SYPHILIS INVESTIGATIVE GUIDELINES

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1. DISEASE REPORTING

1.1. Purpose of Reporting and Surveillance

1. To assess trends in disease patterns, understand the impact of syphilis and better target population-level disease prevention efforts.
2. To assure adequate treatment for infected individuals and their contacts, curtail infectiousness, and prevent complications of late syphilis (e.g., late neurologic complications, cardiovascular disease).
3. To prevent congenital syphilis by screening and treatment of infected pregnant women.

1.2. Legal Reporting Requirements for Health Care Providers, Facilities, and Laboratories

1. Health care providers and health care facilities are required to report the case or suspected case to the local health authority per NAC 441A.230 and 441A.695. The report must include: the disease or suspected disease; name, address, telephone number of the case or suspected case; name, address, and telephone number of the health care provider making the report; occupation, employer, age, sex, race, ethnicity and DOB of the case or suspected case; date of diagnosis, and date of onset.
2. Laboratories are required to report the case or suspected case to the local health authority per NAC 441A.235. The report must include date and result of the test or examination performed; name, address and, if available telephone number of the person from whom the specimen was obtained; the name of the health care provider who ordered the test or examination; and the name and the address or telephone number of the medical laboratory making the report.

1.3. Local Health Department and Priority Responsibilities

1. Disease Investigation Specialists (DIS) review laboratory and health care provider case reports in which initial laboratory or physician report is made. Document all cases and related information in surveillance system, EpiTrax. DIS includes Disease Investigation and Intervention Specialists (DIIS) and Public Health Investigators (PHI).
2. Report all confirmed/probable cases to the Nevada Division of Public and Behavioral Health, Office of State Epidemiology (OSE) via EpiTrax and email the OSE Surveillance Manager within the first working day after identifying a congenital syphilis case or suspected congenital syphilis case.
3. Local health jurisdiction staff should inform health care providers of the importance of instructing patients to refer sex partners for evaluation and treatment.

2. DISEASE AND ITS EPIDEMIOLOGY

2.1. Etiologic Agent

Treponema pallidum, a bacterium of the order Spirochaetales. The agent is difficult to culture.

2.2. Description of Illness

Syphilis is a complex, systemic, sexually transmitted infection that can cause serious health effects without adequate treatment. Symptoms of syphilis can look like many other infections. Left untreated, syphilis progresses through stages that are often

separated by long periods of latency. Case definitions and laboratory criteria for staging are presented in section three below.

2.2.1. *Primary Syphilis*

Primary syphilis is the first stage after an incubation period of 10–90 days (average 21 days), characterized by an ulcer (chancre, sore, or primary lesion) that is typically concave, with a raised border. It is typically painless, appears at the site of inoculation, generally the genitalia or anus. Primary lesions can occur at other sites of inoculation such as the lip, breast or mouth and might be located at ordinarily invisible locations such as the cervix, vagina or rectum. Commonly, only one lesion is present, but more than one ulcer might be present. Inguinal lymphadenopathy is common. The primary lesion persists for 1–5 weeks (3 weeks average) then goes away. This is the most infectious stage of syphilis. Treponemal and non-treponemal tests might be negative when a primary syphilis ulcer first appears. If appropriate treatment is not administered, the infection progresses to the secondary stage.

2.2.2. *Secondary Syphilis*

Skin rash and mucous membrane lesions characterize the secondary stage. The rash usually does not cause itching. After the primary lesion disappears, a latency period of 0–10 weeks (average of 4 weeks) typically ensues, after which the secondary stage appears in about 25% of individuals with untreated infection. Common symptoms include a generalized body rash, lymphadenopathy, mucous patches, patchy hair loss (alopecia), and malaise. Rash is famously protean, often appears as faint coppery macules on palms of hands ("palmar") and soles of feet ("plantar"). Secondary symptoms typically persist from 1–6 weeks. In some cases, the primary ulcer may still be present when secondary symptoms start to appear. One ordinarily finds both treponemal and non-treponemal tests to be reactive during secondary syphilis. The signs and symptoms of secondary syphilis will resolve with or without treatment, but without treatment, the infection will progress to the latent and late stages of disease.

2.2.3. *Latent Syphilis*

During latent syphilis, *T. pallidum* organisms persist in the body of the infected person but no symptoms manifest. Latent syphilis is divided into two categories: *early non-primary non-secondary syphilis*, which is defined as an infection of one year or less, and *unknown duration or late* which is an infection lasting >1 year or unknown duration.

A. *Early non-primary non-secondary*
   This stage applies when an initial infection occurred within the previous 12 months, but there are no signs or symptoms of primary or secondary syphilis. In some instances, earliest date of infection (exposure) can be inferred from a documented negative serologic test collected before the current diagnosis, or from onset of documented signs of primary or secondary syphilis.
B. *Unknown duration or late*
   This stage applies when an initial infection occurred >12 months previously or in which there is insufficient evidence to conclude that infection was acquired during the previous 12 months. In many instances, exact date of infection (exposure) cannot be known or constrained with certainty. These

cases should be classified as unknown duration or late syphilis. If the case remains untreated, syphilis can persist for the remainder of the person's life.

2.2.4. Clinical Manifestations of Syphilis

Neurologic, ocular, or otic manifestations (neurosyphilis, ocular syphilis, or otosyphilis) can occur during any stage and should be reported along with the appropriate stage. Clinical manifestations most commonly include inflammatory lesions of the cardiovascular system, skin, and bone. Less commonly, late syphilis causes clinical manifestations in other anatomic locations such as the respiratory tract, mouth, eye, viscera, lymph nodes, or skeletal muscle.

A. *Neurosyphilis*

An infection of the central nervous system with *T. pallidum*. Laboratory findings include a reactive treponemal serologic test for syphilis and a reactive VDRL test in cerebrospinal fluid (CSF). Manifestations include syphilitic meningitis, meningovascular syphilis, general paresis including dementia, and tabes dorsalis. Concurrent HIV infection might change the appearance and behavior of the primary and secondary micro-cutaneous lesions and increase the risk of CNS disease in patients with Syphilis. Health care providers should consider neurosyphilis in the differential diagnosis of HIV infected individuals with CNS symptoms and ocular and otologic complaints.

B. *Ocular Syphilis*

An infection of the eye with *T. pallidum*. Ocular syphilis can involve almost any eye structure, but posterior uveitis and panuveitis are the most common. Additional manifestations may include anterior uveitis, optic neuropathy, retinal vasculitis and interstitial keratitis. Ocular syphilis may lead to decreased visual acuity including permanent blindness. Ocular syphilis can be associated with neurosyphilis.

C. *Otic Syphilis*

An infection of the cochlea and vestibule of the ear with *T. pallidum*. Manifestations include sensorineural hearing loss, tinnitus, and vertigo.

