

Clinical Overview of Congenital Syphilis

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March 16, 2023



This material is the result of work supported with resources and the use of facilities at the (list facility name), located in the Phoenix Area of the Indian Health Service.

Dr. McAuley is a federal employee and serves as the Clinical Director of the Whiteriver Service Unit in Whiteriver, Arizona

The contents do not represent the views of the Indian Health Service or the United States Government

Who should be screened for syphilis?

US Preventive Services Task Force Grade A Recommendations

- ***“The USPSTF recommends early screening for syphilis infection in all pregnant women”.***
- All pregnant women are at risk. All pregnant women should be tested for syphilis as early as possible when they first present to care. If a woman has not received prenatal care prior to delivery, she should be tested at the time she presents for delivery.
- ***“The USPSTF continues to recommend screening for syphilis in nonpregnant persons who are at increased risk for infection”.***
- Population: Asymptomatic, nonpregnant adolescents and adults who are at increased risk for syphilis infection

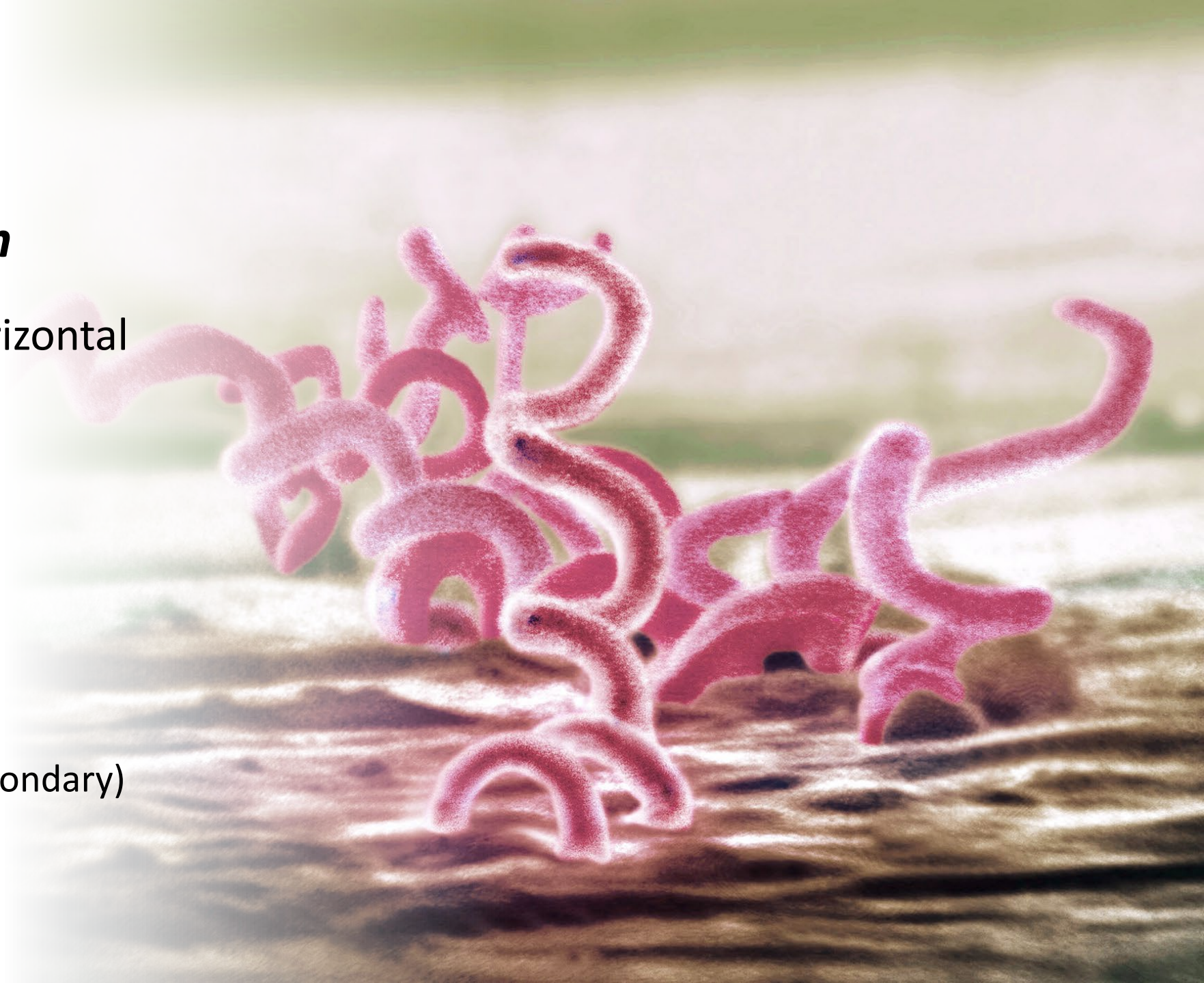
Syphilis Screening Recommendation by the I H S Chief Medical Officer, October 25, 2022

- Annual syphilis testing for persons aged 13-64 to eliminate syphilis transmission by early case recognition.
 - An annual EHR reminder should be turned on at all sites to facilitate testing for two years or until incidence rates decrease locally to baseline.
- Adoption of an STI/HIV/Viral hepatitis testing bundle at all sites to screen broadly:
 - Syphilis screening test with reflex RPR and TPPA
 - Pregnancy test
- Adoption of "Golden Ticket Testing": On-demand, no-provider/no nurse, lab visits for testing, including the above bundle
- Enhance screening rates by screening outside the hospital/clinic in the community
- Field treatments for syphilis by PHNs with Benzathine Penicillin.

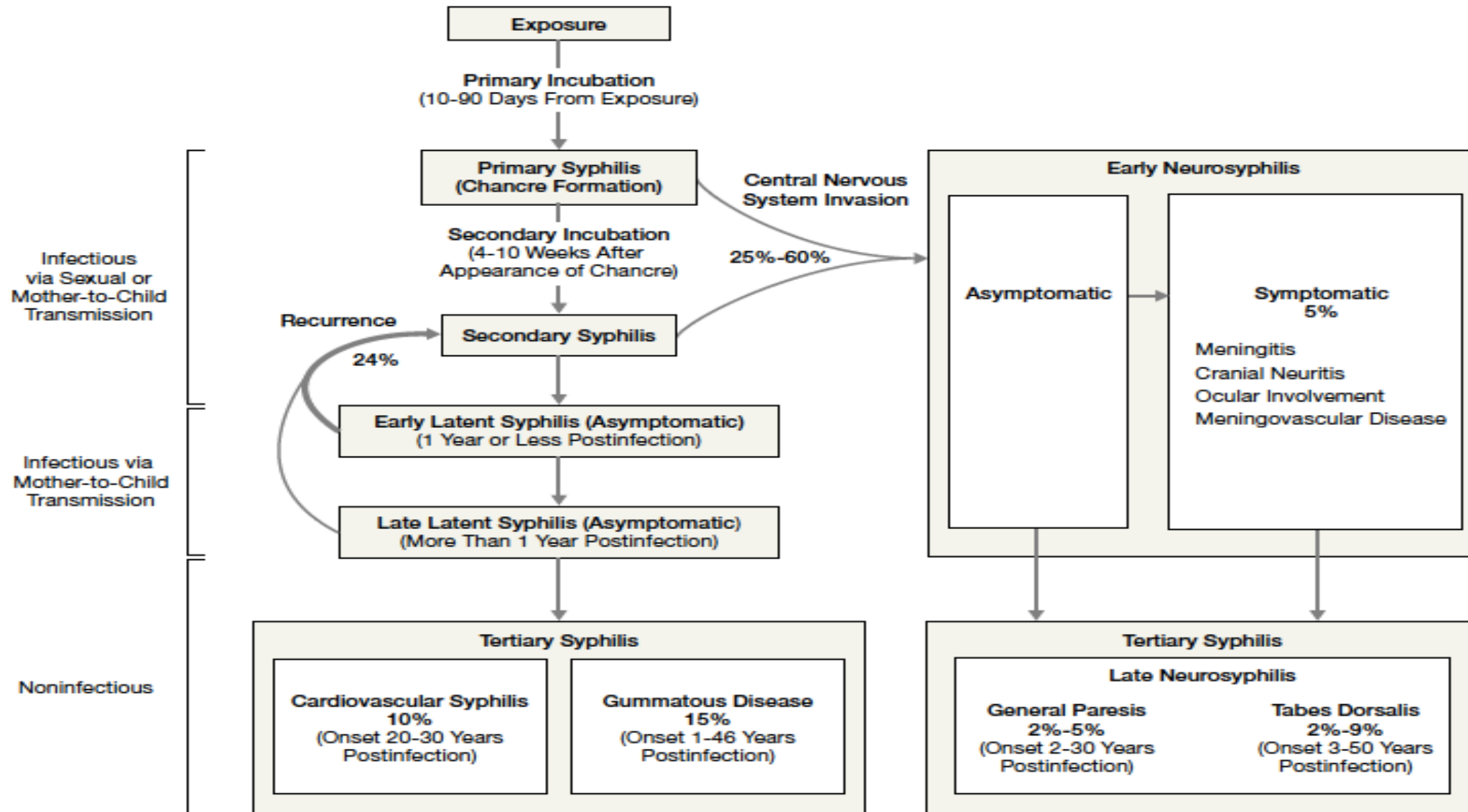


Syphilis

- ***Treponema pallidum***
- Sexual, vertical, and horizontal transmission
- **Curable with penicillin**
- 4 stages
 1. Primary
 2. Secondary
 3. Early (non-primary, non-secondary)
 4. Unknown duration or late

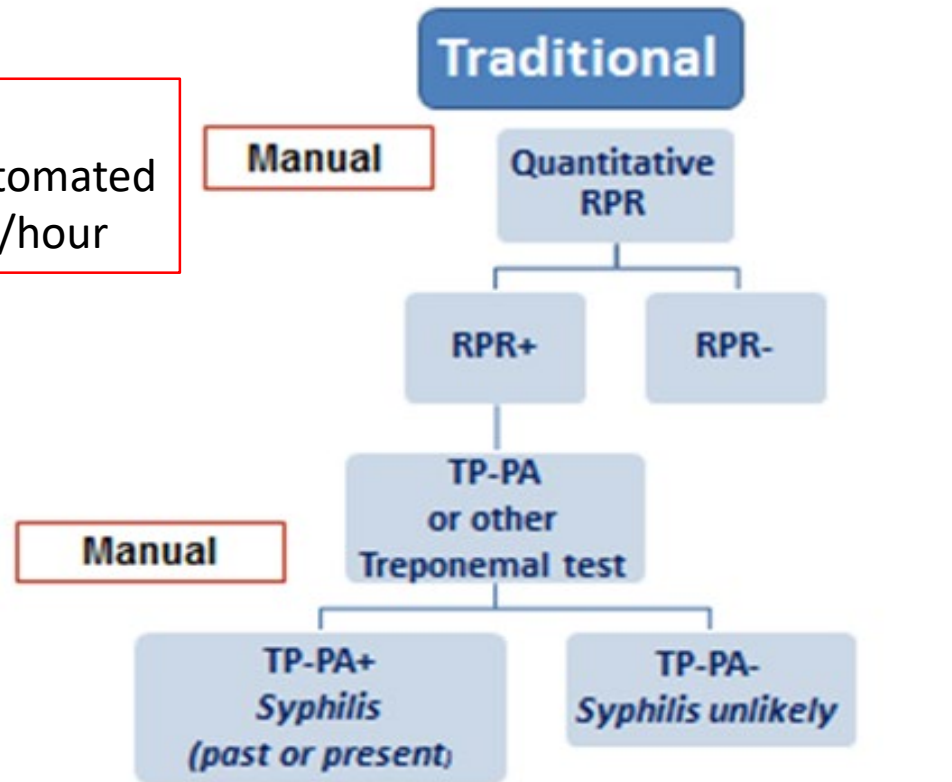


Natural History of Untreated Syphilis



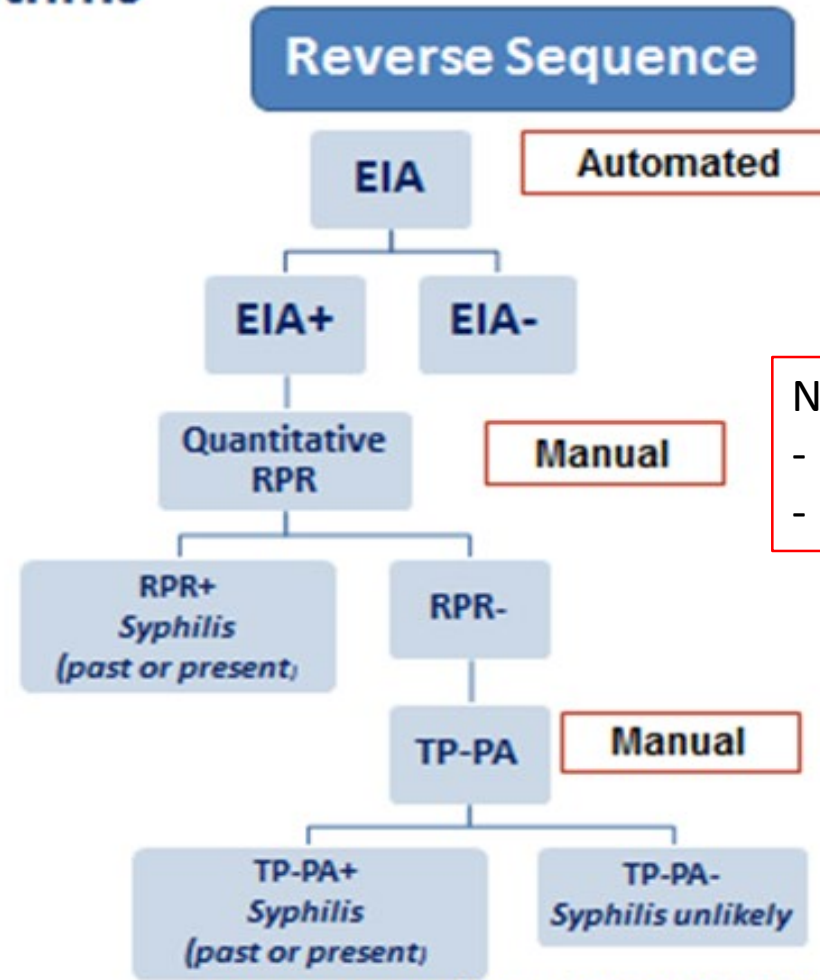
Serologic Diagnosis of Syphilis

Syphilis Serologic Screening Algorithms



RPR – Rapid plasma reagin
 TP-PA – *Treponema pallidum* particle agglutination
 EIA – Enzyme immunoassay

