

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

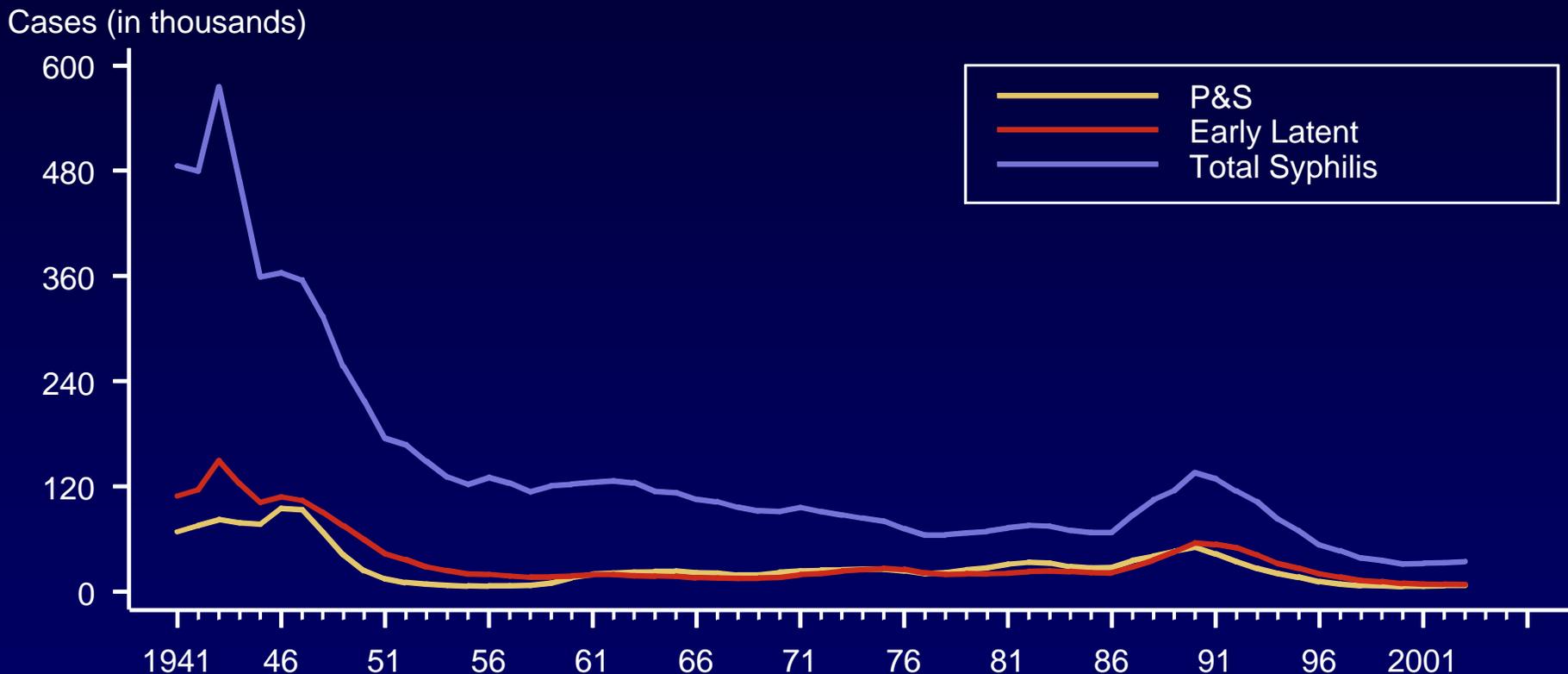
Transmission

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

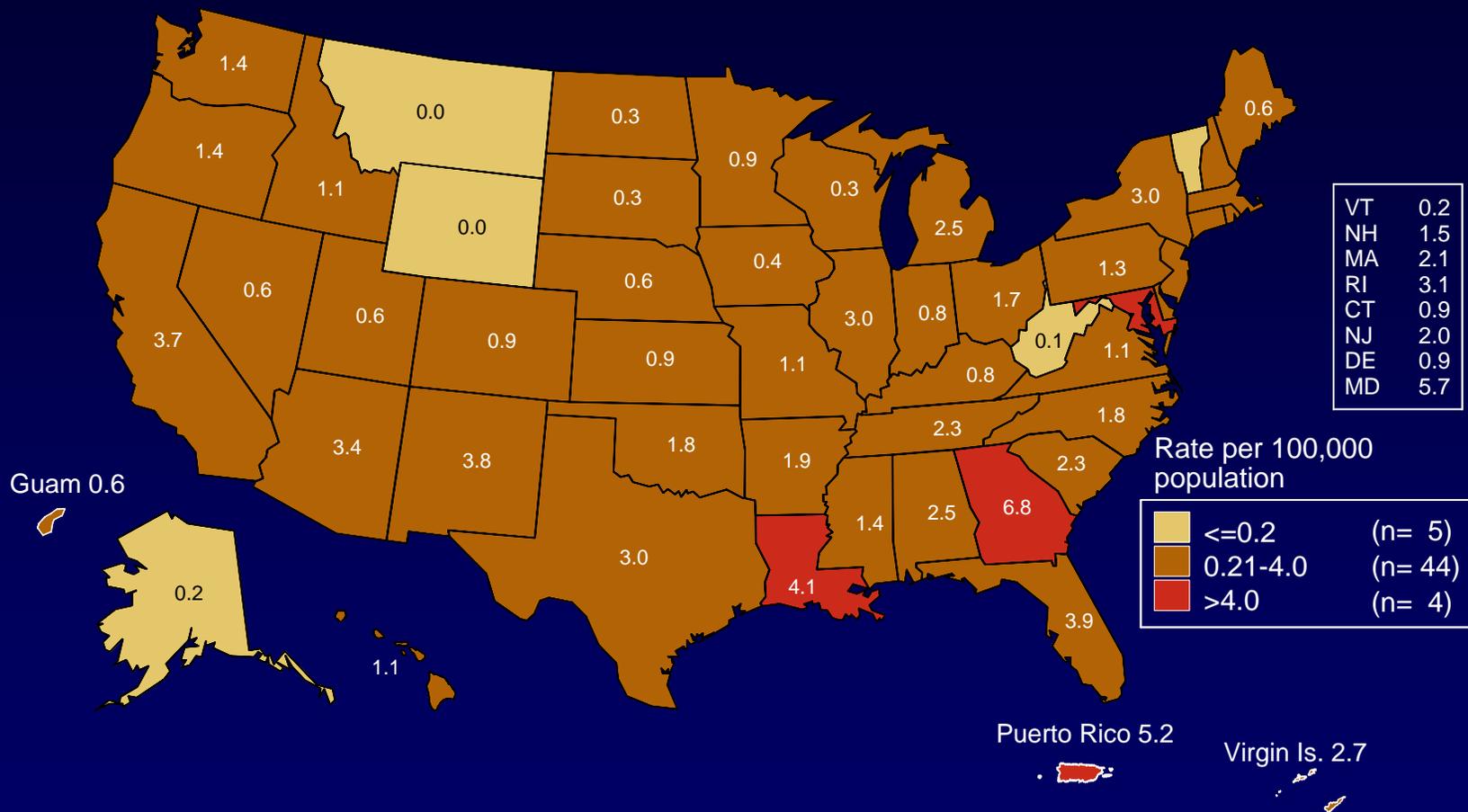
Disease Trends in the U.S.

