Syphilis

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Module 2:   Self-Study Lessons 2nd Edition
Lesson 3:   Syphilis

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Introduction

Syphilis is a systemic infection caused by *Treponema pallidum*, a spirochete bacterium that is transmitted primarily through sexual activity or with vertical transmission during pregnancy. Cases of syphilis, including congenital syphilis, have risen substantially in recent years in the United States. In the absence of treatment, persons who acquire *T. pallidum* remain chronically infected and can develop an array of clinical manifestations. Syphilis characteristically progresses in stages (primary, secondary, latent, and tertiary), with episodes of active clinical disease interrupted by periods of latent infection; neurologic manifestations can occur at any of these stages (Figure 1).[1,2] Chronic disease can result in significant morbidity, potentially affecting nearly every organ system, and rarely, can result in death. In addition, untreated syphilis in pregnant women can lead to fetal demise and devastating congenital infection for the neonate.

Epidemiology in the United States

2020 Syphilis Surveillance Data

Although surveillance reporting of syphilis cases includes data for multiple syphilis stages, the reported cases for primary and secondary syphilis most accurately represent new infections. During the past 80 years in the United States, the incidence of syphilis has fluctuated (Figure 2).[3] Since the year 2000, the reported number of syphilis cases in the United States has dramatically increased, peaking at 133,945 reported cases (of all stages) in 2020 (Figure 3).[3] In 2020, a total of 41,655 cases of primary and secondary syphilis were reported, which represents a 75% increase from 2015 and the highest reported number of cases since 1992.[3] In recent years, there reported cases of syphilis in women have increased, in conjunction with a sharp increase in the number of cases of congenital syphilis.[3] The following summarizes several key epidemiologic features for syphilis as reported in the United States for the year 2020.[3] Note: the Centers for Disease Control and Prevention (CDC) surveillance report provides data on gender that is based on sex assigned at birth (male and female) and therefore the terms male and female are used below.[3]

- **Sex**: The rate of reported primary and secondary syphilis cases among males (20.8 cases per 100,000 men) was approximately 4-fold higher than among women (4.7 cases per 100,000 women). For both men and women, rates of reported primary and secondary syphilis increased significantly from 2015 to 2020, with a 235% increase in women and a 53% increase in men (Figure 4).
- **Sex Partner**: Men who have sex with men (MSM) accounted for 38% of reported cases of primary and secondary syphilis; an additional 5% of the reported cases involved men who have sex with both men and women (Figure 5).
- **Age**: The highest rates of reported primary and secondary cases of syphilis in both males and females occurred in persons 25 to 29 years of age. For males, the age group with the second highest rate was 30 to 44 years. For females, the age group with the second highest rate was 20 to 24 years (Figure 6).
- **Race/Ethnicity**: The rate of primary and secondary syphilis was highest among Black persons (34 cases per 100,000 persons) and next highest among American Indian/Alaska Native individuals (Figure 7). The racial differences in syphilis prevalence are likely impacted by differential access to quality sexual health care and differences in sexual network characteristics, rather than differences in sexual behavior.
- **Region and State**: The West had the highest rate of reported primary and secondary syphilis (16.7 per 100,000 persons), followed by the South (13.2 per 100,000 persons). The five states with the highest rates of reported cases of primary and secondary syphilis were (in descending order) Nevada and Mississippi (both with 24.9), Alaska, Oklahoma, and New Mexico; rates were extremely high in the District of Columbia (Figure 8).
- **Congenital Syphilis**: The number of reported congenital syphilis cases has consistently risen in recent years—during the 8-year period from 2012-2020, the number of yearly cases increased by an alarming 543% (from 334 to 2,148 cases) (Figure 9). The recent increases in rates of congenital syphilis parallel the rise in primary and secondary syphilis among women.
- **HIV Coinfection**: In cases of primary and secondary syphilis when the HIV status of the person diagnosed was known, HIV coinfection was present in 46% of MSM and in 8% of men who have sex only with women. For women diagnosed with primary and secondary syphilis, 6% were identified as having HIV (when the HIV status was known). Among MSM who do not have HIV, a diagnosis of primary or secondary syphilis is associated with a significantly increased risk of subsequently acquiring HIV.[4] [Q] Syphilis Epidemiology

Factors Associated with Syphilis Diagnosis

Persons with the highest rates of syphilis include MSM and individuals with HIV (men or women).[3,5] Additional factors associated with an increased rate of syphilis include age younger than 29 years, a history of incarceration, methamphetamine use, injection drug use, and exchanging sex for money or drugs.[5,6,7]

Among MSM, the use of methamphetamine has been associated with a substantially increased risk of acquiring syphilis.[7]

Impact

Untreated syphilis can result in major morbidity and rarely in death. In the United States, the estimated lifetime cost for syphilis infections acquired in 2018 was $173.7 million.[8] This estimate correlated with an approximate lifetime cost per syphilis infection of $1,190. The overall lifetime medical cost for syphilis represented about 1% of the $15.9 billion lifetime cost for all sexually transmitted infections acquired in the United States in 2018; notably, HIV accounted for approximately $13.7 billion of those total lifetime medical costs.[8]

Microbiology, Pathogenesis, and Transmission

Organism and Classification

The etiologic agent in syphilis is *Treponema pallidum*—from the Greek terms trepo ("to turn") and nema ("thread") and the Latin term pallida ("pale").[9] *Treponema pallidum* belongs to the spirochete class and is a corkscrew-shaped, motile microaerophilic bacterium that cannot be viewed by normal light microscopy (Figure 10). Isolation of *T. pallidum* was first performed using a live rabbit-model in vivo system, but subsequently, successful cultivation and propagation of *T. pallium* has been achieved using in vitro tissue culture.[10,11,12] This spirochete bacterium is thin (0.1 to 0.18 micrometers in diameter) and 6 to 20 micrometers in length (Figure 11).[13] *Treponema pallidum* has been erroneously described as a gram-negative bacterium, but this organism lacks lipopolysaccharide (LPS), a hallmark of gram-negative organisms.[14][Q] Biology of Treponema pallidum

Transmission

The major routes of transmission for *T. pallidum* are sexual (during the primary and secondary stages of syphilis) and hematogenous (in utero via transplacental spread to a fetus).[15] During sexual transmission, *T. pallidum* enters the body via skin and mucous membranes through macroscopic and microscopic abrasions during sexual contact.[14] Persons who acquire *T. pallidum* are contagious to their sex partners throughout the primary and secondary stages of infection—when lesions or rash are present.[14,16] Although sexual transmission of *T. pallidum* usually results from contact at genital mucous membranes, it can also occur at other body areas, including the mouth, anorectal areas, and cutaneous lesions. Maternal transmission predominantly occurs via transplacental passage of *T. pallidum* during maternal spirochetemia; less often, transmission can occur if the newborn has contact with maternal genital lesions at the time of delivery.[14,17] In contrast to sexual transmission of syphilis, which nearly always occurs in early stages of syphilis, vertical transmission can occur during any stage of syphilis. Other forms of hematogenous transmission of *T. pallidum* are rare: transfusion-associated syphilis has been virtually eliminated in the United States, and transmission through needle-sharing with injection drug use is infrequent.[15] [Q] Transmission of Treponema pallidum

Clinical Manifestations

Syphilis has often been called "the great imitator" because so many of the signs and symptoms may be difficult to differentiate from those of other diseases.[15,18,19,20] Early after infection, before clinical signs or symptoms appear, *T. pallidum* can spread to the circulatory system, the lymphatic system, regional lymph nodes, and the central nervous system. Early clinical manifestations (primary and secondary stages) predominantly involve the skin and mucosal surfaces, although secondary syphilis may be accompanied by systemic manifestations.[15,21] Latent disease has no clinical signs or symptoms, but late manifestations (seen after years of infection) may affect virtually any organ system. Neurosyphilis, ocular syphilis, and otosyphilis can occur at any stage of infection. Obtaining a detailed history is critical for determining the duration of infection and assessing for the possibility of reinfection. Assessment should include the following:

- A history of syphilis (if yes, obtain results of previous serologic tests for comparison)
- Known contact with someone with primary, secondary, or early latent syphilis
- Signs or symptoms of syphilis in the past 12 months

Primary Syphilis

Following the inoculation of *T. pallidum* at the entry site, organisms proliferate, sensitize lymphocytes, and activate macrophages, causing the formation of a primary lesion or "chancre" at the site of inoculation.[16] If clinically evident, the chancre appears about 2 to 3 weeks (range 10 to 90 days) after the acquisition of *T. pallidum*.[2,15] Chancres progress from a papule to an ulcer, which is typically painless, round to oval, indurated, well-circumscribed, with a clean base and heaped up margins.[1] Less often, individuals with primary syphilis may develop multiple, painful anogenital lesions.[22] The most common sites where chancres develop include the penis (Figure 12), labia, perianal region, or mouth (Figure 13).[1,15] Regional firm lymphadenopathy often develops in proximity to primary syphilitic lesions.[23,24] Syphilitic chancres are highly infectious and heal spontaneously (without treatment) in approximately 3 to 8 weeks.[2,15] If untreated, persons with primary syphilis may subsequently develop other manifestations of syphilis. Evaluation of any sexually active persons with a genital or perianal ulcer should include testing for syphilis and genital herpes.[25]

Secondary Syphilis

Secondary lesions reflect hematogenous dissemination of *T. pallidum* and generally appear 4 to 10 weeks after the onset of the primary chancre.[2] In fewer than 10% of cases, primary and secondary stages may overlap.[15] Signs and symptoms of secondary syphilis are often the first observed clinical manifestation of syphilis, as primary lesions are often overlooked or not recognized.[15] Relapses of secondary symptoms occur in up to 25% of untreated persons.[2] A wide array of manifestations can occur with secondary syphilis:[1,20]

- **Generalized Body Rash**: A generalized body rash occurs in more than 75% of persons with secondary syphilis and is usually nonpruritic. The red or copper-colored lesions are typically 1 to 2 cm in size and can appear as any combination of macular, papular, squamous, or pustular forms. The rash characteristically involves the chest, back, palms, and soles (Figure 14).
- **Lymphadenopathy**: Approximately 50 to 86% of persons with secondary syphilis develop lymphadenopathy, which may be diffuse.
- **Systemic Symptoms**: Patients often present with malaise, fever, and other nonspecific constitutional symptoms.
- **Mucous Patches**: The development of mucous patches occurs in 6 to 30% of patients and manifest as flat patches located in the oral cavity (Figure 15), pharynx, larynx, or genital region.
- **Condylomata Lata**: Approximately 10 to 20% of persons with secondary syphilis will have condylomata lata lesions, which appear as moist, heaped-up, wart-like papules in warm intertriginous areas (most commonly gluteal folds, perineum, and perianal) (Figure 16); these lesions are highly

contagious.
- **Alopecia**: About 5% of patients develop patchy alopecia, most often in the occipital or bitemporal scalp region, but some patients will have loss of the lateral region of the eyebrows.
- **Visceral Organ Involvement**: In some cases, syphilis may involve one or more visceral organs, including the liver, kidney, lungs, gastrointestinal tract, and spleen. The most common visceral organ manifestations are nephritis and hepatitis (with a high alkaline phosphatase level).[Q] Condylomata Lata

Latent Syphilis

Latent syphilis is a stage of syphilis characterized by the persistence of *T. pallidum* organisms in the body without causing signs or symptoms. Periods of clinical latency may occur between the primary and secondary stages, between secondary relapses, and after the secondary stage. The diagnosis of latent syphilis is made when an individual has (1) seroreactivity indicating infection with *T. pallidum*, (2) no past diagnosis of syphilis, and (3) no active manifestations of syphilis.[26] Latent syphilis is classified into early latent and late latent.[26,27] When evaluating an individual with latent syphilis, the health care provider should inquire about prior symptoms of primary or secondary syphilis, determine whether sexual contact occurred with a partner with primary or secondary syphilis within the past year, perform an examination to look for syphilis-related manifestations, and review all prior syphilis serologic test results.

- **Early Latent Syphilis (Infection of Less than 1 Year in Duration)**: Persons with latent syphilis are classified in the subcategory of early latent syphilis if they have no clinical signs or symptoms of syphilis and ANY of the following:[26]
  - A documented seroconversion within the prior 12 months
  - A sustained (longer than 2 weeks) fourfold or greater increase in the titer in the prior 12 months in a person previously treated for syphilis
  - Unequivocal symptoms of primary or secondary syphilis within the prior 12 months
  - Contact in the prior 12 months with a sex partner who had untreated primary, secondary, or early latent syphilis
  - Documented reactive nontreponemal and treponemal tests, and the only possible exposure occurred during the previous 12 months
- **Late Latent Syphilis (Infection Greater than 1 Year in Duration)**: Persons are considered to have late latent syphilis (or syphilis of unknown duration) if they meet ALL the following criteria:[26]
  - A reactive nontreponemal and treponemal test and no past diagnosis of syphilis
  - No clinical manifestations of syphilis
  - They do not meet criteria for early latent syphilis [Q] Classification of Latent Syphilis

Tertiary Syphilis

Tertiary syphilis is rare because of the widespread availability of antibiotics, enhanced screening for syphilis, and treatment for early syphilis. Without treatment, however, approximately 30% will progress to the tertiary stage at 2 to 50 years after the original infection.[1] Tertiary syphilis most often manifests as gummatous lesions and cardiovascular syphilis; late neurosyphilis, such as general paresis, tabes dorsalis, and psychiatric manifestations, are also often categorized as tertiary syphilis.[1] Otic and ocular syphilis are less common manifestations of tertiary syphilis.[1] Gummatous lesions are formed by a proliferative granulomatous process and can form in almost any tissue or organ.[1,15] The destructive lesions can clinically mimic carcinoma. Cardiovascular syphilis is indicated by pathologic lesions of the aortic vasa vasorum, can manifest as an ascending aortic aneurysm, aortic valve insufficiency, or coronary artery disease.[15]

Neurosyphilis

Neurosyphilis occurs when *T. pallidum* invades the central nervous system, and this may occur at any stage of syphilis; neurosyphilis is categorized as early neurosyphilis and late neurosyphilis.[2,28] Ocular and otic

involvement can occur with early or late infection.[1]

- **Early Neurosyphilis**: Cerebrospinal fluid (CSF) abnormalities can occur in 50 to 60% of persons with early syphilis and are of unknown significance in the absence of neurologic signs or symptoms.[29,30] The most common manifestation of early neurosyphilis is meningeal syphilis, which usually occurs weeks to months (and almost always within a year) after initial infection.[28] Symptomatic syphilitic meningitis often resembles aseptic meningitis, and symptoms may include fever, headache, and stiff neck; with basilar involvement, cranial nerve abnormalities can develop, particularly cranial nerves II, VI, and VIII.[28] Meningovascular syphilis typically develops 5 to 12 years after initial infection, but it can occur earlier. Meningovascular syphilis, which results from *T. pallidum* infection and inflammation of small and medium central nervous system blood vessels, most often manifests as a stroke-like syndrome with seizures.[31]
- **Late Neurosyphilis**: Late forms of neurosyphilis usually occur multiple years or even decades (typically at least 15 years) after infection.[1,28] In the modern era, this type of neurosyphilis is rarely seen. Clinical manifestations include general paresis and tabes dorsalis but can present with a wide variety of neurologic symptoms, including dementia.[2,28]

[Q] Manifestations of Neurosyphilis

Ocular Syphilis

Since *T. pallidum* can potentially infect any part of the eye, a broad range of symptoms and manifestations associated with ocular syphilis may occur with or without neurosyphilis.[32,33,34] Ocular syphilis can develop at any stage of syphilis and can cause acute or chronic symptoms.[33] Although ocular syphilis can involve virtually any region of the eye, the most common clinical presentation is uveitis—anterior, posterior, or panuveitis (Figure 17).[33,34] Other described manifestations include lid involvement, episcleritis, vitritis, papillitis, interstitial keratitis, retinitis, and optic neuritis.[33] The clinical presentation of ocular syphilis can have significant overlap with other infectious and noninfectious eye diseases. Persons with syphilis who have ocular complaints should have a complete cranial nerve evaluation and receive a referral to an ophthalmologist for an immediate evaluation.[26] In addition, if any cranial nerve abnormalities are present, a lumbar puncture should be performed with cerebrospinal fluid analysis to determine if concomitant neurosyphilis is present.[26]