D. *Late Clinical Manifestations*

Late clinical manifestations (tertiary syphilis) usually develop only after a period of 15-30 years of untreated infection. Manifestations include inflammatory lesions of the cardiovascular system, skin, and bone. Rarely, the upper and lower respiratory tracts, mouth, eye, abdominal organs, reproductive organs, lymph nodes, and skeletal muscle may be involved. In addition, certain neurologic manifestations such as general paresis and tabes dorsalis are also late clinical manifestations of syphilis.

2.2.5. Congenital Syphilis

Congenital syphilis occurs when *T. pallidum* is transmitted from a pregnant individual with syphilis to the fetus. Transmission can occur during any trimester and any stage of syphilis, but the risk is higher when a pregnant individual is in the primary or secondary stage. Congenital syphilis can cause miscarriage or stillbirth and may cause infant death due to complications associated with preterm delivery or generalized systemic disease. Other effects of congenital syphilis include brain or nerve involvement, blindness, deafness, bone deformities, and liver and kidney damage. A CDC Congenital Syphilis Case

Investigation and Report form must be completed for all cases in which maternal, infant, or syphilitic stillbirth criteria are met.

2.3. Reservoirs

Humans

2.4. Modes of Transmission

1. Sexual - Direct contact with infectious exudates from obvious or concealed moist, primary or secondary lesions of skin, and with mucous membranes of infected people during sexual intercourse. Direct physical contact with primary lesions is highly infectious. Transmission by physical contact with a dry rash is thought to be rare. Other secondary lesions such mucous patches and condylomata lata (wart-like rash of genital and occasionally other intertriginous areas) and are believed to be more infectious than dry rashes. Sexual abuse must be suspected in any child with acquired syphilis. Evaluation by the local child protective services agency is warranted.
2. Vertical - Transmitted from mother to fetus *in utero* or during delivery. Infected infants may have moist mucocutaneous lesions that are more widespread than in adult syphilis and are a potential source of infection when those lesions are present.

2.5. Incubation period and Period of Communicability

The incubation period for Syphilis is 10 to 90 days, (average 21 days).

2.6. Period of Communicability

Syphilis is transmissible whenever moist mucocutaneous lesions are present. In secondary syphilis, mucous patches and condylomata lata are believed to be more infectious than dry rashes. Although latent syphilis is not transmitted sexually, pregnant persons can pass the infection to the fetus during any stage of infection.

2.7. Treatment

Refer to the most recent CDC treatment guidelines: https://www.cdc.gov/std/treatment-guidelines/default.htm.

2.8. Syphilis in Nevada

Refer to the most recent Nevada STD Fast Facts Report for statistics on Syphilis on the Office of Analytics' Data Dashboard & Report Catalog.

3. CASE DEFINITIONS, DIAGNOSIS, AND LABORATORY SERVICES

Note: According to the Centers for Disease Control and Prevention, case definitions are periodically revised using the Council of State and Territorial Epidemiologists' (CSTE) Position Statements. The 2018 Syphilis case definitions are still in effect as of 2023.

3.1. Primary Syphilis

1. Clinical Description

A stage of infection with *Treponema pallidum* characterized by one or more ulcerative lesions (chancres), which might differ considerably in clinical appearance.

2. Laboratory Criteria for Diagnosis
   A. Confirmatory
      i. Demonstration of *T. pallidum* by darkfield microscopy in a clinical specimen that was not obtained from the oropharynx and is not potentially contaminated by stool, OR
      ii. Demonstration of *T. pallidum* by polymerase chain reaction (PCR) or equivalent direct molecular methods in any clinical specimen.
   B. Supportive (see Appendix A and Appendix B)
      i. A reactive nontreponemal serologic test (Venereal Disease Research Laboratory [VDRL], rapid plasma reagin [RPR], or equivalent serologic methods), OR
      ii. A reactive treponemal serologic test (*T. pallidum* particle agglutination [TP-PA], enzyme immunoassay [EIA], chemiluminescence immunoassay [CIA], or equivalent serologic methods).
   C. Case Classification
      i. Probable: A case that meets the clinical description of primary syphilis and the supportive laboratory criteria.
      ii. Confirmed: A case that meets the clinical description of primary syphilis and the confirmatory laboratory criteria.

3.2. Secondary Syphilis

1. Clinical Description
   A stage of infection caused by *T. pallidum* characterized by localized or diffuse mucocutaneous lesions (e.g., rash), often with generalized lymphadenopathy. Other signs can include mucous patches, condylomata lata, and alopecia. The primary ulcerative lesion may still be present.
2. Laboratory Criteria for Diagnosis
   A. Confirmatory:
      i. Demonstration of *T. pallidum* by darkfield microscopy in a clinical specimen that was not obtained from the oropharynx and is not potentially contaminated by stool, OR
      ii. Demonstration of *T. pallidum* by polymerase chain reaction (PCR) or equivalent direct molecular methods in any clinical specimen.
   B. Supportive:
      i. A reactive nontreponemal serologic test (Venereal Disease Research Laboratory [VDRL], rapid plasma reagin [RPR], or equivalent serologic methods), AND
      ii. A reactive treponemal serologic test (*T. pallidum* particle agglutination [TP-PA], enzyme immunoassay [EIA], chemiluminescence immunoassay [CIA], or equivalent serologic methods).
3. Case Classification
   A. Probable: A case that meets the clinical description of secondary syphilis and the supportive laboratory criteria.
   B. Confirmed: A case that meets the clinical description of secondary syphilis and the confirmatory laboratory criteria.

3.3. Early Non-Primary Non-Secondary Syphilis

1. Clinical Description
   A stage of infection caused by *T. pallidum* in which initial infection has occurred within the previous 12 months, but there are no signs or symptoms of primary or secondary syphilis.
2. Laboratory Criteria for Diagnosis
   Supportive: A current nontreponemal test titer demonstrating fourfold or greater increase from the last nontreponemal test titer, unless there is evidence that this increase was not sustained for >2 weeks (see Appendix C).
3. Case Classification
   A. Confirmed: cannot be confirmed
   B. Probable: A person with no clinical signs or symptoms of primary or secondary syphilis who has one of the following:
      i. No prior history of syphilis, AND a current reactive nontreponemal test (e.g., VDRL, RPR, or equivalent serologic methods), AND a current reactive treponemal test (e.g., TP-PA, EIA, CIA, or equivalent serologic methods), OR
      ii. A prior history of syphilis and meets the supportive laboratory criteria. AND evidence of having acquired the infection within the previous 12 months based on one or more of the following criteria:
         a. Documented seroconversion or fourfold or greater increase in titer of a nontreponemal test (Appendix C) during the previous 12 months, unless there is evidence that this increase was not sustained for >2 weeks
         b. Documented seroconversion of a treponemal test during the previous 12 months
         c. A history of symptoms consistent with primary or secondary syphilis during the previous 12 months
         d. Meets epidemiologic criteria:
            - A history of sexual exposure to a partner within the previous 12 months who had primary, secondary, or early non-primary non-secondary syphilis (documented independently as duration <12 months).
            - Only sexual contact (sexual debut) was within the previous 12 months.

