Indian Health Service

Syphilis Response: Best Practices

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NATIONAL HIV/HCV/STI CLINICAL COORDINATOR

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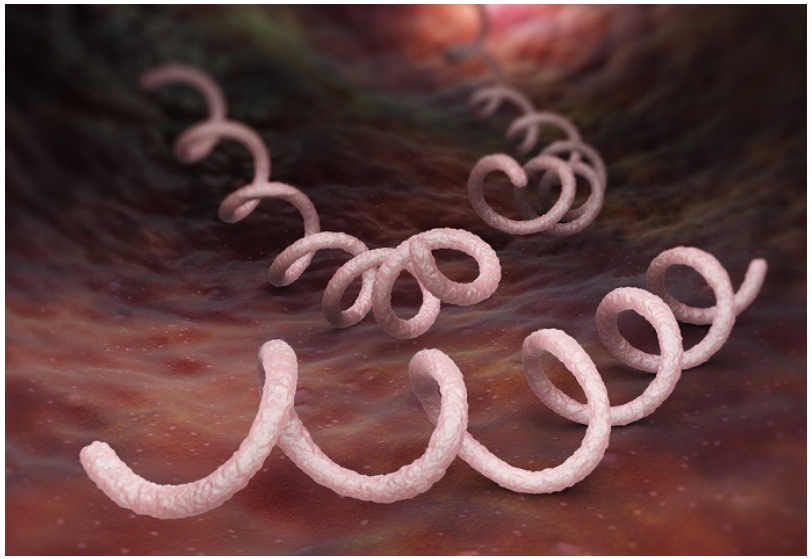
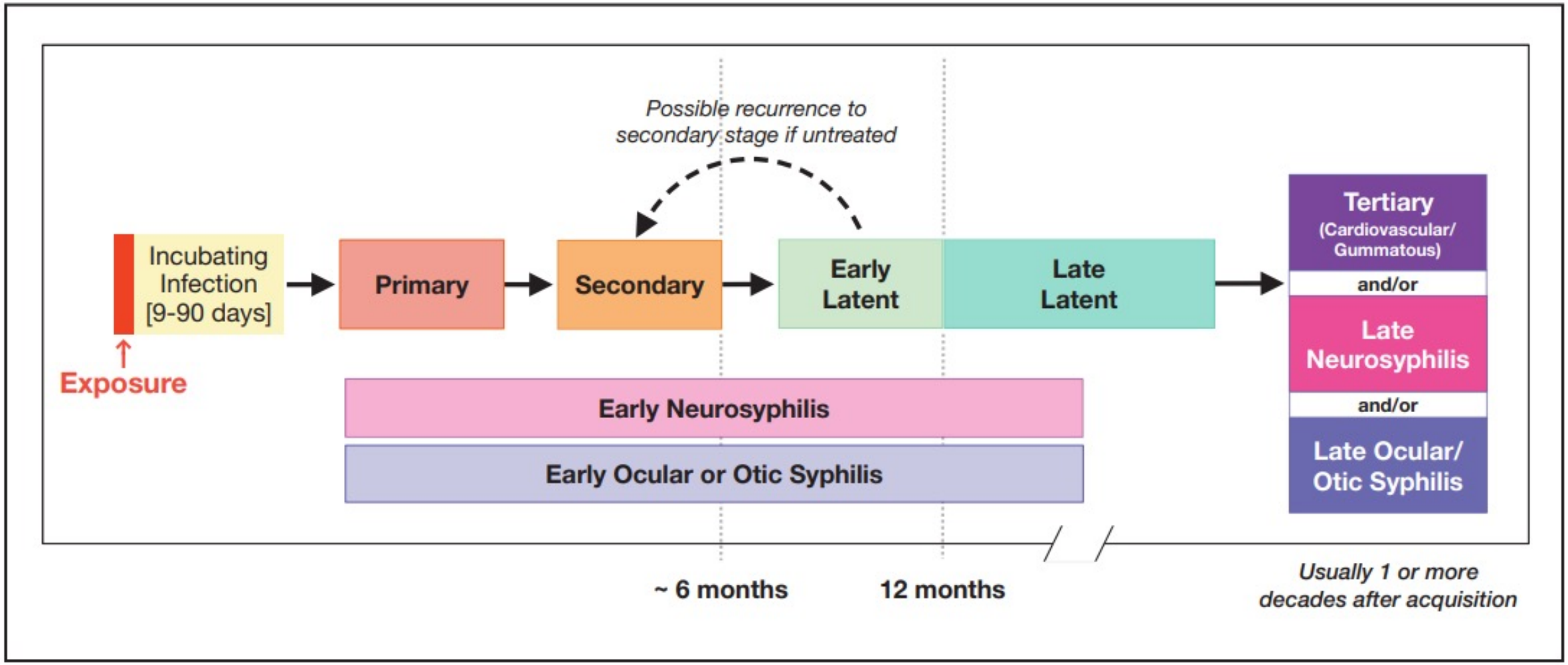
Syphilis

- Sexually transmitted infection (STI) caused by the bacterium *Treponema pallidum*
- Sexual, vertical and horizontal transmission
- Average time between syphilis acquisition and start of symptoms is 21 days (can range from 10-90 days)

