Syphilis, Syphilis in Pregnancy, and Congenital Syphilis

Investigative Guidelines

August 2023

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. Identify cases of syphilis and prevent transmission
2. Ensure adequate treatment and follow-up for individuals with syphilis
3. Ensure appropriate management, including screening and presumptive treatment, of sexual contacts
4. Describe the epidemiology of syphilis in Oregon

1.2 Laboratory and Physician Reporting Requirements

1. Licensed laboratories must report all positive test results indicating syphilis infection to the Local Public Health Authority (LPHA) within one working day (OAR 333-018-0000; 333-018-0015)[1]
2. Clinicians must report lab-confirmed and clinically suspect cases of syphilis to the LPHA within one working day (OAR 333-018-0000; 333-018-0015)[1]
3. Health care providers, health care facilities, and licensed laboratories shall cooperate with public health authorities in the investigation and control of syphilis infections (OAR 333-019-0002)[2]

1.3 Local Public Health Authority Reporting and Follow-up Responsibilities

1. LPHA must begin follow-up case investigation within two working days of receiving the initial provider or laboratory report.
2. LPHA must report all cases to the OHA STD Program through the Oregon Public Health Epidemiology User System (Orpheus) by the end of the calendar week of initial provider or lab report (OAR 333-018-0020)[1]
3. LPHA must conduct case investigations and manage sexual contacts by following procedures outlined in these Investigative Guidelines (OAR 333-019-0000, ORS 433.006)[2,3]

2. DISEASE AND EPIDEMIOLOGY

2.1 Etiologic Agent

The etiologic agent in syphilis is *Treponema pallidum* subspecies *pallidum*, a spirochete (corkscrew-shaped) bacterium.

Of all the subspecies of *T. pallidum*, only *T. pallidum* subsp. *pallidum* is transmitted routinely by sexual contact. The other *T. pallidum* subspecies are transmitted non-sexually (e.g., yaws, pinta).

2.2 Description of Illness

Syphilis is called “the great imitator” because many of the signs and symptoms mimic those of other diseases. If untreated, syphilis infection progresses through stages that are often separated by periods without any symptoms (latency). Neurosyphilis, ocular syphilis, and otosyphilis can occur at any stage of infection.

During the incubation period, before clinical signs or symptoms appear, *T. pallidum* can spread to the circulatory, lymphatic, and central nervous systems.

Early Syphilis: clinical manifestations mainly involve the skin and mucosal surfaces, although secondary syphilis often has systemic manifestations.

- **Primary syphilis**
  - A chancre is the defining feature of primary syphilis
  - A chancre is a small round or oval skin ulcer with a smooth base and firm raised borders that appears where *T. pallidum* entered the body:
    - Most commonly appear on the penis, labia, perianal area, or mouth
    - May go unnoticed, especially if located inside the vagina, foreskin, or rectum
    - Resolve spontaneously within a few weeks, even without treatment
  - Classic primary syphilis is defined by a single painless chancre BUT multiple chancres are common and can be painful (multiple chancres on genitals are often misdiagnosed as herpes simplex virus [HSV] infection)
- **Secondary syphilis**
  - Skin and mucous membrane lesions are the defining feature of secondary syphilis. A lesion is an area of abnormal tissue anywhere in or on the body. While only one type of lesion is associated with primary syphilis (chancre), different lesions are found in secondary syphilis:
    - Rashes can appear anywhere on the body, vary widely in appearance, and do not usually cause itching
      - The characteristic secondary rash appears on the hands and feet, and often the torso
    - Other secondary lesions may include:
      - Mucous patches in the mouth or genital area
      - Condyloma lata in the genital or rectal area
      - Alopecia
  - Symptoms generally appear about 4 to 10 weeks after the onset of the primary chancre (chancres may still be present when secondary symptoms develop)

  - Widespread dissemination of *T. pallidum* throughout the body via the bloodstream causes fever, headaches, muscle aches, malaise, and lymphadenopathy
  - Even without treatment, lesions and symptoms typically resolve spontaneously within a few weeks, but can persist for months
  - If untreated, secondary symptoms can reappear after a latency period

Latent Syphilis: characterized by the persistence of *T. pallidum* in the body without clinical signs or symptoms.

- **Early non-primary non-secondary (early latent) stage**:
  - Occurs when an individual is asymptomatic and there is evidence that the infection was acquired in the 12 months prior to diagnosis
  - Can occur between the primary and secondary stages, after the secondary stage, or between secondary relapses
- **Late or unknown duration (late latent) stage**:
  - Occurs when an individual is asymptomatic and the infection was acquired more than 12 months prior to diagnosis **OR** the time of infection cannot be determined with certainty

Neurosyphilis, Ocular Syphilis, and Otic Syphilis: clinical manifestations that can occur during any stage.

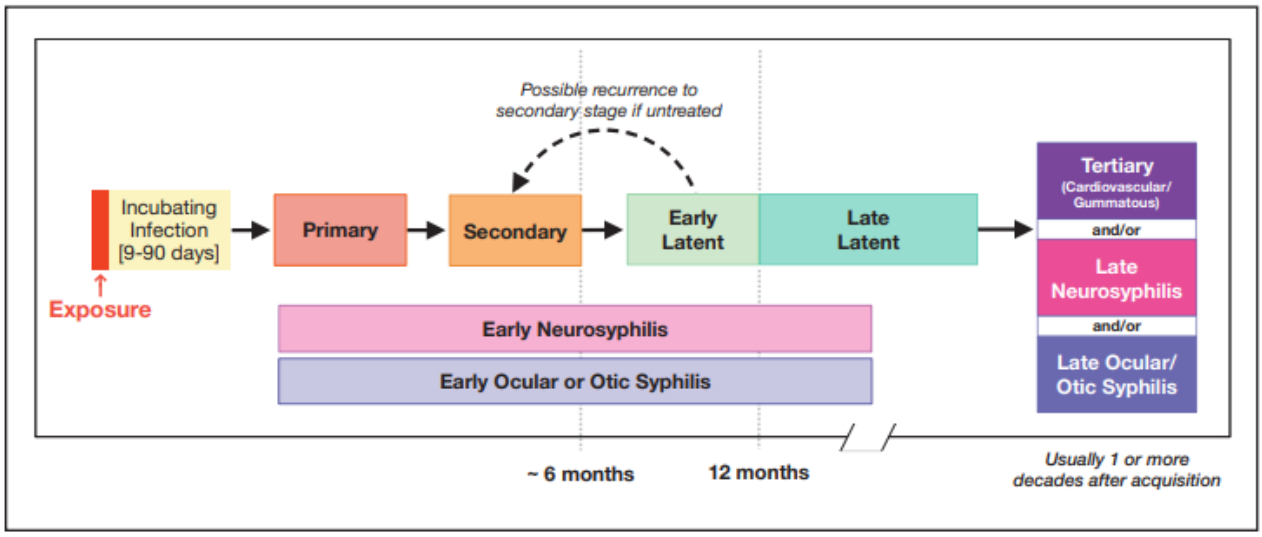
- **Neurosyphilis** can manifest as meningitis or stroke, cognitive dysfunction, motor or sensory deficits, and/or cranial nerve palsies
- **Ocular syphilis** can involve any eye structure but usually manifests as panuveitis or posterior uveitis
  - May cause permanent vision loss
  - Occurs with or without neurosyphilis
- **Otosyphilis** can manifest as hearing loss, tinnitus, and/or vertigo
  - May cause permanent hearing loss
  - Occurs with or without neurosyphilis

Late Clinical Manifestations (Tertiary Syphilis)

- Usually only develop after 15–30 years of untreated infection
- Can affect virtually any organ system including the cardiovascular system, central nervous system, and skin.

See **Figure 1** for a graphical summary of the natural history of syphilis.

Figure 1. The Natural History of Untreated Syphilis



Source: New York City Department of Health and Mental Hygiene, and the New York City STD Prevention Training Center. The Diagnosis and Management of Syphilis: An Update and Review. March 2019. Available at www.nycptc.org

2.3 Reservoirs

Humans are the only reservoir for *T. pallidum*.

2.4 Modes of Transmission

Sexual transmission:

- *T. pallidum* enters the body via skin and mucous membranes through abrasions during sexual contact
- Persons are infectious throughout the primary and secondary stages, when lesions are present
- Usually results from contact with genital mucous membranes, but it can also occur from contact with the mouth, rectum, and cutaneous lesions

Vertical transmission:

- Results in fetal infection
- Occurs primarily via transplacental passage of *T. pallidum*
- Can occur during any stage of syphilis
- Can also occur if a newborn has contact with genital syphilis lesions at the time of delivery

Other forms of syphilis transmission are rare. Transfusion-associated syphilis has been virtually eliminated in the United States and transmission through needle-sharing is infrequent.

2.5 Incubation Period

The earliest sign of syphilis, a primary chancre, usually appears about 2 to 3 weeks after *T. pallidum* infection. Blood tests usually detect infection within 21 days of exposure but may take up to 6 weeks to show seroconversion.

2.6 Period of Communicability

Syphilis is spread by sexual contact—it is not spread through casual contact such as shaking hands. A person acquires syphilis when their mucous membranes (vulva, vagina, penis, anus, mouth) come into contact with bacteria-rich lesions (chancres, rash, condyloma lata, or mucous patches). These bacteria-rich lesions occur in primary and secondary syphilis and may not be visible.

2.7 Treatment

See the CDC 2021 STI Treatment Guidelines for detailed treatment information.[4] Refer to **Table 1** for treatment recommendations for syphilis in non-pregnant adults. Refer to **Table 2** for treatment recommendations for neurosyphilis, ocular syphilis, and otosyphilis. Refer to the Syphilis in Pregnancy and Congenital Syphilis Investigative Guidelines for treatment recommendations for pregnant people and infants/children.

Table 1. Treatment Recommendations for Syphilis in Non-Pregnant Adults

Stages	Recommended Regimen	Alternative Regimen if True Penicillin Allergy*
Primary, Secondary, and Early Non-Primary Non-Secondary	Benzathine penicillin G (Bicillin L-A) 2.4 million units IM in a single dose	Doxycycline 100 mg orally twice daily for 14 days **OR** Skin testing for penicillin allergy and desensitization
Unknown Duration or Late	Benzathine penicillin G (Bicillin L-A) 7.2 million units total IM as three doses of 2.4 million units each at 7-day intervals	Doxycycline 100 mg orally twice daily for 28 days **OR** Skin testing for penicillin allergy and desensitization

* Approximately 10% of all U.S. patients report having a penicillin allergy. However, less than 1% of the population is truly allergic to penicillin. Refer to the CDC 2021 STI Treatment Guidelines and the Is it Really a Penicillin Allergy? fact sheet for guidance on evaluating a reported penicillin allergy.

- For unknown duration or late syphilis, the optimal interval between benzathine penicillin G doses is 7 days; an interval of 6-9 days is acceptable.
    - For people without pregnancy capacity, it is not necessary to restart treatment if intervals between doses are outside this range.
    - For non-pregnant people with pregnancy capacity, adherence to the 6–9-day interval is strongly encouraged to reduce the risk of congenital syphilis in a future pregnancy.
- **For pregnant patients with unknown duration or late syphilis, the dosing interval is critical. A 7-day interval is ideal and a 6–9-day interval is acceptable. If any doses are given outside this interval,**

the treatment series must be restarted. Refer to the Syphilis in Pregnancy Investigative Guidelines for further guidance on treatment in pregnancy.

Table 2. Treatment Recommendations for Clinical Manifestations of Syphilis

Clinical Manifestations	Recommended Regimen
Neurosyphilis, Ocular Syphilis, or Otosyphilis	Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units intravenously every 4 hours or continuous infusion, for 10-14 days

- Ceftriaxone 2 grams IV daily for 14 days is an alternative regimen for non-pregnant patients. Ceftriaxone is not a CDC-recommended first-line therapy but may be appropriate for patients who:
  - Are not comfortable with an infusion pump **OR**
  - Cannot administer treatment at home due to unstable/unsafe housing

3. CASE DEFINITIONS, DIAGNOSIS, AND LABORATORY SERVICES

3.1 Syphilis Stages

See the CDC 2018 Syphilis Surveillance Case Definition page for more information on the stages below.[5] The CDC adult syphilis surveillance staging flowchart (see Appendix A) is a useful tool for determining surveillance stage.

Since RPR testing is the most common form of nontreponemal testing, the terms "nontreponemal serologic testing" and "RPR" are used interchangeably throughout this section.

3.1.1 Primary Syphilis

1. Clinical Description
   - Stage characterized by one or more chancres
2. Laboratory Criteria
   - Confirmatory: *T. pallidum* by darkfield microscopy (only available at Multnomah Co. Health Department) or PCR or equivalent direct molecular methods
   - Supportive: Reactive serologic test for syphilis (RPR *or* treponemal test)
3. Case Classification
   - **Confirmed (rare):** Clinically compatible case with evidence of *T. pallidum* by darkfield microscopy or PCR or equivalent direct molecular methods
     - Confirmed criteria is NOT met by biopsy results or staining done with samples taken from lesions. If a darkfield exam (which does not involve staining) is not done, then a case is not confirmed.

- **Presumptive:** Clinically compatible case (must have chancre(s)) with at least one reactive serologic test (RPR *or* treponemal test)

3.1.2 Secondary Syphilis

1. Clinical Description
   - Stage characterized by a localized or diffuse rash. Other signs may include mucous patches, condyloma lata, and alopecia.
     - Secondary lesions may develop before primary chancres have fully resolved. If both primary and secondary signs are present, this is staged as secondary syphilis.
2. Laboratory Criteria
   - Confirmatory: *T. pallidum* by darkfield microscopy (only available at Multnomah Co. Health Department) or PCR or equivalent direct molecular methods
   - Supportive: Reactive RPR and reactive treponemal test
3. Case Classification
   - **Confirmed (rare):** Clinically compatible case with evidence of *T. pallidum* by darkfield microscopy or PCR or equivalent direct molecular methods
     - Confirmed criteria is NOT met by biopsy results or staining done with samples taken from lesions. If a darkfield exam (which does not involve staining) is not done, then a case is not confirmed.
   - **Presumptive:** Clinically compatible case (must have rash, mucous patches, condyloma lata, or alopecia) with reactive RPR **and** reactive treponemal test

3.1.3 Early Non-Primary Non-Secondary Syphilis

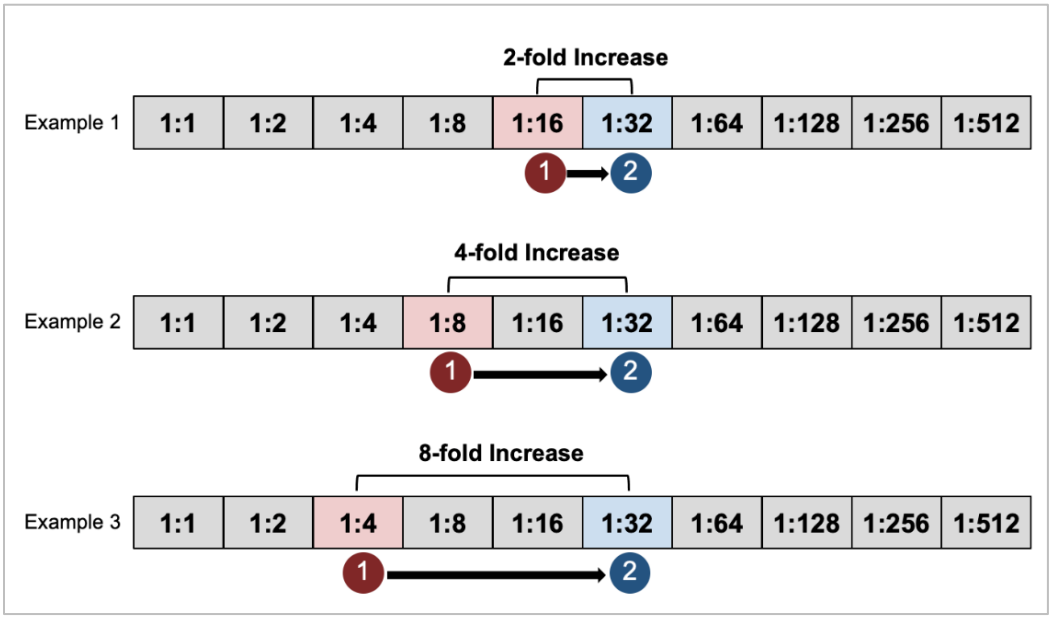
1. Clinical Description
   - Stage in which initial infection occurred within the previous 12 months and there are no signs or symptoms of primary or secondary syphilis
2. Laboratory Criteria
   - No past diagnosis of syphilis, and a reactive RPR and treponemal test ***OR***
   - History of syphilis treatment, and a current RPR titer showing a fourfold or greater increase from the last titer (unless the increase was not sustained for >2 weeks). Refer to **Figure 2** for examples of increases in titers.
3. Case Classification
   - **Confirmed:** Cannot be confirmed. Can only be classified as presumptive.
   - **Presumptive:** No clinical signs or symptoms of primary or secondary syphilis and evidence of acquiring the infection within the previous 12 months based on one or more of the following:
     - Documented RPR seroconversion or at least a fourfold increase in titer in the past 12 months (unless the increase was not sustained for >2 weeks)
     - Documented treponemal test seroconversion in the past 12 months
     - History of symptoms consistent with primary or secondary syphilis in the past 12 months

- History of sexual exposure to a partner in the past 12 months who had primary, secondary, or early non-primary non-secondary syphilis (partner's stage must be documented in medical records and/or Orpheus)
- Only sexual contact ever was in the past 12 months

3.1.4 Unknown Duration or Late Syphilis

1. Clinical Description
   - Stage in which there are no signs or symptoms of primary or secondary syphilis and a) initial infection occurred >12 months ago or b) there is not enough evidence to prove the infection was acquired in the past 12 months
2. Laboratory Criteria
   - No past diagnosis of syphilis, and a reactive RPR and treponemal test
     OR
   - History of syphilis treatment, and a current RPR titer showing a fourfold or greater increase from the last titer (unless the increase was not sustained for >2 weeks). Refer to **Figure 2** for examples of increases in titers.
     OR
   - Likely or verified neurologic, ocular, otic, or late clinical manifestations without a current RPR titer showing a fourfold or greater increase
3. Case Classification
   - **Confirmed:** Cannot be confirmed. Can only be classified as presumptive.
   - **Presumptive:** No clinical signs or symptoms of primary or secondary syphilis, no evidence of having acquired the disease in the past 12 months, and meets laboratory criteria

*Figure 2. 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. Figure from National STD Curriculum Syphilis Quick Reference.

3.2 Syphilis Complications

See the CDC 2018 Syphilis Surveillance Case Definition page for more information on the manifestations below. Note that for Orpheus documentation of these conditions, LPHA staff are only expected to select the criteria that are met—it is not necessary to know the classification category (e.g., possible, likely, or verified). Refer to the Syphilis Case Report and Data Entry Manual for guidance on Orpheus documentation.

3.2.1 Neurologic Manifestations

Neurosyphilis can occur at any stage of syphilis. A case should be staged appropriately and neurological manifestations, if present, should be documented in the case record.

1. Clinical Description
   - Infection of the central nervous system with *T. pallidum*, as shown by manifestations including cranial nerve dysfunction, meningitis, meningovascular syphilis, stroke, altered mental status, tabes dorsalis, and general paresis
   - Symptoms include: severe headache; muscle weakness or paralysis; numbness; changes in mental status (trouble focusing, confusion, personality changes); and dementia (problems with memory, thinking, and/or making decisions)
2. Classification of Neurologic Manifestations
   - **Possible:** Reactive RPR and treponemal test **AND** clinical symptoms or signs consistent with neurosyphilis without other known causes
   - **Likely:** Reactive RPR and treponemal test with both of the following:
     - Clinical symptoms or signs consistent with neurosyphilis without other known causes of these abnormalities,

     AND
     - Elevated cerebrospinal fluid (CSF) protein (>50 mg/dl2) or white blood cell (WBC) count (>5 WBC/mm3) without other known causes
   - **Verified:** Reactive RPR and treponemal test with both of the following:
     - Clinical symptoms or signs that are consistent with neurosyphilis without other known causes

     AND
     - A reactive CSF VDRL in the absence of grossly bloody contamination, defined as a red blood cell (RBC) concentration of over 6000 per cubic millimeter in the CSF

3.2.2 Ocular Manifestations

Ocular syphilis can occur at any stage of syphilis. A case should be staged appropriately and ocular manifestations, if present, should be documented in the

case record. Ocular syphilis is an emergency—permanent vision loss can occur if not treated promptly.

1. Clinical Description
    - Infection of any eye structure with *T. pallidum*, as shown by manifestations including posterior uveitis, panuveitis, anterior uveitis, optic neuropathy, retinal vasculitis, and interstitial keratitis
    - Symptoms include: eye pain or redness, light sensitivity, floating spots in the field of vision (“floaters”), and changes in vision (blurry vision or vision loss)
2. Classification of Ocular Manifestations
    - **Possible:** Reactive RPR and treponemal test **AND** clinical symptoms or signs consistent with ocular syphilis without other known causes
    - **Likely:** Reactive RPR and treponemal test with both of the following:
        - Clinical symptoms or signs consistent with ocular syphilis without other known causes of these abnormalities,

        AND
        - Findings on exam by an ophthalmologist that are consistent with ocular syphilis without other known causes
    - **Verified (rare):** Reactive RPR and treponemal test with both of the following:
        - Clinical symptoms or signs that are consistent with ocular syphilis without other known causes

        AND
        - *T. pallidum* in eye fluid by darkfield microscopy or PCR

3.2.3 Otic Manifestations

Otosyphilis can occur at any stage of syphilis. A case should be staged appropriately and otic manifestations, if present, should be documented in the case record. Otosyphilis is an emergency—permanent hearing loss can occur if not treated promptly.

1. Clinical Description
    - Infection of the cochleovestibular system with *T. pallidum*, as shown by manifestations including sensorineural hearing loss, tinnitus, and vertigo
    - Symptoms include hearing loss; tinnitus (ringing, buzzing, roaring, or hissing in the ears); balance difficulties; and dizziness or vertigo
2. Classification of Otic Manifestations
    - **Possible:** Reactive RPR and treponemal test **AND** clinical symptoms or signs consistent with otosyphilis without other known causes
    - **Likely:** Reactive RPR and treponemal test with both of the following:
        - Clinical symptoms or signs consistent with otosyphilis without other known causes of these abnormalities,

        AND
        - Findings on exam by an otolaryngologist that are consistent with otosyphilis without other known causes
    - **Verified (rare):** Reactive RPR and treponemal test with both of the following:

- Clinical symptoms or signs that are consistent with otosyphilis without other known causes

AND

- *T. pallidum* in inner ear fluid by darkfield microscopy or PCR

3.2.4 Late Clinical Manifestations (extremely rare)

Late clinical manifestations of syphilis (tertiary syphilis) usually develop only after a period of 15-30 years of untreated infection. The case should be reported with the appropriate stage of infection (unknown duration or late syphilis in most cases) and late clinical manifestations, if present, should be documented in the case report.

1. Clinical Description
   - Late clinical manifestations of syphilis may include inflammatory lesions of the cardiovascular system, skin, bone, or other tissue
2. Classification of Late Clinical Manifestations of Syphilis
   - **Possible:** Not an option for late clinical manifestations
   - **Likely:** Reactive RPR and treponemal test with either of the following:
     - Characteristic abnormalities or lesions of the cardiovascular system, skin, bone, or other tissue, without other known causes

     OR

     - Clinical signs and symptoms consistent with late neurologic manifestations of syphilis and either elevated CSF protein (>50 mg/dl2) or CSF WBC count (>5 WBC/mm3) without other known causes
   - **Verified:** Reactive RPR and treponemal test and either of the following:
     - Characteristic abnormalities or lesions of the cardiovascular system, skin, bone, or other tissue without other known causes, in combination with either *T. pallidum* by special stains or PCR, or pathologic changes that are consistent with *T. pallidum* infection on histologic examination

     OR

     - Clinical signs and symptoms consistent with late neurologic manifestations of syphilis and a reactive CSF VDRL

3.3 Diagnosis

3.3.1 Direct Detection of *T. Pallidum*

Darkfield microscopy and molecular tests (e.g., PCR) for detecting *T. pallidum* directly from of lesion fluid or tissue are the definitive methods for immediate diagnosis of primary or secondary syphilis.

The only darkfield microscope currently in use in Oregon is at the Multnomah County Health Department.

3.3.2 Serological Tests for Syphilis

Refer to **Table 3** for information and frequently asked questions about nontreponemal and treponemal serological tests for syphilis. The California PTC

Clinical Interpretation of Syphilis Screening Algorithms Resource for Local Health Jurisdictions (see Appendix B) includes descriptions of the traditional and reverse syphilis screening algorithms and results.

