphilis

- Rare, develops in a subset of untreated syphilis infections
- Appears 10-30 years after infection, can be fatal
- Can affect multiple organ systems including: brain, nerves, heart, blood vessels, eyes, liver, bones, joints



Neurologic Manifestations of Syphilis

- **Can occur at any stage**

Neurosyphilis (Nervous System)	Ocular Syphilis (Visual System)	Otosyphilis (Auditory/Vestibular System)
<ul style="list-style-type: none">- Severe headache- Trouble with muscle movements- Paralysis- Numbness- Altered mental status	<ul style="list-style-type: none">- Eye pain or redness- Floating spots in field of vision- Sensitivity to light- Can lead to permanent blindness	<ul style="list-style-type: none">- Ringing in ears (tinnitus)- Balance difficulties- Vertigo- Can lead to permanent hearing loss

Congenital Syphilis Transmission

How

- Transplacental during maternal spirochetemia
- Direct contact with an infectious lesion during birth
- Not transferred into breast milk

When during gestation?

- At any time during gestation with increasing frequency as gestation advances.

Transmission according to syphilis stage:

- | | |
|----------------------------------|-------------------|
| • Primary or secondary syphilis: | 60% to 90% |
| • Early latent: | 40% |
| • Late latent syphilis: | 10% |

Congenital Syphilis

- Occurs when a pregnant person with syphilis passes the infection on to their baby during pregnancy
- Testing for pregnant people is recommended at the **first prenatal visit, during the third trimester (28 weeks), and at the time of delivery**
- Any person who delivers a **stillborn infant after 20 weeks gestation** should receive testing for syphilis
- Untreated syphilis in pregnant people results in infant death in **up to 40 percent** of cases



Barriers to Diagnosis and Treatment of Syphilis During Pregnancy

- **Risk factors**

- Poor access to prenatal care
- Lack of syphilis testing during pregnancy
- Lack of adequate treatment of confirmed syphilis during pregnancy
- Mother coinfecting with HIV

- **Social vulnerabilities**

- Homelessness
- Substance abuse
- Incarceration

Syphilis Screening Guidelines

CDC

- Asymptomatic persons at increased risk*
- MSM - at least annually
 - Every 3 to 6 months if at increased risk
- All pregnant women at the first prenatal visit, and at 28 weeks of gestation and at delivery if at high risk**

IHS

- **Annual syphilis testing for persons ages 13 and older**
 - For at least 2 consecutive years
- Turn on the annual Electronic Health Record reminder at all sites
- Provide three-point syphilis testing for all pregnant people

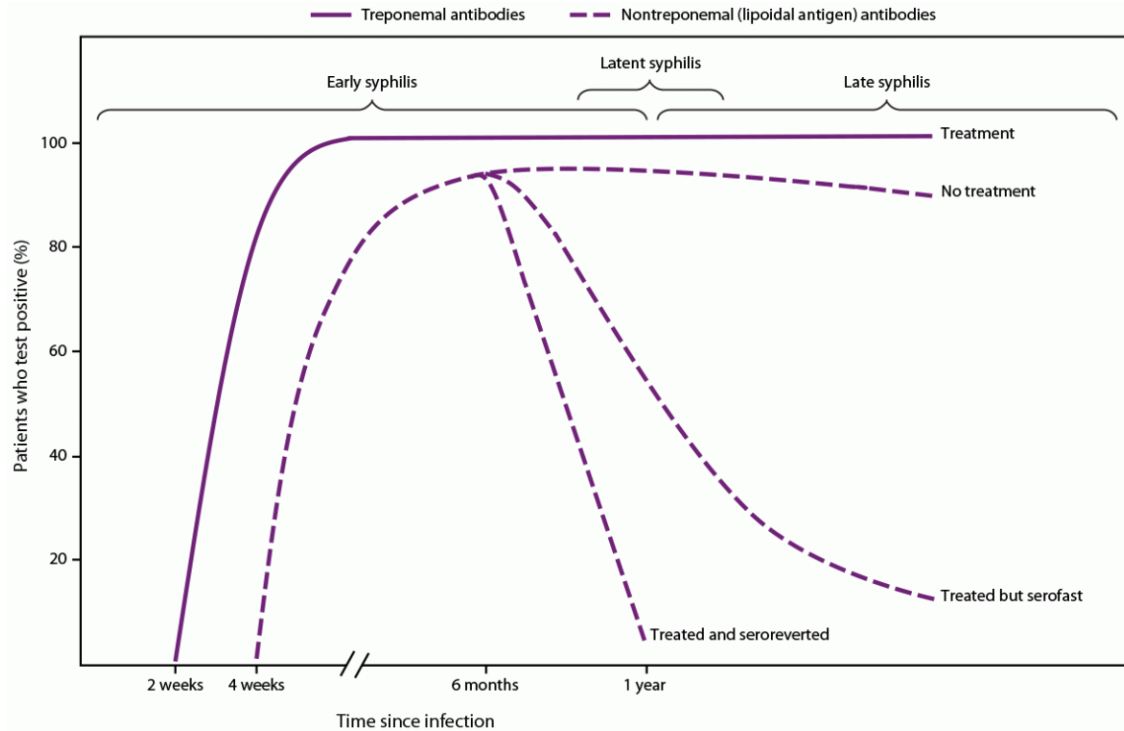
* History of incarceration or transactional sex work, residence in region with high rates, race/ethnicity with high rates, male < 29 yo

