The Reemergence of Syphilis

Clinical Pearls for Consideration

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KEYWORDS

• Syphilis • STI • Epidemiology • Men who have sex with men (MSM)

KEY POINTS

- Although nearly eradicated in the United States by 1998, syphilis incidence rates have been increasing since 2000.
- Rates of congenital syphilis and syphilitic stillbirths have increased significantly in the past 5 years.
- Syphilis disproportionately affects people of color, men who have sex with men, and transgender women.
- Syphilis is the "great imitator" and nurses should consider a diagnosis of syphilis in people with classic and less common symptoms.

INTRODUCTION

Although nearly eradicated in the United States by 1998, syphilis incidence rates have been increasing since 2000.[1] Nurses, positioned throughout the health care system, are equipped to screen for, diagnose, and treat syphilis in its primary, secondary, and tertiary stages. This article describes the history of syphilis, reviews current guidelines for diagnosis and treatment, and introduces strategies for reducing rates of new syphilis infections.

HISTORY

Syphilis is known as the "great imitator" due to varied clinical presentations and the potential time interval between infection and symptom onset. Syphilis is the oldest known sexually transmitted infection (STI).[2] *Treponema pallidum* was identified as the causative bacterium for syphilis by Fritz Schaudinn and Erich Hoffmann in Germany in 1905, and the first diagnostic test for the infection was invented in 1906.[2]

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Initially treated with highly toxic and ineffective mercury and arsphenamine,[3] in 1943, John Mahoney introduced penicillin, revolutionizing the treatment of syphilis.[3] Penicillin remains the mainstay of syphilis treatment nearly 80 years after its introduction.

Development of diagnostic and treatment guidelines has been fraught with ethical lapses, including the inhumane treatment of human subjects.[4–10] In 1837, a French-American physician, Philippe Ricord, demonstrated that gonorrhea and syphilis were distinct STIs by injecting 17 prisoners in Parisian jails.[2] Ricord also is credited as the first to describe the primary, secondary, and latent stages of syphilis. The US Public Health Service did similarly inoculate 1300 Guatemalan sex workers, prisoners, mental health patients, and soldiers with syphilis and gonorrhea from 1946 to 1948 while treating just more than half of those human subjects.[6,7] The infamous "ethically impossible"[8] Tuskegee Syphilis Study also notoriously and knowingly withheld penicillin treatment from hundreds of primarily rural and poor Black American men infected with syphilis for 40 years (1932–1972).[8,9] These experiments accelerated health disparities while decreasing health care utilization and health-seeking behaviors among populations that continue to have a disproportionately high incidence of multiple health problems, including syphilis.[10]

MICROBIOLOGY

T pallidum, the syphilis spirochete, is deemed the "stealth pathogen."[11] Adept at dissemination and immune evasion, syphilis infection can lead to chronic latent and tertiary infection.[11] Left untreated, syphilis infection can span decades. Despite being the oldest and earliest discovered STI, understanding of syphilis has not kept pace with knowledge of other bacterial infections. Pathogenic species of treponemes defy study due to being slow growing, poorly tolerant of desiccation and temperature extremes, and nearly unculturable.[11,12] Despite *T pallidum* being one of the first bacterial genomes to be sequenced, its pathogenesis, virulence, and gene expression are still incompletely understood.[12,13]

Spirochetes can deftly penetrate mucous membranes or breaks in skin barrier from sexual activity. Their morphology propels their dissemination. They lack surface-exposed lipoproteins that activate macrophages and dendritic cells, allowing evasion from destruction by the immune system.[12] *T pallidum* is the most virulent *Treponema* subspecies and easily crosses the blood-brain barrier and the maternal-fetal placenta.[11]

CLINICAL PRESENTATION

Recognition of primary and secondary (P&S) syphilis is crucial to decreasing disease transmission. Syphilis should be included in the differential diagnosis of any sexually active person with a rash or genital lesion. A solitary, painless, indurated genital chancre (ulcer) smaller than 2 cm is the hallmark of primary syphilis infection.[1,14–16] The chancre heals spontaneously in approximately 3 weeks to 4 weeks and is 98% specific and 31% sensitive in identifying primary infection.[17] Clinical findings of secondary syphilis may include fever, swollen glands, patchy hair loss, condyloma lata, oral or perineal gray or white patches, and other skin rashes.[1,14] The rash associated with secondary syphilis usually is nonpruritic and symmetrically distributed and may involve the palms and soles.

After the P&S stages of syphilis, patients progress to either latent or tertiary syphilis. Latent syphilis is defined as either early or late and based on the interval since initial infection. Early latent syphilis occurs within 12 months of exposure. Late latent syphilis

can be defined as either greater than 1 year since initial infection or unknown time since exposure. Tertiary syphilis may occur 1 year to decades after initial infection.

