Syphilis

Treponema pallidum

Learning Objectives

Upon completion of this content, the learner will be able to

1. Describe the epidemiology of syphilis in the U.S.
2. Describe the pathogenesis of *T. pallidum*.
3. Discuss the clinical manifestations of syphilis.
4. Identify common methods used in the diagnosis of syphilis.
5. List the CDC-recommended treatment regimens for syphilis.
6. Summarize appropriate prevention counseling messages for patients with syphilis.
7. Describe public health measures for the prevention of syphilis.

Lessons

I. Epidemiology: Disease in the U.S.
II. Pathogenesis
III. Clinical manifestations
IV. Diagnosis
V. Patient management
VI. Prevention

Lesson I: Epidemiology: Disease in the U.S.

Syphilis Definition

- Sexually acquired infection
- Etiologic agent: *Treponema pallidum*
- Disease progresses in stages
- May become chronic without treatment

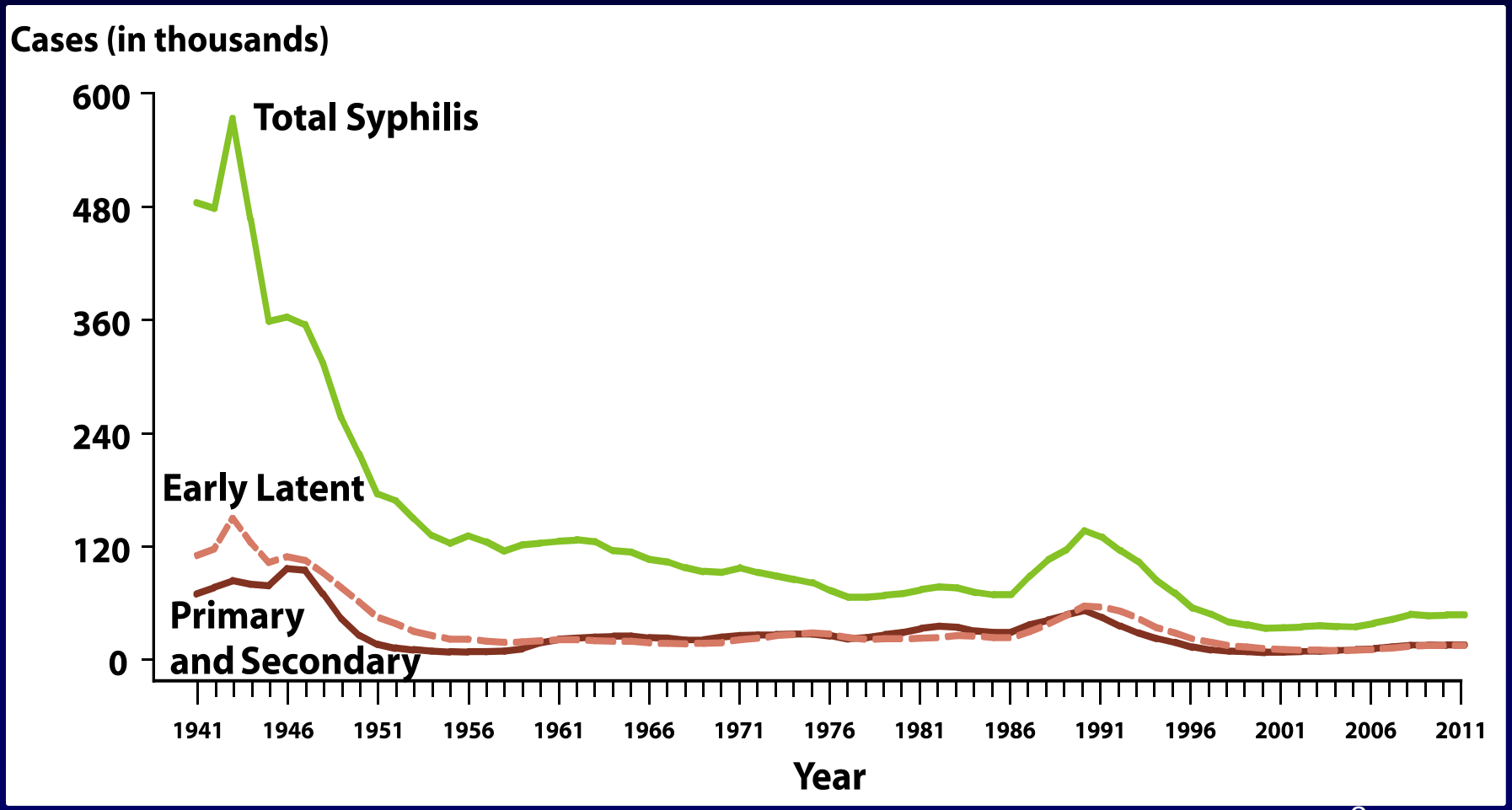
Transmission

- Sexual and vertical
- Most contagious to sex partners during the primary and secondary stages

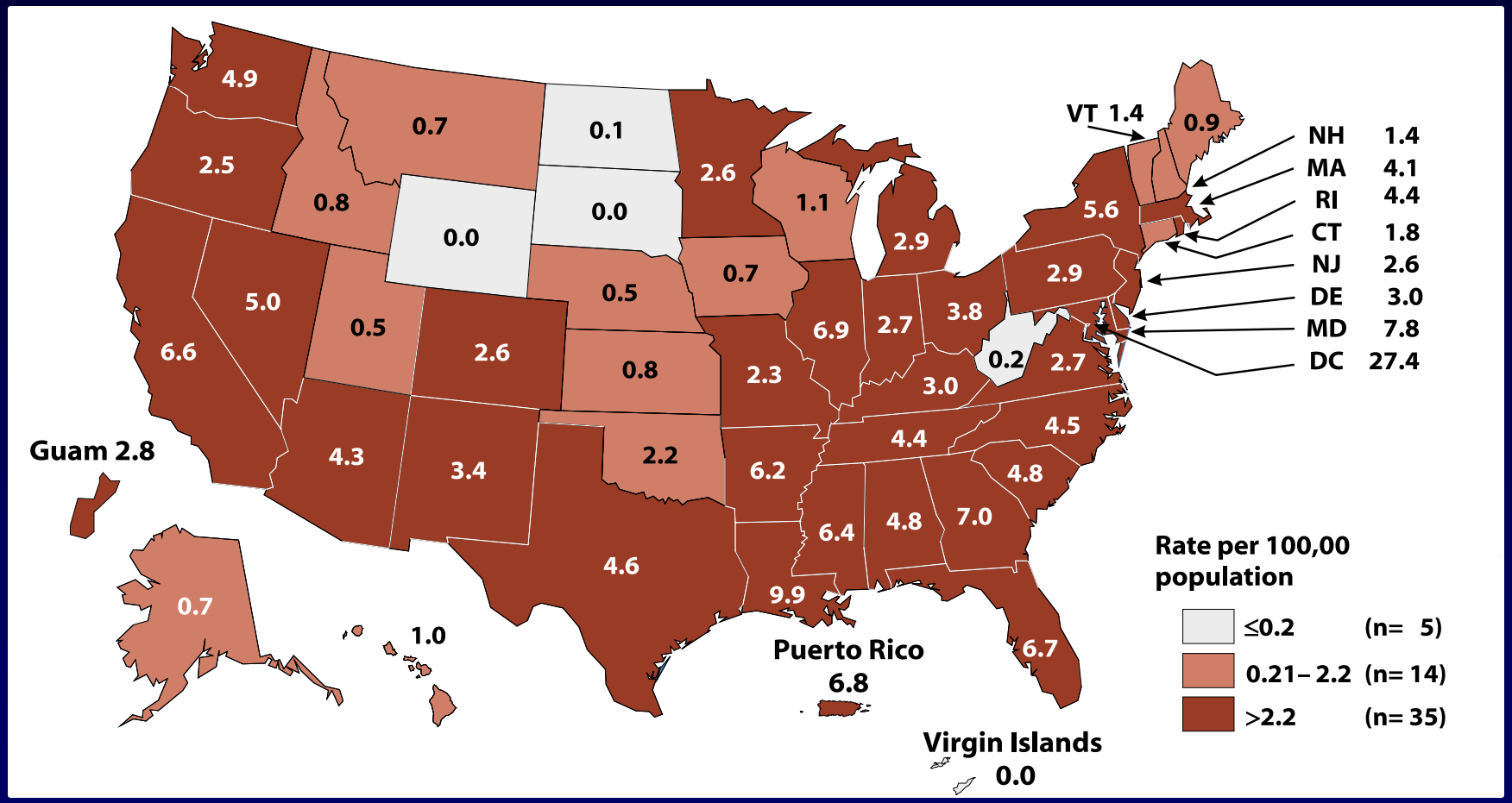
Disease Trends in the U.S.

