JAMA | Review

Syphilis
A Review

Franco J. Chevalier, MD, MPH; Oliver Bacon, MD, MPH; Kelly A. Johnson, MD, MPH; Stephanie E. Cohen, MD, MPH

IMPORTANCE Syphilis is an infectious disease caused by *Treponema pallidum*, a gram-negative, spirochete bacterium. Worldwide, an estimated 8 million adults aged 18 to 49 years acquired syphilis in 2022. From 2019 to 2023, US syphilis cases increased by 61% overall, with diagnoses among females increasing by 112% and congenital syphilis cases increasing by 106%.

OBSERVATIONS Syphilis is transmitted via contact with infectious lesions during vaginal, anal, or oral sex or via the placenta during pregnancy. Individuals at increased risk for syphilis include people with HIV, those engaging in condomless sex with multiple partners, and men who have sex with men (MSM)—who comprised one-third (32.7%) of all males with primary and secondary syphilis in 2023. Early syphilis is defined as syphilis in the first year after infection and includes symptomatic (primary and secondary) and asymptomatic (early latent) stages. Primary syphilis is characterized by painless anogenital lesions. Secondary syphilis is associated with a diffuse rash, mucocutaneous lesions, and lymphadenopathy. Syphilis diagnosed more than a year after infection is referred to as *late syphilis* and includes asymptomatic (late latent) and symptomatic (tertiary) stages. Neurosyphilis, which can occur at any stage, can lead to meningitis, uveitis, hearing loss, or stroke. In pregnancy, up to 40% of fetuses with in-utero exposure to syphilis are stillborn or die from their infection during infancy. The diagnosis of syphilis relies on serologic reactivity along with a clinical history and presentation consistent with active or latent syphilis infection. The recommended treatment for syphilis is benzathine penicillin G administered as intramuscular doses of 2.4 million units: a single injection for early stage and 3 weekly injections for late latent stage syphilis. Strategies to identify and prevent syphilis infections include (1) screening of sexually active people aged 15 to 44 years at least once and at least annually for those at increased risk, (2) screening 3 times in pregnant individuals (at the first prenatal visit, during the third trimester, and at delivery), (3) counseling about condom use, and (4) offering doxycycline postexposure prophylaxis (200-mg doxycycline taken within 72 hours after sex as postexposure prophylaxis) to MSM and transgender women with a history of a sexually transmitted infection in the past year.

CONCLUSIONS AND RELEVANCE Syphilis infections, including congenital syphilis, have increased in the US and worldwide over the past decade. First-line treatment for syphilis is benzathine penicillin G. Routine syphilis screening of all pregnant patients and all sexually active people aged 15 to 44 years and use of doxycycline postexposure prophylaxis in individuals at risk for syphilis infection are recommended strategies to decrease syphilis transmission.

Multimedia

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Author Affiliations: San Francisco Department of Public Health, San Francisco, California (Chevalier, Bacon, Cohen); University of California, San Francisco (Chevalier, Bacon, Johnson, Cohen).

Corresponding Author: Stephanie E. Cohen, MD, MPH, San Francisco Department of Public Health, 25 Van Ness Ave, San Francisco, CA 94102 (Stephanie.Cohen@sfdph.org).

JAMA. doi:10.1001/jama.2025.17362
Published online October 16, 2025. Corrected on October 24, 2025.

Syphilis is a sexually or vertically transmitted infection caused by the spirochete *Treponema pallidum* subspecies pallidum that progresses through several stages: (1) a primary stage characterized by a chancre—an indurated, painless ulcer at the site of exposure; (2) a secondary stage associated with diffuse rash, mucocutaneous lesions, and lymphadenopathy; (3) a latent stage of subclinical infection detected by reactive serologic tests; and (4) a tertiary stage involving end-organ damage. *T pallidum* can affect nearly every organ and, if left untreated, can cause blindness, deafness, psychosis, dementia, and peripheral nerve damage. In-utero exposure can lead to stillbirth. Congenital syphilis can cause severe neonatal complications such as neurological damage (blindness, deafness, developmental delays), organ damage (hepatomegaly, nephrotic syndrome, myocarditis), and lifelong disabilities (intellectual disability, malformed teeth, skeletal abnormalities).[1] This review summarizes current evidence regarding the epidemiology, diagnosis, treatment, and prevention of syphilis; updates in syphilis screening guidelines; and prevention tools.

Methods

We searched PubMed using medical subject headings for English-language studies on the epidemiology, diagnosis, treatment, and prevention of syphilis published between January 1, 2011, and May 28, 2025, and reviewed national syphilis surveillance data. Randomized clinical trials (RCTs), meta-analyses, systematic reviews, and national and international clinical practice guidelines were prioritized for inclusion. We included a total of 91 articles, including 11 systematic reviews or meta-analyses, 25 observational studies, 24 narrative reviews, 9 RCTs and secondary analyses of RCTs, 15 clinical and laboratory protocol guidelines, 3 policy documents, 3 surveillance reports, and 1 nonrandomized laboratory study.

Epidemiology

Syphilis diagnoses have increased worldwide over the past several decades. In 2022, an estimated 8 million adults aged 18 to 49 years acquired syphilis worldwide.[2] In the US, syphilis diagnoses reached a historic low in 2000, with only 9756 primary and secondary reported cases (2.1 per 100 000 persons).[3] However, over the last 25 years, the annual rate of syphilis diagnoses in the US has steadily increased. In 2023, there were 53 007 primary and secondary syphilis cases reported in the US (15.8 cases per 100 000 persons), 209 253 total syphilis cases (62.5 cases per 100 000), and 3882 congenital syphilis cases (105.8 per 100 000 live births).[3] Between 2019 and 2023, annual rates of primary and secondary syphilis and total syphilis increased among both males and females, among all age groups, and in all regions of the US (**Table 1**).[3]

In 2023, 32.7% of all primary and secondary syphilis cases among males in the US were among men who have sex with men (MSM), of whom, nearly half (41.0%) were living with HIV.[3] From 2019 to 2023, the number of cases of primary and secondary syphilis in the US increased 112.0% in females (6493 in 2019 to 13 763 in 2023), increased 20.9% in males overall (32 402 in 2019 to 39 188 in 2023), and decreased by 5.7% among MSM (18 381 in 2019 to 17 331 in 2023).[3] Due to increases in primary and secondary syphilis among women, congenital syphilis cases have increased 106% in the US from 2019 to 2023 (from 1884 to 3882 cases). An estimated 88% of 3761 congenital syphilis cases reported in the US in 2022 could have been prevented with timely testing and adequate treatment during pregnancy.[4,5]

In 2023, diagnosis rates were highest among American Indian or Alaska Native persons (58.2 per 100 000), followed by Black or African American (39.7 per 100 000), Native Hawaiian or Other Pacific Islander (24.3 per 100 000), and Hispanic or Latino (16.9 per 100 000) individuals.[3] These disparities reflect differences in the prevalence of syphilis in sexual networks, access to health care, and social determinants of health (eg, socioeconomic status, substance use, homelessness, stigma, discrimination, structural racism).[6]

Clinical Manifestations, Evaluation, and Syphilis Staging

Transmission

Transmission occurs primarily through direct contact with infectious lesions during vaginal, anal, or oral sex; transplacentally from mother to fetus; and, rarely, via blood transfusion or organ transplant. Following inoculation, *T pallidum* rapidly disseminates via lymphatic and hematogenous routes, establishing infection in multiple organs. Mucocutaneous lesions that develop during the primary and secondary stages of syphilis contain a high burden of spirochetes. Infectivity persists in the first year after syphilis acquisition and wanes over time.[7] The percentage of sexual contacts exposed to syphilis who become infected was estimated to be 32.6% in a meta-analysis of 36 397 sexual contacts across 32 studies.[8] Vertical transmission from an infected pregnant individual to fetus can occur at any stage of pregnancy, with highest rates of in-utero transmission in untreated pregnant individuals with primary or second-