Tertiary syphilis may be characterized as gummatous, cardiovascular, and/or neurologic.[1,14] Gummata are noncancerourous granulomatous lesions found in multiple tissues, including the brain, liver, testes, bone, and skin. Cardiovascular complications of tertiary syphilis can include valve disorders and aortic aneurysm.[1,14] Central nervous system infection can occur at any stage. Early neurosyphilis findings include hearing and vision changes, meningitis, and altered mental status.[18] Tabes dorsalis occurs 10 years to 30 years after primary infection and is the result of an untreated syphilis infection that slowly degenerates nerve tissue, resulting in weakness, diminished reflexes, unsteady gait, joint pain, loss of coordination, paralysis, personality changes, dementia, deafness, visual impairment, and impaired pupillary reaction to light.[18] **Fig. 1** and **Table 1** describes the stages of syphilis. Symptoms correlate with stages and infection transmission.

DIAGNOSIS AND TREATMENT

The threshold for serologic testing should be low. The US Preventive Services Task Force (USPSTF) recommends routine screening in adolescents and adults at high risk,[19] defined as men who have sex with men (MSM) and individuals with human immunodeficiency virus (HIV).[1] Risk factors dependent on prevalence include men under age 29, sex work, drug use, and history of incarceration within the past 12 months.[1] Testing should be offered to anyone with increased risk factors or signs and symptoms of P&S infection.

Because of antepartum fetal infection and congenital syphilis (CS), all pregnant women require screening. The USPSTF[20] and the Centers for Disease Control and Prevention (CDC)[1] recommend screening all pregnant women at their first prenatal visit. Multiple state laws mandate screening at the first prenatal visit and in the third trimester.[21]

Syphilis must be diagnosed with serologic testing because *T pallidum* is difficult to culture. Diagnosis is based on treponemal (fluorescent treponemal antibody absorption [FTA-ABS], enzyme-linked immunoassays [EIAs], and treponemal pallidum particle agglutination [TP-PA]) and nontreponemal (Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]) serologic testing, as shown in **Table 2**. Treponemal tests detect antibodies to *T pallidum* proteins. Nontreponemal tests detect antibodies to damaged host cells and lipoidal antigens.[22] Nontreponemal serology historically has been the standard, initial, cost-effective screening in the United States and still is recommended by the CDC. Reactive RPR results are recorded as quantitative titers. RPR may remain nonreactive, however, for up to 4 weeks after initial infection and often is negative in primary syphilis.[23] A negative RPR, in the absence of treatment, 3 months after potential exposure, rules out syphilis infection.[1,23] Traditionally, treponemal testing is used to confirm reactive nontreponemal results.[23,24] Reverse sequence screening, or initially testing with treponemal and confirmed by nontreponemal serology, has gained favor due to immunoassay automation. Inconclusive results should be verified, as demonstrated in **Table 3**. Patients with syphilis should be screened routinely for chlamydia, gonorrhea, and HIV.[1,23,25] Further testing is warranted for persons with clinical signs of neurosyphilis or tabes dorsalis.[25–27] A diagnosis of neurosyphilis depends on a combination of neurologic symptoms, reactive serology tests, and cerebrospinal fluid (CSF) tests, including CSF cell count, CSF protein, and a reactive CSF-VDRL.[1,27] In both the United States and Canada, all jurisdictions require reporting of new syphilis diagnoses to public health authorities.