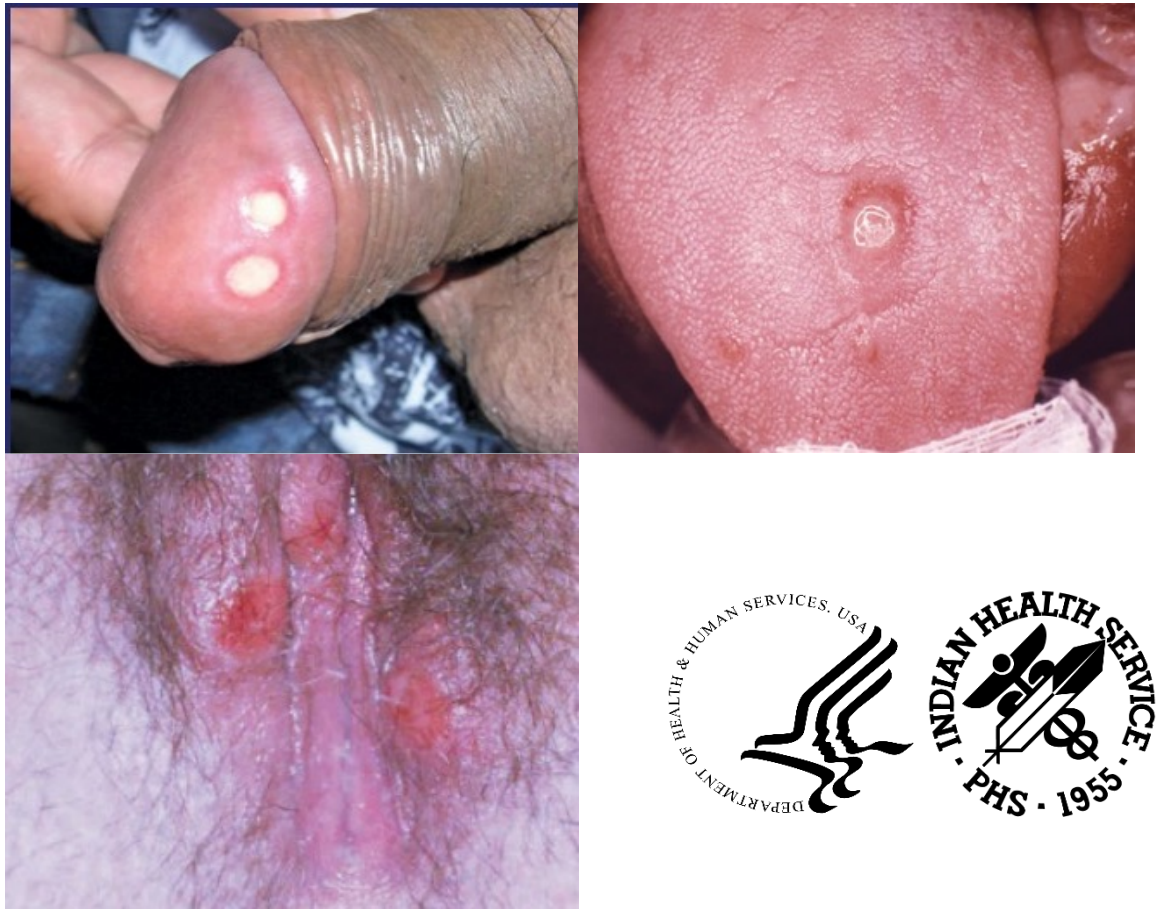


The Natural History of Untreated Syphilis



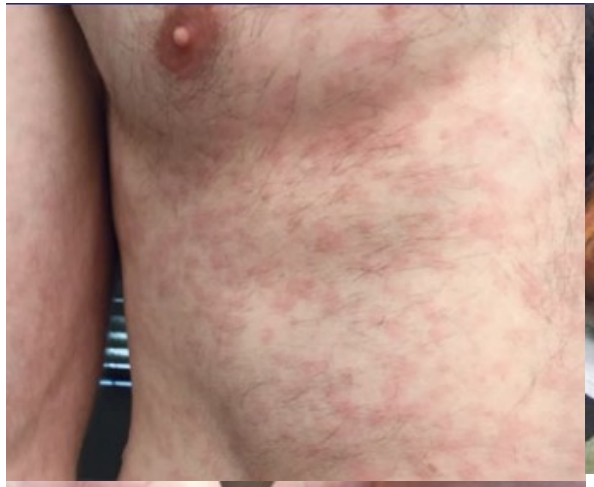
Primary Syphilis

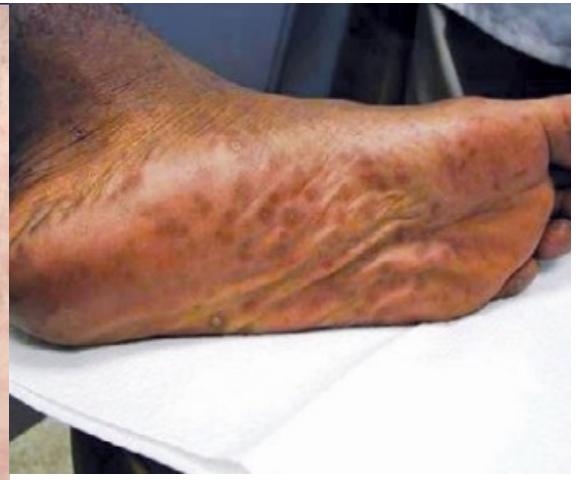
- A single chancre marks the onset of primary syphilis (can be multiple)
- Usually firm, round, and painless Located where syphilis enters the body
- Can appear in locations that are difficult to notice (anus, vagina)
- Lasts 3 to 6 weeks and heals regardless of whether a person receives treatment
-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

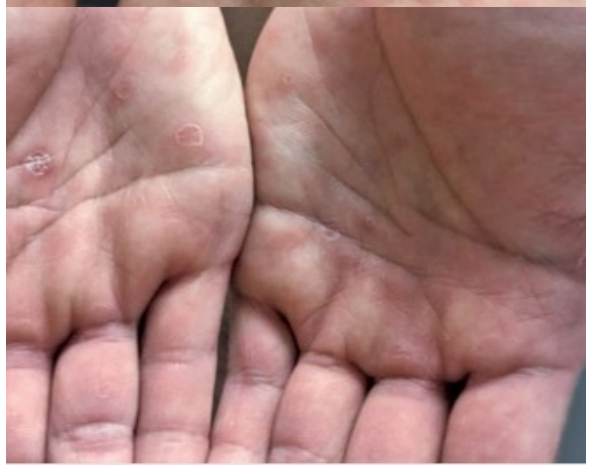


Secondary Syphilis

- Skin rashes and/or mucous membrane lesions (sores in the mouth, vagina or anus) mark the second stage of symptoms
- Usually does not itch, may appear as rough, red, brown spots
- May be accompanied by fever, swollen lymphs, 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 stage

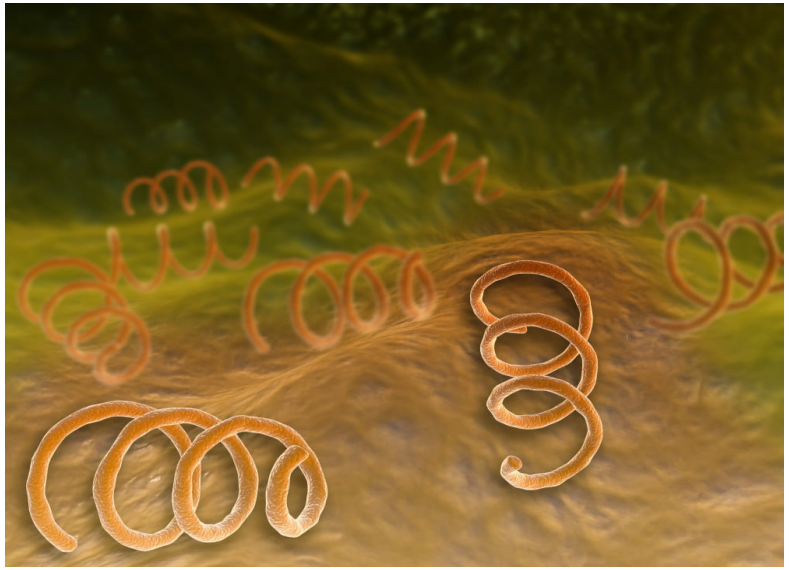






Latent Syphilis

- Latent (hidden) stage of syphilis is when there are no visible signs or symptoms of syphilis
- Early latent syphilis is latent syphilis where infection occurs **within the past 12 months**
- Late latent syphilis is latent syphilis 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



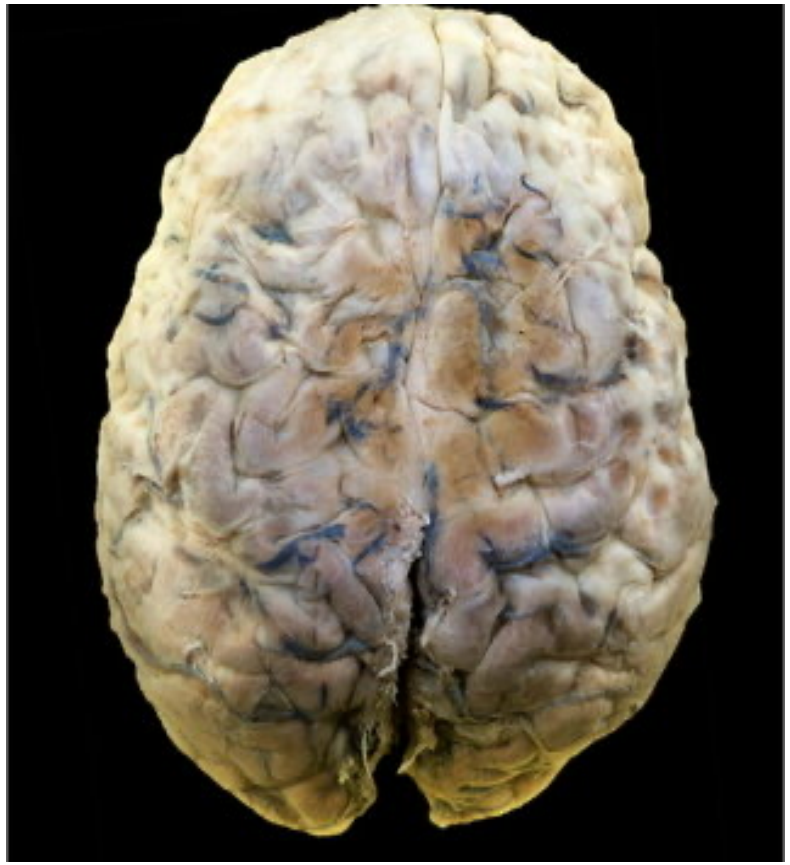
Neurologic Manifestations of Syphilis

Can occur at any stage

Neurosyphilis (Nervous System)	**Ocular Syphilis** (Visual System)	**Otosyphilis** (Auditory/Vestibular System)
- Severe headache - Trouble with muscle movements - Paralysis - Numbness - Altered mental status	- Eye pain or redness - Floating spots in field of vision - Sensitivity to light - Can lead to permanent blindness	- Ringing in ears (tinnitus) - Balance difficulties - Vertigo - Can lead to permanent hearing loss