- Distributed widely throughout the U.S. in the 1940s
- After the 1940s, declined rapidly with the introduction of penicillin therapy and broad-based public health programs
- 1986–90: 83% increase in the incidence of primary and secondary syphilis
- 1990s: reported cases of syphilis declined 89.7% to an all-time low in 2000
- Remains a public health problem in the U.S.
- MSM an important risk population

Syphilis—Reported Cases by Stage of Infection: United States, 1941–2011

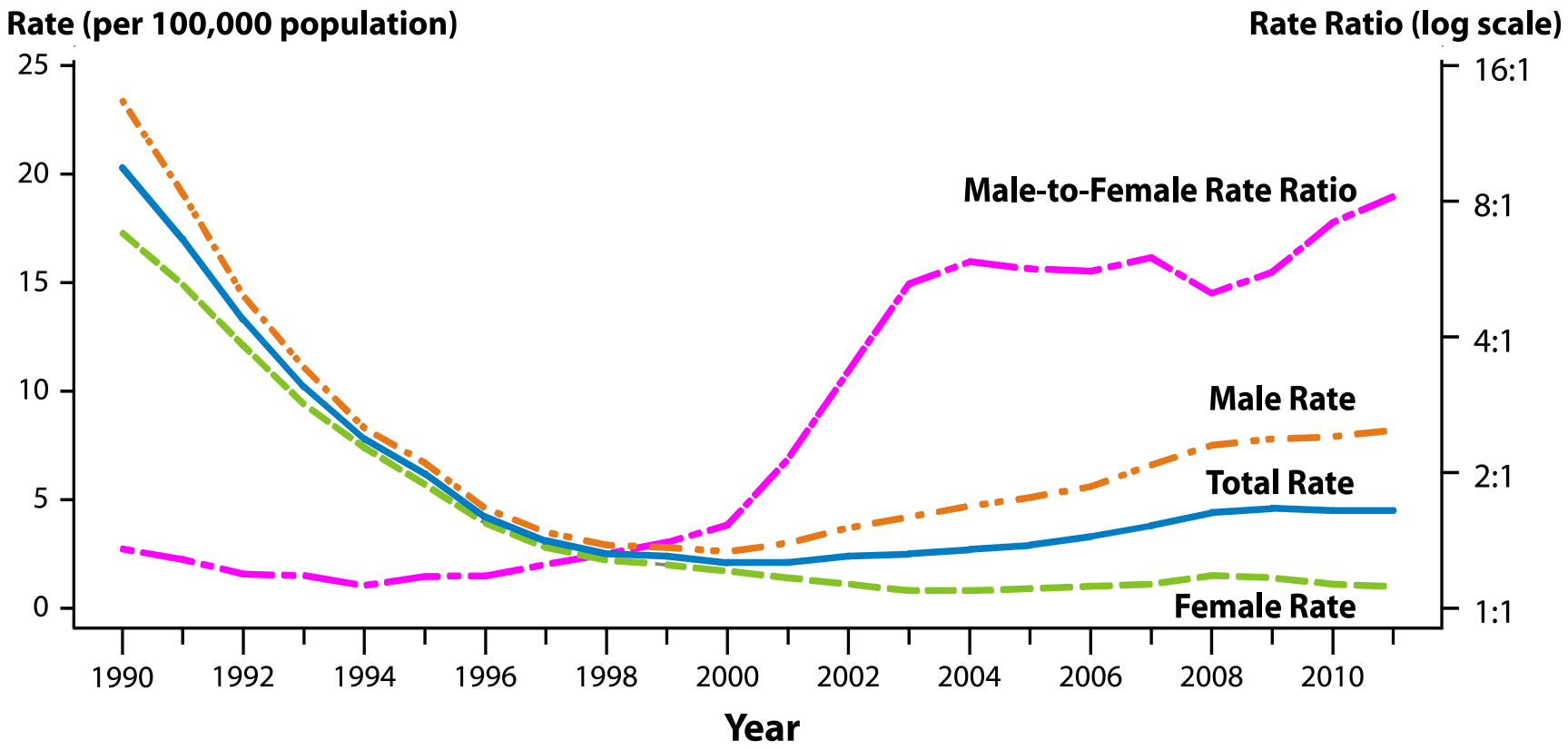


Primary and Secondary Syphilis—Rates by State: United States and Outlying Areas, 2011

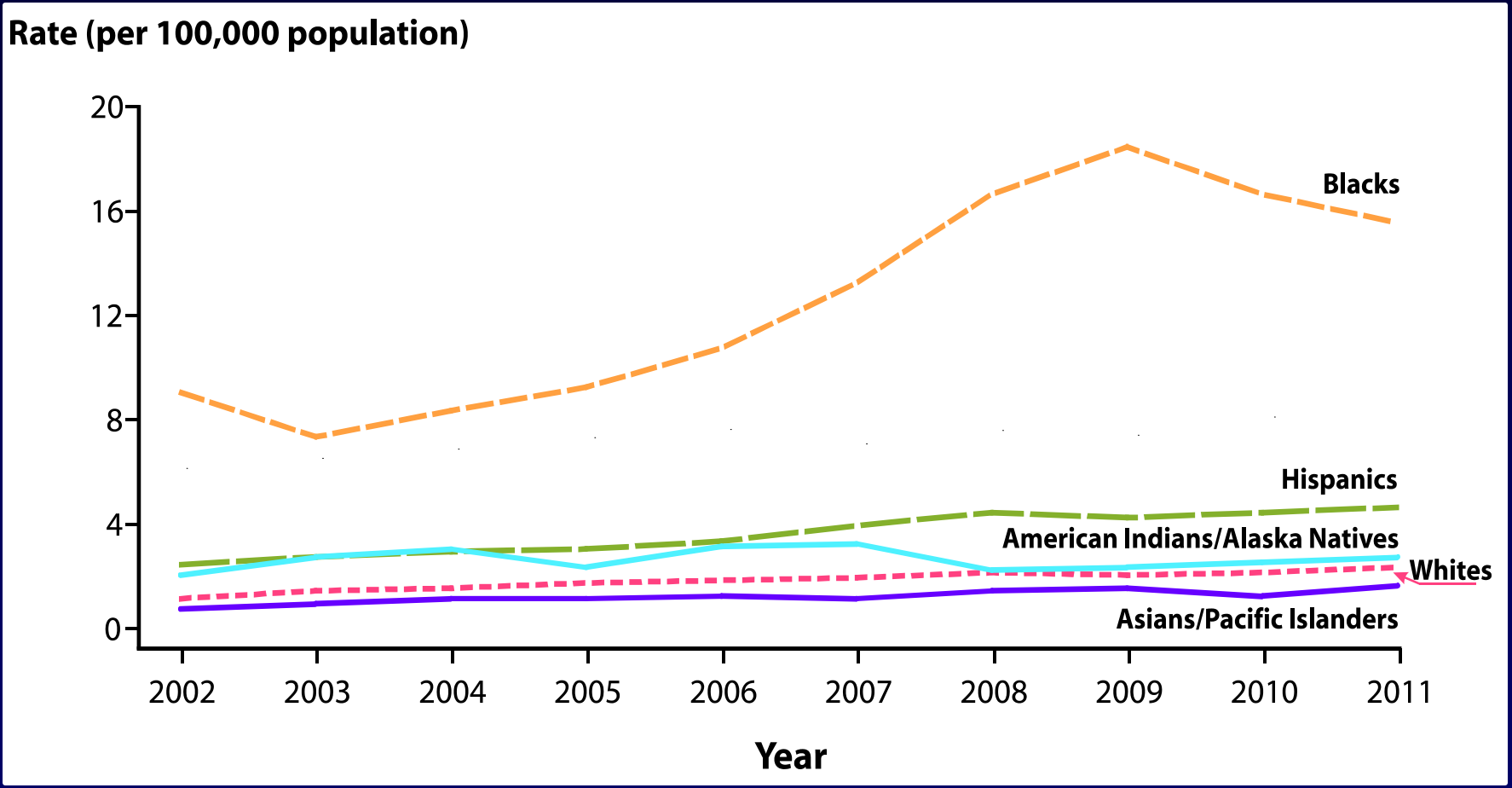


NOTE: The total rate of primary and secondary syphilis for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 4.5 per 100,000 population.