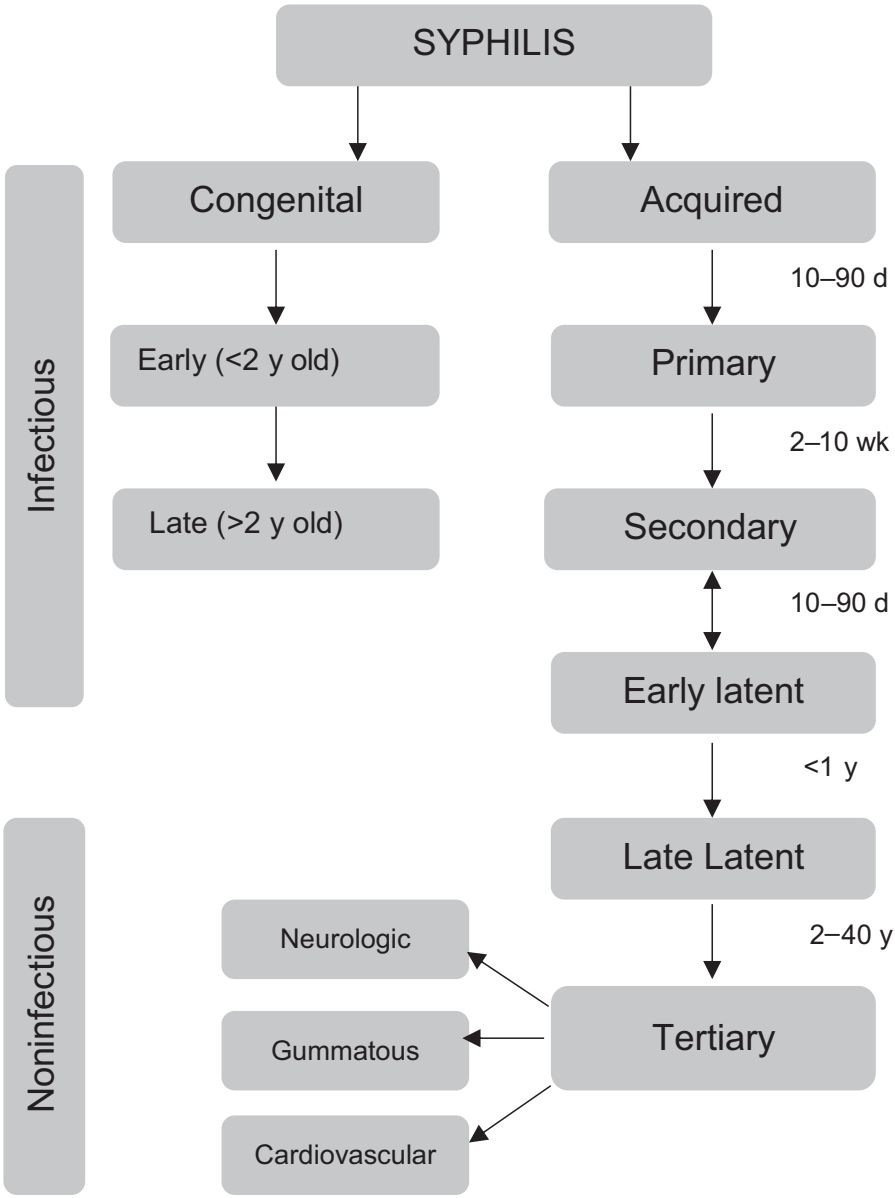


Fig. 1. Stages of syphilis. (*Data from* Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019. Available at: https://www.cdc.gov/std/stats18/STDSurveillance2018-full-report.pdf; and From Centers for Disease Control and Prevention. Sexually Transmitted Diseases: Syphilis – CDC Fact Sheet. Available at: https://www.cdc.gov/std/syphilis/stdfact-syphilis.htm; with permission; and Aguinaldo J. TORCH(Z) Congenital Infections. St. George's University, Masters of Public Health Program. Available at: http://mph.sgu.edu/mphblog/2017/05/16/torchz-congenital-infections/; with permission.)

Table 1
Stages of syphilis

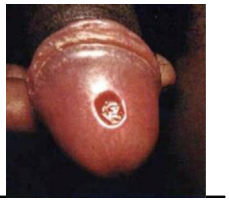
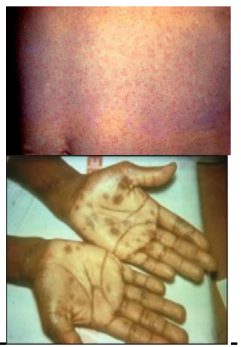
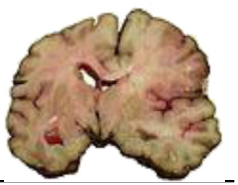
Primary stage	Onset 10–90 d postexposure Duration 3–6 wk	Single chancre; usually firm, round, and painless; <2 cm; and located where *T pallidum* enters the body	
Secondary stage	Onset 4–10 wk after primary Duration varies, usually 2 mo	Rash of multiple locations and morphologies, especially palms of hands and soles of feet; fever; swollen nodes; sore throat; patchy hair loss; headaches and neurologic changes; weight loss; myalgias; fatigue	
Latent stage	Onset at end of secondary stage Duration 1–20 y	Asymptomatic May experience multiple relapses of secondary syphilis before returning to latent stage	

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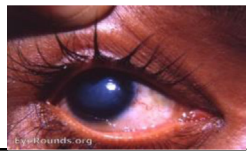
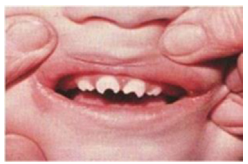
Table 1 (*continued*)			
Tertiary stage	May occur at any point or never occur	Dependent on affected organs Gummata, cardiovascular, ocular syphilis, neurosyphilis Tabes dorsalis	
Congenital	Contracted through placenta or during labor and delivery	Saddle nose, Hutchinson teeth, interstitial keratitis, deafness, skeletal deformities, neurosyphilis	

Data from Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019.