**IPatient lives in a community with high syphilis morbidity or is at risk for syphilis acquisition during pregnancy (SUD, STIs during pregnancy, multiple partners, a new partner, partner with STIs)

Serologic Tests for Syphilis

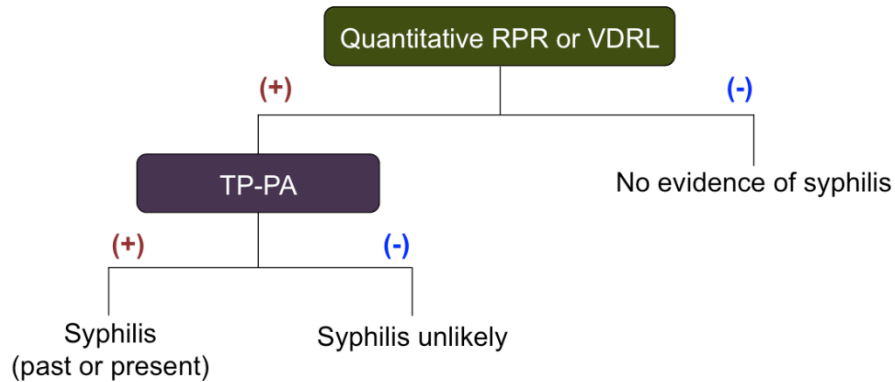
Nontreponemal	Treponemal
VDRL, RPR	CIE, EIA, FTA-ABS, TP-PA, rapid tests
Measure IgG and IgM to cardiolipin-cholesterol- lecithin antigen	Measure IgG and IgM to Treponemal antigens
Qualitative or quantitative	Qualitative
May be used as a screening test	Preferred screening test More specific and sensitive than Non treponemal test
Titer used to follow response to therapy	Generally, remain reactive for life

Serologic response to infection with *Treponema pallidum*, the causative agent of syphilis