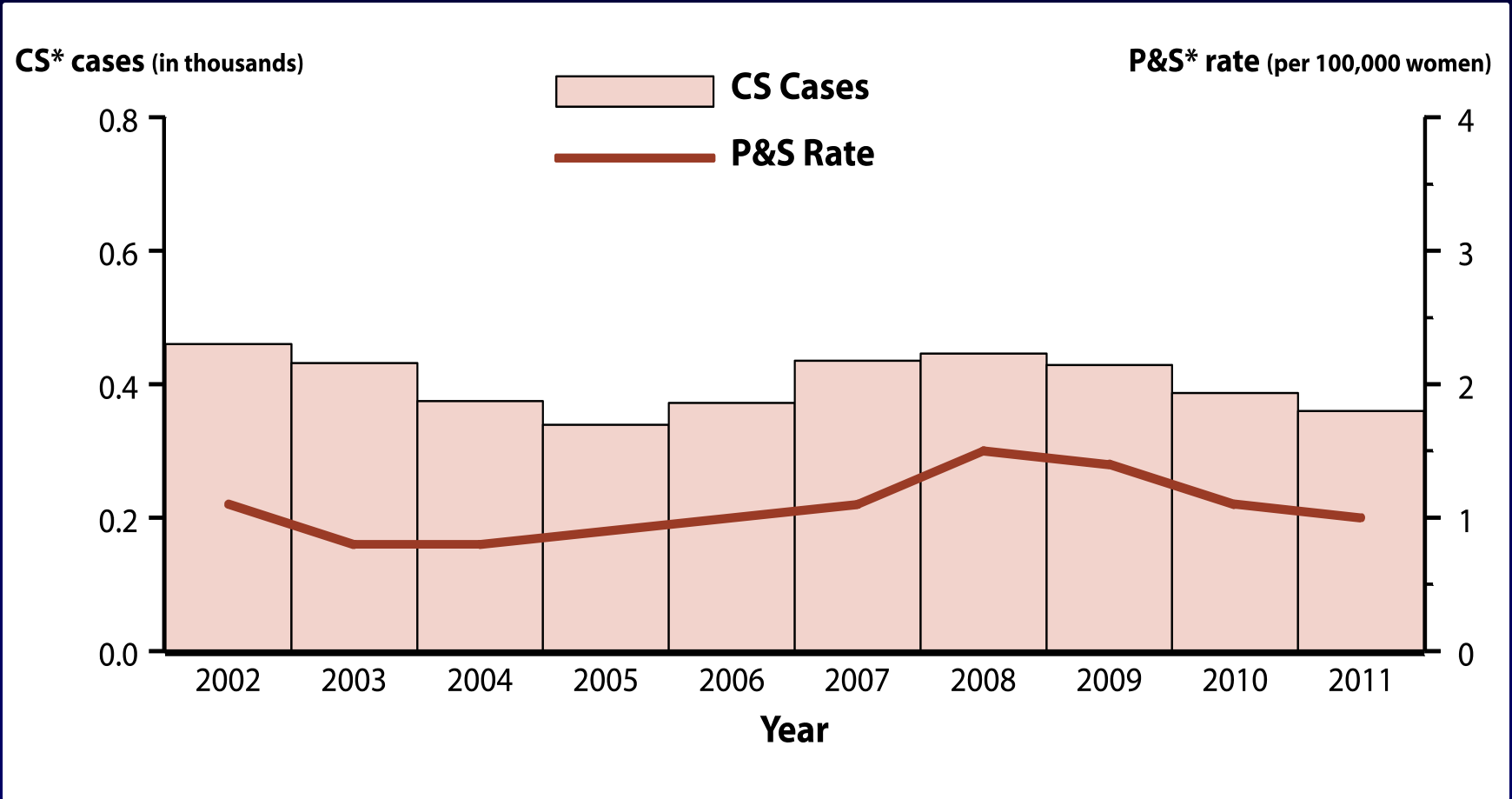
Primary and Secondary Syphilis—Rates by Sex and Male-to-Female Rate Ratios: United States, 1990–2011



Primary and Secondary Syphilis—Rates by Race/Ethnicity: United States, 2002–2011



Congenital Syphilis—Reported Cases Among Infants by Year of Birth and Rates of Primary and Secondary Syphilis Among Women: United States, 2002–2011



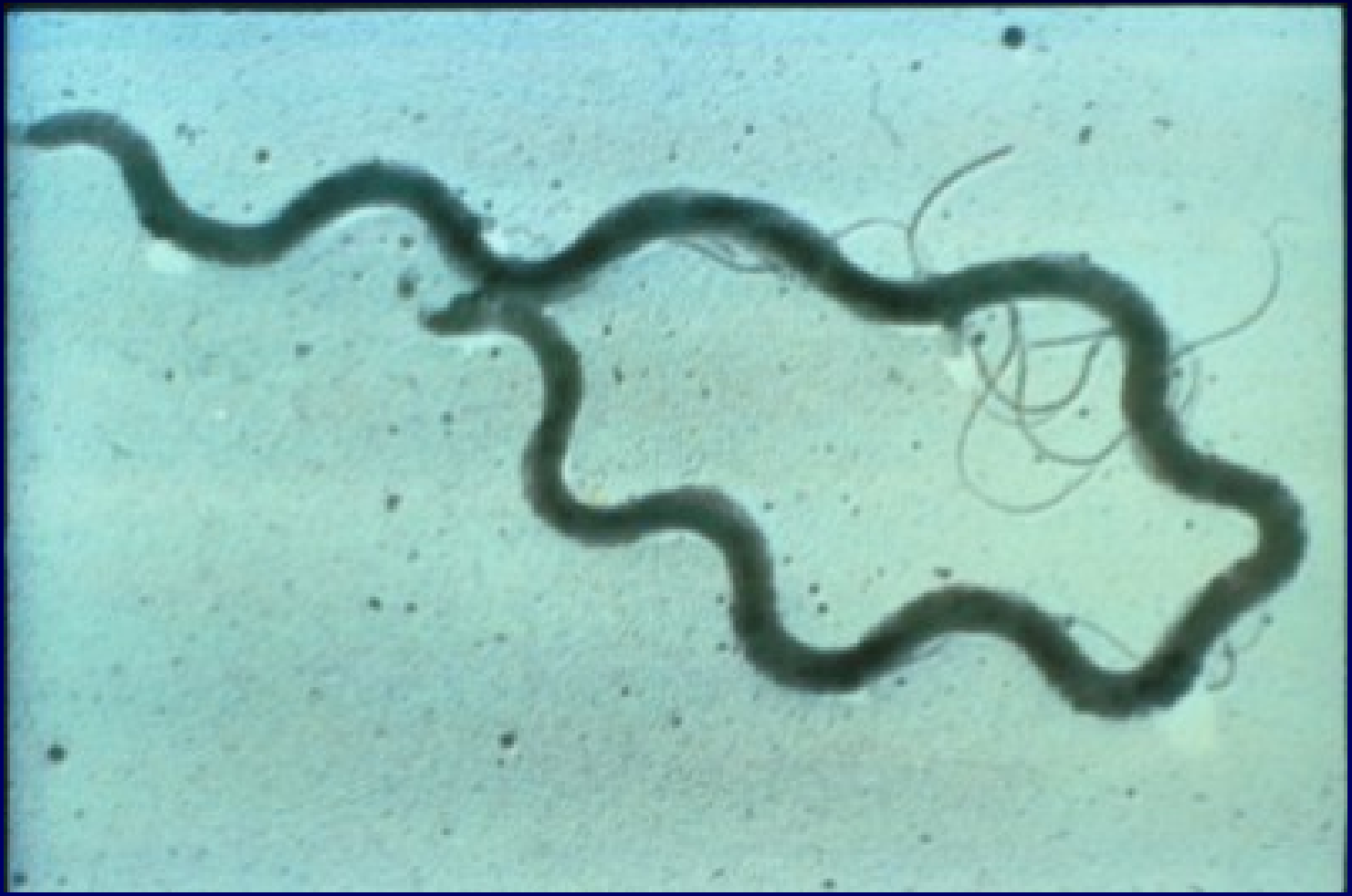
* CS = congenital syphilis; P&S = primary and secondary syphilis.