Table 2
Diagnostic testing for syphilis

Nontreponemal serologic	VDRL or RPR	Considerations Use of only 1 type of serologic test is insufficient for diagnosis and can result in false-negative and false-positive results. Nontreponemal test should be done first, and, if reactive, must be followed by treponemal testing to confirm diagnosis. Follow-up with RPR to track response to treatment and disease activity. Few treponemal tests are approved for use in the United States.
Treponemal serologic	FTA-ABS tests TP-PA assay EIAs, CLIAs , immunoblots, or rapid treponemal assays	
Direct detection: PCR, dark-field microscopy, direct fluorescent antibody	Not widely commercially available	Definitive diagnosis

Data from CDC Sexually Transmitted Infection Treatment Guidelines 2015. Diagnostic Considerations And CDC Discordant results from reverse sequence syphilis screening–five laboratories, United States, 2006-2010.

Parenteral penicillin G is the preferred treatment of all individuals and all stages of syphilis.[28] Parenteral penicillin G is the only acceptable therapy for syphilis during pregnancy.[28] Pregnant women who report penicillin allergy should be desensitized and treated with penicillin.[28,29] The duration and preparation of penicillin G treatment depend on syphilis stage and clinical manifestations, as shown in **Table 4**. Penicillin G benzathine, 2.4 million U, injected intramuscularly (IM) in a single dose, appropriately treats adults with P&S and early latent syphilis. Treatment with penicillin G procaine is not appropriate and should be carefully avoided. Infants and children with P&S syphilis should receive penicillin G benzathine, 50,000 U/kg IM, up to the adult dose of 2.4 million U, in a single dose. Treat late latent and tertiary syphilis with penicillin G benzathine, 2.4 million U IM weekly for 3 weeks. Neurosyphilis is treated with aqueous crystalline penicillin G, 18 million U to 24 million U, intravenously, daily for 10 days

Table 3
Inconclusive diagnostic testing for syphilis

Test Results	Conclusion
Positive reactive RPR with negative EIA/CLIA and TP-PA	False-positive RPR
Positive EIA/CLIA with negative confirmatory TP-PA and negative RPR	False-positive vs early infection
Positive EIA/CLIA with indeterminant confirmatory TP-PA and negative RPR	New infection vs waning antibodies from previous treated infection

Data from CDC Sexually Transmitted Infection Treatment Guidelines 2015. Diagnostic Considerations And CDC Discordant results from reverse sequence syphilis screening–five laboratories, United States, 2006-2010.

Table 4
Syphilis treatment guidelines in immunocompetent people

Stage	First Line	Alternate	Considerations
Primary, secondary, and early latent	Penicillin G benzathine, 2.4 million U IM once	Tetracycline, 500 mg PO QID for 14 d *OR* Doxycycline, 100 mg PO BID for 14 d	6-mo and 12-mo serologic and clinical evaluation HIV testing at diagnosis and at 3 mo in areas of high prevalence
Latent >1 y	Penicillin G benzathine, 2.4 million U IM weekly for 3 wk	Tetracycline 500 mg PO QID for 28 d *OR* Doxycycline, 100 mg PO BID for 28 d	Consider ophthalmic and CSF evaluation if neurologic symptoms present 6-mo and 12-mo serologic and clinical evaluation HIV testing at diagnosis in all patients
Tertiary	Penicillin G benzathine, 2.4 million U IM weekly for 3 wk	Tetracycline, 500 mg PO QID for 28 d *OR* Doxycycline, 100 mg PO BID for 28 d	
Pregnancy	Parenteral penicillin G benzathine per corresponding stage of infection	No appropriate alternative Attempt to desensitize penicillin allergy	Treatment must be 30 d prior to delivery. Serologic titers at 28–32 wk gestation and at delivery
Contacts	Penicillin G benzathine, 2.4 million U IM	Tetracycline, 500 mg PO QID for 14 d *OR* Doxycycline, 100 mg PO BID for 14 d	Provide nonjudgmental help contacting partners confidentially, to reduce reinfection and transmission

Contacts have had sex with person with early syphilis within 90 d.
Data from CDC Sexually Transmitted Infection Treatment Guidelines 2015.

to 14 days. Individuals receiving treatment, especially in P&S stages, should be informed that they may experience Jarisch-Herxheimer reaction, including fever, myalgias, and headache, in the first 24 hours of treatment. Comprehensive treatment guidelines are available from the CDC.[28]

