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The Return of an Old Foe: Syphilis Among Women

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Abstract

Over 10 years, the reported incidence of primary and secondary syphilis increased among women at 6 times the rate compared with men (636% vs. 103%). Untreated syphilis can lead to life-altering complications including permanent vision and hearing loss, congenital syphilis, and increased HIV acquisition. Syphilis diagnosis and staging require current and prior laboratory results, physical examination, and history. The preferred treatment for syphilis is long-acting penicillin G benzathine. Partner testing and treatment are critical to prevent re-infection and further community transmission. Innovative strategies are needed to prevent and treat syphilis among women, especially those without regular access to health care.

Keywords

syphilis; congenital syphilis; sexually transmitted infections (STIs); infections; women

Syphilis, a sexually transmitted infection (STI) caused by the spirochete bacterium *Treponema pallidum*, has long been recognized as a significant public health concern. The earliest diagnosis of the infection dates to the late 15th century in Europe, where it spread rapidly among French soldiers causing debilitating symptoms.¹ The name “syphilis” comes from an Italian poem entitled *Syphilis sive Morbus Gallicus*, which describes the character of Syphilus, cursed by a terrible infection as punishment for offending the gods.¹ The infection spread through Europe, the Americas, Asia, and Africa largely unchecked until the discovery of penicillin coupled with subsequent mass treatment campaigns in the 1940s.¹ While syphilis had been declining, the early 2000s saw a resurgence of the disease globally, particularly among men who have sex with men.^{1,2} Syphilis presents unique challenges in its diagnosis and treatment, especially among women and during pregnancy. While men comprise most cases from 2013 to 2023 in the United States, primary and secondary syphilis among women increased at 6 times the rate with a 636% increase compared with a 103%

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increase in men.³ This highlights the need for a focus on syphilis among women as well as comprehensive testing and treatment strategies led by clinicians who care for women.³ This chapter will explore the epidemiology, clinical manifestations, diagnosis, and treatment of syphilis among women outside of pregnancy.

SYPHILIS PATHOPHYSIOLOGY

T. pallidum is a small corkscrew-shaped, gram-negative spirochete bacterium.⁴ While other gram-negative bacteria have a peptidoglycan layer sandwiched between an outer membrane and cytoplasm, *T. pallidum* lacks an outer membrane and has relatively few integral proteins.⁴ These factors contribute to the lack of antigenicity of the organism and its ability to evade the innate immune system.⁴ *T. pallidum* is most often transmitted sexually through direct exposure to a lesion containing the bacteria but can also be transmitted vertically during pregnancy to the fetus and through microabrasions in the skin.⁵ It can cause an infection at any site of inoculation with lesions most often found near the anus, genitals, or mouth.² The risk of sexual transmission is highest during primary and secondary syphilis as syphilis lesions such as chancres and condylomata lata have a high bacterial load.^{5,6} Latent stages of syphilis are less infectious, though some people can move from latent stages of syphilis back to symptomatic stages, especially if they are co-infected with HIV.⁶ Syphilis can additionally augment the acquisition and transmission of HIV in many ways.⁷ Exposure to the ulcerative lesions of syphilis can increase the probability of HIV transmission due to the lack of an intact epithelial cell barrier and an increased number of HIV-containing macrophages and lymphocytes.⁷ Syphilis can also cause a pro-inflammatory state, which can upregulate viral replication of HIV and thus increase the risk of HIV transmission.⁷

SYPHILIS EPIDEMIOLOGY

In the early 2000s, syphilis cases in the United States were at record lows since the inception of national syphilis data reporting.⁸ However, beginning in 2000 syphilis cases continued to rise yearly throughout the United States, initially among gay, bisexual, and other men who have sex with men and then in all segments of the sexually active population.⁸ Among reproductive-aged women in 2023, the highest rate of primary and secondary syphilis was reported among 25 to 29-year-olds (22.7 per 100,000).⁸ Rising in parallel with increases in syphilis among reproductive-aged women in the United States are reported cases of congenital syphilis; in 2023 there were 3882 cases of congenital syphilis (CS) in the United States, which is a 740% increase since 2014.⁸ Studies have shown that syphilitic infections are more common among women reporting substance use and that women who are pregnant with substance use and syphilitic infections were twice as likely than those without substance use to have a CS outcome.^{8–10}

There is a disproportionate impact of syphilis in the United States on people in racial and ethnic minority groups, especially people identified as American Indian, Alaskan Native, or Black/African American, which highlights the role of systemic racism and implicit bias in syphilis epidemiology.⁸ People from some racial and ethnic minority groups might have reduced access to health care due to geographic isolation, lack of insurance coverage, and language and cultural barriers to treatment, among other obstacles.⁹ Mistrust in the

medical system is also an important consideration when screening and treating for syphilis in the United States, particularly given the history of syphilis research.^{10,11} The US Public Health Service conducted several studies of the natural course of syphilis and transmission dynamics among men who were identified as Black or African American, prisoners, sex workers, and people hospitalized with mental illness.¹¹ These instances have furthered barriers to syphilis care that persist today.