Lesson II: Pathogenesis

Microbiology

- Etiologic agent: *Treponema pallidum*, subspecies *pallidum*
  - Corkscrew-shaped, motile microaerophilic bacterium
  - Cannot be cultured in vitro
  - Cannot be viewed by normal light microscopy

Treponema pallidum



Electron photomicrograph, 36,000 x.

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Treponema pallidum on Darkfield Microscopy

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Pathology

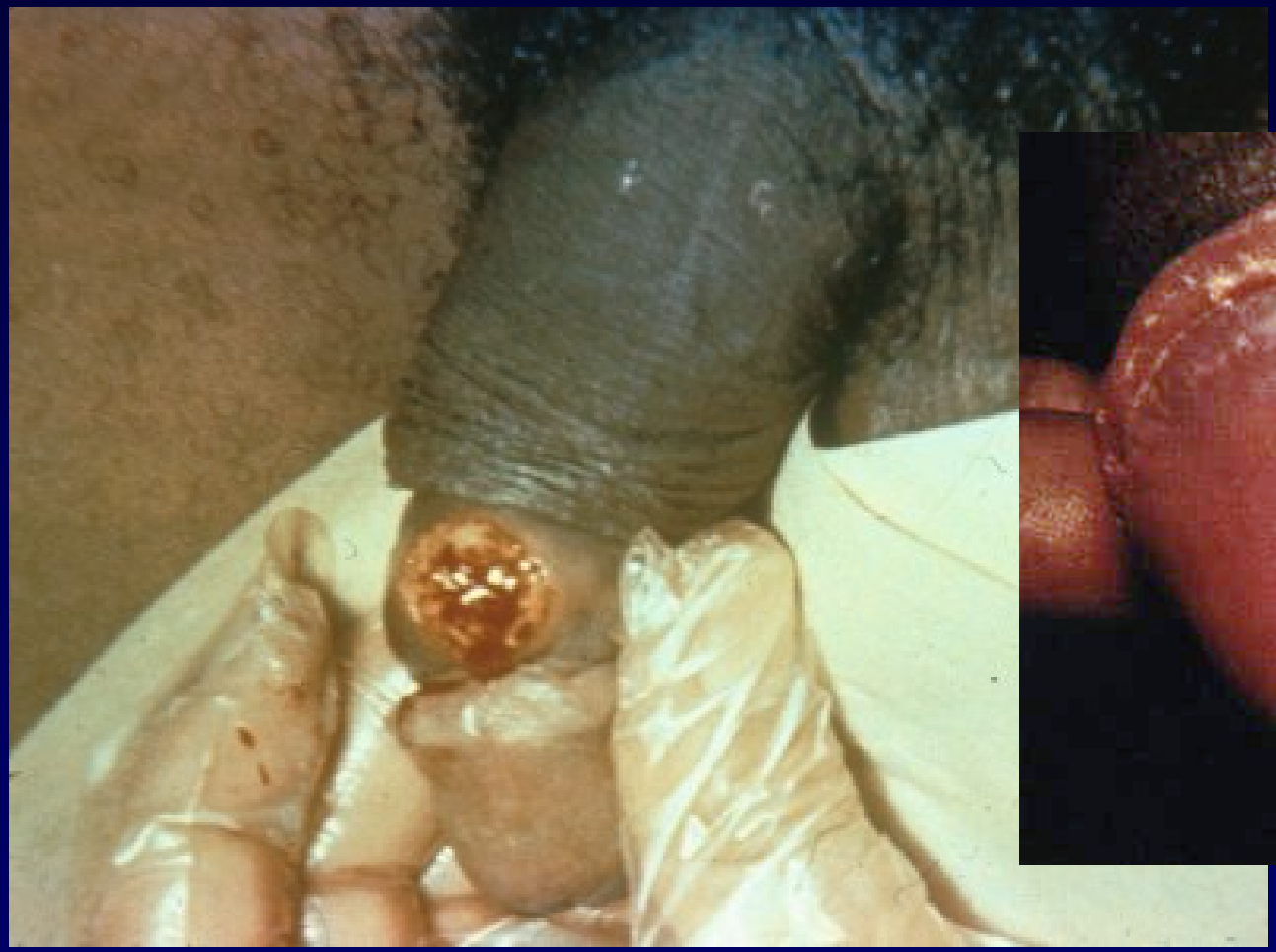
- Penetration:
  - *T. pallidum* enters the body via skin and mucous membranes through abrasions during sexual contact
  - Transmitted transplacentally from mother to fetus during pregnancy
- Dissemination:
  - Travels via the circulatory system (including the lymphatic system and regional lymph nodes) throughout the body
  - Invasion of the central nervous system (CNS) can occur during any stage of syphilis.

Lesson III: Clinical Manifestations

Primary Syphilis

- Primary lesion or "chancre" develops at the site of inoculation.
- Chancre
  - Progresses from macule to papule to ulcer;
  - Typically painless, indurated, and has a clean base;
  - Highly infectious;
  - Heals spontaneously within 3 to 6 weeks; and
  - Multiple lesions can occur.
- Regional lymphadenopathy: classically rubbery, painless, bilateral
- Serologic tests for syphilis may not be positive during early primary syphilis.