EPIDEMIOLOGY

Rates of once-rare syphilis are increasing globally, especially affecting Black men, HIV-positive people, and MSM.[1] In 2018, 115,045 total cases of all stages of syphilis were reported in the United States, the highest number of total cases since 1991.[1] This represents a 13.3% increase from 2017 (101,584 cases). Since nearly eradicated at the end of the 1990s, syphilis incidence continues to increase across ethnic groups (**Tables 5** and **6**; see **Table 8**), age and sex (**Fig. 2**), and geographic regions (**Tables 7** and **8**). **Fig. 3** shows the distribution of total P&S cases in 2018. The greatest percent increases from 2017 to 2018 have occurred in men ages 20 to 34, Black men, MSM, and people who use drugs. Incidence in all women and women of childbearing age, however, also has increased (172.7% and 165.4%, respectively) from 2014 to 2018.[1]

CS rates have paralleled the increases observed in women. CS rates in the United States have risen 153% since 2013 (9.2 cases per 100,000 live births), which was the first increase since 2008. Seventy percent of CS cases were reported from just 5 states (Texas, Florida, California, Arizona, and Louisiana), but most states reported

Table 5
Comparing rates of primary and secondary syphilis the United States by ethnicity, 1998 versus 2018

Race/Ethnicity	1998	2018
American Indians/Alaskan Natives	2.8	15.5
Blacks	17.1	28.1
Hispanics	1.5	13
Whites	0.5	6.0
Asians	0.4	4.6

[a] Rate per 100,000 population.
Data from Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019.

at least 1 case of CS in 2018.[1] The United States 2018 CS rate (33.1 cases per 100,000 live births) represents a 39.7% increase from to 2017 and a 185.3% increase from 2014 (**Table 9**). Syphilitic stillbirths also have increased from 63 in 2017 to 78 in 2018. There was a 22% increase in newborn deaths from syphilis from 77 in 2017 to 94 in 2018.

Drivers of the Epidemic

Multiple determinants drive these trends. These determinants include but are not limited to health-seeking behaviors, access to care, risk-taking behaviors, and provider education and training.[10,30,31] Health-seeking behaviors are limited partly by lack of trust in the health care system,[10] limited awareness about syphilis risk,[1] and the belief that syphilis is a disease of antiquity.[1,2] Access to care is impeded in part by poverty, stigma, lack of transportation, and unstable housing.[1,10,30,31] Reduced access also results from the high cost of care and inadequate or no insurance coverage. Healthy People 2020 cites the lack of availability of services as a limiting factor for access.[31] Health inequity contributes to a higher syphilis incidence and prevalence in ethnic and sexual minority groups (see **Table 8**).

Lack of access has been further exacerbated by budget cuts, including Title X federal grants that fund reproductive health services in the United States.[32,33] The domestic gag rule, instituted in 2019 and applied to clinics receiving Title X funding, prohibits the provision of or referral to abortion services. This rule impacted more than 900 women's health clinics nationwide, including health departments, federally

Table 6
Increasing rates of primary and secondary syphilis in the United States by ethnicity from 2017 to 2018

Race/Ethnicity	Increase (%)
American Indian/Alaskan Natives	40.9
Multiracial	22.1
Native Hawaiians/Pacific Islanders	19.0
Blacks	17.1
Hispanics	13.0
Whites	11.1

Data from Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019.

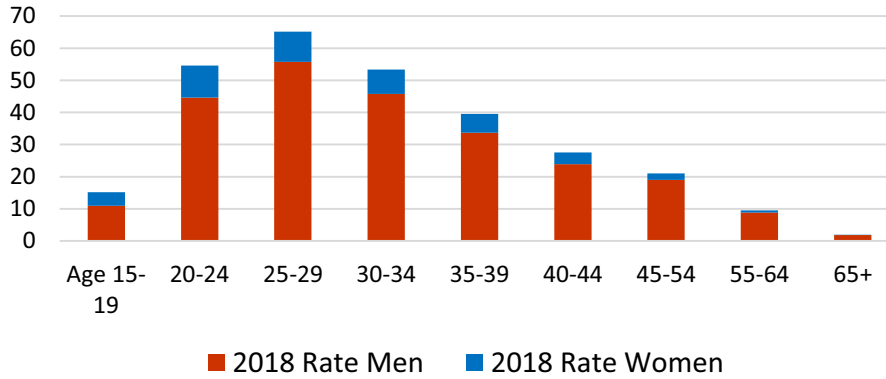


Fig. 2. US rate of cases of P&S syphilis by age and sex, 2018. Rate per 100,000 population. (*Data from* Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019. Available at: https://www.cdc.gov/std/stats18/STDSurveillance2018-full-report.pdf.)

qualified health centers, and other nonprofit providers. Latinas account for one-third and women of color account for more than half of patients served in Title X sites. Twenty-three percent of Title X sites have declared that they will not use Title X funds as result of this rule, having an impact on early prenatal care and screening for P&S syphilis and CS. Budget cuts have made it difficult for clinics to offer free STI screening and treatment.[1,32,33]

