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# SYPHILIS

**STD/HIV**  
Prevention  
Training  
*Center of New England*

A Project of the Division of STD Prevention  
Massachusetts Department of Public Health  
Funded by the CDC



# SYPHILIS

## OBJECTIVES

- 1 Describe the changing epidemiologic trends of syphilis.
- 2 Define each stage of syphilis and describe their respective clinical manifestations.
- 3 Describe the diagnostic value of darkfield microscopy, as well as proper specimen collection, procedure and interpretation for the test.
- 4 Explain the difference between nontreponemal and treponemal tests, as well as their value for diagnosis in the different stages of syphilis and their use for follow-up.
- 5 Choose the appropriate treatment for each stage of syphilis and describe proper post treatment follow-up.
- 6 Identify conditions for CSF evaluation and retreatment considerations.
- 7 Explain the evaluation of, treatment for, and follow-up of syphilis in pregnant women.
- 8 Describe the relationship between syphilis and HIV, and the management of syphilis in HIV infected persons.
- 9 Describe the management of sexual partners of persons infected with syphilis.

## 1.0 BIOLOGY

*Treponema pallidum* is a member of the family Spirochaetaceae. *T. pallidum* belongs to the genus *Treponema*, which also includes the pathogens *T. pertenue* (yaws), *T. carateum* (pinta), and *T. pallidum* var. *Bosnia* (Bejel - endemic syphilis).

***T. pallidum* is a tightly coiled, corkscrew-shaped microaerophilic bacterium** that is 6 - 20  $\mu\text{m}$  in length (average 10 -14, about the length of a white blood cell) and 0.4 - 0.75  $\mu\text{m}$  (average 0.5  $\mu\text{m}$ ) in width. **The organism is too thin to be observed by light microscopy.** Therefore, darkfield microscopy or electron microscopy is required to visualize the organism. *T. pallidum* **cannot be cultured in vitro**. It has been cultured in vivo most commonly by inoculating rabbits (RTT: rabbit infectivity testing).

## 1.1 PATHOGENESIS

The organism enters the body via skin and mucous membranes **through micro or macro abrasions**. The smaller the inoculum, the longer the incubation period.

- ä Some organisms lodge at the entry site, proliferate, sensitize lymphocytes and activate macrophages, resulting in the primary lesion or chancre developing at the site of inoculation.
- ä **The hematogenous spread of the organism occurs in 50% of persons 3 to 6 weeks after the appearance of the chancre.** Signs and symptoms of secondary syphilis are then present, and primary and secondary stages of syphilis may overlap. Clinically, generalized or localized rashes can occur along with mucosal lesions (see clinical manifestations on page 6). The eruptions or rashes may be mild or florid depending on the patient's immune response. Titers of serologic tests for syphilis are generally highest during that period. Patients are immune to reinfection, but cannot clear the infection without adequate treatment.
- ä Eventually, the host suppresses the infection enough so that no lesions are clinically apparent. This is called the latency period. The patient is immune to reinfection, but cannot clear the infection without adequate treatment. Immunity is lost after treatment.

The infection then remains asymptomatic in 60% to 85% of untreated patients. In some, the infection may progress to the tertiary stage within 1 to 20 years.

### NOTES:

## 1.2 EPIDEMIOLOGY

### INCIDENCE TRENDS IN THE USA

The rates of primary and secondary syphilis (P&S) are at their lowest level since reporting began in 1941. Rates of P&S have declined by 88% from 1990 to 1999.

Syphilis remains an important problem in the south and in some urban areas in other regions of the country. In 1999 large outbreaks occurred in several states and recently, outbreaks of syphilis in men who have sex with men have been reported.

Since syphilis rates are at the lowest levels ever seen in the US and the disease is concentrated in 28 counties (1% of total counties in the US), the CDC launched a national campaign to eliminate syphilis. With special funds assisting the areas with highest prevalence of disease, the CDC hopes to achieve the goals of <1000 cases of primary and secondary syphilis annually and >90% of counties syphilis-free by 2005 using the following strategies: enhanced surveillance, rapid outbreak response, expanded clinical and laboratory services, enhanced health promotion and strengthened community involvement and partnerships.

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### TRANSMISSION AND INCUBATION

Transmission of Treponema pallidum generally occurs by **sexual contact** with an acquisition rate of 40% after exposure to an infected person. Other means of transmission include **passage through the placenta (vertical transmission)**, kissing, transfusion of fresh blood, and direct inoculation such as by needlestick.

**Patients are most infectious early on** (during the stages of primary and secondary syphilis), and less so in the early latent stages (< 1 year duration). It may be possible to transmit the infection up to 4 years after initial acquisition.