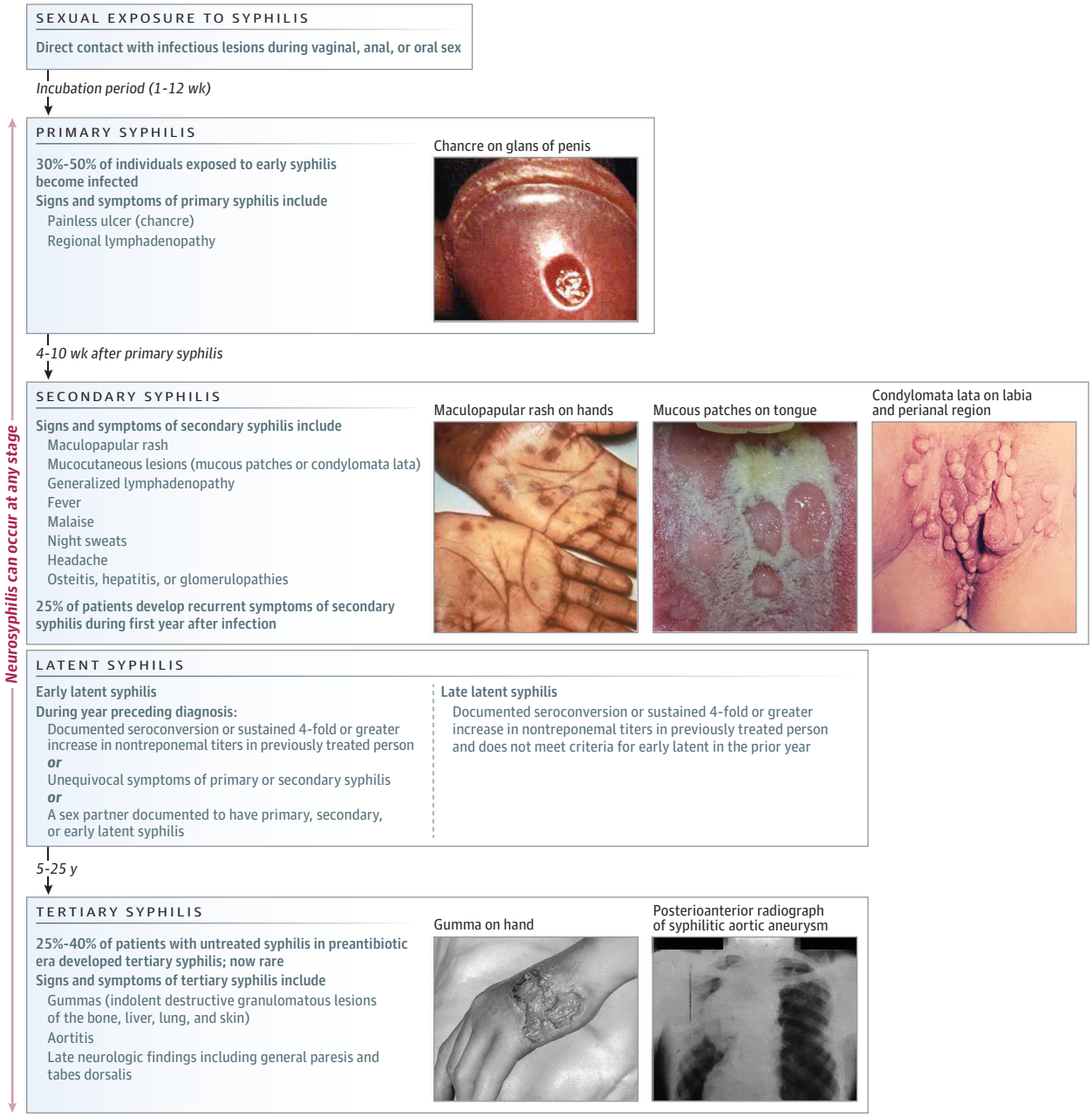
Table 1. Epidemiology of Syphilis in the US, 2019-2023

	No. of newly reported syphilis cases by year of diagnosis (annual rate per 100 000 persons)				
Subtype	2019	2020	2021	2022	2023
Total syphilis[a]	129 827 (39.6)	133 960 (40.4)	176 739 (53.3)	207 269 (62.2)	209 253 (62.5)
Congenital syphilis[b]	1884 (50.3)	2163 (59.9)	2881 (78.6)	3769 (102.8)	3882 (105.8)
Primary and secondary syphilis					
Male and female	38 992 (11.9)	41 655 (12.6)	53 767 (16.2)	59 016 (17.7)	53 007 (15.8)
Male	32 402 (20.0)	33646 (20.5)	41 349 (25.2)	44 309 (26.8)	39 188 (23.6)
Female	6493 (3.9)	7901 (4.7)	12 265 (7.3)	14 652 (8.7)	13 763 (8.1)

[a] Includes primary, secondary, early latent, and late latent syphilis.

[b] Number of reported congenital syphilis cases per 100 000 live births.

Figure 1. Progression of Syphilis After Sexual Exposure



Images used are from the Centers for Disease Control and Prevention's Public Health Image Library.

ary syphilis in the third trimester of pregnancy (60%-100%) compared with pregnant individuals with early latent (40%) or late latent (<8%) stages.[1]

Clinical Presentation

Primary Syphilis

Primary syphilis presents 7 to 90 days (median of 21 days) after exposure as a painless ulcer (chancre) at the site of inoculation, most commonly on the base of the glans penis, vulva, perianal, or intraanal area, and may be associated with nontender regional lymphadenopathy (**Figure 1** and **Table 2**).[9-11] Without treatment, the chancre heals within 1 to 3 weeks. The lesions of primary syphilis may be unnoticed due to their location and lack of pain, contributing to missed opportunities for diagnosis.[12]

Secondary Syphilis

Hematogenous dissemination of treponemes leads to secondary syphilis, which occurs 4 to 10 weeks after primary syphilis and presents as cutaneous lesions including diffuse, symmetric, maculopapular rash (involving the palms and soles in 70% to 90% of patients), mucosal lesions, and condyloma lata (moist, wart-like intertriginous lesions).[13] During hematogenous dissemination, the primary ulcerative lesion may still be present.[9,11,14] The rash of secondary syphilis may mimic other dermatologic condi-