Primary Syphilis—Penile Chancre



Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

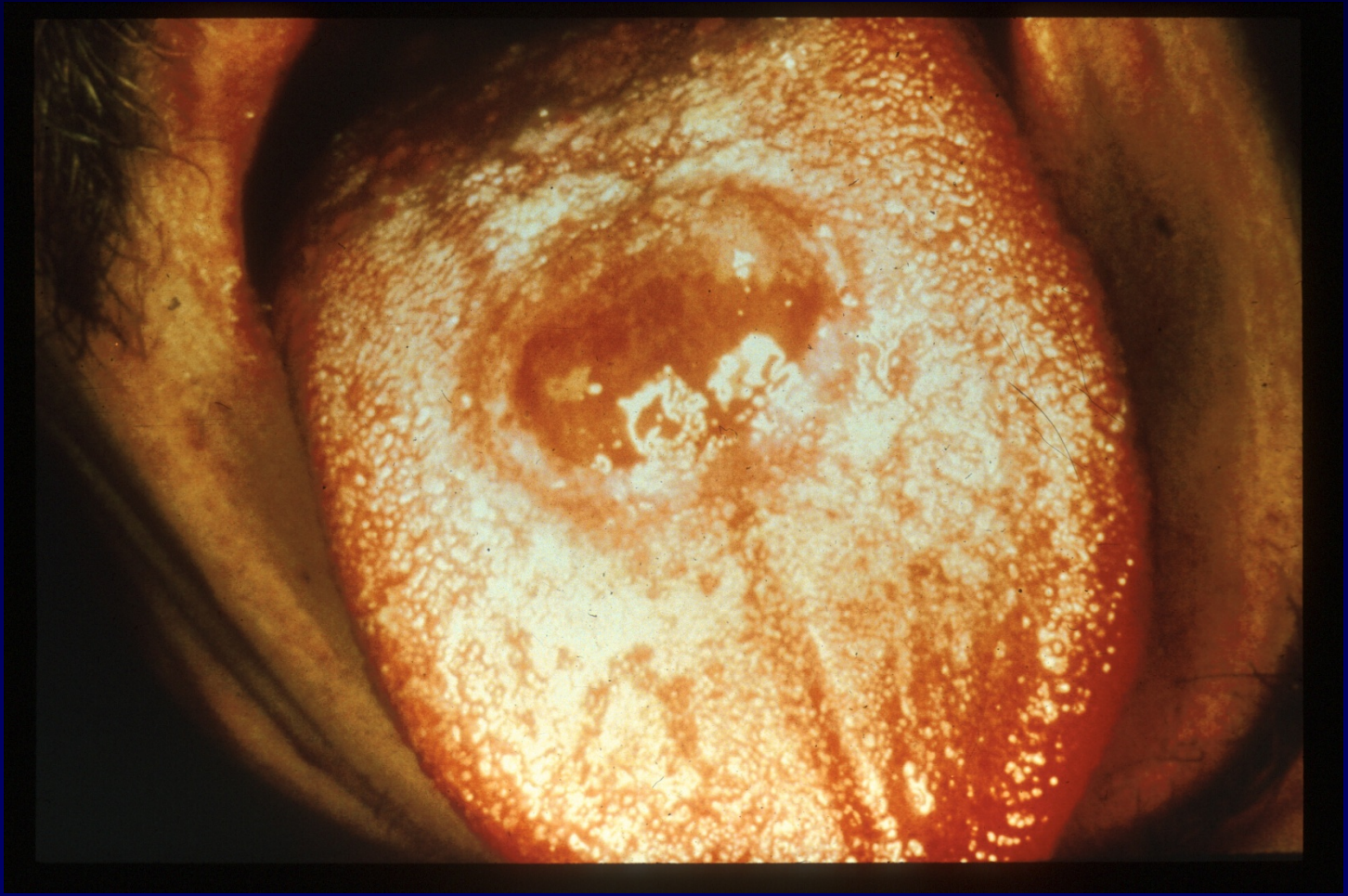
Primary Syphilis—Labial Chancre

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Primary Syphilis—Perianal Chancre

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Primary Syphilis—Chancre of the Tongue



Source: CDC/ NCHSTP/ Division of STD Prevention /STD Clinical Slides

Secondary Syphilis

- Secondary lesions occur several weeks after the primary chancre appears; and may persist for weeks to months.
- Primary and secondary stages may overlap
- Mucocutaneous lesions most common
- Clinical Manifestations:
  - Rash (75%–100%)
  - Lymphadenopathy (50%–86%)
  - Malaise
  - Mucous patches (6%–30%)
  - Condylomata lata (10%–20%)
  - Alopecia (5%)
  - Liver and kidney involvement can occur
  - Splenomegaly is occasionally present
- Serologic tests are usually highest in titer during this stage.

Secondary Syphilis—Papulosquamous Rash

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Secondary Syphilis—Palmar/Plantar Rash

Source: Seattle STD/HIV Prevention Training Center at the University of Washington, UW HSCER Slide Bank

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Secondary Syphilis—Generalized Body Rash

Source: Cincinnati STD/HIV Prevention Training Center

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Secondary Syphilis—Papulo-pustular Rash

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Secondary Syphilis—Condylomata lata

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Secondary Syphilis—Nickel/Dime Lesions

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Secondary Syphilis—Alopecia

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

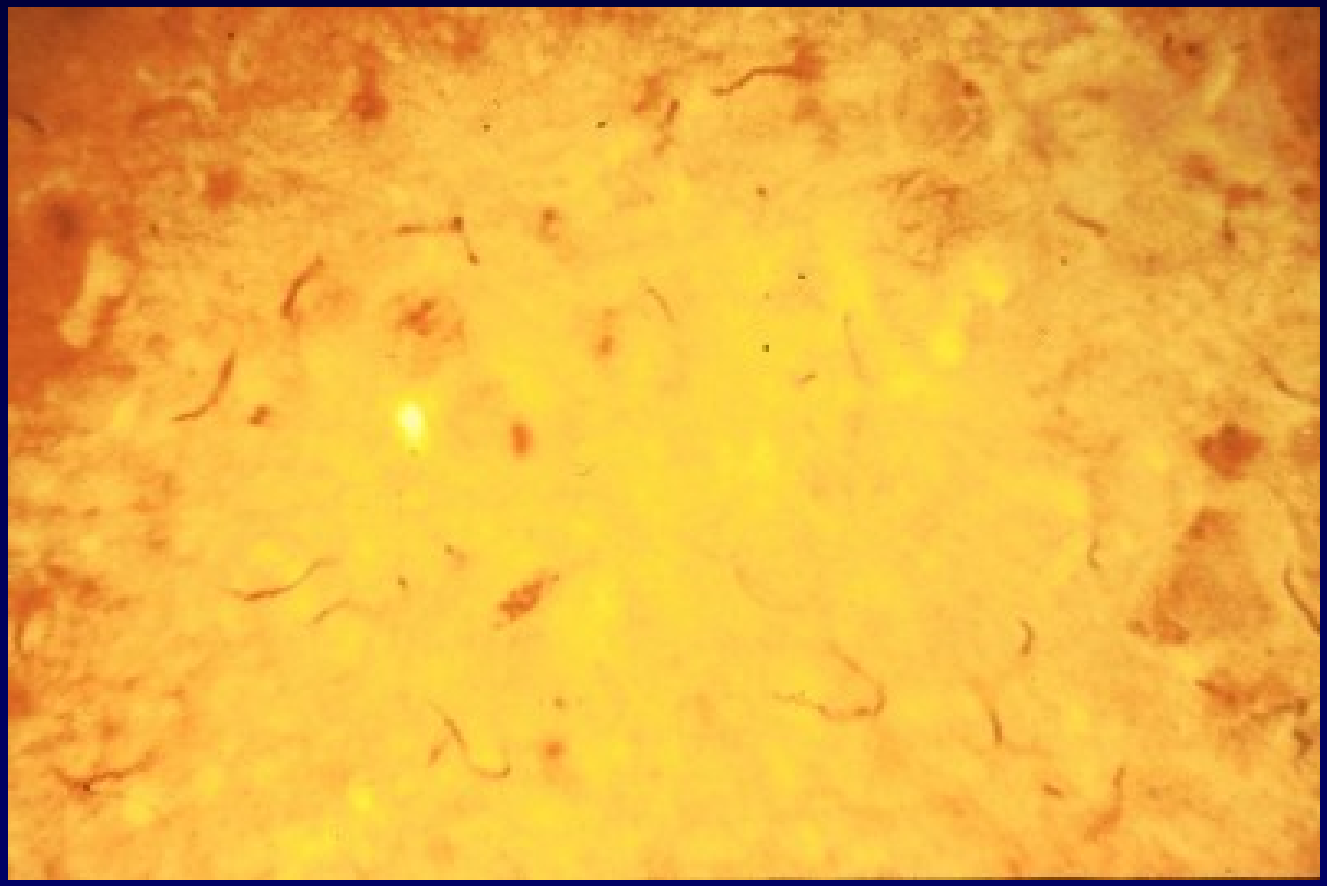
Latent Syphilis

- Host suppresses infection, but no lesions are clinically apparent
- Only evidence is a positive serologic test
- May occur between primary and secondary stages, between secondary relapses, and after secondary stage
- Categories:
  - Early latent: <1 year duration
  - Late latent: ≥1 year duration

Neurosyphilis

- Occurs when *T. pallidum* invades the central nervous system (CNS)
- May occur at any stage of syphilis
- Can be asymptomatic
- Early neurosyphilis occurs a few months to a few years after infection
  - Clinical manifestations can include acute syphilitic meningitis, meningovascular syphilis, and ocular involvement
- Neurologic involvement can occur decades after infection and is rarely seen
  - Clinical manifestations can include general paresis, tabes dorsalis, and ocular involvement
- Ocular involvement can occur in early or late neurosyphilis.