Otosyphilis

Otic involvement from *T. pallidum* infection can occur at any stage of syphilis, and persons with otosyphilis usually present with hearing loss, tinnitus, or vertigo, or a combination of these manifestations.[35,36] The hearing loss with otosyphilis is typically sensorineural and can involve one or both ears.[35,36] Otosyphilis can develop with other syphilis manifestations, including neurosyphilis or ocular syphilis. Thus, individuals with suspected or diagnosed otosyphilis should undergo an initial screening evaluation for neurosyphilis and ocular syphilis.[36] Persons with a suspected diagnosis of otosyphilis should receive a referral for an immediate evaluation by an otolaryngologist.[26] Individuals with a positive serologic test for syphilis who have isolated auditory symptoms and a normal neurologic examination do not require lumbar puncture with cerebrospinal fluid examination.[26]

Congenital Syphilis

Congenital syphilis occurs when *T. pallidum* is transmitted from a pregnant woman with syphilis to her fetus.[14,17] Less often, perinatal transmission of *T. pallidum* can occur at the time of the delivery if the newborn has contact with maternal genital lesions.[14,17] Untreated syphilis during pregnancy may result in a wide range of outcomes, including infant death, stillbirth, birth of an infant with clinical signs or symptoms, and birth of infant with no documented signs or symptoms (Figure 18).[3,37,38] Transmission to the fetus in pregnancy can occur during any stage of syphilis, but the risk is much higher with primary or secondary

syphilis, especially if the mother acquires *T. pallidum* in the third trimester of pregnancy.[3] Fetal infection can occur during any trimester of pregnancy. Congenital syphilis is traditionally classified as either early or late disease.[16] Early manifestations occur within the first two years of life, and late manifestations occur after two years of age. Although infants with congenital syphilis most often display some early manifestations, some do not have clinical manifestations of active disease at the time of birth or early in life. Accordingly, regardless of symptoms, all neonates with a reactive serologic test for syphilis or who are at risk for congenital should undergo a thorough examination for signs or symptoms of congenital syphilis, as well as testing for HIV.[26]

- **Early Congenital Syphilis**: Early congenital syphilis is usually defined as manifestations of syphilis in infants and children younger than 2 years of age, with more common abnormalities that include the following:[17,39]
  - Rhinitis and nasal discharge
  - Hepatosplenomegaly
  - Jaundice
  - Bone involvement (osteochondritis, diaphyseal osteomyelitis, and periostitis)
  - Skin rash (begins as a maculopapular rash and may progress to form bullous or desquamating lesions)
  - Ophthalmic disorders (cataracts, glaucoma, interstitial keratitis, optic neuritis, chorioretinitis, and pigmentary chorioretinopathy)
  - Generalized lymphadenopathy
  - Hematologic abnormalities (anemia and thrombocytopenia)
  - Neurologic (pseudoparalysis of an extremity)
- **Late Congenital Syphilis**: Late congenital syphilis is generally defined as manifestations of syphilis in children older than 2 years of age, which typically result from scarring and chronic inflammatory changes from persistent infection and inflammation, and may manifest with one or more of the following disorders:[17,39,40]
  - Facial changes (frontal bossing due to periostitis, saddle deformity of the nose due to destruction of cartilage)
  - Perforation of the hard palate (Figure 19)
  - Abnormal tooth development (Hutchinson's teeth (Figure 20) and mulberry molars)
  - Bone abnormalities (shortened maxilla, tibial thickening [saber shins])
  - Ophthalmic disorders (interstitial keratitis, glaucoma, optic atrophy)
  - Deafness

Laboratory Diagnosis

The laboratory diagnosis of syphilis is challenging and requires using a combination of clinical and laboratory criteria to differentiate active infection, prior infection, and absence of infection.[41,42] Serologic testing remains the primary tool for diagnosis in most patients with syphilis, and these tests include nontreponemal and treponemal tests.[41,43,44] *Treponema pallidum* cannot be cultivated in artificial media, but the organism can be grown using special techniques that involve inoculation in rabbits. The following summarizes the different test types used for diagnosing syphilis. All persons diagnosed with syphilis should also have HIV testing.

Direct Detection of *Treponema pallidum*

Dark-Field Microscopy

Dark-field microscopy of lesion exudate or tissue is a definitive method for making an immediate diagnosis of primary or secondary syphilis.[26,41] *Treponema pallidum* cannot be viewed by normal light microscopy. Dark-field microscopy can identify *T. pallidum* with its spiral shape, a total length of 6 to 20 micrometers, and corkscrew motion (Figure 21).[45] Dark-field microscopy is infrequently used in clinical practice because most facilities do not have dark-field microscopy, and most clinicians do not know how to appropriately obtain specimens. The specificity of dark-field on oral specimens is extremely poor due to the abundant non-syphilitic oral *Treponema* species.

Polymerase Chain Reaction

Although polymerase chain reaction (PCR) testing is sometimes used for research purposes, there is no FDA-approved PCR test for syphilis at present.

Direct Fluorescent Antibody Test

The direct fluorescent antibody test can detect *T. pallidum* antigens in tissue samples. The test uses antibodies specific to pathogenic treponemes and can generally identify *T. pallidum* in samples—such as oral or rectal lesions—that may have background nonpathogenic spirochetes.[42]

Tissue Staining

Silver staining and immunohistochemical staining of tissue samples can demonstrate characteristic spirochetes on clinical biopsy specimens.[41]

Serologic Testing for Syphilis

Serologic testing for syphilis involves the use of two types of serologic tests—treponemal and nontreponemal.[43] Use of only one type of serologic test is insufficient for diagnosis since each test used alone has major limitations, including false-positive results in persons without syphilis and the inability for treponemal tests to distinguish between recent and distant infection.

Treponemal Serologic Tests

The treponemal serologic tests include various enzyme immunoassays (EIAs) and chemiluminescence immunoassays (CIAs), as well as the *T. pallidum* particle agglutination (TP-PA) and fluorescent treponemal antibody absorption (FTA-ABS) tests.[41] These tests measure antibodies directed against *T. pallidum* antigens by enzyme immunoassay immunofluorescence (Figure 22) or particle agglutination; most detect IgG only, whereas some detect both IgM and IgG. These qualitative tests most often remain reactive for life, even after adequate treatment, but 15 to 25% of persons treated during the primary stage of syphilis eventually revert to being serologically nonreactive with a treponemal serologic test.[46]

Nontreponemal Serologic Tests

The commonly used nontreponemal tests are the Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR) tests.[41] The nontreponemal tests, which measure antibodies directed against lipoidal antigens, such as cardiolipin and lecithin, are not specific for *T. pallidum*.[47] Positive test results are then reported as a quantitative titer, which typically correlates with disease activity.[26] A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary to demonstrate a clinically significant difference.[43] Titer comparisons should be performed at least 3 months apart. The nontreponemal tests are labor-intensive to perform, and biologic false-positive tests can occur from multiple causes, including pregnancy, autoimmune diseases, HIV, hepatitis C virus, other treponemal infections, and immunizations.[47] For monitoring persons with syphilis, sequential serologic tests should use the same testing method (VDRL or RPR) and preferably in the same laboratory. Further, when evaluating congenital syphilis, the neonate and mother should have the same type of nontreponemal test used for comparison. Several years after effective syphilis treatment, the nontreponemal tests usually become nonreactive (or persist at a very low titer).[43] In addition, some individuals with syphilis will have seroreversion to a negative syphilis test even without syphilis treatment.

Performance of Serologic Tests for Syphilis

The common patterns for serologic reactivity with syphilis tests depend on the specific test used, the stage of syphilis, and whether the person has received treatment for syphilis.[43,44,48] The sensitivity of serologic testing also varies based on the test used and the stage of syphilis (Table 1).[42,44] Serologic testing for syphilis has the highest yield for secondary syphilis. Serologic tests for syphilis may be negative during very early primary syphilis, especially with nontreponemal tests.[43,48] Thus, when serologic tests do not correspond with clinical findings suggestive of primary syphilis, presumptive treatment is recommended if the person has known risk factors for syphilis; in this setting, use of other tests, such as dark-field microscopy, biopsy, or PCR, should be considered.

- **False-Positive Reactions**: With both nontreponemal and treponemal serologic tests for syphilis, false-positive reactions can occur.[49] The most common causes of false-positive test results include older age, autoimmune disorders, cardiovascular disease, pregnancy, malaria, leprosy, other spirochete infections, and recent immunizations.[26,50]
- **False-Negative Reaction ("Prozone Effect")**: False-negative reactions infrequently occur with nontreponemal testing due to the "prozone effect."[51] The prozone effect occurs when very high serum antibodies supersaturate the antigens used in the nontreponemal assay, thereby interfering with the antigen-antibody lattice network needed to visualize a flocculation reaction.[51,52] Overall, this occurs in less than 2% of cases of syphilis.[51,53] This false-negative reaction is most likely to occur in patients with secondary syphilis and HIV infection. If clinical suspicion of secondary syphilis is high and the nontreponemal testing is negative, the clinician should alert the laboratory of a suspected prozone effect, and the laboratory should reevaluate the clinical sample after diluting the serum, typically a 1/16 dilution.[Q] Prozone Effect

Prior Serologic Testing for Syphilis

The health care professional should determine the date and results of the most recent serologic test for syphilis, even if the person under evaluation reports no history of the disease. Prior results, if available, are particularly helpful when evaluating an individual who has a low titer for a nontreponemal serologic test for syphilis, no signs or symptoms that suggest a clinical diagnosis of syphilis, and no known contact with an early case of syphilis. Local health departments may be able to provide information on whether the person has been reported as having had syphilis in the past, including reported serologic test results and treatment history.

Serologic Testing Algorithms

Given that treponemal and nontreponemal tests each have significant advantages and disadvantages, these lab tests are used together as part of a screening algorithm in order to maximize sensitivity and specificity for the detection of syphilis infection. Clinicians should be aware of their institution's chosen method for syphilis serologic testing. The two main serologic testing algorithms used by laboratories are traditional sequence screening and reverse sequence screening. The major advantages of using the reverse sequence algorithm, when compared with the traditional screening method, include improved detection of early primary and treated infection, lower cost of the initial screening test, and reduced laboratory time and effort with the initial screening test. The CDC, however, does not recommend one screening method over the other.

Traditional Screening Algorithm

The traditional syphilis screening algorithm uses initial screening with a nontreponemal test (VDRL or RPR), with further testing on a positive initial test using a treponemal test (TP-PA or EIA) (Figure 23).[14,26] Persons who have an initial negative nontreponemal test are considered unlikely to have syphilis, unless they have early syphilis from a recent exposure. Persons with a positive initial nontreponemal result require a treponemal test (usually TP-PA); if this treponemal test is positive, then a diagnosis is confirmed.[26] If the treponemal test is negative, then a diagnosis of syphilis is unlikely, and the positive nontreponemal test may represent a biologic false-positive test result.

Reverse Sequence Screening Algorithm

The reverse sequence screening algorithm uses a treponemal test (EIAs or CIAs) as the initial screening test (Figure 24).[54] A negative initial treponemal result essentially rules out the diagnosis of syphilis, except for persons with a very recent exposure to *T. pallidum*. A positive initial EIA or CIA test requires further testing with a quantitative nontreponemal test (e.g. RPR or VDRL).[26,54] If this nontreponemal test is positive and there is no history of prior treatment for syphilis, then a diagnosis of syphilis is confirmed, and treatment is indicated. With a positive initial treponemal test (EIA or CIA) and a negative nontreponemal test (RPR or VDRL), a second different treponemal test (TP-PA) should be performed.[26,54] If this second treponemal test is negative, then syphilis is unlikely. If, however, the sequence of tests is a positive treponemal test, a negative nontreponemal test, and a positive second treponemal test, then several possible scenarios exist: prior treated syphilis, early syphilis, untreated latent syphilis, or a false-positive test. In this situation, those with a prior history of syphilis treatment do not require further management unless there has been a known reexposure to syphilis after completing prior treatment. Those without a prior history of treatment should be offered treatment, typically for late latent syphilis, unless their history or examination indicates a recent exposure or other syphilis-related complications, such as neurologic involvement.[54]

Positive Titers in Persons Previously Treated for Syphilis

Although persons with early syphilis who are treated usually have a fourfold or greater decline in nontreponemal titers within 12 months after treatment, some fail to achieve seroreversion at month 12.[55] Persons previously treated for syphilis who had a documented adequate reduction in nontreponemal titer after treatment may have a persistent low-positive nontreponemal titer that does not significantly change; this is referred to as "lack of seroreversion" or "serofast state", and does not require additional therapy. Persons with prior treatment who have nontreponemal titers that are higher or unchanged (the titer did not decline 4-fold) from the pretreatment values are either treatment failures or have been reinfected with *T. pallidum*.

Laboratory Evaluation for Neurosyphilis

All persons with a positive serologic test for syphilis and any new neurologic signs or symptoms should have a lumbar puncture with cerebrospinal fluid (CSF) analysis.[26] Persons with ocular syphilis or otosyphilis do not require CSF examination, unless they have concomitant neurologic symptoms or signs.[26] In this situation, the laboratory diagnosis of neurosyphilis should take into account the CSF white blood cell count, CSF protein (in persons without HIV), and CSF VDRL.[26] An elevated CSF white blood cell count and elevated CSF

protein can support the diagnosis of neurosyphilis, but are not diagnostic, since these findings are common in persons with untreated primary and secondary syphilis, even without any neurologic abnormalities.[56] The CSF VDRL has high specificity, but the sensitivity is low; the CSF RPR is not recommended for evaluation of neurosyphilis.[26,28,57] The diagnosis of neurosyphilis is considered highly likely if a person has the following three findings: a positive serologic test, neurologic clinical manifestations, and a positive CSF VDRL (in the absence of blood contamination of the CSF). Because of the low sensitivity of CSF VDRL, when this test is negative and a person has suspected neurosyphilis, additional testing should occur with a CSF treponemal test (FTA-ABS).[56,58] Persons who have a negative CSF FTA-ABS (or TP-PA) are highly unlikely to have neurosyphilis.[26] In addition, CSF protein is not used for diagnosing neurosyphilis in persons with HIV.

Diagnosis of Syphilis in Persons with HIV

In general, the clinical course and diagnostic evaluation of syphilis in persons with HIV is similar to that in persons without HIV.[26] Although not common, unusual serologic responses among persons with HIV can occur. If the clinical suspicion of syphilis is high and the serologic tests for syphilis are negative, then use of other tests (e.g. biopsy of the lesion or rash) should be considered. Conventional therapy is usually effective. Several studies have shown that CSF abnormalities (mononuclear pleocytosis and elevated protein) are more common in persons with HIV who have a CD4 count of 350 cells/mm^3 or less and/or a nontreponemal serologic test titer of greater than or equal to 1:32.[26] For persons with HIV, a lumbar puncture with CSF examination should be reserved for those with neurologic manifestations.[26] Since persons with HIV may have slight elevations in CSF white blood cell counts at baseline, some experts suggest using a higher cutoff (white blood cell count greater than 20 cells/mm^3) to improve the specificity of this test as a component of the neurosyphilis diagnosis.[56]

Diagnosis of Syphilis in Infants and Children

The diagnosis of congenital syphilis is often difficult since maternal nontreponemal and treponemal IgG antibodies can be transferred through the placenta to the fetus; the treponemal antibodies can persist for 15 months or longer.[26] Evaluation and treatment of congenital syphilis is complex and should ideally include expert consultation. The decision to treat a neonate (aged fewer than 30 days) is based on (1) identification of syphilis in the mother; (2) adequacy of maternal treatment; (3) clinical, laboratory, and radiographic evidence of disease in the neonate; and (4) comparison of maternal and neonatal nontreponemal serologic titers.[26] Based on the evaluation and test results, neonates are classified as:[26]

- Proven or highly probable congenital syphilis, *or*
- Possible congenital syphilis, *or*
- Congenital syphilis less likely, *or*
- Congenital syphilis is unlikely.