Table 3. Frequently Asked Questions about Nontreponemal and Treponemal Tests

FAQs	***Nontreponemal Tests***	***Treponemal Tests***
What are the common test names?	The two nontreponemal tests are the rapid plasma reagin (RPR) and the VDRL. The RPR is the most common nontreponemal serological (blood) test. The VDRL is mainly used for CSF testing. Refer to **Table 4** for examples of syphilis test names on lab reports.	There are several types of treponemal tests, including enzyme or chemiluminescence immunoassays (EIA/CIA); *Treponema pallidum* particle agglutination assay (TP-PA); and fluorescent treponemal antibody absorption test (FTA). Refer to **Table 4** for examples of syphilis test names on lab reports.
Is the test specific to syphilis?	No. "Nontreponemal" means the antibodies detected by these tests are not responding to treponemal bacteria. Biologic false positive results can be due to many causes, such as pregnancy, autoimmune diseases, and HIV.	Yes. Treponemal tests detect antibodies specific to *T. pallidum*.
Is the test qualitative or quantitative?	Both. An initial nontreponemal result is qualitative. If reactive, it reflexes to a quantitative result known as a titer. The titer is the measurement of antibodies through diluting a person's blood to determine the highest dilution at which a reactive result (agglutination/flocculation) is still produced. A 1:2 titer indicates a low concentration of antibodies, as none were detected after only two dilutions. A 1:128 titer indicates a high concentration of antibodies, as none were detected after eight dilutions.	Treponemal test results are qualitative. If a numerical value is reported with a reactive result (e.g., FTA 4+), it should be ignored.

How soon does the test become positive?	Nontreponemal tests will typically be reactive by 21 days after infection.	Treponemal tests will typically be reactive by 21 days after infection. EIA/CIA and TP-PA tests may become positive sooner than nontreponemal tests.
Can the test be used to monitor for treatment response and reinfection?	Yes. A baseline titer should be done on or as close to the day of treatment initiation as possible so that treatment response can be determined accurately. Only titers of the same nontreponemal test type should be compared.	No. Treponemal tests remain positive for life, even after treatment. They are not useful for monitoring treatment response or diagnosing a new infection in anyone with syphilis history.
Does the test become negative after treatment?	Nontreponemal tests often become negative after treatment, but it is also common for a low titer to persist for life (known as serofast state). Even without treatment, titers drop over time.	No. See above.
How should equivocal/indeterminate results be handled?	If the traditional screening algorithm is followed, an equivocal/indeterminate RPR result should be followed by a treponemal test. If the reverse screening algorithm is followed, a second treponemal test may be necessary.	No matter which screening algorithm is followed, a second treponemal test may be necessary if the first treponemal test result is equivocal/indeterminate.

Table 4. Examples of Syphilis Test Names on Lab Reports

	Test Type	**Examples of Test Names on Lab Reports**
Nontreponemal Tests (qualitative and quantitative)	RPR	RPR Ser Ql RPR Ser Titr RPR Titer
	VDRL	VDRL Ser Ql VDRL Quantitative

Treponemal Tests (qualitative only)	FTA	FTA-ABS T pallidum Ab Ser Ql IF
	TPPA	TPPA TP-PA T pallidum Ab Particle Agglutination
	EIA/CIA*	Syphilis TP T pallidum Ab Ser Ql T pallidum Ab Ser Ql IA T pallidum IgG+IgM Ser Ql IA Treponemal AB IgG Treponemal AB TOT

* If labs with the same specimen date include two EIA/CIA tests with different names, label the first Trep AB 1 and the second Trep AB 2 in Orpheus. Refer to the Syphilis Case Report and Data Entry Manual for guidance.

3.4 Services Available at Oregon State Public Health Laboratory (OSPHL)

The OSPHL conducts serologic syphilis screening using a treponemal CIA test (Syph-TP) that reflexes to an RPR. If these produce conflicting results, the TP-PA test is run as a reflex "tiebreaker" treponemal test. For patients with a history of syphilis and a recently documented (within past year) positive treponemal test, an "RPR only" should be ordered. For a visual representation of the OSPHL testing algorithm, refer to the Syphilis Testing Algorithm (pdf). Refer to the OSPHL Lab Test Menu, available at www.healthoregon.org/labtests, for additional information.

4. CASE INVESTIGATION

4.1 Provider Records

- Review medical records for the visits associated with syphilis lab results to obtain clinical, treatment, and risk information
- If electronic health records are not accessible, contact the provider by phone, fax, or query letter to request the necessary information
- If appropriate, inform the provider that a public health professional will contact the patient to discuss the syphilis diagnosis
- Refer to the STD Program's Syphilis Case Report and Data Entry Manual for guidance on entering data in Orpheus

4.2 Case Interview

4.2.1 Cases Prioritized for Investigation

An interview should be attempted for the following cases:

- All primary, secondary, and early non-primary non-secondary cases
- All cases involving pregnant and pregnancy-capable individuals regardless of stage. Refer to the Syphilis in Pregnancy Investigative Guidelines for guidance on investigations in pregnancy.

- Late or unknown duration syphilis cases that are suspicious for early syphilis should be investigated per LPHA protocol. Many factors can suggest early infection, including:
  - High titer (≥1:16)
  - Recent exposure to syphilis of unknown stage or suspected early syphilis
  - Concurrent/recent diagnosis of another STD

4.2.2 Interview Methods

- In-person interviews are preferable but interviews by phone and other methods are also acceptable.
- If the client cannot be reached by traditional methods (e.g., calls, texts, mailed letters, field or clinic-based visit), consider using technology-based tools such as social media sites and mobile apps to contact cases. Any method should be used in accordance with LPHA policies.
- Try contacting a case at least three times before closing the investigation
  - Attempts should be made on alternate days and times of day
  - Refer to §4.4 for resources that can assist with locating individuals.
- Maintain client privacy throughout the case investigation and interview
- Document all attempts to contact the client in real time when possible, or on the day of each attempt at minimum

4.2.3 Interview Exceptions

- The importance of an interview may be outweighed by a person's physical or mental health needs or other issues
- LPHAs can decide that an interview is not indicated and document the reason in the case record
- Examples of interview exceptions include:
  - If syphilis testing is done following sexual assault or during hospitalization for a serious medical condition that is not STD-related
  - If a case involves a person younger than 13 years old
    - Consult a supervisor about how to proceed
    - Case investigators are mandatory reporters required by law to report suspected child abuse (ORS 419B.005)
- If an interview is not conducted, obtain necessary information from the electronic health record

4.3 Management of Partners

4.3.1 Interview Periods

- Sexual contacts of a person diagnosed with primary, secondary, or early non-primary non-secondary syphilis are at high risk of acquiring the infection
- Interview periods help identify partners at risk of infection. The interview period is the time from the earliest date the case could have been infected to the date of treatment.
- Refer to **Table 5** for interview periods based on the case's stage ("case" refers to a person with presumptive or confirmed syphilis)

- All partners within the appropriate interview period should be confidentially notified of the exposure and need for evaluation
- Prioritize identifying partners when congenital syphilis is a risk (i.e., case or any partners are pregnant or pregnancy-capable)
- If a case has not had sex within the interview period, the most recent contact should be tested and presumptively treated if follow-up is uncertain

Table 5. Interview Periods by Stage

Stage	Interview Period
Primary	90 days before date of onset of primary chancre through date of treatment
Secondary	6.5 months before date of onset of secondary symptoms through date of treatment
Early Non-Primary Non-Secondary	1 year before start of treatment

4.3.2 Partner Notification

- **If LPHA is handling notification:**
  - Contact named partners within two working days of the initial case interview and refer for evaluation, testing, and treatment
  - If partners cannot be reached by traditional methods (e.g., calls, texts, mailed letters, field or clinic-based visit), consider using technology-based tools such as social media sites and mobile apps to contact cases. Any method should be used in accordance with LPHA policies.
  - Try to contact partners at least three times
    - Attempts should be made on alternate days and times of day
    - Refer to §4.4 for resources that can assist with locating individuals
- **If the case chooses to notify partners:**
  - Advise the case that LPHA staff can help arrange partner testing/treatment and encourage the case to share the staff's contact information with partners
  - If possible, contact the case again to offer LPHA notification and treatment referral if partner treatment cannot be verified within a reasonable time frame (2–5 days)

4.3.3 Partner Testing/Treatment

- Partners from **within 90 days** before case's diagnosis (or onset of symptoms) of early syphilis (primary, secondary, early non-primary non-secondary syphilis):
  - Test and presumptively treat for early syphilis
  - Contacts to late or unknown duration syphilis cases that are suspicious for early infection should also be tested and presumptively treated
- Partners from **>90 days** before case's diagnosis (or onset of symptoms) of early syphilis (primary, secondary, early non-primary non-secondary syphilis):
  - Test and presumptively treat for early syphilis if follow-up is uncertain

        - If positive: stage based on clinical and serologic evaluation and treat (if not treated presumptively)
        - If negative: no treatment is needed
- Long-term partners of a case diagnosed with late/unknown duration syphilis should be evaluated for syphilis and treated based on the clinical and serological findings

4.4 Requesting Locating Searches and Out-of-State Records

1. **Locating Searches**
   If LPHA staff and the provider cannot locate a case or contact using the available contact information, there are two useful resources available:
   - Request that State STD Program staff conduct an Accurint search for the person's current/recent addresses and phone numbers
     - Searches are prioritized for the following:
       - Early syphilis cases
       - Pregnant cases/contacts
       - Cases with unknown pregnancy status
   - Search Orestar to find mailing and residential addresses for Oregon residents
   - Search sites with correctional/judicial information:
     - VISOR to see if a person is currently in a correctional facility or has been recently released
     - Oregon Department of Corrections to see if a person is in an Oregon state prison
     - Oregon Judicial Department to find information on court records, community supervision, name changes, etc.
2. **Out-of-State Records**
   - Out-of-state syphilis records should mainly be requested to:
     - Determine whether there is a new infection based on a comparison of the current and previous titers **OR**
     - Obtain documentation of past syphilis care for persons who are pregnant or pregnancy-capable
   - Clinical management should not be delayed while waiting on out-of-state records, especially if there is a risk of loss to follow-up
     - In many cases, records do not exist or are incomplete
   - Records should not be requested for persons without pregnancy capacity with a current titer 1:2 or lower
     - A fourfold increase could not have occurred (a change from non-reactive to 1:2 is not considered a fourfold increase)
     - It is only necessary for public health to review past treatment for pregnant and pregnancy-capable individuals, not for all people with syphilis history outside Oregon
     - LPHAs have discretion to request records in this scenario if there is a compelling clinical need (e.g., clinical manifestations of syphilis)

4.5 Case/Contact Transfers and Other Orpheus Issues

Refer to the STD Program's Syphilis Case Report and Data Entry Manual for guidance on Orpheus-specific issues including transferring cases/contacts to other Oregon jurisdictions or out of state.

5. CONTROLLING FURTHER SPREAD

5.1 Education

- Persons diagnosed with early syphilis (primary, secondary, or early non-primary non-secondary stages) should be advised to:
  - Complete treatment
  - Avoid all types of sex until treatment has been completed (either Bicillin L-A or doxycycline) and any skin lesions have resolved.
  - Avoid all types of sex with untreated partners until they have been treated and their skin lesions have resolved
- Other key education messages for people at risk of acquiring syphilis and other STIs:
  - Use condoms as often as possible
  - Get checked for HIV and other STIs
  - Talk to partners about testing
  - Know about STI PEP (DoxyPEP) and HIV pre- and post-exposure prophylaxis (PrEP and PEP)
    - Transgender women and gay, bisexual, and other men who have sex with men, on diagnosis of chlamydia, should be offered doxycycline postexposure prophylaxis for bacterial sexually transmitted infections (doxyPEP). Providers should use their clinical judgement and shared decision-making to inform use of doxyPEP with populations that are not part of CDC recommendations. See the CDC doxyPEP guidelines for more information.
    - PrEP education and referrals should be provided to anyone diagnosed with or at risk for syphilis. Refer to the OHA PrEP/PEP page for additional information.
    - Visit the AETC site for a list of PrEP providers in Oregon and southwest Washington State
  - Talk with a provider about contraceptive options if not currently seeking pregnancy
  - Utilize syringe service programs (for those using/injecting drugs)
  - Stay up to date on vaccinations as appropriate, including for HPV and hepatitis A and B

5.2 Recommendations for Clinical Follow-Up

- **Primary, Secondary, and Early Non-Primary Non-Secondary Syphilis**
  - If signs/symptoms persist/return or titer increases fourfold or more:
    - Reinfection is most likely. Repeat treatment for early syphilis and retest for HIV.

        - If the person has neurological symptoms or had no sexual exposure in the prior 3-6 months, conduct CSF exam and retest for HIV.
    - If titer does not decrease fourfold within 12 months:
        - Evaluate for neurosyphilis and retest for HIV
        - Consider treating with benzathine penicillin G (Bicillin L-A) 2.4 million units for 3 weeks or treat for neurosyphilis if indicated
- **Late or Unknown Duration Syphilis**
    - If primary or secondary signs/symptoms occur or titer increases at least fourfold:
        - Reinfection is most likely. Treat based on stage and retest for HIV.
        - If the person has neurological symptoms or had no sexual exposure in the prior 12 months, conduct CSF exam and retest for HIV.
    - If titer does not decrease fourfold within 24 months:
        - Evaluate for neurosyphilis and retest for HIV
        - Consider retreating with benzathine penicillin G (Bicillin L-A) 2.4 million units for 3 weeks or treat for neurosyphilis if indicated

See **Table 6** for the recommended frequency of titer monitoring by stage of infection.

Table 6. Recommended Follow-Up of Treated Syphilis Cases

Stage of Infection	**Follow-Up RPR titers**	
	HIV Negative	HIV Positive
Primary, Secondary, Early Non-Primary Non-Secondary	6 months 12 months	3 months 6 months 9 months 12 months 24 months
Late or Unknown Duration	6 months 12 months 24 months	6 months 12 months 18 months 24 months

6. MANAGING SPECIAL SITUATIONS

6.1 Syphilis Case has Multiple Reportable Infections

- Check in Orpheus to see if a person diagnosed with syphilis has any other new reportable infections, especially other STI or HIV (may depend on Orpheus disease group access)
- Coordinate case investigations to reduce duplication and communication with case:
    - Combine questions for all infections in one interview session rather than having multiple people contact the case to ask different questions

- Obtain partner information based on interview periods for each STI/HIV

6.2 Jarisch-Herxheimer Reaction

- The Jarisch-Herxheimer reaction is a flu-like reaction involving fever, headache, and muscle aches, that can occur after initiation of syphilis treatment
  - The reaction usually begins within 2 hours of treatment initiation, peaks at approximately 8 hours, and resolves in 24-36 hours
  - In most cases no treatment is required
- It is a reaction to the rapid killing of *T. pallidum* bacteria and is **not** an allergic reaction to syphilis treatment
- It occurs most often in early syphilis, likely because bacterial loads are higher during these stages
- Refer to the Syphilis in Pregnancy Investigative Guidelines for guidance on the Jarisch-Herxheimer reaction in pregnancy

6.3 Syphilis among Persons Living with HIV (PLWH)

- Persons with syphilis who also have an HIV diagnosis and are not on antiretroviral therapy should be immediately linked to HIV care
  - Contact the OHA HIV Surveillance Program for assistance with these HIV cases
- Unusual syphilis test results can occur among PLWH but are rare
  - Post-treatment titers may be higher than expected (high serofast) or fluctuate
  - False-negative tests and delayed seroreactivity (detectable immune response to syphilis) have also been seen
- Treatment for all stages and for neuro/ocular/otic syphilis is the same regardless of HIV status
- All persons with HIV and syphilis coinfection should receive a careful neurologic, ocular, and otic examination
  - PLWH who have early syphilis might be at increased risk for neurologic complications
  - Ocular syphilis has been reported more frequently among PLWH

7. FAQ

STAGING

1. A patient who was treated for syphilis in the past now has primary symptoms, but their titer hasn't increased fourfold above their last titer. Is this a case?
   - Yes, this is a new case. Symptoms matter more than the titer in deciding whether it is a case—if someone previously treated for syphilis now has primary or secondary symptoms, then it is a new case no matter the current titer. See §3.1.
2. A patient with no syphilis history has primary chancres. The treponemal test is reactive but the RPR is negative. Is this a case?

- Yes. Primary syphilis is the only stage that does not require both a reactive RPR and a reactive treponemal test. If a primary chancre is present and at least one syphilis test is reactive, then the criteria for presumptive primary syphilis are met. See §3.1.1.

3. A patient requested syphilis testing following a "recent exposure" per the visit notes. They have a reactive treponemal test and RPR titer 1:16. They reported no syphilis signs/symptoms, and none were noted on exam. The provider diagnosed this as "primary syphilis." Should I stage it as primary since that's what the provider said?
   - No. Surveillance staging must be consistent with the CDC syphilis surveillance case definition and is separate from clinical staging. This is how we ensure that a primary syphilis case reported in Oregon is the same as a primary syphilis case reported in all other states. If a chancre is not present, then this is not a primary case (see §3.1.1). Consult the CDC adult syphilis surveillance staging flowchart to determine the appropriate stage.
4. A patient with no syphilis history has secondary signs/symptoms. The ED provider only ordered an RPR, which is reactive with a 1:8 titer. Is this a case?
   - Most likely. However, the surveillance case definition for secondary syphilis requires a reactive treponemal test. If the patient has not yet been treated, then another blood draw can be done at time of treatment. If a treponemal test is not done, then this will be a "No Case" in Orpheus. See §3.1.2.
5. An asymptomatic case said they have a partner who had syphilis recently. The partner might have had a sore on their penis. Can I stage my case as early non-primary non-secondary since it sounds like this recent partner has early syphilis?
   - The partner needs to have a documented case of early syphilis to meet the criteria for this stage. If the partner has an early syphilis case documented in medical records or Orpheus, then your case can be staged as early non-primary non-secondary. If there is no documentation of the partner's early syphilis, then this stage's criteria is not met. See §3.1.3. Note that a provider may choose to treat with three Bicillin L-A doses even if the early non-primary non-secondary case definition is met since clinical and surveillance staging can differ.

TREATMENT

1. A patient was accidentally treated with only 1.2 million units of benzathine penicillin G (Bicillin L-A). Do they need to return for a full dose?
   - The other half of the dose should be given within 7 days. If the patient can't return until more than 7 days later, they should then be given the full 2.4 million units. Consult the STD Program if this scenario occurs with a pregnant patient.
2. A patient has an RPR titer 1:4, a positive treponemal test, and no syphilis signs/symptoms. They have syphilis history, but there is no documentation of previous titers or treatment and the patient can't remember being treated. What should be done?
   - The most cautious approach is to stage and treat as though there is no syphilis history. This person would be staged as late/unknown duration and treated with three Bicillin L-A doses unless they meet criteria for early non-primary non-secondary syphilis (see §3.1.3). For pregnant and pregnancy-capable people especially, this cautious approach is necessary to reduce the risk of congenital syphilis.

3. We received new labs for a case reported a year ago in which no treatment is documented. Should we add these labs to the existing case record, or create a new record?
    - This needs to be decided on a case-by-case basis. Factors to consider include whether current signs/symptoms are present and how the current titer compares to the previous titer. It is also important to determine if treatment was eventually obtained after the initial case investigation concluded. If treatment was not completed, the current titer is less than fourfold the previous titer, and there are no current signs/symptoms, then the new labs can be added to the existing case record. If the current provider is unaware that treatment was not completed and does not plan to treat, they should be advised of the need for treatment completion.

FOLLOW-UP

1. A patient was appropriately treated <12 months ago and their titer hasn't dropped fourfold yet. They don't have any syphilis symptoms. Does anything need to be done?
    - No. It can take up to 12 months for the titer to drop fourfold in primary and secondary cases, and up to 24 months in unknown duration or late cases. See §5.2.
2. A patient was appropriately treated for early syphilis over 12 months ago, but the high baseline titer has not dropped and they are asymptomatic. How should this be managed?
    - This patient should be evaluated for reinfection, HIV infection, and neurosyphilis. If doxycycline was prescribed for the initial infection, retreatment with Bicillin L-A should be considered since doxycycline regimens are difficult to complete. See §5.2 for additional recommendations.

GLOSSARY

CSF: Cerebrospinal fluid. CSF testing can indicate whether there is central nervous system involvement in a syphilis infection.

CBC: Complete Blood Count. A complete blood count is a set of tests that provide information about the cells in a person's blood. The CBC indicates the counts of white blood cells, red blood cells, and platelets, and the hemoglobin and hematocrit.

Early syphilis: Any of the stages that occur in the first 12 months of infection: primary, secondary, and early non-primary non-secondary syphilis.

IM: Intramuscular. An IM injection delivers medication, such as benzathine penicillin G for syphilis, into a muscle.

PCR: Polymerase chain reaction test is a laboratory technique for rapidly producing (amplifying) many copies of a specific segment of genetic material, e.g., *T. pallidum* DNA in syphilis.

RPR: Rapid plasma reagin test is a nontreponemal serologic (blood) test. Unlike treponemal tests, the RPR measures antibodies that are not specific for *T. pallidum* bacteria and may be reactive due to conditions other than syphilis, including pregnancy.

Treponemal test: Treponemal tests measure antibodies directed against *T. pallidum* bacteria. Treponemal serologic (blood) tests include enzyme immunoassays (EIAs) and

chemiluminescence immunoassays (CIAs), *T. pallidum* particle agglutination (TP-PA), and fluorescent treponemal antibody absorption (FTA-ABS) tests. These qualitative tests usually remain reactive for life, regardless of treatment.

VDRL: Venereal Disease Research Laboratory test is a nontreponemal test that can be done on blood and CSF. Mostly used in CSF testing in congenital syphilis and neurosyphilis evaluations. The RPR is the more common nontreponemal serologic (blood) test in Oregon.

REFERENCES

1. Oregon Administrative Rules. Oregon Health Authority Chapter 333 Public Health Division, Division 18 Disease Reporting. https://secure.sos.state.or.us/oard/viewSingleRule.action?ruleVrsnRsn=292908
2. Oregon Administrative Rules. Oregon Health Authority Public Health Division Chapter 333 Division 19 Investigation and Control of Diseases: General Powers and Responsibilities. https://secure.sos.state.or.us/oard/viewSingleRule.action?ruleVrsnRsn=292879
3. Oregon Revised Statutes. Chapter 433 Disease and Condition Control. https://www.oregonlegislature.gov/bills_laws/ors/ors433.html
4. CDC Sexually Transmitted Infections Treatment Guidelines, 2021. https://www.cdc.gov/std/treatment-guidelines/default.htm
5. CDC National Notifiable Diseases Surveillance System (NNDSS) Syphilis (*Treponema pallidum*) 2018 Case Definition. https://ndc.services.cdc.gov/case-definitions/syphilis-2018/

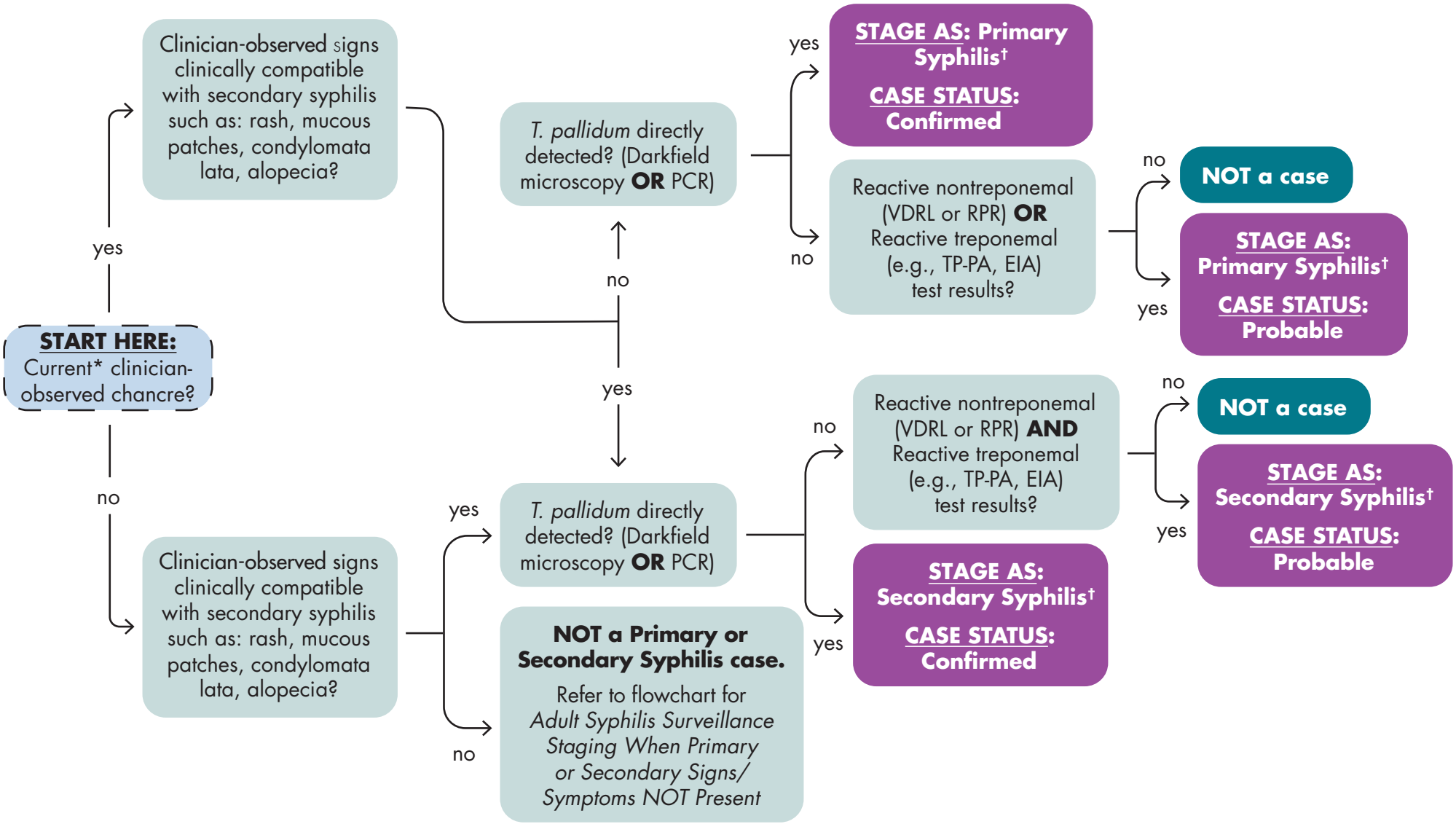
UPDATE LOG

July 2023. Extensively rewritten and reformatted. (Garai, Gonzalez Pena, Menza)
August 2024. Broken links and appendices updated. Confirmatory criteria and direct detection methods in §3 updated. Education on DoxyPEP added. (Garai)

Appendix A

ADULT SYPHILIS SURVEILLANCE STAGING WHEN PRIMARY OR SECONDARY SYPHILIS SIGNS/SYMPTOMS ARE PRESENT

(Not to be used as guidance for treatment)



*Current refers to the anchoring date of the original diagnosis, such as at time of original clinical diagnosis or positive screening test.