Syphilis testing algorithms

Traditional Sequence



Reverse Sequence

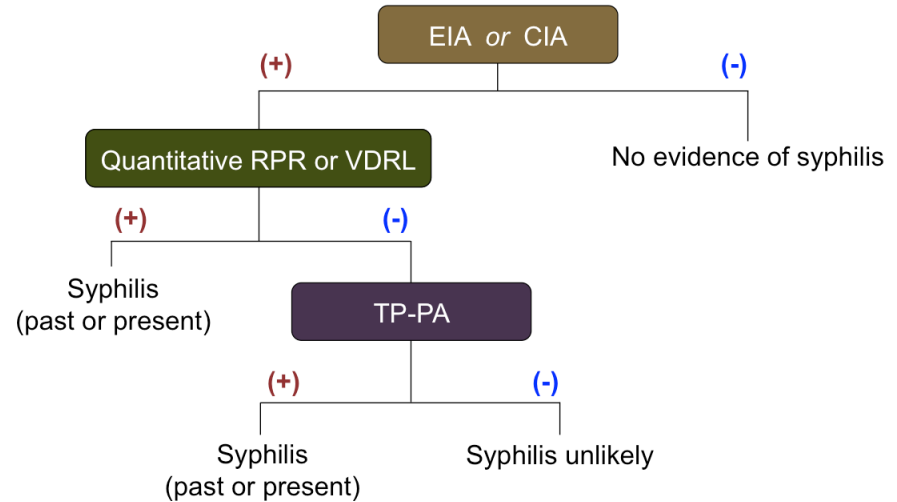


Table 1. Sensitivity and Specificity of Serologic Tests for Syphilis

Test	Sensitivity during stage of infection, % (range)				Specificity, % (range)
	Primary	Secondary	Latent	Late	
Nontreponemal tests					
VDRL [14]	78 (74–87)	100	96 (88–100)	71 (37–94)	98 (96–99)
TRUST [14]	85 (77–86)	100	98 (95–100)	NA	99 (98–99)
RPR [14]	86 (77–99)	100	98 (95–100)	73	98 (93–99)
Early treponemal tests					
MHA-TP [15]	76 (69–90)	100	97 (97–100)	94	99 (98–100)
TPPA [16]	88 (86–100)	100	100	NA	96 (95–100)
TPHA [17]	86	100	100	99	96
FTA-ABS [14]	84 (70–100)	100	100	96	97 (94–100)
Enzyme immunoassays					
IgG-ELISA [18]	100	100	100	NA	100
IgM-EIA [19]	93	85	64	NA	NA
ICE [20]	77	100	100	100	99
Immunochemiluminescence assays					
CLIA [21]	98	100	100	100	99

NOTE. CLIA, chemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption assay; ICE, immune-capture EIA; MHA-TP, microhemagglutination assay for *Treponema pallidum*; NA, not available; TPHA, *T. pallidum* hemagglutination assay; TPPA, *T. pallidum* particle agglutination; TRUST, toluidine red unheated serum test.

Arlene C. Seña, Becky L. White, P. Frederick Sparling, Novel *Treponema pallidum* Serologic Tests: A Paradigm Shift in Syphilis Screening for the 21st Century, *Clinical Infectious Diseases*, Volume 51, Issue 6, 15 September 2010, Pages 700–708,

Syphilis Testing:

Causes of Biological False Positives

Non-Treponemal Tests (RPR/VDRL)

- Autoimmune disease
- Pregnancy
- Injection drug use
- Advanced age
- Other infections (HIV, HBV)
- Recent vaccination
- Chronic liver disease
- False positive occurs in 1-2% of US patients; titer usually 1:8 or less

Treponemal Tests (TP-AB, TPPA, EIA, CIA)

- Autoimmune disease
- Other spirochetes
- Pregnancy
- Inflammatory disease
- Severe gingivitis
- Advanced age (>50 years),
- Tumor
- Dialysis
- Systemic infections unrelated to syphilis (TB, rickettsial diseases, endocarditis, malaria)

Rapid/Point-of-Care Testing

Health Check:

Rapid syphilis test (10 minute results)

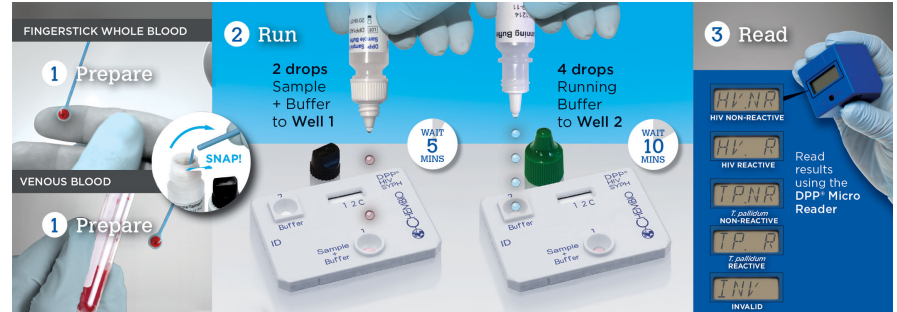
Treponemal antibody test



Chembio:

Dual rapid HIV-Syphilis test (15 minute results)

HIV-1/2 antibody test / Treponemal antibody test



Treatment

- **Rapid Treatment**
 - Treat immediately after rapid test results
- **Presumptive Treatment**
 - Symptomatic patients
 - Patients with known exposure
- **Targeted treatment**
 - Based on laboratory results