Risk-taking behaviors, such as decreased or incorrect condom use, are fueled by drug use,[34–36] technology,[37] and age.[1,38] People who use drugs report higher-risk sexual behaviors, including multiple partners and lack of condom use. Drug use has more than doubled among heterosexual people with P&S syphilis from 2013 to 2017.[25] Although the greatest proportion of P&S syphilis occurs in MSM, sexually disinhibiting drug use increased most in women and heterosexual men (men who have sex with women [MSW]) with P&S syphilis, and included injection drug use, methamphetamine use, heroin use, and sex with people who inject drugs.[25] Although the number of MSM cases reporting injection drug use, methamphetamine use, and heroin use increased slightly, the proportion of MSM with P&S cases reporting use of these drugs did not. Injection drug use by women increased from 4.0% in 2013% to 10.5% in 2017, and MSW cases reporting injection drug use increased from 2.8% to 6.3%. By region, injection drug use was highest in the West and lowest in the Northeast. Injection drug use was most prevalent among Alaskan Natives/American Indians and whites.

Table 7
Comparing rates (per 100,000 population) of primary and secondary syphilis by US geographic region, 1998 versus 2018

Region	1998	2018
South	5.1	7.1
West	1.0	15.0
Midwest	1.5	13
Northeast	0.8	8.7

Data from Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2018.* Atlanta: U.S. Department of Health and Human Services; 2019.

Table 8
Rate increase of primary and secondary syphilis, 2017 to 2018, by region and ethnicity

	Rate Increase, 2017–2018 (%)
By US geographic region	
South	15.6
West	15.4
Midwest	16.4
Northeast	10.1
By ethnicity	
Black	17.1
Multiple	22.1
American Indian	40.9
Native Hawaiian	19.1
White	11.1
Asian	9.5

Data from Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019.

Methamphetamine use in women with P&S syphilis increased from 6.2% to 16.6% from 2013 to 2017. Methamphetamine use among MSW affected by P&S syphilis increased from 5.0% to 13.3%. The proportion of MSM with P&S syphilis cases reporting methamphetamine use decreased from 9.2% to 8.0%. The proportion of P&S syphilis cases that used heroin more than doubled among female cases and more than tripled among MSW cases but remained stable among MSM cases.[25]

Increased risk-taking behaviors also may be attributable to increased technology and dating apps.[37] With the rise of dating and hookup apps, such as Grindr, Tinder, and Scruff, it is not only easier to meet anonymous sex partners but also more difficult to track them down to facilitate partner treatment.

Risk-taking behaviors are historically higher in youth and adolescents; 15-year-old to 24-year-old individuals account for more than half of all new STIs in the United States but represent only one-quarter of the entire population.[1] In 2018, the rate of P&S syphilis among 15-year-old to 24-year-old women was 7.2 cases per 100,000

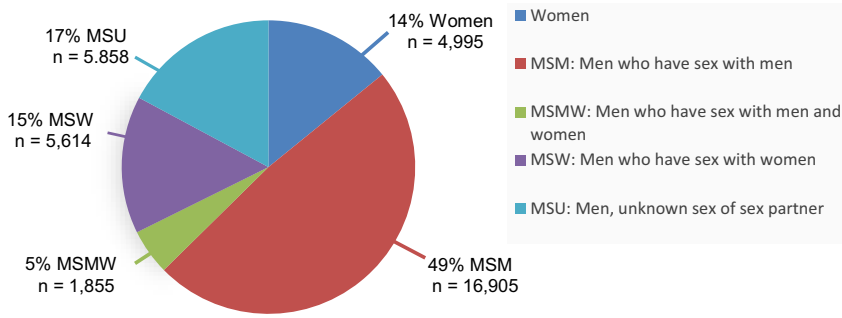


Fig. 3. Distribution of cases of P&S syphilis, 2018. (*Data from* Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019. Available at: https://www.cdc.gov/std/stats18/STDSurveillance2018-full-report.pdf.)

Table 9
Congenital syphilis in the United States

Group	Rate 2014	Rate 2018	Percentage increase 2014-2018
CS total	11.4	33.1	185.5
CS black	38.2	86.6	126.7
CS Hispanic	12.2	44.7	266.9
CS white	3.7	13.5	264.8

[a] Rate per 100,000 live births.

Data from Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019.

women, a 28.6% increase from 2017 (5.6 cases per 100,000 women) and a 100.0% increase from 2014 (3.6 cases per 100,000 women). Among 15-year-old to 24-year-old male cases in 2018, the rate was 28.2 cases per 100,000, a 7.2% increase from 2017 (26.3 per 100,000 male cases) and a 44.6% increase from 2014 (19.5 per 100,000 male cases).[1] These high rates may be attributed to both increased screening efforts and increased incidence.