COMPLICATIONS OF UNTREATED SYPHILIS

Untreated syphilis can lead to significant sequelae for adults and adolescents, including permanent vision and hearing loss, cardiovascular problems, and neurological changes such as mood changes, memory loss, dementia, and psychosis.¹² Further complications might include tabes dorsalis, a degeneration of the spinal cord leading to impaired balance, pain, incontinence, and sensory disturbances, as well as stroke.¹² Chronic pain and mobility issues have been reported due to tissue destruction and joint damage.¹³ Cardiovascular complications can lead to aortic aneurysms or aortic valve disease, potentially causing heart failure or death.¹² About 30% of people with untreated syphilis will progress to tertiary syphilis, which is rarely seen in the United States.¹² And, of course, untreated syphilis during pregnancy can lead to CS.

SYPHILIS SCREENING

The Centers for Disease Control (CDC) recommends screening for syphilis in people who are sexually active and who live in communities with high rates of syphilis.¹⁴ Communities with high rates of syphilis are defined as those with primary and secondary syphilis rates among women 15 to 44 years at or above 4.6 per 100,00 people, based on the Healthy People 2030 syphilis goal.¹⁴ County-level primary and secondary syphilis rates among women of reproductive age can be found at www.cdc.gov/sti-statistics/county-level-syphilis-data/index.html; these data are updated annually (Fig. 1).¹⁵ Screening for syphilis among sexually active women can also be considered based on certain characteristics such as race/ethnicity and a history of incarceration or transactional sex work.^{3,16} The American College of Obstetricians and Gynecologists (ACOG) currently recommends screening for syphilis 3 times during every pregnancy: at the first prenatal visit or encounter with the health system, in the third trimester, and at delivery.¹⁷ CDC specifies that third-trimester screening should occur at 28 weeks gestation as this allows for enough time to adequately treat syphilis and prevent CS.¹⁴ For sexually active people in certain populations, screening for syphilis should occur at least annually and more frequently based on sexual behaviors as well as local epidemiology.^{16,18} Screening recommendations for other populations can be found in the CDC STI Treatment Guidelines.¹⁶

SYPHILIS CLINICAL PRESENTATION

The clinical presentation of syphilis is dependent on the syphilis stage (Table 1, Fig. 2). Primary syphilis classically presents ~21 days after exposure and is most often described as a single painless chancre.¹³ However, presentation can vary, and lesions can be painful and multiple, and enlargement of nearby lymph nodes is common.¹³ Painful lesions are

more common with co-infections, such as herpes or mpox.¹⁶ Multiple lesions can occur from multiple sites of inoculation or auto-inoculation when tissue folds onto itself.¹³ As lesions might be painless and in hard-to-see areas, such as the cervix, vagina, anus, and oral cavity, they can go unnoticed by patients; because of this, a thorough urogenital and oral examination by a clinician is important.¹² Chancres will go away on their own without treatment, but a person still has syphilis and is still able to transmit syphilis.¹⁶

Secondary syphilis typically presents 3 to 6 weeks after primary syphilis.¹³ Secondary syphilis presents as a systemic illness with generalized fever, malaise, headache, and myalgias.¹⁶ A rash is also commonly seen that is macular or papular in nature and can involve the trunk, extremities, palms of the hands, and soles of the feet.¹³ While the latter hand and foot rashes are commonly associated with secondary syphilis, they are not necessary to make a diagnosis of secondary syphilis.¹³ Additional secondary syphilis physical examination findings include mucosal patches which are white patches on the mouth or tongue.¹³ Condylomata lata can also be present and are raised gray to white lesions typically near the mouth or perineum that are usually flatter and moister than condyloma acuminatum (ie, genital warts).¹³ Less common findings of secondary syphilis include alopecia, hepatitis, and renal abnormalities.¹⁹ Some signs and symptoms of secondary syphilis overlap with common findings during pregnancy and, as such, clinical suspicion for syphilis must be high when a reproductive-aged woman presents with these findings.