New – ASI
 - Fully automated
 - 190 test/hour

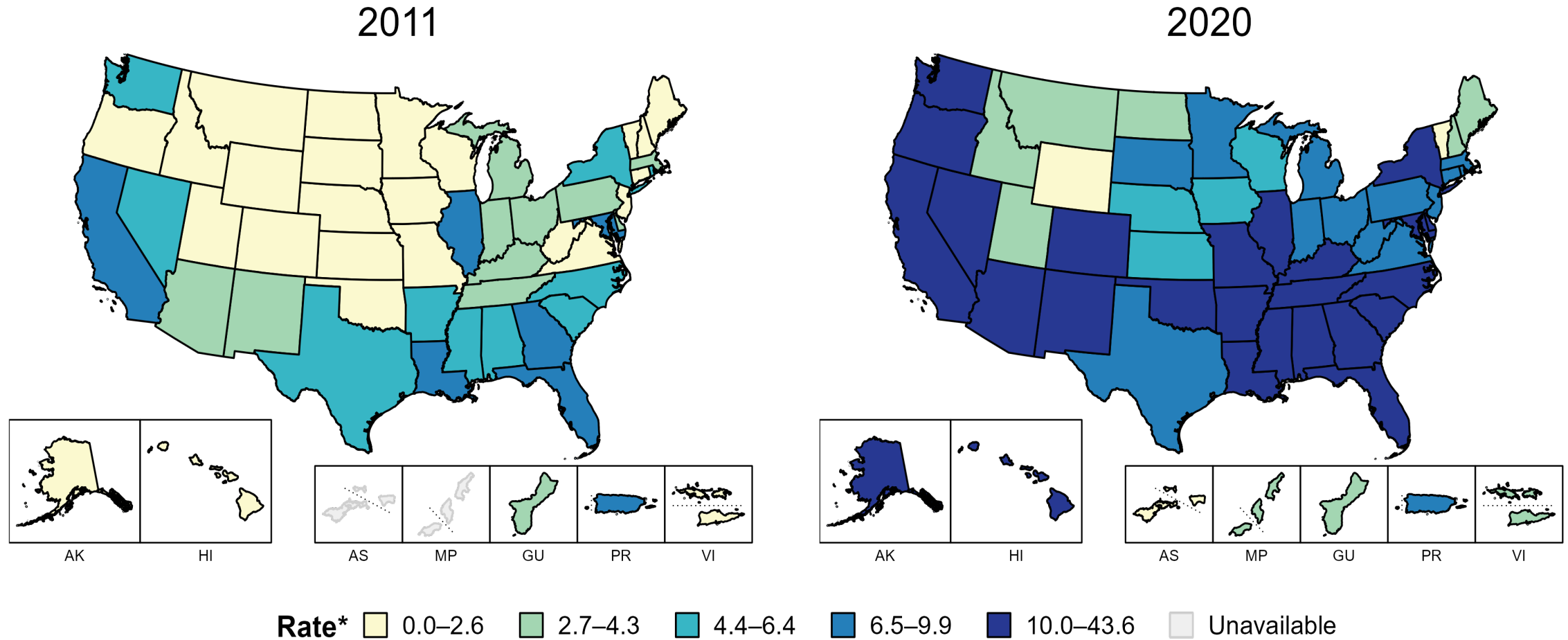


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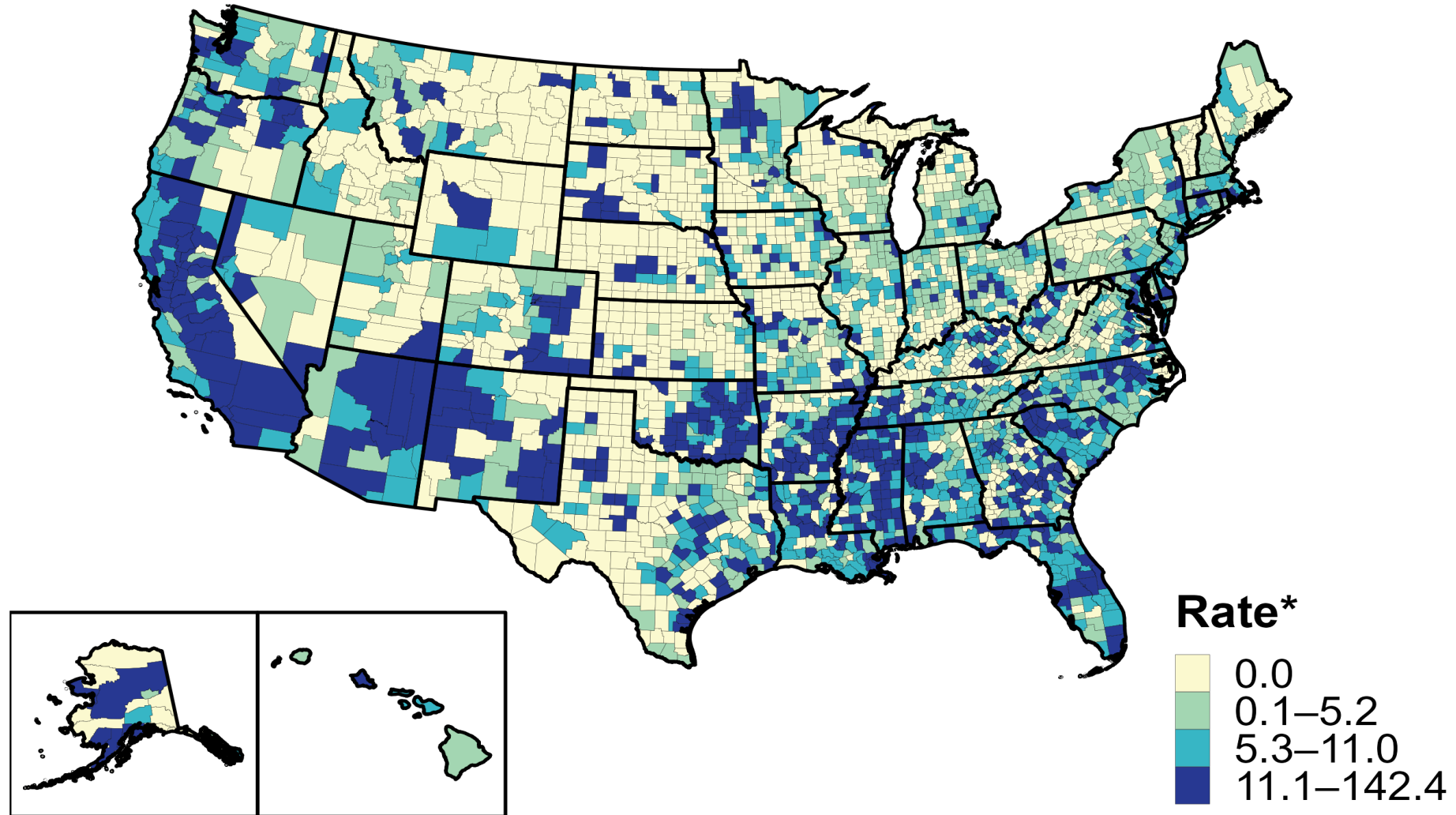
Reverse sequence syphilis screening; 2011 CDC DSTDP webinar

Chembio POC combination HIV 1/2 and TPPA just FDA approved. Syphilis Health Check POC TPPA previously FDA cleared.

Primary and Secondary Syphilis — Rates of Reported Cases by State, United States and Territories, 2011 and 2020



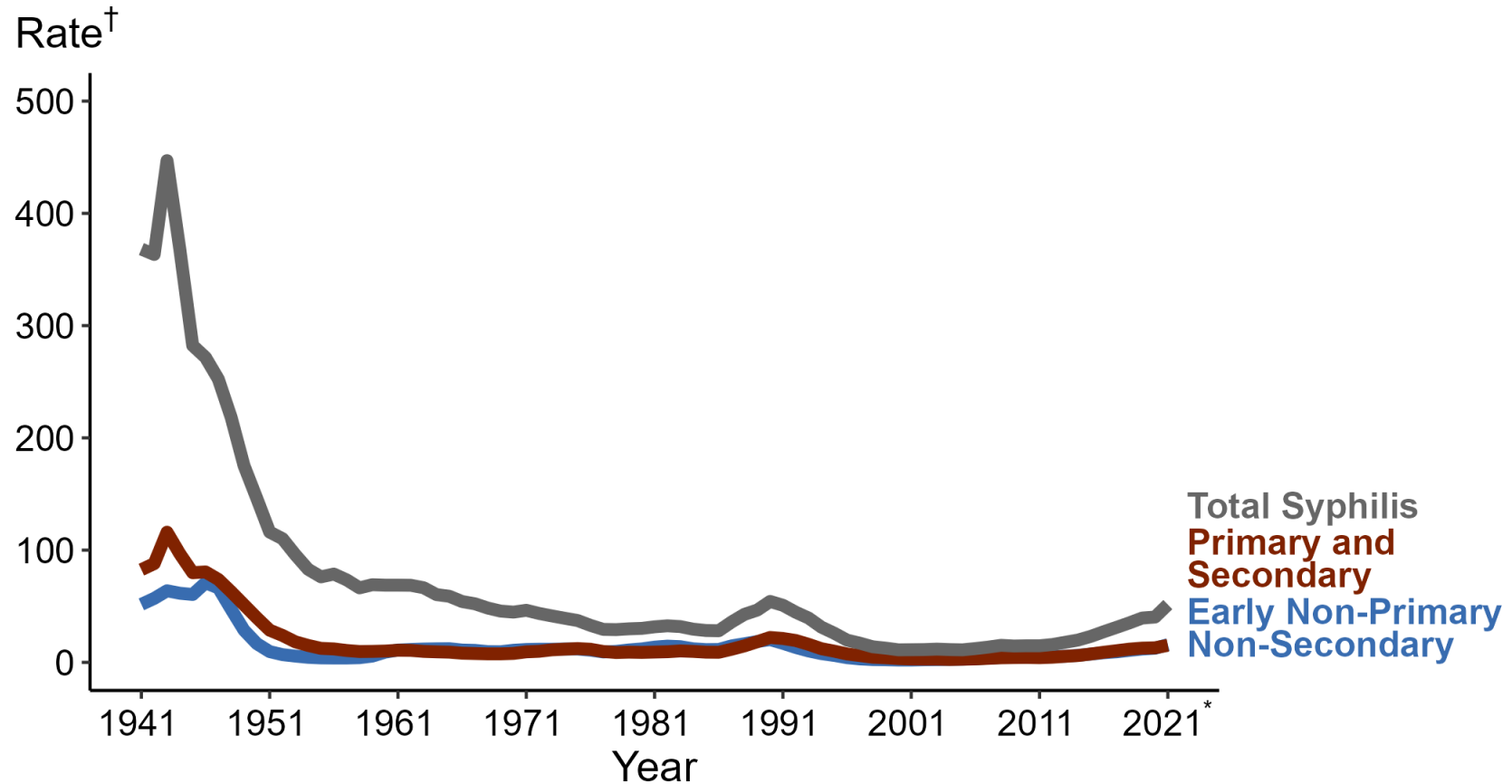
Primary and Secondary Syphilis — Rates of Reported Cases by County, United States, 2020