Education and training of both the health care providers and the public are important factors in the syphilis epidemic. One in 3 providers has not received further training on STIs after graduation.[1,25] Sexual education in schools is limited and at times nonexistent and also may contribute to the epidemic.[38] Only 24 states mandate sex education. The California Healthy Youth Act went into effect in 2016 and is the most comprehensive sex education legislation in the United States. It includes education specific to students who identify as lesbian, gay, bisexual, transgender, or queer. The Act requires sexual education in seventh grade and in high school and mandates education on consent and harassment. The law has been met with resistance from conservative groups. Critics maintain that the content is not age appropriate. Similar protests challenge progressive sex education legislation in several states.[38]

Syphilis Among Men Who Have Sex with Men and Transgender Women

The diverse population of MSM is disproportionately affected with syphilis and coinfection with HIV.[1,25,39] Gay and bisexual men and transgender women who have sex with men are impacted biologically with increased susceptibility of rectal and oral mucosa to infection transmission, behaviorally in some instances due to frequent partner changes, and structurally due to stigma, bigotry, and lack of culturally competent care.[40]

Some have proposed that HIV pre-exposure prophylaxis (PrEP) has contributed to the increased syphilis incidence[41] because it may afford false security in STI prevention, increase higher-risk sexual behavior, and decrease condom use.[42,43] A 2016 meta-analysis showed that rates of new diagnoses among MSM using PrEP were 44.6-times greater for syphilis, 25.3 times greater for gonorrhea, and 11.2-times greater for chlamydia compared with MSM not taking PrEP.[43] The PROUD randomized control trial, however, strongly supported the efficacy of PrEP in preventing HIV-1, without noting new cases of other STIs.[44] It is important to consider that syphilis incidence has been rising since 2001, well before PrEP was approved by the Food and Drug Administration in 2012. PrEP adoption has been slow in locations and populations with concerning epidemiology. Syphilis incidence is increasing significantly in young adult MSM, people in the South, and in Native American individuals, all groups who have been less likely to utilize PrEP.[1,39,41] It is certain that P&S syphilis facilitates HIV transmission because sores or breaks in the skin allow the virus to enter the body

more easily.[39,40] Despite the possibility of risk compensation, the benefits of HIV PrEP outweigh any possible risk of increase in syphilis infection.

STRATEGIES TO DECREASE THE TREND

Identifying and staging syphilis properly are key to appropriate treatment planning and follow-up. Syphilis may be difficult to diagnose, but it is easy to treat. Penicillin remains the most effective treatment, despite a concerning increase in penicillin resistant strains of syphilis**.** Penicillin cannot reverse damage caused by syphilis, only eradicate the infection. Early diagnosis is key to decreasing incidence and morbidity.[1,28] Nurses should routinely collect and revise detailed patient sexual histories, including sex partners, anatomic risk of exposure, and risk factors. Interviews should be supportive, open-ended, and nonbiased. Nontreponemal screening tests should be done at least annually on sexually active MSM, including those with HIV infection or taking PrEP. Screen as frequently as every 3 months to 6 months in all individuals if there is drug use or multiple sex partners.[23,28] All individuals with an oral, anal, or vaginal sex partner who have been recently diagnosed with syphilis should be screened. Screen all pregnant women at the initial prenatal visit and in the last trimester. Ensure partner treatment to prevent reinfection.[23,28]

Serologic and clinical follow-up are essential. Nontreponemal titers should decrease 4-fold within 6 months to 12 months and ongoing elevation in titers may indicate treatment failure.[28] Indirect nontreponemal tests (RPR and VRDL) are not diagnostic without clinical and treponemal confirmation.[11,12,22]

An emerging strategy for the early detection of syphilis includes the use of reverse sequence screening and emerging technologies for direct detection of *T pallidum.* Current CDC guidelines[1] call for the initial syphilis diagnosis to be based on indirect nontreponemal testing (RPR and VDRL) followed by treponemal testing (polymerase chain reaction [PCR], TP-TA, and FTA-ABS) (**Fig. 4**). A study of 15 cases of syphilis diagnosed between January 2013 and September 2018 at a clinic in Spain, however, demonstrated that treponemal testing (chemiluminescence immunoassays [CLIAs] and EIAs) were useful in diagnosing early syphilis. Of 158 total individuals diagnosed with syphilis, 15 subjects had negative nontreponemal tests (RPR), and 14 of 15 had syphilis detected by treponemal testing in early primary syphilis. Treponemal PCR detected *T pallidum* in the primary lesion exudate of 8 subjects. The study promotes reverse sequence treponemal testing as the future of initial screening, given diagnostic sensitivity, speed, and low cost.[45] This assertion should be further evaluated as a potential strategy to reverse the current epidemiologic trend through prompt diagnosis. **Fig. 4** compares traditional screening to reverse screening. Although reverse screening algorithms (ie, treponemal testing confirmed by nontreponemal testing) recently have gained favor due to immunoassay automation, the CDC currently continues to recommend the traditional screening algorithm.