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

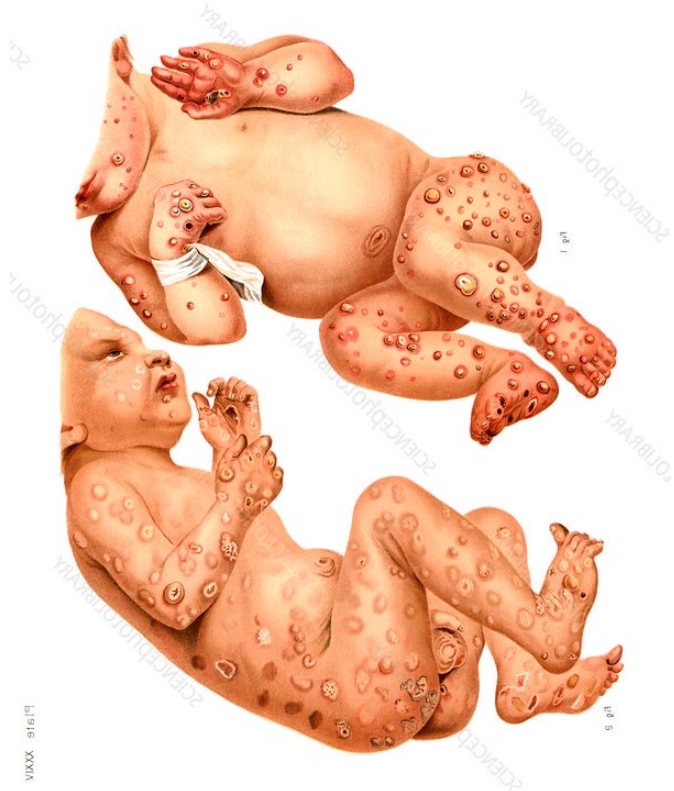


Congenital Syphilis

- Occurs when a pregnant person with syphilis passes the infection on to their baby during pregnancy
- Several factors are considered to determine if a baby has congenital syphilis:
  - Results of maternal syphilis blood test and, if diagnosed with syphilis, whether syphilis was adequately treated during pregnancy
  - Results of baby's syphilis blood test, a physical exam of baby, spinal tap, imaging
- A baby born alive with syphilis may be asymptomatic. However, without immediate treatment, the baby may develop serious problems (developmental delays, seizures, death) within a few weeks

Congenital Syphilis

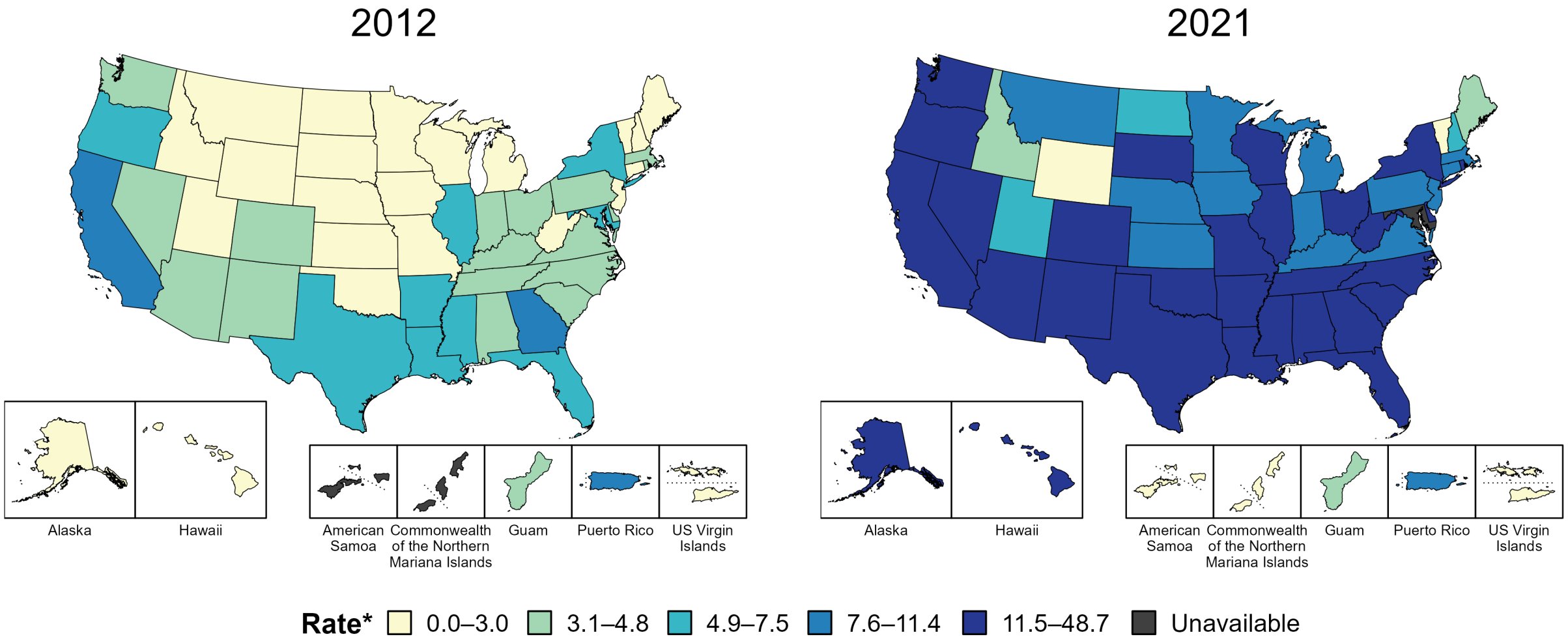
- Testing for pregnant people is recommended at the **first prenatal visit, during the third trimester (28 weeks), and at the time of delivery**
- Any person who delivers a **stillborn infant after 20 weeks gestation** should receive testing for syphilis
- Untreated syphilis in pregnant people results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



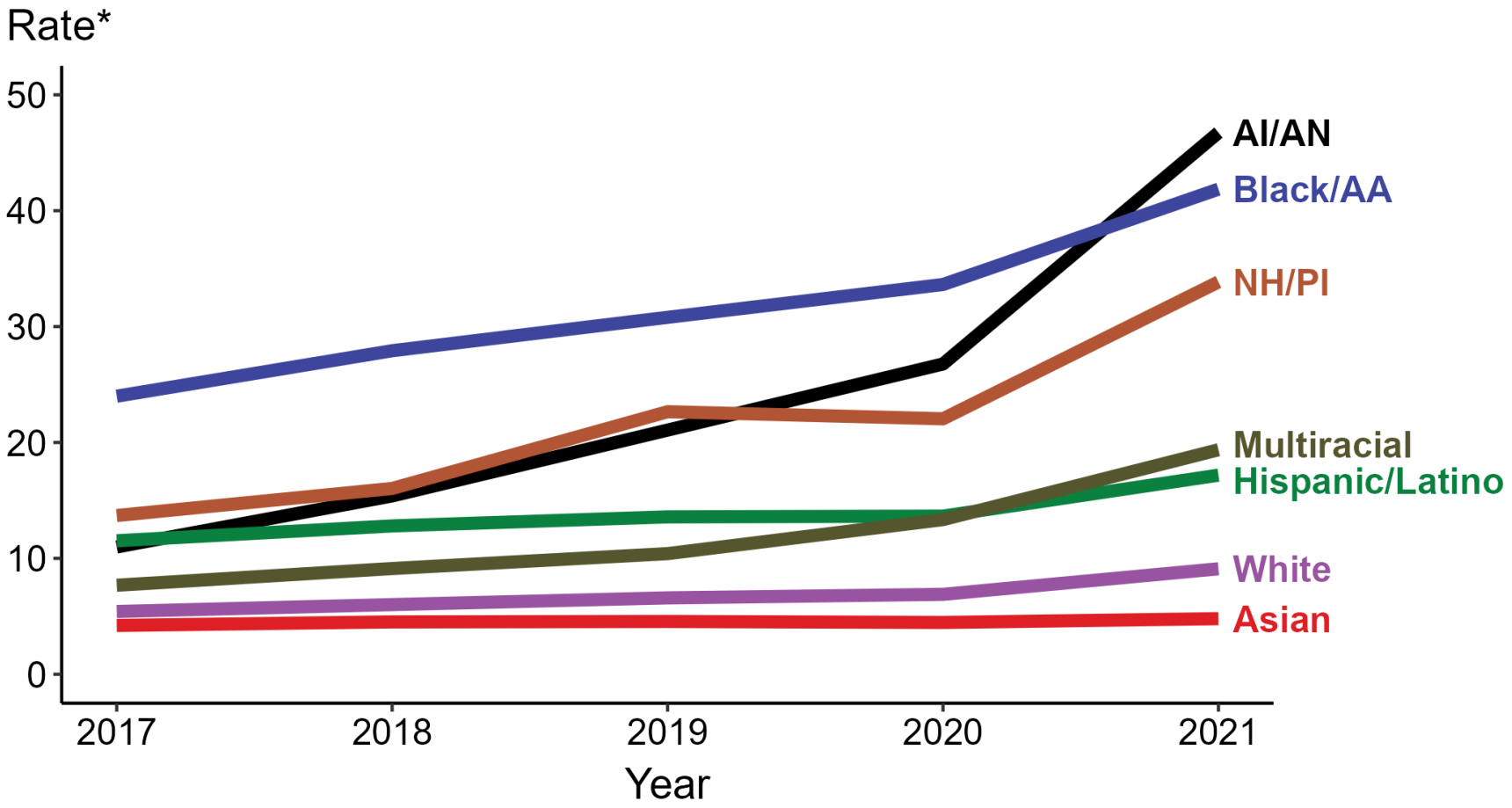
Congenital Syphilis

- Syphilitic Stillbirth is defined as a fetal death that occurs **after 20-week gestation** OR in which the **fetus weighs >500g** AND **the mother had untreated or inadequately treated syphilis at delivery**
- Adequate treatment is defined as the completion of a penicillin-based regimen, in accordance with CDC treatment guidelines, appropriate for the stage of infection, **initiated 30 or more days before delivery**