- Distributed widely throughout the U.S. in the 1940s
- Declined rapidly after introduction of penicillin therapy and broad-based public health programs
- 1986-90: 85% increase in the incidence of primary and secondary syphilis
- During the 1990s, reported cases of syphilis decreased approximately 15% per year to an all-time low in 2000
- Rates remain high in:
 - Rural areas in the South
 - Some urban areas throughout the U.S
- Recent outbreaks have occurred among subpopulations of men who have sex with men (MSM)

Syphilis — Reported cases by stage of infection: United States, 1941–2003



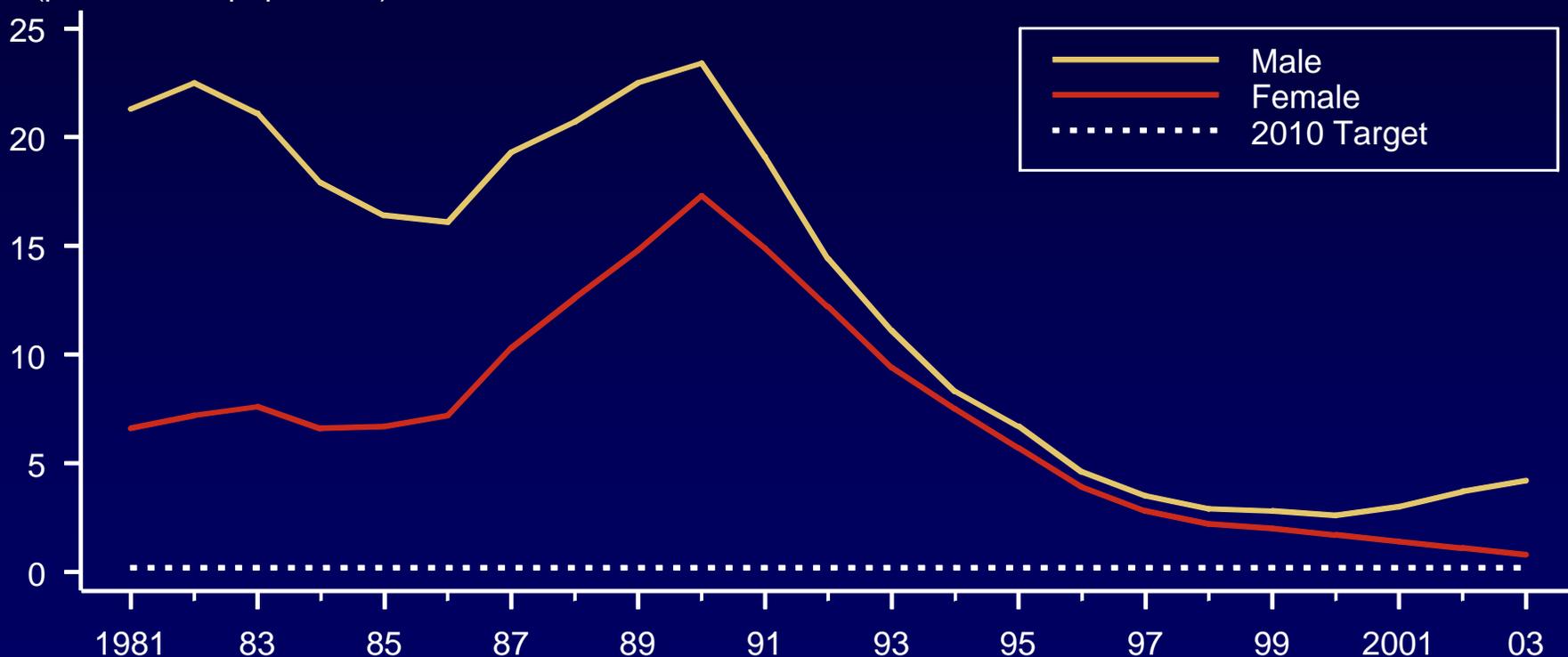
Primary and secondary syphilis — Rates by state: United States and outlying areas, 2003



Note: The total rate of primary and secondary syphilis for the United States and outlying areas (Guam, Puerto Rico and Virgin Islands) was 2.5 per 100,000 population. The Healthy People 2010 target is 0.2 case per 100,000 population.