The incubation period is between 9 and 90 days, with an average of 21 days.

#### KEY POINTS:

- Syphilis is not evenly distributed in US (50% of cases in 1% of counties, concentrated in southeast)
- Incubation period up to 90 days (average 21 days)
- Most infectious early in the disease (primary, secondary, early latent)



## 1.3 CLINICAL MANIFESTATIONS

Syphilis is characterized by episodes of active disease and by periods of latent infection. Early clinical manifestations primarily involve the skin and mucosal surfaces. Latent disease has no clinical signs or symptoms. Late manifestations may affect virtually any organ system. Primary and secondary stages are considered to be new or incident infections, whereas other stages are considered prevalent infections.

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### PRIMARY SYPHILIS

**Chancere:** Begins as a macule/papule which progressively erodes into a **clean based, painless, indurated ulcer** with smooth firm borders. It may be present at any site of inoculation. Extragenital chancres may be less easily recognized in areas such as the fingers, breasts, etc. Chancres involving the cervix, or rectum will often go undiagnosed. **Although usually singular, multiple chancres can occur in at least 25% of cases**, and are more common in HIV infected persons (up to 70% of cases in one study). Chancres will be unnoticed in 15-30% of patients. Spontaneous resolution, usually without scarring, occurs within 1 - 6 weeks (Generally three weeks or more).

Regional lymphadenopathy: **is classically painless**, discrete, **rubbery**, and bilateral.

Differential diagnosis: Herpes simplex virus infections, chancroid, granuloma inguinale (donovanosis), lymphogranuloma venereum (LGV), fixed drug eruption, trauma, furuncle, squamous cell carcinoma, HIV infection, Behcet's syndrome.

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### SECONDARY SYPHILIS

Symptoms occur generally 3-6 weeks after the primary stage.

Constitutional symptoms: malaise, fever, headache, anorexia, arthralgias, pharyngitis, myalgias. Hepatosplenomegaly may also be present, as well as a patchy alopecia (resolves with treatment) and loss of lateral portion of eyebrows.

Rash: The appearance may vary. Initially, it may be a very faint macular rash. It can be macular, papular, pustular, scaling, follicular or combination. It is generally nonpruritic. Palms and soles involved in 60% of cases. The eruptions or rashes may be mild or florid, depending on the patient's immune response.

#### KEY POINTS:

- Primary syphilis: painless, indurated ulcer; may be multiple in 25% of cases
- Secondary syphilis: rash, constitutional symptoms, condyloma lata, mucous patches, generalized adenopathy, etc.



Generalized lymphadenopathy: Is present in 86% of cases.

Mucous patches: Are present in 5 to 30% of cases. They are white flat patches with erythematous borders involving the mouth, pharynx, larynx and genitals.

Condyloma lata: Are present in 5 to 25% of cases. These are heaped, moist, wart-like papules that enlarge in warm intertriginous areas such as gluteal folds, nasolabial folds, axillae, between toes, under breasts, anus/vulva/scrotum, etc. These lesions are teeming with treponemes.

Signs and symptoms resolve spontaneously in 2-10 weeks, or may persist for months (up to 26 weeks). As previously stated, primary and secondary syphilis often overlap. Signs and symptoms of secondary syphilis can coexist with those of primary syphilis.

Differential diagnosis of cutaneous lesions: Ptyriasis rosea, measles, erythema multiforme, tinea, sarcoidosis, granuloma annulare, lichen planus, Rocky Mountain spotted fever, drug allergy, HIV infection, Hepatitis B, etc.

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## LATENT SYPHILIS

Is defined as the presence of a positive serology in the absence of evidence of clinical disease

early latent < 1 year duration

late latent > 1 year duration

A diagnosis of early latent syphilis should be made only if there is a documented seroconversion in the last year, unequivocal history of symptoms of primary or secondary syphilis in the last year, or if the patient had a sex partner with primary, secondary or early latent syphilis in the last year. All others should be considered to have syphilis of unknown duration, and should be treated as if they had late latent syphilis.

**Recurrence of symptoms of primary or secondary syphilis can occur in 25% of untreated cases**, usually within the first year after infection. 90% of relapses occur by the end of the first 12 months. "Chancre redux" (chancriform lesion) may recur at the site of the initial chancre. Cutaneous secondary lesions occur. **Patients are considered relatively noninfectious after 4 years**, and resistant to reinfection if untreated.

The latent stage can last 2 to 50 years.