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

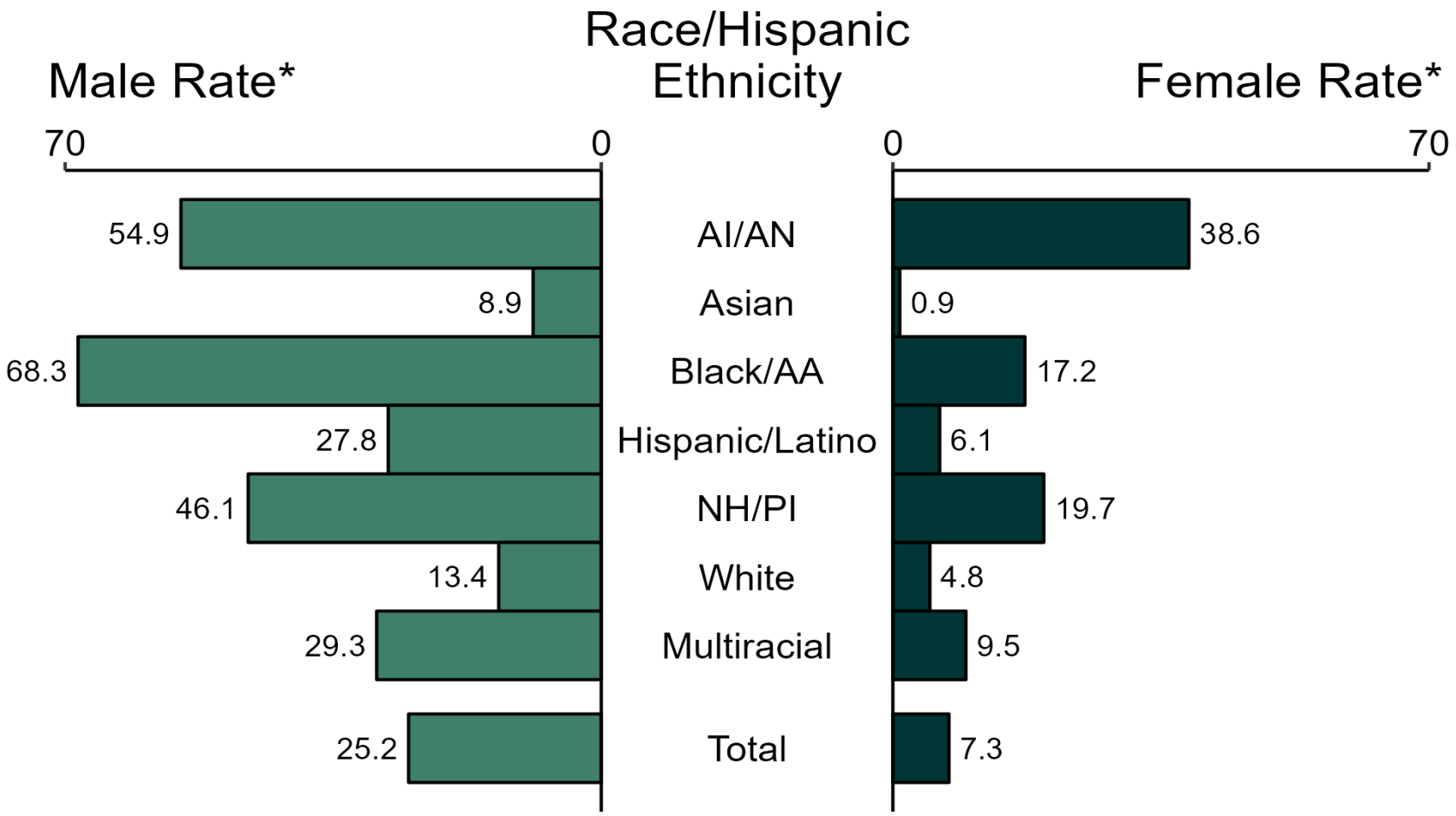


Primary and Secondary Syphilis — Rates of Reported Cases by Race/Hispanic Ethnicity, United States, 2017–2021