Latent infections have no clinical manifestations and can only be diagnosed using laboratory testing.¹⁶ Early latent infections are asymptomatic syphilis infections acquired within the preceding year; late latent infections include asymptomatic syphilis infections acquired more than a year ago.⁶ The only way to diagnose early latent syphilis is to identify one of the following clinical or historical facts within the preceding year: negative syphilis testing, adequate syphilis treatment for a given stage of syphilis, classic primary or secondary syphilis signs or symptoms, or a known syphilis exposure.¹⁶ Asymptomatic infections with uncertain acquisition timing are classified as latent syphilis of unknown duration.⁶

Neurosyphilis, ocular syphilis, and otosyphilis can occur at any time during a syphilitic infection.²⁰ Any person presenting for a syphilis evaluation should be asked about signs and symptoms possibly consistent with 1 of these 3 types of syphilis because they require different treatment, and the long-term consequences of not receiving the proper treatment can be devastating. If signs and symptoms consistent with possible neurosyphilis, ocular syphilis, or otosyphilis are identified, the person should immediately be evaluated by a specialist with capacity for the appropriate evaluation.¹⁶ Signs or symptoms of early neurosyphilis are those associated with meningitis such as headache, confusion, and hydrocephalus.²⁰ Ocular syphilis and otosyphilis might present with or without other findings consistent with neurosyphilis; ocular syphilis usually presents with vision changes, uveitis, or conjunctivitis and otosyphilis with hearing loss with or without tinnitus and vertigo.²⁰

Tertiary syphilis refers to prolonged syphilitic infections, typically 10 to more than 30 years in duration, and has findings such as cardiovascular syphilis, gummas, memory loss, or late neurosyphilis findings such as general paresis and tabes dorsalis.⁹

SYPHILIS DIAGNOSIS

Syphilis diagnosis and staging requires a combination of current and prior laboratory test results (if available), physical examination, and a thorough medical and sexual history. Knowledge of prior syphilis laboratory test results often requires consultation with the health department. A medical and social history should include information about prior syphilis diagnoses and details of treatment as well as a sexual history.²¹

A definitive diagnosis of syphilis is made by darkfield microscopy, which is time-intensive and not often available.¹¹ Gram stain and microscopy are inadequate due to the poor uptake of dye by *T. pallidum*, and culture is only available in research settings.¹⁸ As such, laboratory testing for syphilis relies mainly on the detection of antibodies; either to nonspecific (lipoidal, also known as nontreponemal) antibodies or the syphilis organism itself (treponemal tests).¹⁸ Both a nontreponemal test and a treponemal test are needed to diagnose syphilis.¹⁸

Nontreponemal tests include rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests; these are nonspecific and detect antibodies to lipoidal antigens usually resulting in titers when reactive.¹⁸ Because nontreponemal tests are usually performed and read manually, there can be variability between laboratories, and it is advisable to run tests at the same facility when comparing results.¹⁸ Some people will remain low-level nontreponemal test reactive even after adequate treatment; this is referred to as a serofast state.¹⁸ Less than 1% of the population will have biological false positive nontreponemal test results because of a reaction to a condition other than syphilis; these people will have a nonreactive treponemal test.¹⁸ Lastly, it is also possible for nontreponemal tests to be falsely negative, usually due to the early stage of the infection in which a person has not developed enough antibodies for the test to be reactive. Rarely, the prozone effect can occur, which is when there are excess antibodies or antigens in a test specimen that interfere with the test's ability to result as positive.¹⁸ This is more likely to occur in patients with HIV co-infection or in patients with secondary syphilis. If there is high clinical suspicion for syphilis in a patient with a positive treponemal test, signs and symptoms of secondary syphilis, and a negative nontreponemal test, the laboratory can be consulted and asked to dilute the specimen before testing to avoid the prozone effect.¹⁸

Treponemal tests detect antibodies specific to *T. pallidum* and result qualitatively as either reactive or nonreactive; they include tests such as the *T. pallidum* particle agglutination assay (TPPA), fluorescent treponemal antibody absorption tests (FTA-ABS), enzyme immunoassays (EIA), and chemiluminescence immunoassays (CIA).¹⁸ Some treponemal tests are automated.¹⁸ Treponemal tests typically remain positive for life in individuals with a history of treated syphilis and, thus, cannot be relied upon alone for diagnosis of a new infection.¹⁸

There are 2 algorithms for syphilis testing: the traditional algorithm, which starts with a nontreponemal test, and the reverse algorithm, which starts with a treponemal test (Fig. 3).¹⁸ For the traditional algorithm, if the nontreponemal test is reactive, a treponemal test is performed to confirm the diagnosis.¹⁸ The reverse algorithm follows a reactive treponemal

test with a confirmatory nontreponemal test; if these 2 test results are discordant, the reverse algorithm adjudicates with a second treponemal test.¹⁸ Both algorithms are acceptable, and they have a 99% concurrence with one another.¹⁸