†Neurologic, ocular, and otic manifestations of syphilis can occur at any stage. After assigning syphilis stage, assess all cases for these clinical manifestations and classify separately as "No," "Verified," "Likely," "Possible," or "Unknown." Late clinical manifestations of syphilis are classified separately as "No," "Verified," "Likely," or "Unknown." For assistance with classification of these manifestations, please see clinical manifestations algorithms.

ACRONYMS: *T. pallidum* = *Treponema pallidum*; PCR = polymerase chain reaction; VDRL = Venereal Disease Research Laboratory; RPR = rapid plasma reagin; TP-PA = *Treponema pallidum* particle agglutination; EIA = enzyme immunoassay

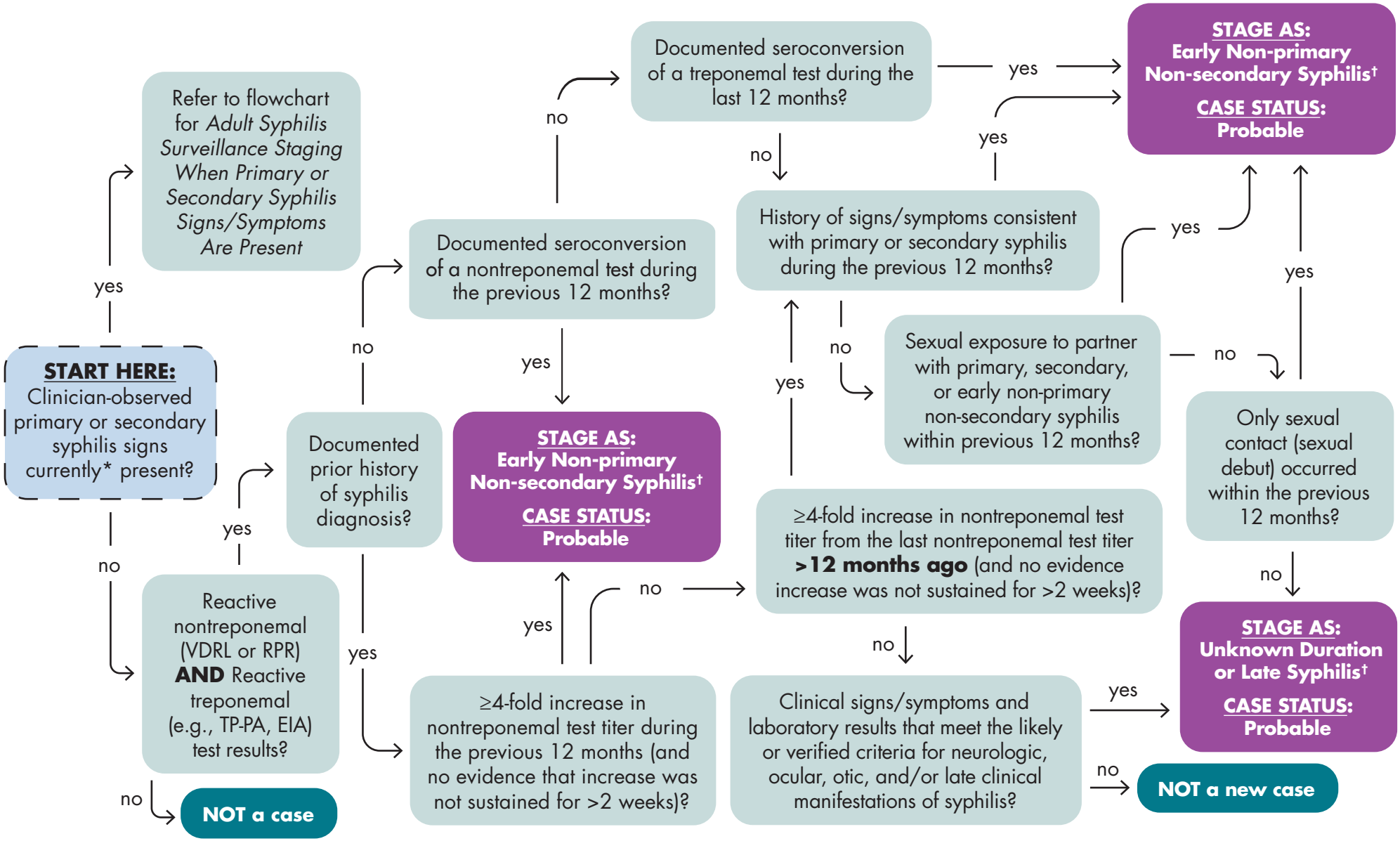
RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

CS328736-A

Updated 6/1/2023

ADULT SYPHILIS SURVEILLANCE STAGING WHEN PRIMARY OR SECONDARY SIGNS/SYMPTOMS NOT PRESENT

(Not to be used as guidance for treatment)



*Current refers to the anchoring date of the original diagnosis, such as at time of original clinical diagnosis or positive screening test.

†Neurologic, ocular, and otic manifestations of syphilis can occur at any stage. After assigning syphilis stage, assess all cases for these clinical manifestations and classify separately as "No," "Verified," "Likely," "Possible," or "Unknown." Late clinical manifestations of syphilis are classified separately as "No," "Verified," "Likely," or "Unknown." For assistance with classification of these manifestations, please see clinical manifestations algorithms.

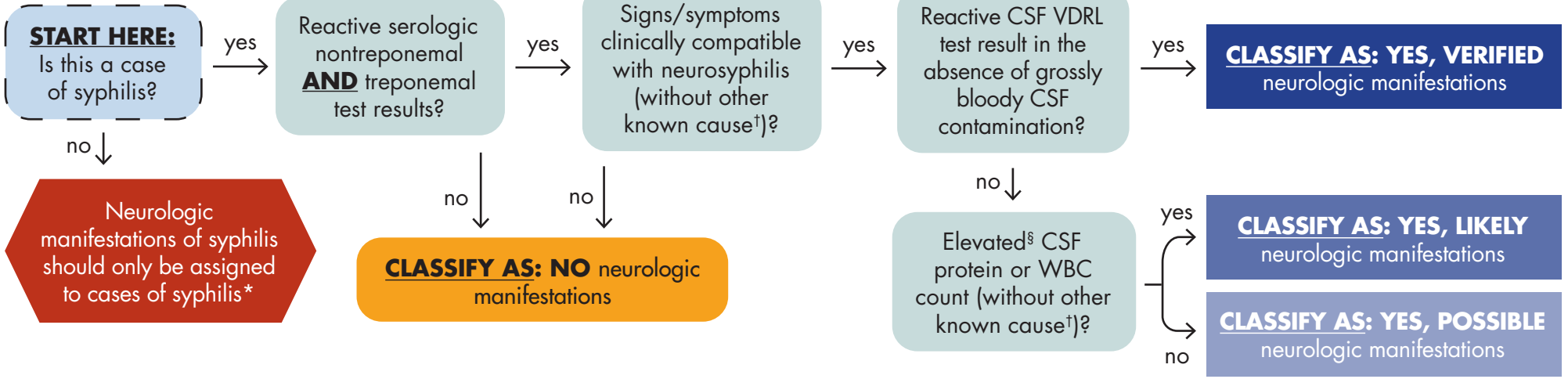
ACRONYMS: VDRL = Venereal Disease Research Laboratory; RPR = rapid plasma reagin; TP-PA = *Treponema pallidum* particle agglutination; EIA = enzyme immunoassay.

RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

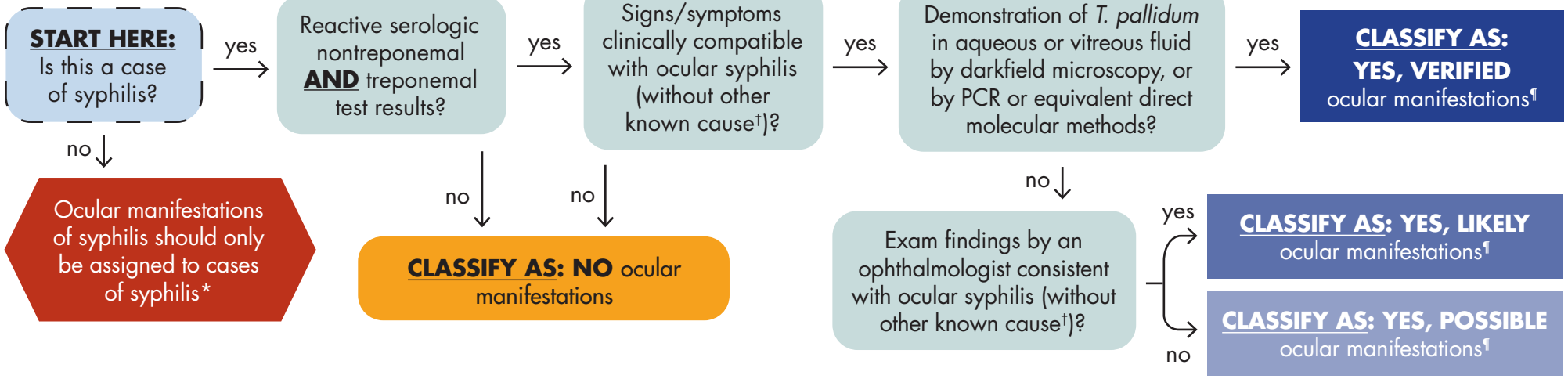
CS328736-A

Updated 6/1/2023

SURVEILLANCE CLASSIFICATION OF NEUROLOGIC MANIFESTATIONS OF SYPHILIS *(Not to be used as guidance for treatment)*



SURVEILLANCE CLASSIFICATION OF OCULAR MANIFESTATIONS OF SYPHILIS *(Not to be used as guidance for treatment)*



*Any case with clinical signs/symptoms and laboratory results that meet the likely or verified criteria for neurologic, ocular, otic, or late clinical manifestations of syphilis and that has no evidence of having acquired the disease within the preceding 12 months meets the Council of State and Territorial Epidemiologists case definition for unknown duration or late syphilis.

†Clinician input may be needed to rule out other possible causes.

§The Council of State and Territorial Epidemiologists case definition for neurologic manifestations of syphilis defines elevated CSF protein as >50 mg/dL and elevated CSF WBC count as >5 WBCs/mm^3. Additional guidance for interpretation of CSF results is available in CDC's STI Treatment Guidelines.

¶Because ocular manifestations are considered signs/symptoms clinically compatible with neurosyphilis, cases classified as having ocular manifestations should also be classified as having neurologic manifestations.

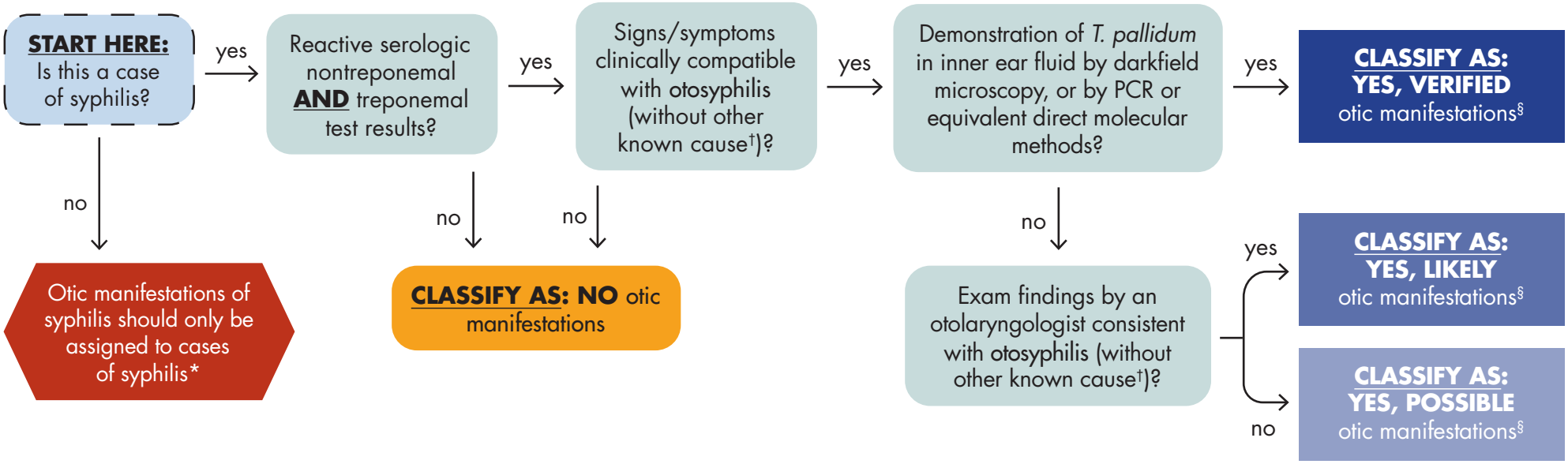
ACRONYMS: CSF = cerebrospinal fluid; VDRL = Venereal Disease Research Laboratory; WBC = white blood cell; *T. pallidum* = *Treponema pallidum*; PCR = polymerase chain reaction

RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

CS328983-A

Updated 5/23/2023

SURVEILLANCE CLASSIFICATION OF OTIC MANIFESTATIONS OF SYPHILIS *(Not to be used as guidance for treatment)*



*Any case with clinical signs/symptoms and laboratory results that meet the likely or verified criteria for neurologic, ocular, otic, or late clinical manifestations of syphilis and that has no evidence of having acquired the disease within the preceding 12 months meets the Council of State and Territorial Epidemiologists case definition for unknown duration or late syphilis.

†Clinician input may be needed to rule out other possible causes.

§Because otic manifestations are considered signs/symptoms clinically compatible with neurosyphilis, cases classified as having otic manifestations should also be classified as having neurologic manifestations.

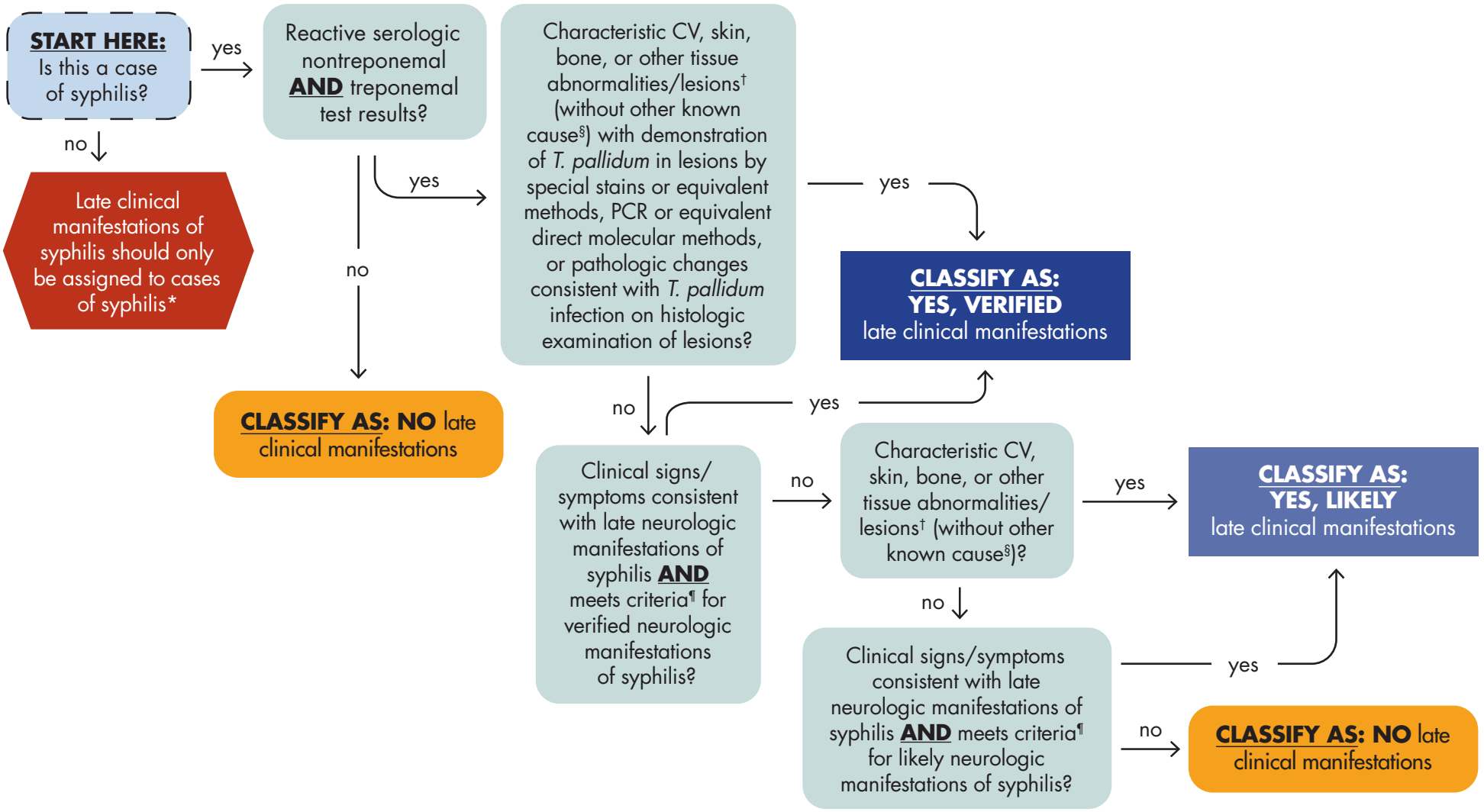
ACRONYMS: *T. pallidum* = *Treponema pallidum*; PCR = polymerase chain reaction

RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

Updated 5/23/2023

CS328983-A

SURVEILLANCE CLASSIFICATION OF LATE CLINICAL MANIFESTATIONS OF SYPHILIS *(Not to be used as guidance for treatment)*



*Any case with clinical signs/symptoms and laboratory results that meet the likely or verified criteria for neurologic, ocular, otic, or late clinical manifestations of syphilis and that has no evidence of having acquired the disease within the preceding 12 months meets the Council of State and Territorial Epidemiologists case definition for unknown duration or late syphilis.

†Additional information about characteristic lesions associated with late clinical manifestations of syphilis is available in CDC's STI Treatment Guidelines.

§Clinician input may be needed to rule out other possible causes.

¶Please see syphilis surveillance case definitions and neurologic manifestations classification algorithm for additional assistance.

ACRONYMS: CV = cardiovascular; *T. pallidum* = *Treponema pallidum*; PCR = polymerase chain reaction

RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

Updated 5/23/2023

CS328983-A

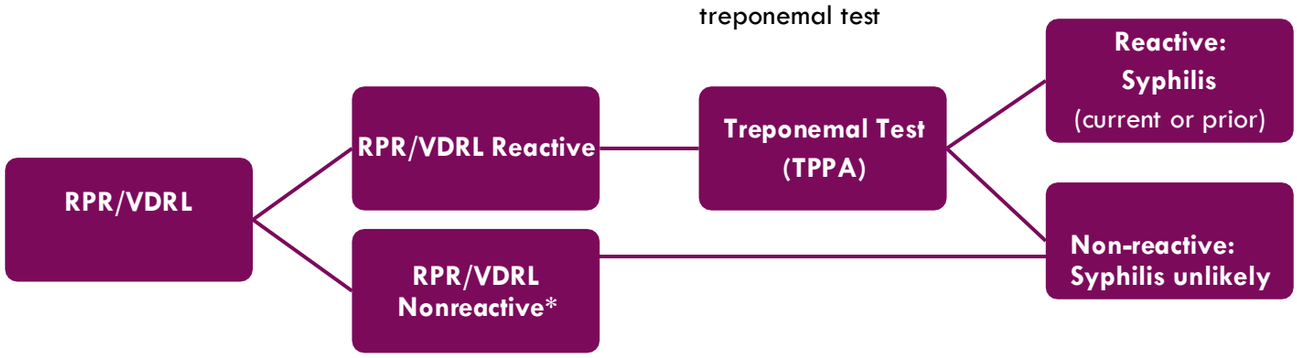
Appendix B

Clinical Interpretation of Syphilis Screening Algorithms

Testing: Traditional Algorithm[a]

1. Screen with non-treponemal test (RPR/VDRL)

2. Confirm reactive non-treponemal test with treponemal test



*Early primary syphilis and late untreated syphilis possible if RPR/VDRL are nonreactive; see below for recommended actions

Table 1: Interpretation of Syphilis Serologies, Traditional Algorithm

Non-Treponemal (RPR/VDRL)	Treponemal (TPPA)	Possible Interpretations	Recommended Actions
Nonreactive	Nonreactive or not done	1. No syphilis 2. Early/incubating syphilis (too early to be detected by serology)	▪ If syphilis unlikely, no further action needed. ▪ If early syphilis suspected, consider ordering a treponemal test (if not done initially) and repeating an RPR/VDRL in 1-2 weeks; if either test is reactive, treat for syphilis. ▪ If concerned for early syphilis (e.g., chancre present or known exposure) treat presumptively. If treating presumptively, repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
	Reactive	1. Prior treated syphilis 2. Untreated syphilis	▪ Treponemal tests (e.g., TPPA) often stay reactive for life; if patient has a history of adequate treatment for syphilis & no new exposures/ symptoms, no further action needed. ▪ If early syphilis suspected (e.g., chancre present or known exposure), treat presumptively according to stage. If treating presumptively, repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion. ▪ If no signs or symptoms, order a second treponemal test (e.g., EIA or CIA); see table 2 for recommendations based on results.
Reactive	Nonreactive	1. False positive RPR or VDRL	▪ Likely false positive (not syphilis).[b] ▪ In pregnancy or in patients at high risk for syphilis, consider rescreening with serologic testing in 2-4 weeks – if unchanged, no action needed.[c]
	Reactive	1. Current syphilis 2. Treated syphilis with residual/ persistent RPR/VDRL titer	▪ If RPR/VDRL is newly reactive, stage and treat. ▪ If previously treated and sustained (≥2 weeks) 4-fold rise in RPR/VDRL titer, manage as treatment failure versus re-infection.[d] ▪ Note that RPR/VDRL may still be reactive after treatment; if there is a fourfold decline within 12-24 months, treatment is considered to have been adequate even if RPR/VDRL remains reactive. ▪ Some treated patients may have a persistent low level RPR/VDRL titer for a prolonged period; re-treatment is not necessary in the absence of new exposures or symptoms.