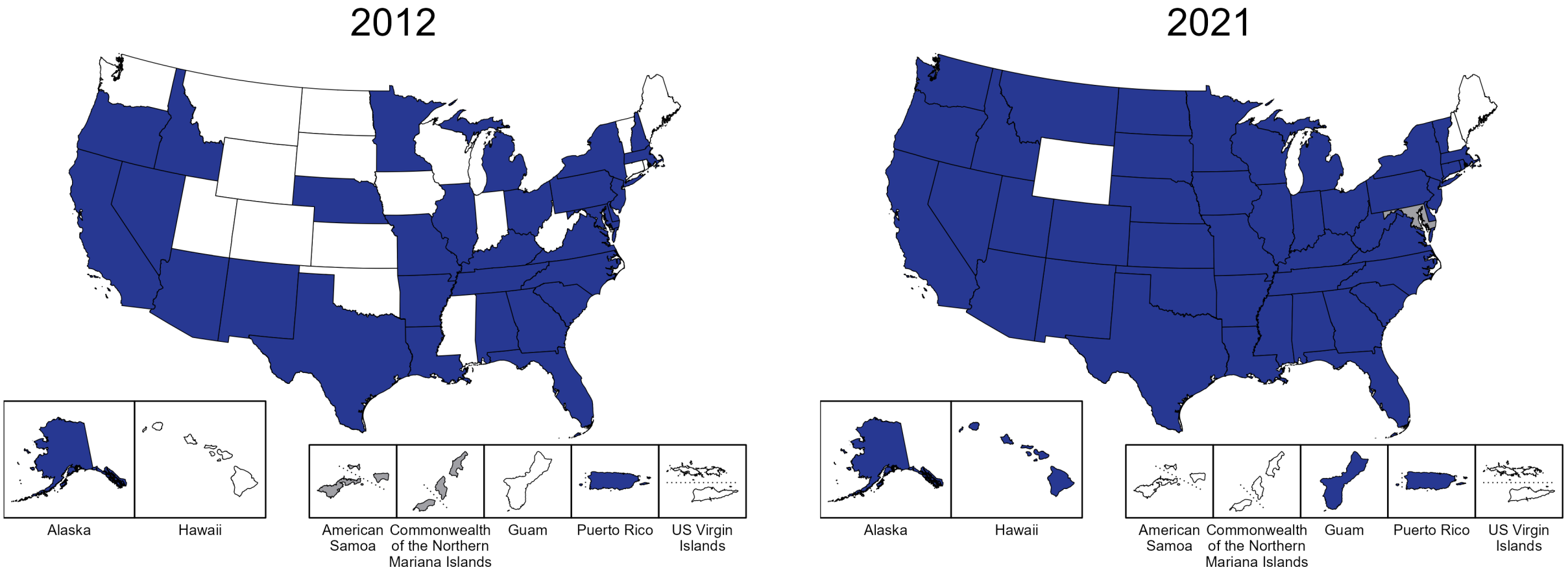
* Per 100,000

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

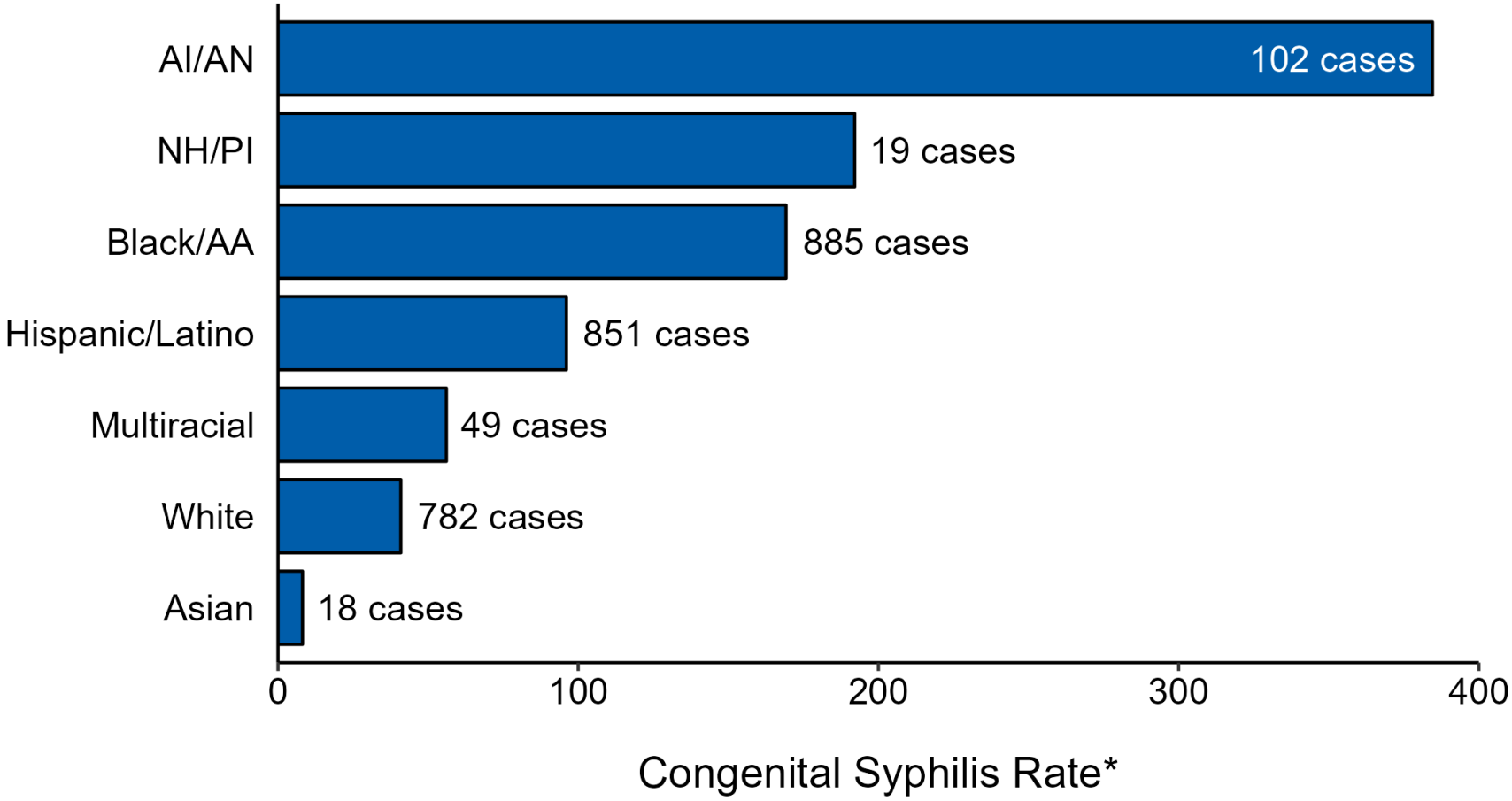


* Per 100,000

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

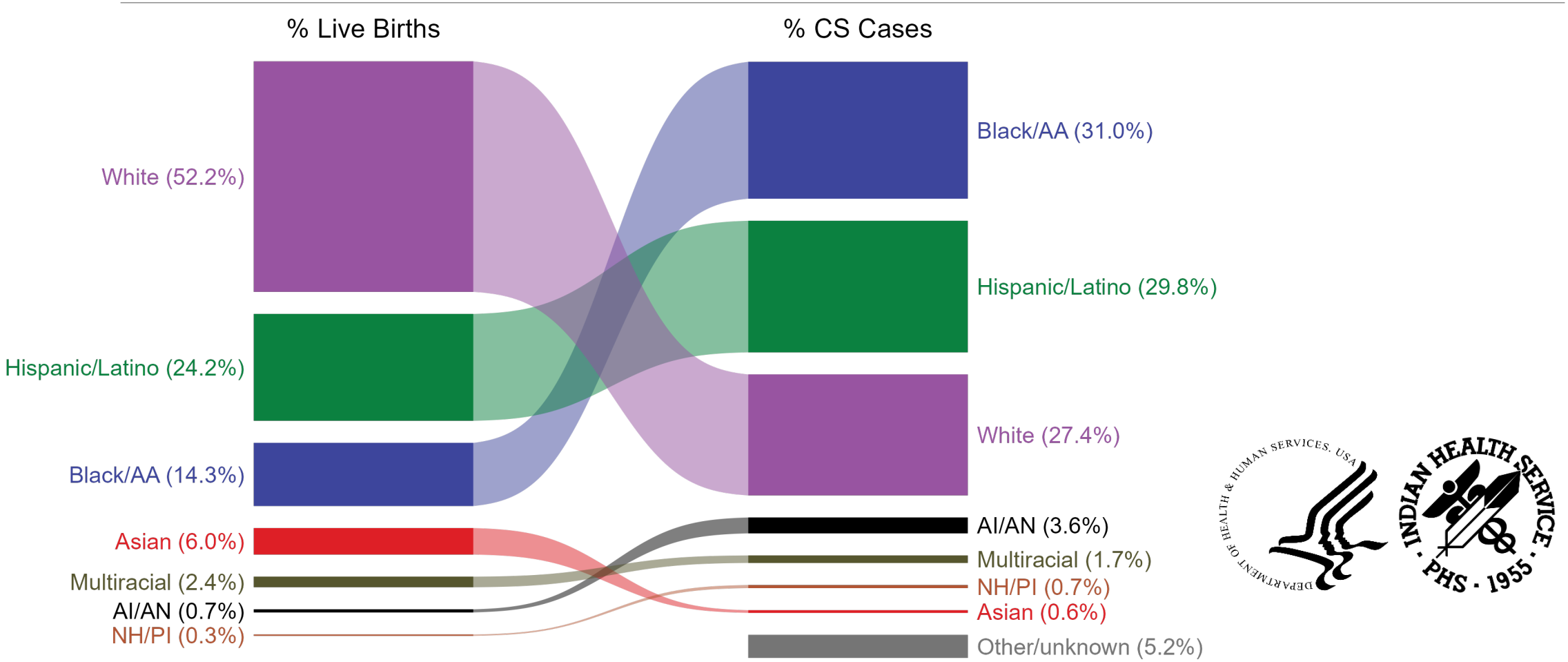


Congenital Syphilis — Case Counts and Rates of Reported Cases by Race/Hispanic Ethnicity of Mother, United States, 2021