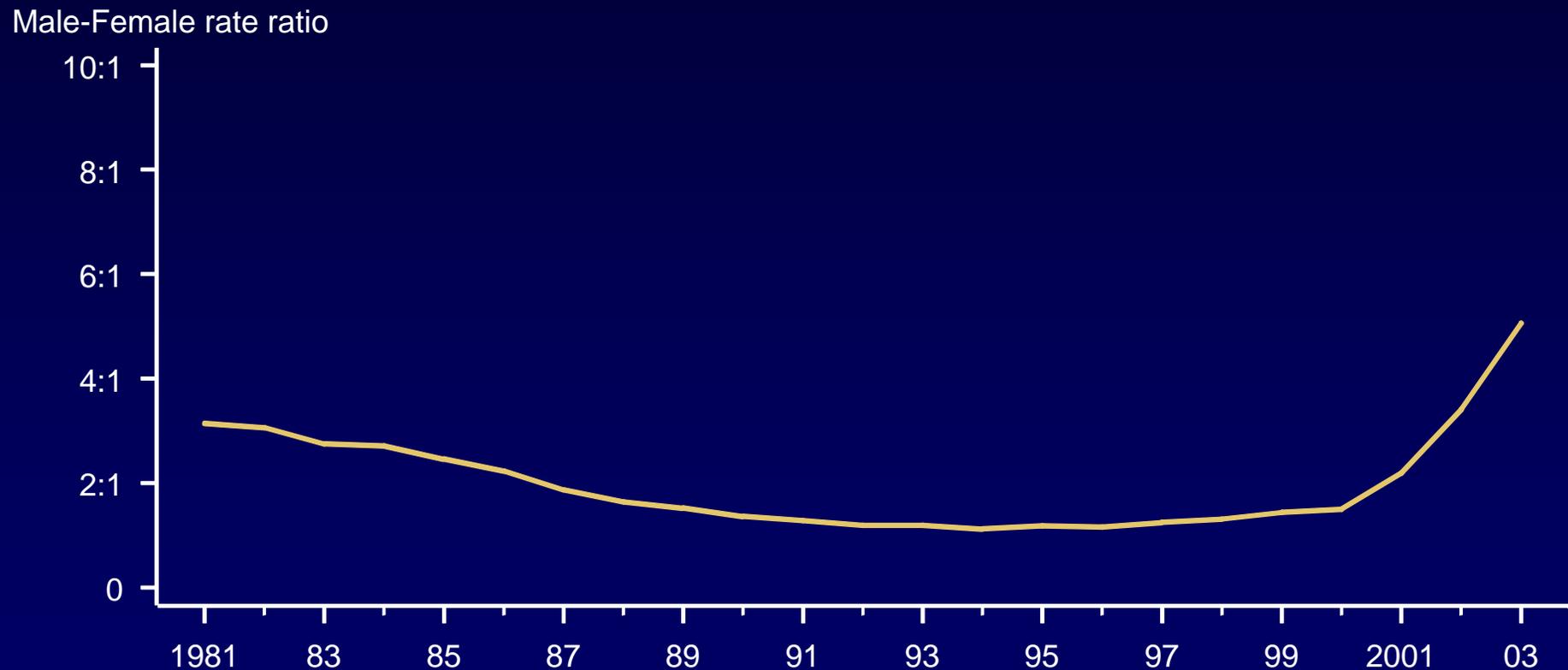
Primary and secondary syphilis — Rates by sex: United States, 1981–2003 and the Healthy People 2010 target

Rate (per 100,000 population)