[a] The traditional algorithm starts with a non-treponemal test (RPR or VDRL) which, if reactive, is followed by a confirmatory treponemal test (TPPA). In interpreting serologies, it is helpful to know which testing algorithm (traditional vs reverse) is being used in your lab.

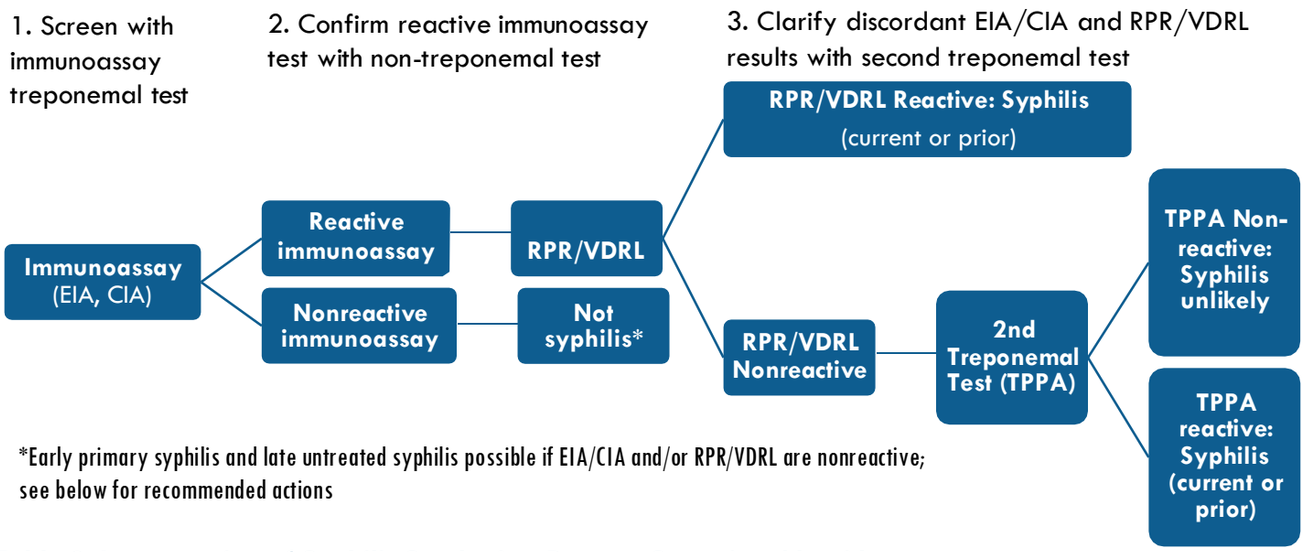
[b] False positives can be seen in pregnancy and/ in patients with autoimmune diseases, Lyme disease, certain viral infections (including HIV), injection drug use, and other conditions.

[c] In California, all pregnant people should be screened for syphilis at least twice during pregnancy: once at either confirmation of pregnancy or at the first pre-natal encounter, and again during the third trimester (ideally between 28-32 weeks). Patients should also be screened at delivery, except those at low risk who have a documented negative screen in the third trimester. See https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/California-STI-Screening-Recommendations.aspx.%20As%20of%20April%202024. As of April 2024, the American College of Obstetrics and Gynecology recommends screening all pregnant patients universally for syphilis three times: once at the first prenatal care visit, again during the third trimester, and again at birth.

[d] For patients determined to have new syphilis or treatment failure, refer to the Centers for Disease Control STD treatment guidelines at https://www.cdc.gov/std/treatment-guidelines/syphilis.htm for treatment and follow up recommendations.

Clinical Interpretation of Syphilis Screening Algorithms

Testing: Reverse Algorithm[a]



*Early primary syphilis and late untreated syphilis possible if EIA/CIA and/or RPR/VDRL are nonreactive; see below for recommended actions

Table 2: Interpretation of Syphilis Serologies, Reverse Screening Algorithm

Immuno-assay (CIA or EIA)	RPR/ VDRL	TPPA	Possible Interpretations	Recommended Actions
Non-reactive	Non-reactive or not done	Non-reactive or not done	1. Syphilis unlikely 2. Early/incubating syphilis (too early to be detected by serology)	▪ If syphilis unlikely, no further action needed. ▪ If immunoassay nonreactive but high clinical suspicion (such as a chancre or known exposure), treat presumptively for early syphilis. If treating presumptively, obtain RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
Reactive	Non-reactive	Non-reactive or not done	1. False positive immunoassay 2. Early/incubating syphilis 3. Latent or prior syphilis (treated or untreated)	▪ If no signs/symptoms and low risk for syphilis, most likely a false positive immunoassay.[b] No further action needed. ▪ If concerned for early infection or in pregnant patients, re-screen in 2-4 weeks.[c] ▪ If signs/symptoms or contact to syphilis, treat presumptively. Repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
		Reactive	1. Latent or prior syphilis (treated or untreated) 2. Early syphilis (prior to RPR/VDRL seroconversion)	▪ No further action needed if patient treated appropriately for syphilis in past, assuming no new exposures/symptoms and a negative clinical exam. ▪ If no symptoms and no known prior adequate treatment, treat presumptively for latent syphilis. ▪ If early syphilis suspected (symptoms or known exposure), treat presumptively. Obtain RPR/VDRL on day of treatment. If nonreactive, repeat in 2-4 weeks to assess for seroconversion.
	Reactive	Not done or Reactive	1. Current syphilis 2. Prior syphilis (treated or untreated)	▪ If RPR/VDRL is newly reactive, stage and treat. ▪ If previously treated and sustained (≥2 weeks) 4-fold rise in RPR/VDRL titer, manage as treatment failure versus re-infection.[d] ▪ If known prior adequate treatment for stage of infection and RPR/VDRL declining appropriately (i.e., a fourfold decline within 12-24 months), no further action needed. ▪ Some treated patients may have a persistent low level RPR/VDRL titer for a prolonged period; re-treatment is not necessary in the absence of new exposures or symptoms.

[a] The reverse algorithm starts with an immunoassay detecting syphilis antibodies which, if reactive, is followed by an RPR/VDRL. If there is a discrepancy between the immunoassay and RPR (one reactive, one nonreactive), a treponemal test (TPPA) serves as the tie-breaker. In interpreting serologies, it is helpful to know which testing algorithm (traditional vs reverse) is being used in your lab.

[b] False positive immunoassays can occur with Lyme disease or non-syphilis treponemal infections.

[c] In California, all pregnant people should be screened for syphilis at least twice during pregnancy: once at either confirmation of pregnancy or at the first pre-natal encounter, and again during the third trimester (ideally between 28-32 weeks). Patients should also be screened at delivery, except those at low risk who have a documented negative screen in the third trimester. See https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/California-STI-Screening-Recommendations.aspx.%20As%20of%20April%202024. As of April 2024, the American College of Obstetrics and Gynecology recommends screening all pregnant patients universally for syphilis three times: once at the first prenatal care visit, again during the third trimester, and again at birth.

[d] For patients determined to have new syphilis or treatment failure, refer to the Centers for Disease Control STD treatment guidelines at https://www.cdc.gov/std/treatment-guidelines/syphilis.htm for treatment and follow up recommendations.

Syphilis in Pregnancy

Investigative Guidelines

August 2023

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. Identify cases of syphilis in pregnancy and prevent vertical transmission
2. Ensure adequate treatment and follow-up for pregnant people with syphilis and the infant
3. Ensure appropriate management, including screening and presumptive treatment, of sexual contacts
4. Describe the epidemiology of syphilis in pregnancy in Oregon

1.2 Laboratory and Physician Reporting Requirements

1. Licensed laboratories must report all positive test results indicating syphilis infection to the Local Public Health Authority within one working day (OAR 333-018-0000; 333-018-0015)[1]
2. Clinicians must report lab-confirmed and clinically suspect cases of syphilis to the Local Public Health Authority within one working day (OAR 333-018-0000; 333-018-0015)[1]
   - Oregon Revised Statute (ORS) 433.017 requires individuals attending a pregnant patient to collect or order the collection of a blood specimen for submission to a licensed laboratory to test for syphilis and selected other infections, unless the pregnant patient declines testing (OAR 333-019-0036)[2,3]
   - Oregon Health Authority recommends that all pregnant people be tested for syphilis three times: 1) at the first prenatal visit or presentation to care, 2) at 28 weeks' gestation, and 3) at delivery
3. Health care providers, health care facilities, and licensed laboratories shall cooperate with public health authorities in the investigation and control of syphilis infections (OAR 333-019-0002)[3]

1.3 Local Public Health Authority Reporting and Follow-up Responsibilities

1. LPHA must begin follow-up case investigation within two working days of receiving the initial provider or laboratory report
2. LPHA must report all cases to the OHA STD Program through the Oregon Public Health Epidemiology User System (Orpheus) by the end of the calendar week of initial provider or laboratory report (OAR 333-018-0020)[1]

3. LPHA must conduct case investigations and manage sexual contacts by following procedures outlined in these Investigative Guidelines (ORS 433.006, OAR 333-019-0000)[2,3]

2. DISEASE AND EPIDEMIOLOGY

2.1 Etiologic Agent

The etiologic agent in syphilis is *Treponema pallidum* subspecies *pallidum*, a spirochete (corkscrew-shaped) bacterium.

Of all the subspecies of *T. pallidum*, only *T. pallidum* subsp. *pallidum* is transmitted routinely by sexual contact. The other *T. pallidum* subspecies are transmitted non-sexually (e.g., yaws, pinta).

2.2 Description of Illness

Syphilis is called “the great imitator” because many of the signs and symptoms mimic those of other diseases. If untreated, syphilis infection progresses through stages that are often separated by periods without any symptoms (latency). Neurosyphilis, ocular syphilis, and otosyphilis can occur at any stage of infection.

During the incubation period, before clinical signs or symptoms appear, *T. pallidum* can spread to the circulatory, lymphatic, and central nervous systems.

Early Syphilis: clinical manifestations mainly involve the skin and mucosal surfaces, although secondary syphilis often has systemic manifestations.

- **Primary syphilis**
  - A chancre is the defining feature of primary syphilis
  - A chancre is a small round or oval skin ulcer with a smooth base and firm raised borders that appears where *T. pallidum* entered the body:
    - Most commonly appear on the penis, labia, perianal area, or mouth
    - May go unnoticed, especially if located inside the vagina, foreskin, or rectum
    - Resolve spontaneously within a few weeks, even without treatment
  - Classic primary syphilis is defined by a single painless chancre BUT multiple chancres are common and can be painful (multiple chancres on genitals are often misdiagnosed as herpes simplex virus [HSV] infection)
- **Secondary syphilis**
  - Skin and mucous membrane lesions are the defining feature of secondary syphilis. A lesion is an area of abnormal tissue anywhere in or on the body. While only one type of lesion is associated with primary syphilis (chancre), different lesions are found in secondary syphilis:

        - Rashes can appear anywhere on the body, vary widely in appearance, and do not usually cause itching
            - The characteristic secondary rash appears on the hands and feet, and often the torso
        - Other secondary lesions may include:
            - Mucous patches in the mouth or genital area
            - Condyloma lata in the genital or rectal area
            - Alopecia
    - Symptoms generally appear about 4 to 10 weeks after the onset of the primary chancre (chancres may still be present when secondary symptoms develop)
    - Widespread dissemination of *T. pallidum* throughout the body via the bloodstream causes fever, headaches, muscle aches, malaise, and lymphadenopathy
    - Even without treatment, lesions and symptoms typically resolve spontaneously within a few weeks, but can persist for months
    - If untreated, secondary symptoms can reappear after a latency period

Latent Syphilis: characterized by the persistence of *T. pallidum* in the body without clinical signs or symptoms.

- **Early non-primary non-secondary (early latent) stage**:
    - Occurs when an individual is asymptomatic and there is evidence that the infection was acquired in the 12 months prior to diagnosis
    - Can occur between the primary and secondary stages, after the secondary stage, or between secondary relapses
- **Late or unknown duration (late latent) stage**:
    - Occurs when an individual is asymptomatic and the infection was acquired more than 12 months prior to diagnosis **OR** the time of infection cannot be determined with certainty

Neurosyphilis, Ocular Syphilis, and Otic Syphilis: clinical manifestations that can occur during any stage.

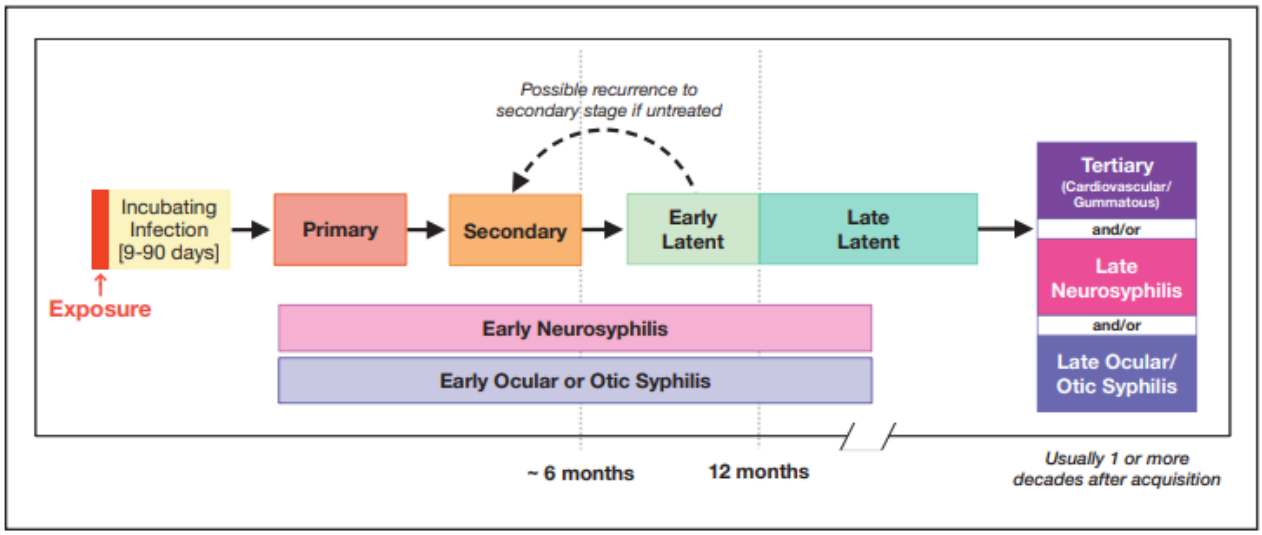
- **Neurosyphilis** can manifest as meningitis or stroke, cognitive dysfunction, motor or sensory deficits, and/or cranial nerve palsies
- **Ocular syphilis** can involve any eye structure but usually manifests as panuveitis or posterior uveitis
    - May cause permanent vision loss
    - Occurs with or without neurosyphilis
- **Otosyphilis** can manifest as hearing loss, tinnitus, and/or vertigo
    - May cause permanent hearing loss
    - Occurs with or without neurosyphilis

Late Clinical Manifestations (Tertiary Syphilis)

- Usually only develop after 15–30 years of untreated infection
- Can affect virtually any organ system including the cardiovascular system, central nervous system, and skin

See **Figure 1** for a graphical summary of the natural history of syphilis.

Figure 1. The Natural History of Untreated Syphilis



Source: New York City Department of Health and Mental Hygiene, and the New York City STD Prevention Training Center. The Diagnosis and Management of Syphilis: An Update and Review. March 2019. Available at www.nycptc.org

2.3 Reservoirs

Humans

2.4 Modes of Transmission

Sexual transmission:

- *T. pallidum* enters the body via skin and mucous membranes through abrasions during sexual contact
- Persons are infectious throughout the primary and secondary stages, when lesions are present
- Usually results from contact with genital mucous membranes, but it can also occur from contact with the mouth, rectum, and cutaneous lesions

Vertical transmission:

- Results in fetal infection
- Occurs primarily via transplacental passage of *T. pallidum*
- Can occur during any stage of syphilis
- Can also occur on contact with genital syphilis lesions at the time of delivery

Other forms of syphilis transmission are rare. Transfusion-associated syphilis has been virtually eliminated in the United States and transmission through needle-sharing is infrequent.

2.5 Incubation Period

The earliest sign of syphilis, a primary chancre, usually appears about 2 to 3 weeks after *T. pallidum* infection. Blood tests usually detect infection within 21 days of exposure but may take up to 6 weeks to show seroconversion.

2.6 Period of Communicability

Syphilis is spread by sexual contact—it is not spread through casual contact such as shaking hands. A person acquires syphilis when their mucous membranes (vulva, vagina, penis, anus, mouth) come into contact with bacteria-rich lesions (chancres, rash, condyloma lata, or mucous patches). These bacteria-rich lesions occur in primary and secondary syphilis and may not be visible.

3. CASE DEFINITIONS, DIAGNOSIS, AND LABORATORY SERVICES—FOR PUBLIC HEALTH STAFF

3.1 Syphilis Stages

See the CDC 2018 Syphilis Surveillance Case Definition page for more information on the stages below.[4] The CDC adult syphilis surveillance staging flowchart (see Appendix A) is a useful tool for determining surveillance stage.

Since RPR testing is the most common form of nontreponemal testing, the terms "nontreponemal serologic testing" and "RPR" are used interchangeably throughout this section.

3.1.1 Primary Syphilis

1. Clinical Description
   - Stage characterized by one or more chancres
2. Laboratory Criteria
   - Confirmatory: *T. pallidum* by darkfield microscopy (only available at Multnomah Co. Health Department) or PCR or equivalent direct molecular methods
   - Supportive: Reactive serologic test for syphilis (RPR *or* treponemal test)
3. Case Classification
   - **Confirmed (rare):** Clinically compatible case with evidence of *T. pallidum* by darkfield microscopy or PCR or equivalent direct molecular methods
     - Confirmed criteria is NOT met by biopsy results or staining done with samples taken from lesions. If a darkfield exam (which does not involve staining) is not done, then a case is not confirmed.
   - **Presumptive:** Clinically compatible case (must have chancre(s)) with at least one reactive serologic test (RPR *or* treponemal test)

3.1.2 Secondary Syphilis

1. Clinical Description

- Stage characterized by a localized or diffuse rash. Other signs may include mucous patches, condyloma lata, and alopecia.
    - Secondary lesions may develop before primary chancres have fully resolved. If both primary and secondary signs are present, this is staged as secondary syphilis.

2. Laboratory Criteria
    - Confirmatory: *T. pallidum* by darkfield microscopy (only available at Multnomah Co. Health Department) or PCR or equivalent direct molecular methods
    - Supportive: Reactive RPR and reactive treponemal test
3. Case Classification
    - **Confirmed (rare):** Clinically compatible case with evidence of *T. pallidum* by darkfield microscopy or PCR or equivalent direct molecular methods
        - Confirmed criteria is NOT met by biopsy results or staining done with samples taken from lesions. If a darkfield exam (which does not involve staining) is not done, then a case is not confirmed.
    - **Presumptive:** Clinically compatible case (must have rash, mucous patches, condyloma lata, or alopecia) with reactive RPR **and** reactive treponemal test

3.1.3 Early Non-Primary Non-Secondary Syphilis

1. Clinical Description
    - Stage in which initial infection occurred within the previous 12 months and there are no signs or symptoms of primary or secondary syphilis
2. Laboratory Criteria
    - No past diagnosis of syphilis, and a reactive RPR and treponemal test
    OR

    History of syphilis treatment, and a current RPR titer showing a fourfold or greater increase from the last titer (unless the increase was not sustained for >2 weeks). Refer to **Figure 2** for examples of increases in titers.
3. Case Classification
    - **Confirmed:** Cannot be confirmed. Can only be classified as presumptive.
    - **Presumptive:** No clinical signs or symptoms of primary or secondary syphilis and evidence of acquiring the infection within the previous 12 months based on one or more of the following:
        - Documented RPR seroconversion or at least a fourfold increase in titer in the past 12 months (unless the increase was not sustained for >2 weeks)
        - Documented treponemal test seroconversion in the past 12 months
        - History of symptoms consistent with primary or secondary syphilis in the past 12 months
        - History of sexual exposure to a partner in the past 12 months who had primary, secondary, or early non-primary non-secondary syphilis (partner's stage must be documented in medical records and/or Orpheus)
        - Only sexual contact ever was in the past 12 months

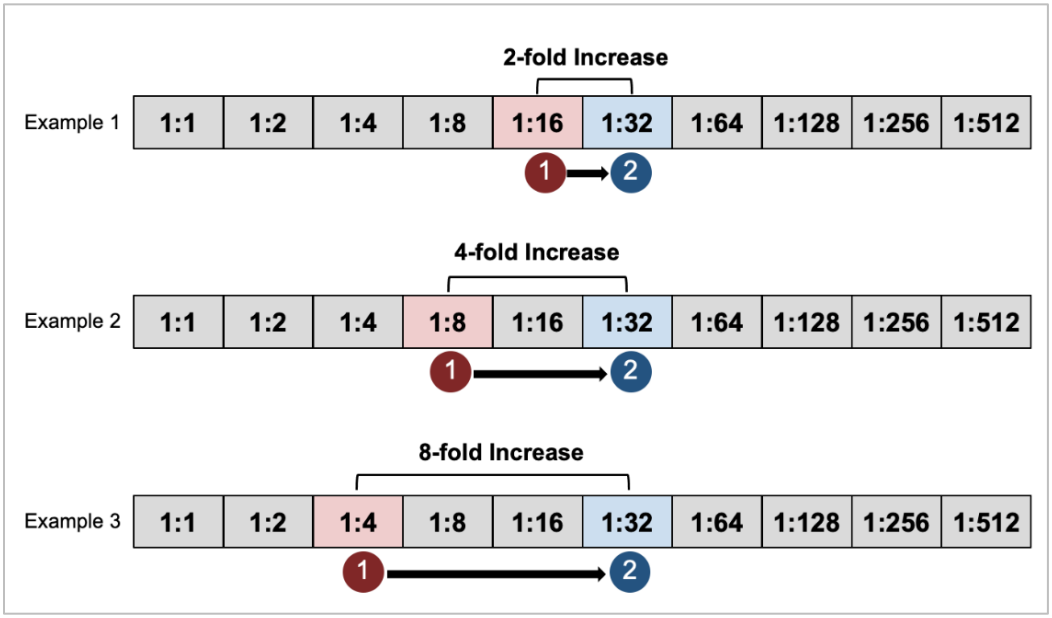
3.1.4 Unknown Duration or Late Syphilis

1. Clinical Description
   - Stage in which there are no signs or symptoms of primary or secondary syphilis and a) initial infection occurred >12 months ago or b) there is not enough evidence to prove the infection was acquired in the past 12 months
2. Laboratory Criteria
   - No past diagnosis of syphilis, and a reactive RPR and treponemal test
   OR

   History of syphilis treatment, and a current RPR titer showing a fourfold or greater increase from the last titer (unless the increase was not sustained for >2 weeks). Refer to **Figure 2** for examples of increases in titers.
   OR

   Likely or verified neurologic, ocular, otic, or late clinical manifestations without a current RPR titer showing a fourfold or greater increase
3. Case Classification
   - **Confirmed:** Cannot be confirmed. Can only be classified as presumptive.
   - **Presumptive:** No clinical signs or symptoms of primary or secondary syphilis, no evidence of having acquired the disease in the past 12 months, and meets laboratory criteria

*Figure 2. 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. Figure from National STD Curriculum Syphilis Quick Reference.

3.2 Complicated Syphilis

See the CDC 2018 Syphilis Surveillance Case Definition page for more information on the manifestations below. Note that for Orpheus documentation of

these conditions, LPHA staff are only expected to select the criteria that are met—it is not necessary to know the classification category (e.g., possible, likely, or verified). Refer to the Syphilis Case Report and Data Entry Manual for guidance on Orpheus documentation.

3.2.1 Neurologic Manifestations

Neurosyphilis can occur at any stage of syphilis. A case should be staged appropriately and neurological manifestations, if present, should be documented in the case record.