The syphilis point-of-care tests currently available in the United States are fingerstick tests (ie, similar to a blood glucose point-of-care test) that are only treponemal tests. As such, while they can be used in people who have not previously been treated for syphilis to presumptively diagnose syphilis and offer an opportunity for immediate treatment, they are not adequate to make a diagnosis of syphilis. These tests have utility for people or settings where phlebotomy is refused or not possible and/or follow-up is difficult. The first syphilis self-test (ie, at-home test) was approved by the FDA on August 16, 2024; it uses similar technology as the current domestically available point-of-care tests.¹⁶ It is important that people who are tested for syphilis with a point-of-care or self-test also have serologic laboratory testing with either the traditional or reverse algorithm for a complete syphilis evaluation as well as electronic laboratory reporting to the health department.

SYPHILIS TREATMENT

Once the diagnosis of syphilis has been made, prompt treatment is critical for preventing sequelae and stopping transmission of the disease. If a person has signs or symptoms suggestive of syphilis or has a known exposure to syphilis, presumptive treatment is reasonable while awaiting serologic laboratory test results.¹⁶ All people who are diagnosed with syphilis should be offered HIV testing and if negative, should be offered HIV pre-exposure prophylaxis (PrEP).¹⁶

First line treatment for syphilis is intramuscular benzathine penicillin G, a formulation of penicillin that hydrolyzes slowly to penicillin G allowing for prolonged bactericidal concentrations of the medication (Table 2).¹⁶ If a person cannot receive benzathine penicillin G due to allergy or refusal of injection, and is not pregnant, doxycycline and tetracycline are acceptable alternatives per current CDC guidelines.¹⁶ Benzathine penicillin G is the only option to treat syphilis during pregnancy and prevent CS. Primary, secondary, and early latent syphilis are treated with a single dose of benzathine penicillin G 2.4 million units (mu).¹⁶ Treatment for late latent, latent of unknown duration, and tertiary syphilis (with a normal CSF evaluation) should be with 3 doses of benzathine penicillin G 2.4 mu given weekly.¹⁶ An acceptable interval between doses is likely 10 to 14 days based on clinical experience, though if a woman is pregnant, the treatment course should be reinitiated if more than 9 days pass between doses.¹⁶

Neurosyphilis, ocular syphilis, and otosyphilis should all be treated with high doses of aqueous crystalline penicillin G, with 18 to 24 mu given intravenously per day, divided into 3 to 4 mu infusions every 4 hours or a continuous infusion for 10 to 14 days.¹⁶ Alternatively, 10 to 14 days of both procaine penicillin 2.4 mu intramuscularly once daily and probenecid 500 mg orally 4 times daily can be given, however, this is not feasible for most clinics as procaine penicillin is no longer manufactured in the United States.¹⁶

The Jarisch-Herxheimer reaction (JHR) is a self-limiting febrile illness that can occur in the 24 hours after syphilis treatment.¹⁶ It is not an allergic reaction.¹⁶ Affecting ~10% to 35% of people, JHR is thought to be due to an inflammatory reaction caused by an increase in cytokines due to treatment, although the exact pathophysiology is unknown.²² Supportive care can be provided, including antipyretics though they have not been demonstrated to prevent JHR from occurring.¹² It is important to discuss the potential for JHRs with patients and describe the self-limited course. In pregnancy, there is a risk of JHR to cause premature labor and fetal distress, however this should not prevent or delay treatment.¹⁶

Syphilis itself is not a contraindication for breastfeeding as *T. pallidum* is too large to be excreted in breast milk.²³ However, lesions or sores on or near the breast pose a risk, so covering lesions, hand-expressing, or pumping should be considered until the sores are healed.²³ Penicillin is compatible with breastfeeding.²⁴ Doxycycline is excreted in small amounts in breast milk and can be considered safe to use in short courses while breastfeeding.^{23,24}

FOLLOW-UP AFTER SYPHILIS TREATMENT

Follow-up titers are compared with titers collected on the first day of a person's syphilis treatment.¹⁶ Quantification of the change in titers is determined based on increases or decreases calculated as "folds;" a 4-fold increase or decrease is a 2-dilution change in titers, which can also be calculated by dividing the titer denominators (eg, 1:8 to 1:32 is a 4-fold increase as 32 divided by 8 is 4). Repeat titers should be collected at 6 and 12 months after treatment; a history and physical examination should also be performed at these times.¹⁶ Additional follow-up should be performed at 24 months after treatment if someone had latent or tertiary syphilis and the titer was reactive at 6 and 12 months.¹⁶ Repeat testing should be performed sooner if someone presents with signs or symptoms of syphilis or a known exposure.¹⁶