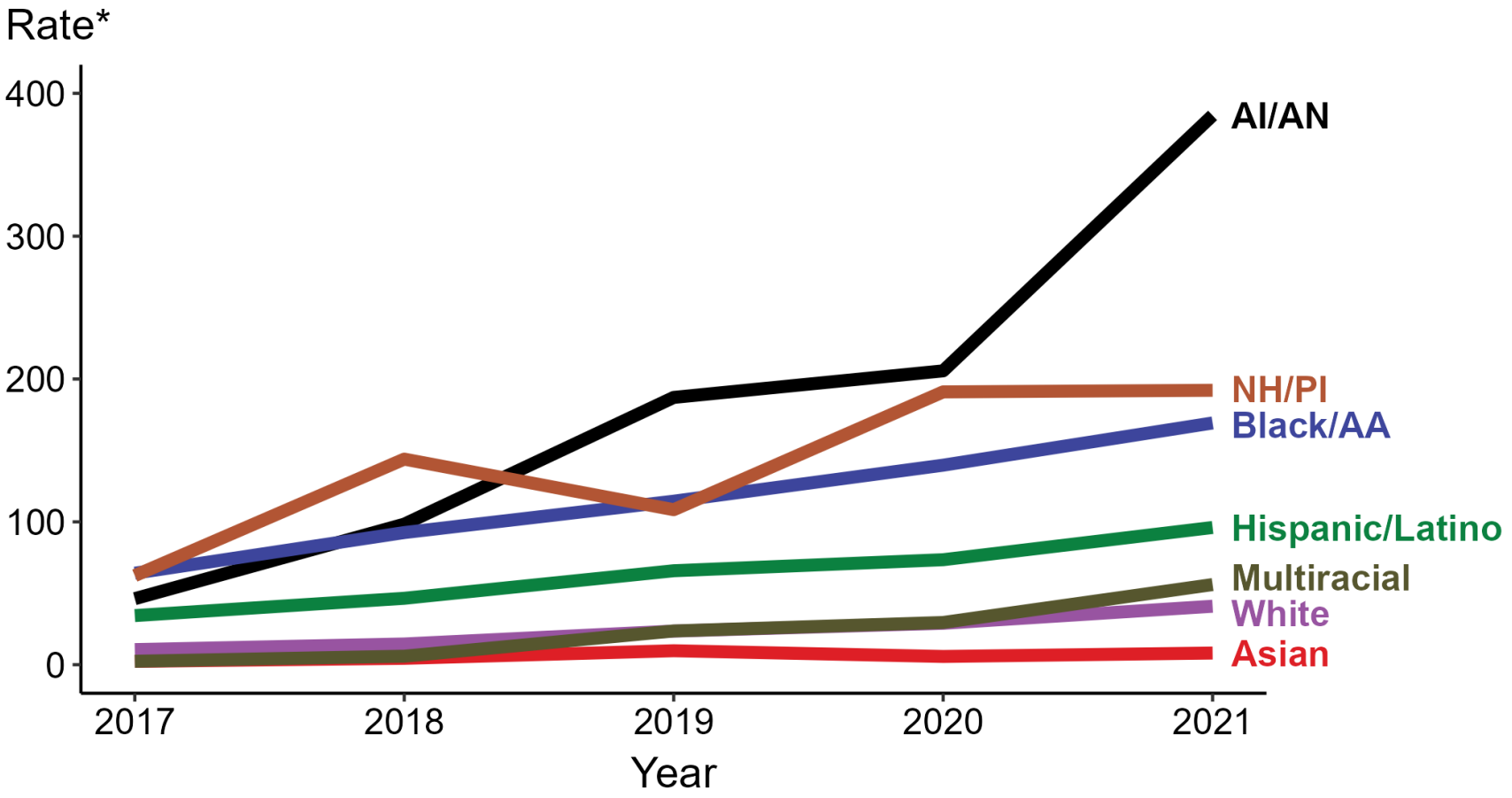


* Per 100,000 live births

Congenital Syphilis — Reported Cases by Race/Hispanic Ethnicity of Mother, United States, 2021



Congenital Syphilis — Rates of Reported Cases by Year of Birth, Race/Hispanic Ethnicity of Mother, United States, 2017–2021



Primary and Secondary Syphilis — Reported Cases and Rates of Reported Cases by State, Ranked by Rates, United States, 2021

Rank	State	Cases	Rate per 100,000 Population
1	South Dakota	436	48.7
2	New Mexico	724	34.2
3	Arkansas	990	32.7
4	Oklahoma	1,225	30.7
5	Nevada	939	29.9
9	**Oregon**	**949**	**22.3**
14	**Washington**	**1,506**	**19.5**
47	**Idaho**	**84**	**4.4**
	US TOTAL	**53,767**	**16.2**

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

Rank	State	Cases	Rate per 100,000 Population
1	Arizona	181	232.3
2	New Mexico	44	205.7
3	Louisiana	110	191.5
4	Mississippi	64	182.0
5	Texas	680	182.0
17	**Oregon**	**27**	**66.0**
19	**Washington**	**53**	**63.2**
34	**Idaho**	**5**	**22.3**
	US TOTAL	**2,855**	**77.9**

CMO letter

- **Annual syphilis testing** for persons aged 13-64 to eliminate syphilis transmission by early case recognition
- **Turn on the annual EHR reminder** at all sites to facilitate testing for two years or until incidence rates decrease locally to baseline
- **Three-point syphilis testing for all pregnant people**: at the first prenatal visit, the beginning of the third trimester, and delivery
- Adoption of an **STI/HIV/Viral hepatitis testing bundle** at all sites to screen broadly:
  - Syphilis screening test with reflex RPR and TPPA
  - HIV serology (with consent if required in the local state jurisdiction)
  - Screening for gonorrhea and chlamydia at three sites: Urine, Pharynx, Rectum
  - Screening for hepatitis B and C
  - Pregnancy test

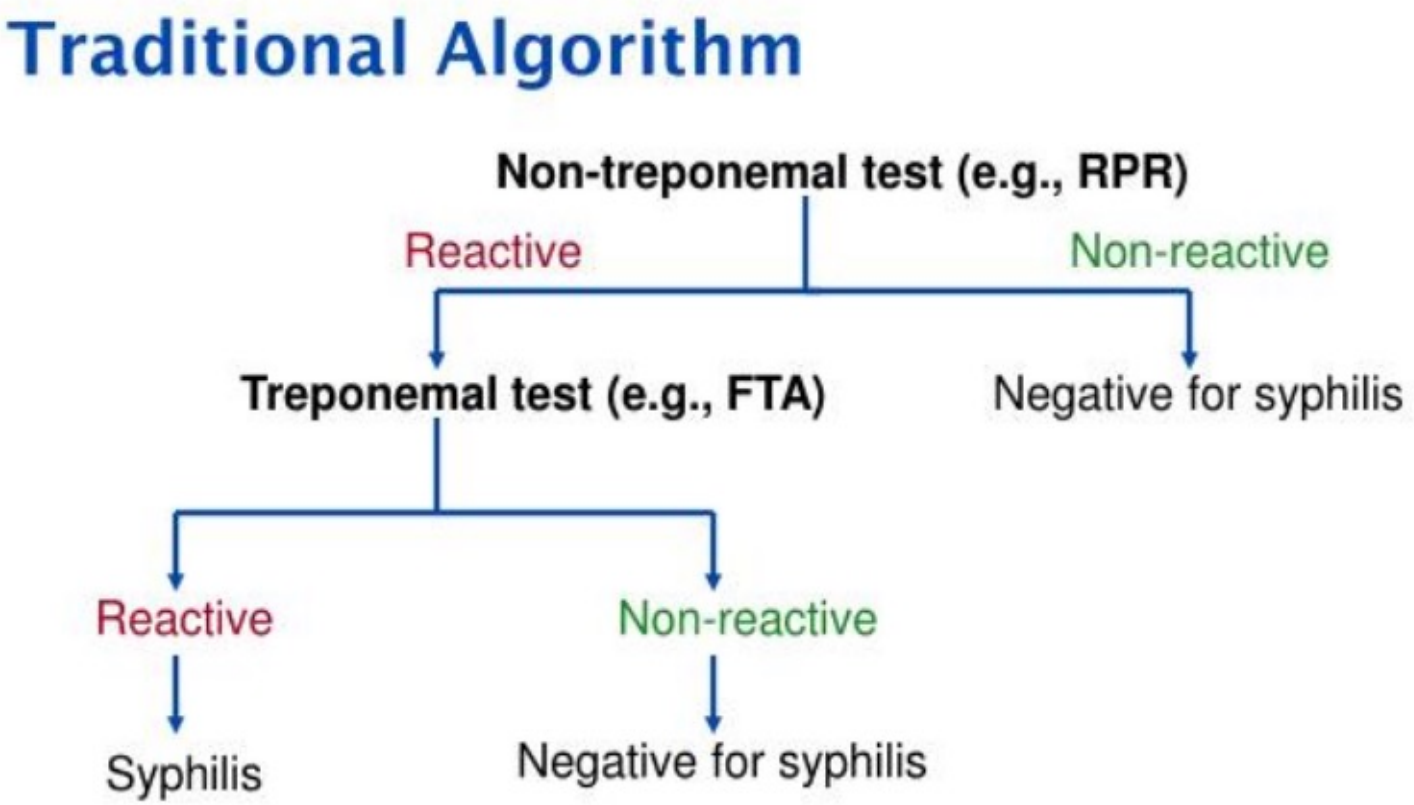
CMO letter

- Adoption of **"Express STI Testing"** Express STI services refer to triage-based STI testing without a full clinical exam, using standing orders
  - Research shows that express STI services increase clinic capacity and reduce the time to treatment
  - Find the Express Testing Guide and Toolkit here. Sample Toolkit for Express STI Resources - Indian Country ECHO
- **Enhance screening rates by screening outside of hospitals and clinics**
  - Field testing at community centers, sporting events, health fairs, correctional settings, or on the street
- Provide **Field treatment for syphilis** for high-risk adults diagnosed with syphilis and their partners. PHNs can provide treatment with Benzathine Penicillin. The Express STI Services Toolkit includes policy examples. For questions, contact Tina Tah or Melissa Wyaco