* Per 100,000

<https://www.cdc.gov/std/statistics/2020/figures.htm>

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

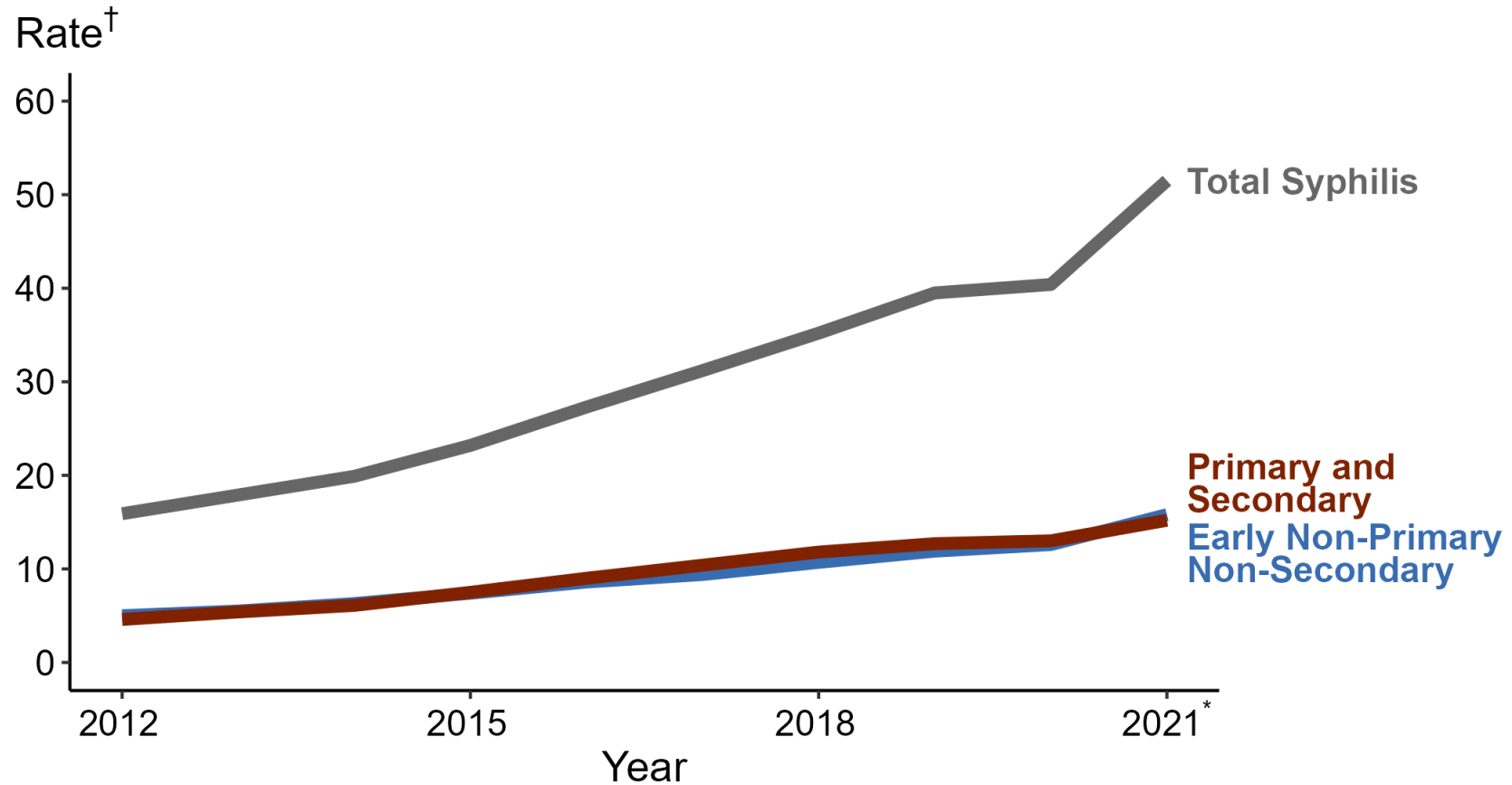


* Reported 2021 data are preliminary as of July 7, 2022

† Per 100,000

<https://www.cdc.gov/std/statistics/2021/default.htm>

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



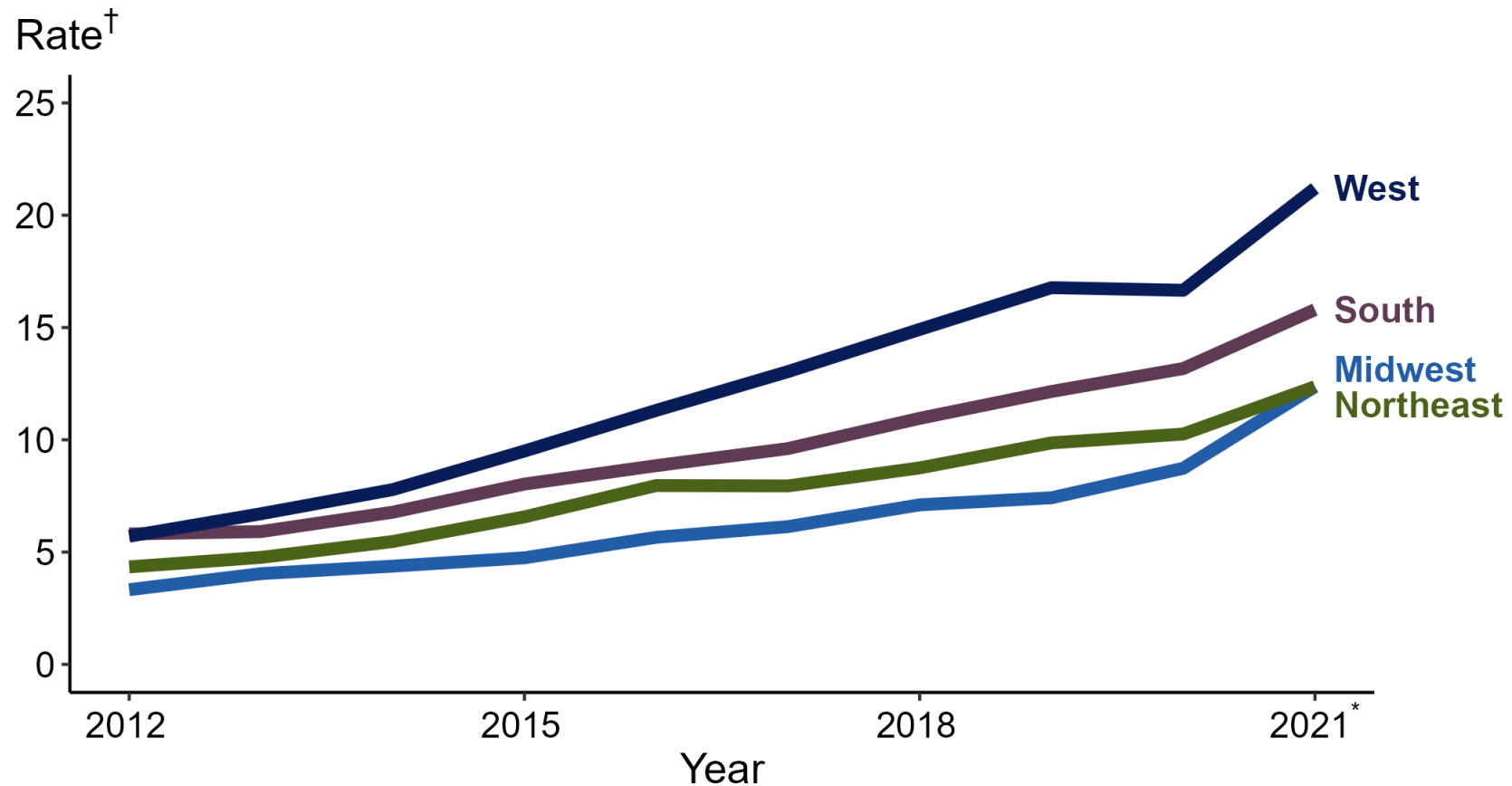
* Reported 2021 data are preliminary as of July 7, 2022

† Per 100,000

<https://www.cdc.gov/std/statistics/2021/default.htm>



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

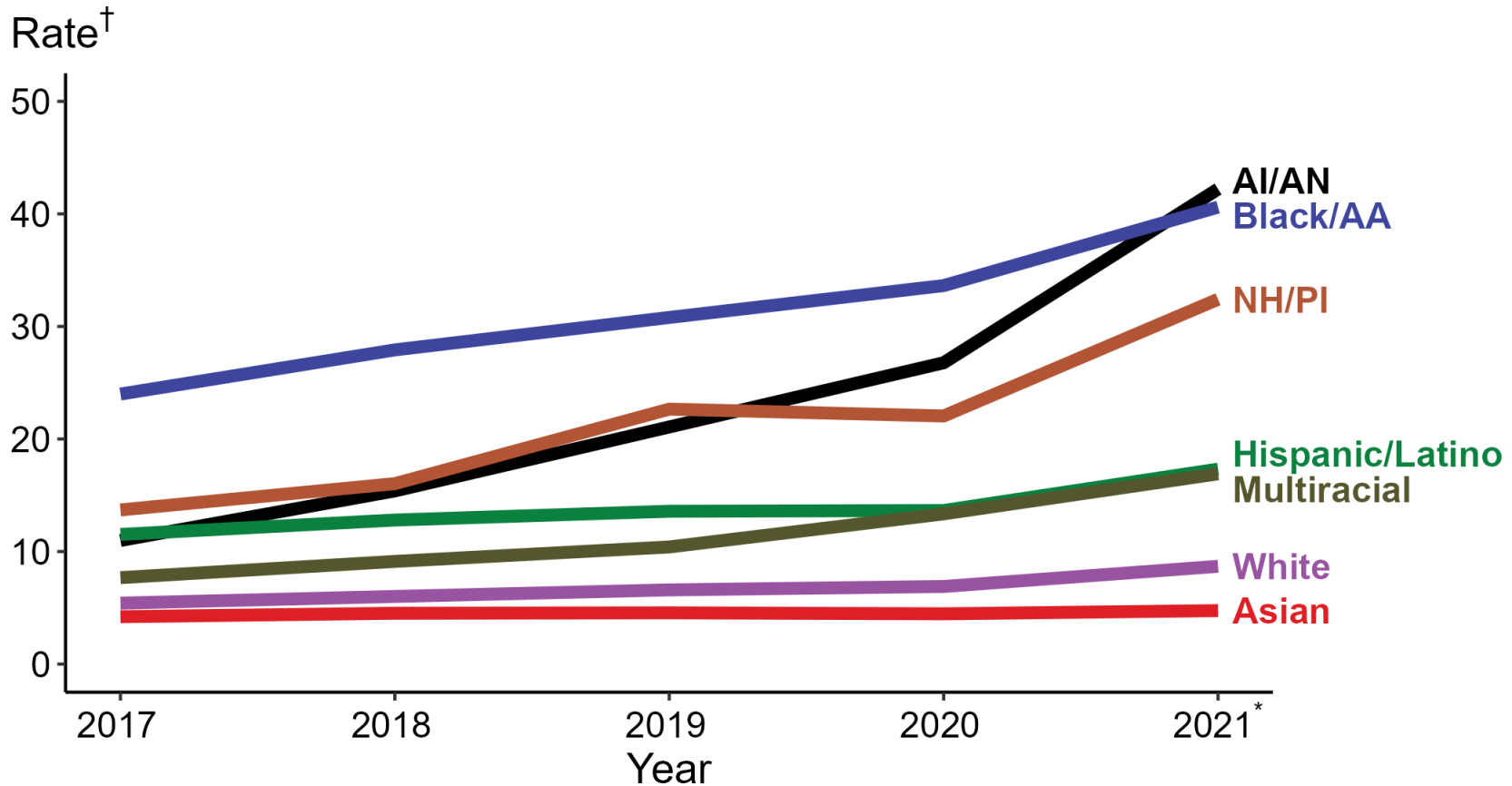


* Reported 2021 data are preliminary as of July 7, 2022

† Per 100,000

<https://www.cdc.gov/std/statistics/2021/default.htm>

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



* Reported 2021 data are preliminary as of July 7, 2022

† Per 100,000

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

<https://www.cdc.gov/std/statistics/2021/default.htm>



Congenital Syphilis

- Transmission follows placental infection with hematogenous spread to the fetus, or the baby can be infected by exposure to an active lesion during delivery.
- The majority of congenital syphilis is asymptomatic.
- It is rare for a fetus to show evidence of infection before 20 weeks gestation.
- Infection can be transmitted during any stage of maternal disease but 60-100% of primary and secondary untreated cases result in transmission, while only 10-15% of late latent cases result in transmission.



Clinical Case

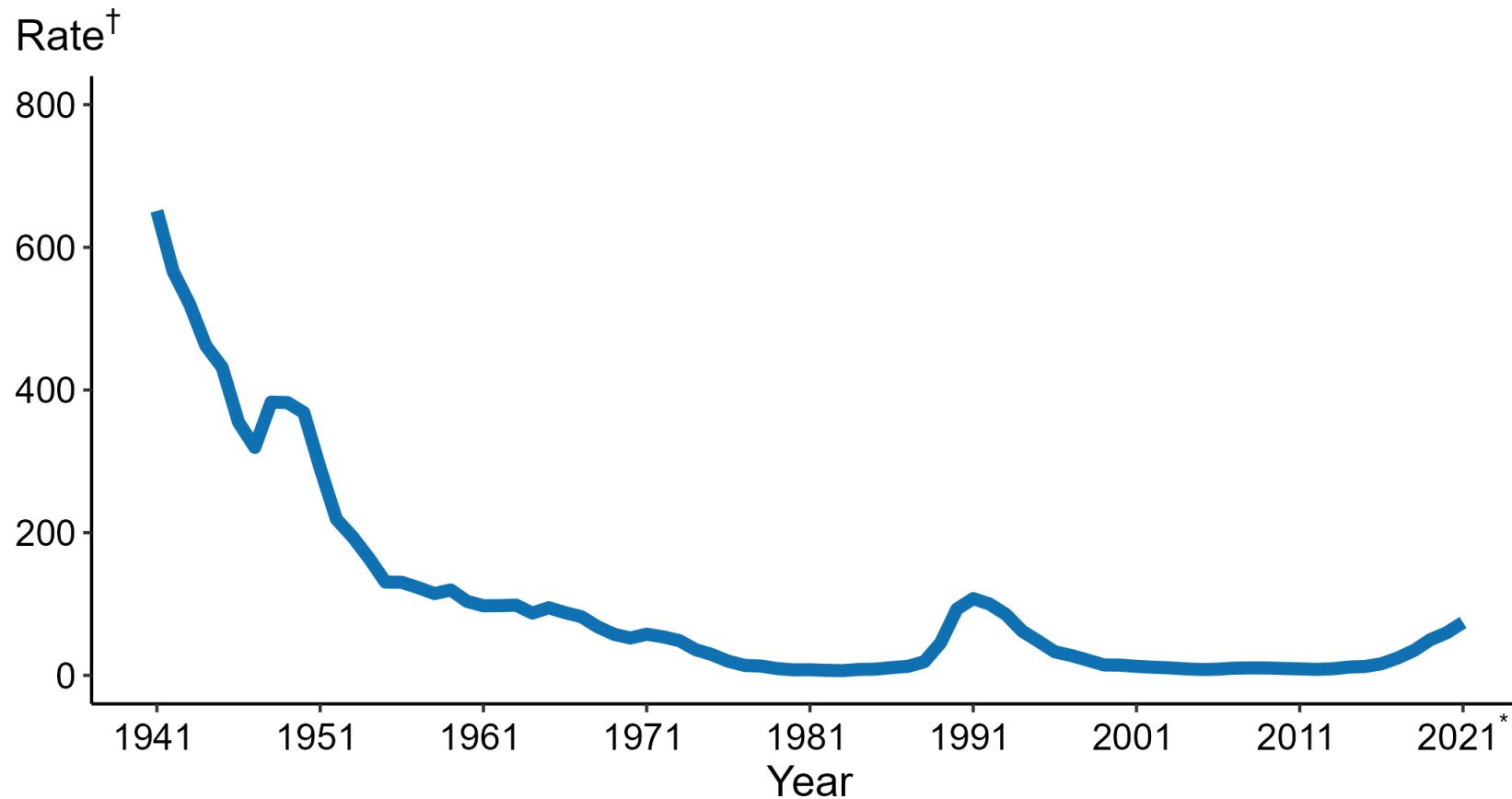
A pregnant woman in her mid-20s with no prenatal care presented at 40+ weeks gestation and gave birth to a 3200 gm baby, Apgar's 8/9. RPR two years prior was negative. RPR at delivery 1:16. Baby had normal new born exam and normal exam at the 2 week visit.