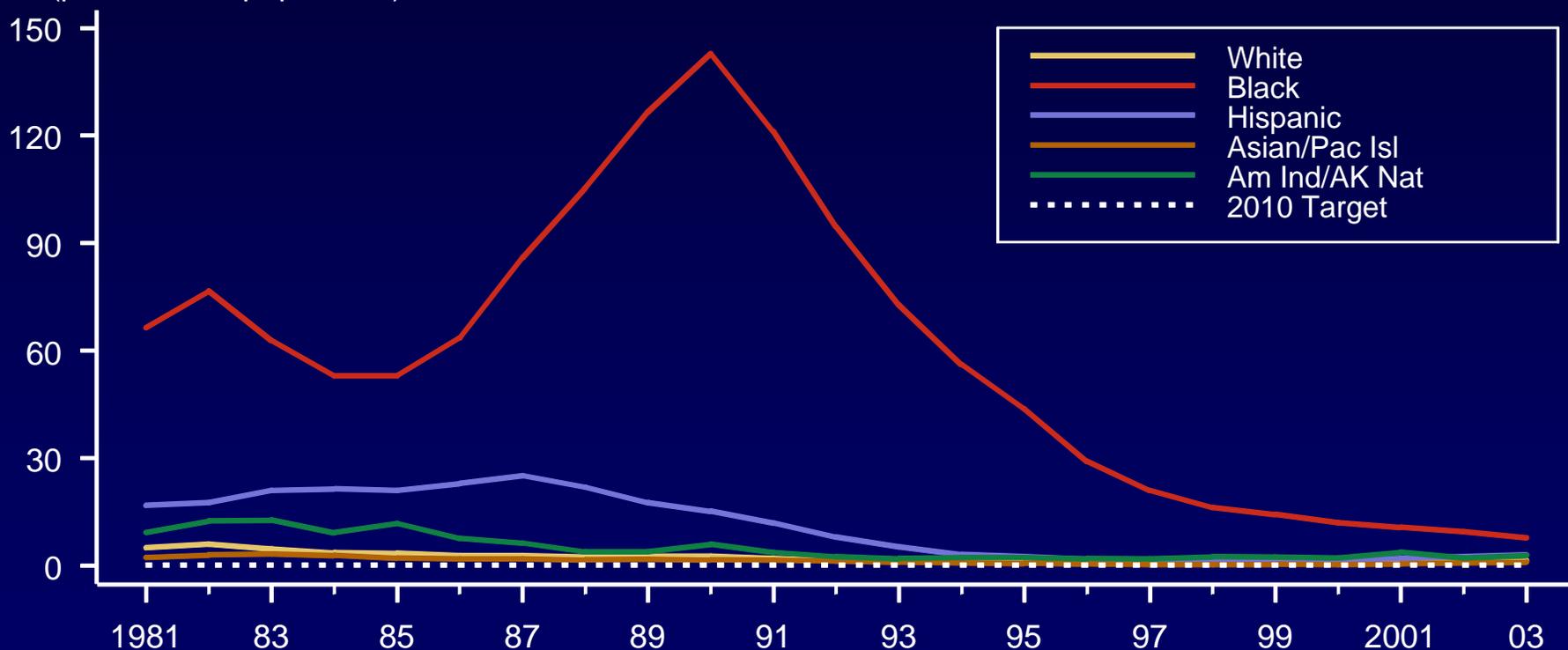
Note: The Healthy People 2010 target for P&S syphilis is 0.2 case per 100,000 population.

Primary and secondary syphilis — Male-to-female rate ratios: United States, 1981–2003



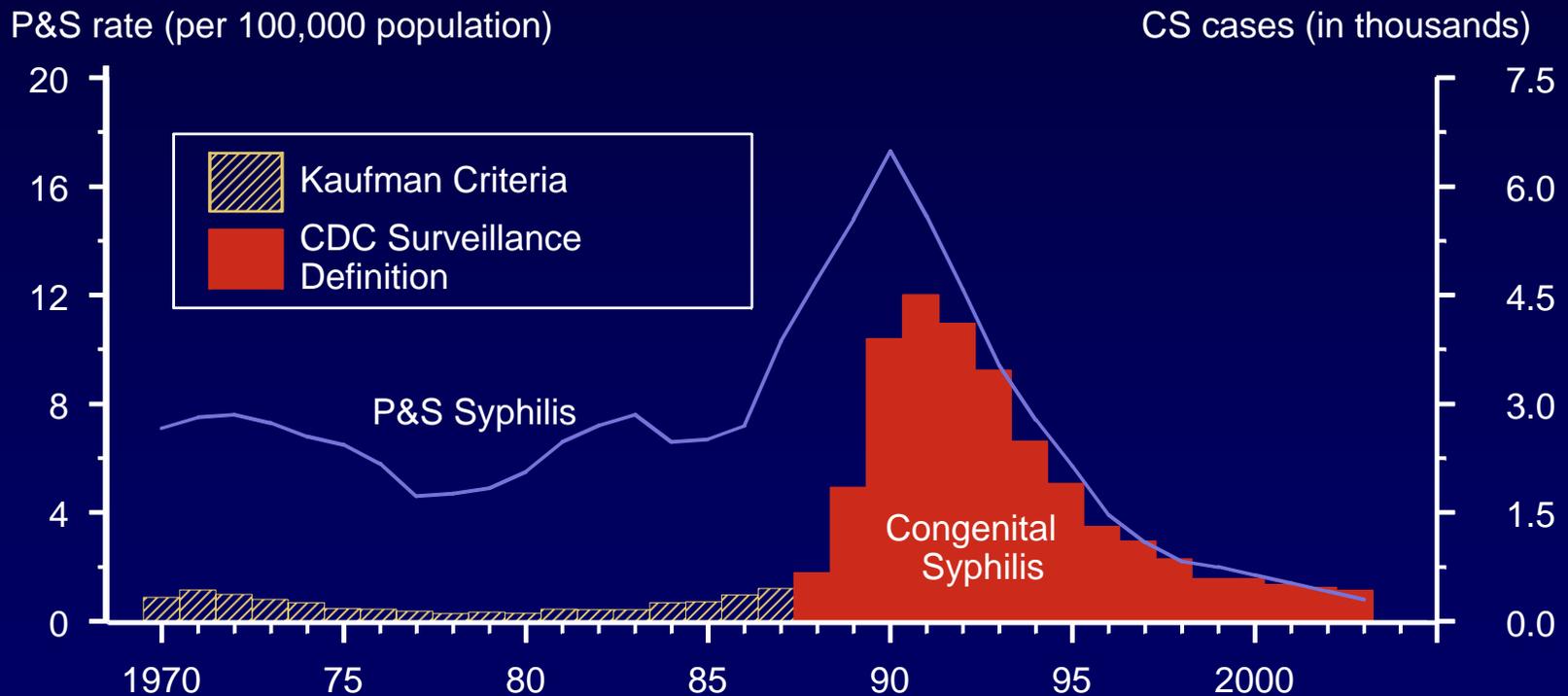
Primary and secondary syphilis — Rates by race and ethnicity: United States, 1981–2003 and the Healthy People 2010 target

Rate (per 100,000 population)



Note: The Healthy People 2010 target for P&S syphilis is 0.2 case per 100,000 population.