1. Clinical Description
   - Infection of the central nervous system with *T. pallidum*, as shown by manifestations including cranial nerve dysfunction, meningitis, meningovascular syphilis, stroke, altered mental status, tabes dorsalis, and general paresis
   - Symptoms include: severe headache; muscle weakness or paralysis; numbness; changes in mental status (trouble focusing, confusion, personality changes); and dementia (problems with memory, thinking, and/or making decisions)
2. Classification of Neurologic Manifestations
   - **Possible:** Reactive RPR and treponemal test **AND** clinical symptoms or signs consistent with neurosyphilis without other known causes
   - **Likely:** Reactive RPR and treponemal test with both of the following:
     - Clinical symptoms or signs consistent with neurosyphilis without other known causes of these abnormalities,

     AND
     - Elevated cerebrospinal fluid (CSF) protein (>50 mg/dl2) or white blood cell (WBC) count (>5 WBC/mm3) without other known causes
   - **Verified:** Reactive RPR and treponemal test with both of the following:
     - Clinical symptoms or signs that are consistent with neurosyphilis without other known causes

     AND
     - A reactive CSF VDRL in the absence of grossly bloody contamination, defined as a red blood cell (RBC) concentration of over 6000 per cubic millimeter in the CSF

3.2.2 Ocular Manifestations

Ocular syphilis can occur at any stage of syphilis. A case should be staged appropriately and ocular manifestations, if present, should be documented in the case record. Ocular syphilis is an emergency—permanent vision loss can occur if not treated promptly.

1. Clinical Description
   - Infection of any eye structure with *T. pallidum*, as shown by manifestations including posterior uveitis, panuveitis, anterior uveitis, optic neuropathy, retinal vasculitis, and interstitial keratitis

- Symptoms include: eye pain or redness, light sensitivity, floating spots in the field of vision (“floaters”), and changes in vision (blurry vision or vision loss)

2. Classification of Ocular Manifestations
   - **Possible:** Reactive RPR and treponemal test **AND** clinical symptoms or signs consistent with ocular syphilis without other known causes
   - **Likely:** Reactive RPR and treponemal test with both of the following:
     - Clinical symptoms or signs consistent with ocular syphilis without other known causes of these abnormalities,

     AND
     - Findings on exam by an ophthalmologist that are consistent with ocular syphilis without other known causes
   - **Verified (rare):** Reactive RPR and treponemal test with both of the following:
     - Clinical symptoms or signs that are consistent with ocular syphilis without other known causes

     AND
     - *T. pallidum* in eye fluid by darkfield microscopy or PCR

3.2.3 Otic Manifestations

Otosyphilis can occur at any stage of syphilis. A case should be staged appropriately and otic manifestations, if present, should be documented in the case record. Otosyphilis is an emergency—permanent hearing loss can occur if not treated promptly.

1. Clinical Description
   - Infection of the cochleovestibular system with *T. pallidum*, as shown by manifestations including sensorineural hearing loss, tinnitus, and vertigo
   - Symptoms include hearing loss; tinnitus (ringing, buzzing, roaring, or hissing in the ears); balance difficulties; and dizziness or vertigo
2. Classification of Otic Manifestations
   - **Possible:** Reactive RPR and treponemal test **AND** clinical symptoms or signs consistent with otosyphilis without other known causes
   - **Likely:** Reactive RPR and treponemal test with both of the following:
     - Clinical symptoms or signs consistent with otosyphilis without other known causes of these abnormalities,

     AND
     - Findings on exam by an otolaryngologist that are consistent with otosyphilis without other known causes
   - **Verified (rare):** Reactive RPR and treponemal test with both of the following:
     - Clinical symptoms or signs that are consistent with otosyphilis without other known causes

     AND
     - *T. pallidum* in inner ear fluid by darkfield microscopy or PCR

3.2.4 Late Clinical Manifestations (extremely rare)

Late clinical manifestations of syphilis (tertiary syphilis) usually develop only after a period of 15-30 years of untreated infection. The case should be reported with the appropriate stage of infection (unknown duration or late syphilis in most cases) and late clinical manifestations, if present, should be documented in the case report.

1. Clinical Description
   - Late clinical manifestations of syphilis may include inflammatory lesions of the cardiovascular system, skin, bone, or other tissue
2. Classification of Late Clinical Manifestations of Syphilis
   - **Possible:** Not an option for late clinical manifestations
   - **Likely:** Reactive RPR and treponemal test with either of the following:
     - Characteristic abnormalities or lesions of the cardiovascular system, skin, bone, or other tissue, without other known causes

     OR
     - Clinical signs and symptoms consistent with late neurologic manifestations of syphilis and either elevated CSF protein (>50 mg/dl2) or CSF WBC count (>5 WBC/mm3) without other known causes
   - **Verified:** Reactive RPR and treponemal test and either of the following:
     - Characteristic abnormalities or lesions of the cardiovascular system, skin, bone, or other tissue without other known causes, in combination with either *T. pallidum* by special stains or PCR, or pathologic changes that are consistent with *T. pallidum* infection on histologic examination

     OR
     - Clinical signs and symptoms consistent with late neurologic manifestations of syphilis and a reactive CSF VDRL

3.3 Diagnosis

3.3.1 Direct Detection of *T. Pallidum*

Darkfield microscopy and molecular tests (e.g., PCR) for detecting T. pallidum directly from of lesion fluid or tissue are the definitive method for immediate diagnosis of primary or secondary syphilis.

The only darkfield microscope currently in use in Oregon is at the Multnomah County Health Department.

3.3.2 Serological Tests for Syphilis

Refer to **Table 1** for information and frequently asked questions about nontreponemal and treponemal serological tests for syphilis. The California PTC Clinical Interpretation of Syphilis Screening Algorithms Resource for Local Health Jurisdictions (see Appendix B) includes descriptions of the traditional and reverse syphilis screening algorithms and results.

Table 1. Frequently Asked Questions about Nontreponemal and Treponemal Tests

FAQ	***Nontreponemal Tests***	***Treponemal Tests***
What are the common test names?	The two nontreponemal tests are the rapid plasma reagin (RPR) and the VDRL. The RPR is the most common nontreponemal serological (blood) test. The VDRL is mainly used for CSF testing. Refer to **Table 2** for examples of syphilis test names on lab reports.	There are several types of treponemal tests, including enzyme or chemiluminescence immunoassays (EIA/CIA); *Treponema pallidum* particle agglutination assay (TP-PA); and fluorescent treponemal antibody absorption test (FTA). Refer to **Table 2** for examples of syphilis test names on lab reports.
Is the test specific to syphilis?	No. "Nontreponemal" means the antibodies detected by these tests are not responding to treponemal bacteria. Biologic false positive results can be due to many causes, such as pregnancy, autoimmune diseases, and HIV.	Yes. Treponemal tests detect antibodies specific to *T. pallidum*.
Is the test qualitative or quantitative?	Both. An initial nontreponemal result is qualitative. If reactive, it reflexes to a quantitative result known as a titer. The titer is the measurement of antibodies through diluting a person's blood to determine the highest dilution at which a reactive result is still produced. A 1:2 titer indicates a low concentration of antibodies, as none were detected after only two dilutions. A 1:128 titer indicates a high concentration of antibodies, as none were detected after eight dilutions.	Treponemal test results are qualitative. If a numerical value is reported with a reactive result (e.g., FTA 4+), it should be ignored.
How soon does the test become positive?	Nontreponemal tests will typically be reactive by 21 days after infection.	Treponemal tests will typically be reactive by 21 days after infection. EIA/CIA and TP-PA tests may become positive sooner than nontreponemal tests.
Can the test be used to monitor for treatment response and reinfection?	Yes. A baseline titer should be done on or as close to the day of treatment initiation as possible so that treatment response can be determined accurately. Only titers of the same nontreponemal test type should be compared.	No. Treponemal tests usually remain positive for life, even after treatment. They are not useful for monitoring treatment response or diagnosing a new infection in anyone with syphilis history.

Does the test become negative after treatment?	Nontreponemal tests often become negative after treatment, but it is also common for a low titer to persist for life (known as serofast state). Even without treatment, titers drop over time.	No. See above.
How should equivocal/indeterminate results be handled?	If the traditional screening algorithm is followed, an equivocal/indeterminate RPR result should be followed by a treponemal test. If the reverse screening algorithm is followed, a second treponemal test may be necessary.	No matter which screening algorithm is used, a second treponemal test may be necessary if the first treponemal test result is equivocal/indeterminate.

Table 2. Examples of Syphilis Test Names on Lab Reports

	Test Type	**Examples of Test Names on Lab Reports**
Nontreponemal Tests (qualitative and quantitative)	RPR	RPR Ser Ql RPR Ser Titr RPR Titer
	VDRL	VDRL Ser Ql VDRL Quantitative
Treponemal Tests (qualitative only)	FTA	FTA-ABS T pallidum Ab Ser Ql IF
	TPPA	TPPA TP-PA T pallidum Ab Particle Agglutination
	EIA/CIA*	Syphilis TP T pallidum Ab Ser Ql T pallidum Ab Ser Ql IA T pallidum IgG+IgM Ser Ql IA Treponemal AB IgG Treponemal AB TOT

* If labs with the same specimen date include two EIA/CIA tests with different names, label the first *Trep AB 1* and the second *Trep AB 2* in Orpheus. Refer to the Syphilis Case Report and Data Entry Manual for guidance.

3.4 Services Available at Oregon State Public Health Laboratory (OSPHL)

The OSPHL conducts serologic syphilis screening using a treponemal CIA test (Syph-TP) that reflexes to an RPR. If these produce conflicting results, the TP-PA test is run as a reflex "tiebreaker" treponemal test. For patients with a history of syphilis and a recently documented (within past year) positive treponemal test, an "RPR only" should be ordered. For a visual representation of the OSPHL testing algorithm, refer to the Syphilis Testing Algorithm (pdf). Refer to the OSPHL Lab Test Menu, available at www.healthoregon.org/labtests, for additional information.

4. CASE INVESTIGATION—FOR PUBLIC HEALTH STAFF

4.1 Provider Records

- Review medical records for the visits associated with syphilis lab results to obtain clinical, treatment, and risk information
- If electronic health records are not accessible, contact the provider by phone, fax, or query letter to request the necessary information
- If appropriate, inform the provider that a public health professional will contact the patient to discuss the syphilis diagnosis
- Refer to the STD Program's Syphilis Case Report and Data Entry Manual for guidance on entering data in Orpheus

4.2 Case Interview

- All pregnant cases should be investigated and interviewed regardless of stage
- Cases with two reactive treponemal tests and a non-reactive RPR and no primary signs should be investigated even though the syphilis surveillance case definition is not met
- Interview methods:
  - In-person interviews are preferable but interviews by phone and other methods are also acceptable
  - If the client cannot be reached by traditional methods (e.g., calls, texts, mailed letters, field or clinic-based visit), consider using technology-based tools such as social media sites and mobile apps to contact cases. Any method should be used in accordance with LPHA policies.
  - Refer to §4.4 for resources that can assist with locating individuals
  - Maintain client privacy throughout the case investigation and interview
  - Document all attempts to contact the client in real time when possible, or on the day of each attempt at minimum

4.3 Management of Partners

4.3.1 Interview Periods

- Sexual contacts of a person diagnosed with primary, secondary, or early non-primary non-secondary syphilis are at high risk of acquiring the infection
- Interview periods help identify partners at risk of infection. The interview period is the time from the earliest date the case could have been infected to the date of treatment.
- Refer to **Table 3** for interview periods based on the case's stage ("case" refers to a person with presumptive or confirmed syphilis)
- All partners within the appropriate interview period should be confidentially notified of the exposure and need for evaluation
- If a case has not had sex within the interview period, the most recent contact should be tested and presumptively treated if follow-up is uncertain

Table 3. Interview Periods by Stage

Stage	Interview Period
Primary	90 days before date of onset of primary chancre through date of treatment
Secondary	6.5 months before date of onset of secondary symptoms through date of treatment
Early Non-Primary Non-Secondary	1 year before start of treatment

4.3.2 Partner Notification

Partner treatment is key to preventing reinfection in pregnancy. All partners who pose a risk of reinfection during the pregnancy need to be identified and contacted so that they can be tested and presumptively treated.

- **If LPHA is handling notification:**
  - Contact named partners within two working days of the initial case interview and refer for evaluation, testing, and treatment
  - If partners cannot be reached by traditional methods (e.g., calls, texts, mailed letters, field or clinic-based visit), consider using technology-based tools such as social media sites and mobile apps to contact cases. Any method should be used in accordance with LPHA policies.
  - Try to contact partners at least three times
    - Attempts should be made on alternate days and times of day
    - Refer to §4.4 for resources that can assist with locating individuals
- **If the case chooses to notify partners:**
  - Advise the case that LPHA staff can help arrange partner testing/treatment and encourage the case to share the staff's contact information with partners
  - If possible, contact the case again to offer LPHA notification and treatment referral if partner treatment cannot be verified within a reasonable time frame (2–5 days)

4.3.3 Partner Testing/Treatment

- Partners from **within 90 days** before case's diagnosis (or onset of symptoms) of early syphilis (primary, secondary, early non-primary non-secondary syphilis):
  - Test and presumptively treat for early syphilis
  - Contacts to late or unknown duration syphilis cases that are suspicious for early infection should also be tested and presumptively treated
- Partners from **>90 days** before case's diagnosis (or onset of symptoms) of early syphilis (primary, secondary, early non-primary non-secondary syphilis):
  - Test and presumptively treat for early syphilis if follow-up is uncertain
    - If positive: stage based on clinical and serologic evaluation and treat (if not treated presumptively)
    - If negative: no treatment is needed

    - Contacts to late or unknown duration syphilis cases that are suspicious for early infection should also be tested and presumptively treated if follow-up is uncertain
- Long-term partners of a case diagnosed with late/unknown duration syphilis should be evaluated for syphilis and treated based on the clinical and serological findings

4.4 Requesting Locating Searches and Out-of-State Records

1. **Locating Searches**
   If LPHA staff and the provider cannot locate a case or contact using the available contact information, there are useful resources available:
   - Request that State STD Program staff conduct an Accurint search for the person's current/recent addresses and phone numbers
     - Searches are prioritized for the following:
       - Early syphilis cases
       - Pregnant cases/contacts
       - Cases with unknown pregnancy status
   - Search Orestar to find mailing and residential addresses for Oregon residents
   - Search sites with correctional/judicial information:
     - VISOR to see if a person is currently in a correctional facility or has been recently released
     - Oregon Department of Corrections to see if a person is in an Oregon state prison
     - Oregon Judicial Department to find information on court records, community supervision, name changes, etc.
2. **Out-of-State Records**
   - Out-of-state syphilis records should mainly be requested to:
     - Determine whether there is a new infection based on a comparison of the current and previous titers **OR**
     - Obtain documentation of past syphilis care for persons who are pregnant or pregnancy-capable
   - Clinical management should not be delayed while waiting on out-of-state records, especially if there is a risk of loss to follow-up
     - In many cases, records do not exist or are incomplete

4.5 Case/Contact Transfers and Other Orpheus Issues

Refer to the STD Program's Syphilis Case Report and Data Entry Manual for guidance on Orpheus-specific issues including transferring cases/contacts to other Oregon jurisdictions or out of state.

5. CLINICAL MANAGEMENT—FOR MEDICAL PROVIDERS

Through proper management of pregnant people and partners with syphilis, congenital syphilis can be prevented. Among pregnant people with syphilis who deliver after 20 weeks' gestation, maternal treatment with penicillin is 98%

effective at preventing congenital syphilis. See the CDC 2021 STI Treatment Guidelines for detailed clinical recommendations.[5]

The OHA/AETC Prenatal Syphilis Screening, Staging, and Management Pocket Guide (see Appendix C) is a helpful tool summarizing clinical recommendations.

Since RPR testing is the most common form of nontreponemal testing, the terms "nontreponemal serologic testing" and "RPR" are used interchangeably throughout this section.

5.1 Serologic Screening

- Screen all pregnant people three times in pregnancy, regardless of perceived risk:
  1. At the first prenatal visit or presentation to care
  2. At 28 weeks' gestation
  3. At delivery
- To diagnose syphilis, order a syphilis screening cascade:
  - Traditional algorithm: RPR with reflex to titer and treponemal test
  - Reverse algorithm: Treponemal test with reflex to RPR and titer

5.1.1 Interpreting Screening Algorithm Results (Note: if the initial test for either algorithm is negative, no further testing will be done)

Reactive treponemal test and reactive RPR and no documented syphilis history: Stage and treat with the appropriate penicillin-based regimen. See §5.2.

Reactive treponemal test and reactive RPR and documented history of syphilis diagnosis and treatment:

- Determine whether additional treatment is needed. If past treatment information is not readily available, treatment should be initiated while waiting for records. See §4.4 for information on requesting out-of-state records.
  - If previous treatment prior to or earlier in pregnancy was inadequate (not completed, not appropriate for stage, or not a CDC-recommended regimen): Treat with the penicillin-based regimen appropriate for the current stage of infection.
  - If the current RPR titer is a fourfold or higher increase over previous titer or syphilis symptoms are present: Treat with the penicillin-based regimen appropriate for the current stage of infection.

Reactive treponemal test and nonreactive RPR: A second treponemal test (different from the first) is needed.

- **If second treponemal test is negative:** Initial reactive treponemal test is most likely a false positive. Manage as follows:
  - The provider should consider ordering repeat testing within 4 weeks to monitor for seroconversion. If both the RPR and second treponemal test remain negative, no treatment is necessary.
  - If follow-up is not likely, pregnant people with an isolated reactive treponemal test and without a history of treated syphilis should be

treated with benzathine penicillin G 2.4 million units for presumptive early syphilis.

- **If second treponemal test is positive:** Either an old infection or a very early infection. If primary syphilis signs are present at time of testing, treat with the appropriate CDC-recommended regimen. If asymptomatic, proceed as follows:
  - If documentation of past completion of CDC-recommended treatment appropriate for stage: no further treatment needed.
  - If previous treatment prior was inadequate (not completed, not appropriate for stage, or not a CDC-recommended regimen): treat with the penicillin-based regimen appropriate for the current stage of infection.
  - If no documentation of treatment, or past treatment was inadequate, treat for late/unknown duration syphilis.

Reactive RPR and nonreactive treponemal test: Determine need for follow-up based on titer:

- If the RPR titer is <1:4, recommend repeat testing in one month to rule out incubating syphilis. If primary syphilis symptoms are present at time of testing, treat with benzathine penicillin G 2.4 million units.
- If the RPR titer is ≥1:4, further investigation is needed to determine risk of syphilis versus biological false positive.
  - If primary symptoms are present at the time of testing, treat with benzathine penicillin G 2.4 million units.
  - If no symptoms are present, repeat testing in one month is recommended to rule out incubating syphilis.

5.2 Treatment in Pregnancy

See the CDC 2021 STI Treatment Guidelines for detailed treatment information.[5] Refer to **Table 4** for treatment recommendations for syphilis in pregnancy.

- Penicillin G is the only effective antibiotic for treating fetal infection and preventing congenital syphilis
- For pregnant people with primary, secondary, or early non-primary non-secondary syphilis, a second dose of benzathine penicillin G 2.4 million units IM can be administered 1 week after the initial dose for additional protection. *This is not required.*
- **For pregnant people with unknown duration or late syphilis, the dosing interval is critical. A 7-day interval is ideal and a 6-9 day interval is acceptable. If any doses are given outside this interval, the treatment series must be restarted.** For example, if the third dose is given 10 days after the second dose, the three-dose regimen should be restarted (in this scenario, the third dose can be considered the first dose of the restarted series).

Table 4. Treatment Recommendations for Syphilis in Non-Pregnant Adults

Stages	Recommended Regimen	If Penicillin Allergy*
Primary, Secondary, and Early Non-Primary Non-Secondary	Benzathine penicillin G (Bicillin L-A) 2.4 million units IM in a single dose	Skin testing for penicillin allergy and desensitization (urgent)
Unknown Duration or Late	Benzathine penicillin G (Bicillin L-A) 7.2 million units total IM as three doses of 2.4 million units each at 7-day intervals	Skin testing for penicillin allergy and desensitization (urgent)

* Approximately 10% of all U.S. patients report having a penicillin allergy. However, less than 1% of the population is truly allergic to penicillin. Refer to the CDC 2021 STI Treatment Guidelines and the Is it Really a Penicillin Allergy? fact sheet for guidance on evaluating a reported penicillin allergy.

Refer to **Table 5** for treatment recommendations for neurosyphilis, ocular syphilis, and otosyphilis in pregnant adults.

Table 5. Treatment Recommendations for Clinical Manifestations of Syphilis

Clinical Manifestations	Recommended Regimen	If Penicillin Allergy
Neurosyphilis, Ocular Syphilis, or Otosyphilis	Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units intravenously every 4 hours or continuous infusion, for 10-14 days	Skin testing for penicillin allergy and desensitization (urgent)

5.3 Sonographic Screening

When syphilis is diagnosed after 20 weeks' gestation, clinical management should include a sonographic fetal evaluation for congenital syphilis. This evaluation should not delay syphilis treatment.

5.4 Titer Monitoring in Pregnancy

- The main reason to check titers following syphilis treatment in pregnancy is to monitor for reinfection. Reinfection is indicated by a fourfold or higher increase in titer and/or syphilis signs/symptoms.
- A fourfold decrease in titer is unlikely before delivery following treatment during pregnancy. Titers should not be done with the expectation of achieving a fourfold decrease in titer or a nonreactive RPR before delivery.
- Titer monitoring in pregnancy:
  - **Diagnosed and treated at or before 24 weeks' gestation:**
    - Titers should NOT be repeated before 8 weeks after treatment initiation. Titers can increase immediately after treatment, likely

related to the treatment response. Unless primary or secondary signs appear, a follow-up titer should not be done until at least 8 weeks after treatment initiation.
        - A titer should be repeated at delivery.
        - Additional titers can be done if there are untreated partners who pose a continuing risk of reinfection during the pregnancy and/or if primary or secondary signs appear. Refer to §4.3 for guidance regarding management of sexual contacts to prevent reinfection.
    - **Diagnosed and treated after 24 weeks' gestation:**
        - A titer should be repeated at delivery.
        - There is little benefit to checking a titer following treatment and before delivery unless primary or secondary signs/symptoms are present or there are untreated partners who pose a continuing risk of reinfection during the pregnancy.
- See the Syphilis Investigative Guidelines for titer monitoring recommendations for non-pregnant adults.

6. CONTROLLING FURTHER SPREAD

6.1 Education

- Pregnant people diagnosed with syphilis should be advised to:
    - Complete treatment
    - Avoid all types of sex until treatment has been completed and any skin lesions have resolved.
    - Avoid all types of sex with untreated partners until the partners have been treated and their skin lesions have resolved
- Other key education messages for people at risk of acquiring syphilis and other STIs:
    - Use condoms as often as possible
    - Get checked for HIV and other STIs
    - Talk to partners about testing
    - Know about STI PEP (DoxyPEP) and HIV pre- and post-exposure prophylaxis (PrEP and PEP)
        - Transgender women and gay, bisexual, and other men who have sex with men, on diagnosis of chlamydia, should be offered doxycycline postexposure prophylaxis for bacterial sexually transmitted infections (doxyPEP). Providers should use their clinical judgement and shared decision-making to inform use of doxyPEP with populations that are not part of CDC recommendations. See the CDC doxyPEP guidelines for more information.
        - PrEP education and referrals should be provided to anyone diagnosed with or at risk for syphilis. Refer to the OHA PrEP/PEP page for additional information.
        - Visit the AETC site for a list of PrEP providers in Oregon and southwest Washington State

- Talk with a provider about contraceptive options if not currently seeking pregnancy
- Utilize syringe service programs (for those using/injecting drugs)
- Stay up to date on vaccinations as appropriate, including for HPV and hepatitis A and B

7. MANAGING SPECIAL SITUATIONS

7.1 Syphilis Case has Multiple Reportable Infections

- Check in Orpheus to see if a pregnant person diagnosed with syphilis has any other new reportable infections, especially other STI or HIV (may depend on Orpheus disease group access)
- Coordinate case investigations to reduce duplication and communication with case:
  - Combine questions for all infections in one interview session rather than having multiple people contact the case to ask different questions
  - Obtain partner information based on interview periods for each STI/HIV

7.2 Jarisch-Herxheimer Reaction

- The Jarisch-Herxheimer reaction is a flu-like reaction involving fever, headache, and muscle aches, that can occur after initiation of syphilis treatment
  - The reaction usually begins within 2 hours of treatment initiation, peaks at approximately 8 hours, and resolves in 24-36 hours
  - In most cases no treatment is required
- It is a reaction to the rapid killing of *T. pallidum* bacteria and is **not** an allergic reaction to syphilis treatment
- It occurs most often in early syphilis, likely because bacterial loads are higher during these stages
- Patients treated during the second half of pregnancy should be advised to seek obstetric care after treatment if they notice fever, contractions, or decreased fetal movement

7.3 Syphilis among Pregnant Persons Living with HIV (PLWH)

- Pregnant persons with syphilis who also have an HIV diagnosis and are not on antiretroviral therapy should be immediately linked to HIV care
  - Contact the OHA HIV Surveillance Program for assistance with these HIV cases
- Unusual syphilis test results can occur among PLWH but are rare
  - Post-treatment titers may be higher than expected (high serofast) or fluctuate
  - False-negative tests and delayed seroreactivity (detectable immune response to syphilis) have also been seen
- Treatment for all stages and for neuro/ocular/otic syphilis is the same regardless of HIV status

- All persons with HIV and syphilis coinfection should receive a careful neurologic, ocular, and otic examination
  - PLWH who have early syphilis might be at increased risk for neurologic complications
  - Ocular syphilis has been reported more frequently among PLWH

GLOSSARY

CSF: Cerebrospinal fluid. CSF testing can indicate whether there is central nervous system involvement in a syphilis infection.