Reporting Requirements

Laws and regulations in all states require clinicians, laboratories, or both to report persons diagnosed with syphilis (including congenital syphilis) to local public health authorities. Reporting can be done by medical providers, laboratories, or both.

Screening for Syphilis

In the United States, the main recommendations for syphilis screening are from the 2021 STI Treatment Guidelines and the 2016 US Preventive Services Task Force (USPSTF) Recommendation Statement on Screening for Syphilis Infection in Nonpregnant Adults and Adolescents.[5,26] These recommendations both identify MSM and persons with HIV as high priority groups for routine syphilis screening.[5,59,60] The following summarizes the most recent syphilis screening recommendations in the 2021 STI Treatment Guidelines.[26,60]

Men and Nonpregnant Women [60]

- Routine syphilis screening is not recommended for (1) men who have sex with women, (2) nonpregnant women who have sex with men, and (3) nonpregnant women who have sex with women.
- For these groups, syphilis screening may be indicated if the individual has increased risk for acquiring syphilis (e.g. history of incarceration, sex in exchange for money or drug, or other epidemiologic factors that may be associated with increased risk).

Men Who Have Sex with Men [60,61]

- For sexually active MSM, perform syphilis screening at least annually.
- More frequent screening (every 3 to 6 months) is recommended for MSM who have an ongoing increased risk for acquiring syphilis (e.g. multiple partners, anonymous partners, and concurrent partners).

Pregnant Women [60,62]

- Syphilis serologic testing should be performed for all pregnant women at their first prenatal visit.
- Syphilis retesting should occur at 28 weeks of gestation and at delivery for women who live in a community with a high syphilis rate and for women considered to have a high risk of acquiring syphilis during the pregnancy (e.g. sex with multiple partners, sex in conjunction with drug use, sex in exchange for money or drugs, late entry to prenatal care, methamphetamine or heroin use, incarceration of the woman or her partner, and unstable housing or homelessness).
- Any woman who delivers a stillborn infant after 20 weeks of gestation should have syphilis serologic testing.
- Screening for syphilis should occur during each pregnancy.

Persons with HIV [60]

- Sexually active persons with HIV should have syphilis serologic screening at their first visit for HIV care and then at least annually thereafter.
- Persons with HIV who have higher risk for acquisition of syphilis should have more frequent screening (every 3 to 6 months).

Transgender and Gender Diverse People [60,63]

- Consider screening at least once a year based on the reported sex activity and relative risk for acquiring syphilis.

Correctional Facilities [64]

- Routine opt-out screening for syphilis in correctional facilities should be performed based on the local area and institutional prevalence of early (primary, secondary, and early latent) infectious syphilis. Correctional facilities should stay apprised of syphilis prevalence as it changes over time.

[Q] Screening for Syphilis

Treatment

General Considerations

Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis.[26] The preparation(s) of penicillin used (e.g. benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of the disease. Benzathine penicillin G is slowly released from the intramuscular site due to extremely low solubility and is also hydrolyzed to penicillin G; the combination of slow absorption and hydrolysis results in prolonged low serum levels of penicillin with this preparation. Benzathine-procaine penicillin coformulations and oral penicillin preparations are not appropriate for the treatment of syphilis.[26] Reports have identified the inappropriate use of benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin G (Bicillin L-A) product.[65]

Treatment of Primary and Secondary Syphilis in Adults

Parenteral penicillin G is effective in resolving clinical symptoms associated with primary and secondary syphilis and prevents late sequelae in those who receive appropriate treatment. The recommended regimen for adults with primary and secondary syphilis is benzathine penicillin G given as 2.4 million units once as a single intramuscular dose (Table 2).[26]

Treatment of Primary or Secondary Syphilis with Penicillin Allergy

For persons who report a penicillin allergy, it is important to determine the severity of the reaction, if the reaction was consistent with an IgE-mediated reaction, and whether the reaction occurred within the prior 10 years. Among all persons who self-report a history of an allergic reaction to penicillin or another beta-lactam antibiotic, only 7.1% had a positive objective test that confirmed the penicillin allergy.[66] In addition, approximately 80% of persons with a true IgE-mediated allergic reaction to penicillin will lose sensitivity to penicillin after 10 years.[67] The optimal treatment of primary and secondary syphilis in persons with a true documented allergy to penicillin is unknown due to limited available data. The following summarizes alternative regimens to consider for persons allergic to penicillin; individuals receiving one of these alternative regimens should have close follow-up after treatment.[26]

- **Doxycycline and Tetracyclin**e: Small studies and clinical experience suggest that oral regimens of doxycycline (100 mg twice daily for 14 days) or tetracycline (500 mg four times daily for 14 days) can be an effective alternative for nonpregnant, penicillin-allergic persons who have primary or secondary syphilis.[68,69] Doxycycline is preferable to tetracycline because of its less frequent dosing and fewer gastrointestinal side effects.
- **Ceftriaxone**: Intramuscular or intravenous ceftriaxone (1 gram daily for 10 days) is considered an effective alternative for treating primary and secondary syphilis in penicillin-allergic persons, but the optimal dose and duration of ceftriaxone in this setting has not been well studied.[70] Note that among persons with a history of penicillin allergy, fewer than 1.0% will have an allergic reaction to a third-generation cephalosporin, such as ceftriaxone.[71]
- **Azithromycin**: Several reports have shown that a single 2-gram oral dose of azithromycin has been effective for treating primary and secondary syphilis, but due to concerns about emerging macrolide resistance and documented treatment failures, azithromycin is not recommended for the treatment of syphilis, even in persons with a penicillin allergy.[72,73]
- **Penicillin Desensitization**: Persons with a penicillin allergy for whom concern exists about adherence or follow-up should undergo penicillin desensitization and then receive treatment with benzathine penicillin G.[Q] Treatment of Secondary Syphilis

Treatment of Latent Syphilis in Adults

The treatment of individuals with latent syphilis requires appropriate classification into early latent syphilis (acquired less than 1 year ago as detailed above) or late latent syphilis (acquired longer than 1 year ago). The main goal of treating persons with latent syphilis is to prevent the development of late syphilis manifestations. Early latent syphilis is treated with intramuscular benzathine penicillin G 2.4 million units given as a single dose; late latent syphilis is treated with intramuscular benzathine penicillin G 7.2 million units total, which is split into three weekly doses, each with 2.4 million units (Table 3).[26] Alternative therapies for treatment of latent syphilis have not been well studied.

Treatment of Latent Syphilis in Persons Allergic to Penicillin

For penicillin-allergic, nonpregnant persons with early latent syphilis, the treatment approach should be the same as penicillin-allergic persons with primary or secondary syphilis. For penicillin-allergic individuals with late latent syphilis, the only acceptable treatment alternatives are a 28-day course of oral therapy with either doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily).[26] Ceftriaxone may be a reasonable option in this setting, but the optimal number of doses or schedule has not been determined, and use of ceftriaxone to treat latent syphilis should involve consultation with a specialist.[26] All persons treated with an alternative regimen should have close serologic and clinical follow-up, especially individuals with HIV. Persons for whom adherence and follow-up are a concern should ideally undergo penicillin desensitization and receive treatment with benzathine penicillin G.[26]

Treatment of Tertiary Syphilis in Adults

The recommended regimen for tertiary syphilis (without evidence of neurosyphilis) is benzathine penicillin G 7.2 million units total divided into three weekly intramuscular injections of 2.4 million units with each dose (Table 4).[26] All persons diagnosed with tertiary syphilis should undergo a CSF examination prior to starting therapy due to the high rates of neurosyphilis that is not clinically apparent.[26] Some experts treat tertiary cardiovascular syphilis with a neurosyphilis regimen, regardless of the CSF results.[26]

Treatment of Tertiary Syphilis in Persons Allergic to Penicillin

Persons diagnosed with tertiary syphilis who have a documented penicillin allergy also should be treated in consultation with an expert; for these individuals, there is inadequate data for any alternative regimens.[26]

Treatment of Neurosyphilis, Ocular Syphilis, and Otosyphilis in adults

The recommended treatment regimen for neurosyphilis, ocular syphilis, and otosyphilis is aqueous crystalline penicillin G 18-24 million units per day, given as 3-4 million units intravenously every 4 hours (or as continuous infusion), for a total of 10 to 14 days (Table 5).[26] If adherence to therapy can be ensured, an acceptable alternative is a 10- to 14-day course of intramuscular procaine penicillin G 2.4 million units once daily plus probenecid 500 mg orally four times a day.[26] Some experts recommend giving additional therapy with intramuscular benzathine penicillin G 2.4 million units once per week for up to 3 weeks—starting after the completion of the 10- to 14-day regimen—to provide a total duration of therapy comparable to the treatment for late latent syphilis; although this approach is often used, data are lacking to support this enhanced treatment regimen.[26] In addition, there is insufficient data to support the use of systemic corticosteroids as adjunctive therapy for neurosyphilis, ocular syphilis, or otosyphilis.

Treatment of Neurosyphilis in Persons Allergic to Penicillin

Limited data suggest that intramuscular or intravenous ceftriaxone 1-2 grams daily for 10 to 14 days can be used as an alternative treatment for persons with neurosyphilis who are allergic to penicillin.[26,74] Other regimens have not been adequately studied for use in persons with neurosyphilis.[Q] Treatment of Neurosyphilis

Treatment of Syphilis in Adults with HIV

The recommended treatment of all stages of syphilis (primary, secondary, latent, or tertiary) and neurosyphilis in persons with HIV is the same as for persons without HIV (Table 6).[26] Available data suggest that persons with HIV may have an increased risk of developing neurologic complications and may have higher rates of treatment failure (based on inadequate serologic response).[26,75] All persons with HIV who are diagnosed with syphilis should undergo careful neurologic, ocular, and otic examination, and those with abnormal findings should promptly undergo lumbar puncture for CSF examination.[26] Initiation of antiretroviral therapy for HIV concurrently with syphilis treatment may improve clinical response to syphilis treatment.[76]

Delays in Treatment Doses

For persons scheduled to receive a weekly 3-dose benzathine penicillin G treatment regimen, unplanned delays can occur between the scheduled weekly doses. When these delays occur, the optimal management is not clear. Although the pharmacokinetic profile of benzathine penicillin G suggests an interval of 7 to 9 days between doses is optimal and preferred, clinical experience suggests that an interval of 10 to 14 days between doses for the treatment of late latent syphilis (or latent syphilis with unknown duration) might be acceptable.[21] For nonpregnant persons, an interval greater than 10 to 14 days warrants restarting therapy. For pregnant women, if an interval between penicillin doses exceeds 9 days, the 3-dose benzathine penicillin G treatment regimen should start over.[26,77]

Treatment of Syphilis in Pregnancy

All pregnant persons diagnosed with syphilis should receive treatment according to stage of infection and whether there is any evidence of neurologic disease. Treatment of pregnant women is a very high priority to minimize the risk of maternal transplacental transmission of *T. pallidum*. All pregnant persons with a diagnosis of syphilis should receive treatment with penicillin, with the exact regimen based on the state of disease and whether neurologic involvement is present. There are no recommended alternative regimens for the treatment of pregnant women with syphilis.[26] Accordingly, pregnant women with syphilis who have an allergy to penicillin should undergo desensitization and receive treatment with penicillin.[26] Some experts recommend giving a second dose of intramuscular benzathine penicillin G 2.4 million units 1 week after the initial dose for pregnant women who have primary, secondary, or early latent infection. Treatment of the mother during the last month of pregnancy or with a drug other than penicillin is not considered adequate treatment for the fetus. Pregnant women should be informed that treatment for syphilis may precipitate early labor and that they should notify an obstetrician if problems develop.

Treatment of Neonates and Infants and Children with Syphilis

The approach to treating congenital syphilis depends on whether the child is younger than 1 month of age (neonate) or ≥1 month of age (infants and children).[26] The evaluation and treatment of congenital syphilis is complex and should include a syphilis expert.

- **Treatment of Neonates**: The treatment recommendations and options for congenital syphilis in neonates vary based on the certainty of the diagnosis: (1) confirmed or highly probable, (2) possible, (3) less likely, or (4) unlikely (Table 7).[26] The recommended regimens for confirmed or highly probable congenital syphilis are aqueous crystalline penicillin G 100,000–150,000 units/kg body weight per day, administered as 50,000 units/kg body weight per dose by IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days; or intramuscular procaine penicillin G 50,000 units/kg body weight per dose in a single daily dose for 10 days.[26] Neonates classified as possible congenital syphilis have the additional option of receiving treatment with intramuscular benzathine penicillin G 50,000 units/kg body weight in a single dose if all laboratory studies are normal and follow-up is assured. For neonates classified as congenital syphilis less likely,

intramuscular benzathine penicillin G 50,000 units/kg body weight in a single dose is the recommended treatment.
- **Treatment of Infants and Children**: The recommended treatment for congenital syphilis in infants or children who are at least 1 month of age is aqueous crystalline penicillin G 200,000–300,000 units/kg body weight per day, administered as 50,000 units/kg body weight by IV every 4–6 hours for 10 days (Table 8).[26]

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is a self-limited reaction associated with initiation of antitreponemal therapy. This reaction represents a systemic inflammatory response following the antimicrobial treatment of *T. pallidum*—it is not an allergic reaction to penicillin. The Jarisch-Herxheimer reaction most often involves persons treated for early syphilis, particularly secondary syphilis, presumably because of the higher bacterial burden during the early stages.[26] When this reaction occurs, it typically begins within several hours after initiation of antimicrobial treatment and nearly always by 24 hours. The Jarisch-Herxheimer reaction is characterized by fever, malaise, nausea, vomiting, and, less frequently, chills, hypotension, or an exacerbation of a secondary syphilis rash.[78] This reaction can be mistaken as an allergic reaction to penicillin. Accordingly, it is important to carefully evaluate any reaction that begins within 24 hours after treatment of syphilis and carefully sort out the likelihood of a Jarisch-Herxheimer reaction versus an allergic reaction to penicillin. The management of Jarisch-Herxheimer is supportive care, primarily with fluids and antipyretics; typically, the reaction resolves spontaneously within 24 hours.[15]

Post-Treatment Follow Up

Post-Treatment Follow-Up Testing

The follow-up of persons with syphilis is extremely important to document response to therapy and to reevaluate for reinfection. The following are general recommendations for follow-up after syphilis treatment.[26]

- **Primary and Secondary Syphilis**: Persons without HIV who are treated for primary or secondary syphilis should be reexamined clinically and serologically 6 months and 12 months following treatment. Clinicians should allow for a full 12 months of follow-up to determine if the titers have declined appropriately (at least 4-fold decrease) in persons treated for primary or secondary syphilis. Individuals with HIV should have post-treatment follow-up for primary or secondary syphilis at 3, 6, 9, 12, and 24 months; since treatment response may be delayed in persons with HIV, a full 24 months of follow-up should be allowed for the response.
- **Latent Syphilis**: Persons without HIV who are treated for latent syphilis should have clinical and nontreponemal serologic follow-up at 6, 12, and 24 months. For persons with HIV, this follow-up should occur at 6, 12, 18, and 24 months. Clinicians should allow for a full 24 months of follow-up to determine if the titers have declined appropriately (at least a 4-fold decrease) in persons treated for latent syphilis.
- **Neurosyphilis, Ocular Syphilis, and Otosyphilis**: Available data suggest that for immunocompetent persons without HIV (and persons with HIV on antiretroviral therapy), a normalization of the RPR titers following syphilis treatment correlates with normalization of abnormal CSF parameters.[79,80] Accordingly, persons treated for neurosyphilis who have good clinical and nontreponemal serologic responses do not require follow-up lumbar puncture and CSF evaluation. The serologic nontreponemal titer follow-up for persons treated for neurosyphilis, ocular syphilis, and otosyphilis should be based on their stage of syphilis and their HIV status. For example, if a person without HIV is concomitantly diagnosed with secondary syphilis and neurosyphilis, their follow-up should be the same as for persons with primary or secondary syphilis—serologic testing at 6 and 12 months following treatment, allowing for a full 12 months of follow-up to determine if the titers have declined appropriately.