Table 2. Stages and Signs of Syphilis Infection

Stage[a]	Symptoms and findings[9,11,12,14,22,24,26,28]	Timeline[9-12,14]	Recommended tests and performance of select syphilis tests[21,29-33]
Primary syphilis	Painless, indurated, well-demarcated ulcer or chancre, generally localized to genital and perianal regions (can be multiple and at times painful) Inguinal lymphadenopathy	Symptoms may present 7 to 90 d after infection May spontaneously resolve, even without treatment, after 2-6 wk	Recommendation: perform 2-step serologic testing (either traditional or reverse-sequence); if available on site, conduct darkfield microscopy of fluid from moist lesions Test performance data: Darkfield microscopy: sensitivity, 58%-100%; specificity, 100% Nontreponemal tests: sensitivity, 50%-92.7%; specificity, published data on the specificity of nontreponemal tests for syphilis by stage are limited Treponemal tests: sensitivity, 95%-100% for TPPA and automated immunoassays and 78%-100% for FTA-ABS; specificity, 98%-100% NAAT: sensitivity, 76%-94% for exudates from primary lesions; specificity, 90%-99%
Secondary syphilis	Mucocutaneous lesions: condyloma lata (rubbery, wart-like lesions in predominantly moist areas), macular, maculopapular, nodular, pustular, or follicular skin rashes predominantly in palms and soles of feet, back/torso region; mucous patches in oropharynx and, less commonly, patchy alopecia or split papule Kidney: glomerulonephritis, nephrotic syndrome Liver: hepatitis Constitutional symptoms: fever, malaise, generalized lymphadenopathy (mostly seen in cervical, epitrochlear, and inguinal nodes), arthralgias, weight loss, etc	Symptoms may develop 4 to 10 wk after the primary lesion Lesions may disappear spontaneously after 3-8 wk	Recommendation: perform 2-step serologic testing (either traditional or reverse-sequence); if available on-site, conduct darkfield microscopy of fluid from moist lesions Test performance data: Darkfield microscopy: sensitivity, 58%-71%; specificity, 100% Nontreponemal tests: sensitivity, 97%-100%; specificity, NA Treponemal tests: sensitivity, 100%; specificity, 98%-100% NAAT: sensitivity, 20%-86% (for exudates from moist secondary lesions; lower from swabs of dry rash); specificity, 92%-98%
Early latent syphilis	No symptoms or findings on examination with a reactive serologic test for syphilis plus (1) a documented nonreactive serologic test or sustained 4-fold or greater increase in titer of a nontreponemal test during the prior year, (2) unequivocal symptoms of primary or secondary syphilis, or (3) a sex partner documented to have primary, secondary, or early latent syphilis during the prior year	Asymptomatic infection in first year after syphilis acquisition	Recommendation: perform 2-step serologic testing (either traditional or reverse-sequence) Test performance data: Nontreponemal tests: sensitivity, 63%-75%; specificity, published data on the specificity of nontreponemal tests for syphilis by stage are limited Treponemal tests (TPPA and automated immunoassays): sensitivity, 97%-100%; specificity, NA
Late latent syphilis	No findings on examination; patients are noninfectious during this stage	Asymptomatic infection diagnosed >1 y after syphilis acquisition	Recommendation: perform 2-step serologic testing (either traditional or reverse-sequence) Tests performance data: Nontreponemal tests: sensitivity, 63%-75%; specificity, NA Treponemal tests: sensitivity, 97%-100%; specificity, NA
Tertiary (late) syphilis	Gummatous disease: generally localized in skin, vascular tissue, and bone; however, can appear anywhere Cardiovascular complications: aortic aneurysms, aortitis, mucinous myocarditis Symptomatic late neurosyphilis	Presents >5-10 y after infection	Recommendations: Two-step serology Nontreponemal tests may be nonreactive due to seroreversion (disappearance of antibodies over time); if there is a clinical suspicion for tertiary syphilis and treponemal test is reactive, proceed with evaluation even if the nontreponemal test is nonreactive Diagnostic workup of suspected tertiary disease is case specific, involving imaging for gummatous disease or vasculitis (including aortitis), and biopsies of potentially affected organs and tissues with immunohistochemical testing specific for *T pallidum* Test performance data: Nontreponemal tests: sensitivity, 43%-64%; specificity, NA Treponemal tests: sensitivity, 97%-100%; specificity, NA

(continued)

tions, including psoriasis, lichen planus, pityriasis rosea, and condyloma acuminata.[13] Systemic symptoms (fever, diffuse lymphadenopathy) may also occur (Figure 1 and Table 2).[13] Secondary syphilis can resolve without treatment; approximately 25% of patients have relapsing episodes of secondary syphilis within the first year.[15] Syphilitic hepatitis occurs in 0.25% to 3% of patients with secondary syphilis and typically presents with a cholestatic pattern of liver injury, often with marked elevation in alkaline phosphatase. Mild elevations in transaminases may also be seen.[16] Kidney involvement (eg, proteinuria, nephrotic syndrome, membranous nephropathy) occurs in 0.3% to 10% of patients with secondary syphilis.[17]

Table 2. Stages and Signs of Syphilis Infection (continued)

Stage[a]	Symptoms and findings[9,11,12,14,22,24,26,28]	Timeline[9-12,14]	Recommended tests and performance of select syphilis tests[21,29-33]
Symptomatic early neurosyphilis	Meningitis: headache, blurred vision, nausea/vomiting Cranial nerve dysfunction: usually III, VII, VIII	Early neurosyphilis can present within the 1 to 2 y after infection	Recommendation: if 2-step serology indicates syphilis infection and neurosyphilis is clinically suspected, obtain CSF for VDRL, cell count and differential, glucose, protein; in the absence of a positive CSF VDRL, any of the following CSF values in a person with clinical picture raise suspicion for neurosyphilis: WBC count >5/μL or elevated protein without other explanation Tests performance data: VDRL is the only FDA-approved test for CSF evaluation No clear reference standard to determine test performance; however, in symptomatic neurosyphilis CSF VDRL: sensitivity, 48%-86%; specificity, 78%-90% Although not FDA-approved for this use, a nonreactive FTA-ABS, a treponemal test, with high sensitivity (91%-100%) but low specificity (55%), has been used to rule out neurosyphilis in cases with low pretest probability
Symptomatic late neurosyphilis	General paresis: personality or mood changes, dementia, cognitive decline, and behavioral defects Tabes dorsalis: sharp stabbing pains in limbs or abdomen; bladder disturbances, rectal incontinence; loss of deep tendon reflexes, proprioception, touch, pain, and vibratory sensation; positive Romberg sign; and gait disturbances	Late neurologic manifestations of syphilis can develop after 15-20 y of infection	Recommendation: if 2-step serology indicates syphilis infection and neurosyphilis is suspected, obtain CSF for VDRL, cell count and differential, glucose, protein; in the absence of a positive CSF VDRL, any of the following CSF values in a person with clinical picture raise suspicion for neurosyphilis: WBC >5/μL and elevated protein In suspected late neurosyphilis, nontreponemal serology may be nonreactive due to seroreversion (disappearance of nontreponemal antibodies over time); therefore, CSF evaluation should proceed if symptoms are present and treponemal test is reactive, even if the nontreponemal test is nonreactive
Ocular and otic syphilis	Ocular syphilis can present as conjunctivitis, scleritis, episcleritis, uveitis, increased intraocular pressure, chorioretinitis, retinitis, vasculitis; patient may report redness of eyes, eye pain, visual disturbances, floaters, flashing lights, visual acuity loss, blindness Otosyphilis can present as sensorineural hearing loss, tinnitus (often precedes hearing loss), and vertigo (sudden or fluctuating) and may include osteitis of temporal bone; patient may report hearing loss, ringing in ears, and dizziness/vertigo	Can occur at any stage of syphilis	Recommendation: if ocular or otic symptoms only, without any other neurologic findings may omit CSF examination, obtain dilated ophthalmologic examination by ophthalmologist (if ocular syphilis suspected), and obtain audiometry (by ENT specialist) (if otosyphilis suspected) If other neurologic symptoms, obtain CSF plus ophthalmologic or ENT evaluation

Abbreviations: CSF, cerebrospinal fluid; ENT, ear, nose, and throat; FDA, US Food and Drug Administration; FTA-ABS, fluorescent treponemal antibody absorption; NA, not available; NAAT, nucleic acid amplification tests; TPPA, *T pallidum* particle agglutination assay; VDRL, venereal disease research laboratory; WBC, white blood cell.

[a] Neurosyphilis, infection of the central nervous system by *T pallidum*, can occur at any stage.