3.4. Unknown Duration or Late Syphilis

1. Clinical Description
   A stage of infection caused by *T. pallidum* in which initial infection occurred >12 months previously or in which there is insufficient evidence to conclude that infection was acquired during the previous 12 months.
2. Laboratory Criteria for Diagnosis
   None noted
3. Case Classification
   A. Confirmed: cannot be confirmed
   B. Probable: A person with no clinical signs or symptoms of primary or secondary syphilis who meets one of the following sets of criteria:
      i. No prior history of syphilis, and a current reactive nontreponemal test (e.g., VDRL, RPR, or equivalent serologic methods), and a current reactive treponemal test (e.g., TP-PA, EIA, CIA, or equivalent serologic methods), OR

ii. A prior history of syphilis, and a current nontreponemal test titer demonstrating fourfold or greater increase from the last nontreponemal test titer, unless there is evidence that this increase was not sustained for >2 weeks, OR
iii. Clinical signs or symptoms and laboratory results that meet the likely or verified criteria for neurologic, ocular, otic, or late clinical manifestations syphilis (see below)
iv. AND who has no evidence of having acquired the disease within the preceding 12 months (see Early Non-Primary Non-Secondary Syphilis)

Comments:

Although cases of syphilis of unknown duration are grouped together with late syphilis for the purposes of surveillance, the conservative clinical and public health responses to these cases will differ when there is uncertainty about the duration of infection. When faced with uncertainty, clinicians should act conservatively and treat unknown duration syphilis as if it were late infection, in accordance with CDC STD guidelines. In contrast, approach all cases as early infections by interviewing for partners and risk, and make final case determinations after thorough investigation. Because this would not be feasible for most STD control programs, programs should consider prioritizing cases of syphilis of unknown duration with higher nontreponemal titers (e.g., 1:32 or higher) for investigation and partner services. Although nontreponemal titers cannot reliably distinguish between early infection (<12 months duration) and late infection (>12 months duration), nontreponemal titers usually are higher early in the course of syphilis infection.

3.5. Congenital Syphilis

1. Clinical Description
   A condition caused by infection in utero with *T. pallidum*. A spectrum of severity exists, from inapparent infection to severe cases that are clinically apparent at birth. An infant or child (aged less than 2 years) may have signs such as hepatosplenomegaly, rash, condylomata lata, snuffles, jaundice (nonviral hepatitis), pseudoparalysis, anemia, or edema (nephrotic syndrome and/or malnutrition). Older children may have stigmata (e.g., interstitial keratitis, nerve deafness, anterior bowing of shins, frontal bossing, mulberry molars, Hutchinson teeth, saddle nose, rhagades, or Clutton joints).
2. Laboratory Criteria for Diagnosis
   A. Demonstration of *T. pallidum* by Darkfield microscopy of lesions, body fluids, or neonatal nasal discharge, OR
   B. Polymerase chain reaction (PCR) or other equivalent direct molecular methods of lesions, neonatal nasal discharge, placenta, umbilical cord, or autopsy material, OR
   C. Immunohistochemistry (IHC), or special stains (e.g., silver staining) of specimens from lesions, placenta, umbilical cord, or autopsy material.
3. Case Classification
   A. Confirmed: A case that is laboratory confirmed by methods listed above.
   B. Probable:
      i. A condition affecting an infant whose mother had untreated or inadequately treated* syphilis at delivery, regardless of signs in the infant, OR

ii. An infant or child who has a reactive non-treponemal test for syphilis (Venereal Disease Research Laboratory [VDRL], rapid plasma reagin [RPR], OR equivalent serologic methods) AND any one of the following:
    a. Evidence of congenital syphilis on physical examination (see Clinical description)
    b. Evidence of congenital syphilis on radiographs of long bones
    c. Reactive cerebrospinal fluid (CSF) venereal disease research laboratory test (VDRL) test
    d. In a non-traumatic lumbar puncture, an elevated CSF leukocyte (white blood cell, WBC) count or protein (without other cause). Suggested parameters for abnormal CSF WBC and protein values:
        - During the first 30 days of life, a CSF WBC count of >15 WBC/mm3 or a CSF protein >120 mg/dl is abnormal.
        - After the first 30 days of life, a CSF WBC count of >5 WBC/mm3 or a CSF protein >40 mg/dl, regardless of CSF serology.

The treating clinician should be consulted to interpret the CSF values for the specific patient.

*Adequate treatment is defined as completion of a penicillin-based regimen, in accordance with CDC treatment guidelines, appropriate for stage of infection, initiated 30 or more days before delivery.

Comments:

Congenital and acquired syphilis may be difficult to distinguish when a child is seropositive after infancy. Signs of congenital syphilis may not be obvious, and stigmata may not yet have developed. Abnormal values for CSF VDRL, WBC count, and protein may be found in either congenital or acquired syphilis. Findings on radiographs of long bones may help because radiographic changes in the metaphysis and epiphysis are considered classic signs of congenitally acquired syphilis. While maternal antibodies can complicate interpretation of serologic tests in an infant, reactive tests past 18 months of age are considered to reflect the status of the child. The decision may ultimately be based on maternal history and clinical judgment. In a young child, the possibility of sexual abuse should be considered as a cause of acquired rather than congenital syphilis, depending on the clinical picture. For reporting purposes, congenital syphilis includes cases of congenitally acquired syphilis among infants and children as well as syphilitic stillbirths.

3.6. Syphilitic Stillbirth

1. Clinical Description
   A fetal death that occurs after a 20-week gestation or in which the fetus weighs greater than 500 grams and the mother had untreated or inadequately treated* syphilis at delivery.

*Adequate treatment is defined as completion of a penicillin-based regimen, in accordance with CDC treatment guidelines, appropriate for stage of infection, initiated 30 or more days before delivery. For reporting purposes, congenital syphilis includes cases of congenitally acquired syphilis among infants and children as well as syphilitic stillbirths.

The following provides guidance for reporting neurologic, ocular, otic, and late clinical manifestations of syphilis. Cases should be reported according to stage of infection, as defined above (e.g., primary syphilis; secondary syphilis; early non-primary, non-secondary syphilis; or unknown duration or late syphilis) and the clinical manifestations should be reported in the case report data, as defined below.

3.7. Neurologic Manifestations

Neurologic manifestations (neurosyphilis) can occur at any stage of syphilis. If the patient has neurologic manifestations of syphilis (verified or likely), the case should be reported with the appropriate stage of infection (as if neurologic manifestations were not present) and neurologic manifestations should be noted in the case report data.