Follow-Up Management

A key reason for close follow-up of persons treated for syphilis is to monitor signs, symptoms, or serologic changes in nontreponemal titers that indicate possible treatment failure or reinfection. Changes in nontreponemal titers are described as a quantitative fold increase (Figure 25) or quantitative fold decrease (Figure 26), based on the comparison of baseline and follow-up nontreponemal titers. In general, the goal is to achieve a 4-fold or greater decline in nontreponemal titer and this is often referred to as having an "adequate serologic response" or "serologic cure". In contrast, the failure to achieve a 4-fold or greater decline in the nontreponemal titer within an appropriate timeframe after treatment is termed "inadequate serologic response" or "lack of serologic response" or "serologic nonresponse".[26,81] Several factors have been identified with a lack of 4-fold decline in nontreponemal titers, including a lower pretreatment titer (e.g. less than 1:8), older age, and later stage of syphilis; a prior history of syphilis treatment is associated with a slower decline in titers.[81,82] The term "serofast" has also been used to describe any persistent nontreponemal titer after treatment, including inadequate serologic response and persistently positive nontreponemal titers despite an appropriate 4-fold decline in titers.[83,84] The following summarizes the recommended evaluation and management of several post-treatment scenarios.[26]

- **Probable Reinfection or Treatment Failure**: Reinfection or treatment failure is likely if any of the following occur: (1) an individual has signs or symptoms that persist or recur, (2) the person experiences new signs or symptoms attributable to primary or secondary syphilis, or (3) repeated serologic testing shows a sustained 4-fold (or greater) increase in nontreponemal titer that persists for

longer than 2 weeks. In any of these situations, HIV testing should be performed, unless the person is known to have HIV. Evaluation for neurosyphilis with lumbar puncture and CSF evaluation is recommended if new neurologic manifestations are present or there are no recent sexual exposures (in the prior 6 months in persons treated for primary or secondary syphilis and the prior 12 months for person treated for latent and other stages of syphilis); treatment is then guided based on the CSF evaluation. In a sexually active person who does not have new neurologic manifestations, or a person in whom the CSF evaluation has ruled out neurosyphilis, retreatment is recommended and should consist of one dose of intramuscular benzathine penicillin G 2.4 million units for those previously diagnosed with primary or secondary syphilis and all others should receive retreatment with three doses of intramuscular benzathine penicillin G 2.4 million units given weekly for 3 weeks.

- **Inadequate Serologic Response**: For persons who fail to achieve at least a post-treatment 4-fold decline in nontreponemal titers within the recommended time frame (12 months for primary or secondary syphilis, 24 months for latent syphilis, and 24 months for any stage of syphilis in persons with HIV), the optimal management is unknown. The evaluation of persons with inadequate serologic response should include, at a minimum, HIV testing, neurologic examination, and a yearly clinical follow-up that includes repeated syphilis serologic studies. Syphilis retreatment is recommended when follow-up cannot be ensured or the person had an initial high titer (greater than 1:32) that did not decrease at least 4-fold in the expected time period; the recommended retreatment regimen is weekly intramuscular injections of benzathine penicillin G 2.4 million units for 3 weeks. In this setting, however, several observational studies did not show short-term or intermediate-term benefit when giving additional antibiotics versus continued monitoring without giving antibiotics, and syphilis nontreponemal titers often fail to decline after retreatment.[83,85] If at any point the person has neurologic signs or symptoms, then analysis of CSF should be performed with treatment guided by the CSF results; some experts would consider performing CSF analysis if a fourfold decline was not achieved in the 12-month post-treatment period, even without neurologic signs or symptoms.
- **Lack of Seroreversion**: Some individuals will achieve a 4-fold or greater decline in the nontreponemal titer after treatment, but have persistently reactive nontreponemal titers; this situation is usually referred to as "lack of seroreversion".[81,86] There is increasing evidence that providing additional antibiotics in these individuals does not change outcomes.[84,85] Therefore, in the absence of clinical evidence for reinfection or new neurologic manifestations, most experts would not recommend retreatment in this setting.

Management of Sex Partners

Evaluation and Treatment of Sex Partners

In general, the transmission of *T. pallidum* between sex partners only occurs when the person with syphilis has mucocutaneous lesions. In general, all persons who have sexual contact with a person diagnosed with primary, secondary, or early latent syphilis infection should undergo evaluation, testing, and treatment for syphilis, as outlined below.[26]

- For persons diagnosed with primary, secondary, or early latent syphilis, all of their sex partners in the 90 days preceding the syphilis diagnosis should be notified, undergo clinical evaluation, have syphilis serologic studies obtained, and receive presumptive treatment for early syphilis, even if serologic test results are negative.
- For persons who had sexual contact with an individual diagnosed with syphilis diagnosed with primary, secondary, or early latent syphilis, but the contact occurred more than 90 days before the syphilis diagnosis, should be notified and undergo clinical evaluation and syphilis serologic testing. The sex partner should be treated presumptively for early syphilis if serologic test results are not immediately available and follow-up is uncertain. Alternatively, if follow-up is reliable, treatment can be based on syphilis serologic test results; for persons with negative serologic tests, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis.
- In some areas or populations with high rates of syphilis, health departments recommend notification and presumptive treatment of sex partners of persons with late latent syphilis who have high nontreponemal serologic test titers (i.e. greater than 1:32) because high titers might be indicative of early syphilis. These partners should be managed as if the index case had early syphilis.
- Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated based on these findings.
- Certain sex partners of persons with syphilis are considered at risk for infection and should be confidentially notified of the exposure and the need for evaluation. These include partners who have had sexual contact within 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis, within 6 months plus duration of symptoms for those with secondary syphilis, and within 1 year for persons with early latent syphilis. For example, if a person had symptoms of secondary syphilis for 1 month, then any sex partner in the prior 4 months should be considered at risk for syphilis and undergo evaluation and treatment.

Expedited Partner Therapy

Expedited partner therapy is not recommended for sexual contacts of persons diagnosed with syphilis.

Counseling and Education

The following summarizes key counseling messages for persons diagnosed with syphilis.

- **Resuming Sexual Activity**: Persons treated for syphilis infection should be informed they can transmit syphilis to others during the primary and secondary stages of syphilis (when mucosal lesions or rashes are present). They should abstain from sexual activity until the following criteria are met: (1) at least 7 days have elapsed since completing syphilis treatment, (2) all mucosal and skin lesions have resolved, and (3) sex partners have been treated for syphilis.
- **Partner Notification**: It is extremely important that persons treated for syphilis understand the importance of partner notification (for all sex partners in the prior 90 days). Partner notification with evaluation and treatment can markedly reduce the spread of STIs in the community, and it also reduces the likelihood of reinfection for the person diagnosed with syphilis.
- **Follow-Up Testing**: It is important that all persons treated for syphilis have follow-up visits for clinical evaluation and serial nontreponemal serologic testing to evaluate response to syphilis treatment.
- **STI Prevention**: At the time a person is receiving treatment for an STI, it is appropriate to provide counseling messages on how to prevent STIs in the future (e.g. limiting the number of sex partners and consistently using condoms).
- **HIV Preexposure Prophylaxis**: Men who have sex with men who are diagnosed with syphilis have a substantial risk for acquiring HIV and therefore should be offered HIV preexposure prophylaxis (PrEP). All other persons diagnosed with syphilis should be evaluated for potential HIV preexposure prophylaxis on a case-by-case basis.

Summary Points

- In the United States, reported cases of syphilis, including congenital syphilis, have steadily increased in recent years. Epidemiologic features associated with increased reported rates of syphilis include male sex, age 25-34 years, MSM, persons with HIV, and persons who are Black.
- Syphilis is a systemic infection caused by *Treponema pallidum*, and in the absence of treatment, this disease can progress in stages. Untreated syphilis is characterized by episodes of active clinical manifestations interrupted by periods of asymptomatic latent infection. Neurosyphilis, ocular syphilis, and otosyphilis can occur during any stage of infection.
- Untreated syphilis in pregnancy can lead to devastating consequences, including stillbirth, neonatal death, and congenital syphilis.
- The laboratory diagnosis of syphilis is challenging and requires using a combination of clinical criteria and laboratory tests (both treponemal and nontreponemal tests) to differentiate active infection, prior infection, and absence of infection.
- The serologic diagnosis of syphilis employs two major algorithms: (1) the traditional screening method that uses a nontreponemal assay as the initial test, or (2) a reverse sequence screening method that uses a treponemal antibody test as the initial test.
- Screening for syphilis is recommended in all pregnant women, men who have sex with men, persons with HIV, and other groups at increased risk for acquisition of syphilis.
- Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis and is effective in resolving clinical symptoms associated with primary and secondary syphilis, as well as preventing late sequelae. The dosing of penicillin depends on the stage of disease; neurologic, ocular, and otosyphilis require more intensive therapy.
- The Jarisch-Herxheimer reaction is a self-limited reaction that can occur after initiation of anti-treponemal therapy; it is characterized by fever, malaise, nausea, vomiting, chills, and exacerbation of a secondary syphilis rash.
- For a person diagnosed with primary, secondary, or early latent syphilis, all of their sex partners within the prior 90 days should undergo evaluation and treatment of syphilis; if no sexual contacts occurred in the 90 days prior to the diagnosis, then the most recent sex partner should have evaluation and presumptive treatment.
- All persons treated for syphilis should have follow-up monitoring with nontreponemal testing to evaluate response to treatment.

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Figures

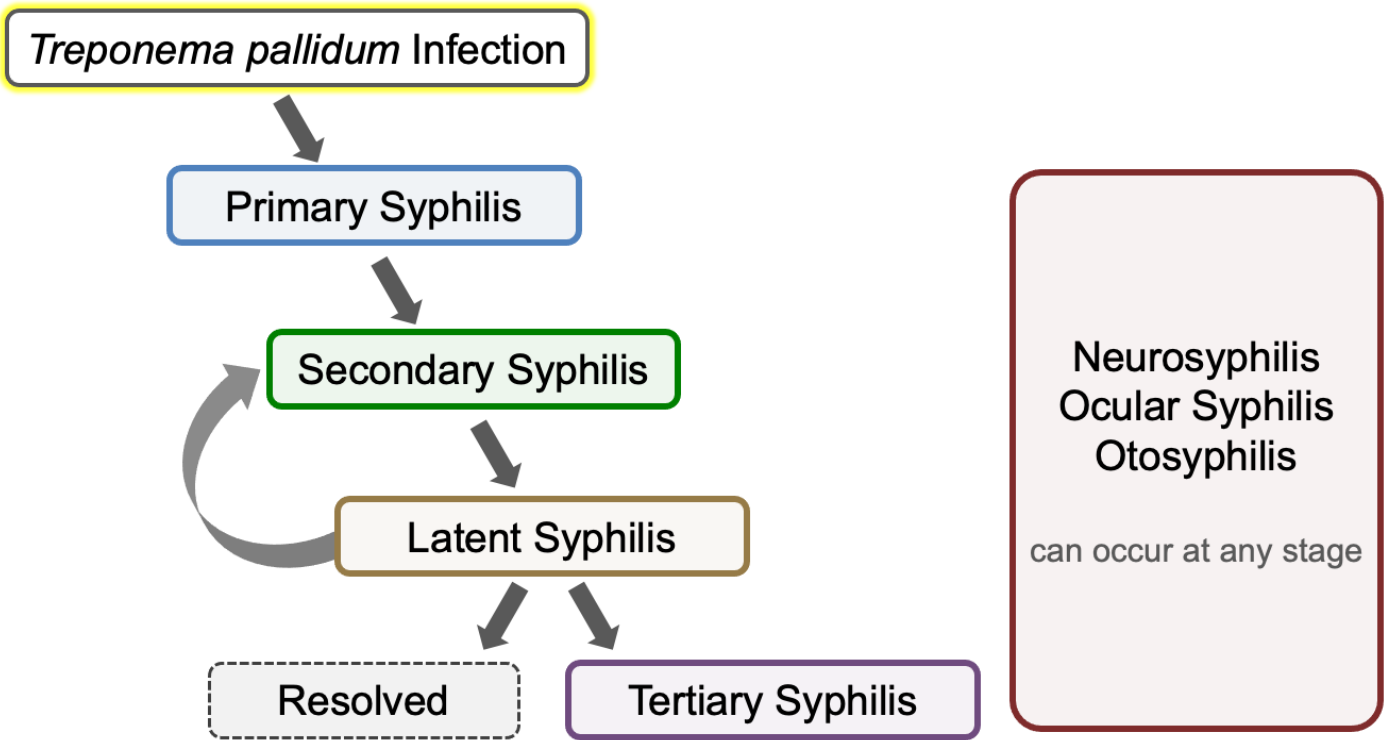**Figure 1 Natural History and Clinical Staging of Syphilis**

Figure 2 Syphilis Cases, United States, 1941-2020

NOTE: Data collection for syphilis began in 1941; however, syphilis became nationally notifiable in 1944. This graphic shows the number of reported cases of syphilis for all stages, primary and secondary, and early non-primary non-secondary.

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2020*. Syphilis. Atlanta: U.S. Department of Health and Human Services; April 2022.
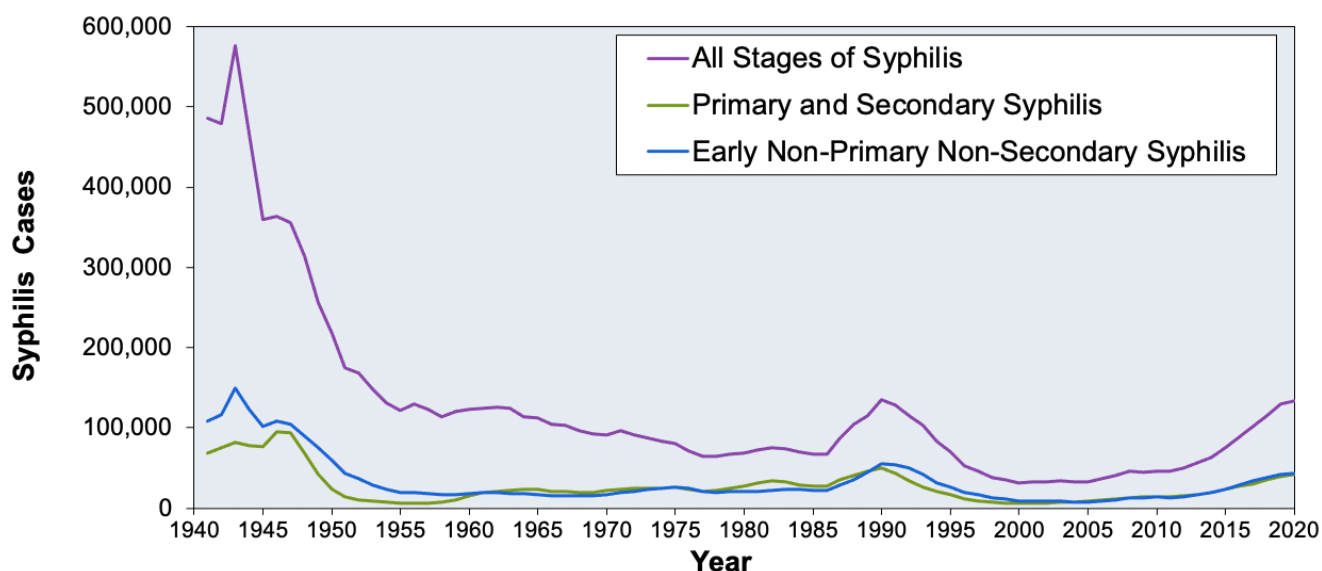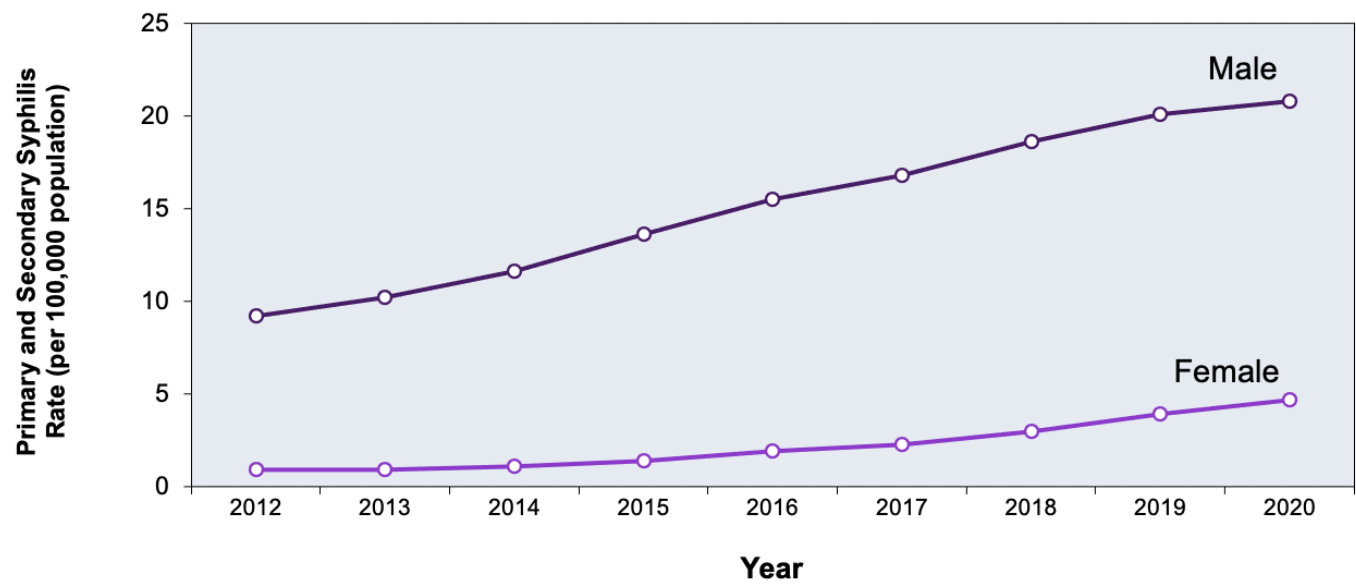
Figure 3 Syphilis Cases, All Stages of Infection, United States, 2000-2020