CASE EXAMPLE

A 22-year-old man in usual good health presented to his nurse practitioner with a rash that started 1 week prior to the office visit. He denied systemic symptoms and exposure to any new detergents, soaps, persons with rash, or outdoor activity. The nurse practitioner took a careful and culturally sensitive sexual history and the patient disclosed regular sexual activity with 2 male partners. The patient reported careful condom use with every sexual encounter. Nontreponemal testing (RPR) was obtained. The RPR and additional STI tests were negative. The patient was referred to dermatology and diagnosed with discoid eczema. He showed no improvement with

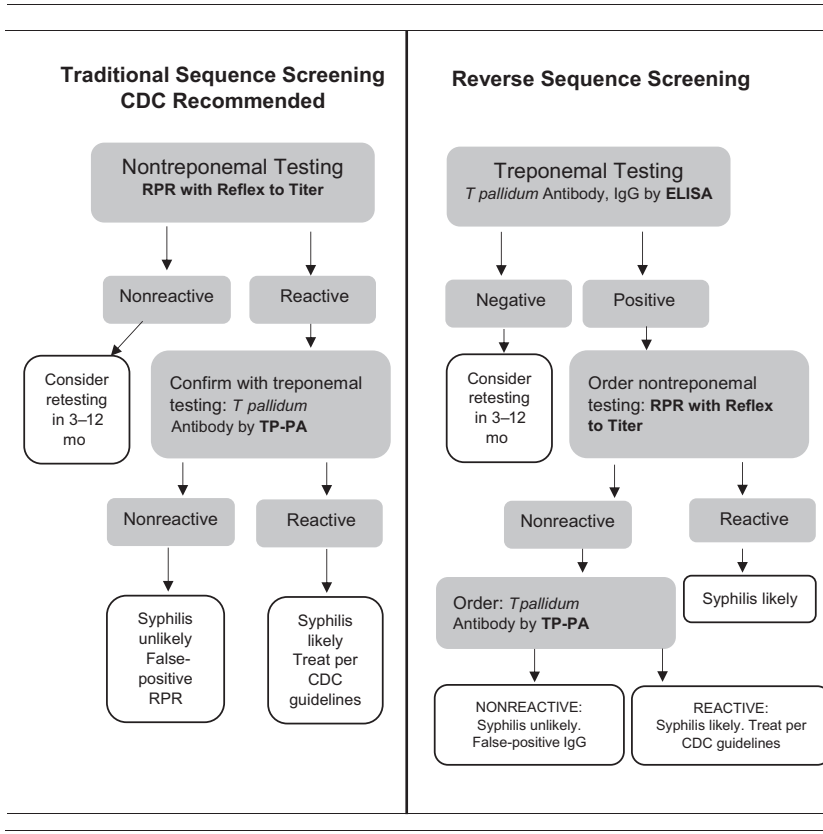


Fig. 4. Syphilis testing algorithms. (*Adapted from* ARUP Consult. Syphilis Testing Algorithms. Arup Laboratories. December 2019. Available at: https://arupconsult.com/algorithm/syphilis-testing-algorithm. With permission ©2019 ARUP Laboratories. All Rights Reserved.)

emollients and topical corticosteroids. About 6 weeks after rash onset, he reported feeling mentally "foggy." While under treatment of his rash, he hit his head during a motor vehicle collision, and subsequent diagnostic imaging of the brain was normal. Seven weeks after initial onset of his rash, the nurse practitioner repeated the RPR and it was positive. A syphilis diagnosis was confirmed with treponemal testing (FTA-ABS). The patient's symptoms of P&S syphilis resolved completely after a single dose of penicillin G benzathine, 2.4 million U IM.

SUMMARY

Nurses must be knowledgeable about and maintain a high index of suspicion for syphilis in patients with clinical signs and symptoms or asymptomatic people at risk. Nontreponemal testing often is negative in the first 4 weeks of infection.[22] So, follow-up testing is essential to identify many cases of P&S syphilis. Nurses may consider the use of a reverse screening algorithm because this may improve diagnostic accuracy in early primary syphilis.

The reemergence of syphilis threatens public health and nurses play an essential role in the screening, diagnosis, and treatment of syphilis in people at risk. Syphilis' reputation as the "great imitator" should remind practicing nurses to be vigilant and

consider a diagnosis of syphilis in patients with both classic and less common symptoms of the disease.

DISCLOSURE

The authors have nothing to disclose.

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