<u>Date</u>	<u>Age</u>	<u>RPR</u>	<u>Intervention</u>
2/20	Birth	1:4 (Mat 1:16)	Neg W/U (CBC, LFTs, Long bone x-ray, CSF), 170,000 U Benzathine PCN IM (DOL 15)
3/30	5 weeks	-	Baby fussy with desquamating rash. PCN 50,000 U/kg q 8hr x 10 days, CSF VDRL NR
4/20	8 weeks	1:128	Post treatment RPR elevated but baby normal exam
6/25	16 weeks	1:8	
2/10	1 year	1:1	Recommend re-evaluation and retreatment but tertiary center declined

Was this congenital syphilis? Was a single dose of IM benzathine penicillin appropriate at birth? Why is the RPR still elevated at one year? Is it a treatment failure?



Congenital Syphilis — Rates of Reported Cases by Year of Birth, United States, 1941–2021*

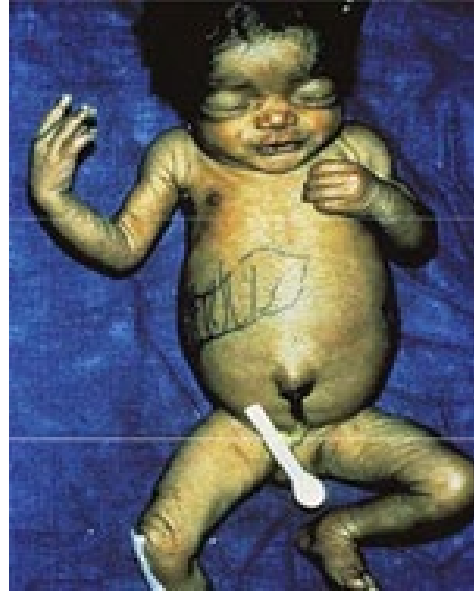


* Reported 2021 data are preliminary as of July 7, 2022

† Per 100,000 live births

<https://www.cdc.gov/std/statistics/2021/default.htm>

Clinical Manifestations of Congenital Syphilis (CS)



<https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/quick-reference-handbook/congenital-syphilis.html>

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
<p>Neonate with:</p> <ul style="list-style-type: none"> • a physical exam consistent with CS • serum quantitative nontreponemal serology 4-fold greater than mother’s or • a positive darkfield or PCR test of placenta, body fluids or positive silver stain of placenta or cord 	<p>Neonate with a normal physical exam and a serum quantitative nontreponemal serologic titer equal to or < 4-fold of the maternal titer at delivery and one of the following:</p> <ul style="list-style-type: none"> • The mother was not treated, was inadequately treated, or has no documentation of treatment. • The mother was treated with erythromycin or a regimen not recommended in these guidelines • The mother received recommended regimen but treatment was initiated <30 days before delivery. 	<p>Neonate with a normal physical examination and a serum quantitative nontreponemal serologic titer equal or <4-fold of the maternal titer at delivery and both of the following are true:</p> <ul style="list-style-type: none"> • The mother was treated during pregnancy, treatment was appropriate for the infection stage, and the treatment regimen was initiated ≥30 days before delivery. • The mother has no evidence of reinfection or relapse 	<p>Neonate with:</p> <ul style="list-style-type: none"> • a normal physical exam • serum quantitative nontreponemal 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
<p>Evaluation: CSF with VDRL, cell ct, protein, CBC/diff, long bone radiographs, neurologic eval (eye, auditory, imaging)</p>	<p>CSF analysis for VDRL, cell count, and protein** CBC, differential, long-bone radiographs</p>	<p>No evaluation is recommended</p>	<p>No evaluation is recommended</p>
<p>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</p>	<p>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 50,000 units/kg</p>	<p>Treatment: Benzathine penicillin G 50,000 units/kg body weight/dose IM in a single dose * Another approach involves not treating the newborn if follow-up is certain but providing close serologic follow-up every 2–3 months for 6 months for infants whose mothers’ nontreponemal titers decreased at least fourfold after therapy for early</p>	<p>No treatment recommended</p> <ul style="list-style-type: none"> • Benzathine penicillin 50,000 units/kg body weight as a single IM injection might be considered, if follow-up is uncertain and the neonate has a reactive nontreponemal test. • Neonates should be followed serologically to ensure the nontreponemal test returns to negative

Syphilitic Stillbirth

Clinical case definition

A fetal death that occurs **after a 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 completion of a penicillin-based regimen, in accordance with CDC treatment guidelines, appropriate for stage of infection, initiated 30 or more days before delivery.

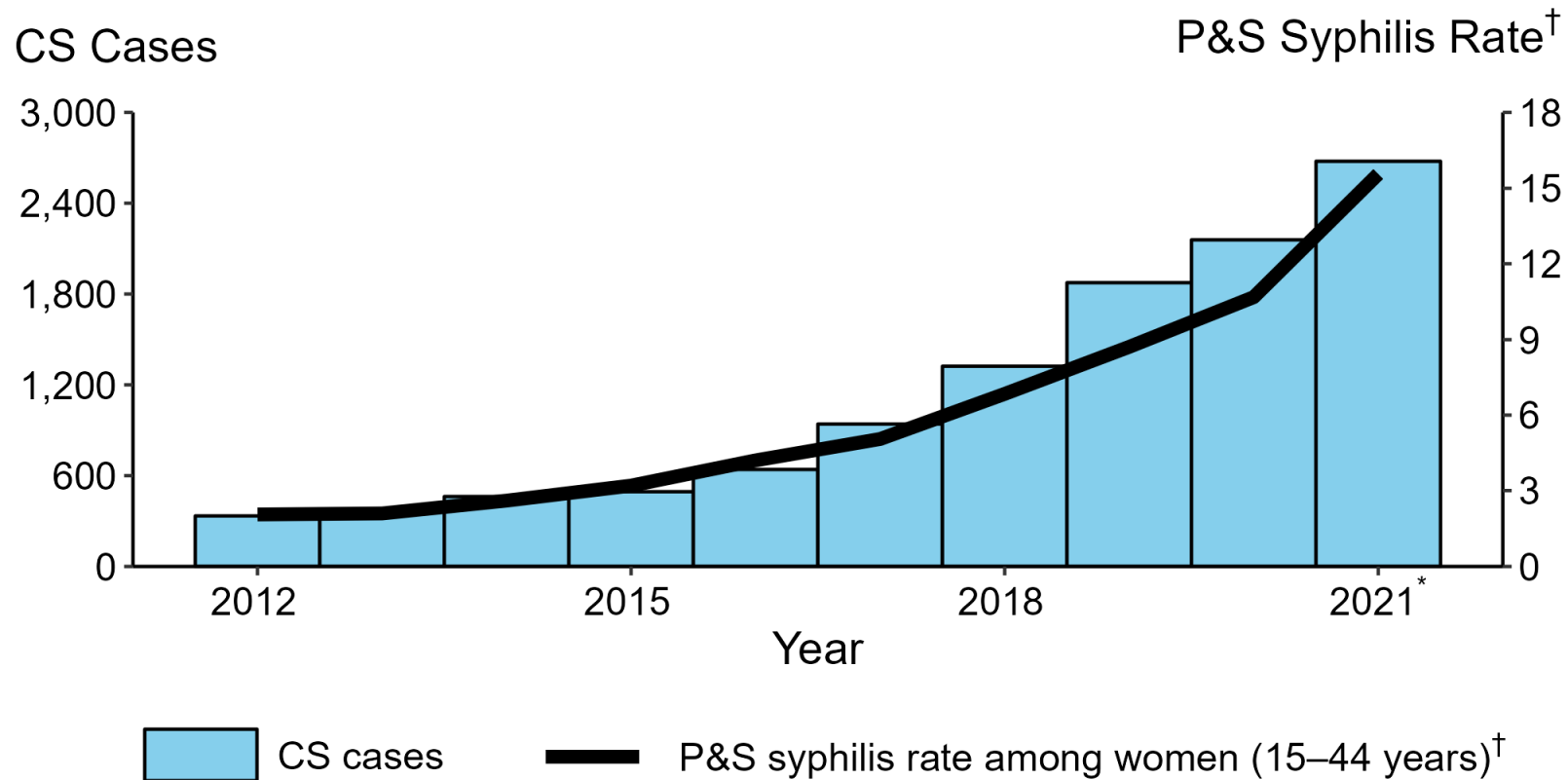
Comments: For **reporting** purposes, congenital syphilis includes:

1. cases of congenitally acquired syphilis among infants and children
2. syphilitic stillbirths

<https://www.cdc.gov/std/statistics/2019/case-definitions.htm>



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*



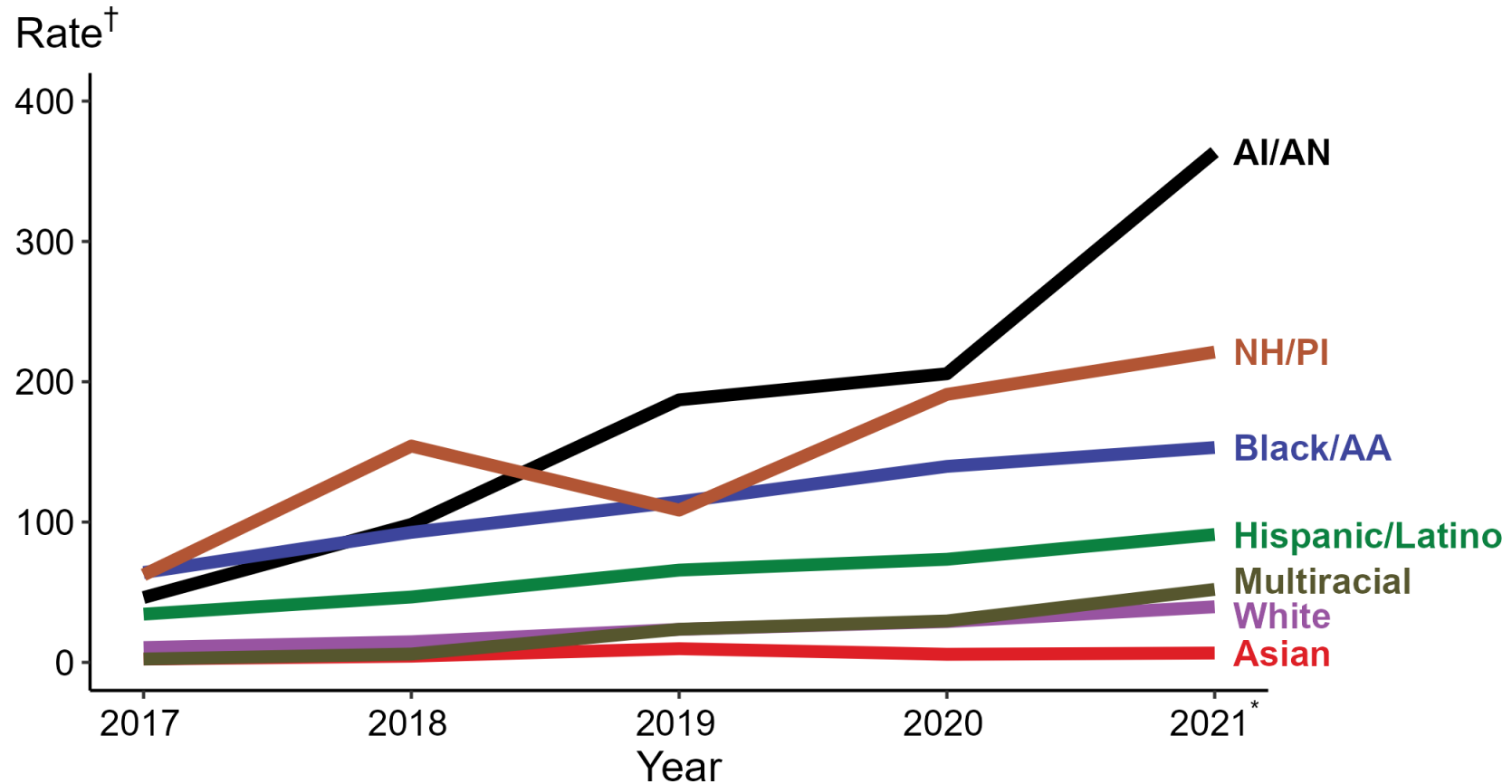
* Reported 2021 data are preliminary as of July 7, 2022