Treatment of syphilis with Penicillin

Stage or Presentation				
Primary	Secondary	Early non-primary, non secondary	Late Latent/ or Unknown Duration	Neurosyphilis, ocular syphilis and otic syphilis
Benzathine penicillin 2.4 million units IM in a single dose	Benzathine penicillin 2.4 million units IM in a single dose	Benzathine penicillin 2.4 million units IM in a single dose	Benzathine penicillin 2.4 million units total administered as 3 doses of 2.4 million units IM each at 1-week intervals	<p>Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units by IV every 4 hours or continuous infusion for 10-14 days</p> <p>Alternative: procaine penicillin G 2.4 million units IM 1x/day PLUS probenecid 500 mg orally 4x/day, both for 10-14 days</p>



<https://www.cdc.gov/std/treatment-guidelines/default.htm>

As of May 2024, I H S has an adequate supply of benzathine penicillin G to treat all syphilis patients

1. Pregnant persons and HIV infected persons with syphilis as well as infants with congenital syphilis should receive priority for treatment with Benzathine penicillin G.

Benzathine penicillin G (Bicillin L-A®) is the only recommended treatment for pregnant people infected or exposed to syphilis.

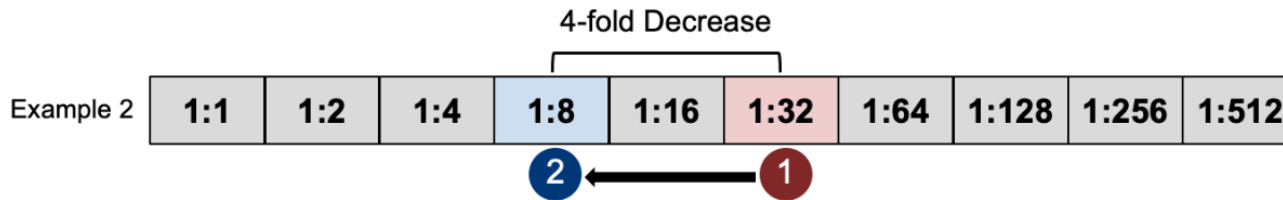
2. Other persons with early syphilis (primary, secondary, early latent) and sexual partners should be treated with Benzathine penicillin G if supplies are adequate to cover high risk patients listed under priority #1.
3. If Benzathine penicillin G supplies are inadequate to cover patients listed as priority #2, treat early syphilis (primary, secondary, early latent) with **doxycycline 100 mg po bid for 14 days** and late latent syphilis or latent syphilis of uncertain duration with **doxycycline 100 mg po bid for 28 days**.
4. (Ceftriaxone 1 gm IV daily for 10 days may be an acceptable second-line alternate treatment for primary and secondary syphilis)

Penicillin Allergy

- **Patients often are incorrectly labeled as allergic to penicillin**
 - Evaluate what symptoms were experienced by patients with reported penicillin allergy. Consider allergy testing.
- **Penicillin allergy causing anaphylaxis is rare**
 - In studies that have incorporated penicillin skin testing and graded oral challenge among persons with reported penicillin allergy, the true rates of allergy are low, ranging from 1.5% to 6.1%.
- **Allergies wane over time:**
 - Approximately 80% of patients with a true IgE-mediated allergic reaction to penicillin have lost the sensitivity after 10 years
- ***Desensitization is recommended for pregnant women diagnosed with syphilis followed by treatment with penicillin.***

Follow-up testing

- **Adequate serologic response to treatment: ≥ 4 -fold decline in nontreponemal titer**
 - Early Syphilis Primary/secondary/early latent: **within 12 months**
 - Late Syphilis: Late Latent, tertiary: **within 24 months**
 - Persons with HIV: **within 24 months**
- **Serofast** (lack of seroreversion):
 - Persistent nontreponemal titer after treatment



“Always Obtain RPR close or on the day of treatment”