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2020*. Syphilis. Atlanta: U.S. Department of Health and Human Services; April 2022.
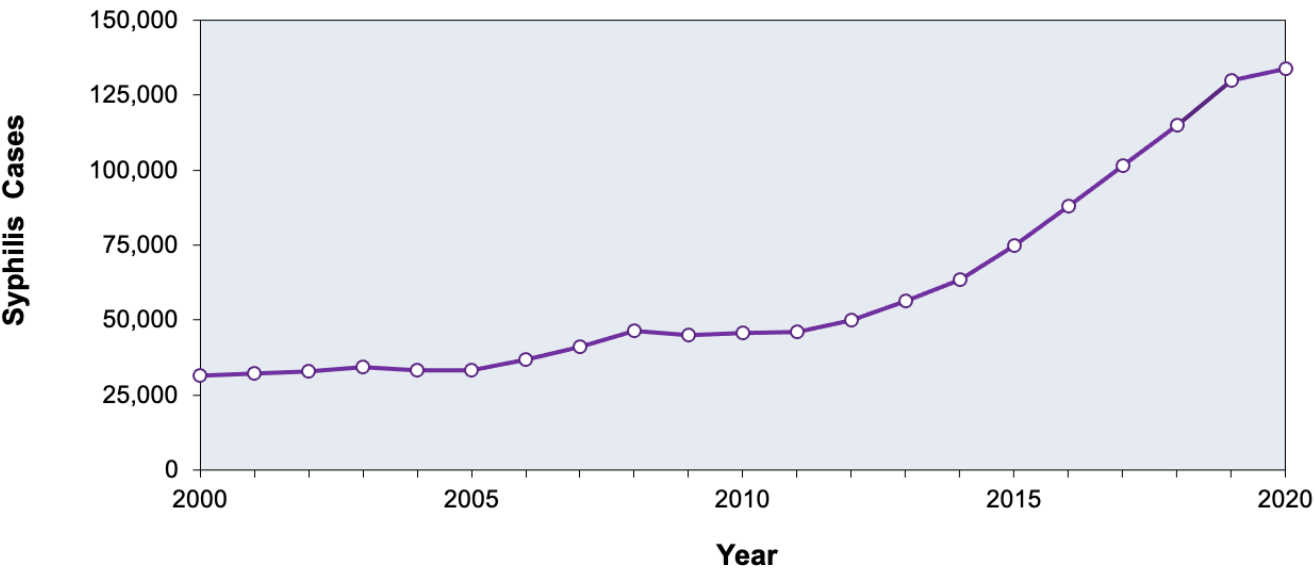
Figure 4 Primary and Secondary Syphilis—Rates by Sex, United States, 2012-2020

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2020*. Syphilis. Atlanta: U.S. Department of Health and Human Services; April 2022.
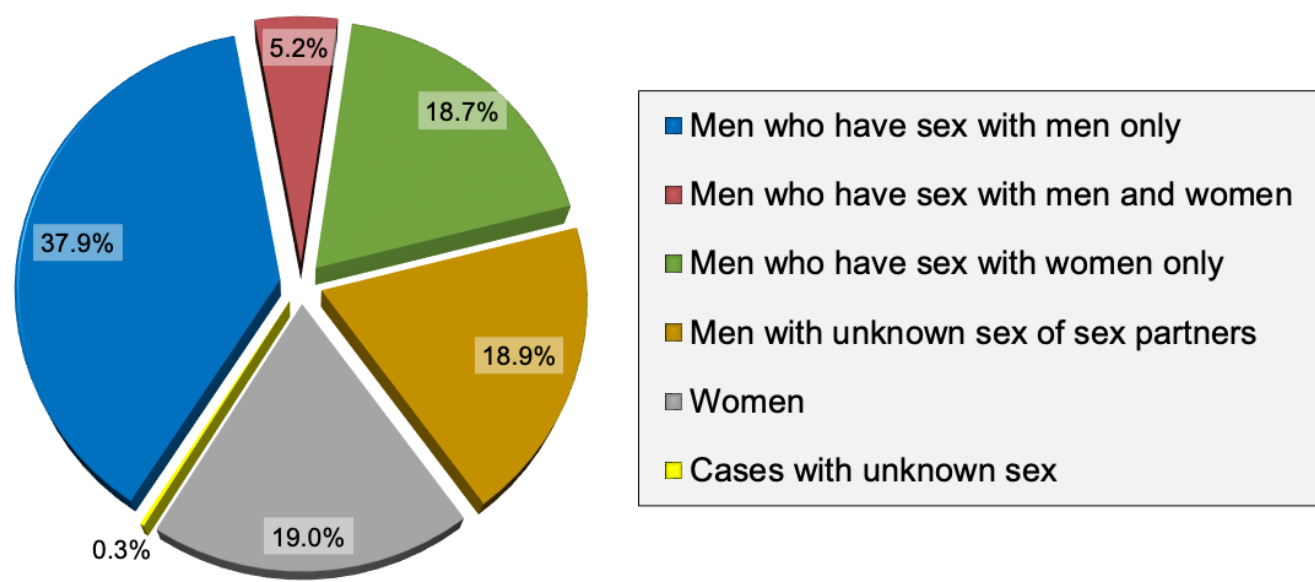
Figure 5 Primary and Secondary Syphilis—Distribution of Cases by Sex and Sex of Sex Partners, United States, 2020

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2020*. Syphilis. Atlanta: U.S. Department of Health and Human Services; April 2022.
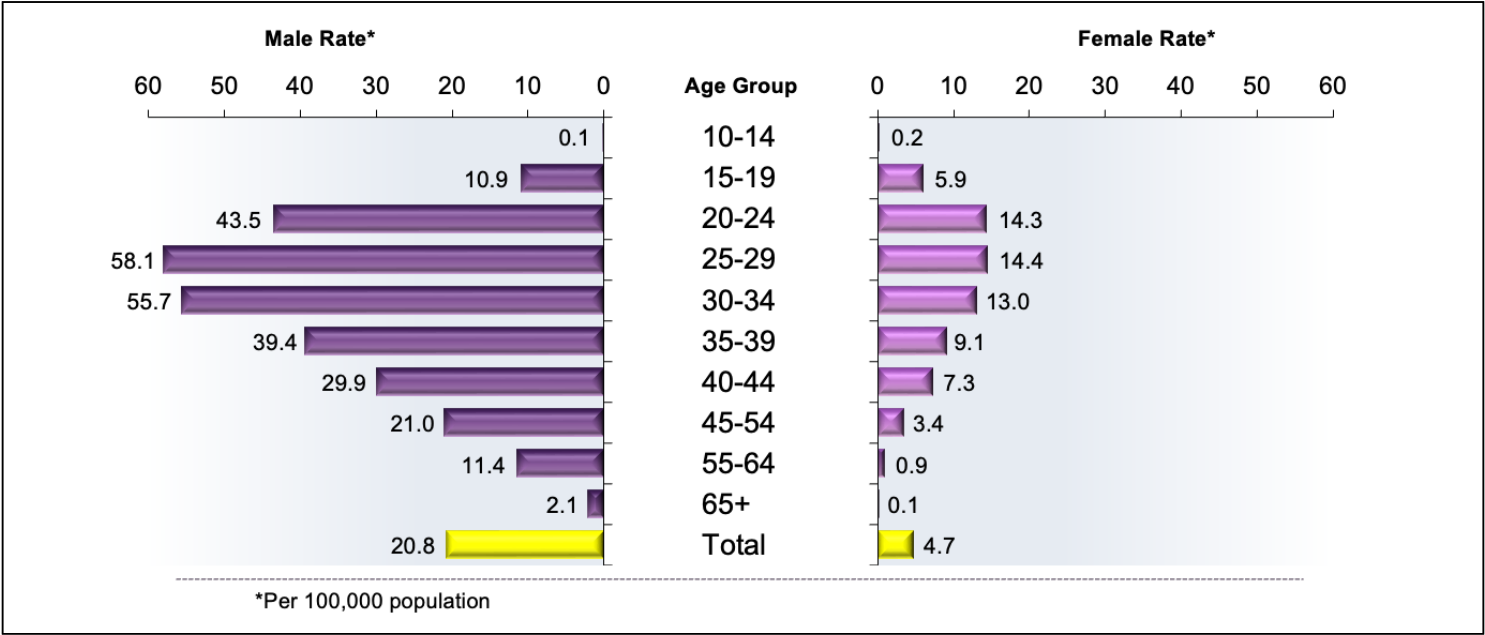
Figure 6 Primary and Secondary Syphilis—Rates by Age and Sex, United States, 2020

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2020*. Syphilis. Atlanta: U.S. Department of Health and Human Services; April 2022.

Male Rate*	Age Group	Female Rate*
0.1	10-14	0.2
10.9	15-19	5.9
43.5	20-24	14.3
58.1	25-29	14.4
55.7	30-34	13.0
39.4	35-39	9.1
29.9	40-44	7.3
21.0	45-54	3.4
11.4	55-64	0.9
2.1	65+	0.1
20.8	Total	4.7

*Per 100,000 population

Figure 7 Primary and Secondary Syphilis—Rates by Race/Ethnicity, United States, 2020

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2020*. Syphilis. Atlanta: U.S. Department of Health and Human Services; April 2022.
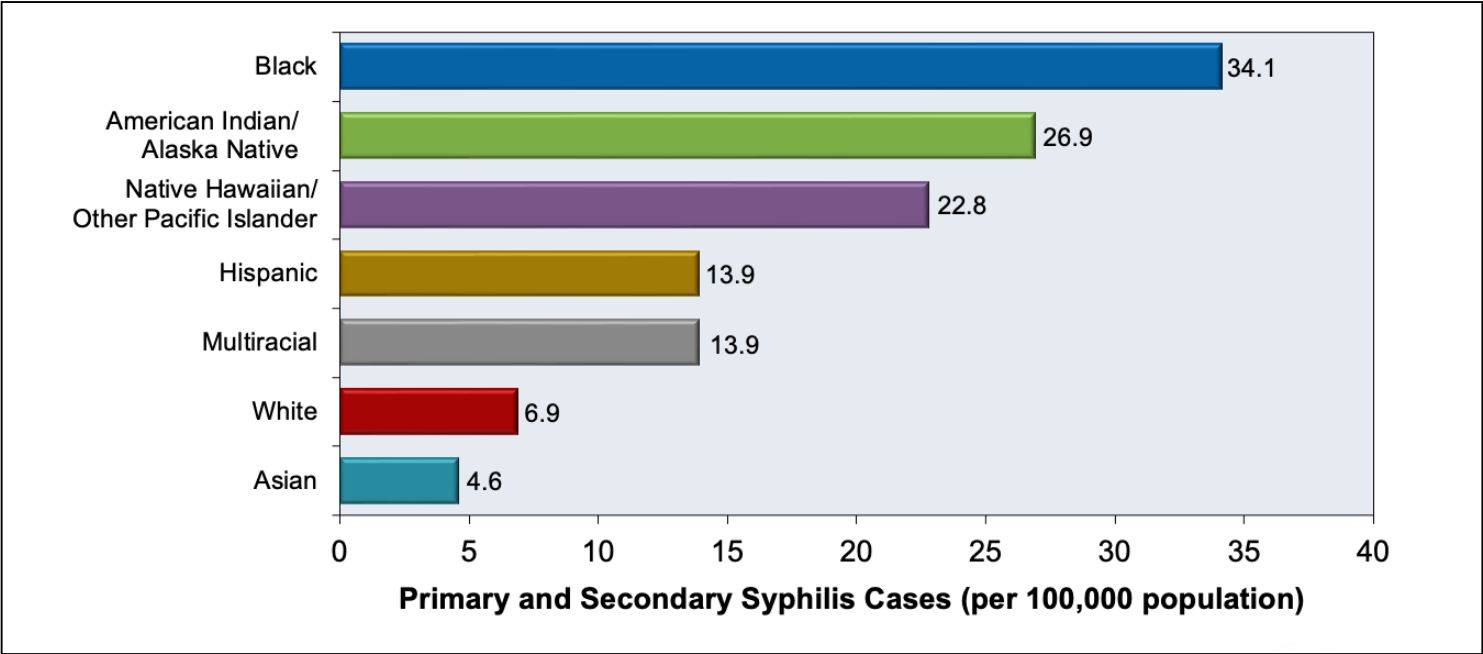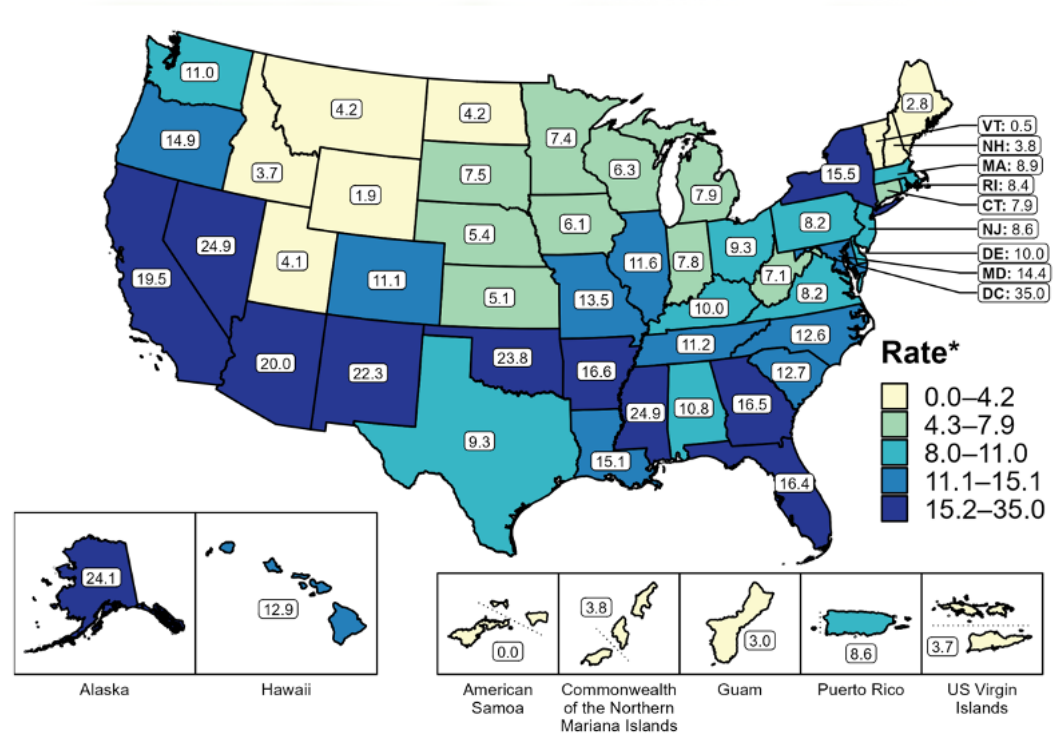
Figure 8 Primary and Secondary Syphilis—Rates by State, United States and Surrounding Areas, 2020

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2020*. Syphilis. Atlanta: U.S. Department of Health and Human Services; April 2022.