Neurosyphilis—Spirochetes in Neural Tissue



Silver stain, 950x

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Tertiary (Late) Syphilis

- Approximately 30% of untreated patients progress to the tertiary stage within 1 to 20 years.
- Rare because of the widespread availability and use of antibiotics
- Manifestations
  - Gummatous lesions
  - Cardiovascular syphilis

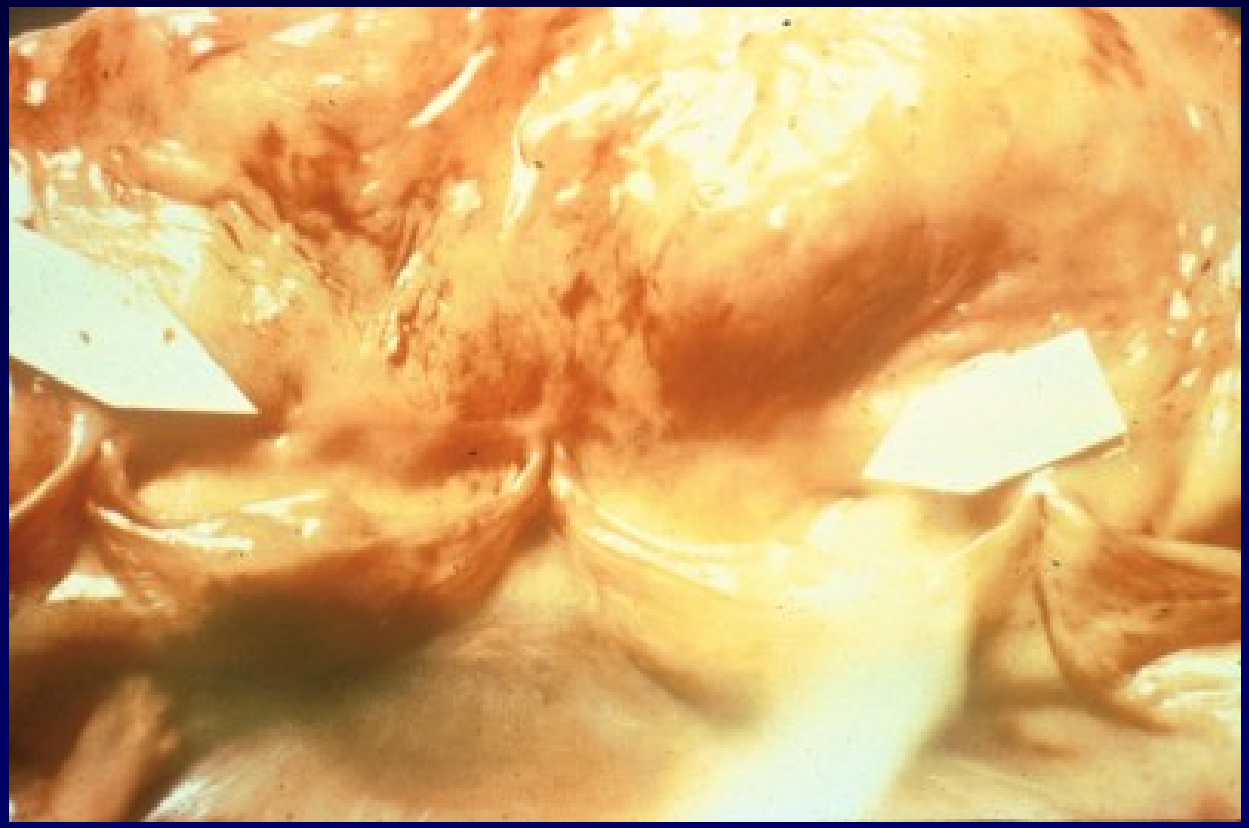
Late Syphilis—Serpiginous Gummata of Forearm

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Late Syphilis - Ulcerating Gumma

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Late Syphilis—Cardiovascular



Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

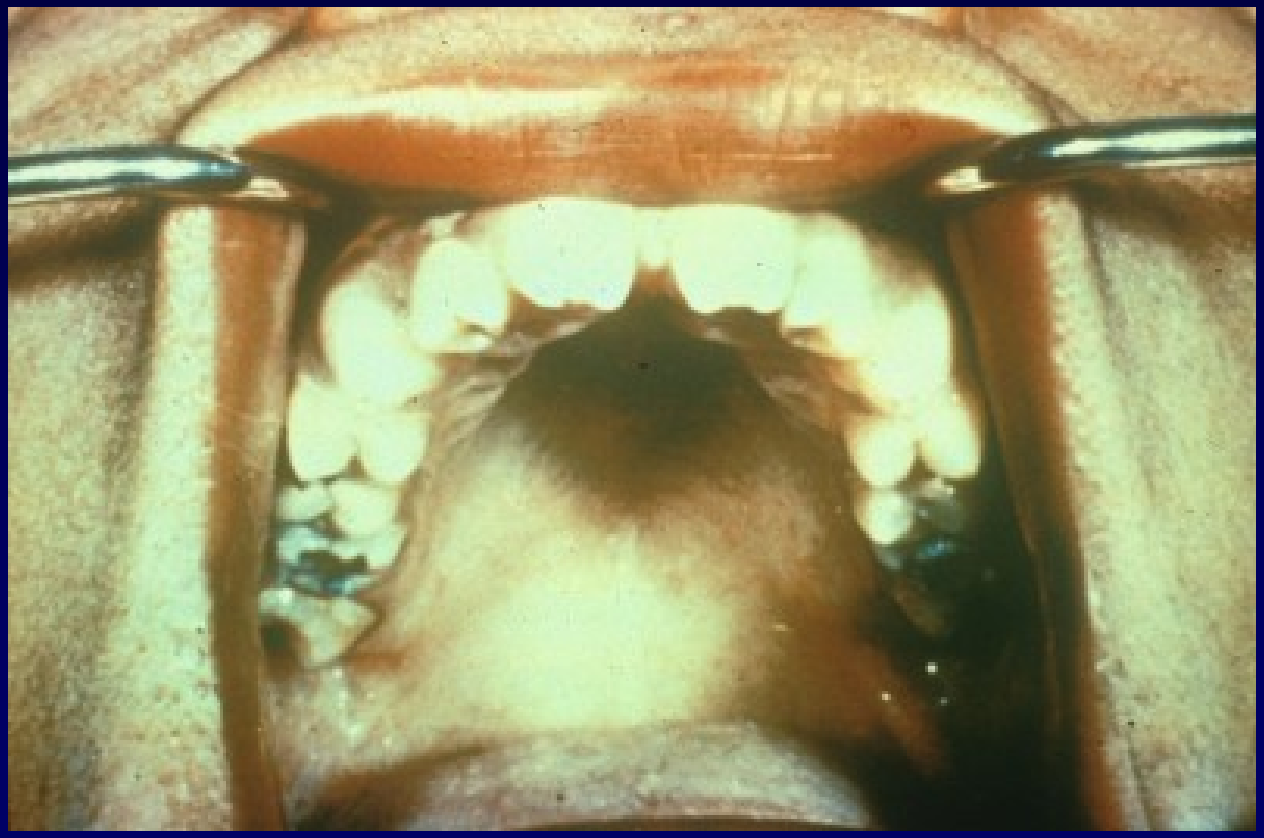
Congenital Syphilis

- Occurs when *T. pallidum* is transmitted from a pregnant woman to her fetus
- May lead to stillbirth, neonatal death, and infant disorders such as deafness, neurologic impairment, and bone deformities
- Transmission can occur during any stage of syphilis; risk is much higher during primary and secondary syphilis
- Fetal infection can occur during any trimester of pregnancy
- Wide spectrum of severity exists; only severe cases are clinically apparent at birth
  - Early lesions (most common): Infants <2 years old; usually inflammatory
  - Late lesions: Children >2 years old; tend to be immunologic and destructive