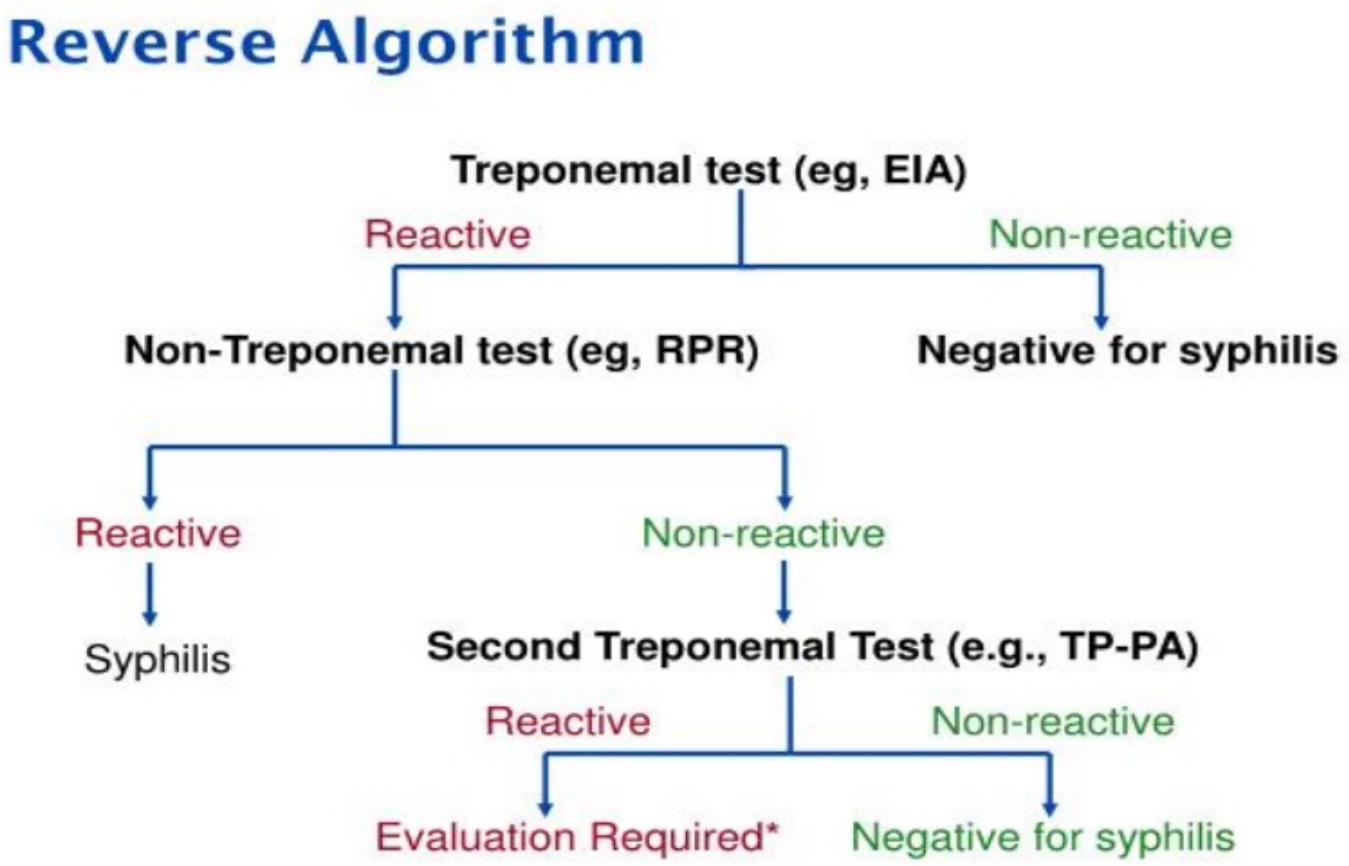
CMO letter

- **Presumptive treatment of syphilis** for anyone having signs or symptoms of syphilis or with known exposure to syphilis
- **Create and build awareness** and encourage people to get tested and treated. There is a new AI/AN-specific national campaign called STOP SYPHILIS
  - The campaign offers handouts, posters, and other print materials, as well as social media posts and short educational videos. All materials are free to order at www.stopsyphilis.org
- Reference the **Syphilis Resources Hub**: https://www.indiancountryecho.org/syphilis-resources/
- *I Want The Kit: In-home specimen collection/lab-based testing (syphilis will be added later this year)
- *Vending machines

Traditional Algorithm



Reverse Algorithm



Rapid/Point-of-Care Testing

Health Check: Rapid syphilis test (10 minute results)

Treponemal antibody test

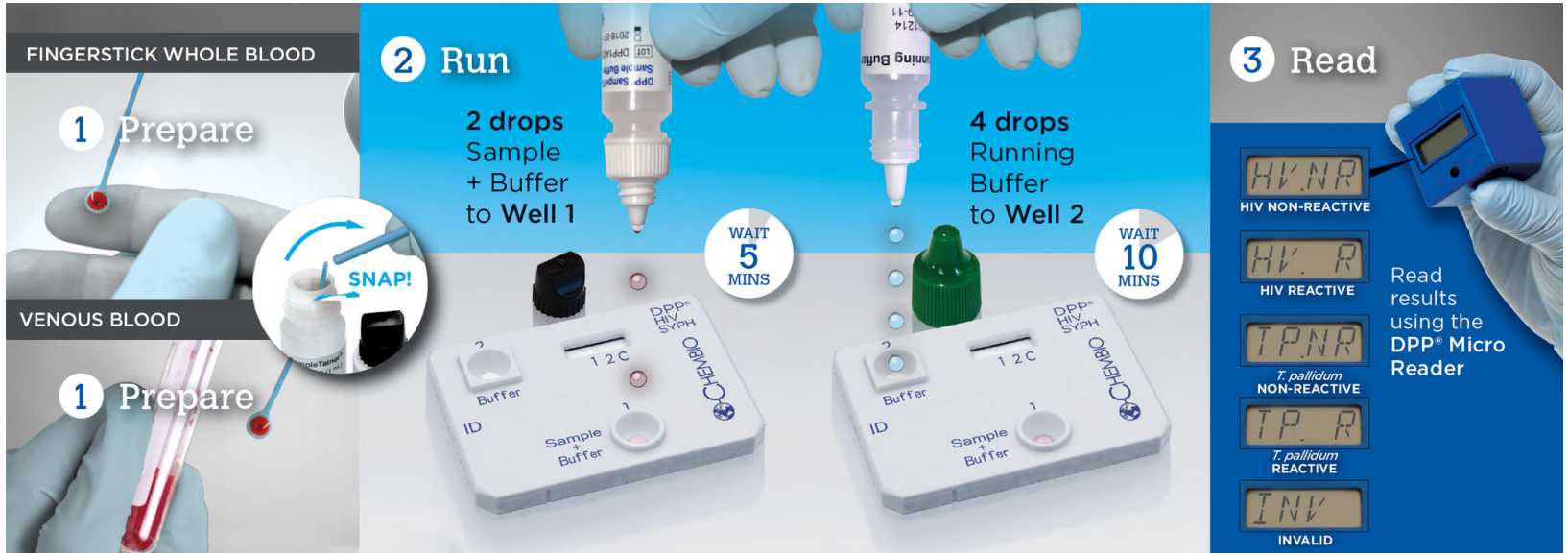
[Diagnostics Direct VSC-11-01 - McKesson Medical-Surgical]

Rapid/Point-of-Care Testing

Chembio: Dual rapid HIV-Syphilis test (15 minute results)

HIV-1/2 antibody test / Treponemal antibody test

[Chembio Diagnostic 65-9502-0 - McKesson Medical-Surgical]



Testing

- Standing Orders
- Express STI Testing
- I Want The Kit: In-home specimen collection/lab-based testing
- Expanded screening to at-risk communities of sexually active adults and adolescents (schools, corrections, emergency department, primary care, obstetrics, dental, community venues, parole centers, work physicals)

Treatment

STAGE		
Primary & Secondary, Early non-primary, non secondary	**Late Latent/or Unknown Duration**	**Neurosyphilis, ocular syphilis and otosyphilis**
Benzathine penicillin 2.4 million units IM in **a single dose** Doxycycline 100mg BID **for 14 days**	Benzathine penicillin 2.4 million units total administered as **3 doses** of 2.4 million units IM each **at 1- week intervals** Doxycycline 100mg BID **for 28 days**	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** Alternative: procaine penicillin G 2.4 million units IM 1x/day PLUS probenecid 500 mg orally 4x/day, **both for 10-14 days**

Treatment (Congenital Syphilis)