Early syphilis: Any of the stages that occur in the first 12 months of infection: primary, secondary, and early non-primary non-secondary syphilis.

IM: Intramuscular. An IM injection delivers medication, such as benzathine penicillin G for syphilis, into a muscle.

PCR: Polymerase chain reaction test is a laboratory technique for rapidly producing (amplifying) many copies of a specific segment of genetic material, e.g., *T. pallidum* DNA in syphilis.

RPR: Rapid Plasma Reagin test is a nontreponemal serologic (blood) test. Unlike treponemal tests, the RPR measures antibodies that are not specific for *T. pallidum* bacteria and may be reactive due to conditions other than syphilis, including pregnancy.

Treponemal test: Treponemal tests measure antibodies directed against *T. pallidum* bacteria. Treponemal serologic (blood) tests include enzyme immunoassays (EIAs) and chemiluminescence immunoassays (CIAs), *T. pallidum* particle agglutination (TP-PA), and fluorescent treponemal antibody absorption (FTA-ABS) tests. These qualitative tests usually remain reactive for life, regardless of treatment.

VDRL: Venereal Disease Research Laboratory test is a nontreponemal test that can be done on blood and CSF. Mostly used in CSF testing in congenital syphilis and neurosyphilis evaluations. The RPR is the more common nontreponemal serologic (blood) test in Oregon.

REFERENCES

1. Oregon Administrative Rules. Oregon Health Authority Chapter 333 Public Health Division, Division 18 Disease Reporting. https://secure.sos.state.or.us/oard/viewSingleRule.action?ruleVrsnRsn=292908
2. Oregon Revised Statutes. Chapter 433 Disease and Condition Control. https://www.oregonlegislature.gov/bills_laws/ors/ors433.html
3. Oregon Administrative Rules. Oregon Health Authority Public Health Division Chapter 333 Division 19 Investigation and Control of Diseases: General Powers and Responsibilities. https://secure.sos.state.or.us/oard/viewSingleRule.action?ruleVrsnRsn=292879

4. CDC National Notifiable Diseases Surveillance System (NNDSS) Syphilis (*Treponema pallidum*) 2018 Case Definition. https://ndc.services.cdc.gov/case-definitions/syphilis-2018/
5. CDC Sexually Transmitted Infections Treatment Guidelines, 2021. https://www.cdc.gov/std/treatment-guidelines/default.htm

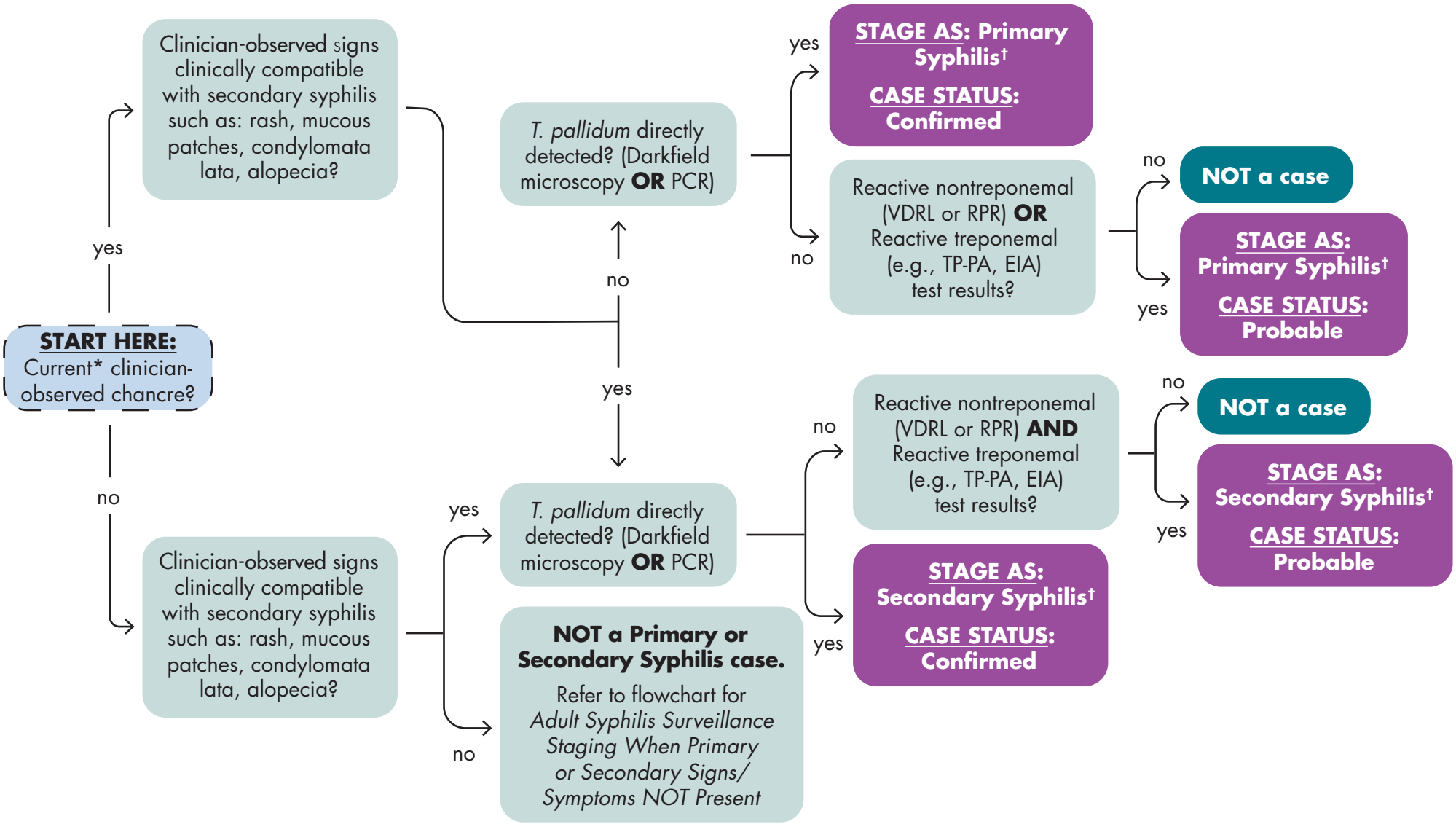
UPDATE LOG

July 2023. Extensively rewritten and reformatted. (Garai, Gonzalez Pena, Menza)
August 2024. Broken links fixed and appendices updated. Confirmatory criteria and direct detection methods in §3 updated. Education on DoxyPEP added. (Garai)

Appendix A

ADULT SYPHILIS SURVEILLANCE STAGING WHEN PRIMARY OR SECONDARY SYPHILIS SIGNS/SYMPTOMS ARE PRESENT

(Not to be used as guidance for treatment)



*Current refers to the anchoring date of the original diagnosis, such as at time of original clinical diagnosis or positive screening test.

†Neurologic, ocular, and otic manifestations of syphilis can occur at any stage. After assigning syphilis stage, assess all cases for these clinical manifestations and classify separately as "No," "Verified," "Likely," "Possible," or "Unknown." Late clinical manifestations of syphilis are classified separately as "No," "Verified," "Likely," or "Unknown." For assistance with classification of these manifestations, please see clinical manifestations algorithms.

ACRONYMS: *T. pallidum* = *Treponema pallidum*; PCR = polymerase chain reaction; VDRL = Venereal Disease Research Laboratory; RPR = rapid plasma reagin; TP-PA = *Treponema pallidum* particle agglutination; EIA = enzyme immunoassay

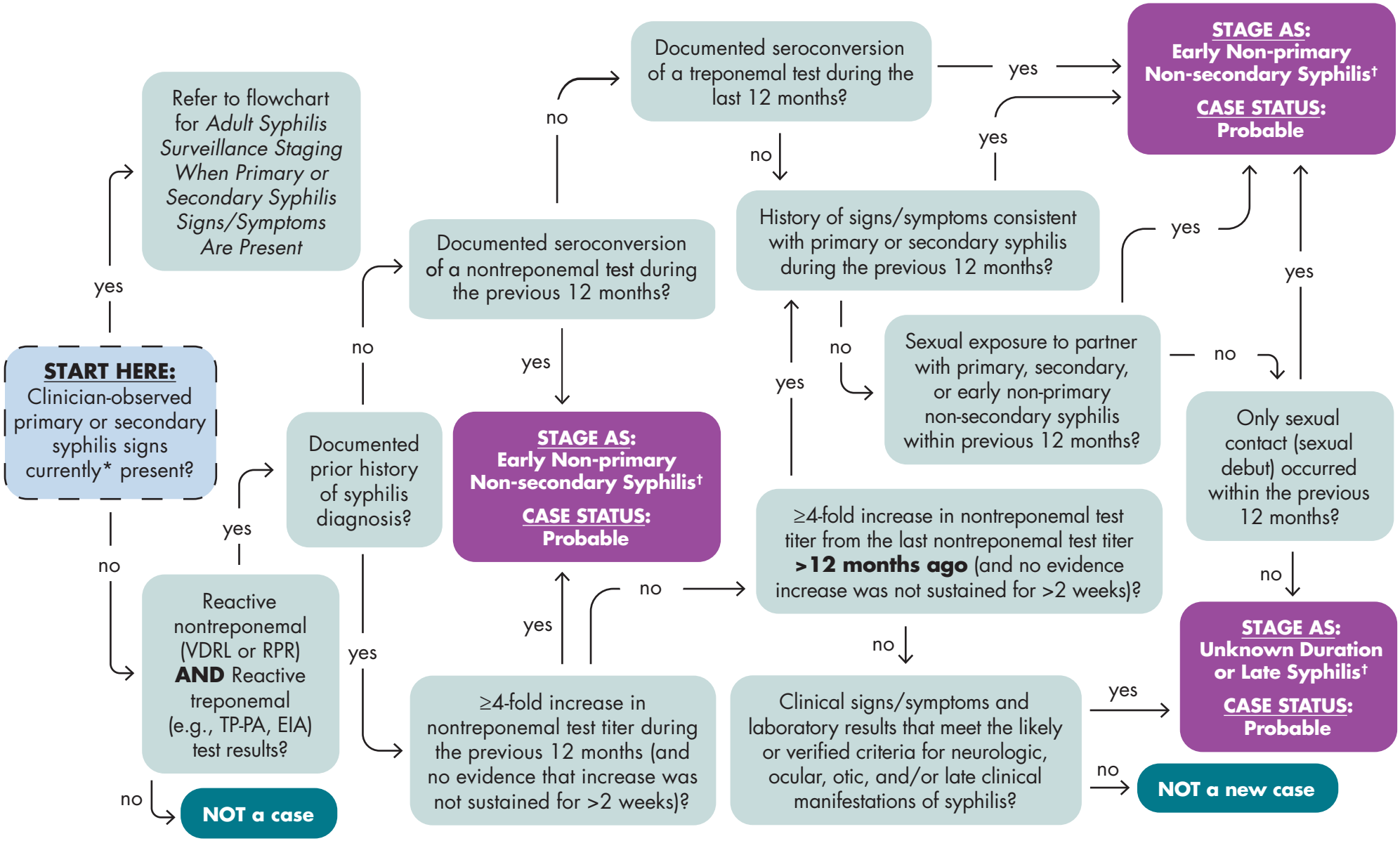
RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

CS328736-A

Updated 6/1/2023

ADULT SYPHILIS SURVEILLANCE STAGING WHEN PRIMARY OR SECONDARY SIGNS/SYMPTOMS NOT PRESENT

(Not to be used as guidance for treatment)



*Current refers to the anchoring date of the original diagnosis, such as at time of original clinical diagnosis or positive screening test.

†Neurologic, ocular, and otic manifestations of syphilis can occur at any stage. After assigning syphilis stage, assess all cases for these clinical manifestations and classify separately as "No," "Verified," "Likely," "Possible," or "Unknown." Late clinical manifestations of syphilis are classified separately as "No," "Verified," "Likely," or "Unknown." For assistance with classification of these manifestations, please see clinical manifestations algorithms.

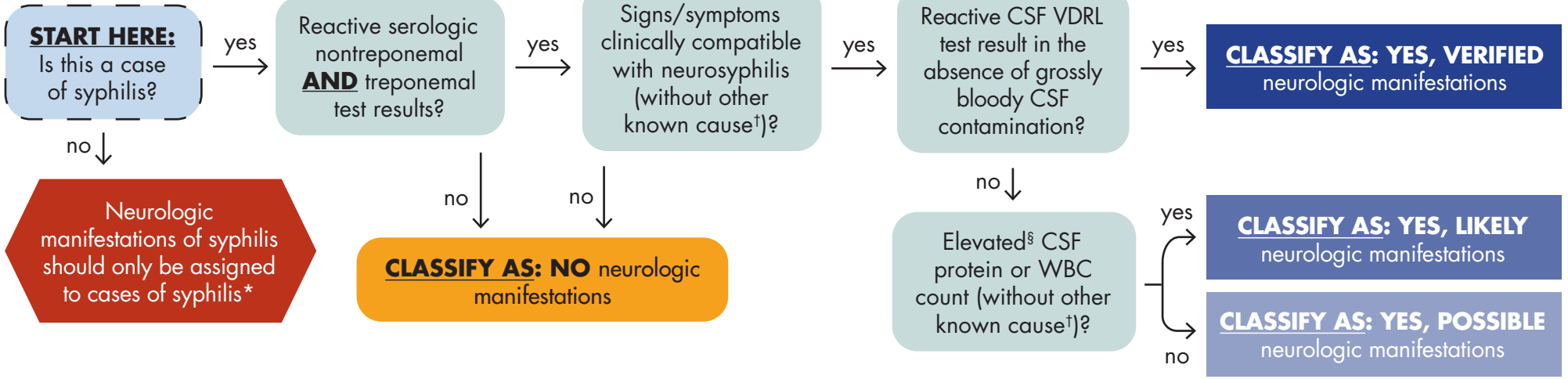
ACRONYMS: VDRL = Venereal Disease Research Laboratory; RPR = rapid plasma reagin; TP-PA = *Treponema pallidum* particle agglutination; EIA = enzyme immunoassay.

RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

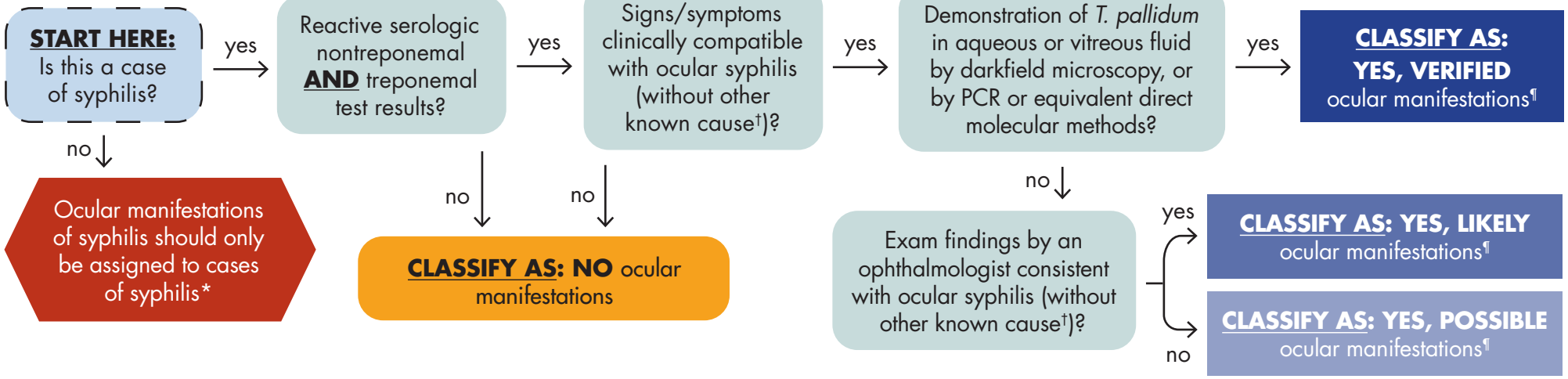
CS328736-A

Updated 6/1/2023

SURVEILLANCE CLASSIFICATION OF NEUROLOGIC MANIFESTATIONS OF SYPHILIS *(Not to be used as guidance for treatment)*



SURVEILLANCE CLASSIFICATION OF OCULAR MANIFESTATIONS OF SYPHILIS *(Not to be used as guidance for treatment)*



*Any case with clinical signs/symptoms and laboratory results that meet the likely or verified criteria for neurologic, ocular, otic, or late clinical manifestations of syphilis and that has no evidence of having acquired the disease within the preceding 12 months meets the Council of State and Territorial Epidemiologists case definition for unknown duration or late syphilis.

†Clinician input may be needed to rule out other possible causes.

§The Council of State and Territorial Epidemiologists case definition for neurologic manifestations of syphilis defines elevated CSF protein as >50 mg/dL and elevated CSF WBC count as >5 WBCs/mm^3. Additional guidance for interpretation of CSF results is available in CDC's STI Treatment Guidelines.

¶Because ocular manifestations are considered signs/symptoms clinically compatible with neurosyphilis, cases classified as having ocular manifestations should also be classified as having neurologic manifestations.

ACRONYMS: CSF = cerebrospinal fluid; VDRL = Venereal Disease Research Laboratory; WBC = white blood cell; *T. pallidum* = *Treponema pallidum*; PCR = polymerase chain reaction

RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

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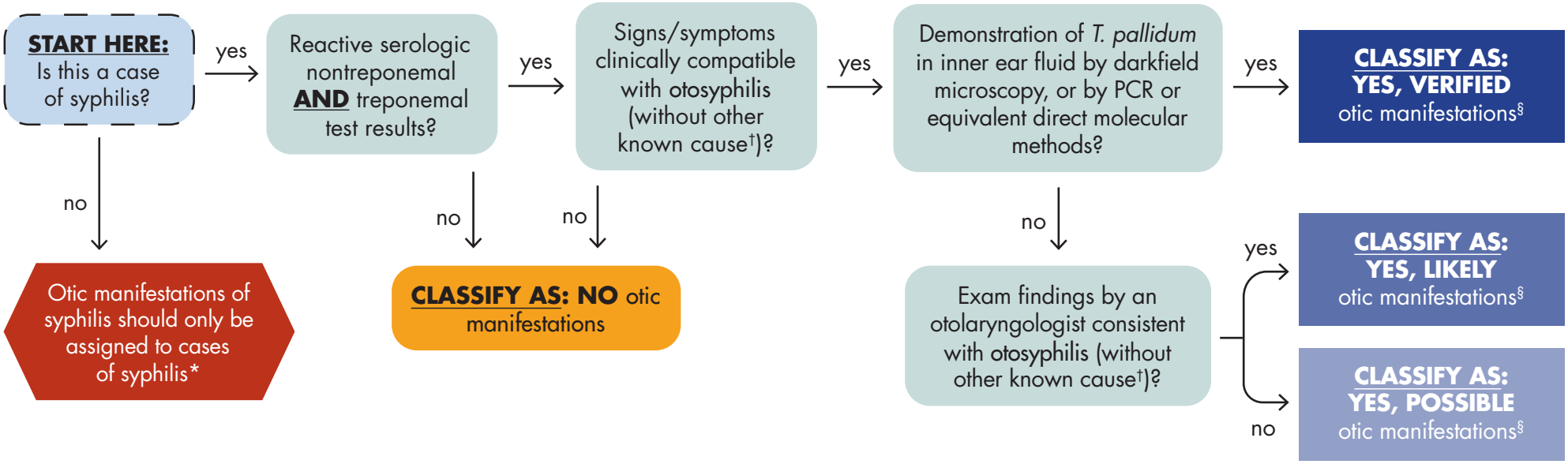
Updated 5/23/2023

SURVEILLANCE CLASSIFICATION OF OTIC MANIFESTATIONS OF SYPHILIS *(Not to be used as guidance for treatment)*



*Any case with clinical signs/symptoms and laboratory results that meet the likely or verified criteria for neurologic, ocular, otic, or late clinical manifestations of syphilis and that has no evidence of having acquired the disease within the preceding 12 months meets the Council of State and Territorial Epidemiologists case definition for unknown duration or late syphilis.

†Clinician input may be needed to rule out other possible causes.

§Because otic manifestations are considered signs/symptoms clinically compatible with neurosyphilis, cases classified as having otic manifestations should also be classified as having neurologic manifestations.

ACRONYMS: *T. pallidum* = *Treponema pallidum*; PCR = polymerase chain reaction

RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

Updated 5/23/2023

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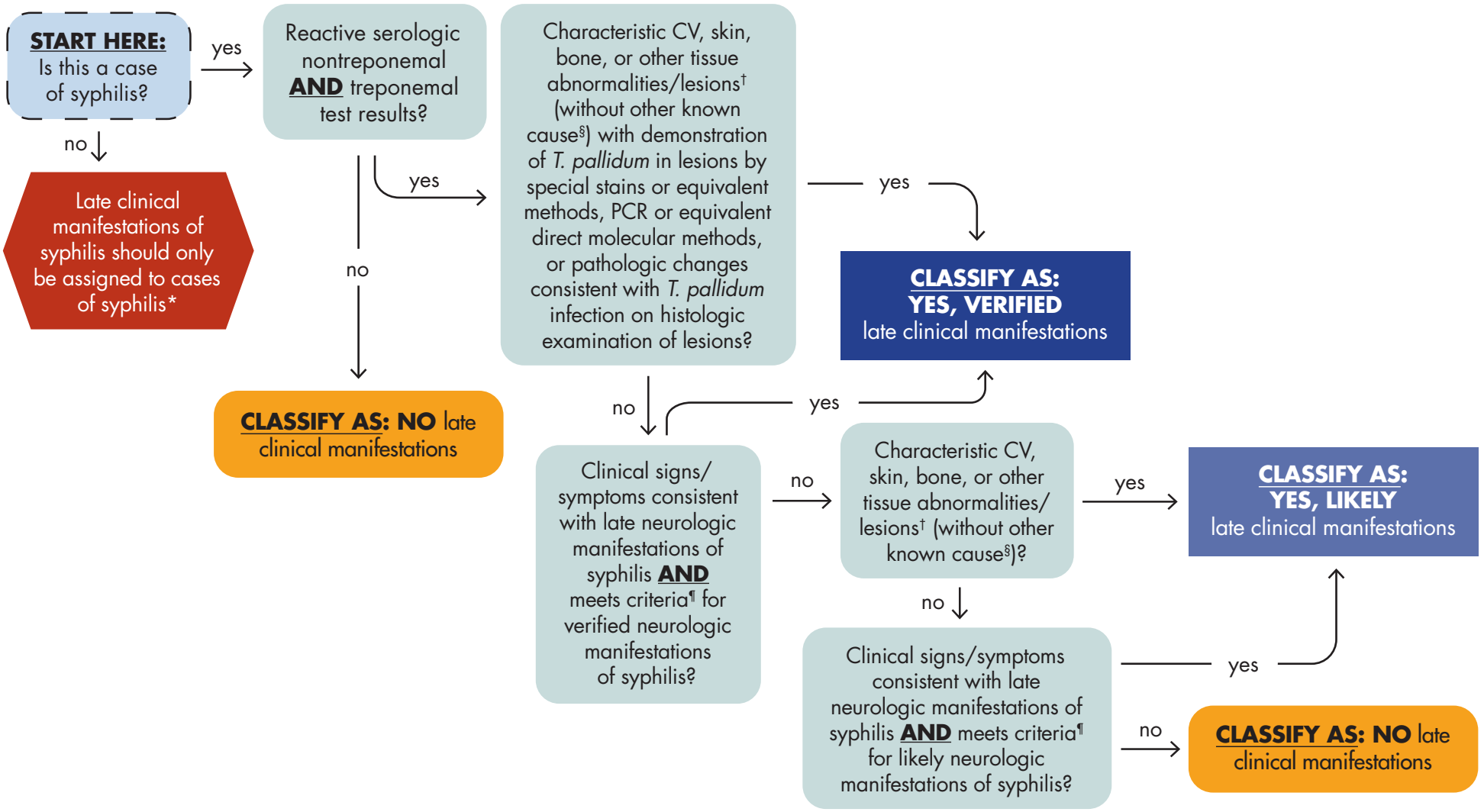
SURVEILLANCE CLASSIFICATION OF LATE CLINICAL MANIFESTATIONS OF SYPHILIS *(Not to be used as guidance for treatment)*



*Any case with clinical signs/symptoms and laboratory results that meet the likely or verified criteria for neurologic, ocular, otic, or late clinical manifestations of syphilis and that has no evidence of having acquired the disease within the preceding 12 months meets the Council of State and Territorial Epidemiologists case definition for unknown duration or late syphilis.