Latent Syphilis

Latent syphilis is asymptomatic, and cases are typically identified through routine serologic screening or testing of an exposed sexual partner. Sexual history and prior syphilis test results are used to differentiate between early latent stage (acquisition in the previous 12 months) and late latent stage (acquisition more than 12 months previously).[18]

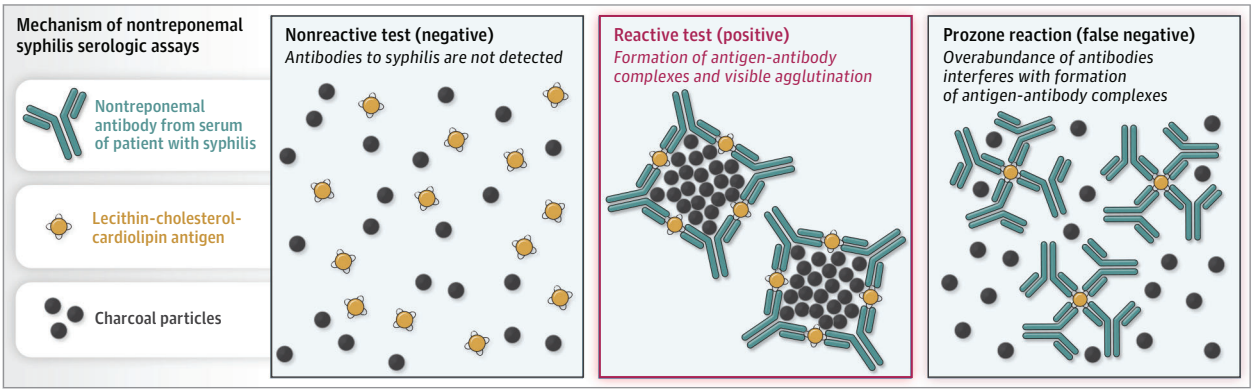
Tertiary Syphilis

Although it is now rare in the US, in the preantibiotic era, signs and symptoms of tertiary syphilis developed after decades in approximately 25% to 40% of untreated individuals (Figure 1 and Table 2).[7,9,19] Syphilitic aortitis is estimated to occur in 10% of patients with tertiary syphilis; cardiovascular complications may include aortic valvular insufficiency, aortic aneurysms, coronary ostial stenosis, myocardial ischemia, and infarction and congestive heart failure.[20] Gummatous syphilis is another rare manifestation of tertiary syphilis characterized by indolent destructive granulomatous lesions of the skin, soft tissues, bony structures, visceral organs, bones, and/or the central nervous system.

Neurosyphilis

Neurologic complications can occur at any stage of syphilis and result from both direct invasion of the central nervous system by *T pallidum* and the accompanying inflammatory response, which can cause vasculitis, perivascular inflammation, and immune-mediated damage to neural structures.[21,22] Early symptomatic neurosyphilis may present with acute meningitis, cranial nerve dysfunction (especially CN II, VI, VII, and VIII), uveitis,[23] optic neuritis, hearing loss, or tinnitus. Ocular syphilis occurs in 1% to 5% of all cases and otic syphilis occurs in 0.4%; these are both more common in early stages of syphilis and in people with HIV.[21,24-26] Late symptomatic neurosyphilis, which is rare since the advent of antibiotics,[27] is associated with meningovascular disease and may present as stroke, general paresis, or tabes dorsalis 15 to 25 years after infection (Figure 1 and Table 2).[21,24,26,28] General paresis (also known as *paretic neurosyphilis* or *dementia paralytica*) results from chronic inflammatory changes in the brain cortex, which may cause memory deficits, personality changes, dementia, seizures, and/or psychiatric symptoms such as depression, mania, or psychosis.[21,22] Tabes dorsalis, caused by degenerative changes of posterior roots and spinal

Figure 2. Prozone Phenomenon



This image was adapted from a review from the New York City STD Prevention Training Center.

cord columns, is characterized by sensory ataxia and lancinating pain (sudden, often brief severe, sharp, stabbing, or electric shock–like pain).[21,22]

Congenital Syphilis

Up to 40% of fetuses infected with congenital syphilis are stillborn or die of their infection in infancy.[1] Among infants with early congenital syphilis (onset before 2 years of age), 30% to 44.5% have signs of the infection, including osteochondritis or periostitis (75% of cases), neurosyphilis (60%), bullous or mucocutaneous rashes (40%), hepatobiliary dysfunction (33%-100%), and anemia and thrombocytopenia (37%). Hepatosplenomegaly and rhinitis may also be seen.[1,34] Late manifestations (onset after 2 years of age) may include dental abnormalities (peg-shaped, notched central incisors), sensorineural hearing loss, ocular abnormalities (interstitial keratitis, glaucoma, optic atrophy), and bony deformities affecting the face (saddle nose) or lower extremities (saber shins).[34]

Assessment

Individuals with characteristic signs or symptoms of syphilis, known exposure to syphilis, or a positive syphilis test result on routine screening require a thorough sexual history, symptom review, and physical examination, with careful inspection of the oropharynx, cranial nerves, skin (including trunk, palms, and soles), lymph nodes, and anogenital region.

Diagnosis

The diagnosis of syphilis relies on serologic reactivity along with a clinical history and presentation consistent with active or latent syphilis infection (Table 2). Direct detection of treponemes in lesion exudates by darkfield microscopy or in tissue samples can be useful, although not always available. *T pallidum* cannot be cultured outside of specialized research laboratories.

Serologic tests for syphilis are classified as nontreponemal or treponemal and are used in a 2-step combination to establish a diagnosis of syphilis infection.[35] Nontreponemal tests (NTTs) or lipoidal antigen tests detect antibodies to lipoidal antigens (cardiolipin, phosphorylcholine, and cholesterol), which are present in both *T pallidum* and host tissues and may be present in other inflammatory conditions including systemic lupus erythematosus and infections including yaws, leprosy, HIV, hepatitis C virus, cytomegalovirus, and parvovirus B19.[29,36] Reactive samples are serially diluted. The highest dilution at which the sample is still reactive is reported as the end point titer. Rarely (<0.3% of samples), an overabundance of antibody can prevent crosslinking of antigen-antibody complexes, leading to a false-negative result (the prozone phenomenon). The prozone phenomenon can be overcome by diluting the sample; repeat testing with dilution should be requested in the setting of a high level of suspicion for syphilis and a nonreactive NTT (**Figure 2**).[37]

NTTs start to become reactive 3 to 4 weeks after infection; appearance may lag behind the earliest signs of primary syphilis by 1 to 2 weeks. Titers peak during secondary syphilis (3-6 months after infection), plateau during latency, and can decline slowly, even in the absence of treatment.[38] Titers should be followed serially to monitor response to treatment. A 4-fold or greater decrease in the NTT titer after treatment represents cure (eg, from 1:64 to 1:16).

Treponemal tests (TTs) detect transient IgM and lifelong IgG antibodies specific for *T pallidum*. Because TTs are reported as reactive or nonreactive, they are not useful for monitoring disease activity or treatment response. In addition, they cannot be used to detect reinfection, because seroreversion of TTs after successful treatment is rare.[30,37]