Congenital syphilis — Reported cases for infants <1 year of age and rates of primary and secondary syphilis among women: U.S., 1970–2003



Note: The surveillance case definition for congenital syphilis changed in 1988.

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.

Treponema pallidum on darkfield microscopy



Pathology

- Penetration:
 - *T. pallidum* enters the body via skin and mucous membranes through abrasions during sexual contact
 - Also transmitted transplacentally
- Dissemination:
 - Travels via the lymphatic system to regional lymph nodes and then throughout the body via the blood stream
 - Invasion of the 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 1 to 6 weeks
 - 25% present with multiple lesions
- Regional lymphadenopathy: classically rubbery, painless, bilateral
- Serologic tests for syphilis may not be positive during early primary syphilis

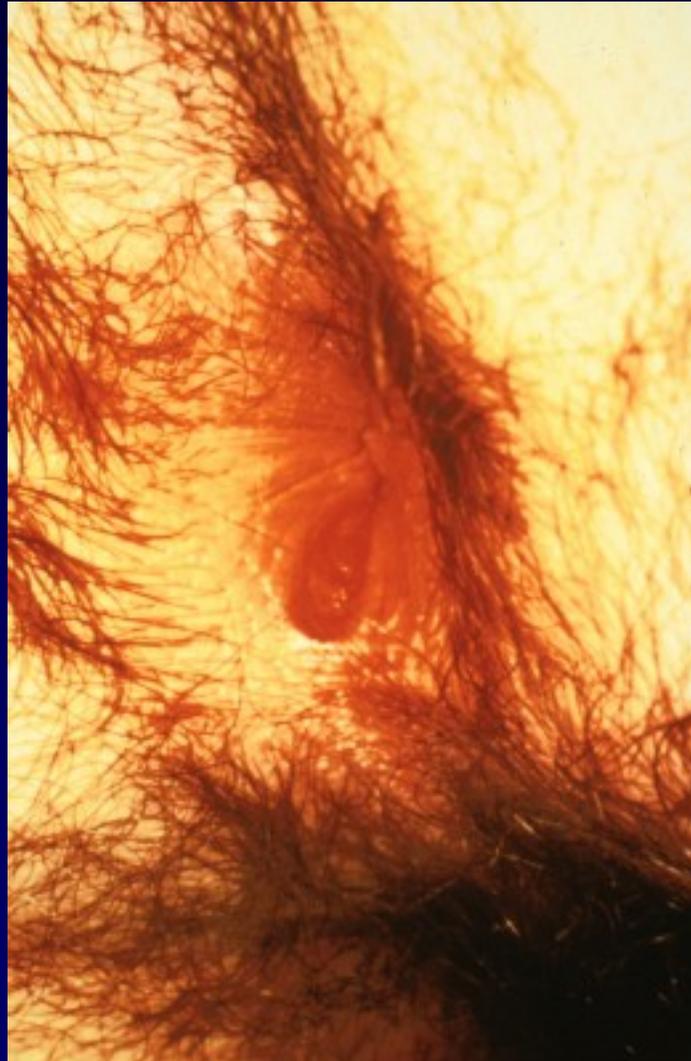
Primary Syphilis- Penile Chancre



Primary Syphilis – Labial Chancre



Primary Syphilis – Perianal Chancre



Syphilis Lesion - Tongue



Secondary Syphilis

- Secondary lesions occur 3 to 6 weeks after the primary chancre appears; may persist for weeks to months
- Primary and secondary stages may overlap
- Mucocutaneous lesions most common
- Manifestations:
 - Rash (75%-100%)
 - Lymphadenopathy (50%-86%)
 - Malaise
 - Mucous patches (6%-30%)
 - Condylomata lata (10%-20%)
 - Alopecia (5%)
- Serologic tests are usually highest in titer during this stage