Treatment failure is defined as a failure of nontreponemal titers to decrease 4-fold after 12 months in primary and secondary syphilis or after 24 months with latent or tertiary syphilis.¹⁶ People with signs or symptoms or who have a 4-fold increase in nontreponemal titers sustained for 2 weeks are likely re-infected or have treatment failure.¹⁶ Given that HIV infection is associated with treatment failure, repeat HIV testing should be performed on anyone with suspected treatment failure.¹⁶ Neurosyphilis is also a cause of treatment failure, so a repeat neurological examination should be performed with CSF evaluation if they did not have sexual exposure to syphilis in the interval since treatment.¹⁶ If neurosyphilis has been excluded, benzathine penicillin G should be repeated according to stage.¹⁶ Additional nuances of syphilis follow-up can be found in the CDC STD Treatment Guidelines, especially around the close follow-up of titers for women who are pregnant.¹⁶

SYPHILIS OPPORTUNITIES FOR PREVENTION

There are many potential avenues for syphilis prevention, both on individual and systemic levels. First, clinician awareness and education are crucial for diagnosis, staging, and treatment to prevent further community transmission. In 1 study in 2021, 70% of residents/

fellows and 44% of non-ID attendings stated they felt very inexperienced in diagnosing and treating syphilis.²⁵ Syphilis is challenging to manage given the need for titer interpretation, complicated follow-up algorithms, and intramuscular treatment. There are many resources to support clinicians in learning about and managing syphilis in women (Table 3). In addition to information provided by medical societies and the CDC, the National STD Curriculum provides syphilis clinical education along with continuing education credits. The STD Clinical Consultation Network is a free resource for clinical support around individual patient syphilis management. Finally, the National Network of STD Clinical Prevention Training Centers can provide syphilis training, consultation, and technical assistance.

Education may also extend to patients and the public about syphilis generally, as well as ways to reduce risk, including condom use, and the importance of regular STI screening. Trusted health care messengers include community health care workers, birth workers, and medical assistants—clinicians who work with women can facilitate syphilis care by working with all of their colleagues to ensure high-quality information about syphilis is available and reinforced with patients. These efforts can prioritize outreach to communities at high risk for syphilis with nonstigmatizing educational efforts.

Syphilis screening is important to enable early diagnosis and treatment, which prevents the long-term complications of untreated syphilis and further community transmission. Point-of-care tests, as discussed above, might have a role in increasing testing in communities with less frequent access to medical care, including people living in rural settings and people with lives complicated by substance use and housing instability.²⁶ Partnerships with health departments are critical in ensuring both the treatment of syphilis in women and partner testing and treatment.

CONCLUSIONS

The burden of syphilis in women has been increasing dramatically in the United States over the last 10 years. A history and physical examination remain important parts of diagnosing, staging, and treating syphilis. While point-of-care tests and self-tests for syphilis are exciting new tools to address syphilis in the United States, both a nontreponemal and treponemal test are needed to diagnose syphilis. Benzathine penicillin G is the standard of care for the treatment of syphilis in all populations and quick access to treatment must be ensured to prevent the long-term complications of untreated syphilis. Research and development around syphilis testing, treatment, management, and potential vaccination will dramatically change the landscape of syphilis in the years to come. Clinicians who work with women are fundamental to addressing syphilis in our communities and a critical part of the multipronged approach that is needed.