† Per 100,000

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

<https://www.cdc.gov/std/statistics/2021/default.htm>

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



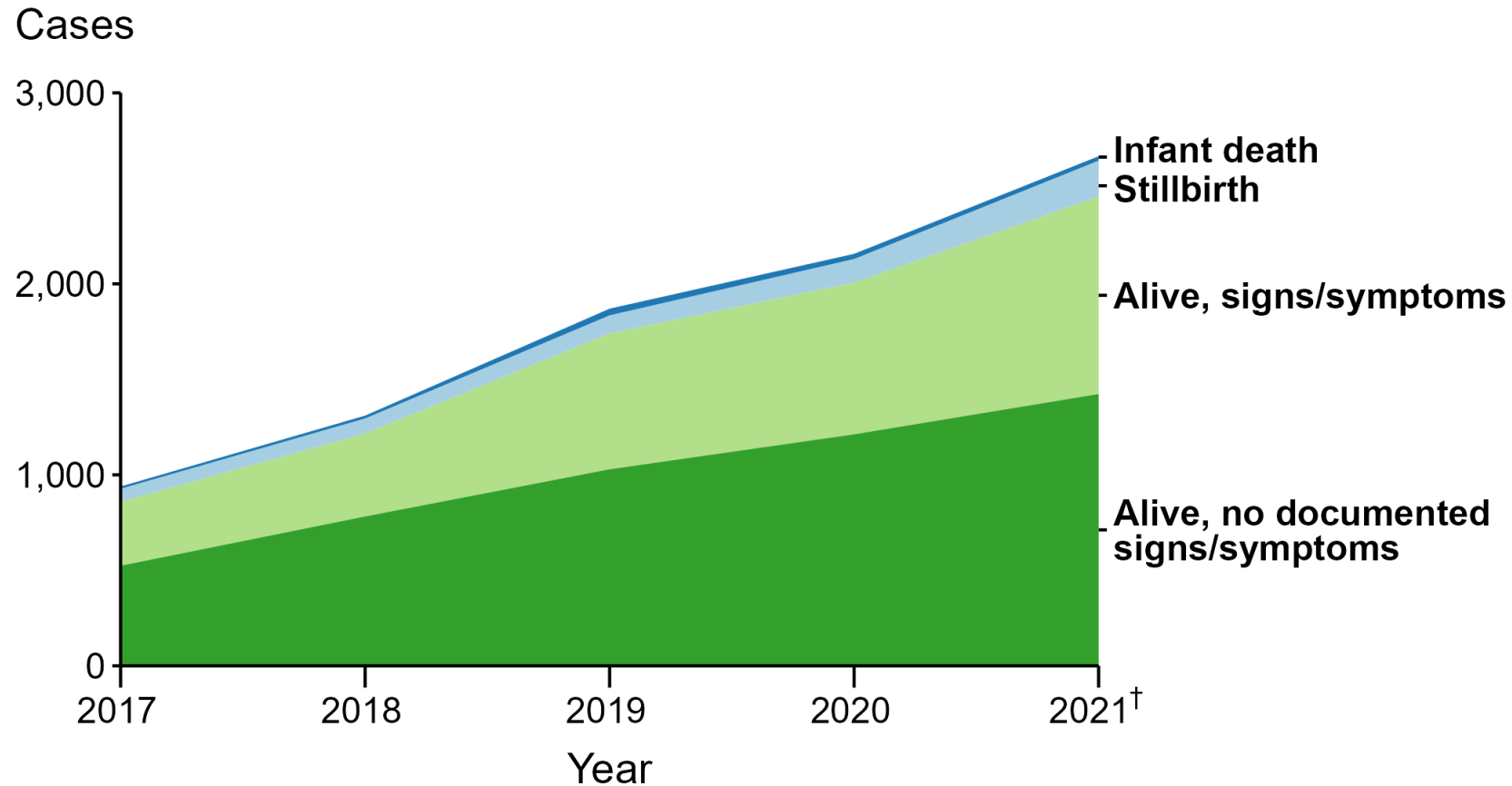
* Reported 2021 data are preliminary as of July 7, 2022

† Per 100,000 live births

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

<https://www.cdc.gov/std/statistics/2021/default.htm>

Congenital Syphilis — Reported Cases by Vital Status and Clinical Signs and Symptoms* of Infection, United States, 2017–2021[†]

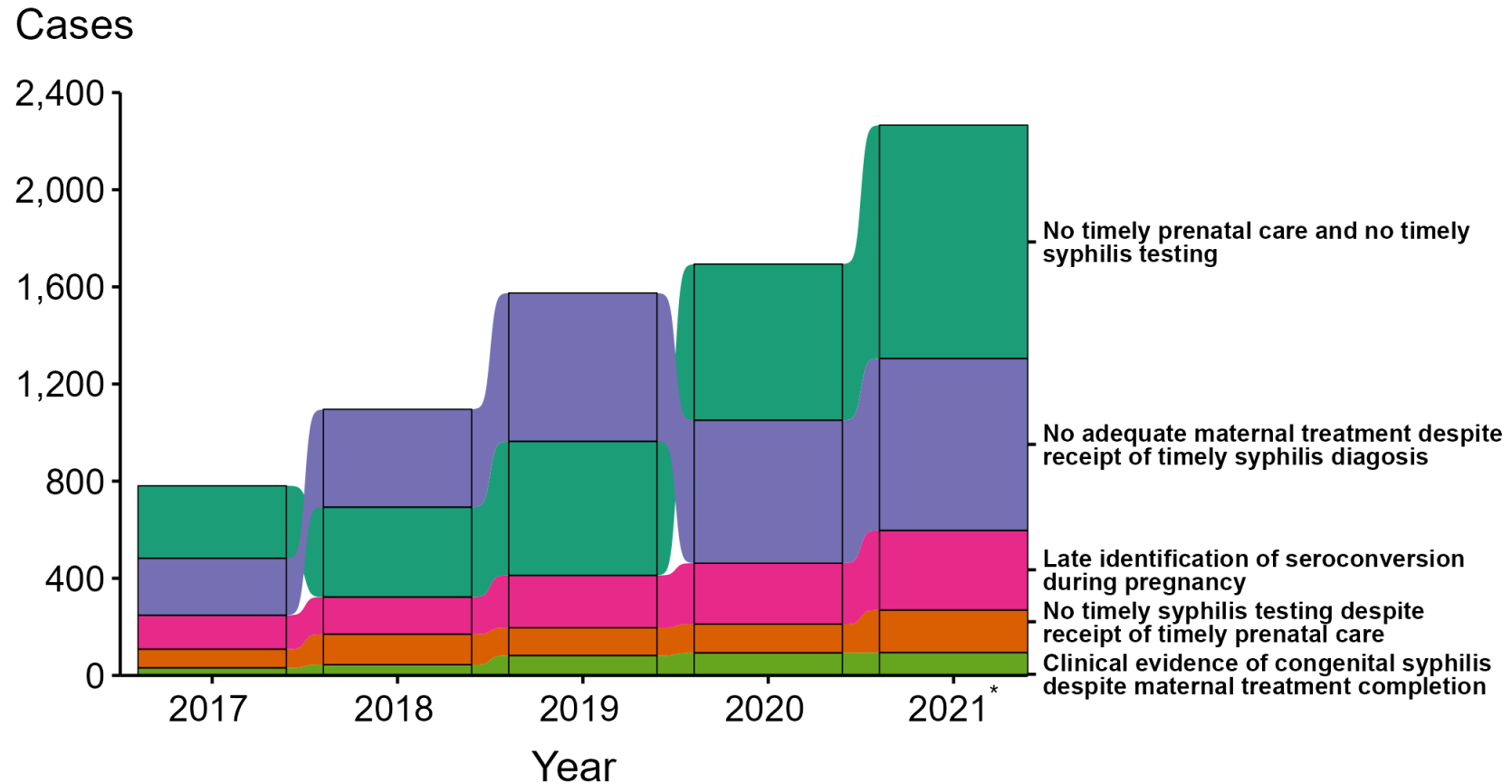


* Infants with signs/symptoms of congenital syphilis have documentation of at least one of the following: long bone changes consistent with congenital syphilis, snuffles, condyloma lata, syphilitic skin rash, pseudoparalysis, hepatosplenomegaly, edema, jaundice due to syphilitic hepatitis, reactive CSF-VDR, elevated CSF WBC or protein, or evidence of direct detection of *T. Pallidum*.

[†] Reported 2021 data are preliminary as of July 7, 2022; <https://www.cdc.gov/std/statistics/2021/default.htm>

NOTE: Of the 8,974 congenital syphilis cases reported during 2017 to 2021, 30 (0.3%) did not have sufficient information to be categorized.

Congenital Syphilis — Missed Prevention Opportunities among Mothers Delivering Infants with Congenital Syphilis, United States, 2017–2021*



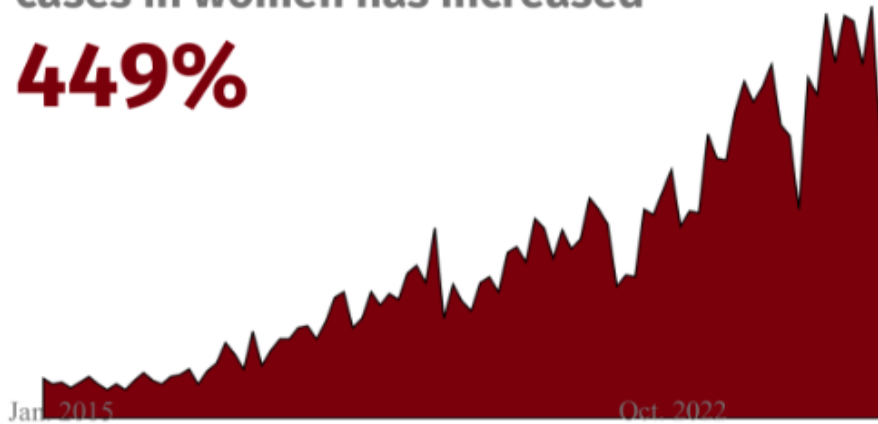
* Reported 2021 data are preliminary as of July 7, 2022

NOTE: Of the 8,974 congenital syphilis cases reported during 2017 to 2021, 1,562 (17.4%) were not able to have the primary missed prevention opportunity identified due to insufficient information provided to CDC related to maternal prenatal care, testing, or treatment. <https://www.cdc.gov/std/statistics/2021/default.htm>

Arizona has an **outbreak of syphilis** among women and babies

Since 2015, the yearly average of **syphilis** cases in women has increased

449%



How can you **protect** yourself?



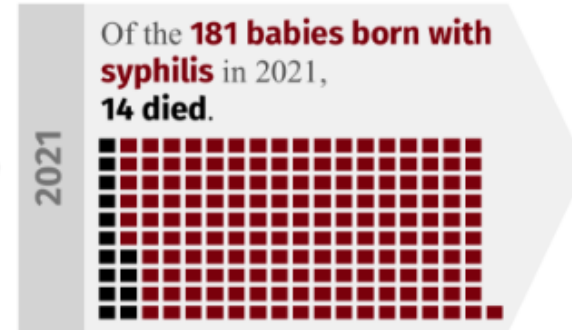
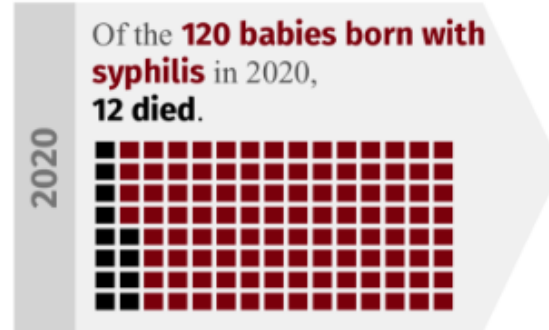
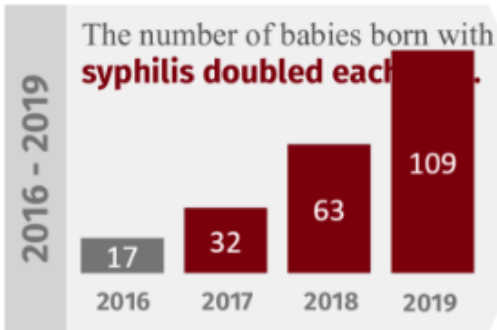
Use condoms when having **ANY** type of sex



Reduce number of sexual partners



Get tested for STDs



Syphilis can lead to problems with the skin, eyes, and brain, **stillbirth, or infant death.**

Up to **40%** of untreated syphilitic pregnancies result in **stillbirth or newborn death**¹