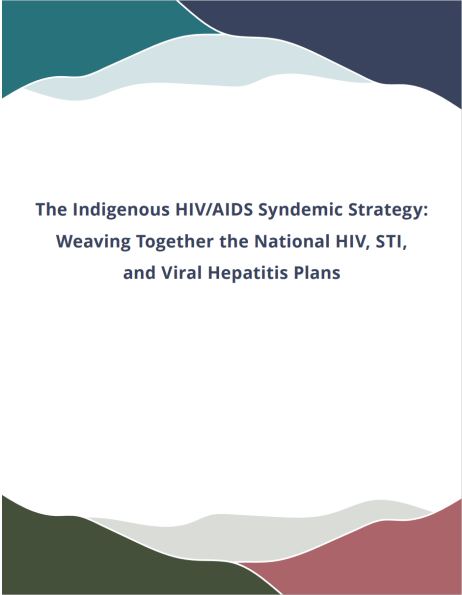
Overlapping Epidemics: “Syndemic” Bundle for Screening

Indian Health Service “Syndemic Bundle”

1. Syphilis screening test with reflex RPR and TPPA
2. HIV serology (with documentation of consent if required in the local state jurisdiction)
3. Screening for gonorrhea and chlamydia at three sites: Urine, Pharynx, Rectum
4. Screening for hepatitis B and C
5. Pregnancy test

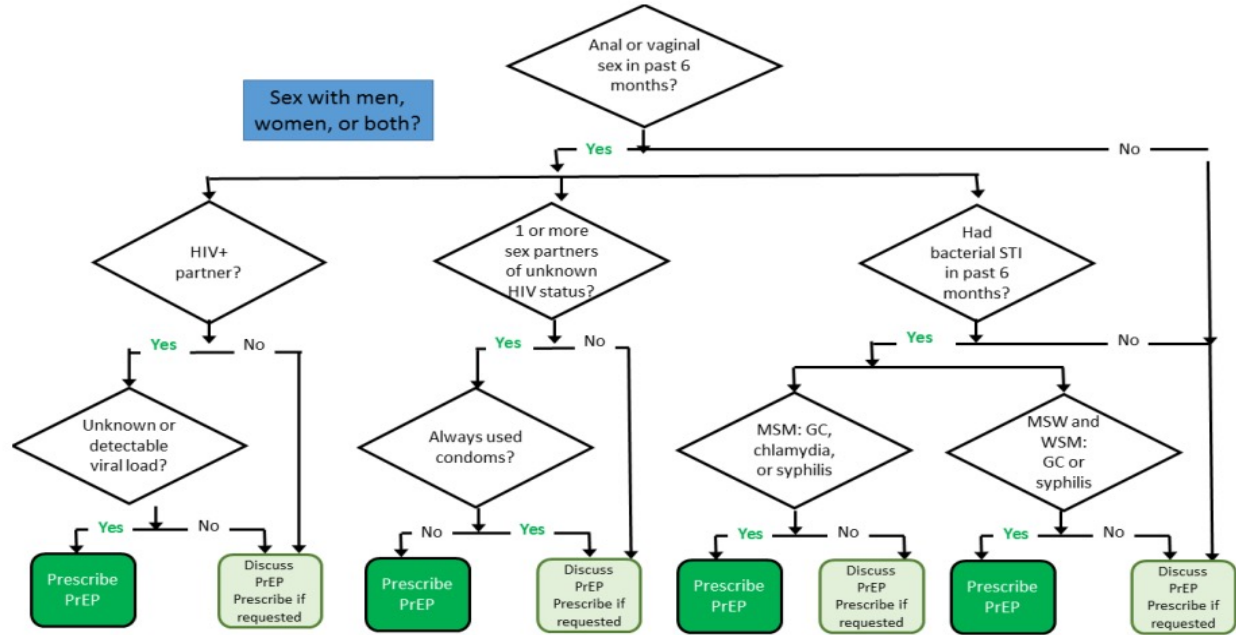
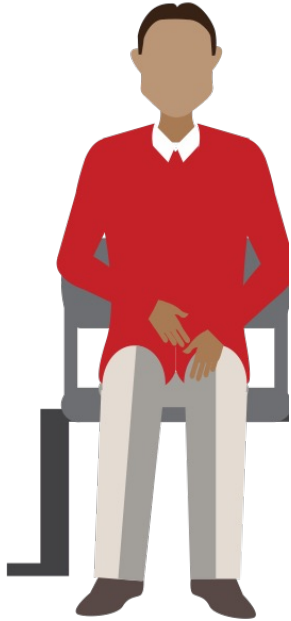
[Stop-Syphilis-Letter-2-15-24.pdf \(indiancountryecho.org\)](#)