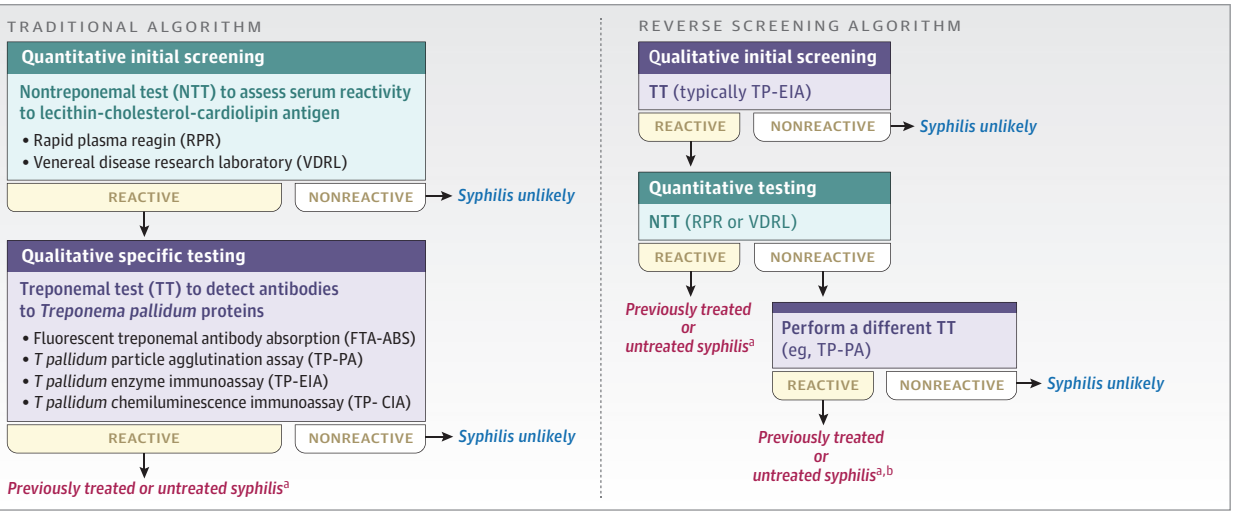
Performance Characteristics of NTTs

The 2 most commonly used NTTs are the rapid plasma reagin and venereal disease research laboratory (VDRL).[37] Using darkfield microscopy as the reference standard, the sensitivity of NTTs for primary syphilis ranges from 63% to 78% in most studies.[29] Using polymerase chain reaction testing of lesions as the reference standard, the sensitivity of the rapid plasma reagin for primary syphilis ranges from 79% to 82% and the specificity from 87% to 91%.[29] The sensitivity of NTTs reaches 100% during secondary and early latent stage syphilis, and declines in late latent and tertiary disease (Table 2).[29,31-33,37,39-41]

Performance Characteristics of TTs

Treponemal tests include manual assays, such as the fluorescent treponemal antibody absorption test, *T pallidum* particle agglutination assay, and microhemagglutination assay for *T pallidum*,

Figure 3. Two-Stage Syphilis Testing



[a]History of syphilis diagnoses, treatments, titers, and a physical examination are needed to differentiate between previously treated and untreated syphilis and for accurate staging and treatment.

[b]Reactive TT results with a nonreactive NTT result indicates prior treated syphilis, untreated late latent syphilis, very early primary syphilis (particularly if a lesion is present), or false-negative NTT result due to prozone (if high clinical suspicion of syphilis).

and automated immunoassays, including chemiluminescence immunoassays and enzyme immunoassays, that use recombinant antigens.[37] The sensitivity and specificity of TTs is 95% to 100% and 98% to 100%, respectively, across all stages (Table 2).[30,37,42]

Serologic Testing Algorithms

In the traditional 2-step testing algorithm, a reactive NTT is reflexed to a TT for confirmation. High-volume clinical laboratories in the US and elsewhere have implemented automated reverse-sequence screening, in which a reactive TT is reflexed to an NTT to assess disease activity. If the NTT result is nonreactive, the sample is reflexed to a second, manual TT (**Figure 3**).[37] Regardless of the algorithm used, a reactive NTT plus reactive TT result suggests a new syphilis diagnosis if the NTT is newly reactive or reinfection if the NTT titer is at least 4-fold higher than the most recent prior titer. A reactive NTT with a nonreactive TT result indicates a biologic false-positive result. Reactive TTs with a nonreactive NTT indicates prior treated syphilis, untreated late latent syphilis, very early primary syphilis (particularly if a lesion is present), or false-negative NTT result due to prozone (if high clinical suspicion of syphilis). All serologic results must be interpreted in the context of the patient's signs, symptoms, and history of syphilis treatment to determine whether there is a new syphilis infection and, if so, the stage (Figure 1, Table 2, and Figure 3).[30]

Point-of-Care Tests

Three point-of-care syphilis tests are approved by the US Food and Drug Administration (FDA). One is available without a prescription and is FDA-approved for home use using fingerstick blood. All are lateral-flow immunochromatographic strip tests that detect treponemal antibodies in whole blood (including fingerstick), serum, or plasma with a sensitivity of 77% to 100% and specificity of 96% to 97% for the detection of early syphilis (using traditional sequence screening algorithm as the reference).[37,49]

Direct Detection Methods

Darkfield microscopy, which uses scattered light to illuminate live, motile spirochetes against a dark background, is no longer widely used because it requires both a darkfield microscope and trained personnel on-site.[50] Immunohistochemical staining of biopsy tissue can identify *T pallidum* with a sensitivity ranging from 64% to 94%, depending on stage and site, and a specificity of 100% for secondary syphilis.[37]

Although no nucleic acid amplification tests for syphilis have been approved by the FDA, several large commercial laboratories offer proprietary nucleic acid amplification tests that can be used to detect *T pallidum* in swabs collected from anogenital lesions, with a sensitivity of 76% to 94% and specificity of 90% to 99% for the detection of primary syphilis.[51]

Neurosyphilis Diagnosis

A positive VDRL result from cerebrospinal fluid (CSF) confirms the diagnosis of neurosyphilis in a person with clinical signs or symptoms of neurosyphilis and a reactive syphilis serology. The specificity of the CSF VDRL is 78% to 90%; its sensitivity in persons with symptoms of neurosyphilis and elevated CSF protein, CSF pleocytosis, or positive *T pallidum* polymerase chain reaction test result is 48% to 86%.[21,37] Treponemal testing in CSF using the fluorescent treponemal antibody absorption test is highly sensitive (91%-100%) but not specific (55%).[52] Patients with ocular or otic syphilis can be treated without a CSF examination, unless they have another indication for lumbar puncture (eg, meningeal signs, seizure, cranial nerve abnormalities, or altered mental status). All patients clinically suspected to have neuro, ocular, or otic syphilis should be empirically treated for neurosyphilis even if the CSF VDRL result is negative (**Table 3**).[21,37]

Table 3. Recommended and Alternative Syphilis Treatment Regimens by Stage of Infection for Nonpregnant and Pregnant Individuals[a,b]