1. Clinical Description
   Infection of the central nervous system with *T. pallidum*, as evidenced by manifestations including syphilitic meningitis, meningovascular syphilis, general paresis, including dementia, and tabes dorsalis.
2. Laboratory Criteria for Diagnosis
   A reactive serologic test for syphilis and a reactive VDRL in CSF, in the absence of grossly bloody contamination of the CSF.
3. Classification of neurologic manifestations (neurosyphilis)
   A. Confirmed: Syphilis of any stage that meets both clinical and laboratory criteria for neurosyphilis.
   B. Possible: Syphilis of any stage and clinical symptoms or signs that are consistent with neurosyphilis without other known causes for these clinical abnormalities.
   C. Likely: Syphilis of any stage, and both of the following:
      i. Clinical symptoms or signs that are consistent with neurosyphilis without other known causes for these clinical abnormalities, AND
      ii. Elevated cerebrospinal fluid (CSF) protein (>50 mg/dL2) or leukocyte count (>5 white blood cells/cubic millimeter CSF) in the absence of other known causes of these abnormalities.

3.8. Ocular Manifestations

Ocular manifestations (ocular syphilis) can occur at any stage of syphilis. If the patient has ocular manifestations of syphilis, the case should be reported with the appropriate stage of infection (as if ocular manifestations were not present) and ocular manifestations should be noted in the case report data.

1. Clinical Description
   Infection of any eye structure with *T. pallidum*, as evidenced by manifestations including posterior uveitis, panuveitis, anterior uveitis, optic neuropathy, and retinal vasculitis. Ocular syphilis may lead to decreased visual acuity including permanent blindness.
2. Laboratory Criteria for Diagnosis
   A reactive serologic test for syphilis and demonstration of *T. pallidum* in aqueous or vitreous fluid by darkfield microscopy, or by polymerase chain reaction (PCR) or equivalent direct molecular methods.
3. Classification of ocular manifestations (ocular syphilis)
   A. Confirmed: Syphilis of any stage that meets both clinical and laboratory criteria for ocular syphilis.

B. Possible: Syphilis of any stage and clinical symptoms or signs that are consistent with ocular syphilis without other known causes for these clinical abnormalities.
C. Likely: Syphilis of any stage, and both of the following:
    i. Clinical symptoms or signs consistent with ocular syphilis without other known causes for these clinical abnormalities, AND
    ii. Findings on exam by an ophthalmologist that are consistent with ocular syphilis in the absence of other known causes for these abnormalities.

3.9. Otic Manifestations

Otic manifestations can occur at any stage of syphilis. If the patient has otic manifestations of syphilis, the case should be reported with the appropriate stage of infection (as if otic manifestations were not present) and otic manifestations should be noted in the case report data.

1. Clinical Description
   Infection of the cochleovestibular system with *T. pallidum*, as evidenced by manifestations including sensorineural hearing loss, tinnitus, and vertigo.
2. Laboratory Criteria for Diagnosis
   A reactive serologic test for syphilis and demonstration of T. pallidum in inner ear fluid by darkfield microscopy, or by PCR or equivalent direct molecular detection techniques.
3. Classification of otic manifestations (otosyphilis)
   A. Confirmed: syphilis at any stage that meets both clinical and laboratory criteria for otosyphilis.
   B. Possible: Syphilis of any stage and clinical symptoms or signs that are consistent with otosyphilis without other known causes for these clinical abnormalities.
   Likely: syphilis of any stage, and both of the following:
      i. Clinical symptoms or signs consistent with otosyphilis without other known causes for these clinical abnormalities, AND
      ii. Findings on exam by an otolaryngologist that are consistent with otosyphilis in the absence of other known causes for these abnormalities.

3.10. Late Clinical Manifestations

Late clinical manifestations of syphilis usually develop only after a period of 15–30 years of untreated infection. Therefore, if the patient has late clinical manifestations of syphilis, the case should be reported with the appropriate stage of infection (for most cases, unknown duration or late syphilis) and late clinical manifestations should be noted in the case report data.

1. Clinical Description
   Late clinical manifestations of syphilis (tertiary syphilis) may include inflammatory lesions of the cardiovascular system (e.g., aortitis, coronary vessel disease), skin (e.g., gummatous lesions), bone (e.g., osteitis), or other tissue. Rarely, other structures (e.g., the upper and lower respiratory tracts, mouth, eye, abdominal organs, reproductive organs, lymph nodes, and skeletal muscle) may be involved. In addition, certain neurologic manifestations (e.g., general paresis and tabes dorsalis) are also late clinical manifestations of syphilis.
2. Laboratory Criteria for Diagnosis

A. A reactive treponemal blood test (EIA, FTA-ABS, or TP-PA), OR
B. Demonstration of T. pallidum in late lesions by fluorescent antibody or special stains (although organisms are rarely visualized in late lesions).

3. Classification of late clinical manifestations of syphilis (tertiary syphilis)
   A. Confirmed: A person with a reactive nontreponemal test (e.g., VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (e.g., TP-PA, EIA, CIA or equivalent serologic methods) and either of the following:
      i. Characteristic abnormalities or lesions of the cardiovascular system (e.g., aortitis, coronary vessel disease), skin (e.g., gummatous lesions), bone (e.g., osteitis), or other tissue in the absence of other known causes of these abnormalities, in combination with either demonstration of T. pallidum in late lesions by special stains or equivalent methods, or by polymerase chain reaction (PCR) or equivalent direct molecular methods, or demonstration of pathologic changes that are consistent with T. pallidum infection on histologic examination of late lesions, OR
      ii. Clinical signs and symptoms consistent with late neurologic manifestations of syphilis (e.g., general paresis, including dementia, or tabes dorsalis) in a case that meets the criteria for verified neurologic manifestations of syphilis (see above).
   B. Likely: A person with a reactive nontreponemal test (e.g., VDRL, RPR, or equivalent serologic methods) and a reactive treponemal test (e.g., TP-PA, EIA, CIA or equivalent serologic methods) with either of the following:
      i. Characteristic abnormalities or lesions of the cardiovascular system (e.g., aortitis, coronary vessel disease), skin (e.g., gummatous lesions), bone (e.g., osteitis), or other tissue, in the absence of other known causes of these abnormalities, OR
      ii. Clinical signs and symptoms consistent with late neurologic manifestations of syphilis (e.g., general paresis, including dementia, or tabes dorsalis) in a case that meets the criteria for likely neurologic manifestations of syphilis (see above)

4. DIAGNOSIS AND LABORATORY SERVICES

4.1. Diagnosis

Demonstration of T. pallidum by darkfield microscopy, fluorescent antibody, or other specific stains in specimens from lesions, placenta, umbilical cord, or autopsy material. Reactive nontreponemal blood test (RPR or VDRL) and treponemal blood test (EIA or TP-PA).

4.2. Tests Available

Serological testing for syphilis can be classified into two categories - treponemal and non-treponemal. As the name suggests, the treponemal tests are aimed at detecting an antigen or an antibody of *T. pallidum*. However, a positive treponemal test cannot necessarily be indicative of an active syphilis infection. This is because antibodies remain in the bloodstream even after several years since contraction of syphilis. Non-

treponemal tests on the other hand, looks for indirect indications of the infection, like the presence of cardiolipins. This is released when a treponeme bacteria damages cells. So, if cardiolipin is found in the blood sample, it indicates an active infection. However, one then needs to take a treponemal test to confirm that increased cardiolipin is in fact a result of a syphilis infection.