Rate*

- 0.0–4.2
- 4.3–7.9
- 8.0–11.0
- 11.1–15.1
- 15.2–35.0

VT: 0.5
NH: 3.8
MA: 8.9
RI: 8.4
CT: 7.9
NJ: 8.6
DE: 10.0
MD: 14.4
DC: 35.0

Alaska — 24.1
Hawaii — 12.9
American Samoa — 0.0
Commonwealth of the Northern Mariana Islands — 3.8
Guam — 3.0
Puerto Rico — 8.6
US Virgin Islands — 3.7

*per 100,000 population

Figure 9 Congenital Syphilis—Reported Cases by Year of Birth, United States, 2005-2020

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2020*. Syphilis. Atlanta: U.S. Department of Health and Human Services; April 2022.
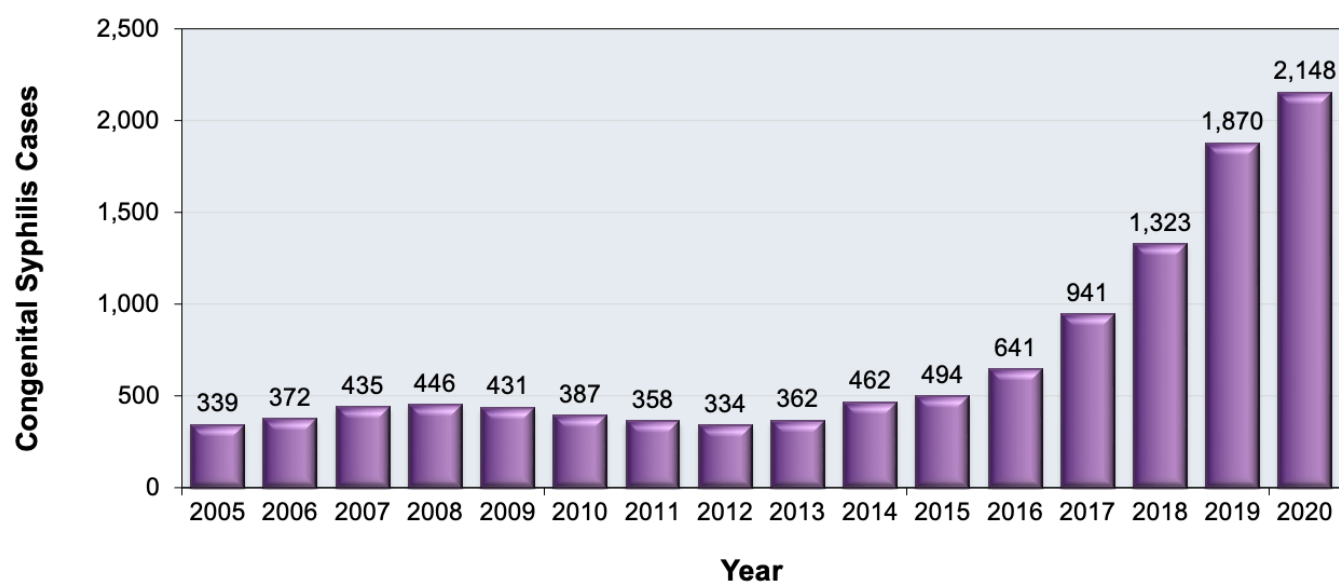
Figure 10 *Treponema pallidum*—Electron Micrograph

This electron micrograph shows the 'corkscrew' shape of *Treponema pallidum* growing in cultures of cottontail rabbit epithelium cells.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Dr. David Cox).

Figure 11 *Treponema pallidum*—Photomicrograph

This photomicrograph shows an isolated *Treponema pallidum* spirochete bacterium approximately 6 to 20 micrometers in length and 0.1 to 0.18 micrometers in width.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Susan Lindsley, 1972).

Figure 12 Primary Syphilis—Penile Chancre

This patient with primary syphilis had a large firm ulcerated lesion on the penis accompanied by right-sided inguinal adenopathy.

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

Figure 14 (Image Series) - Secondary Syphilis—Rash (Image Series) - Figure 14 (Image Series) - Secondary Syphilis—Rash
Image 14A: Diffuse Rash on Chest

This patient with secondary syphilis developed a diffuse erythematous macular rash prominent on the chest, back, palms, and soles.

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

Figure 14 (Image Series) - Secondary Syphilis—Rash
Image 14B: Diffuse Rash on Back

This patient with secondary syphilis developed a diffuse erythematous macular rash prominent on the chest and back.

Photograph credit: David H. Spach, MD

Figure 14 (Image Series) - Secondary Syphilis—Rash
Image 14C: Maculopapular Rash on Palms of Hands

Source: photograph from Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

Figure 14 (Image Series) - Secondary Syphilis—Rash
Image 14D: Maculopapular Rash on Feet

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

Figure 15 Secondary Syphilis—Oral Lesions

This patient with secondary syphilis had multiple shallow ulcerations on the tongue (black arrows).

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County Sexual Health Clinic

Figure 16 Secondary Syphilis—Condylomata lata

This patient with secondary syphilis developed multiple vulvar and intertriginous condylomata lata lesions; these lesions typically appear as moist, gray, raised papules, often resembling warts (condyloma acuminata).

Photograph credit: Centers for Disease Control and Prevention Public Health Image Library (CDC/J.Pledger, 1976).

Figure 17 Normal Eye Anatomy

The uvea includes three structures: iris, ciliary body, and choroid

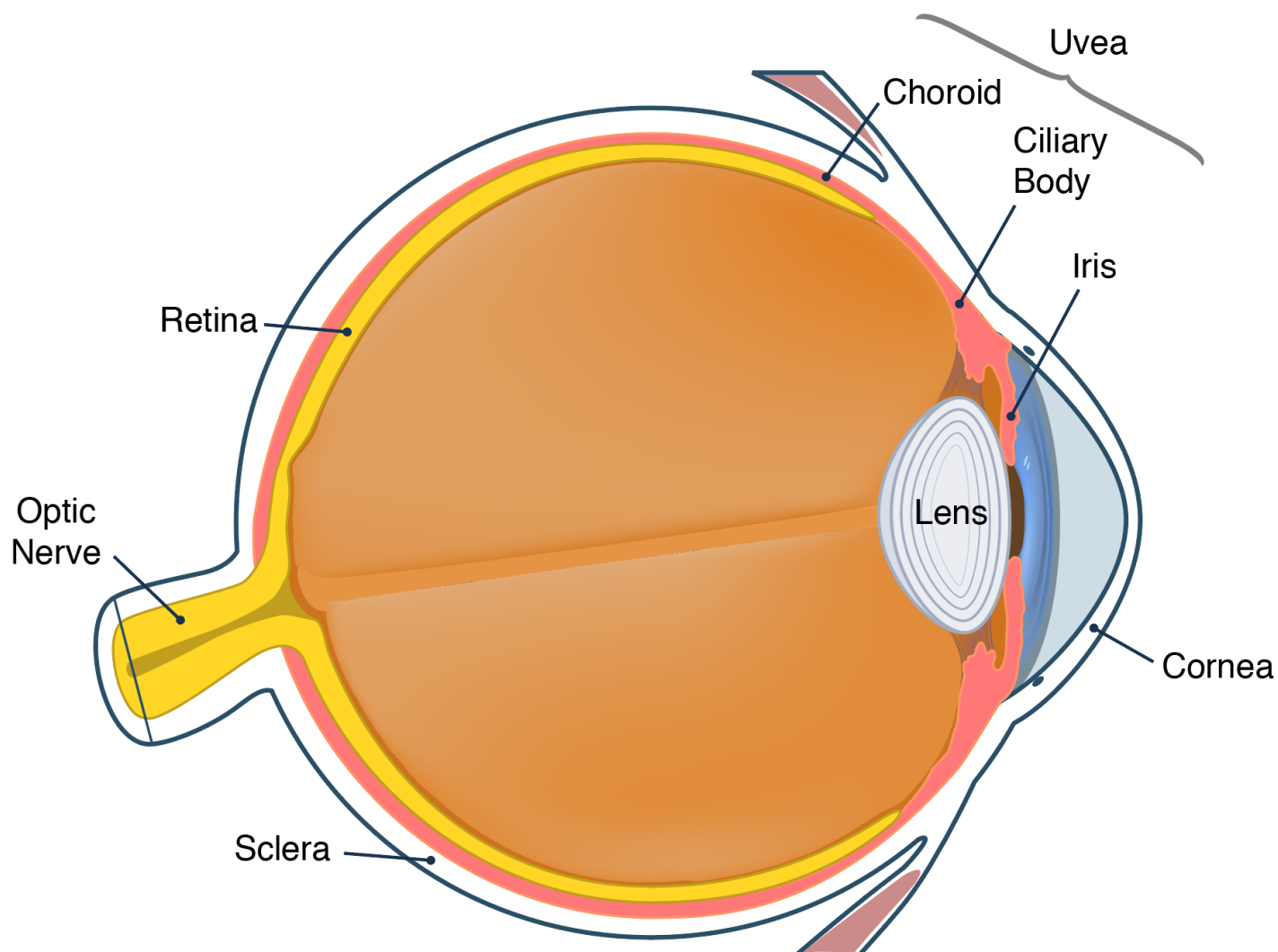Illustration by David Ehlert, Cognition Studio, Inc.

Figure 18 Congenital Syphilis — Reported Cases by Vital Status and Clinical Signs and Symptoms* of Infection, United States, 2015–2019

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

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2019*. Syphilis. Atlanta: U.S. Department of Health and Human Services; April 2021.
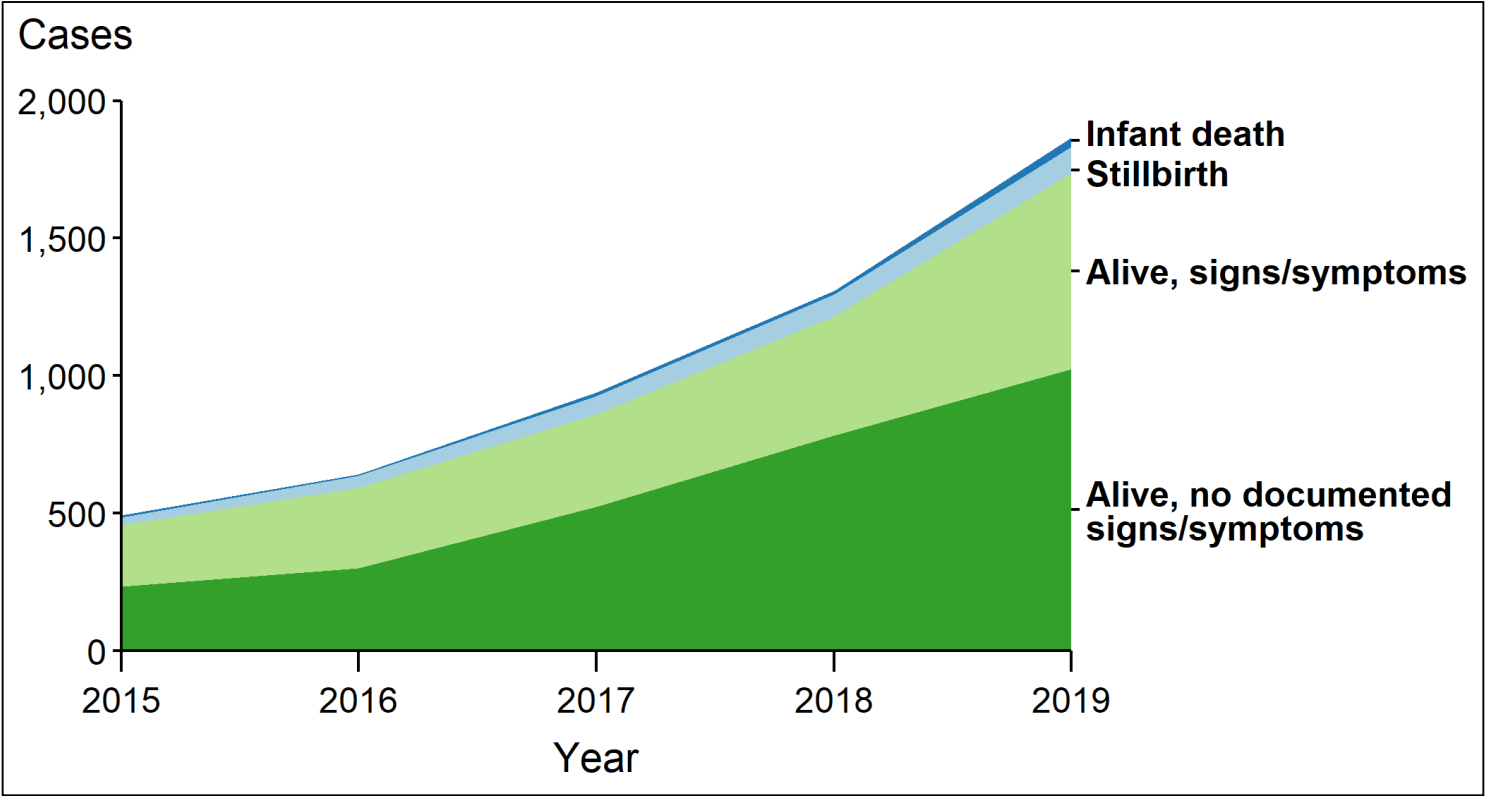
Figure 19 Congenital Syphilis—Palatal Perforation

This photograph shows an intraoral view of a perforation in the hard palate caused by congenital syphilis.