	Recommended regimen	Alternative regimens[c]	Common adverse effects of recommended and alternative regimens
Outside of pregnancy			
Primary, secondary, and early latent stage syphilis	Benzathine penicillin G (BPG) 2.4 million units intramuscularly for 1 dose[d]	Doxycycline 100 mg orally twice per day for 14 d Tetracycline 500 mg orally 4 times per day for 14 d Ceftriaxone 1 g intramuscularly or intravenously daily for 10-14 d	Recommended medications:[43] Penicillin G: nausea, vomiting, diarrhea, nonspecific rashes, injection site pain or redness with intramuscular formulations True IgE-mediated penicillin allergies (ie, anaphylaxis, angioedema) are rare, affecting less than 1% of the US population Jarisch-Herxheimer reactions (posttreatment transient worsening of symptoms) may occur in up to 50%-75% of patients treated for primary and secondary syphilis[44-46]; common symptoms include fever, chills, headache, myalgias, and rash Alternative medications: Tetracyclines (including doxycycline): nausea/vomiting, diarrhea, drug-induced esophagitis, photosensitivity (in 6%-42% of patients)[47] Ceftriaxone: rashes (3% of patients), diarrhea (2%), cholestatic hepatitis (3%), allergic reactions in people with cephalosporin allergies Procaine penicillin G[g] with probenecid: penicillin adverse effects as above; probenecid also associated with nausea, vomiting, dizziness, and headache
Late latent or syphilis of unknown duration	BPG administered as 3 doses of 2.4 million units intramuscularly, given at 1-wk intervals[d,e]	Doxycycline 100 mg orally twice per day for 28 d Tetracycline 500 mg orally 4 times per day for 28 d	
Neuro, ocular, and otic syphilis	Aqueous crystalline penicillin G: 18-24 million units daily, given as 3-4 units intravenously every 4 h or as a continuous infusion for 10-14 d[f]	Procaine penicillin G[g] 2.4 million units intramuscularly daily plus oral probenecid 500 mg 4 times daily, both given for 10-14 d Ceftriaxone 1-2 g intramuscularly or intravenously daily for 10-14 d	
During pregnancy			
Primary, secondary, and early latent syphilis	BPG 2.4 million units intramuscularly × 1[d]	None	Common penicillin adverse effects as listed above
Late latent or syphilis of unknown duration	BPG administered as 3 doses of 2.4 million units intramuscularly, given at 1-wk intervals[d,h]	None	
Neuro, ocular, and otic syphilis	Aqueous crystalline penicillin G: 18-24 million units daily, given as 3-4 units intravenously every 4 h, or as a continuous infusion, for 10-14 d[f]	Procaine penicillin G[g] 2.4 million units intramuscularly daily plus oral probenecid 500 mg 4 times daily, both given for 10-14 d	
Congenital syphilis			
Infants with signs/symptoms of congenital syphilis on physical examination, long bone radiographic imaging, or cerebrospinal fluid analysis; also applies to infants with nontreponemal titers that are 4-fold higher than their birthing parent at delivery	Aqueous crystalline penicillin G: 100 000-150 000 units/kg/d, administered as 50 000 units/kg/dose intravenously every 12 h during the first 7 d of life and every 8 h thereafter for a total of 10 d	None	Common penicillin adverse effects as listed above
Infants whose birthing parents were treated inadequately during pregnancy but who have no abnormalities on examination, cerebrospinal fluid analysis, or long bone radiographic imaging (if follow-up is certain)	BPG 50 000 units/kg/dose intramuscularly in a single dose[i]	None	

[a] Recommended and alternative treatment options do not differ by HIV status.

[b] Following treatment, nontreponemal titers should be measured every 3 to 6 months. A 4-fold decline in titer is expected by 12 months following treatment for primary and secondary syphilis and by 24 months following treatment for latent syphilis or in people with HIV.

[c] Recommended regimens are first-line treatment. Alternative regimens should only be used when recommended regimens are contraindicated, such as in cases of serious drug allergies.

[d] Each 2.4 million–unit dose of BPG can be administered either all at once or as 2 divided doses of 1.2 million units; the 2 techniques are equally well tolerated and equally selected by patients when given the choice.[48]

[e] Although pharmacologic considerations suggest that 7-9 days between BPG injections is optimal for ensuring treponemicidal drug levels, the Centers for Disease Control and Prevention suggests, based on clinical experience, that intervals of up to 10-14 days may be acceptable in nonpregnant people before restarting the full 3-dose treatment series.[44]

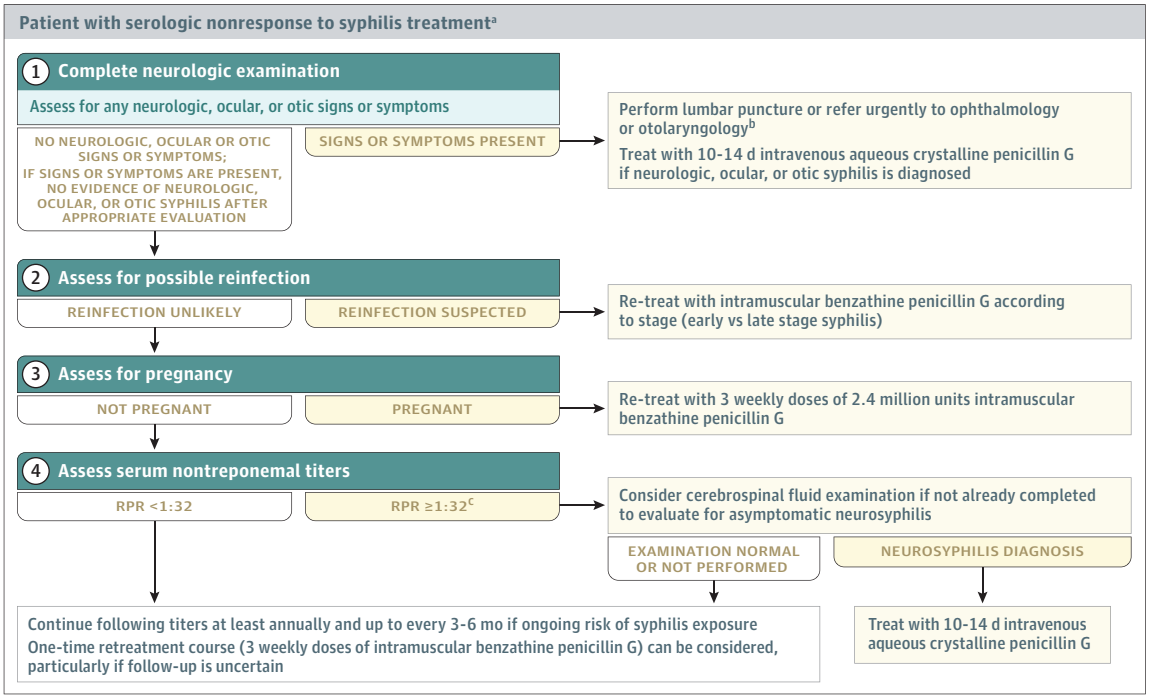
[f] Because the duration of therapy for neuro, ocular, and otic syphilis is shorter than that for late latent syphilis, some experts will give an additional 1-3 intramuscular injections of 2.4 million units of BPG following treatment for neurosyphilis to achieve a comparable duration of therapy.

[g] Procaine penicillin G is no longer available as of June 2023.

[h] Every effort should be made to ensure pregnant people are treated at strict 7-day intervals. BPG treatment intervals >9 days are not acceptable in pregnancy.[44]

[i] A single dose of intramuscular BPG can also be considered, but is not required, for asymptomatic infants whose birthing parents were treated adequately for their stage of syphilis either before or during pregnancy. To be considered adequate during pregnancy, treatment must consist of a penicillin-based regimen initiated 30 or more days before delivery.

Figure 4. Approach to the Clinical Management of Patients With Serologic Nonresponse[a]



[a]Serologic nonresponses occurs among people with treated syphilis infections in whom nontreponemal titers fail to decrease by 4-fold within the expected timeframe (ie, within up to 12 months for primary and secondary syphilis or up to 24 months for latent syphilis or in people with HIV).

[b]A lumbar puncture is indicated in patients with clinical neurologic findings, such as signs/symptoms of meningitis or stroke, cranial nerve dysfunction, or motor or sensory deficits. Patients with isolated ocular or otic symptoms should be referred urgently to ophthalmology or otolaryngology, respectively; a cerebrospinal fluid examination is unnecessary prior to the treatment of isolated ocular or otic syphilis.