Congenital Syphilis—Mucous Patches

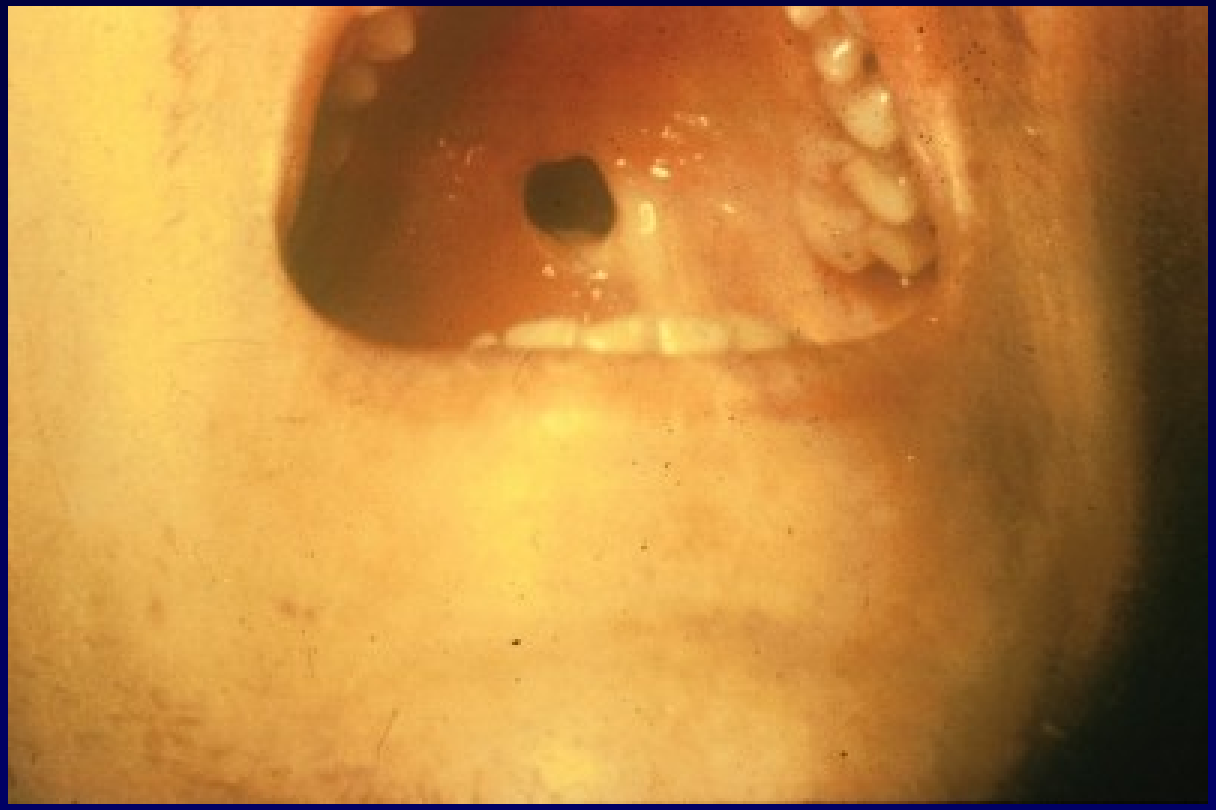
Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Congenital Syphilis—Hutchinson's Teeth



Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Congenital Syphilis—Perforation of Palate



Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Lesson IV: Syphilis Diagnosis

Aspects of Syphilis Diagnosis

1. Clinical history
2. Physical examination
3. Laboratory diagnosis

Clinical History

Assess

- History of syphilis
- Known contact to an early case of syphilis
- Typical signs or symptoms of syphilis in the past 12 months
- Most recent serologic test for syphilis

Physical Examination

- Oral cavity
- Lymph nodes
- Skin of torso
- Palms and soles
- Genitalia and perianal area
- Neurologic examination
- Abdomen

Laboratory Diagnosis

- Identification of *Treponema pallidum* in lesion exudate or tissue
  - Darkfield microscopy
  - Tests to detect *T. pallidum*
- Serologic tests to allow a presumptive diagnosis
  - Nontreponemal tests
  - Treponemal tests

Darkfield Microscopy

- What to look for
  - *T. pallidum* morphology and motility
- Advantage
  - Definitive immediate diagnosis
  - Rapid results
- Disadvantages
  - Requires specialized equipment and an experienced microscopist
  - Possible confusion with other pathogenic and nonpathogenic spirochetes
  - Must be performed immediately
  - Generally not recommended on oral lesions
  - Possibility of false-negatives

Serologic Tests for Syphilis

- Two types
  - Treponemal (qualitative)
  - Nontreponemal (qualitative and quantitative)
- The use of only one type of serologic test is insufficient for diagnosis

Nontreponemal Serologic Tests

- Principles
  - Measure antibody directed against a cardiolipin-lecithin-cholesterol antigen
  - Not specific for *T. pallidum*
  - Titers usually correlate with disease activity and results are reported quantitatively
  - May be reactive for life, referred to as “serofast”
- Nontreponemal tests include VDRL, RPR, TRUST, USR

Nontreponemal Serologic Tests (continued)

Advantages

- Rapid and inexpensive
- Easy to perform and can be done in clinic or office
- Quantitative
- Used to follow response to therapy
- Can be used to evaluate possible reinfection

Disadvantages

- May be insensitive in certain stages
- False-positive reactions may occur
- Prozone effect may cause a false-negative reaction (rare)

Treponemal Serologic Tests

- Principles
  - Measure antibody directed against *T. pallidum* antigens
  - Qualitative
  - Usually reactive for life
  - Titers should not be used to assess treatment response
- Treponemal tests include TP-PA, FTA-ABS, EIA, and CIA

Sensitivity of Serological Tests in Untreated Syphilis

	Stage of Disease (Percent Positive [Range])			
Test	**Primary**	**Secondary**	**Latent**	**Tertiary**
VDRL	78 (74–87)	100	95 (88–100)	71 (37–94)
RPR	86 (77–99)	100	98 (95–100)	73
FTA-ABS*	84 (70–100)	100	100	96
Treponemal Agglutination*	76 (69–90)	100	97 (97–100)	94
EIA	93	100	100	

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

Causes of False-Positive Reactions in Serologic Tests for Syphilis

Disease	RPR/VDRL	FTA-ABS	TP-PA
Age		Yes	
Autoimmune Diseases	Yes	Yes	
Cardiovascular Disease		Yes	Yes
Dermatologic Diseases	Yes	Yes	--
Drug Abuse	Yes	Yes	
Febrile Illness	Yes		
Glucosamine/chondroitin sulfate		Possibly	
Leprosy	Yes	No	--
Lyme disease		Yes	
Malaria	Yes	No	
Pinta, Yaws	Yes	Yes	Yes
Recent Immunizations	Yes	--	--
STD other than Syphilis		Yes	

Source: Syphilis Reference Guide, CDC/National Center for Infectious Diseases, 2002

Diagnosis of Latent Syphilis

- Criteria for early latent syphilis, if within the year preceding the evaluation
  - Documented seroconversion or 4-fold increase in comparison with a serologic titer
  - Unequivocal symptoms of primary or secondary syphilis reported by patient
  - Contact to an infectious case of syphilis
  - Only possible exposure occurred within past 12 months
- Patients with latent syphilis of unknown duration should be managed clinically as if they have late latent syphilis.
- Public health laws require that all cases of syphilis be reported to the state/local health department.

CNS Disease Diagnostic Issues

- CNS disease can occur during any stage of syphilis.
- Conventional therapy is effective for the vast majority of immuno-competent patients with asymptomatic CNS involvement in primary and secondary syphilis.

Indications for CSF Examination

- Patients with syphilis who demonstrate any of the following criteria should have a prompt CSF evaluation:
  - Neurologic or ophthalmic signs or symptoms
  - Evidence of active tertiary syphilis (e.g., gummatous lesions)
  - Treatment failure
  - HIV infection with a CD4 count ≤350 and/or a nontreponemal serologic test titer of ≥1:32

Diagnosis of CNS Disease

- No test can be used alone to diagnose neurosyphilis.
- VDRL-CSF: highly specific, but insensitive
- Diagnosis usually depends on the following factors:
  - Reactive serologic test results
  - Abnormalities of CSF cell count or protein
  - A reactive VDRL-CSF with or without clinical manifestations
- CSF leukocyte count usually is elevated (>5 WBCs/mm^3) in patients with neurosyphilis.
- The VDRL-CSF is the standard serologic test for CSF, and when reactive in the absence of contamination of the CSF with blood, it is considered diagnostic of neurosyphilis. However, in early syphilis it can be of unknown prognostics significance.