Non-treponemal serologic tests - Non-treponemal serologic tests for syphilis include VDRL (Venereal Disease Research Laboratory) test and RPR (Rapid Plasma Reagin). The titer should be determined when the test is reactive and a second specimen obtained to verify the reaction.

Treponemal Tests -Treponemal tests can be used for screening, utilizing a rapid test (such as the Rapid Syphilis Health Check) or enzyme immunoassay (EIA) format. These include FTA-ABS (Fluorescent treponemal antibody absorption) test, TPHA and MHA-TP (Treponema pallidum hemagglutination assay) and the TP-PA test (Treponema pallidum particle agglutination assay).

Important Points in the Interpretation of the RPR:

- More than a reactive RPR is needed to justify the diagnosis of syphilis.
- A reactive RPR in the absence of syphilis is called a Biologic False Positive (BFP) or “syphilis infection”. A BFP must always be proven not to represent syphilis.
- The RPR is not necessarily reactive in primary syphilis, and it usually does not become reactive until one to three weeks after the appearance of the chancre.
- A patient may have late syphilis, either acquired or congenital, and have a non-reactive RPR. A negative non-treponemal test does not rule out syphilis.
- A patient with secondary syphilis could have a non-reactive undiluted RPR due to a prozone reaction. If a secondary syphilis case is suspected, a request for dilutions should be specifically made. In secondary syphilis, the TP-PA (MHA-TP) is always positive.
- If the patient receives treatment past one year being infected, the RPR may remain reactive in low titer or in the high pre-treatment titer range for life. In such cases, a cure is not based on serologic reversal, and treatment need not be repeated unless there is other evidence of re-infection.
- A fourfold (2 dilution) rise in the titer (e.g., 1:2 to 1:8) performed by the same laboratory is considered evidence of need for re-treatment. There are exceptions to artificial rises in titer. Reinfection may be ruled out.
- Every pregnant woman with a reactive serologic test for syphilis should be referred to the Sexual Health Clinic or a provider of choice for evaluation and follow up testing.
- A reactive VDRL-CSF test performed on a sample of spinal fluid always represents syphilis unless proved otherwise. Central nervous system involvement (except in cases of tabes dorsalis) is also indicated by elevations of spinal fluid white cell count and total protein.

5. ROUTINE SURVEILLANCE AND CASE INVESTIGATION

1. Receive report from hospital, health care provider’s office, laboratory or public.
2. Obtain health care provider’s name and phone number if not indicated on report.
3. Contact healthcare provider to obtain the following if not already reported:

a. Demographics
b. Lab results
c. Clinical notes, signs and symptoms
d. Treatment information
e. Pregnancy
    i. *Refer to Congenital Syphilis protocol if client is pregnant.*

4. Complete the Local Health Department (LHD) case status in the Administrative tab.
    a. Most classifications for syphilis will be probable based on clinical criteria and supportive laboratory testing. (e.g., all cases of early non-primary and unknown duration or late syphilis will be classified as probable)
    b. Cases classified as confirmed must have the following:
        i. A case that meets the clinical description of primary syphilis or secondary syphilis AND
        ii. Demonstration of *T. pallidum* by darkfield microscopy in a clinical specimen that was not obtained from the oropharynx and is not potentially contaminated by stool, OR
        iii. Demonstration of *T. pallidum* by polymerase chain reaction (PCR) or equivalent direct molecular methods in any clinical specimen.
    c. If, during an investigation, it is determined that a person is not infected/not re-infected with syphilis (e.g., clients with record search history; not a 4-fold increase) the case classification will be not a case (NAC).
5. Case Follow Up – *See investigation priority grid and Syphilis reactor grid.* If the case meets the criteria for closure, select a disposition and skip to number 12. Criteria for closure encompasses case status and can include other factors such as re-interview completed, number of efforts captured to attempt notification/interview/re-interview, and completion of all required fields (e.g., demographics, staging, dispositions).
6. Contact case for notification and interview.
7. Collect pertinent information using the interview record form in EpiTrax.
8. Ensure that proper referrals to services needed and physician referrals are completed for each person that tests positive for syphilis.
9. Ensure that the client has access to and is treated for syphilis.
10. Offer and encourage other STD and HIV testing if not done at the time of syphilis testing.
11. Offer partner services.
    a. Management of Sexual Partners - All sexual partners and/or needle sharing partners within the interview period should be offered testing and counseling to reduce risk of infection. Contact investigation and partner notification are required for cases assigned to disease investigation staff.
    b. DIIS will attempt to notify partners within one business day of collecting contact information.
    c. Partners will be assessed for risk and provided education and counseling for reducing their risk.
    d. Refer to local Internet Partner Services (IPS) procedure for notification of partners, as needed. For local health authorities that need guidance on how to develop a local protocol, refer to: https://www.cdc.gov/std/program/ips/components.htm.

e. Jurisdiction for a case belongs to the local health authority for a patient's county of residence. All partners identified as out of jurisdiction (OOJ) will be entered into EpiTrax with the STD disposition indicated as Sent Out of Jurisdiction. Please see below for additional information.
f. Refer to CDC Passport to Partner Services: https://www.cdc.gov/hiv/effective-interventions/diagnose/partner-services/index.html

12. Provide education and risk reduction counseling.
13. All clients testing positive should be re-interviewed for additional information regarding partners, risk, education, etc.
14. Out of Jurisdiction (OOJ) Cases and Contacts.
15. If the local health authority that receives the initial report discovers that the case resides in a different county, they will transfer the case to the appropriate jurisdiction via EpiTrax by updating the home address and jurisdiction in the case record and marking it for transferring the case via EpiTrax.
16. b) If the local health authority that receives the initial report discovers that the case does not reside in Nevada, they will mark the case as OOJ and transfer the case to DPBH so that the ICCR coordinator can transfer the case to the appropriate state.
17. c) If the patient identifies a partner who lives outside of the local health jurisdiction, the contact will be transferred to the appropriate jurisdiction via EpiTrax by entering the contact's address and appropriate jurisdiction and transferring the contact via EpiTrax.
18. d) For partners residing out of state, local health authority staff will enter the available demographic information into EpiTrax and transfer the case via EpiTrax to DPBH so that the ICCR coordinator can forward the contact to the appropriate state.

6. CONTROL MEASURES

1. Ensure adequate and appropriate treatment is provided as soon as possible. Verify treatment with provider or pharmacy.

2. Provide referrals as needed.
This may include referrals for mental health, additional counseling, housing, substance abuse/addictions, etc. Referrals should be provided when the DIIS identifies areas that may be a barrier for the client to access medical care.

3. Provide risk reduction counseling for the case and their partners

4. Provide education
- Advise clients about risk of complication if left untreated.
- Advise prenatal clients about risk of untreated Syphilis infection in pregnancy and about the need for repeat STI screening in third trimester.
- Counsel on risk of re-infection.
- Stress the importance of testing/treating sexual partner(s).
- Advise client to avoid intercourse until 7 days after patient and partner (s) complete treatments to avoid reinfection.
- Counsel on safer sex practices and use of condoms.
- Advise sexual activity with untested/untreated partner(s) may result in infection.
- Counsel on need for follow-up testing to ensure appropriate response to treatment.