Photograph credit: Centers for Disease Control and Prevention Public Health Image Library (CDC/Robert E. Sumpter, 1967).
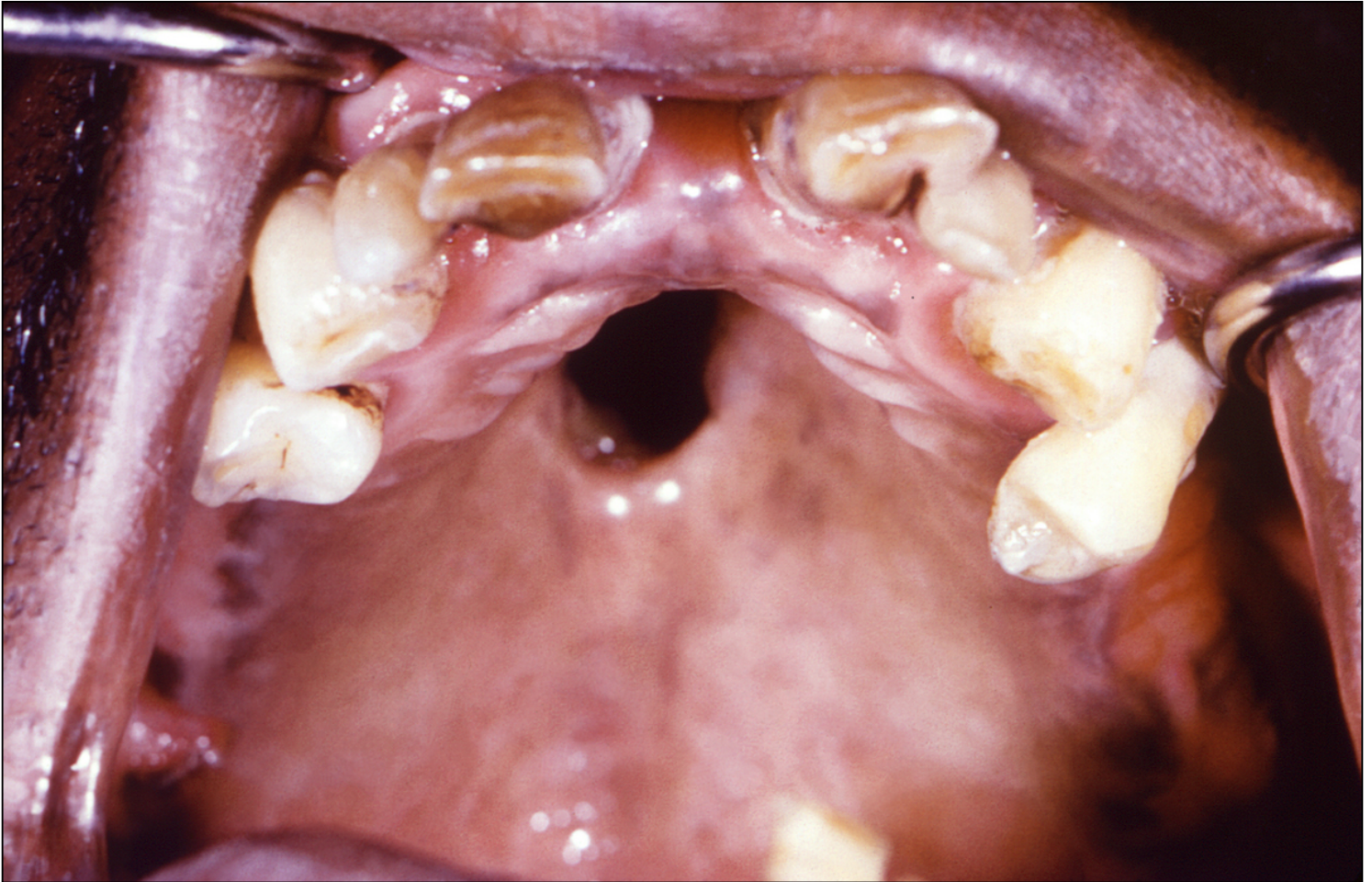
Figure 20 Congenital Syphilis—Hutchinson's Teeth

This photograph demonstrates the triangular-shaped deformity of an upper central incisor (top arrow) and a lower lateral incisor (lower arrow) dentition within the oral cavity of a person with a history of congenital syphilis. These dental abnormalities are known as Hutchinson incisors.

Photograph credit: Centers for Disease Control and Prevention Public Health Image Library (CDCRobert E. Sumpter, 1967).
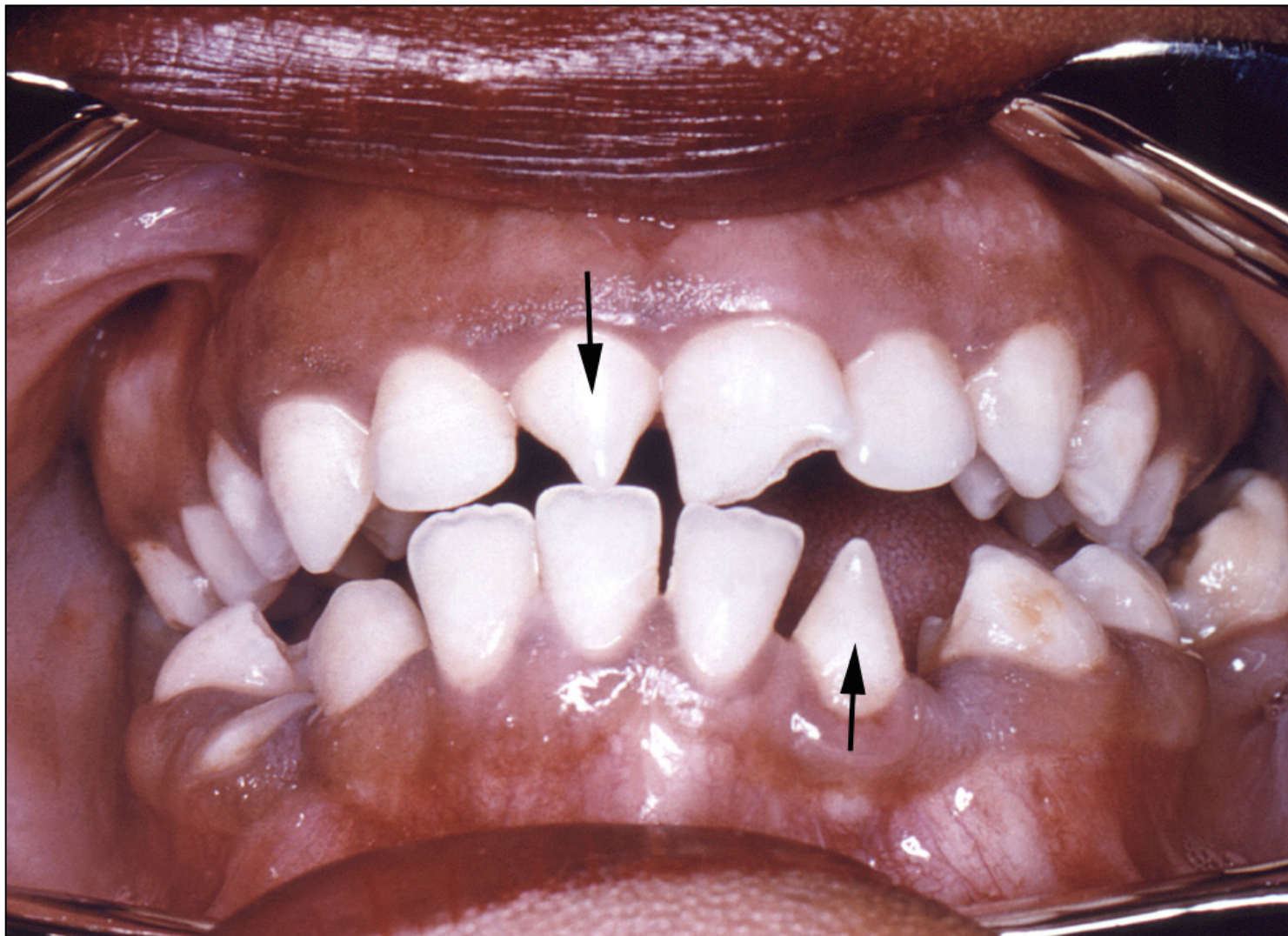
Figure 21 *Treponema pallidum*—Dark-Field Microscopy

This photomicrograph shows the typical 'corkscrew' appearance of several *Treponema pallidum* spirochetes with the dark-field microscopy technique.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Renelle Woodall, 1969).

Figure 22 *Treponema pallidum* Indirect Fluorescent Antibody (FA) Serologic Test

The fluorescent treponemal antibody absorption (FTA-ABS) test uses indirect fluorescent antibody technique in serum samples. This image shows abundant *Treponema pallidum* spirochetes with the use of a sample treated with Fluorescent Treponemal Antibody (FTA) antigen. The specimen shown here is enhanced by ultraviolet (UV) illumination.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Russell, 1967).
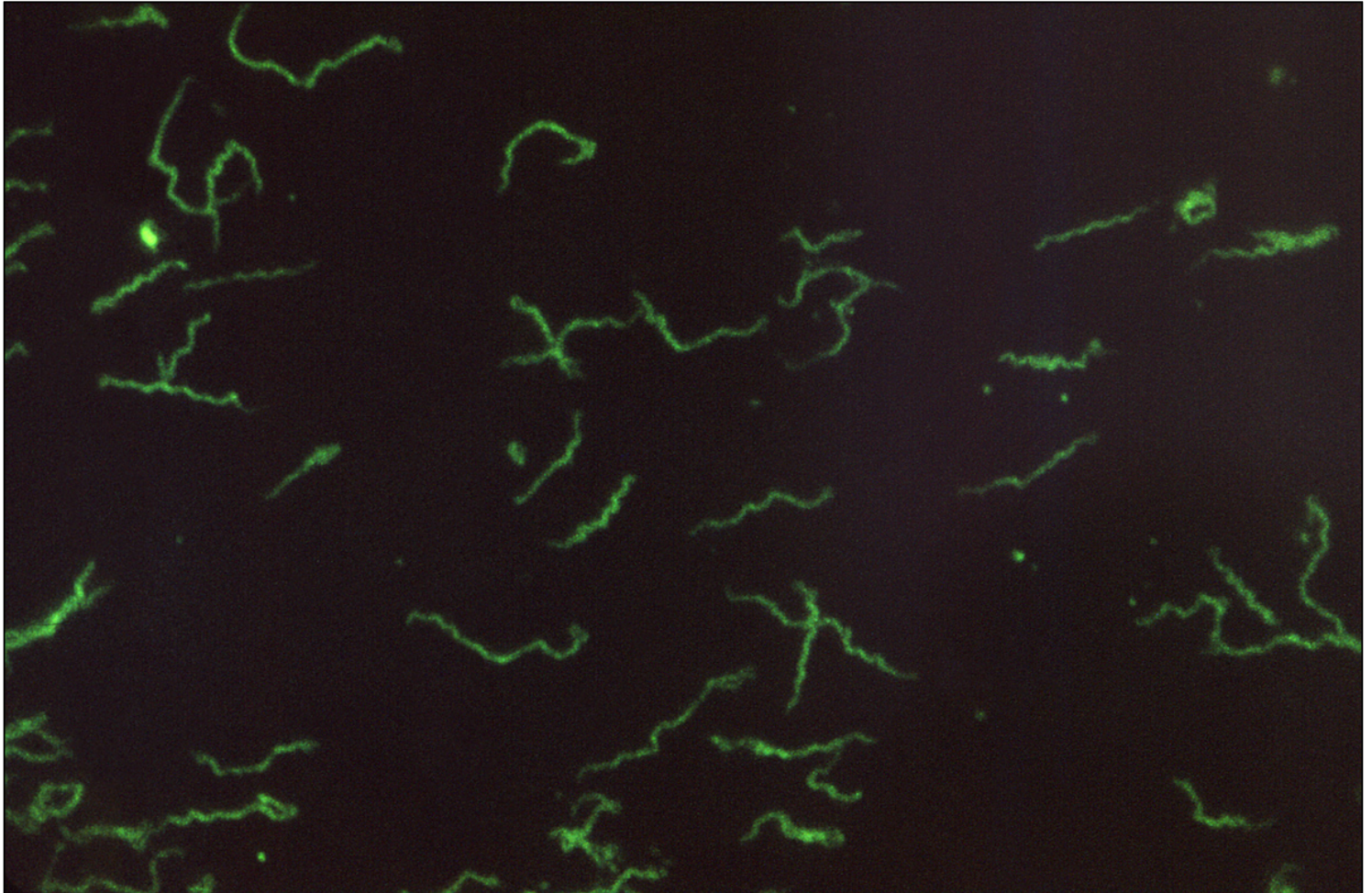
Figure 23 Syphilis Serologic Screening—Traditional Sequence Algorithm

The traditional (standard) serologic screening sequence algorithm uses a quantitative nontreponemal test (RPR or VDRL) for screening followed by a treponemal test for confirmation of positive screening tests. Abbreviations: RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = *Treponema pallidum* particle agglutination.

Source: Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60:133-7.
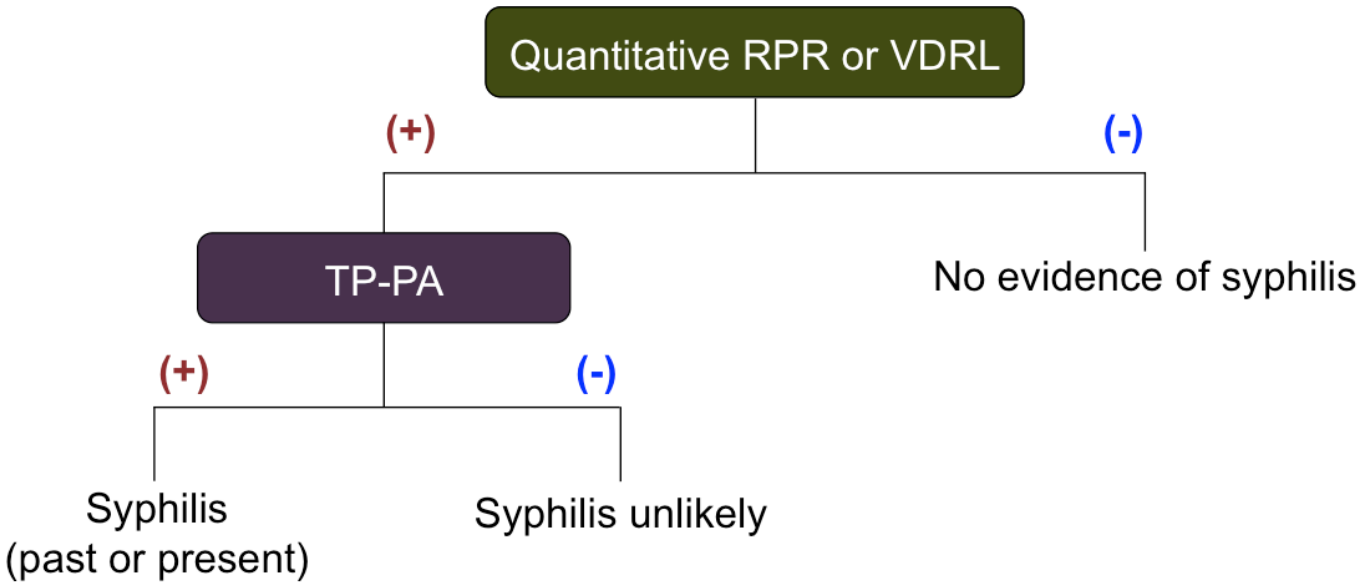
Figure 24 Syphilis Serologic Screening—Reverse Sequence Algorithm

The reverse serologic screening algorithm uses an initial treponemal test for screening, followed by a nontreponemal test confirmation. A specimen with reactive EIA/CIA results should be tested reflexively with a quantitative nontreponemal test (RPR or VDRL). Abbreviations: EIA = enzyme immunoassay; CIA = chemiluminescence immunoassays; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = *Treponema pallidum* particle agglutination.

Source: Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60:133-7.

Figure 25 Examples of Increases in Nontreponemal Titers

This graphic shows three examples of increases in nontreponemal titers when comparing two tests. Test number 1 is represented as red and test number 2 as blue.