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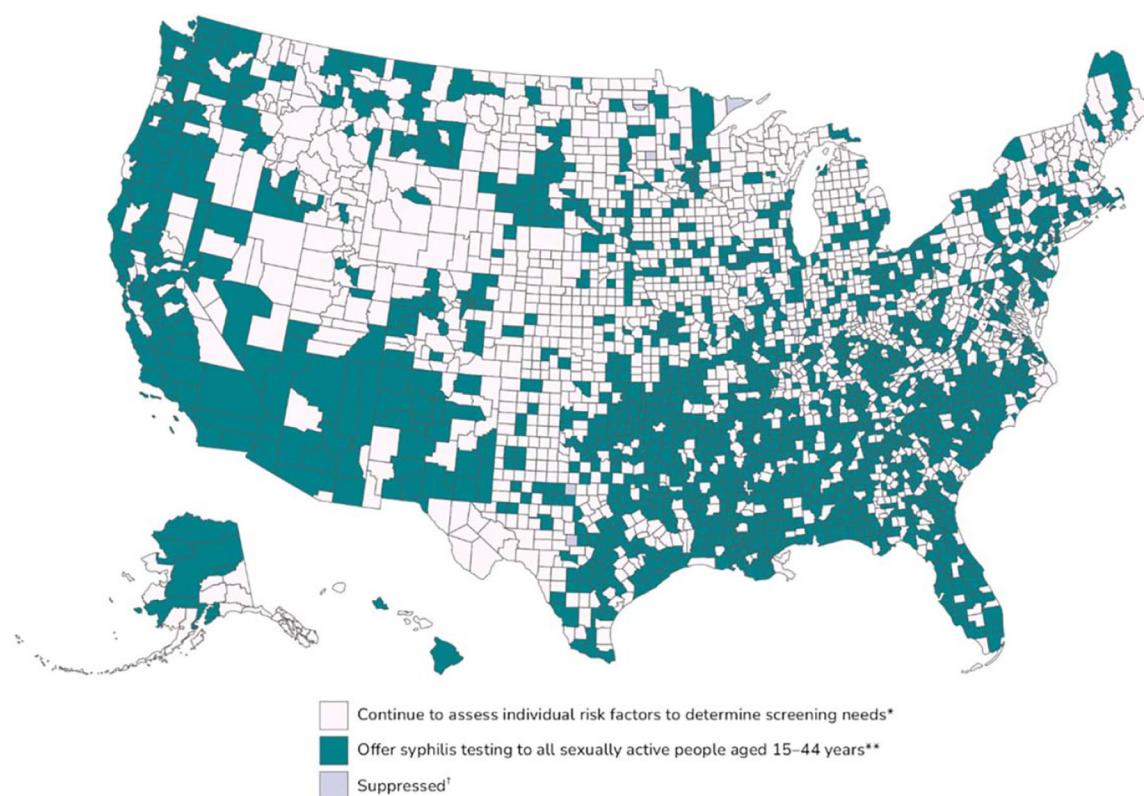


FIGURE 1.

County-level map of primary and secondary syphilis rates among women aged 14 to 44, 2023, updated annually. Reproduced with permission from the Centers for Disease Control and Prevention. *In counties with a rate of primary and secondary syphilis among women aged 15 to 44 years less than or equal to 4.6 per 100,000 people, providers should continue to assess individual risk factors to determine screening needs, as outlined in existing screening guidelines. **Offer syphilis testing to all sexually active people aged 15 to 44 years in counties with a rate of primary and secondary syphilis among women aged 15 to 44 years that is greater than 4.6 per 100,000 people.