[c]Some experts would recommend using a cutoff of RPR >1:64, though the odds ratios for asymptomatic neurosyphilis are similar at RPR cutoffs of >1:32 and >1:64 (5.12 and 5.69, respectively).[54]

Treatment

Penicillin is the first-line treatment for syphilis (Table 3). US and European guidelines recommend benzathine penicillin G (BPG) administered as intramuscular doses of 2.4 million units: a single dose for early stage (primary, secondary, and early latent) and 3 weekly BPG injections for late latent stage and for tertiary syphilis with a normal CSF examination. Neurosyphilis, ocular syphilis, and otic syphilis are treated with intravenous aqueous crystalline penicillin G, 18 million to 24 million units per day, given as 3 million to 4 million units intravenous every 4 hours or via continuous infusion for 10 to 14 days (Table 3). Due to insufficient clinical, pharmacologic, and/or safety data, there are no alternatives to penicillin for the treatment of syphilis in pregnancy.[53]

The efficacy of penicillin for the treatment of syphilis is high; a systematic review of studies including 11 102 patients with early syphilis reported 90% to 100% treatment success rate.[44,54,55] True IgE-mediated penicillin allergies (eg, anaphylaxis or angioedema) are rare, affecting less than 1% of the US population[43]; most people with syphilis can be safely treated with BPG. For patients with reported penicillin allergies, clinicians should obtain a thorough history regarding penicillin exposures and symptoms, refer for penicillin skin testing, and administer an oral challenge (250 mg of amoxicillin) in a monitored clinical setting for patients with negative skin test results or a low-risk penicillin allergy history.[44,56]

For nonpregnant people (except those with neurosyphilis or ocular, otic, or tertiary syphilis), alternative treatment options include oral doxycycline for 14 to 28 days (depending on stage of syphilis) and ceftriaxone (1 g intramuscular or intravenous daily for 10 days for primary and secondary syphilis) (Table 3).[47,48] Given intermittent BPG shortages, studies are ongoing to evaluate BPG alternatives such as oral cefixime for 10 days, oral linezolid for 10 days, and the combination of ceftriaxone and doxycycline.[57] A 2024 RCT comparing linezolid (600 mg orally for 5 days) with a single BPG injection for the treatment of early syphilis was terminated early after linezolid failed to meet prespecified noninferiority criteria, demonstrating treatment response rates of 70% (vs 100% for BPG).[58] An RCT of 58 men with HIV reported that oral cefixime (400 mg twice daily) and BPG resulted in a similar percentage of patients with treatment response (87% vs 93% for early syphilis in the per-protocol analysis), although the study was underpowered and response to treatment was lower with cefixime in the intention-to-treat analysis (56% vs 81% with BPG).[59]

Infants with signs or symptoms of congenital syphilis on physical examination, long bone radiographic imaging, or CSF examination or those whose NTT titers at delivery are at least 4-fold higher than their birthing parent should be treated with intravenous aqueous crystalline penicillin G (100 000-150 000 units/kg/d for a total of 10 days). Asymptomatic infants whose birthing parents received no or inadequate treatment for syphilis during pregnancy and whose evaluations demonstrate no abnormalities can be treated with

Box. Commonly Asked Questions About Syphilis

1. Which asymptomatic nonpregnant individuals should be screened for syphilis?
All sexually active people aged 15 to 44 years living in counties with a primary and secondary syphilis rate among females exceeding 4.6 cases per 100 000 population per year should have at least 1 lifetime screen for syphilis (72% of US population). Sexually active individuals at increased risk, including men who have sex with men, people with HIV, those taking HIV preexposure prophylaxis and/or doxycycline postexposure prophylaxis, or those with multiple or anonymous partners, should be screened at least annually and up to every 3 to 6 months.

2. How can congenital syphilis be prevented?
Prevention of congenital syphilis can be achieved by prenatal screening and treatment of maternal syphilis during pregnancy. All pregnant patients should be screened for syphilis at their first prenatal visit, in the third trimester, and at delivery. For pregnant people diagnosed with syphilis, treatment should be initiated as soon as possible to reduce the risk of congenital syphilis.

3. Over what period do nontreponemal titers decrease after successful treatment of syphilis in adults and adolescents and what is recommended if the titers do not decline 4-fold?
Nontreponemal titers should decline 4-fold by 12 months after treatment of primary or secondary syphilis and after 24 months after treatment of latent syphilis or in people with HIV. If titers have not declined 4-fold at these points, the patient should be assessed for repeat syphilis infection and for signs or symptoms of neurosyphilis (**Figure 4**).

a single dose of intramuscular BPG (50 000 units/kg/dose) if follow-up is certain. A single dose of intramuscular BPG can also be considered, but is not required, for asymptomatic infants whose birthing parents were treated adequately for their stage of syphilis either before or during pregnancy.[44] Adequate treatment during pregnancy must consist of a penicillin-based regimen initiated 30 or more days before delivery.

Serologic Response

NTT titers that decrease by at least 4-fold (eg, from 1:16 to 1:4) indicate an adequate response to treatment. This decrease in titers may take up to 12 months in primary and secondary syphilis and up to 24 months in people with HIV or those with latent infections.[44] The Centers for Disease Control and Prevention (CDC) recommends repeating NTT titer measurements at 6 and 12 months after treatment for primary and secondary syphilis and at 6, 12, and 24 months following treatment for latent syphilis. More frequent NTT monitoring (every 3 months) is recommended for people with HIV and those with ongoing risk of syphilis reexposures. A 4-fold or higher increase in NTT titers sustained for 2 or more weeks indicates reinfection and necessitates repeat treatment.

Serologic Nonresponse

Serologic nonresponse occurs when NTT titers do not decline by 4-fold within 12 to 24 months following treatment. In a systematic review of 20 studies with a total of 8834 participants, serologic nonresponse occurred in 11.2% (IQR, 5.8%-31.9%) of patients treated for syphilis of any stage at greater than or equal to 12 months after treatment.[60] Serologic nonresponse may be caused by lack of pathogen clearance, reinfection, or ongoing production of nontreponemal antibodies despite *T pallidum* clearance.[60] Risk factors for serologic nonresponse include later stages of syphilis infection, lower initial NTT titers (<1:8), and age older than 34 to 40 years.[44,60] Patients with serologic nonresponse should be assessed for neurologic, hearing, or vision concerns (ie, blurry vision, vision loss, eye pain, red eye)[25]; individuals with ocular and otic symptoms should be urgently referred to ophthalmology or otolaryngology, and those with other neurologic findings (eg, meningeal signs, cranial nerve abnormalities or altered mental status) should undergo a lumbar puncture to evaluate for neurosyphilis. In the absence of signs or symptoms of neurosyphilis or ocular or otic syphilis, patients with serologic nonresponse should be evaluated for reinfection based on examination and sexual history. If there is concern for reinfection, patients should receive repeat treatment according to their syphilis stage. Even in the absence of concern for reinfection, pregnant patients with serologic nonresponse should be offered repeat treatment with 3 weekly doses of intramuscular BPG. Outside of pregnancy or suspected reinfection, if NTT titers remain high (≥1:32), a lumbar puncture should be considered.[61] In cases in which the CSF examination results are normal or the examination is not performed, a 1-time repeat treatment with 3 weekly doses of intramuscular BPG can be considered (**Figure 4**).[44,62]

The Serofast State

Despite a 4-fold decline in NTT titers, some patients—up to 27% at 400 days after treatment in a study of early syphilis[63]—remain serofast, meaning that they have a persistently reactive NTT. The serofast state does not indicate treatment failure and is more common with HIV co-infection, age older than 30 years, multiple sex partners (>5 in the last 6 months), lower (≤1:32) baseline NTT titers, and stage of syphilis (later stages at diagnosis are more likely to become serofast).[44,64] Current data do not support treating patients in a serofast state with additional doses of penicillin.[65]

Prognosis

Primary, secondary, early latent, and late latent syphilis are curable with appropriate treatment. Neurosyphilis, ocular syphilis, and otic syphilis can result in long-term sequelae, despite successful treatment. In a 2019 study, hearing improved by audiogram in only 11 of 34 patients (32.4%) with otosyphilis after treatment with intravenous penicillin over 14 days.[66] In a 2020 retrospective cohort study, vision improved in only 24 of 67 eyes (35.8%) after treatment for ocular syphilis among patients who had already developed blindness before starting treatment.[67] Reinfection occurs in 5.9% to 22% of MSM.[68,69]