Illustration by David H. Spach, MD

2-fold Increase

| Example 1 | 1:1 | 1:2 | 1:4 | 1:8 | 1:16 | 1:32 | 1:64 | 1:128 | 1:256 | 1:512 |

4-fold Increase

| Example 2 | 1:1 | 1:2 | 1:4 | 1:8 | 1:16 | 1:32 | 1:64 | 1:128 | 1:256 | 1:512 |

8-fold Increase

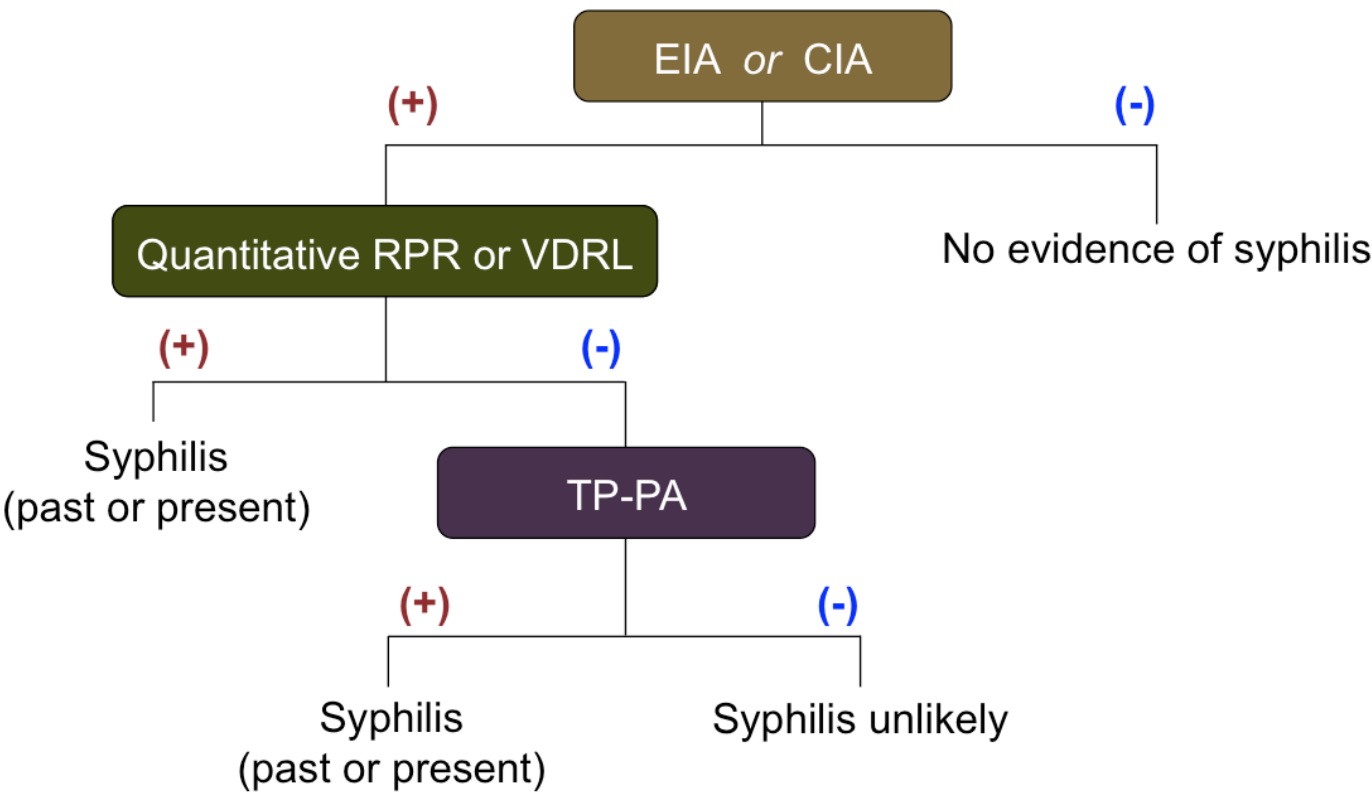| Example 3 | 1:1 | 1:2 | 1:4 | 1:8 | 1:16 | 1:32 | 1:64 | 1:128 | 1:256 | 1:512 |

Figure 26 Examples of Decreases in Nontreponemal Titers

This graphic shows three examples of decreases in nontreponemal titers when comparing two tests. Test number 1 is represented as red and test number 2 as blue.
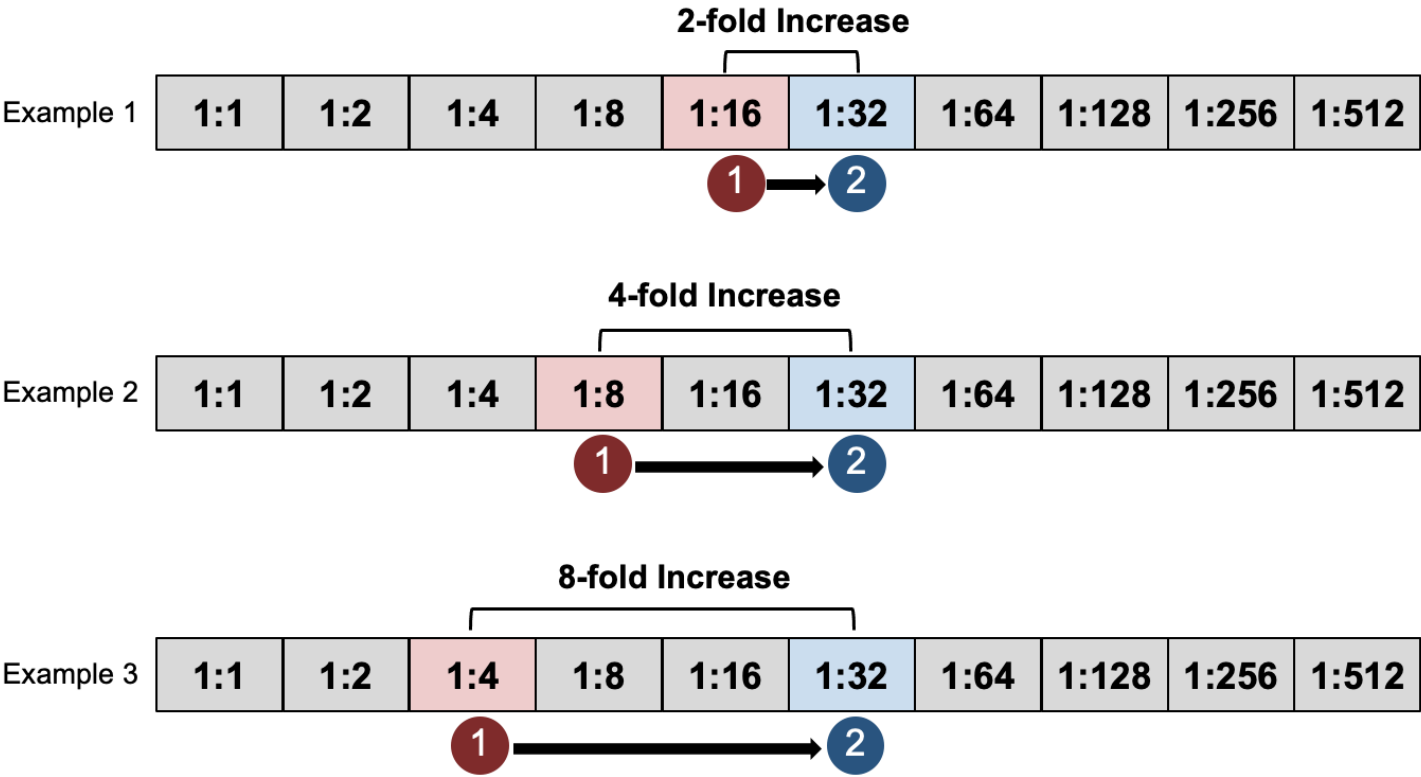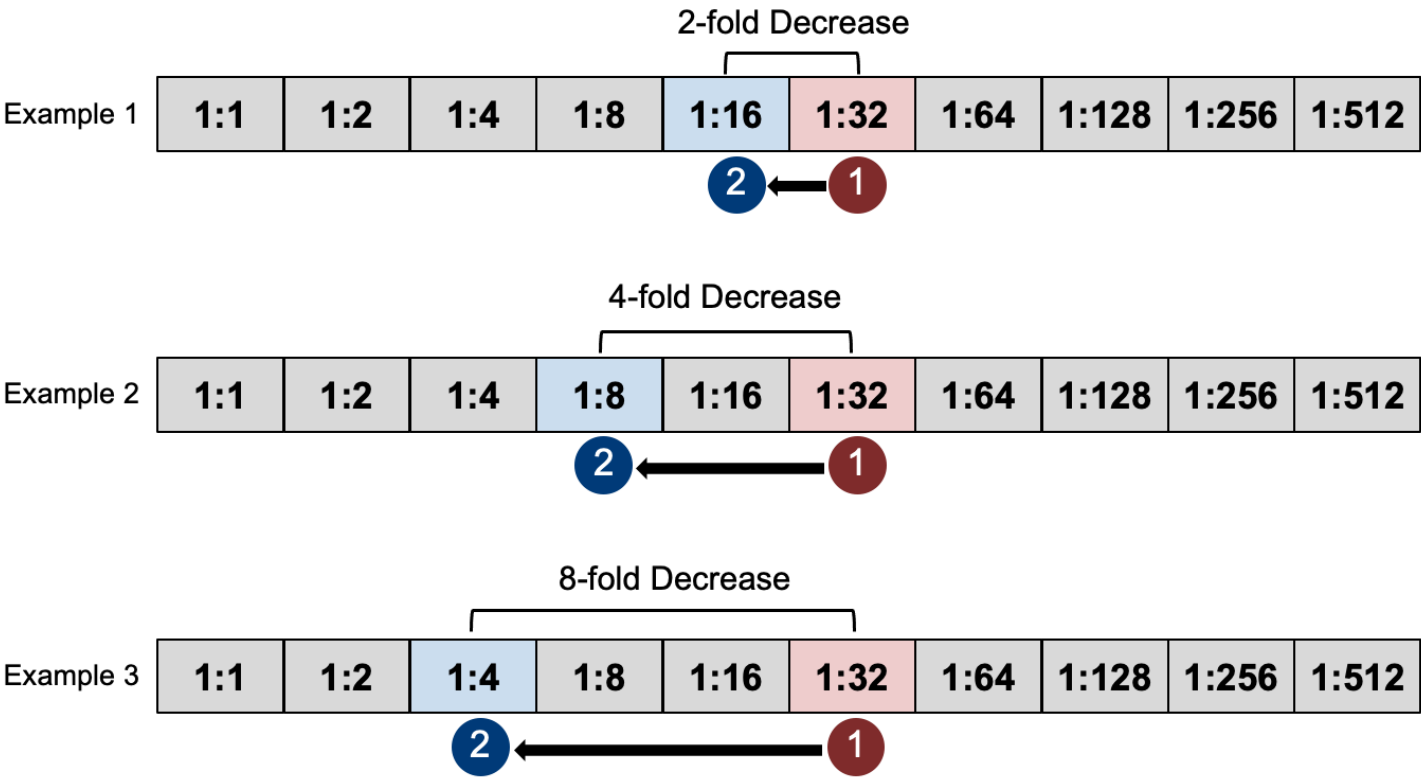
Illustration by David H. Spach, MD

Table 1.

Sensitivity and Specificity of Common Serological Tests in Untreated Syphilis

Test	Sensitivity During Stage of Infection, % (range)				Specificity, % range
	Primary	Secondary	Latent	Late	
VDRL	78 (74-87)	100	96 (88-100)	71 (37-94)	98 (96-99)
RPR	86 (77-99)	100	98 (95-100)	73	98 (93-99)
FTA-ABS	84 (70-100)	100	100	96	97 (94-100)
TP-PA	88 (86-100)	100	100	NA	96 (95-100)
ELISA (IgG)	100	100	100	NA	100

*FTA-ABS and TP-PA are generally considered equally sensitive in the primary stage of disease.

Abbreviations
NA = not available
VDRL = Venereal Disease Research Laboratory
RPR = Rapid Plasma Reagin
FTA-ABS = Fluorescent Treponemal Antibody Absorbed
TP-PA = *Treponema pallidum*-Particle agglutination
ELISA= Enzyme Linked Immunoassay

Source:

- Seña AC, White BL, Sparling PF. Novel *Treponema pallidum* serologic tests: a paradigm shift in syphilis screening for the 21st century. Clin Infect Dis. 2010;51:700-8. [PubMed Abstract]

Table 2. 2021 STI Treatment Guidelines: Syphilis
Treatment of Primary and Secondary Syphilis Among Adults*

*Recommendations for treating syphilis among persons with HIV infection and pregnant women are not addressed in this table.

Recommended Regimen
Benzathine penicillin G *2.4 million units IM in a single dose*
Note: Available data demonstrate that use of additional doses of benzathine penicillin G, amoxicillin, or other antibiotics do not enhance efficacy when used to treat primary and secondary syphilis, regardless of HIV status.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Syphilis. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 3. 2021 STI Treatment Guidelines: Syphilis
Treatment of Latent Syphilis Among Adults*

*Recommendations for treating syphilis in persons with HIV and pregnant women are not addressed in this table.

Recommended Regimen for Early Latent Syphilis

Benzathine penicillin G
2.4 million units IM in a single dose

Note: Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early latent syphilis do not enhance efficacy, regardless of HIV status.

Recommended Regimen for Late Latent Syphilis

Benzathine penicillin G
7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Syphilis. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 4. 2021 STI Treatment Guidelines: Syphilis
Treatment of Tertiary Syphilis Among Adults

Recommended Regimen for Treatment of Tertiary Syphilis with Normal CSF Examination
Benzathine penicillin G *7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals*

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Syphilis. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 5. 2021 STI Treatment Guidelines: Syphilis
Treatment of Neurosyphilis, Ocular Syphilis, or Otosyphilis Among Adults

Recommended Regimen
Aqueous crystalline penicillin G *18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days*

Alternative Regimen		
Procaine penicillin G *2.4 million units IM once daily for 10-14 days*	**+**	**Probenecid** *500 mg orally four times a day for 10–14 days*
Note: If compliance with therapy can be ensured, this alternative regimen might be considered.		

The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin G, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Syphilis. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 6. 2021 STI Treatment Guidelines: Syphilis
Treatment of Syphilis Among Persons with HIV Infection

Recommended Regimen for Treatment of Primary and Secondary Syphilis
Benzathine penicillin G *2.4 million units IM in a single dose*
Note: Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis among persons with HIV infection do not result in enhanced efficacy.

Recommended Regimen for Treatment of Early Latent Syphilis
Benzathine penicillin G *2.4 million units IM in a single dose*

Recommended Regimen for Treatment of Late Latent or Latent Syphilis of Unknown Duration
Benzathine penicillin G *7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals*

Recommended Regimen for Treatment of Neurosyphilis, Ocular Syphilis, and Otic Syphilis
Aqueous crystalline penicillin G *18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days*
Note: The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Alternative Regimen for Treatment of Neurosyphilis, Ocular Syphilis, and Otic Syphilis	
Procaine penicillin G *2.4 million units IM once daily for 10-14 days* +	**Probenecid** *500 mg orally four times a day for 10–14 days*
If compliance with therapy can be ensured, this alternative regimen might be considered. Note: The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin G, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.	

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Syphilis. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 7. 2021 STI Treatment Guidelines: Syphilis
Treatment of Congenital Syphilis in Neonates

Recommended Regimens for Confirmed or Highly Probable Congenital Syphilis
Aqueous crystalline penicillin G *100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days*
Recommended Regimens for Confirmed or Highly Probable Congenital Syphilis
Procaine penicillin G *50,000 units/kg body weight/dose IM in a single daily dose for 10 days*
Recommended Regimens for Possible Congenital Syphilis
Aqueous crystalline penicillin G *100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days*
Recommended Regimens for Possible Congenital Syphilis
Procaine penicillin G *50,000 units/kg body weight/dose IM in a single daily dose for 10 days*
Recommended Regimens for Possible Congenital Syphilis
Benzathine penicillin G *50,000 units/kg body weight/dose IM in a single dose*
Recommended Regimen when Congenital Syphilis Less Likely
Benzathine penicillin G *50,000 units/kg body weight/dose IM in a single dose**
Note: *Another approach involves not treating the newborn if follow-up is certain but providing close serologic follow-up every 2–3 months for 6 months for infants whose mothers' nontreponemal titers decreased at least fourfold after therapy for early syphilis or remained stable for low- titer, latent syphilis (e.g. VDRL <1:2 or RPR <1:4).
Recommended Regimen when Congenital Syphilis Unlikely Note: No treatment is required. However, any neonate with reactive nontreponemal tests should be followed serologically to ensure the nontreponemal test returns to negative. Benzathine penicillin G 50,000 units/kg body weight as a single IM injection might be considered, particularly if follow-up is uncertain and the neonate has a reactive nontreponemal test.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Syphilis. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]

Table 8. 2021 STI Treatment Guidelines: Syphilis
Treatment of Congenital Syphilis Among Infants and Children

Infants and children aged ≥1 month who receive a syphilis diagnosis should have birth and maternal medical records reviewed to assess whether they have congenital or acquired syphilis.

Recommended Regimen
Aqueous crystalline penicillin G *200,000–300,000 units/kg body weight/day by IV, administered as 50,000 units/kg body weight every 4–6 hours for 10 days*

Infants and children aged ≥1 month with primary or secondary syphilis should be managed by a pediatric infectious disease specialist and evaluated for sexual abuse (e.g. through consultation with child-protection services)

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Syphilis. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [2021 STI Treatment Guidelines]