Secondary Syphilis - Papulosquamous Rash



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



Secondary Syphilis - Condylomata lata



Secondary Syphilis – Nickel/Dime Lesions



Secondary Syphilis - Alopecia



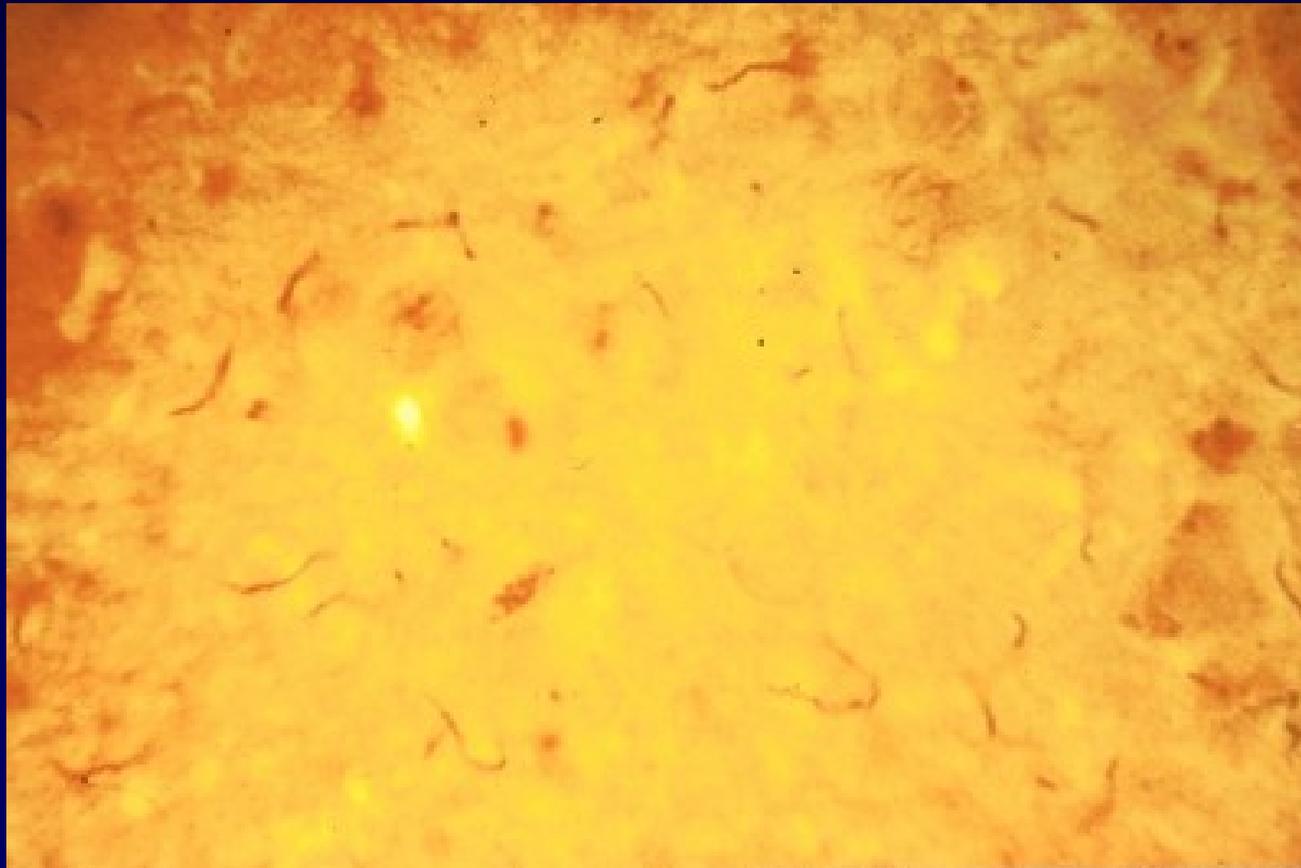
Latent Syphilis

- Host suppresses the infection enough so that no lesions are clinically apparent
- Only evidence is positive serologic test for syphilis
- 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 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 include acute syphilitic meningitis, meningovascular syphilis, ocular involvement
- Late neurosyphilis occurs decades after infection and is rarely seen
 - Clinical manifestations include general paresis, tabes dorsalis, ocular involvement

Neurosypphilis - Spirochetes in Neural Tissue



Silver stain, 950x

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

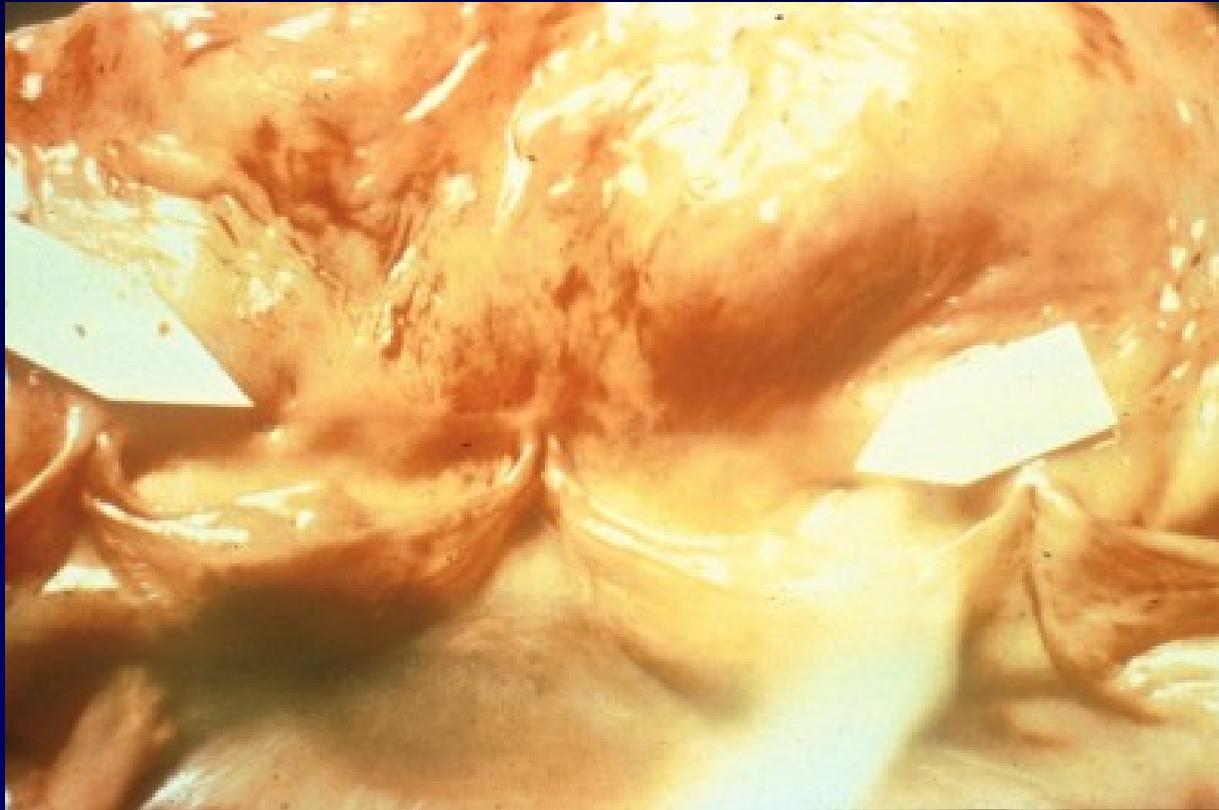
Late Syphilis - Serpiginous Gummata of Forearm