- Offer Chlamydia, Gonorrhea and HIV testing.

Comment:

Management of Partners/Contacts: Contact investigation and partner notification may be provided by the local health authority as determined by available resources using standard partner follow-up methods. Patient confidentiality must be preserved throughout the follow-up process. Telephone contact and interview or face-to-face approaches are acceptable. Electronic communication such as text and email might be acceptable alternatives if confidentiality, privacy and security can be reasonably assured.

7. MANAGING SPECIAL SITUATIONS

7.1. Pregnancy

Nevada Revised Statute (NRS) 442.010 requires an examination for the discovery of syphilis pursuant to section 1 must be performed:

a) During the first trimester of pregnancy at the first visit to a physician or other person permitted by law to attend upon pregnant people, a non-hospital medical facility or an emergency department or labor and deliver unit of a hospital;
b) During the third trimester of pregnancy between the 27th and 36th week of gestation; and
c) At delivery for a pregnant person who:
    1. Should be routinely tested for infection with syphilis, as recommended by the Centers for Disease Control and Prevention;
    2. Lives in an area designated by the Division as having high syphilis morbidity;
    3. Did not receive prenatal care;
    4. Or delivers a stillborn infant after 20 weeks of gestation.

Additional details can be found in NRS 442.010.

7.2. Co-infection with HIV/AIDS

All persons who have syphilis should be tested for HIV infection and other sexually transmitted infections including gonorrhea and chlamydia. Consider retesting for HIV after 3 months if the first HIV test is negative. Though uncommon, unusual serologic responses have been observed among HIV-infected persons who have syphilis. Most commonly, serologic titers have been higher than expected, but false negative serologic tests and delayed appearance of antibodies have been reported. Serologic titers should be interpreted in the usual manner for diagnosis and treatment of *T. pallidum* infection. Unless neurologic symptoms are present, cerebrospinal fluid examination is not necessary in individuals with HIV and syphilis.

7.3. Outbreak Investigation

Refer to applicable local Outbreak Response Plan.

8. ROUTINE PREVENTION

8.1. Vaccine Recommendations

No vaccine currently exists for syphilis.

8.2. Education

Key individual STD prevention messages include:

Abstinence
The most reliable way to avoid infection is to not have sex (i.e., anal, vaginal or oral) (https://www.cdc.gov/std/prevention/default.htm).
If you have, or plan to have, more than one sex partner:

- Use a latex condom and lubricant every time you have sex.
- Get tested for asymptomatic STDs including HIV.
- If you are a man who has had sex with other men (MSM), get tested at least once a year.
- If you are a woman who is planning to get pregnant or who is pregnant, get tested for syphilis and HIV as soon as possible, before you have your baby. Ask your health care provider about being tested for other STDs.
- Talk about STDs, including HIV, with each partner before you have sex.
- Learn as much as you can about each partner's past behavior (sex and drug use).
- Ask your partners if they have recently been treated for an STD or have been tested for HIV; encourage those who have not been tested to do so.

8.3. Prevention

Key STD prevention strategies include:

STD prevention counseling, testing, and referral services – Individuals at risk for STD should be offered counseling regarding methods to eliminate or reduce their risk and testing so that they can be aware of their status and take steps to protect their own health and that of their partners.

Partner Services (or Partner Notification) with strong linkages to prevention and treatment/care services – Sexual partners of STD-infected persons have been exposed to an STD and are at-risk of being infected. Partner services locate these individuals based on information provided by the patient and provide counseling and education about the exposure as well as services to prevent infection or, if infected, linkages to care.

Prevention for high-risk populations – Prevention interventions for high-risk populations at high-risk for STDs, including HIV-infected persons, are critical to reducing the spread of STDs and HIV and ensure that those at highest risk of acquiring or transmitting these diseases are given the tools necessary to protect themselves and others from HIV infection. Prevention includes targeted health education and risk reduction, health communication programs, and public information programs for at-risk populations and the general public.

HIV Prevention and Care – For people at high risk of acquiring HIV, which may include for example some MSM patients and some people who inject drugs, referral to HIV testing (if

HIV status is not already known) and referral to PrEP (Pre-exposure Prophylaxis for HIV) navigation or evaluation is key in preventing acquisition of HIV.

For people living with HIV who are not receiving medical care or who are not virally suppressed, referral to HIV case management and medical care for HIV infection are key in promoting individual health as well as preventing spread of HIV.

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REFERENCES

Centers for Disease Control and Prevention (2023). Partner Services. Available: https://www.cdc.gov/hiv/effective-interventions/diagnose/partner-services/index.html

Centers for Disease Control and Prevention (2022). Syphilis – CDC Detailed Fact Sheet. Available: https://www.cdc.gov/std/syphilis/stdfact-syphilis-detailed.htm.

Centers for Disease Control and Prevention (2022). Syphilis – Sexually Transmitted Infections Treatment Guidelines, 2021. Available: https://www.cdc.gov/std/treatment-guidelines/syphilis.htm

Centers for Disease Control and Prevention (2021). Syphilis (Treponema pallidum) 2018 Case Definition. Available: https://ndc.services.cdc.gov/case-definitions/syphilis-2018/

Centers for Disease Control and Prevention (2020). 4 Internet Partner Services (IPS) Components. Available: https://www.cdc.gov/std/program/ips/components.htm

Centers for Disease Control and Prevention (2003). Recommendations for Public health Surveillance of Syphilis in the United States. Atlanta, GA: U.S. Department of health and Human Services.

Illinois Department of Public Health (no date). Increasing Early Syphilis Cases in Illinois – Syphilis Laboratory Tests https://dph.illinois.gov/content/dam/soi/en/web/idph/files/publications/publicationsohpsyphilis-testing-and-lab-interpretation.pdf

Nevada Administrative Code 441A. Available: https://www.leg.state.nv.us/nac/nac-441a.html

Nevada Revised Statute 442.010. Available: https://www.leg.state.nv.us/NRS/NRS-442.html#NRS442Sec010

Nevada Revised Statute 441A. Available: https://www.leg.state.nv.us/nrs/nrs-441a.html

Nevada Senate Bill No. 211. Available: https://www.leg.state.nv.us/Session/81st2021/Bills/SB/SB211_EN.pdf

Nevada Senate Bill No. 304. Available: https://www.leg.state.nv.us/Session/75th2009/Bills/SB/SB304_EN.pdf

Nicoll D, Lu CM, McPhee SJ. Guide to Diagnostic Tests, Seventh Edition.