### KEYPOINTS:

- Latent syphilis: defined as a positive serology in the absence of symptoms
- Early latent: infection of < 1 year duration, as evidenced by one of the following: documented seroconversion, unequivocal signs/symptoms of primary or secondary syphilis or sexual contact with case of primary, secondary or early latent syphilis
- Late latent: infection of > 1 year duration

## TERTIARY SYPHILIS

### A. LATE BENIGN SYPHILIS OR GUMMATOUS SYPHILIS

Granulomatous lesions, called gummas, are present in soft tissues, skeleton and viscera. These are the result of an immune response to treponemal antigens, and there is some debate as to whether treponemas are present in these lesions.

The "gumma" is felt to be a marked inflammatory response to a small number of organisms. Pathologically, it is a granuloma with coagulative necrosis. There can be involvement of any organ system, and lesions may occur in the skeletal, spinal, soft tissues (breasts), mucosal areas, as well as in the eye, viscera (lung, stomach, liver, heart) and the brain.

Skin: indurated nodular lesions, brownish red in color that may ulcerate.

Subcutaneous lesions: "the solitary gumma"

Upper respiratory tract: involvement may include the hard palate, nasal septum, oropharynx (pharyngitis with ulceration), larynx (hoarseness)

Gastro-intestinal tract: eosophagus (mistaken for carcinoma), hepatic gumma

The average onset is 4 to 12 years.

### B. CARDIOVASCULAR SYPHILIS

Predilection for the vasa vasorum of the proximal aorta, with development of endarteritis. All three layers of the aorta are affected. Luetic **aneurysms** most commonly involve the thoracic aorta and proximal ascending aorta. May present as aortic insufficiency. Dissections do not occur. Coronary artery disease occurs due to the obliteration of the coronary ostia by an endarteritis. Involvement is usually present only in the ostia or proximal portion of the arteries. **Aortic regurgitation** occurs in  $\frac{1}{3}$  of patients with cardiovascular syphilis and is due to dilatation of the aortic root. Cardiovascular syphilis is due to an ongoing inflammatory process. Organisms may not be present in tissue. **Antibiotic therapy is not helpful in the treatment of cardiovascular syphilis**, as the complications are due to degenerative changes. **However, treatment will prevent further complications of syphilis.**

NOTES:

Patients may present fifteen to thirty years after the acquisition of the initial infection. It can occasionally appear sooner, but the average onset is 15 years. This condition is now very rarely encountered.

### C. NEUROSYPHILIS :

Central nervous system involvement occurs early in infection. If syphilis is left untreated, clinical neurological manifestations may occur early or late in the course of the disease. The manifestations of neurosyphilis vary.

Asymptomatic neurosyphilis	31%	
Syphilitic meningitis	6%	
Meningovascular syphilis	10%	
General Paresis	12%	(Parenchymatous disease)
Tabes	30%	(Parenchymatous disease)
Mixed tabes/GP	3%	(parenchymatous disease)
Optic neuritis	3%	(Parenchymatous disease)
Deafness	1%	
Meningomyelitis and other spinal cord involvement	3%	
Gummatous lesions	1%	

*(Adapted from Holmes KK, Sexually Transmitted Disease, 1999; chapter 36, p.489)*

These data are taken from studies dating back to the mid century in the pre-penicillin era. Late manifestations may be less common nowadays because of screening and treatment early in the disease. Proportionately, acute presentations of neurosyphilis may be more common in recent years often coexisting with HIV infection (see ref #56).

**Note: Over 40% of early syphilis patients have treponemal invasion of the central nervous system.** Recent evidence suggests that this finding may not be very clinically significant, although the extent of its prognostic significance is not well known. It appears that conventional therapy is adequate to prevent sequelae, as evidenced by the rare occurrence of CNS manifestations following recommended treatment for early syphilis. According to a recent study (see reference # 53), the detection of *T. pallidum* in the CSF in early syphilis was not more common in HIV infected persons, apparently was not predictive of symptomatic neurosyphilis and was not linked to higher rates of serologically defined treatment failures.

#### NOTES:

The diagnosis of neurosyphilis can be difficult to make. Laboratory tests (other than the CSF VDRL) used in the diagnosis are nonspecific including an elevated cell count ( $>5$  WBC/mm<sup>3</sup>), or an elevated protein level ( $> 40$  mg/dL). The CSF VDRL is the standard serologic test for syphilis. When reactive in the absence of substantial blood contamination of the CSF, it is considered diagnostic of neurosyphilis. However, the CSF VDRL can be negative when neurosyphilis is present. In one study of neurosyphilis, the nontreponemal test was positive in only 50% of patients. Some experts recommend performing a CSF FTA-ABS. Although this test is not specific (false positives may occur), it is believed to be highly sensitive. A negative CSF FTA-ABS, according to some authorities, excludes neurosyphilis. Newer techniques are being applied to the diagnosis of neurosyphilis including the polymerase chain reaction (PCR), and various enzyme immunoassays for detecting IgG and IgM.