Late Syphilis - Ulcerating Gumma



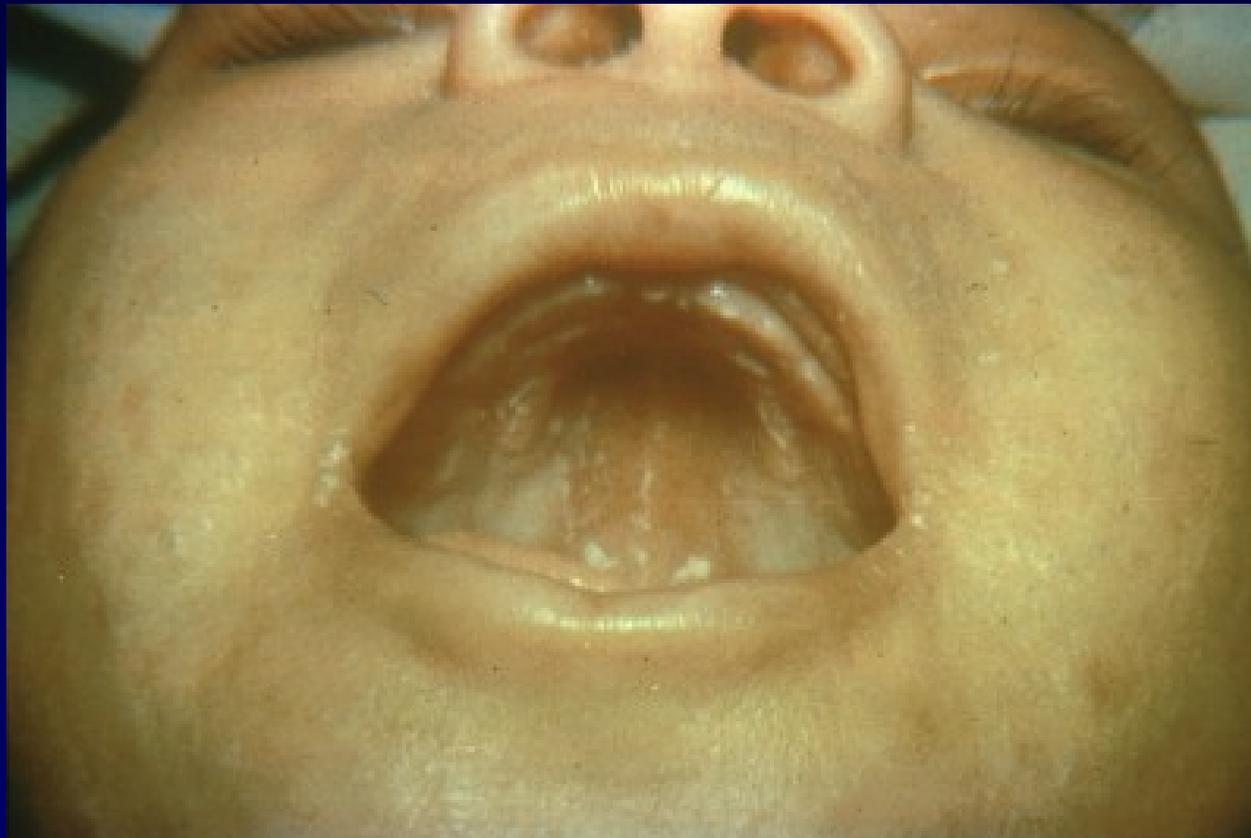
Late Syphilis--Cardiovascular



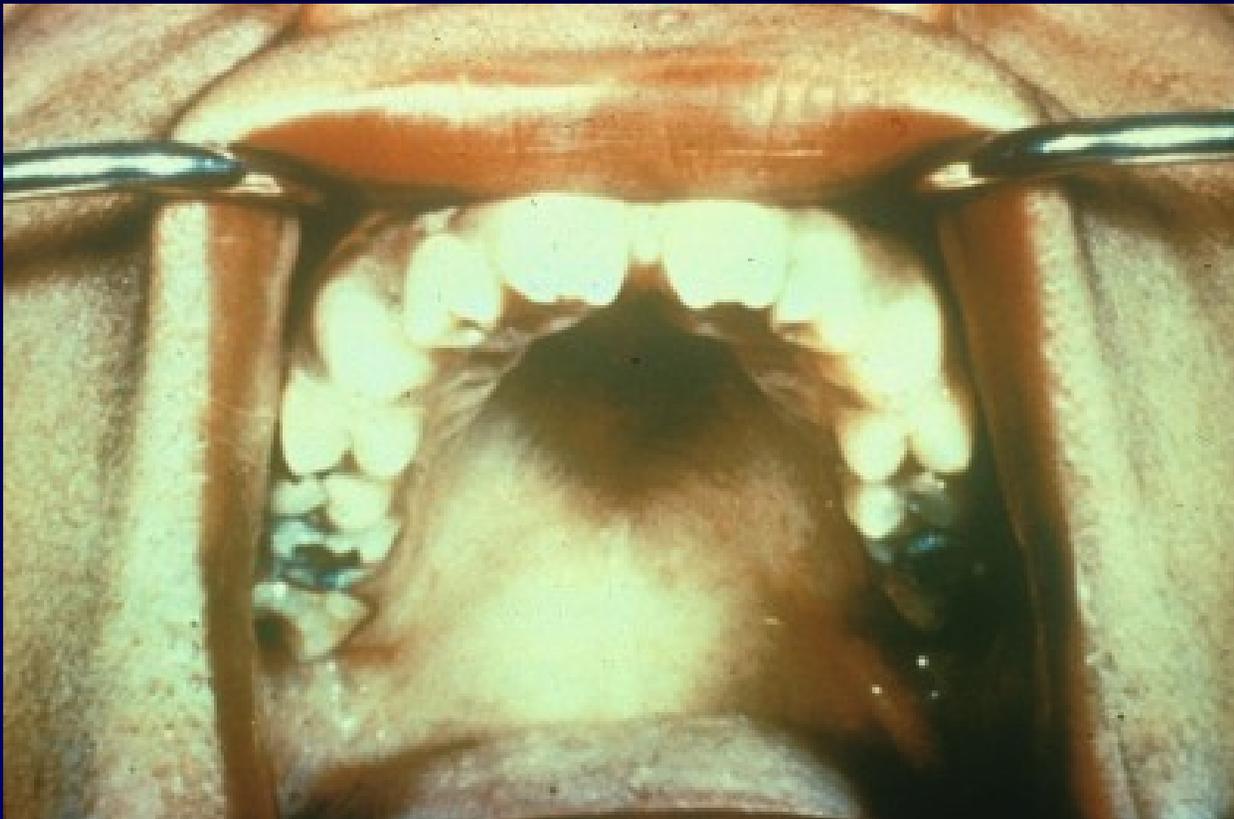
Congenital Syphilis

- Occurs when *T. pallidum* is transmitted from a pregnant woman with syphilis to her fetus
- May lead to stillbirth, neonatal death, and infant disorders such as deafness, neurologic impairment, and bone deformities
- Transmission to the fetus in pregnancy 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



Congenital Syphilis - Hutchinson's Teeth



Congenital Syphilis - Perforation of Palate



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

Laboratory Diagnosis

- Identification of *Treponema pallidum* in lesions
 - Darkfield microscopy
 - Direct fluorescent antibody - *T. pallidum* (DFA-TP)
- Serologic tests
 - Nontreponemal tests
 - Treponemal tests

Darkfield Microscopy

- What to look for:
 - *T. pallidum* morphology and motility
- Advantage:
 - Definitive immediate diagnosis
- 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

Direct Fluorescent Antibody-- *T. pallidum* (DFA-TP)

- Identifies *T. pallidum* in direct lesion smear by immunofluorescence
- Advantages:
 - Commercially available
 - Compares favorably with darkfield microscopy
- Disadvantages:
 - Turnaround time 1-2 days

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
- 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
- Treponemal tests include TP-PA, FTA-ABS, EIA

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
Pregnancy	Yes*		
Recent Immunizations	Yes	--	--
STD other than Syphilis		Yes	

*May cause increase in titer in women previously successfully treated for syphilis

Diagnosis of Latent Syphilis

- Criteria for early latent syphilis:
 - Documented seroconversion or 4-fold increase in comparison with a serologic titer obtained within the year preceding the evaluation
 - Unequivocal symptoms of primary or secondary syphilis reported by patient in past 12 months
 - 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.

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., aortitis, gumma, and iritis),
 - Treatment failure, or
 - HIV infection with late latent syphilis or syphilis of unknown duration.

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, or
 - A reactive VDRL-CSF with or without clinical manifestations.