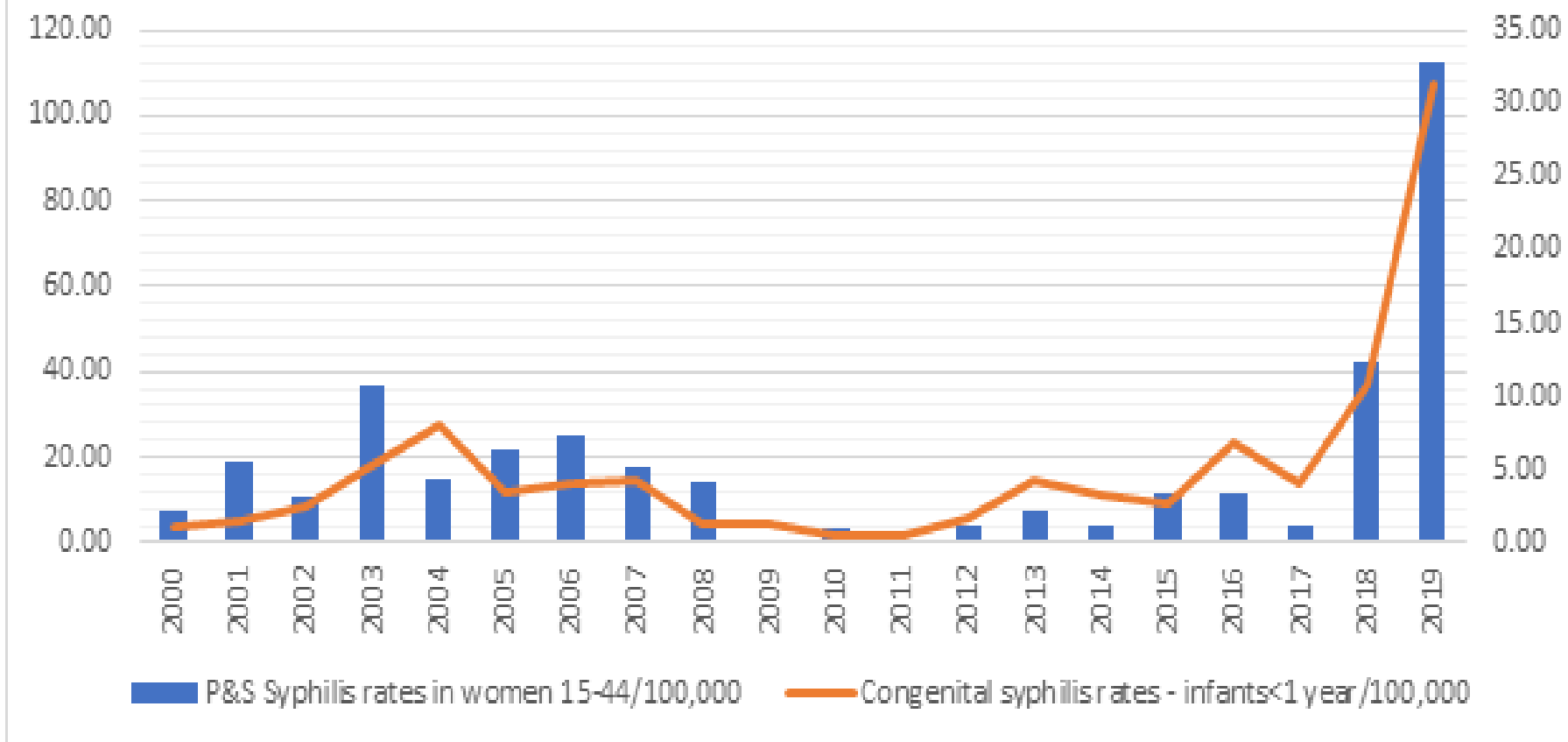
Babies who survive spend about **10 days** in the hospital

77% of babies were symptomatic in 2019.

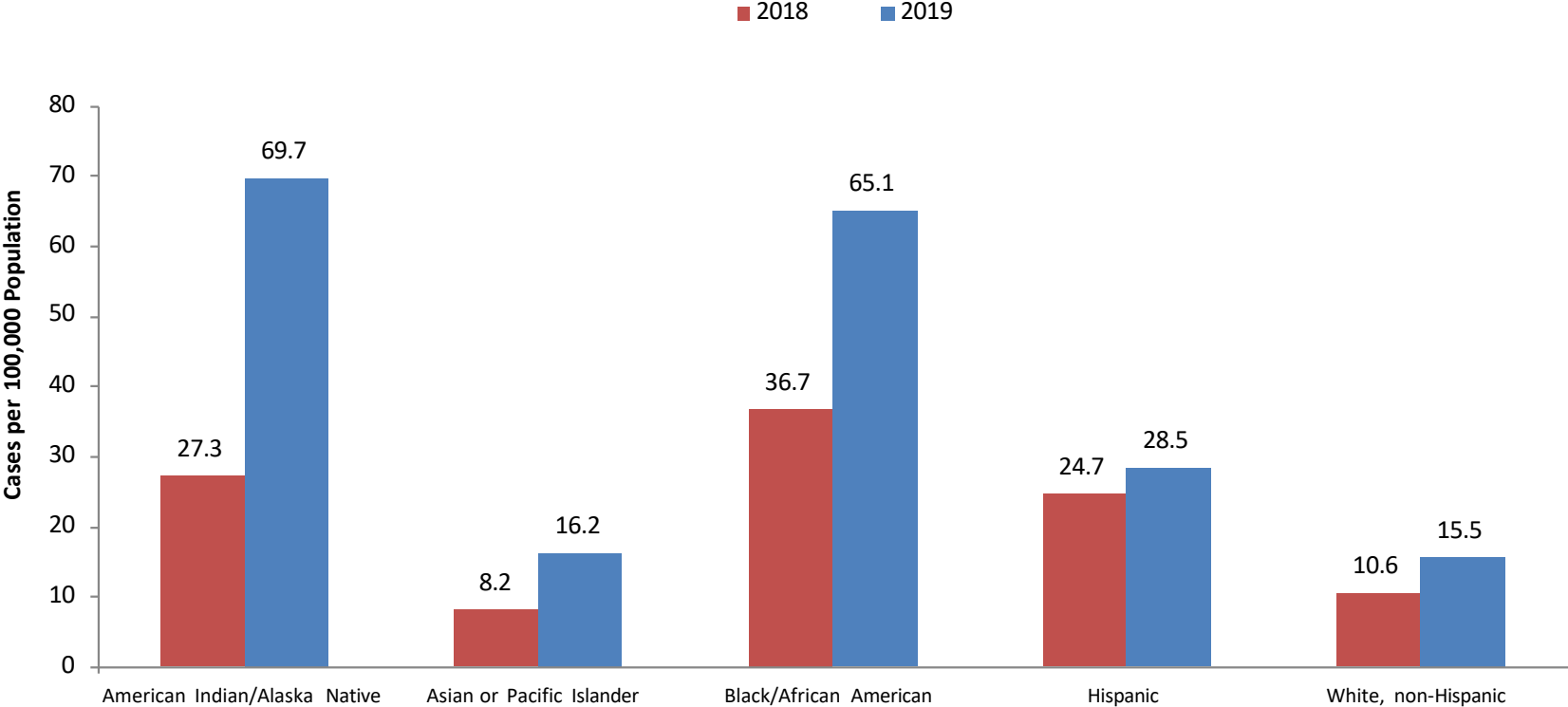
[1] Centers for Disease Control and Prevention. "STD Facts – Congenital Syphilis" [Online] Available: <https://www.cdc.gov/std/syphilis/stdfact-congenital-syphilis.htm>

Infographic Updated: 1/11/2023 – Case counts from the current year may change as the data are still pending. There is a 3 month lag in this report to help ensure accurate counts.

Congenital Syphilis rates in infants <1 year/ 100,000 population and Primary and Secondary Syphilis rates in women aged 15 - 44/ 100,000 population, New Mexico, 2000 - 2019



Primary, Secondary, and Early Latent Syphilis Rates by Race/Ethnicity, NM, 2018 – 2019



Treatment of syphilis: Overview

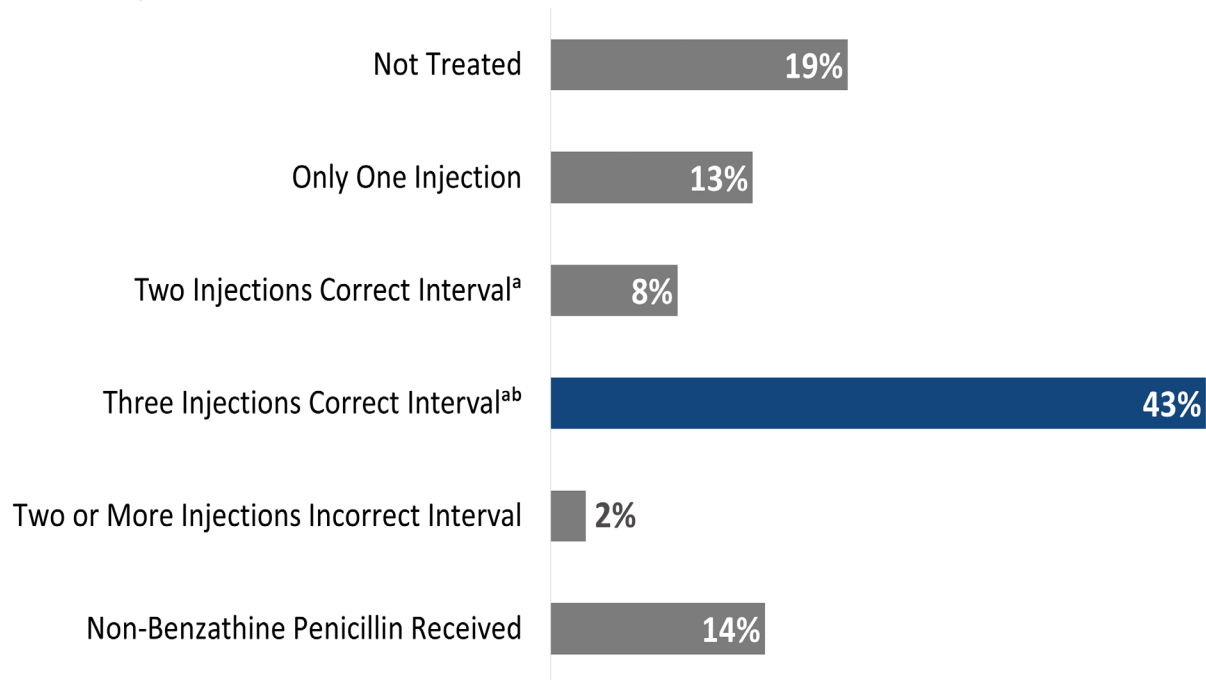
Stage				
Primary	Secondary	Early non-primary, non secondary	Late Latent/ or Unknown Duration	Neurosyphilis, ocular syphilis and otosyphilis
Benzathine penicillin 2.4 million units IM in a single dose	Benzathine penicillin 2.4 million units IM in a single dose	Benzathine penicillin 2.4 million units 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>

Syphilis Treatment Compliance: Benzathine Penicillin Treatment Rates Among People with Late Latent and Unknown Duration Syphilis in Maricopa County, Arizona

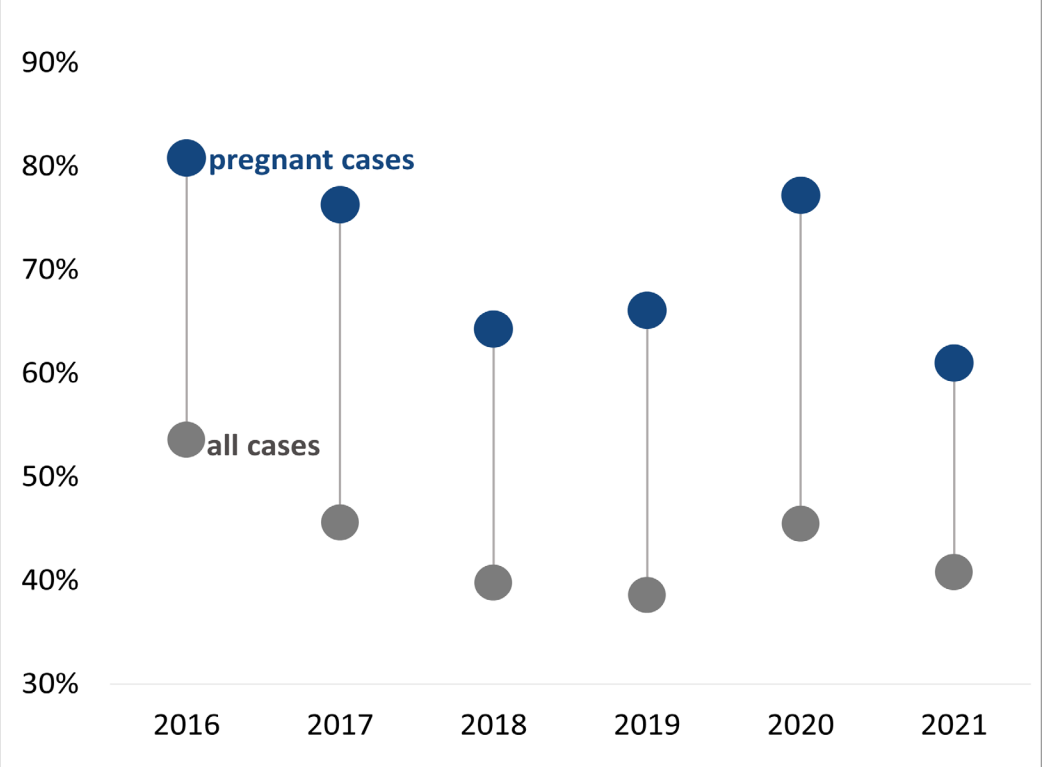
The treatment completion rate for **all 3 injections of benzathine penicillin G** was **43%** at 7-9 days between doses from 2016-2021 (n = 5,372 cases).