Effect of HIV Infection on Syphilis

- Syphilis and HIV infections commonly coexist.
- Clinical course is similar to non-HIV-infected patients.
- Although uncommon, unusual serologic responses can occur.
- If clinical suspicion of syphilis is high and the serologic tests are negative, then use of other tests (e.g., biopsy of the lesion or rash) should be considered.
- Conventional therapy is effective.

Lesson V: Patient Management

Therapy for Primary, Secondary, and Early Latent Syphilis

- Benzathine penicillin G 2.4 million units intramuscularly in a single dose (Bicillin L-A®)
- If penicillin allergic
  - Doxycycline 100 mg orally twice daily for 14 days, or
  - Tetracycline 500 mg orally 4 times daily for 14 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2010. MMWR 2010;59 (No. RR-12).

Therapy for Late Latent Syphilis

- Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units intramuscularly each at 1-week intervals
- If penicillin allergic
  - Doxycycline 100 mg orally twice daily for 28 days or
  - Tetracycline 500 mg orally 4 times daily for 28 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2010. MMWR 2010;59 (No. RR-12).

Therapy for Tertiary Syphilis

- Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units intramuscularly each at 1-week intervals
- If penicillin allergic
  - Doxycycline 100 mg orally twice daily for 28 days or
  - Tetracycline 500 mg orally 4 times daily for 28 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2010. MMWR 2010;59 (No. RR-12).

Therapy for Neurosyphilis

- 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 to14 days intravenously
- Alternative regimen (if compliance can be ensured)
  - Procaine penicillin 2.4 million units intramuscularly once daily PLUS Probenecid 500 mg orally 4 times a day, both for 10 to14 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2010. MMWR 2010;59 (No. RR-12).

Therapy for Syphilis in Pregnancy

- Treat with penicillin according to stage of infection.
- Erythromycin is no longer an acceptable alternative drug in penicillin-allergic patients.
- Patients who are skin-test-reactive to penicillin should be desensitized in the hospital and treated with penicillin.
- Some evidence suggests that additional therapy can be beneficial for pregnant women in some settings.

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2010. MMWR 2010;59 (No. RR-12).

Jarisch-Herxheimer Reaction

- Self-limited reaction to antitreponemal therapy
  - Fever, malaise, nausea/vomiting; may be associated with chills and exacerbation of secondary rash
- Occurs within 24 hours after therapy
- Not an allergic reaction to penicillin
- More frequent after treatment with penicillin and treatment of early syphilis
- Antipyretics can be used to manage symptoms, but they have not been proven to prevent this reaction.
- Pregnant women should be informed of this possible reaction, that it may precipitate early labor, and to call obstetrician if problems develop.

Syphilis and HIV/Other STDs

- HIV infected persons with primary, secondary, and early latent syphilis should receive a single intramuscular dose of 2.4 MU of benzathine penicillin.
- Penicillin-allergic patients with syphilis and HIV whose compliance cannot be ensured should be desensitized and treated with penicillin.
- All patients who have syphilis should be tested for HIV infection.
- Consider screening persons with syphilis for other STDs, based on risk.

Follow-Up

- Primary or secondary syphilis
  - Reexamine at 6 and 12 months.
  - Follow-up titers should be compared to the maximum or baseline nontreponemal titer obtained on day of treatment.
- Latent syphilis
  - Reexamine at 6, 12, and 24 months.
- HIV-infected patients
  - 3, 6, 9, 12 and 24 months for primary or secondary syphilis
  - 6, 12, 18, and 24 months for latent syphilis
- Neurosyphilis
  - Serologic testing as above
  - Repeat CSF examination at 6-month intervals until normal

Treatment Failure

- Indications of probable treatment failure or reinfection include
  - Persistent or recurring clinical signs or symptoms
  - Sustained 4-fold increase in titer
  - Titer fails to show a 4-fold decrease within 6–12 months
- Retreat and re-evaluate for HIV infection.
- CSF examination can be considered.

Lesson VI: Prevention

Patient Counseling and Education

- Nature of the disease
- Transmission
- Treatment and follow-up
- Risk reduction

Management of Sex Partners

- For sex partners of patients with syphilis in any stage
  - Draw syphilis serology
  - Perform physical exam
- For sex partners of patients with primary, secondary, or early latent syphilis
  - Treat presumptively as for early syphilis at the time of examination, unless
    - The nontreponemal test result is known and negative and
    - The last sexual contact with the patient is > 90 days prior to examination.

Screening Recommendations

- Screen pregnant women at least at first prenatal visit.
  - In high prevalence communities, or patients at risk
    - Test twice during the third trimester, at 28 weeks, and at delivery, in addition to routine early screening.
  - Any woman who delivers a stillborn infant after 20 weeks gestation should be tested for syphilis.
- Screen other populations based on local prevalence and the patient's risk behaviors.

Reporting

- Laws and regulations in all states require that persons diagnosed with syphilis are reported to public health authorities. Reporting can be provider or laboratory based.
- The follow-up of patients with early syphilis is a public health priority.

Case Study

History

- Stan Carter is a 19-year-old male who presents to the STD clinic.
- Chief complaint is a penile lesion for 1 week
- Last sexual exposure was 3 weeks prior, without a condom.
- No history of recent travel
- Predominantly female partners (3 in the last 6 months), and occasional male partners (2 in the past year)
- Last HIV antibody test (2 months prior) was negative

Physical Exam

- No oral, perianal, or extra-genital lesions
- Genital exam discloses a lesion on the ventral side near/at the frenulum. Lesion is red, indurated, clean-based, and non-tender.
- Two enlarged tender right inguinal nodes, 1.5 cm x 1 cm
- Scrotal contents without masses or tenderness
- No urethral discharge
- No rashes on torso, palms, or soles. No alopecia. Neurologic exam with normal limits.

Questions

1. What are the possible etiologic agents that should be considered in the differential diagnosis?
2. What is the *most likely* diagnosis?
3. Which laboratory tests would be appropriate to order or perform?

Stat Lab Results

The results of stat laboratory tests showed the following:

RPR: Nonreactive

Darkfield examination of penile lesion: Positive for *T. pallidum*

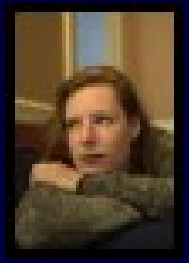
4. What is the diagnosis?
5. What is the appropriate treatment?

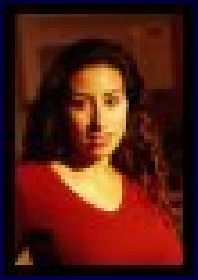
Reference Lab Results

- RPR: Nonreactive
- FTA-ABS: Reactive
- HSV culture: Negative
- Gonorrhea NAAT: Negative
- Chlamydia NAAT: Negative
- HIV antibody test: Negative

6. Do the reference laboratory results change the diagnosis?
7. Who is responsible for reporting this case to the local health department?

Stan's Sex Partners



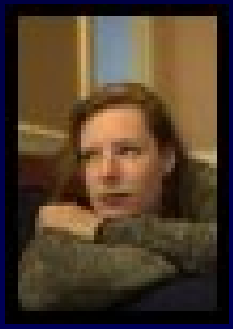


Tracy – last sexual exposure 3 weeks ago
Danielle – last sexual exposure 6 weeks ago
Jonathan – last sexual exposure 1 month ago
Tony – last sexual exposure 8 months ago
Carrie – last sexual exposure 6 months ago

8. Which of Stan's partners should be evaluated and treated prophylactically, even if their test results are negative?

Sex Partner Follow-Up

Stan's partner, Tracy, is found to be infected and is diagnosed with primary syphilis. She is also in her second trimester of pregnancy and is allergic to penicillin.



9. What is the appropriate treatment for Tracy?

Follow-Up

Stan returned to the clinic for a follow-up exam 1 week later. Results were as follows

- His penile lesion was almost completely healed.
- He had not experienced a Jarisch-Herxheimer reaction.
- The RPR (repeated at the follow-up visit because the initial one was negative) was 1:2.

10. What type of follow-up evaluation will Stan need?

11. What are appropriate prevention counseling messages for patients with syphilis?