Office of Analytics (2022). Data Dashboards & Reports Catalog. Available: https://dhhs.nv.gov/Programs/Office_of_Analytics/OFFICE_OF_ANALYTICS_-_DATA___REPORTS/

Oregon Health Authority (2019). Syphilis Investigative Guidelines Available: file:///C:/Users/hgp1/Downloads/cdc_48172_DS1.pdf

Soreng K., Levy R., Falike Y (2014). Serologic Testing for Syphilis: Benefits and Challenges of a Reverse Algorithm.

Southern Nevada Health District Office of Disease Surveillance (2021). Syphilis Investigative Protocol.

Spach D., Ramchandani M. (2022). Syphilis. National STD Curriculum. Available: https://www.std.uw.edu/go/comprehensive-study/syphilis/core-concept/all

Washington State Department of Health (2022). Syphilis Investigative Reporting Guidelines.

APPENDIX A

Common Syphilis Serologic Tests

Test	Full Name	Type	Target	Notes
RPR	Rapid Plasma Reagin	Non-treponemal	Cardiolipin Antibodies	Quantitative results reported as a titer.
VDRL	Venereal Disease Research Laboratory	Non-treponemal	Cardiolipin Antibodies	Quantitative results reported as a titer. Only test approved for CSF (cerebrospinal fluid) specimens
FTA-ABS	Fluorescent Treponemal Antibody-Absorption	Treponemal	*T. pallidum Antibodies*	
TP-PA	*Treponema pallidum*-particle agglutination	Treponemal	*T. pallidum Antibodies*	
MHA-TP	Microhemagglutination-*Treponema pallidum*	Treponemal	*T. pallidum Antibodies*	
EIA	Enzyme immunoassay	Treponemal	*T. pallidum Antibodies*	May be initial test in reverse sequencing algorithm.
CIA	Chemiluminescent immunoassay	Treponemal	*T. pallidum Antibodies*	May be initial test in reverse sequencing algorithm.

Source: Illinois Department of Public Health
https://dph.illinois.gov/content/dam/soi/en/web/idph/files/publications/publicationsohpsyphilis-testing-and-lab-interpretation.pdf
Note: This table is not exhaustive of all the tests available for diagnosing syphilis.

Serologic Diagnostic Tests:

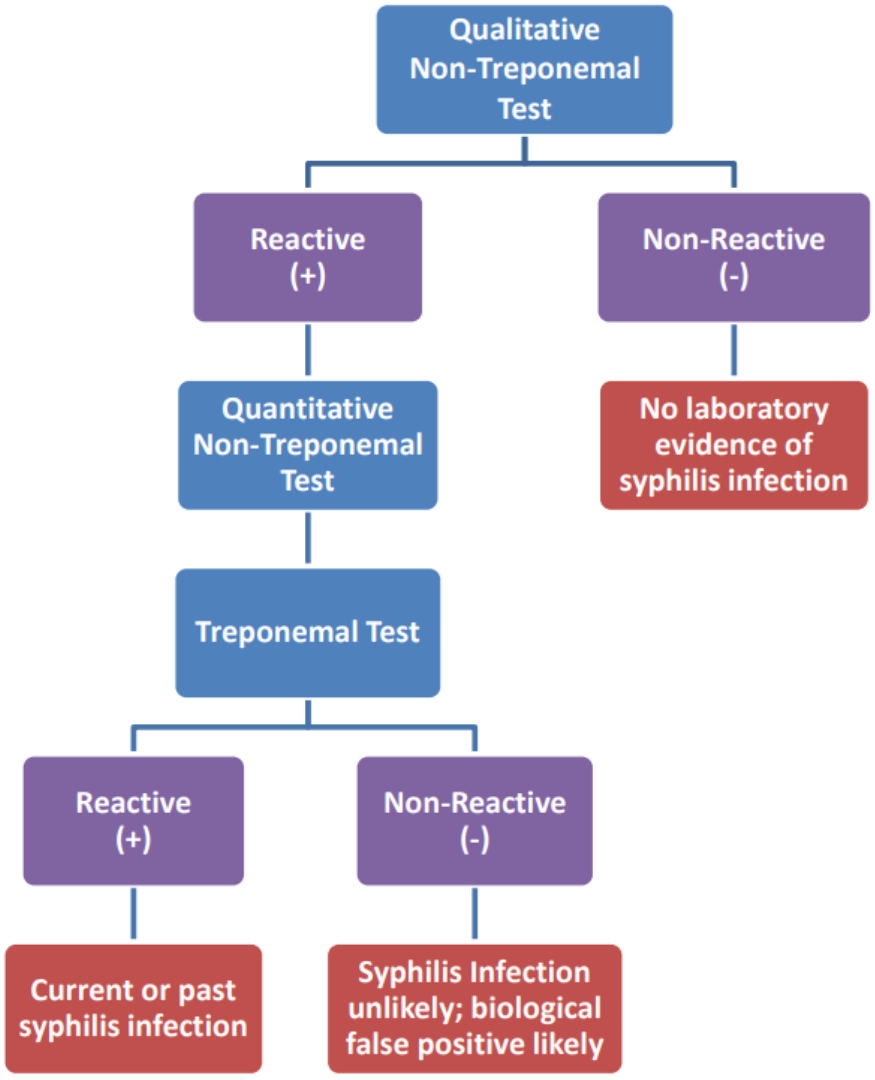
Non-treponemal tests, also called screening tests (RPR and VDRL), do not detect antibodies specific for syphilis and are based upon the reactivity of serum from infected patients to a cardiolipin-cholesterollecithin antigen (regain). RPR and VDRL results should have a quantitative titer reported with them (1:2, 1:4, 1:8, etc.). A reactive RPR must also have a reactive treponemal test to be considered a case of syphilis as false positives are possible. Changes in titer are followed after treatment to detect a therapeutic response and to assess for new infection. With adequate treatment, most individuals will return to a non-reactive RPR. Some individuals may maintain a low titer RPR for life despite adequate treatment (serofast). False negatives can also occur with this test, most often during early acute infection.

Treponemal tests, also called confirmatory tests (FTA, TP-PA, EIA), detect antibodies specific to syphilis. Treponemal antibodies will appear earlier after acute infection than non-treponemal antibodies. The antibodies detected in these tests usually remain detectable for life even after successful treatment. Thus, a reactive treponemal test can indicate current or past syphilis infection.