†Additional information about characteristic lesions associated with late clinical manifestations of syphilis is available in CDC's STI Treatment Guidelines.

§Clinician input may be needed to rule out other possible causes.

¶Please see syphilis surveillance case definitions and neurologic manifestations classification algorithm for additional assistance.

ACRONYMS: CV = cardiovascular; *T. pallidum* = *Treponema pallidum*; PCR = polymerase chain reaction

RESOURCES: Syphilis case definitions; Syphilis treatment guidelines; Partner services

Updated 5/23/2023

CS328983-A

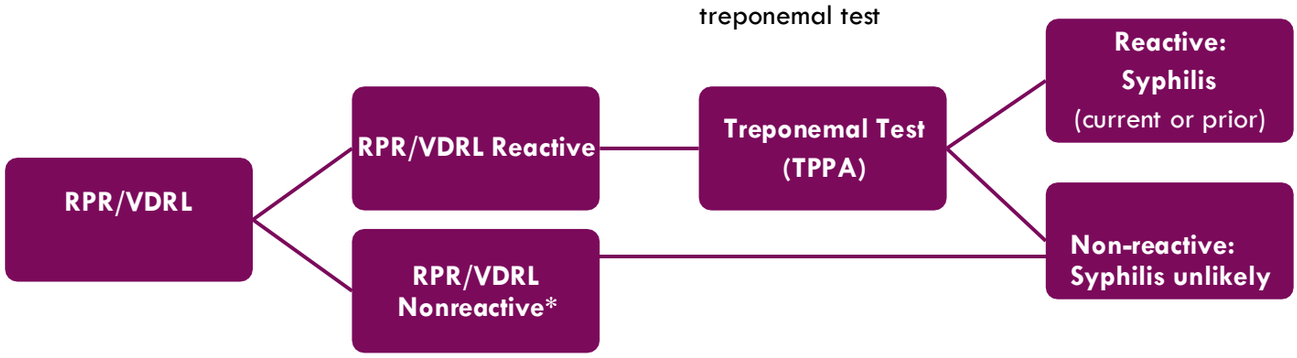
Appendix B

Clinical Interpretation of Syphilis Screening Algorithms

Testing: Traditional Algorithm[a]

1. Screen with non-treponemal test (RPR/VDRL)

2. Confirm reactive non-treponemal test with treponemal test



*Early primary syphilis and late untreated syphilis possible if RPR/VDRL are nonreactive; see below for recommended actions

Table 1: Interpretation of Syphilis Serologies, Traditional Algorithm

Non-Treponemal (RPR/VDRL)	Treponemal (TPPA)	Possible Interpretations	Recommended Actions
Nonreactive	Nonreactive or not done	1. No syphilis 2. Early/incubating syphilis (too early to be detected by serology)	▪ If syphilis unlikely, no further action needed. ▪ If early syphilis suspected, consider ordering a treponemal test (if not done initially) and repeating an RPR/VDRL in 1-2 weeks; if either test is reactive, treat for syphilis. ▪ If concerned for early syphilis (e.g., chancre present or known exposure) treat presumptively. If treating presumptively, repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
	Reactive	1. Prior treated syphilis 2. Untreated syphilis	▪ Treponemal tests (e.g., TPPA) often stay reactive for life; if patient has a history of adequate treatment for syphilis & no new exposures/ symptoms, no further action needed. ▪ If early syphilis suspected (e.g., chancre present or known exposure), treat presumptively according to stage. If treating presumptively, repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion. ▪ If no signs or symptoms, order a second treponemal test (e.g., EIA or CIA); see table 2 for recommendations based on results.
Reactive	Nonreactive	1. False positive RPR or VDRL	▪ Likely false positive (not syphilis).[b] ▪ In pregnancy or in patients at high risk for syphilis, consider rescreening with serologic testing in 2-4 weeks – if unchanged, no action needed.[c]
	Reactive	1. Current syphilis 2. Treated syphilis with residual/ persistent RPR/VDRL titer	▪ If RPR/VDRL is newly reactive, stage and treat. ▪ If previously treated and sustained (≥2 weeks) 4-fold rise in RPR/VDRL titer, manage as treatment failure versus re-infection.[d] ▪ Note that RPR/VDRL may still be reactive after treatment; if there is a fourfold decline within 12-24 months, treatment is considered to have been adequate even if RPR/VDRL remains reactive. ▪ Some treated patients may have a persistent low level RPR/VDRL titer for a prolonged period; re-treatment is not necessary in the absence of new exposures or symptoms.

[a] The traditional algorithm starts with a non-treponemal test (RPR or VDRL) which, if reactive, is followed by a confirmatory treponemal test (TPPA). In interpreting serologies, it is helpful to know which testing algorithm (traditional vs reverse) is being used in your lab.

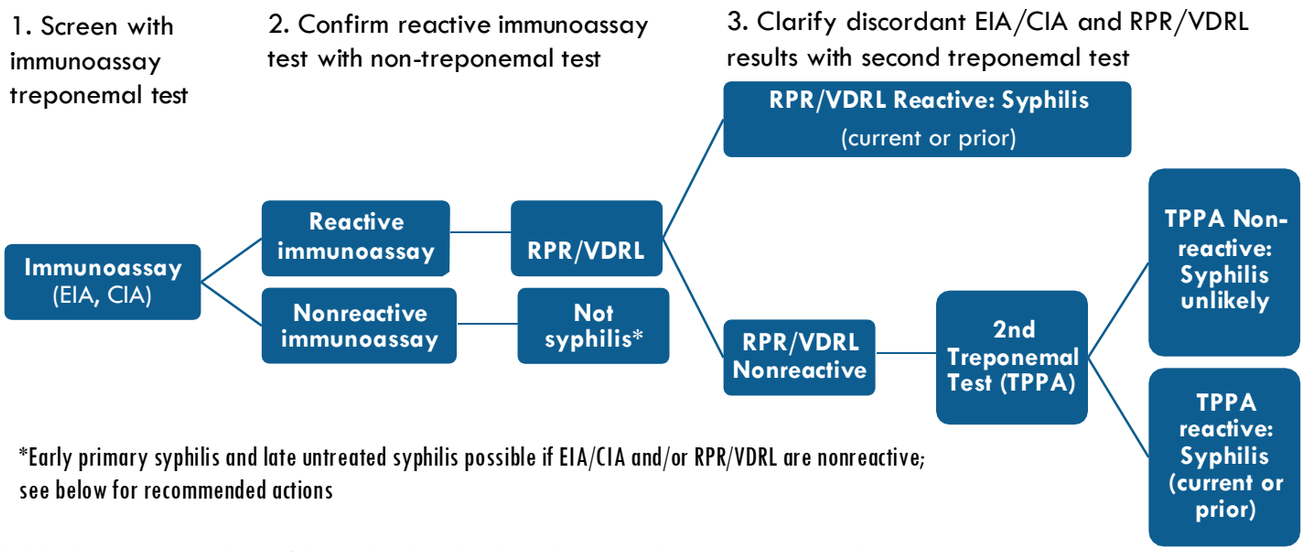
[b] False positives can be seen in pregnancy and/ in patients with autoimmune diseases, Lyme disease, certain viral infections (including HIV), injection drug use, and other conditions.

[c] In California, all pregnant people should be screened for syphilis at least twice during pregnancy: once at either confirmation of pregnancy or at the first pre-natal encounter, and again during the third trimester (ideally between 28-32 weeks). Patients should also be screened at delivery, except those at low risk who have a documented negative screen in the third trimester. See https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/California-STI-Screening-Recommendations.aspx.%20As%20of%20April%202024. As of April 2024, the American College of Obstetrics and Gynecology recommends screening all pregnant patients universally for syphilis three times: once at the first prenatal care visit, again during the third trimester, and again at birth.

[d] For patients determined to have new syphilis or treatment failure, refer to the Centers for Disease Control STD treatment guidelines at https://www.cdc.gov/std/treatment-guidelines/syphilis.htm for treatment and follow up recommendations.

Clinical Interpretation of Syphilis Screening Algorithms

Testing: Reverse Algorithm[a]



*Early primary syphilis and late untreated syphilis possible if EIA/CIA and/or RPR/VDRL are nonreactive; see below for recommended actions

Table 2: Interpretation of Syphilis Serologies, Reverse Screening Algorithm

Immuno-assay (CIA or EIA)	RPR/ VDRL	TPPA	Possible Interpretations	Recommended Actions
Non-reactive	Non-reactive or not done	Non-reactive or not done	1. Syphilis unlikely 2. Early/incubating syphilis (too early to be detected by serology)	▪ If syphilis unlikely, no further action needed. ▪ If immunoassay nonreactive but high clinical suspicion (such as a chancre or known exposure), treat presumptively for early syphilis. If treating presumptively, obtain RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
Reactive	Non-reactive	Non-reactive or not done	1. False positive immunoassay 2. Early/incubating syphilis 3. Latent or prior syphilis (treated or untreated)	▪ If no signs/symptoms and low risk for syphilis, most likely a false positive immunoassay.[b] No further action needed. ▪ If concerned for early infection or in pregnant patients, re-screen in 2-4 weeks.[c] ▪ If signs/symptoms or contact to syphilis, treat presumptively. Repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
		Reactive	1. Latent or prior syphilis (treated or untreated) 2. Early syphilis (prior to RPR/VDRL seroconversion)	▪ No further action needed if patient treated appropriately for syphilis in past, assuming no new exposures/symptoms and a negative clinical exam. ▪ If no symptoms and no known prior adequate treatment, treat presumptively for latent syphilis. ▪ If early syphilis suspected (symptoms or known exposure), treat presumptively. Obtain RPR/VDRL on day of treatment. If nonreactive, repeat in 2-4 weeks to assess for seroconversion.
	Reactive	Not done or Reactive	1. Current syphilis 2. Prior syphilis (treated or untreated)	▪ If RPR/VDRL is newly reactive, stage and treat. ▪ If previously treated and sustained (≥2 weeks) 4-fold rise in RPR/VDRL titer, manage as treatment failure versus re-infection.[d] ▪ If known prior adequate treatment for stage of infection and RPR/VDRL declining appropriately (i.e., a fourfold decline within 12-24 months), no further action needed. ▪ Some treated patients may have a persistent low level RPR/VDRL titer for a prolonged period; re-treatment is not necessary in the absence of new exposures or symptoms.

[a] The reverse algorithm starts with an immunoassay detecting syphilis antibodies which, if reactive, is followed by an RPR/VDRL. If there is a discrepancy between the immunoassay and RPR (one reactive, one nonreactive), a treponemal test (TPPA) serves as the tie-breaker. In interpreting serologies, it is helpful to know which testing algorithm (traditional vs reverse) is being used in your lab.

[b] False positive immunoassays can occur with Lyme disease or non-syphilis treponemal infections.

[c] In California, all pregnant people should be screened for syphilis at least twice during pregnancy: once at either confirmation of pregnancy or at the first pre-natal encounter, and again during the third trimester (ideally between 28-32 weeks). Patients should also be screened at delivery, except those at low risk who have a documented negative screen in the third trimester. See https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/California-STI-Screening-Recommendations.aspx.%20As%20of%20April%202024. As of April 2024, the American College of Obstetrics and Gynecology recommends screening all pregnant patients universally for syphilis three times: once at the first prenatal care visit, again during the third trimester, and again at birth.

[d] For patients determined to have new syphilis or treatment failure, refer to the Centers for Disease Control STD treatment guidelines at https://www.cdc.gov/std/treatment-guidelines/syphilis.htm for treatment and follow up recommendations.

Appendix C

Prenatal Syphilis Screening, Staging, and Management for Congenital Syphilis Prevention

Screen

Screen all patients at three points in pregnancy:

❶ First prenatal visit or time of pregnancy testing **❷ 28 weeks' gestation** **❸ Delivery**

Initial diagnosis requires both a non-treponemal test (RPR) and confirmatory treponemal test (TP-PA, FTA-ABS, EIA/CIA)

Stage / Treat / Monitor

SYPHILIS DIAGNOSIS			RISK FACTORS FOR SYPHILIS IN PREGNANCY
Stage: Primary + Chancre; Secondary + Rash and/or other signs[1]; Early Latent NO symptoms, and infection occurred within the past year[2]	**Stage:** Late Latent or Unknown Duration — NO symptoms, and infection does not meet criteria for early latent[2]	**Stage:** Neurosyphilis/ Ocular/ Otosyphilis[3] — + CNS signs or symptoms; + CSF findings on lumbar puncture (LP)	**If there is no record of syphilis screening in pregnancy or screening history is unknown, screen patients with any of these risks (particularly those who attend ED, urgent care, detention/correctional, and/or substance use treatment settings):**
Treat: Benzathine penicillin G 2.4 Million Units Intramuscularly (IM) Once. *Certain evidence indicates that additional therapy is beneficial for early syphilis in pregnancy. A second dose of benzathine penicillin G 2.4 million units IM can be given 7 days after the initial dose.*	**Treat:** Benzathine penicillin G 2.4 Million Units IM every 7 days, for 3 doses (7.2 Million Units total). *A 6-9 day interval between doses is acceptable. If any doses are late or missed, re-start the entire 3-dose series.*	**Treat:** Aqueous 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. See 2021 CDC STI Treatment Guidelines for non-intravenous alternative regimen.	• Limited or no prenatal care • Injection drug use (or partner who uses injection drugs) • Methamphetamine or heroin use (any method) • Houselessness or unstably housed • Criminal justice involvement within previous 12 months (or partner with criminal justice involvement) • Living with HIV or hepatitis C • Other STI diagnosed within previous 12 months • Multiple sex partners, a new partner, or partner with other partners

Monitor:

If syphilis treated at/before 24 weeks' gestation, wait at least 8 weeks to repeat titer and repeat again at delivery. Repeat sooner if reinfection or treatment failure is suspected. If treated after 24 weeks' gestation, repeat titer at delivery. Consider more frequent monitoring if at high risk for reinfection in pregnancy (see risks at right).

If syphilis diagnosed after 20 weeks' gestation, management should include a fetal ultrasound to look for congenital syphilis.

Post-treatment serologic response during pregnancy varies widely. Many women do not experience a fourfold decline by delivery. If sustained (>2 weeks) fourfold increase occurs after treatment completion, evaluate for reinfection and neurosyphilis.

1. Signs of secondary syphilis also include condyloma lata, patchy alopecia, and mucous patches.
2. Persons can receive a diagnosis of early latent if, during the prior 12 months, they had a) seroconversion or sustained fourfold titer rise (RPR); b) unequivocal symptoms of primary or secondary syphilis; or c) a sex partner with primary, secondary, or early latent syphilis.
3. Neurosyphilis, ocular, and otic syphilis can occur at any stage. Patients need a full neurologic exam including ophthalmic and otic; If clinical evidence of neurologic involvement is observed (e.g. cognitive dysfunction, motor or sensory deficits, cranial nerve palsies, or symptoms or signs of meningitis or stroke), a CSF examination should be performed before treatment. If only ocular/otic manifestations without other abnormalities on neuro exam, CSF evaluation not necessary before starting treatment for neurosyphilis.

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Last Updated: 3/31/22

Important Considerations for Syphilis Treatment in Pregnancy

Screen early, treat as soon as possible
Treatment failure, and subsequent congenital syphilis, has been associated with treatment later in the pregnancy

Treatment is safe and highly effective for both the pregnant person and fetus

Benzathine Penicillin G (Bicillin L-A) is the ONLY recommended therapy for syphilis during pregnancy

Someone with signs, symptoms, or exposure to syphilis should receive treatment for early disease regardless of whether serology results are available

ADDITIONAL RESOURCES

- **For detailed treatment guidelines,** including penicillin allergy recommendations, see the CDC 2021 STI Treatment Guidelines: www.cdc.gov/std/treatment-guidelines
- **For clinical questions:**
  - Contact Dr. Tim Menza at the Oregon Health Authority (TIMOTHY.W.MENZA@dhsoha.state.or.us), or
  - Enter your consult online at the STD Clinical Consultation Network: stdccn.org

What if my patient is allergic to penicillin?

- **Verify the nature of the allergy.** Approximately 10% of the population reports a penicillin allergy, but less than 1% of the whole population has a true IgE-mediated allergy.
- **Symptoms of an IgE-mediated (type 1) allergy include:** Hives, angioedema, wheezing and shortness of breath, and anaphylaxis. Reactions typically occur within 1 hour of exposure.
- **Refer for penicillin skin testing** if the nature of the allergy is uncertain or cannot be determined.
- **Refer for desensitization with penicillin** if the skin test is positive or the patient has a true penicillin allergy.
- **Desensitization should be performed.** Serious allergic reactions can occur. Consult an allergist.
- **Treat the patient with benzathine penicillin G.** Treat according to appropriate stage of syphilis (see opposite page for treatment regimen).

FOR MORE INFORMATION ABOUT IgE-MEDIATED PENICILLIN ALLERGY:
www.cdc.gov/antibiotic-use/community/pdfs/penicillin-factsheet.pdf
www.cdc.gov/std/treatment-guidelines/penicillin-allergy.htm

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Oregon Health Authority

AETC AIDS Education & Training Center Oregon AETC

END HIV

Congenital Syphilis

Investigative Guidelines

August 2023

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. Identify cases of syphilis in pregnancy and prevent vertical transmission
2. Ensure adequate treatment and follow-up for pregnant people with syphilis and the infant
3. Ensure appropriate management, including screening and presumptive treatment, of sexual contacts of pregnant people with syphilis
4. Describe the epidemiology of congenital syphilis in Oregon

1.2 Laboratory and Physician Reporting Requirements

1. Licensed laboratories must report all positive test results indicating syphilis infection to the Local Public Health Authority within one working day (OAR 333-018-0000; 333-018-0015)[1]
2. Clinicians must report lab-confirmed and clinically suspect cases of syphilis to the Local Public Health Authority within one working day (OAR 333-018-0000; 333-018-0015)[1]
   - Oregon Revised Statute (ORS) 433.017 requires individuals attending a pregnant patient to collect or order the collection of a blood specimen for submission to a licensed laboratory to test for syphilis and selected other infections, unless the pregnant patient declines testing (OAR 333-019-0036)[2,3]
   - Oregon Health Authority recommends that all pregnant people be tested for syphilis three times: 1) at the first prenatal visit or presentation to care, 2) at 28 weeks' gestation, and 3) at delivery
3. Health care providers, health care facilities, and licensed laboratories shall cooperate with public health authorities in the investigation and control of syphilis infections (OAR 333-019-0002)[3]

1.3 Local Public Health Authority Reporting and Follow-up Responsibilities

1. LPHA must begin follow-up case investigation within two working days of receiving the initial provider or laboratory report
2. LPHA must report all congenital syphilis cases (including syphilitic stillbirths) to the OHA STD Program through the Oregon Public Health Epidemiology User System (Orpheus) by the end of the calendar week of initial provider or laboratory report (OAR 333-018-0020)[1]

3. LPHA must conduct case investigations and manage sexual contacts by following procedures outlined in these Investigative Guidelines (ORS 433.006, OAR 333-019-0000)[2,3]

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

The etiologic agent in syphilis is Treponema pallidum subspecies pallidum, a spirochete (corkscrew-shaped) bacterium.

Of all the subspecies of T. pallidum, only T. pallidum subsp. pallidum is transmitted routinely by sexual contact. The other T. pallidum subspecies are transmitted non-sexually (e.g., yaws, pinta).

2.2 Description of Illness

- **Early Congenital Syphilis (infant or child <2 years old):** Manifestations can include rhinitis (“snuffles”), long bone abnormalities, severe anemia, enlarged liver and spleen, jaundice, meningitis, or skin rashes
  - Infants with congenital syphilis may not have any symptoms at birth but can develop serious problems without treatment
- **Late Congenital Syphilis (child ≥2 years old):** Manifestations can include saddle nose, tibial thickening (“saber shins”), joint swelling (“Clutton joints”), perforation of hard palate, abnormal tooth development (“Hutchinson teeth” or “mulberry molars”), corneal inflammation, or brain and nerve problems causing blindness and deafness
- **Syphilitic Stillbirth:** Fetal death that occurs after a 20-week gestation or in which the fetus weighs >500 g and the birthing person had untreated or inadequately treated syphilis at delivery
  - Inadequate treatment consists of any nonpenicillin therapy; penicillin therapy initiated <30 days before delivery; incomplete therapy or dosing intervals outside of 6-9 days for treatment of late/unknown duration syphilis

2.3 Reservoirs

Humans

2.4 Modes of Transmission

Vertical transmission results in fetal infection:

- Occurs primarily via transplacental passage of *T. pallidum*
- Can occur during any stage of syphilis
- Can also occur on contact with genital syphilis lesions at the time of delivery

2.5 Incubation Period

Symptoms of congenital syphilis may not appear until several weeks or months after birth and, in some cases, may take years to appear. Early congenital syphilis typically manifests within the first 3 months of life. In late congenital syphilis, symptoms do not usually become apparent until two to five years of age.

2.6 Period of Communicability

Congenital syphilis risk is related to the syphilis stage during pregnancy, with the highest risk occurring during the primary and secondary stages:

- Untreated primary or secondary syphilis in pregnancy results in a 25% risk of stillbirth, a 14% risk of neonatal death, a 41% risk of a live infant with congenital syphilis, and a 20% chance of a non-infected infant
- Untreated late syphilis in pregnancy results in a 12% risk of stillbirth, a 9% risk of neonatal death, a 2% risk of giving birth to an infant with congenital syphilis, and a 77% chance of a non-infected infant[4]

3. CASE DEFINITIONS—FOR PUBLIC HEALTH STAFF

Public health staff determine whether the congenital syphilis surveillance case definition is met. Clinicians consult appropriate guidelines and use clinical judgement in evaluating and treating infants of people with syphilis in pregnancy. The CDC clinical scenarios (§4) do not perfectly align with the CDC congenital syphilis surveillance case definition.

3.1 Congenital Syphilis

See the CDC 2018 Syphilis Surveillance Case Definition page for further information on congenital syphilis case criteria and diagnosis.[5]

The Congenital Syphilis Case Classification Flow Chart (see Appendix A) is useful in determining whether the congenital syphilis surveillance case definition is met.

Since RPR testing is the most common form of nontreponemal testing, the terms "nontreponemal serologic testing" and "RPR" are used interchangeably throughout these guidelines. The nontreponemal test performed on the infant should be the same type of nontreponemal test performed on the birthing person.

3.1.1 Confirmed Congenital Syphilis

Confirmed through demonstration of *T. pallidum* in fetus/infant by:

- Darkfield microscopy of lesions, body fluids, or neonatal nasal discharge

OR

- PCR of lesions, neonatal nasal discharge, placenta, umbilical cord, or autopsy material

OR

- Immunohistochemistry or special stains (e.g., silver staining) of specimens from lesions, placenta, umbilical cord, or autopsy material

3.1.2 Presumptive Congenital Syphilis (must meet maternal and/or infant criteria)

1. **Maternal Criteria:** Birthing parent had untreated or inadequately treated syphilis at delivery regardless of signs in the infant
   - Adequate treatment is defined as completion of a penicillin-based regimen, in accordance with CDC treatment guidelines, appropriate for stage of infection, initiated ≥30 days before delivery

OR

2. **Infant Criteria:** Infant with a reactive RPR **AND** any one of the following:
   - Any evidence of congenital syphilis on physical examination
     - Infant or child <2 years old: hepatosplenomegaly, rash, condyloma lata, snuffles, jaundice caused by liver dysfunction (e.g., cholestatic jaundice, direct hyperbilirubinemia, conjugated hyperbilirubinemia, or nonviral hepatitis), pseudoparalysis, anemia, or edema
     - Child ≥2 years old: interstitial keratitis, nerve deafness, anterior bowing of shins, frontal bossing, mulberry molars, Hutchinson teeth, saddle nose, skin fissures, or Clutton joints
   - Any evidence of congenital syphilis on X-rays of long bones (*X-rays only recommended in CDC clinical scenarios 1 and 2*; see §4.2.1)
   - Evidence of congenital syphilis on a non-traumatic lumbar puncture/cerebrospinal fluid (CSF) exam (*CSF exam only recommended in CDC clinical scenarios 1 and 2; see §4.2.1*):
     - A reactive CSF VDRL test
     - Elevated CSF leukocyte (white blood cell, or WBC) count **or** protein (without other cause). CDC-suggested parameters for abnormal CSF values:
       - ≤30 days of life, a CSF WBC count >15 WBC/mm3 or a CSF protein >120 mg/dl
       - >30 days of life, a CSF WBC count >5 WBC/mm3 or a CSF protein >40 mg/dl, even if CSF VDRL is nonreactive.