Scenario 1: Confirmed, proven or highly probable congenital syphilis	Scenario 2: Possible congenital syphilis	Scenario 3: Congenital syphilis less likely	Scenario 4: Congenital syphilis unlikely
Neonate with a physical exam consistent with CS, nontreponemal serology 4-fold greater than mother's	Normal physical exam and a serum nontrep titer equal to or < 4-fold of the maternal titer at delivery and one of the following: 1) The mother was not treated, was inadequately treated, or has no documentation of treatment 2) The mother was treated with erythromycin or a regimen not recommended in these guidelines 3) The mother received recommended regimen but treatment was initiated <30 days before delivery	Neonate with a normal physical examination and a serum nontrep titer equal or <4-fold of the maternal titer at delivery and both of the following are true: The mother was treated during pregnancy and the mother has no evidence of reinfection or relapse	Neonate with: a normal physical exam, serum nontrep serology equal to or less than 4-fold mother's at delivery and, mother's treatment was adequate before pregnancy, mother's nontreponemal titer remained low and stable before and during pregnancy and at delivery
Evaluation: CSF with VDRL, cell count, protein, CBC/diff, long bone radiographs, neuro eval (eye, auditory)	CSF with VDRL, cell count, CBC/ diff, long-bone radiographs	No evaluation is recommended	No evaluation is recommended
Treatment: **Aqueous crystalline penicillin G** 100,000–150,000 units/kg/body wt./day, administered as 50,000 units/kg body wt./dose IV q 12 hours during the first 7 days of life and q 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	**Treatment**: **Aqueous crystalline penicillin G** 100,000–150,000 units/kg/body wt./day, administered as 50,000 units/kg body wt./dose IV q 12 hours during the first 7 days of life and q 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 OR **Benzathine penicillin G** 50,000 units/kg body weight/dose IM in a single dose	**Treatment:** **Benzathine penicillin** G 50,000 units/kg body weight/dose IM in a single dose	**No treatment recommended**

Post-Treatment Follow Up (P&S)

- Clinical and serologic evaluation should be performed **at 6 and 12 months after treatment**
- Persons who have symptoms that persist/recur and those with at least a **fourfold increase** in nontreponemal test titer likely were reinfected or experienced treatment failure. Among persons who have neurologic findings, a CSF examination is recommended
- Failure of nontreponemal test titers to **decrease fourfold within 12 months** after therapy for primary or secondary syphilis might be indicative of treatment failure. At a minimum, these persons should receive additional neurologic examinations, clinical and serologic follow-up annually. If additional follow-up cannot be ensured, retreatment is recommended
- For retreatment, weekly injections of benzathine penicillin G 2.4 million units intramuscularly (IM) for 3 weeks is recommended, unless CSF examination indicates that neurosyphilis is present

Post-Treatment Follow Up (Congenital Syphilis)

- **All neonates with reactive nontreponemal tests should receive follow-up exams and serologic testing every 2–3 months until the test becomes nonreactive**
- For a neonate who was not treated because congenital syphilis was considered less likely or unlikely, nontreponemal antibody titers should decrease by age 3 months and be **nonreactive by age 6 months**. **If the nontreponemal test is still reactive, the infant is likely infected and should be treated**
- Treated neonates who exhibit **persistent nontreponemal test titers by age 6–12 months should be reevaluated through CSF examination**. Retreatment with a 10-day course of a penicillin G regimen might be indicated
- Neonates with a negative nontreponemal test at birth and whose mothers were seroreactive at delivery should be **retested at age 3 months**.
- Neonates whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless they exhibit persistent nontreponemal serologic test titers at age 6–12 months.

Treatment

- Rapid Treatment
  - Treat immediately after rapid test results
- Presumptive Treatment
  - Symptomatic patients
  - Patients with known exposure

Penicillin Shortage

- Increased demand
- Discontinuation of Penicillin (PCN) Procaine
- Global issue (FDA exploring importation)
- Bicillin L-A is a sole source product from Pfizer
- Pfizer is prioritizing production of 1.2 and 2.4 mu syringes
- Producing at maximum capacity

Penicillin Shortage

- Penicillin G benzathine should only be used to treat syphilis
- Appropriate staging
- Assess likelihood of adherence
- Prioritize pregnant people
- Prioritize people living with HIV

Jarisch-Herxheimer Reaction

- An acute febrile reaction accompanied by headache and myalgia that can occur **within the first 24 hours** after the initiation of any syphilis therapy
- It is a reaction to treatment and not an allergic reaction to penicillin
- Occurs most frequently among persons who have early syphilis, presumably because bacterial loads are higher during these stages
- Antipyretics can be used to manage symptoms
- The Jarisch-Herxheimer reaction might induce early labor or cause fetal distress in pregnant women; however, **this should not prevent or delay therapy**

Field Based Screening and Treatment

Considerations:

- Personnel: avoid providing care alone – team with PHN, pharmacist, tribal STI worker, or any other approved staff
- Confirm that there is adequate cell phone service and emergency services (911 and EMS) are available
- Screen for exclusionary criteria: history of true penicillin allergy and/or serious complications
- Ensure all supplies and equipment are available for transport

Allergies

- Penicillin G is contraindicated in patients with known hypersensitivity to penicillin. However, **fewer than 1%** of the whole population are truly allergic to penicillin
- Approximately 80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years
- Correctly identifying those who are not truly penicillin-allergic can decrease the unnecessary use of broad-spectrum antibiotics

Allergies

Evaluate the patient for a true penicillin allergy (IgE-mediated) by conducting a history and physical, and when appropriate, a skin test and challenge dose

- History and physical: What kinds of reactions occurred? How long ago did the reaction occur? How was the reaction managed? What was the outcome?
- Characteristics of an IgE-mediated (Type 1) reaction: **Occur immediately or usually within one hour**. Hives, angioedema, wheezing and shortness of breath, anaphylaxis
- Anaphylaxis: Requires **at least two of the following symptoms**: Skin (hives, flushing, itching, angioedema), Respiratory (cough, nasal congestion, shortness of breath, chest tightness, wheezing, choking, change in voice quality), Cardiovascular (hypotension, syncope, tachy/bradycardia, tunnel vision, chest pain, sense of impending doom, loss of consciousness), Gastrointestinal (nausea, vomiting, cramping, diarrhea)
- Penicillin Skin Test
- Challenge Doses

Allergies

- If penicillin allergy is ruled out, **remove from the allergy list** on patient's electronic health record
- Pregnant people with confirmed hypersensitivity to penicillin should be desensitized to receive penicillin

Field Based Screening and Treatment

- Anaphylaxis Management:
  - Often occurs within 15-30 minutes of medication administration
  - Administer Epinephrine as soon as possible
  - Contact emergency medical services
  - Transfer patient to a higher level of medical care
  - Document in EHR

DoxyPEP: Post Exposure Prophylaxis

Take **1 dose of Doxycycline 200mg** 24-72 hours after condomless sex

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- Found a **65% reduction in chlamydia, gonorrhea, and syphilis** among men who have sex with men (MSM) and transgender women
- CDC has acknowledged that providers and patients have started to use DoxyPEP off-label and provided considerations for its use:
    - A reminder that current studies have shown promise among MSM and transgender women, but not among cis-gender women
    - Only Doxycycline has been studied, no other antibiotics

DoxyPEP: Post Exposure Prophylaxis

- Further analyses are needed to determine the effects of intermittent doxycycline use on antimicrobial resistance and long-term effects on the gut
- Doxycycline is contraindicated for pregnant people. Doxycycline may cause fatty liver disease in pregnant people and fetal tooth staining

DoxyPrEP (Pre-Exposure Prophylaxis)

Take **Doxycycline 100mg daily** prior to having condomless sex

In a pilot study, 30 MSM living with HIV with previous syphilis (two or more episodes since HIV diagnosis) were randomly assigned to doxycycline 100 mg for 48 weeks versus a financial incentive–based behavioral intervention

Results: **73% reduction in any bacterial STI** at any site for the intervention group, without substantial differences in sexual behavior

Implementation

- 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
- 3-6 month schedule: Provide enough meds and replenish after STI screening
- If having signs and symptoms of an STI: patient's should come in for immediate screening and treatment per traditional protocol, and abstain until 1 week post treatment

Case Management

- Case investigation
- Contact tracing
  - Expedited partner therapy
- Utilizing non-clinical partners
- Treatment Adherence Support
  - Multiple Bicillin injections
  - Follow up on Doxycycline adherence

Communication

- Patient: Internet partner services
  - Text messaging
  - Email
  - Social media
    - IHS Headquarters currently working on policies to expand communication options to include internet partner services
- Clinicians: Obtaining medical records
  - HIPPA Release

Incentives

- Used to enhance screening and adherence to treatment
- IHS Headquarters currently working on policies to allow the direct transfer of federal funds to service areas
- Criteria of what is allowed/not allowed to be purchased

Resources

- Indian Country ECHO

http://www.indiancountryecho.org

- Syphilis Resource Hub

https://www.indiancountryecho.org/syphilis-resources

- Stopsyphilis.org
- ID Consults

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