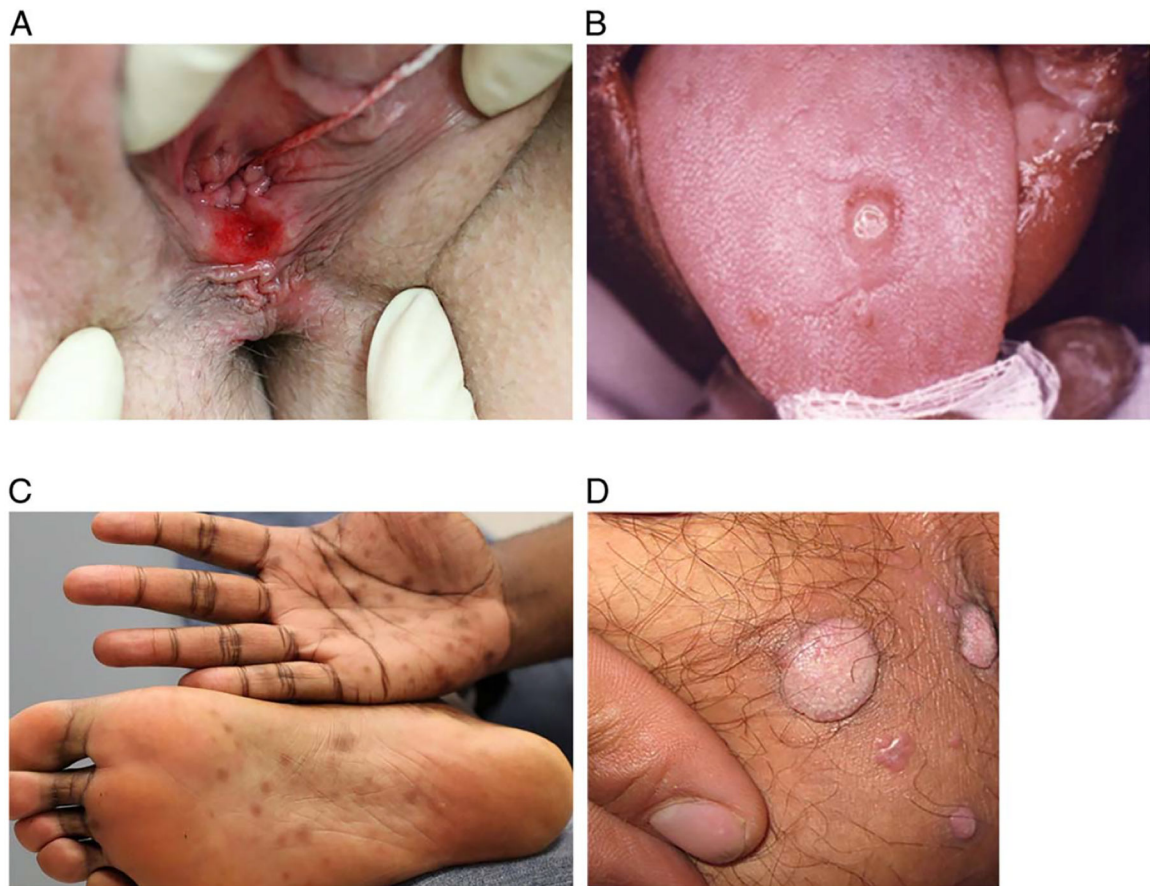
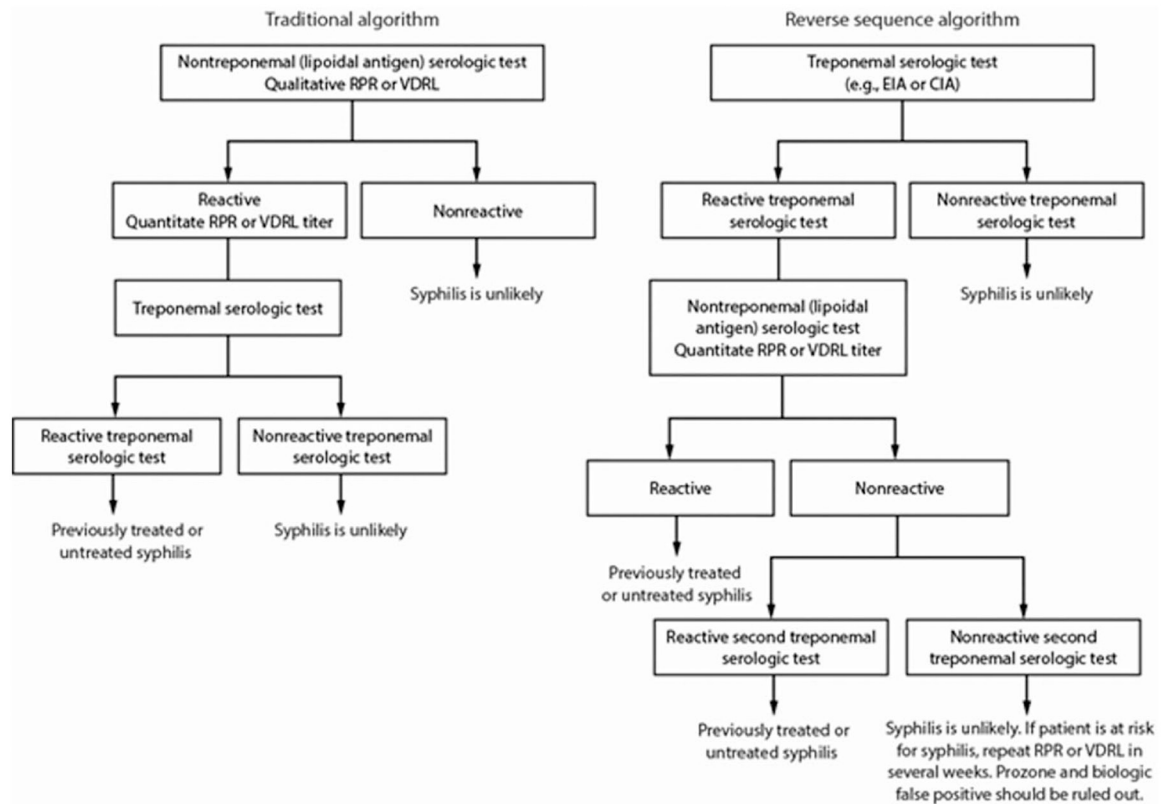


FIGURE 2.

Syphilis signs. (A) Chancre inside vaginal opening found in primary syphilis. (B) Chancre on the tongue found in primary syphilis. (C) Rashes found in secondary syphilis. (D) Condyloma lata lesions found in secondary syphilis. (Reproduced with permission from the Orange County Health Care Agency [Dr. Christopher Ried] and Centers for Disease Control and Prevention).