^aValidated: Captures Communicable Disease Investigator (CDI) documentation of each individual injection

^bNon-validated: Captures CDI documentation of patient reported "3 injections with benzathine penicillin at 1 week intervals" from 2016-2019

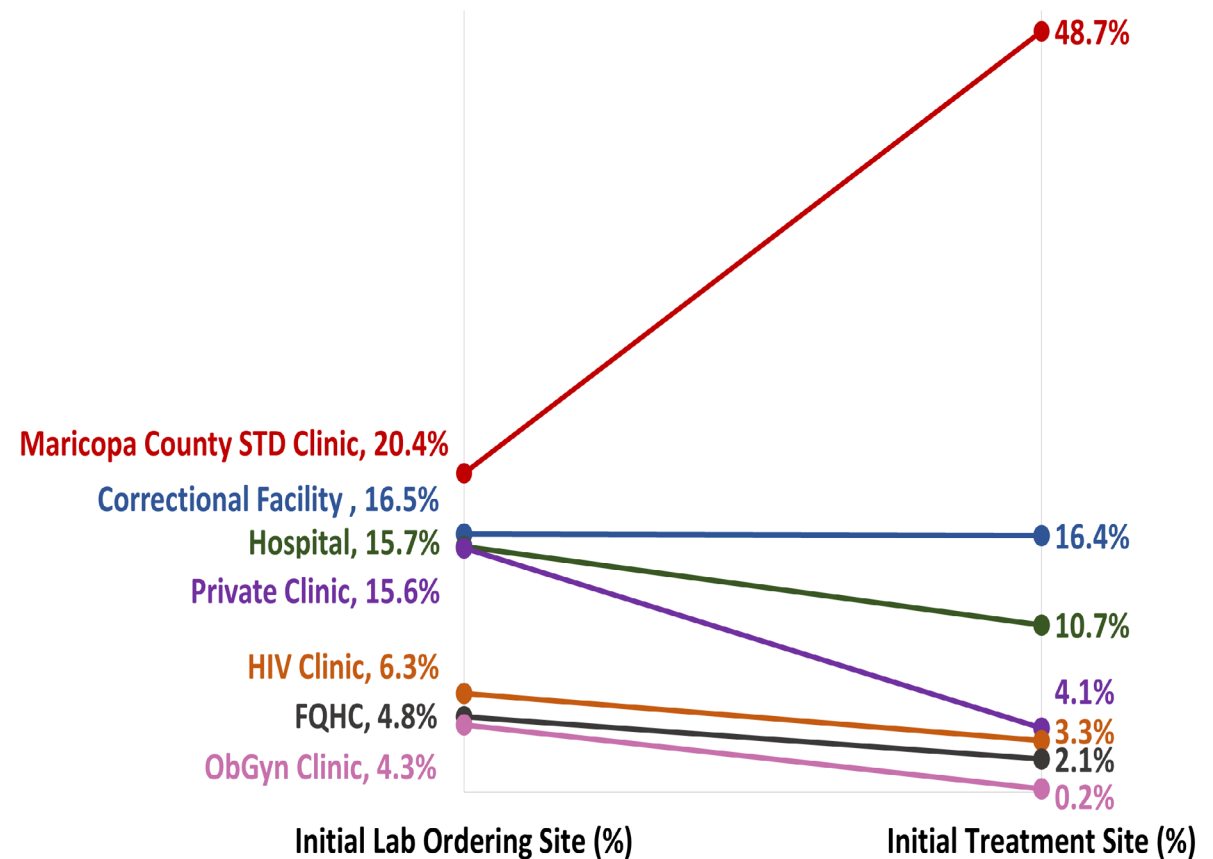
The treatment completion rate for all 3 injections of benzathine penicillin G at 7-9 days between doses was higher among **pregnant cases** when compared to **all cases**.



Access to benzathine penicillin for syphilis patients, Maricopa County, AZ 2021 (n = 2977)

Site Category	Initial Lab Ordering Site (n)	Initial Lab Ordering Site AND Initial Treatment Site (n)	Proportion (%)
Maricopa County STD Clinic	607	594	98%
Correctional Facility	492	466	95%
Hospital	468	196	42%
Private Clinic	434	97	22%
HIV Clinic	200	100	50%
FQHC	145	49	34%
ObGyn	129	6	5%
Hospital ER/Urgent Care	126	15	12%
Indian Health Service	115	105	91%
Community Health Center	58	50	86%
Laboratory	55	0	0%
Blood Bank	37	0	0%
Mental Health	35	7	20%
Military	32	24	75%
Family Planning/Planned Parenthood	16	10	63%
Drug Treatment	16	1	6%
School based Clinic	9	8	89%
Other Health Department	3	3	100%

Among syphilis cases that received penicillin as initial treatment (n = 2,977), **Maricopa County STD Clinic treated nearly 50%** despite only serving as the initial lab ordering site for 20% of cases.



Clinical Case

23 yo pregnant female (G1P0) presents for her first prenatal visit. She denies symptoms other than morning sickness. Her EGA is 10 weeks

She has no other medical conditions. She is allergic to penicillin which causes throat swelling.

Her prenatal labs reveal a positive syphilis EIA and an RPR of 1:512. She denies recent symptoms of syphilis and she is no longer in contact with her sexual partner. Her last sexual encounter was 3 weeks ago.

She lives 40 miles away and used medical transport to get to clinic today.

What is the ideal clinical management for this patient with syphilis?

- Administer benzathine penicillin 2.4 MU now as she is unlikely to be truly allergic to penicillin.
- Begin treatment with doxycycline 100 mg BID as an alternative regimen for treatment of syphilis since she is allergic to penicillin
- Ask her to return to clinic at her convenience for penicillin desensitization and treatment
- Admit her to the hospital for penicillin desensitization followed by the first injection of benzathine penicillin 2.4 MU of a 3 weekly dose series.
- Retest her for syphilis as test results may be false positive since she is pregnant

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Penicillin Allergy

- Patients often are incorrectly labeled as allergic to penicillin
 - Evaluate what symptoms were experienced by patients with reported penicillin allergy
- 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.***

Maternal Screening for Syphilis

1. All pregnant women should be tested for syphilis early in pregnancy at the **first prenatal visit** or at the time of pregnancy confirmation
2. In **high prevalence areas or who are at high individual risk***, retesting at 28 weeks and delivery is recommended. High-risk* pregnant women should be screened at **delivery**.
3. No mother or baby should be discharged from the hospital without documentation of maternal syphilis testing (during pregnancy and/or delivery)
4. Women who experience a **fetal death** at ≥ 20 weeks should be tested for syphilis.

*Examples of high risk: ***multiple prior STIs, recent incarceration, substance misuse, homelessness, transactional sex***

<https://www.cdc.gov/std/statistics/2019/case-definitions.htm>





Clinical Considerations for Syphilis Outbreak Response

Expand syphilis case finding

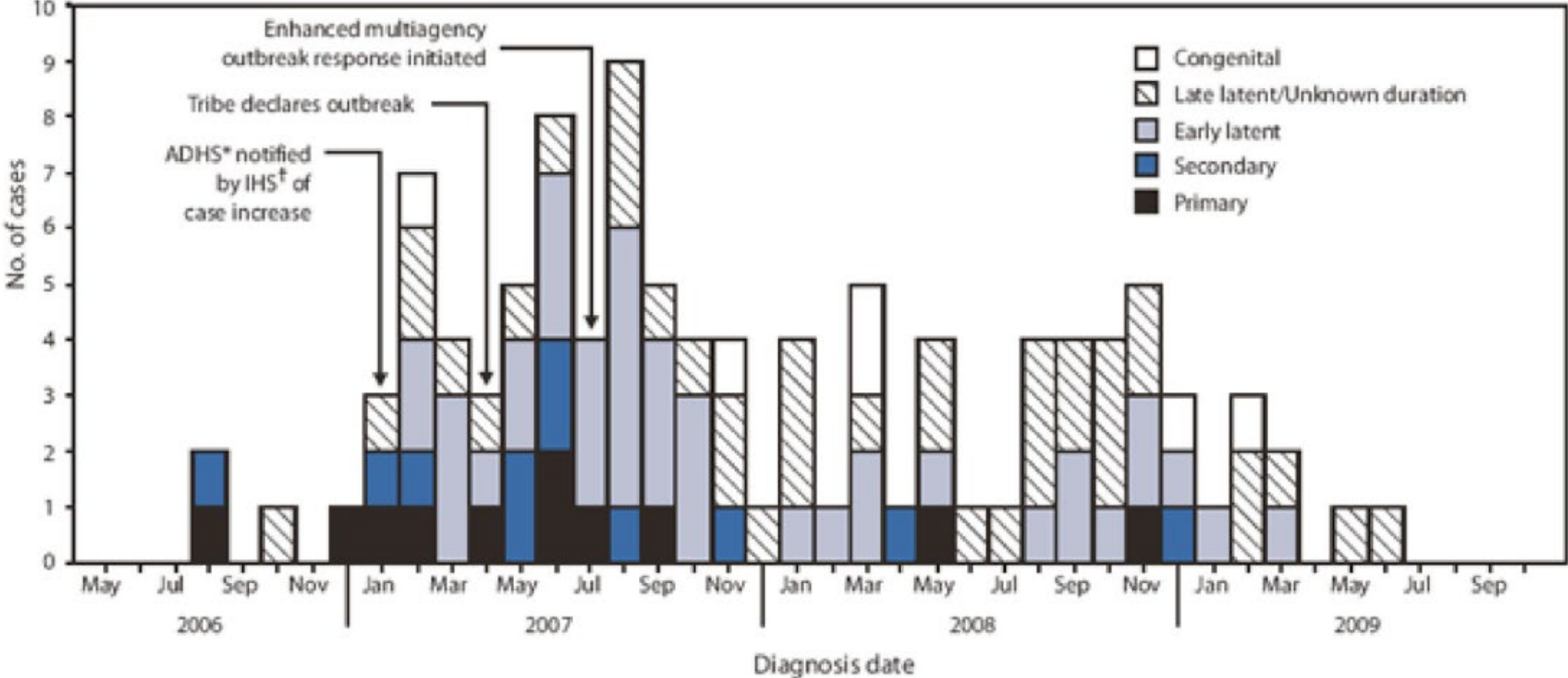
- Expand syphilis screening to populations at risk
 - Health facility- Emergency departments, OB/GYN, primary care, behavioral health
 - **** (Consider Test-only Visits)**
 - Community-based – schools, community events, corrections, work/school physicals
- Implement screening reminders in E H Rs, automated order sets, and customized treatment orders for syphilis and other STIs
- **Ensure 3-time point syphilis screening during pregnancy/delivery in high-prevalence settings or among high-risk populations.**
- Test women with syphilis for pregnancy

Public Health Considerations for Syphilis Outbreak Response

Provide prompt, stage-based treatment of cases and sexual partners

- a) Link providers and case managers to public health investigative staff for effective disease intervention and community prevention (*case investigation with identification and treatment of sexual partners*)
- b) Provide **presumptive** treatment of (1) symptomatic persons and (2) sexual partners of cases
- c) Ensure access to prompt treatment (either health facility or field-based) using designated **case management** pathways
- d) Endeavor to identify patients with **early syphilis** which requires only one injection of benzathine penicillin.
- e) Repeat day of treatment RPR if most recent test is ≥ 6 days old
- f) Clinical consultative “rounds” to share and discuss case staging and treatment

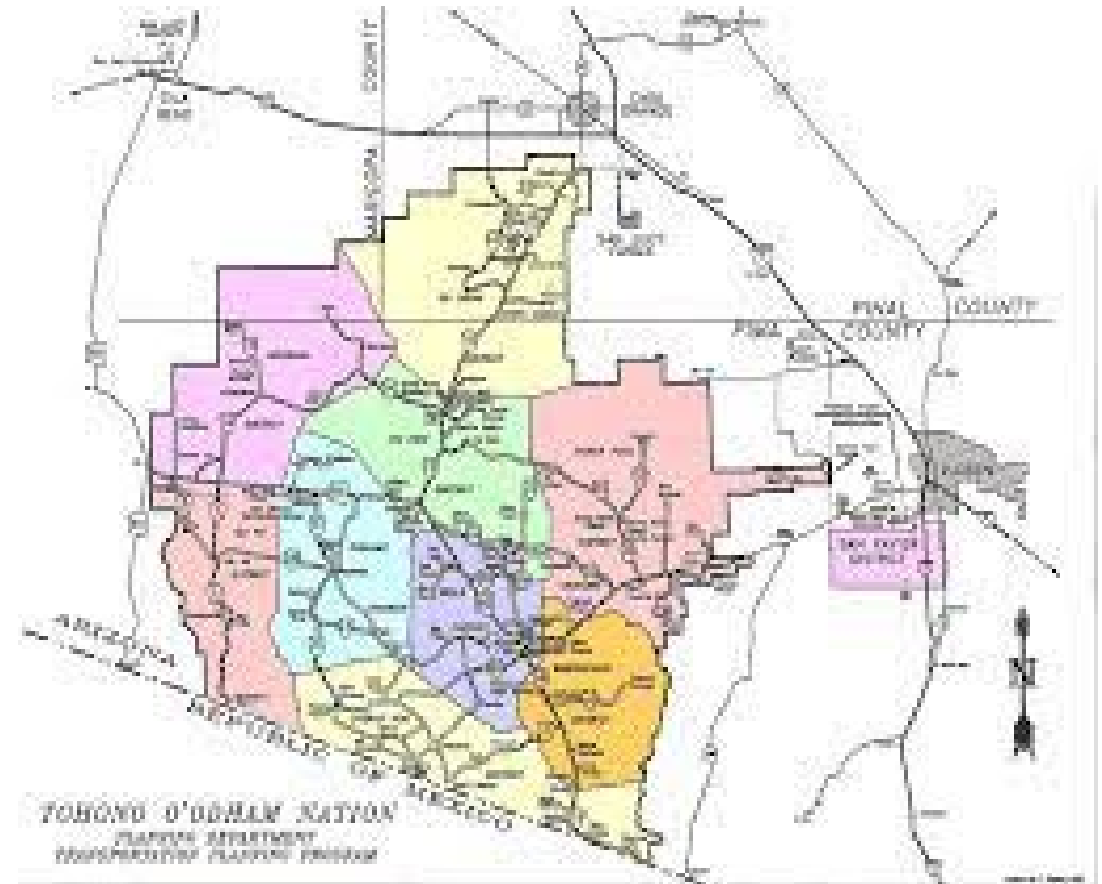
Southern Arizona Syphilis Outbreak, 2007-2009