3.2 Syphilitic Stillbirth

Fetal death that occurs after a 20-week gestation or in which the fetus weighs >500 g and the birthing person 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 days before delivery

4. CLINICAL MANAGEMENT—FOR MEDICAL PROVIDERS

The information in this section is adapted from the CDC 2021 STI Treatment Guidelines, which outline infant evaluation and treatment based on specific clinical scenarios.[6]

When a baby is born to a person with syphilis, the priority is to determine which clinical scenario applies. Clinicians consult appropriate guidelines and use clinical judgement in evaluating and treating infants of people with syphilis in pregnancy. Public health staff determine whether the congenital syphilis surveillance case definition is met (§3.2). The CDC clinical scenarios do not align with the CDC congenital syphilis surveillance case definition.

Serologic RPR testing should be performed on the infant's serum. Umbilical cord blood can become contaminated with maternal blood and yield a false-positive result and Wharton's jelly within the umbilical cord can yield a false-negative result.

Treponemal testing on the infant's serum is not recommended because it is difficult to interpret, as passively transferred maternal antibodies can persist for >15 months.

4.1 Management of Infants Aged <1 Month

Infants exposed to syphilis in utero should be examined for signs of congenital syphilis. Pathologic examination of the placenta or umbilical cord using specific staining (e.g., silver) or a *T. pallidum* PCR test should be considered, including in cases of stillbirth.

Diagnosis of congenital syphilis can be difficult. Maternal nontreponemal and treponemal antibodies can be transferred through the placenta to the fetus, complicating the interpretation of reactive serologic tests for infants. Treatment decisions frequently must be made based on identification of maternal syphilis; adequacy of maternal treatment; clinical, laboratory, or radiographic evidence of syphilis in the infant; and comparison of maternal (at delivery) and infant titers.

4.1.1 Infant Evaluation and Treatment: if maternal reactive RPR and treponemal tests in pregnancy and reactive RPR at delivery (including for cases diagnosed at delivery)

The OHA/AETC Congenital Syphilis Evaluation and Treatment Pocket Guide (see Appendix B) is a helpful flowchart for determining which clinical scenario below applies if the birthing person had reactive RPR and treponemal tests in pregnancy and a reactive RPR at delivery (including for cases diagnosed at delivery).

Scenario 1: Confirmed Proven or Highly Likely Congenital Syphilis

Infant with:

- Abnormal physical exam consistent with congenital syphilis **OR**
- RPR titer that is fourfold or greater higher than the maternal titer at delivery **OR**
- Positive dark-field test or PCR of placenta, cord, lesions or body fluids or a positive silver stain of the placenta or cord

Recommended Evaluation:

- CSF analysis for VDRL, white blood cell count, and protein
- Complete blood count (CBC) and differential and platelet count
- Long-bone X-rays
- Other tests as clinically indicated (e.g., chest X-ray, liver function tests, ophthalmologic exam)

Recommended Treatment:

- Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose by IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days

Scenario 2: Possible Congenital Syphilis

Infant with a normal physical exam **AND** an RPR titer ≤fourfold of the maternal titer at delivery **AND** one of the following:

- Inadequate or no maternal treatment or no documentation of treatment
- Maternal treatment with non-penicillin G regimen
- Maternal treatment was **initiated** <30 days before delivery

Recommended Evaluation:

- CSF analysis for VDRL, white blood cell count, and protein
- Complete blood count (CBC) and differential and platelet count
- Long-bone X-rays

Recommended Treatment:

- Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose by IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days *if any part of the evaluation is abnormal or not performed, the CSF is grossly contaminated, or follow-up as described in §4.2.3 is uncertain.*

OR

- Benzathine penicillin G 50,000 units/kg body weight/dose IM in a single dose *if all the recommended evaluation is performed, all results are available and normal, and follow-up as described in §4.2.3 is certain.*

Additional Considerations:

Infants born to birthing people with untreated early syphilis at the time of delivery may not have a reactive RPR and may have a normal clinical and laboratory evaluation. In this setting, the infant may have incubating or very early syphilis that is not yet clinically apparent. Therefore, even if follow-up as described in §4.3.2 is certain, infants should be treated with the 10-day regimen.

Scenario 3: Congenital Syphilis Less Likely

Infant with a normal physical exam **AND** an RPR titer ≤fourfold of the maternal titer at delivery **AND** both of the following are true:

- Birthing person was treated during pregnancy, treatment was appropriate for the syphilis stage, and the treatment regimen was initiated ≥30 days before delivery
- There is no evidence of maternal reinfection (i.e., no symptoms and titer has not increased fourfold or more)

Recommended Evaluation: None

Recommended Treatment:
- Benzathine penicillin G 50,000 units/kg body weight/dose IM in a single dose
- If follow-up is certain and maternal RPR titers decreased at least fourfold after therapy for early syphilis or remained stable for low-titer, latent syphilis (e.g., RPR<1:4), close RPR follow-up every 2-3 months for 6 months can be pursued instead of treatment.

Scenario 4: Congenital Syphilis Unlikely

Infant with a normal physical exam and an RPR titer ≤fourfold of the maternal titer at delivery **AND** both of the following are true:
- Maternal treatment was adequate before pregnancy
- Maternal RPR titers remained low and stable before and during pregnancy and at delivery

Recommended Evaluation: None

Recommended Treatment:
- No treatment required
- Benzathine penicillin G 50,000 units/kg body weight as a single IM injection should be considered if follow-up is uncertain and the infant has a reactive RPR

4.1.2 Infant Evaluation and Treatment: if maternal reactive treponemal tests and a nonreactive RPR

1. **Reactive maternal treponemal tests with a nonreactive RPR during pregnancy:**
   - Congenital syphilis is highly unlikely for infants born to people with a nonreactive RPR after adequate treatment for syphilis during pregnancy or documentation of adequate treatment before pregnancy (with no evidence of reinfection)
   - If the maternal RPR remains nonreactive at delivery and the infant has a normal physical examination and nonreactive RPR, manage like *Scenario 4: Congenital Syphilis Unlikely* scenario above. Benzathine penicillin G 50,000 units/kg body weight as a single IM injection might be considered if syphilis exposure is possible within 1 month before delivery and follow-up is uncertain.
2. **One reactive maternal treponemal test (e.g., EIA reactive, RPR nonreactive, TP-PA nonreactive) during pregnancy:**
   - Congenital syphilis is unlikely for infants born to people screened with the reverse sequence algorithm with an isolated reactive maternal treponemal test

- If the infant has a normal physical examination and the risk for maternal syphilis is low, no evaluation and treatment are recommended for the infant
- If maternal syphilis exposure is possible or unknown, repeat testing within 1 month is recommended to evaluate for early infection

3. **Reactive maternal treponemal test at delivery and no previous syphilis history or testing:**
   - Confirmatory testing is needed
   - If late or no prenatal care, the infant should be evaluated and treated with a 10-day course of penicillin as recommended in *Scenario 1: Confirmed Proven or Highly Likely Congenital Syphilis* above unless/until maternal syphilis is ruled out

4.1.3 Infant Follow-Up

- All infants with a reactive RPR at birth should receive thorough follow-up examinations and RPR testing every 2–3 months until the test becomes nonreactive*. Treponemal tests should not be used to evaluate infant infection status or treatment response*—these results are qualitative and passive transfer of maternal treponemal antibodies might persist for >15 months.
  - Treated infants who have persistent RPR titers by age 6–12 months should be reevaluated through CSF examination and managed in consultation with an expert. Retreatment with a 10-day course of a penicillin G regimen might be indicated.
  - For infants who were not treated because congenital syphilis was considered less likely or unlikely, RPR titers should decrease by age 3 months and be nonreactive by age 6 months, indicating that the reactive test result was caused by passive transfer of maternal antibodies
    - If the RPR is nonreactive at age 6 months, no further evaluation or treatment is needed
    - If the RPR is still reactive at age 6 months, the infant is likely infected and should be treated
- Infants with a negative RPR at birth born to people with a reactive RPR at delivery should be retested at age 3 months to rule out incubating congenital syphilis
- Infants whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless they exhibit persistent RPR titers at age 6–12 months. Persistent RPR titers and CSF abnormalities should be managed in consultation with an expert.

4.2 Management of Infants and Children Aged ≥1 Month

- Infants and children aged ≥1 month with reactive RPR and/or treponemal tests for syphilis should be examined thoroughly and have maternal serology and records reviewed to assess whether they have congenital or acquired syphilis
  - In the case of extremely early or incubating syphilis at the time of delivery, all maternal serologic tests might have been negative

  - Any infant or child at risk for congenital syphilis should receive a full evaluation and testing for HIV infection
- International adoptee, immigrant, or refugee children from countries where treponemal infections (e.g., yaws or pinta) are endemic might have reactive RPR and treponemal tests, which cannot distinguish between syphilis and other subspecies of *T. pallidum*. These children might also have syphilis and should be evaluated for congenital syphilis.

Recommended Evaluation:
- CSF analysis for VDRL, white blood cell count, and protein
- Complete blood count (CBC) and differential and platelet count
- Other tests as clinically indicated (e.g., chest X-ray, liver function tests, ophthalmologic exam)

Recommended Treatment:
- Aqueous crystalline penicillin G 200,000–300,000 units/kg body weight by IV, administered as 50,000 units/kg body weight every 4–6 hours for 10 days
- If there are no clinical manifestations of congenital syphilis and the evaluation is normal, treatment with up to 3 weekly doses of benzathine penicillin G 50,000 units/kg body weight IM can be considered
- These treatment regimens should also be adequate for children who might have other treponemal infections

Follow-up:
- Thorough follow-up examinations and RPR testing of infants/children treated for congenital syphilis after the first 30 days of life should be performed every 3 months until the test becomes nonreactive or the titer has decreased fourfold. *Treponemal tests should not be used to evaluate infant infection status or treatment response*—these results are qualitative and passive transfer of maternal treponemal antibodies might persist for >15 months.
- The titer response after therapy might be slower than for infants aged <1 month
- If titers increase at any point for >2 weeks or do not decrease fourfold after 12–18 months, the infant/child should be evaluated (e.g., CSF examination), treated with a 10-day course of parenteral penicillin G, and managed in consultation with an expert.
- Infants/children whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless their RPR titers do not decrease fourfold after 12–18 months. After 18 months of follow-up, abnormal CSF results that persist and cannot be attributed to other ongoing illness indicate that retreatment is needed for possible neurosyphilis and should be managed in consultation with an expert.

5. MANAGING SPECIAL SITUATIONS

5.1 Infants Placed in Department of Human Services (DHS) Custody

When an infant is classified as a CS case and/or has a reactive RPR at birth, and is placed in DHS custody:

- The county investigating the CS case should attempt to obtain information about where in Oregon the child will be residing and contact information for the child's pediatrician if known
- The county investigating the CS case should then give the county where the child is residing access to the infant's Orpheus case record to enable any necessary follow-up

GLOSSARY

CSF: Cerebrospinal fluid. CSF testing can indicate whether there is central nervous system involvement in a syphilis infection.

CBC: Complete Blood Count. A complete blood count is a set of tests that provide information about the cells in a person's blood. The CBC indicates the counts of white blood cells, red blood cells, and platelets, and the hemoglobin and hematocrit.

Early syphilis: Any of the stages that occur in the first 12 months of infection: primary, secondary, and early non-primary non-secondary syphilis.

IM: Intramuscular. An IM injection delivers medication, such as benzathine penicillin G for syphilis, into a muscle.

PCR: Polymerase chain reaction test is a laboratory technique for rapidly producing (amplifying) many copies of a specific segment of genetic material, e.g., *T. pallidum* DNA in syphilis.

RPR: Rapid plasma reagin test is a nontreponemal serologic (blood) test. Unlike treponemal tests, the RPR measures antibodies that are not specific for *T. pallidum* bacteria and may be reactive due to conditions other than syphilis, including pregnancy.

Treponemal test: Treponemal tests measure antibodies directed against *T. pallidum* bacteria. Treponemal serologic (blood) tests include enzyme immunoassays (EIAs) and chemiluminescence immunoassays (CIAs), *T. pallidum* particle agglutination (TP-PA), and fluorescent treponemal antibody absorption (FTA-ABS) tests. These qualitative tests usually remain reactive for life, regardless of treatment.

VDRL: Venereal Disease Research Laboratory test is a nontreponemal test that can be done on blood and CSF. Mostly used in CSF testing in congenital syphilis and neurosyphilis evaluations. The RPR is the more common nontreponemal serologic (blood) test in Oregon.

REFERENCES

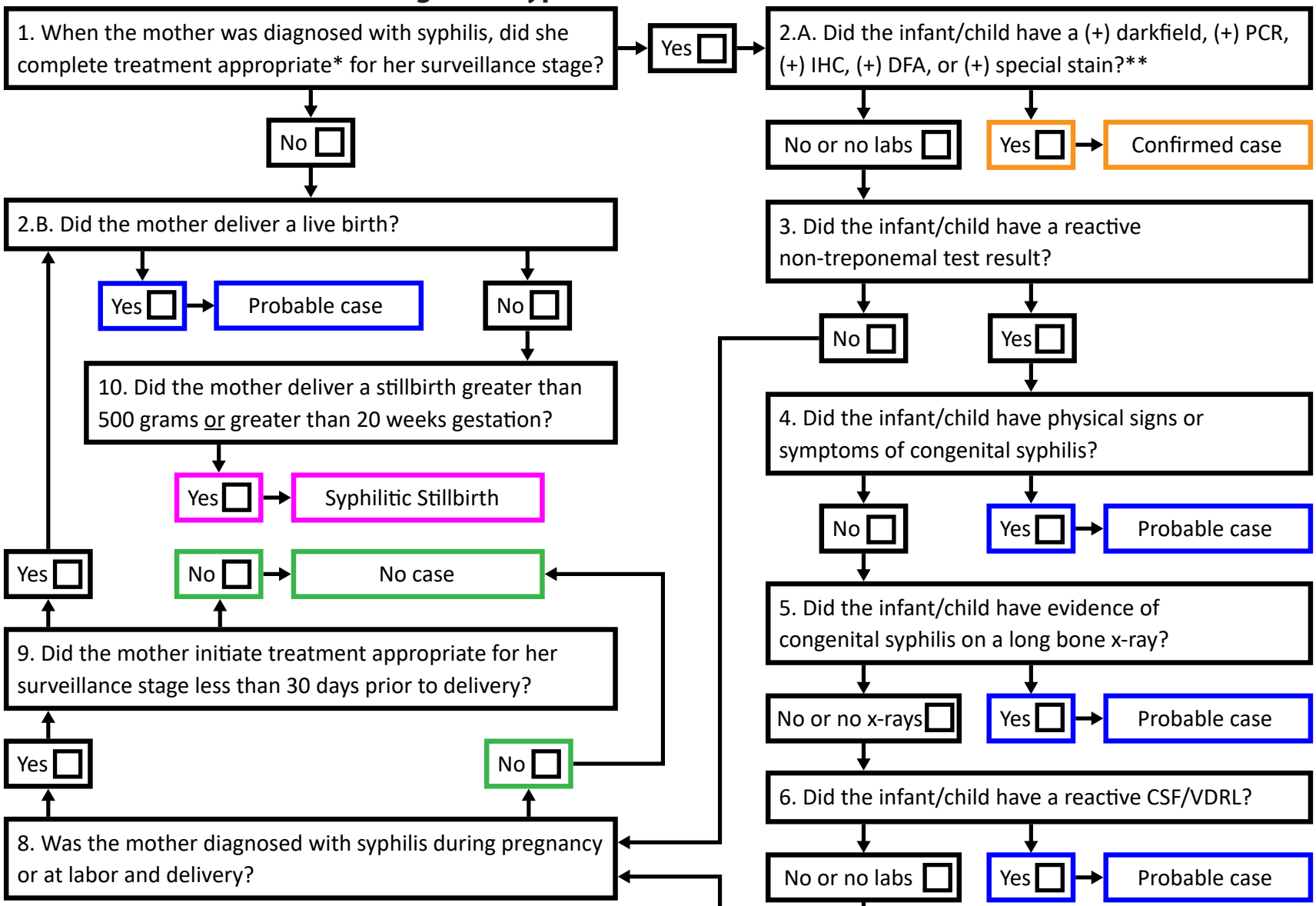
1. Oregon Administrative Rules. Oregon Health Authority Chapter 333 Public Health Division, Division 18 Disease Reporting. https://secure.sos.state.or.us/oard/viewSingleRule.action?ruleVrsnRsn=292908
2. Oregon Revised Statutes. Chapter 433 Disease and Condition Control. https://www.oregonlegislature.gov/bills_laws/ors/ors433.html
3. Oregon Administrative Rules. Oregon Health Authority Public Health Division Chapter 333 Division 19 Investigation and Control of Diseases: General Powers and Responsibilities. https://secure.sos.state.or.us/oard/viewSingleRule.action?ruleVrsnRsn=292879
4. Ingraham NR. The value of penicillin alone in the prevention and treatment of congenital syphilis. Acta Dermato Veneriologica. 1951;31:60–88.
5. CDC National Notifiable Diseases Surveillance System (NNDSS) Syphilis (*Treponema pallidum*) 2018 Case Definition. https://ndc.services.cdc.gov/case-definitions/syphilis-2018/
6. CDC Sexually Transmitted Infections Treatment Guidelines, 2021. https://www.cdc.gov/std/treatment-guidelines/default.htm

UPDATE LOG

July 2023. First draft. (Jillian Garai, Yuritzy Gonzalez Pena, Timothy Menza)

Appendix A

Congenital Syphilis Case Classification Flow Chart



* appropriate treatment is defined as completion of a therapy regimen as outlined in the current CDC treatment guidelines at the time of diagnosis or in the event of two dilution titer rise. Special consideration for treatment regimens for pregnant women can be found here.

** regardless of mother's treatment, if the answer to 2A is "Yes," the congenital syphilis case is confirmed.

CDC Congenital Syphilis Case Definition

Considerations when following this flow chart:

- If an infant has a reactive darkfield, polymerase chain reaction (PCR), immunohistochemistry (IHC), direct fluorescent antibodies (DFA), or special stain test that is reactive for *Treponema pallidum* then regardless of mother's treatment history or infant's serological findings this will be a **confirmed case.**
- If mother did not complete treatment appropriate to her surveillance stage of syphilis (verify surveillance stage upon congenital syphilis case report) **OR** initiated treatment less than 30 days prior to delivery and had a live birth- the infant will be classified as a **probable case.**
- For a **probable case** to occur based on clinical manifestations an infant must have a reactive non-treponemal test **AND**
  - ◊ Positive CSF VDRL **OR**
  - ◊ Elevated CSF WBC (without other cause): Elevated CSF WBC is defined as greater than 15 WBC/mm^3 for the first 30 days of life and greater than 5 WBC/mm^3 after the first 30 days of life **OR**
  - ◊ Elevated CSF protein (without other cause): Elevated CSF protein defined as greater than 120 mg/dl for the first 30 days of life and greater 40 mg/dl for after the first 30 days of life **OR**
  - ◊ Evidence of congenital syphilis on a long bone x-ray (bowing of the long bones) **OR**
  - ◊ Any one of the following clinical manifestations outlined on the flow chart (without other cause)
    - ♦ Common physical signs and symptoms of congenital syphilis in infants are:
      - ∗ Hepatosplenomegaly (enlarged liver and spleen)
      - ∗ Rash
      - ∗ condyloma lata
      - ∗ Snuffles (nasal discharge)
      - ∗ Jaundice (yellowing of the tissues)
      - ∗ Pseudoparalysis of the extremities
      - ∗ Edema (tissue swelling from excess fluid)
      - ∗ Nerve deafness
    - ♦ Common physical signs and symptoms of congenital syphilis in an older child are:
      - ∗ Ocular issues (cataracts, keratitis)
      - ∗ Nerve deafness
      - ∗ Dental issues (mulberry molars, Hutchinson teeth)
      - ∗ Facial and skin abnormalities (frontal bossing, saddle nose, rhagades)
      - ∗ Limb and extremities abnormalities (anterior bowing of the shins, Clutton joints)
- If a fetal demise occurred at greater than 500 grams **OR** roughly 20 weeks gestation or greater **AND** if mother did not complete treatment appropriate to her surveillance stage of syphilis (verify surveillance stage upon congenital syphilis case report) **OR** initiated treatment less than 30 days prior to delivery then the infant will be classified as a **congenital syphilis stillbirth.**

Additional Considerations: If mother is a documented biological false positive during the current pregnancy and a NR treponemal test is obtained from labor and delivery, no case report is needed. If mother has never met case criteria at the time of delivery, no case report is needed.

Appendix B

CONGENITAL SYPHILIS (CS)

Evaluation and treatment of infants (<30 days old) exposed to syphilis in utero*

Start

INFANTS AND BIRTHING PARENT (e.g., mother) SHOULD HAVE SERUM RPR TITER DRAWN AT DELIVERY

Infant and Maternal Criteria

Infant Criteria:
- CS findings on physical exam
- Infant titer ≥fourfold higher than mother's titer
- + darkfield or PCR of placenta, cord, lesions, or body fluid
- + silver stain of placenta or cord

No to all

Maternal Criteria:
- Not treated
- Inadequately treated§
- Treatment undocumented
- Treated with a non-penicillin G regimen
- Initiated treatment <30 days before delivery

No to all

Additional Maternal Criteria:
- Adequately treated with penicillin G regimen appropriate for stage, initiated ≥30 days before delivery

AND

- No concern for reinfection or treatment failure

Yes to any

Scenario 1: Proven or Highly Probable CS

Yes to any

Scenario 2: Possible CS ||

Yes to both

Scenario 3: Less Likely CS

Infant Evaluation

- **CSF analysis†** VDRL, cell count, and protein
- **Complete blood count (CBC),** differential, and platelet count
- **Long-bone radiographs**
- **Tests as clinically indicated by signs on physical exam**

- **CSF analysis†** VDRL, cell count, and protein
- **CBC,** differential, and platelet count
- **Long-bone radiographs**

No additional infant evaluation

Review Maternal Titers & Stage:
- ≥4 fold decrease in titer after treatment for early syphilis

OR

- Stable titer for low-titer, latent syphilis (RPR < 1:4)

Any abnormalities, results not available, *OR* follow-up¶ uncertain

No abnormalities *AND* follow-up¶ certain

No to both *OR* follow-up¶ uncertain

Yes to either *AND* follow-up¶ certain

Infant Treatment

Aqueous crystalline penicillin G‡
100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days

Benzathine penicillin G
50,000 units/kg/dose IM in a single dose

No treatment indicated
with close serologic follow-up of infant every 2-3 months for 6 months

* Scenario 4: CS Unlikely is not shown. This scenario covers infants with normal physical exam and RPR titer ≤fourfold of the maternal titer at delivery, and the mother was adequately treated prior to becoming pregnant and sustained RPR titers ≤1:4 throughout pregnancy.

† CSF test results obtained during the neonatal period can be difficult to interpret; normal values differ by gestational age.

‡ Alternative: Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days

§ Adequate treatment for syphilis in a pregnant person refers to the appropriate penicillin regimen recommended by the CDC initiated at least 30 days prior to delivery.

|| Evaluation is not necessary if a 10-day course of parenteral therapy is administered, although such evaluations might be useful. If the neonate's nontreponemal test is nonreactive and the mother's risk for untreated syphilis is low, a single IM dose of benzathine penicillin G (BPG) can be considered without evaluation.

¶ All neonates with reactive nontreponemal tests should receive careful follow-up examinations and serologic testing (i.e., a nontreponemal test) every 2–3 months until the test becomes nonreactive. Neonates with a negative nontreponemal test at birth whose mothers were seroreactive at delivery should be retested at 3 months to rule out serologically negative incubating congenital syphilis at the time of birth.

FOR MORE INFORMATION ABOUT SCENARIO 4 MANAGEMENT, TREATMENT OF SYPHILIS IN PREGNANCY, NEONATAL CSF INTERPRETATION, AND CS INFANT FOLLOW-UP, PLEASE REFER TO THE CDC 2021 STI TREATMENT GUIDELINES.

Oregon Health Authority

Last updated: 3/22/22

AETC AIDS Education & Training Center Oregon AETC

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