## SYPHILIS AND CONCOMITANT HIV INFECTION

Patients who are HIV infected represent a special challenge in the management of syphilitic infection. Alterations in the clinical manifestations, serologic responses, occurrence of complications and the efficacy of treatment regimens have been reported. Alterations in clinical manifestations include:

- A. Gummatous lesions reported involving skin, groin, penis, calf, thigh, oral cavity, and cerebrum.
- B. Lues maligna
- C. Increased incidence of ophthalmic involvement including uveitis, retinal necrosis, optic neuritis
- D. Increased incidence of otic syphilis
- E. Syphilitic gastritis
- F. Neurosyphilis - Reports suggest that HIV infected patients have early neurological involvement and a higher risk of developing neurosyphilis than HIV sero-negative patients, despite previous therapy for syphilis. Reports also suggest a more rapid progression of disease, with symptomatic neurosyphilis likely to occur sooner after infection in the HIV infected patient compared with the HIV sero-negative patient. This, however, was not documented in a recent prospective study, although lost to follow-up was close to 50% and the study followed patients for only 12 months. Syphilitic meningitis occurs more commonly in HIV infected patients. HIV infected patients are more likely to be younger, have higher CSF WBC count and higher CSF protein levels.

### KEYPOINTS:

- Treponemal invasion of CNS common in early syphilis, but most do not develop neurosyphilis
- Symptomatic neurosyphilis may occur at any stage of infection
- CSF VDRL not 100% sensitive, so must evaluate for CSF pleocytosis or increased protein

- G. A recent study demonstrated that HIV infected persons were more likely to have multiple ulcers in primary syphilis (70% vs 34% – see ref #53).

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## CONGENITAL SYPHILIS

Transmission of the infection to the fetus can occur before 18 weeks of gestation, in which case inflammation is absent. Pathogenesis may depend more on the immune response of the fetus than on the cytopathogenic effect of *T. pallidum*. **Adequate therapy of pregnant women during the first or second trimester is effective to treat the fetus in most cases.**

### Vertical Transmission (*Holmes KK et al, 1999*)

- Virtually **100% in untreated maternal primary and secondary syphilis**, resulting in 50% prematurity/perinatal death and 50% congenital syphilis.
- **80% in untreated maternal early latent syphilis**, resulting in 20% perinatal death, 20% prematurity and 40% congenital syphilis.
- **30% in untreated maternal late latent syphilis**, resulting in 11% perinatal death, 9% prematurity and 10% congenital syphilis.

Recent data suggests that untreated syphilis during pregnancy is a risk factor for vertical HIV transmission (see ref #53).

**Early congenital syphilis** (>2 years old): most syphilitic infants will lack manifestations at birth, but signs will appear within the third month of life. In  $\frac{2}{3}$  of cases, the signs will appear in the third to sixth week of life. **Neonates born with overt manifestations of syphilis at birth are usually severely affected and carry a worse prognosis. Lesions are usually inflammatory and exudative.** Hepatosplenomegaly is present in 50% of cases, generalized lymphadenopathy in 20% to 50% of cases, nasal discharge ("snuffles") in 20%, cutaneous lesions in 30% to 60%, skeletal involvement in 70% (osteochondritis, epiphysitis and periostitis). Hematologic abnormalities include anemia and thrombocytosis. 40 to 60% of syphilitic infants have abnormal CSF findings and 10% have overt meningitis.

**Late congenital syphilis (> 2 years old): lesions tend to be allergic and destructive.**

Interstitial keratitis is most common. Other manifestations include VIII nerve deafness, bone and teeth involvement (Hutchinson's incisors, mulberry molars, saber shins).