- CSF leukocyte count usually is elevated (>5 WBCs/mm³) 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.

Effect of HIV Infection on Syphilis

- Syphilis and HIV infections commonly coexist.
- Clinical course is similar to non-HIV-infected patients.
- Serological tests for syphilis are usually equivalent in sensitivity in HIV-infected and non-infected persons.
- Conventional therapy is usually effective.
- Some investigators feel that HIV-infected patients may be more likely to present with symptomatic neurosyphilis.

Lesson V: Patient Management

Therapy for Primary, Secondary, and Early Latent Syphilis

- Benzathine penicillin G 2.4 million units IM in a single dose
- If penicillin allergic:
 - Doxycycline 100 mg orally twice daily for 14 days, or
 - Tetracycline 500 mg orally 4 times daily for 14 days

Therapy for Late Latent Syphilis or Latent Syphilis of Unknown Duration

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

Therapy for Tertiary Syphilis without Neurologic Involvement

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

Therapy for Neurosyphilis

- Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion for 10-14 days IV
- Alternative regimen (if compliance can be ensured):
 - Procaine penicillin 2.4 million units IM once daily PLUS Probenecid 500 mg orally 4 times a day, both for 10-14 days

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.

Jarisch-Herxheimer Reaction

- Self-limited reaction to anti-treponemal 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
- 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

- 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
 - Re-examine 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
 - Re-examine at 6, 12, 18, and 24 months
- HIV-infected patients
 - 3, 6, 9, and 12 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 months
- Retreat and re-evaluate for HIV infection
- Some specialists recommend CSF examination

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 by clinicians, labs, or both.
- 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: penile lesion x 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: 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 WNL.

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 culture: Negative

Chlamydia DNA-probe: 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?