**FIGURE 3.**

Algorithms that can be applied to screening for syphilis with serologic tests. Centers for Disease Control and Prevention Laboratory Recommendations for Syphilis Testing in the United States, 2024. Reproduced with permission from the Centers for Disease Control and Prevention. CIA indicates chemiluminescence immunoassay; EIA, enzyme immunoassay; RPR, rapid plasma regain; TPPA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory.

TABLE 1.
Syphilis Stages With Common Signs and Symptoms

Syphilis stage	Common signs and symptoms
Primary syphilis	Painless chancre (though might be painful and more than 1)
Secondary syphilis	Palms of hands or soles of feet rash
	Reddish brown maculopapular body rash
	Condylomata lata
	Mucous patches
	Alopecia
	Fever
	Fatigue
	Hepatitis
	Lymphadenopathy
	Malaise
	Renal abnormalities
Early latent syphilis	None (less than 1 year since infection)
Late latent syphilis	None (more than 1 year since infection)
Tertiary syphilis	Cardiovascular problems (dilated aorta, aortic regurgitation)
	Gummas (soft tumor-like growth)
	Psychiatric manifestations (memory loss, personality changes)
	Late neurosyphilis (general paresis, tabes dorsalis)
Neurosyphilis *	Meningitis (headache, confusion, and hydrocephalus)
	General paresis
	Tabes dorsalis
Ocular syphilis *	Vision changes
	Uveitis
	Conjunctivitis
Otosyphilis *	Hearing loss
	Tinnitus
	Vertigo

Centers for Disease Control and Prevention STI Treatment Guidelines, 2021.

* Neurosyphilis, ocular syphilis, and otosyphilis can occur at any time during a syphilitic infection. Any patient presenting for a syphilis evaluation should be asked about signs and symptoms possibly consistent with 1 of these 3 types of syphilis.

TABLE 2.

Syphilis Treatment by Stage

	Recommended regimen	Alternative regimen
Primary, secondary, or early latent syphilis	Benzathine penicillin G 2.4 million units (mu) intramuscularly (IM) in a single dose	Doxycycline 100 mg twice daily for 14 d OR tetracycline 500 mg 4 times daily for 14 d
Late latent or latent of unknown duration syphilis	Benzathine penicillin G 7.2 mu total, administered as 3 doses of 2.4 mu IM each at 1-week intervals*	Doxycycline 100 mg twice daily for 28 d OR tetracycline 500 mg 4 times daily for 28 d
Tertiary syphilis (with normal CSF evaluation)	Benzathine penicillin G 7.2 mu total, administered as 3 doses of 2.4 mu IM each at 1-week intervals*	None specified; consult with an infectious disease specialist
Neurosyphilis, ocular syphilis, or otosyphilis	Aqueous crystalline penicillin G 18–24 mu per day, administered as 3–4 mu intravenously every 4 h or continuous infusion for 10–14 d	Procaine penicillin 2.4 mu IM daily for 10–14 d AND probenecid 500 mg orally 4 times daily for 10–14 d

Centers for Disease Control and Prevention STI Treatment Guidelines, 2021.

* An acceptable interval between doses is likely 10 to 14 days based on clinical experience, though if a woman is pregnant, the treatment course should be reinitiated if more than 9 days pass between doses.

TABLE 3.

Syphilis Clinical Resources

Title	Host	Website link
STI Treatment Guidelines	Centers for Disease Control and Prevention (CDC)	https://www.cdc.gov/std/treatment-guidelines/provider-resources.htm
National STD Curriculum	University of Washington STD Prevention Training Center	https://www.std.uw.edu/
National Network of STD Clinical Prevention Training Centers	National Network of STD Clinical Prevention Training Centers	https://www.nnptc.org/
STD Clinical Consultation Network	National Network of STD Clinical Prevention Training Centers	https://www.stdccn.org/
A Guide to Taking a Sexual History	CDC	https://www.cdc.gov/sti/hcp/clinical-guidance/taking-a-sexual-history.html
2023 STI Surveillance Report	CDC	https://www.cdc.gov/sti-statistics/annual/index.html
National Center for HIV, Viral Hepatitis, STIs, and Tuberculosis Prevention AtlasPlus	CDC	https://www.cdc.gov/nchhstp/about/atlasplus.html
County-Level Syphilis Rates to Direct Screening Efforts	CDC	www.cdc.gov/sti-statistics/county-level-syphilis-data/index.html
Screening for Syphilis in Pregnancy	American College of Obstetrics and Gynecology (ACOG)	https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2024/04/screening-for-syphilis-in-pregnancy
State Prenatal Syphilis Screenings Laws and Regulations	CDC	https://www.cdc.gov/syphilis/hcp/prenatal-screening-laws/index.html