<https://www.indiancountryecho.org/indigenous-hiv-aids-syndemic-strategy/>



The Indigenous HIV/AIDS Syndemic Strategy:
Weaving Together the National HIV, STI,
and Viral Hepatitis Plans

HIV Pre-exposure Prophylaxis (PrEP)



[US Public Health Service: PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE, A CLINICAL PRACTICE GUIDELINE \(cdc.gov\)](https://www.cdc.gov/hiv/prep/2021-update)

DoxyPEP

Prevention of chlamydia, gonorrhea, and syphilis

- Take 1 dose of Doxycycline 200mg
< 72 hours after condomless sex
- **Who should receive DoxyPEP?**
 - Men who have sex with men (MSM)/Trans Women (TGW) on HIV PrEP or living with HIV
 - If not on HIV PrEP, MSM/TGW with history of STIs within the past 12 months, sex work, chemsex (sex under the influence of drugs)



Case 1:

HPI:

- 20 yo cis-gender female who has sex with cis-gender males, presents for a pregnancy test only. She reports last had oral and vaginal sex without protective barrier 3 weeks ago and had 2 partners over the past 6 months. No current signs or symptoms, and doesn't recollect any in the past year
- Never tested for HIV; last gonorrhea/chlamydia (urine only) and RPR tests were 11 months ago, all negative

Social History:

- Denies drug use, reports unstable housing and transportation, no regular access to phone

Labs in Office

- Rapid pregnancy test: **negative**
- Agrees to rapid HIV/Syphilis test in office when offered incentive
- HIV: **non-reactive**; Syphilis (treponemal antibody): **reactive**

Case 1:

What are the recommended next steps? (Check all that apply)

- A. No further testing necessary, as initial reason for the visit (pregnancy testing) already completed
- B. Draw serum HIV, test for gonorrhea and chlamydia in the urine and throat
- C. Draw RPR, wait for results (~1 week) to determine treatment
- D. Draw RPR and immediately administer 2.4 MU IM injection of benzathine penicillin for early latent stage syphilis
- E. Draw RPR and immediately administer 2.4 MU IM injection of benzathine penicillin weekly x 3 weeks (total 7.2 MU) for late latent stage syphilis

References

- ❖ CDC STD 2021 Treatment Guideline: <https://www.cdc.gov/std/treatment-guidelines/default.htm>
- ❖ STD Prevention Training Centers: <https://www.cdc.gov/std/projects/nnptc.htm>
- ❖ STD online self-study: <https://www.std.uw.edu/>
- ❖ CDC self-study: <http://www.cdc.gov/std/training/std101/home.htm>
- ❖ USPS Task Force: <https://www.uspreventiveservicestaskforce.org/uspstf/>

Resources

- National Clinician Consultation Center
<http://nccc.ucsf.edu/>
 - HIV Management
 - Perinatal HIV
 - HIV PrEP
 - HIV PEP line
 - HCV Management
 - Substance Use Management
- Present on ECHO
- <https://hsc.unm.edu/scaetc/programs-services/echo.html>
- AETC National HIV Curriculum
<https://aidsetc.org/nhc>
- AETC National Coordinating Resource Center
<https://targethiv.org/library/aetc-national-coordinating-resource-center-0>
- HIVMA Resource Directory
<https://www.hivma.org/globalassets/ektron-import/hivma/hivma-resource-directory.pdf>
- Additional trainings
scaetcecho@salud.unm.edu
- www.scaetc.org

IHS/Tribal Resources

- Sexually Transmitted Infections (STI) Initiative: STI Toolkit. https://www.ihs.gov/sites/nptc/themes/responsive2017/display_objects/documents/sti/Express-STI-Guide.pdf
- <https://www.indiancountryecho.org/resource-hubs/syphilis-resources/> The STOP SYPHILIS campaign offers free materials, including print materials, social media posts, and short educational videos.
- Go to www.stopsyphilis.org For questions about field testing and treatment policies and procedures, contact Tina Tah, Public Health Nursing Consultant, by e-mail at tina.tah@ihs.gov