Prevention

Screening of individuals at elevated risk, prompt treatment of confirmed cases, and prophylactic treatment of exposed contacts are the cornerstones of syphilis control.[70-73] Syphilis is a nationally reportable condition in the US, which facilitates public health follow-up, including contact tracing and partner notification. Clinicians should advise patients diagnosed with syphilis to inform recent sexual partners; partners should undergo testing and empiric treatment for syphilis. At least annual (and up to every 3-6 months) syphilis screen-

Table 4. Recommended Approaches to Syphilis Screening

Population	Centers for Diseases Control and Prevention (CDC)	US Preventive Services Task Force (USPSTF)	American College of Obstetricians and Gynecologists (ACOG)
Nonpregnant adults	Screen all sexually active people aged 15-44 y in counties with primary and secondary syphilis rates among females >4.6/100 000[5] (applies to 72% of the US population) At least annual syphilis screening for men who have sex with men (MSM) and people with HIV; consider for transgender and gender-diverse people More frequent screening (up to 3-6 mo) for individuals with increased vulnerability (eg, MSM taking PrEP, people living with HIV, those with a history of incarceration or transactional sex, if risk behaviors persist, or if they or their sex partners have multiple partners)[44] Screen asymptomatic patients at increased risk[44]	All nonpregnant adolescents and adults should be screened for syphilis if at increased risk for infections[71]	
During pregnancy	Screen all pregnant patients at the first prenatal visit[44] Retest at 28 weeks' gestation and at delivery if at increased risk due to local syphilis prevalence or personal risk (eg, substance use, STIs during pregnancy, multiple partners, a new partner, or partners with STIs)[44]	All pregnant patients should be screened for syphilis as early during pregnancy as possible[77]	Screen all pregnant patients at the first prenatal care visit, followed by universal rescreening during the third trimester and at delivery (not risk based)[76]

Abbreviations: PrEP, preexposure prophylaxis; STI, sexually transmitted infection.

Table 5. Recommended Approaches to Doxycycline Postexposure Prophylaxis (DoxyPEP)

	DoxyPEP recommendations by organization	
Population	Centers for Disease Control and Prevention (CDC)[85]	International AIDS Society[86]
MSM and transgender women	MSM and transgender women with a history of bacterial STI(s) in the past year should be counseled on and offered doxyPEP through shared decision-making as part of comprehensive sexual health DoxyPEP could also be discussed through shared decision-making with MSM and transgender women who have not had a bacterial STI during the prior year but who will be participating in sexual activities known to increase risk of STI exposure	DoxyPEP is recommended within 72 h after condomless sex for cisgender MSM and transgender women, regardless of HIV status
Other populations and comments	Clinicians should use their clinical judgement and shared decision-making to inform use of doxyPEP with populations not part of CDC recommendations (eg, cisgender women, cisgender heterosexual men, transgender men, and other queer and nonbinary persons assigned female at birth)	Pharmacokinetic modeling suggests that doxyPEP is effective for vaginal exposures and is recommended on a case-by-case basis for cisgender women at risk

Abbreviations: MSM, men who have sex with men; STI, sexually transmitted infection.

ing and doxycycline postexposure prophylaxis (doxyPEP) should be offered to patients with ongoing risk of exposure.[68,69] Preventive strategies, including risk reduction counseling to decrease number and concurrency of sexual partners and increased condom usage, are also recommended.[74,75]

Screening

Routine syphilis screening facilitates timely diagnosis and treatment of infected individuals. In 2023, the CDC expanded syphilis screening guidelines such that all sexually active people between the ages of 15 and 44 years should be offered screening if living in counties with a primary and secondary syphilis rate among females exceeding 4.6 cases per 100 000 population per year, a threshold exceeded by 72% of the US population (**Box**).[5] In 2024, the American College of Obstetricians and Gynecologists recommended screening for all pregnant people at the first prenatal visit, during the third trimester, and again at delivery.[76] In 2025, the US Preventive Services Task Force recommended all pregnant women be screened for syphilis early in pregnancy or at the first medical visit, which could be as late as admission for delivery (Grade A).[77] MSM, people with HIV, and those with increased vulnerability to exposure (ie, history of incarceration or transactional sex) should be screened at least annually (and up to every 3-6 months) (**Table 4**).[44]

DoxyPEP

DoxyPEP, a prevention strategy in which individuals take 200 mg of doxycycline within 72 hours after condomless oral, anal, or vaginal sex reduces the relative risk of syphilis infection in MSM and transgender women by 77% to 88% per quarter, and the absolute risk by 18.7% to 21.2% per quarter.[78-82] An RCT conducted in Kenya reported that doxyPEP was not effective at reducing syphilis in cisgender women, though this may have been explained by low adherence to the intervention.[83,84] CDC doxyPEP clinical guidelines recommend (Grade A1) that clinicians counsel MSM and transgender women with a history of a sexually transmitted infection (STI) in the past year about the benefits and harms of using doxyPEP (**Table 5**).[85,86] In San Francisco, a 2025 ecologic analysis assessing the association between doxyPEP implementation and citywide STI incidence found a sustained decrease of −51.39% (95% CI, −58.21% to −43.46%) in early syphilis infections in MSM and transgender women, but not in cisgender women, demonstrating that doxyPEP

has the potential to reduce the population-level incidence of syphilis.[87] Although doxycycline resistance in *T pallidum* has not been found clinically or derived in vitro with exposure to subtherapeutic doses of doxycycline,[88] there is concern that doxyPEP could contribute to antibiotic resistance in other organisms, such as *Staphylococcus aureus*, *Neisseria gonorrhoeae*, group A *Streptococcus*, or *Escherichia coli*, where doxycycline resistance already occurs.[78,79,83] Ongoing surveillance and resistance monitoring is needed as doxyPEP becomes more widely used.

Vaccines

There are no licensed vaccines for the prevention of syphilis infection. However, syphilis vaccine research may benefit from recent advances, including the successful cultivation of *T pallidum* in vitro and a rabbit animal model.[89] The development of an effective syphilis vaccine will be essential for syphilis control.[90]

Practical Considerations

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction—a posttreatment transient worsening of symptoms (eg, fever, chills, headache, myalgias, and rash) due to release of inflammatory cytokines—occurs in up to 50% to 75% of patients treated for primary or secondary syphilis at a median (IQR) time of 4.9 (3.0-9.2) hours after BPG administration. The median (IQR) symptom duration is 12.8 (5.0-24.0) hours.[91] The Jarisch-Herxheimer reaction does not constitute a penicillin allergy.[44-46]

Limitations

This narrative review has several limitations. First, only studies published in English were included. Second, the quality of study evidence was not reviewed. Third, relevant articles may have been missed. Fourth, some recommendations are based on limited data, observational studies, or expert opinion.

Conclusions

Syphilis infections, including congenital syphilis, have increased in the US and worldwide over the past decade. First-line treatment for syphilis is benzathine penicillin G. Routine syphilis screening of all pregnant patients and all sexually active people aged 15 to 44 years and use of doxyPEP in individuals at risk for syphilis are recommended to decrease syphilis transmission.

ARTICLE INFORMATION

Accepted for Publication: August 28, 2025.

Published Online: October 16, 2025. doi:10.1001/jama.2025.17362

Correction: This article was corrected on October 24, 2025, to correct typographical errors in the text and tables.

Conflict of Interest Disclosures: Dr Cohen reported receiving nonfinancial support from Mayne Pharma (donated medications to doxyPEP study), nonfinancial support from Hologic (donated test kits for doxyPEP study), and nonfinancial support from Cepheid (donated test kits for doxyPEP study). No other disclosures were reported.

Additional Contributions: We would like to acknowledge Khalil Ghanem, MD, PhD (Johns Hopkins University), for his contributions to the clinical approach to serologic nonresponse discussed in this article. He did not receive compensation for his contribution.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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