Johnson M, et al. Syphilis Outbreak Among American Indians --- Arizona, 2007–2009. *MMWR Morb Mortal Wkly Rep.* 2010 February 19; 59(6): 158–161

Southern Arizona Syphilis Response

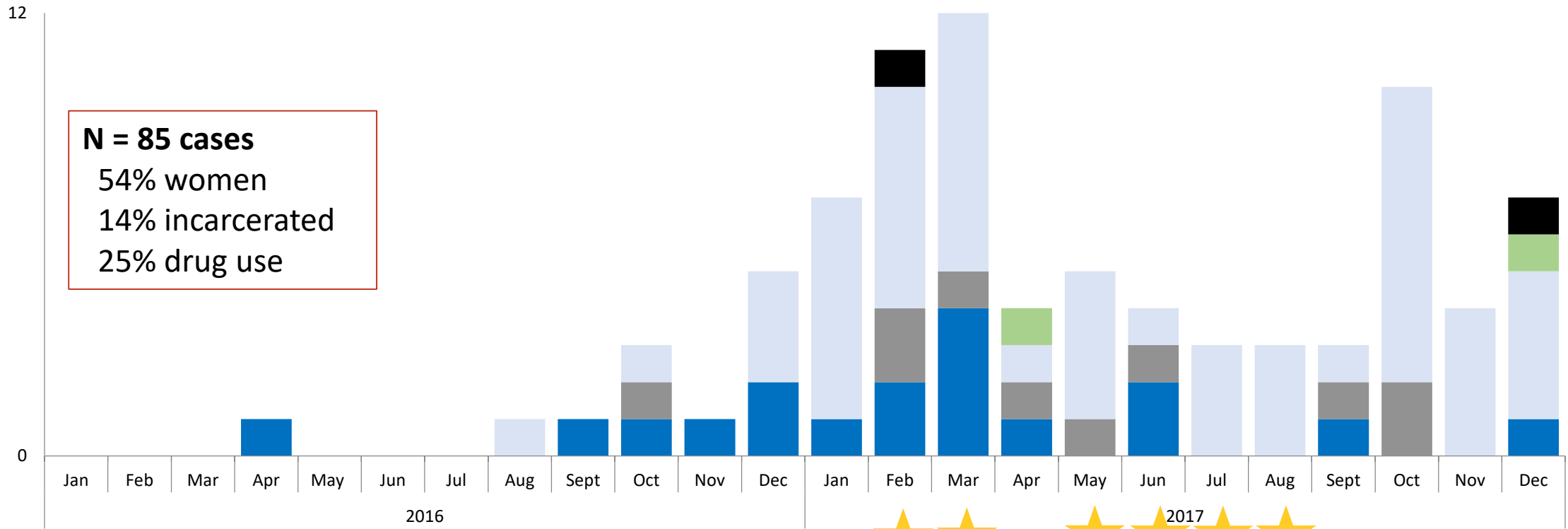
- Identification of syphilis, HIV, chlamydia, and gonorrhea screening program on the reservation to include:
 1. Clinic- and hospital-based screening of all persons aged 12–55 years receiving health care (including pregnant women),
 2. Screening of all incarcerated adults and juvenile detainees,
 3. Screening of students at seven high schools and of youths at six social events,
 4. Screening of workers at two worksites, and door-to-door screening in seven of the reservation's 11 districts.
 5. Case investigation and clinical management of sexual partners
 6. Community awareness campaign





Central Arizona, 2016-2017

Primary **Secondary** **Early** **Late** **Congenital**



★ ★ ★ ★ ★

Screening

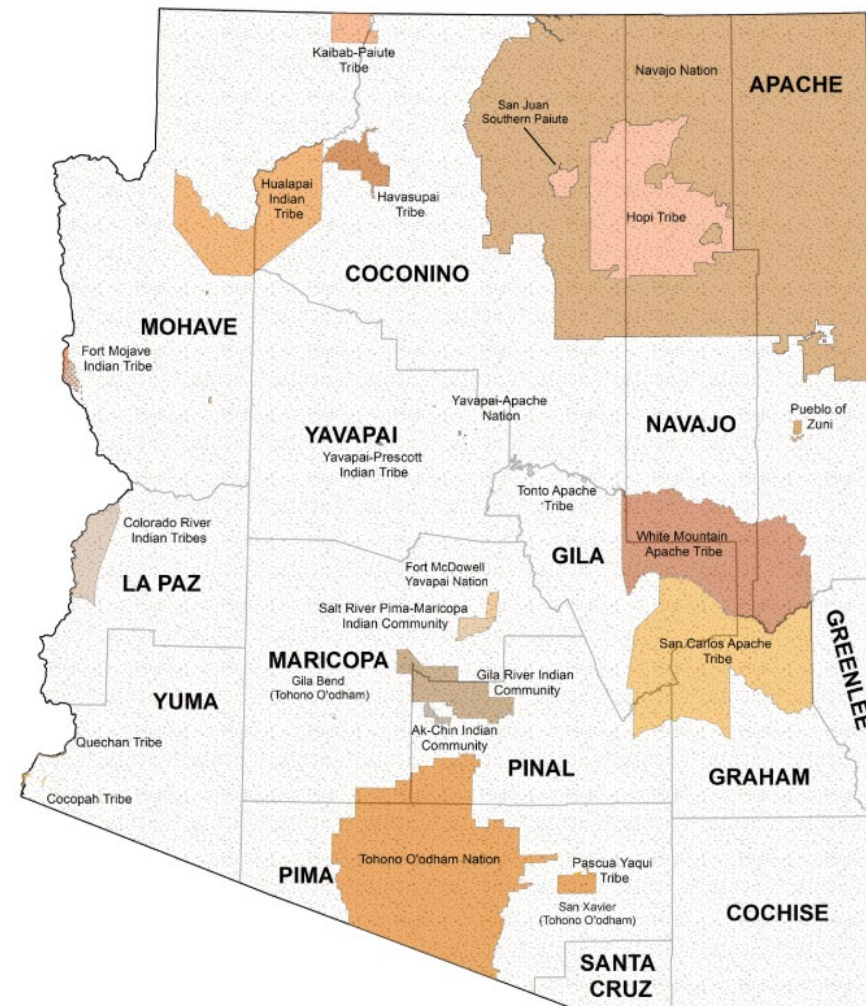
No BPG*

★ Site Visit
 *Benzathine penicillin

Central Arizona, 2016-2017

Methods of Case Finding	
Partner Services	51%
Screening	32%
<i>Provider screen (74%)</i>	
<i>Prenatal screen (11%)</i>	
<i>Jail screen (7%)</i>	
<i>Community screen (7%)</i>	
Self-Referral	14%
Referred by partner	2%

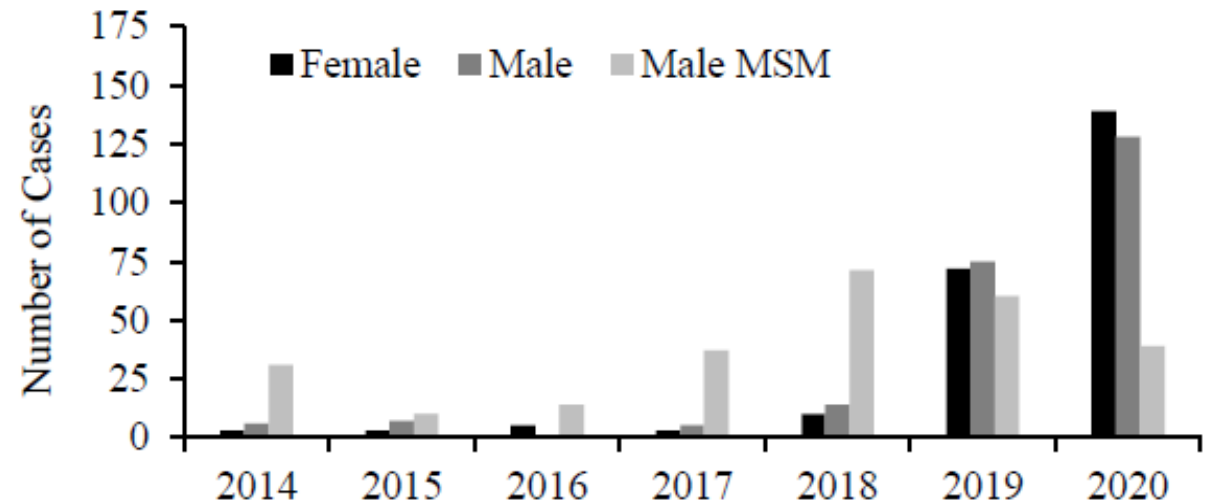
Tribal Homelands In Arizona



Alaska 2018-2020

- Ongoing increase 2018-2020
 - 361 cases in 2020
 - (49% increase from 2019)
 - 167 (55%) were in males
 - 150 (49%) American Indian/Alaska Native people, 90 (29%) White persons, 23 (8%) were in Black persons,
 - 104 (34%) were diagnosed with at least one other STD or had known HIV infection.
 - Eight infants with congenital syphilis born to mothers who reported inconsistent or no prenatal care

Figure. Primary, Secondary, and Early Latent Syphilis by Transmission Category — Alaska, 2014–2020 (N=733)*



* *Male: men who did not self-identify as having sex with men*
Male MSM: men who self-identified as having sex with men

Syphilis Outbreak Update, Alaska 2020. State of Alaska Epidemiology Bulletin.

http://www.epi.alaska.gov/bulletins/docs/b2021_08.pdf

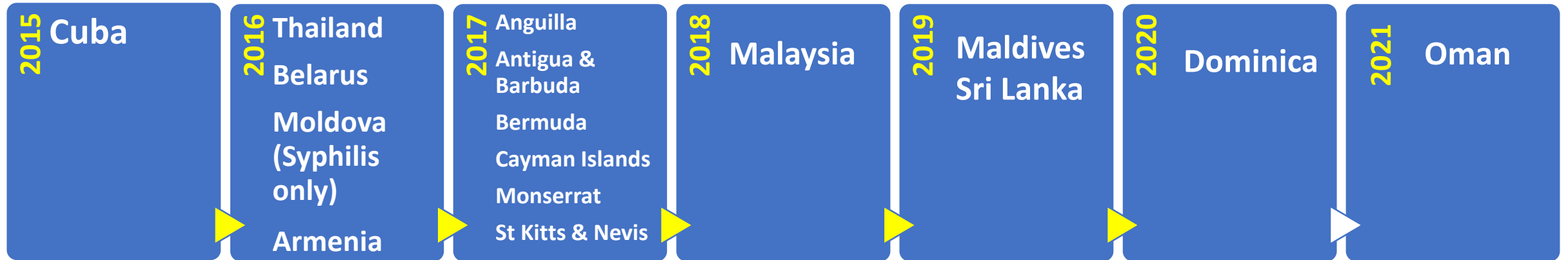
Whiteriver Service Unit

Prior to 2018 WRSU had 0-2 syphilis cases per year. In 2018 the number began to rise and by 2021 there were over 130 cases per year. In 2022 WRSU initiated a multipronged approach to address the outbreak:

- Educational sessions for clinical staff
- Updated EHR reminders for all patients over 13 years of age (age stratified)
- Initiated POC TPPA testing – Field, pharmacy, community events
- New automated RPR implemented with ordering of RPR for all ER and Inpatients who had a blood draw (age appropriate and based upon time since last RPR). ~6,500 RPRs to date.
- Door-to-door campaign (POC TPPA) with WMAT
- PHN field delivery of IM PCN
- Updated PCN allergy desensitization protocol
- Updated standing orders and initiated ‘golden ticket testing’



16 Countries/Territories validated by WHO for the Elimination of Mother-to-Child Transmission of HIV and/or syphilis



- [Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV, syphilis and hepatitis B virus \(who.int\)](https://www.who.int/initiatives/triple-elimination-initiative-of-mother-to-child-transmission-of-hiv-syphilis-and-hepatitis-b/validation)
- <https://www.who.int/initiatives/triple-elimination-initiative-of-mother-to-child-transmission-of-hiv-syphilis-and-hepatitis-b/validation>



Provider Education Resources

- **CDC STD Treatment Guidelines:** <https://www.cdc.gov/std/treatment-guidelines/default.htm>
- **Indian Country Infectious Disease ECHO:** www.IndianCountryECHO.org
- **CDC STD Prevention Training Centers:** <https://www.cdc.gov/std/training/default.htm>
- **University of Washington STD CME sessions:** <https://www.std.uw.edu/>
- **California Prevention Training Center Online:** https://www.stdhivtraining.org/online_courses.html
- **Johns Hopkins STD Prevention Training:** <https://www.stdpreventiontraining.com/>
- **New York City STD/HIV Prevention Training Center:** <https://www.nycptc.org/>
- **CDC STD Surveillance:** <https://www.cdc.gov/std/statistics/2019/default.htm>
- **CDC STD Hotline:** <https://www.usa.gov/federal-agencies/cdc-national-std-hotline>