APPENDIX B

Syphilis Screening Algorithms

Traditional Syphilis Testing Algorithm

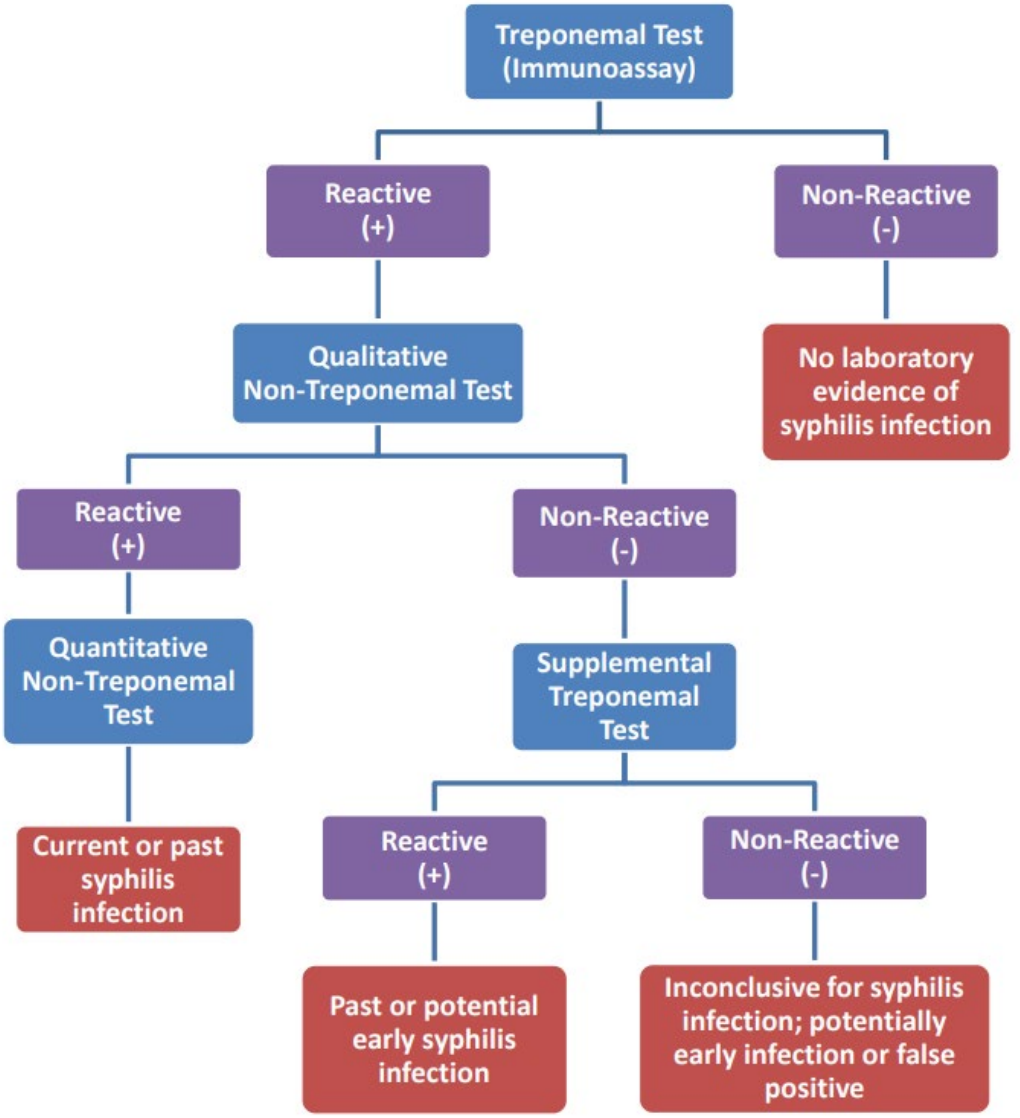


Source: Illinois Department of Public Health
https://dph.illinois.gov/content/dam/soi/en/web/idph/files/publications/publicationsohpsyphilis-testing-and-lab-interpretation.pdf

Note:

The traditional testing algorithm for syphilis begins testing with the non-treponemal test. If the non-treponemal test is reactive, a treponemal test is then used to confirm syphilis infection.

Reverse Syphilis Testing Algorithm



Source: Illinois Department of Public Health
https://dph.illinois.gov/content/dam/soi/en/web/idph/files/publications/publicationsohpsyphilis-testing-and-lab-interpretation.pdf

Note:

The reverse testing algorithm for syphilis begins testing with a treponemal test. If this test is reactive, a non-treponemal test is performed. When the non-treponemal test is non-reactive, a second treponemal test is performed to determine if the first treponemal test was a false positive.

APPENDIX C

Examples of Increases in Nontreponemal Titers

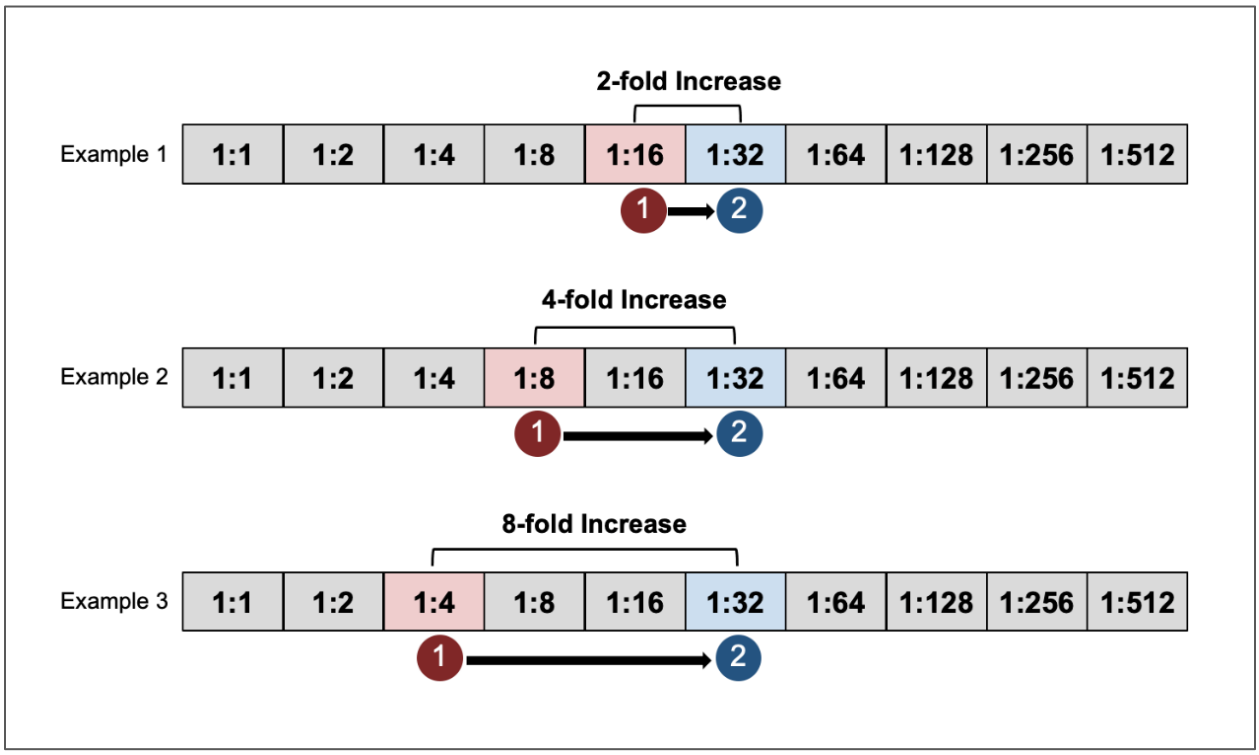


Illustration credit: David H. Spach, MD; National STD Curriculum

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