#### KEYPOINTS:

- Genital ulcerations are a risk factor in the development of HIV infection.
- An increased incidence of HIV infection has been noted in patients with syphilis and vice versa.
- **ALL patients with syphilis should be counseled on HIV infection, and HIV testing should be recommended. In addition, all patients who are HIV positive should be tested for syphilis.**



For more information on the clinical manifestations and management of congenital syphilis, consult ref #2, ch 84 and ref # 3

## 1.4 LABORATORY DIAGNOSIS

### DARKFIELD (DF) MICROSCOPY

**Provides a rapid and inexpensive definite diagnosis by direct visualization of *T. pallidum*.** Best means of diagnosis for primary (chancre) and secondary (condyloma lata, weeping cutaneous lesions) syphilis. It requires a **specialized microscope condenser** and an **experienced microscopist** because *T. pallidum* may be confused with other non pathogenic treponemes or artefacts. It must be performed immediately. *T. Pallidum* can be identified by its size (10-20 microns) and its mobility (corkscrew motion, pending and flaring at sharp angles). DF **cannot be used for oral lesions** because *T. pallidum* may be confused with a spirochete very similar in morphology, *T. denticola*, a nonpathogenic treponema often inhabiting the oral cavity.

Sensitivity of the DF will vary with the duration of the lesion, and is estimated to be at best 80%. The use of topical agents (soap, ointments) on the lesion interferes with interpretation (immobilized *T. pallidum*). **A negative DF does not exclude the diagnosis of syphilis.**

### DIRECT FLUORESCENT ANTIBODY-*T. PALLIDUM* (DFA-TP)

Identification of (*T. pallidum*) in direct lesion smear by immunofluorescent polyclonal antiserum. Reagent is adsorbed to remove most cross reactive antibody. It can be used for oral lesions and is commercially available. The test is only available in certain research laboratory. The monoclonal antibody test is not commercially available.

Although it compares favorably with DF, and does not require immediate processing, it currently has limited value in the clinical setting because of its limited availability and lack of immediate result.

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NOTES:



## SEROLOGICAL TESTING

### A. NONTREPONEMAL TESTS (VDRL, RPR)

**Detect a group of antibodies IgM and IgG (reagin) directed against the cardiolipin-lecithin-cholesterol antigen.** The reaction may be microscopic (Venereal Disease Research Laboratory test eg VDRL) or macroscopic (Rapid Plasma Reagin eg RPR). They **are not specific for *T. pallidum*** and their sensitivity varies with stage of infection.

Nontreponemal tests (RPR, VDRL) are used to screen for syphilis and assess response to treatment. A positive nontreponemal test must be confirmed with a treponemal test for a diagnosis of syphilis. After adequate treatment, 97% of patients with primary syphilis should have a negative RPR/VDRL within one year. The greater the duration of untreated disease (i.e. infection of more than 1 year), the greater the time needed to achieve seronegativity.

Are inexpensive, rapid, easy to perform, and can be done in the clinic (rapid RPR card test). These tests can be used for qualitative and quantitative assessments.

They are usually positive before the disappearance of the chancre, but may be negative early in primary syphilis.

**Biological false positives (BFP)** (positive nontreponemal test and negative treponemal test) occur, and are classified as acute (lasting for < 6 months) or chronic (lasting > 6 months). Although titers in BFP reactions are generally low (eg < 1:8), some may be higher. Over 10% of injecting drug users have BFP titers > 1:8.

**A prozone reaction** can occur if large amounts of antibody are present, which is often the case in secondary syphilis. Serum samples will test negative because the excess of antibody blocks the antigen-antibody reaction. This can occur in 1 to 2% of cases of 2<sup>nd</sup> syphilis. If this is suspected, the serum sample should be diluted and the test redone.

The same test (RPR or VDRL), and ideally done at the same laboratory, should be used to follow serologic titers. RPR titers are generally slightly higher than VDRL titers.

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## Potential Causes of False Positive Serologic Tests for Syphilis

### Nontreponemal tests (VDRL, RPR)

<p><b>Acute:</b> viral hepatitis infectious mononucleosis varicella measles, mumps viral pneumonia tuberculosis other viral infections immunizations pregnancy malaria bacterial infections chancroid, LGV mycoplasma pneumoniae rickettsial disease</p>	<p><b>Chronic:</b> HIV connective tissue disease lupus erythematosus injection drug use* aging leprosy malignancy multiple myeloma chronic liver disease multiple blood transfusions advanced cancer</p>
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\* A recent study demonstrated that only 20.5% of injecting drug users with a previous BFP reaction tested again BFP in subsequent visits (see ref #61)

### Treponemal Tests (FTA-ABS, MHA-TP\*)

In general, the MHA-TP gives fewer false positive results than the FTA-ABS

<p><b>Acute:</b> Lyme disease (FTA) malaria leprosy leptospirosis relapsing fever infectious mononucleosis non syphilis treponemal diseases yaws &amp; pinta</p>	<p><b>Chronic:</b> discoid lupus injecting drug use systemic lupus erythematosus</p>
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(Adapted from Hook EW, Carra CM. *Acquired Syphilis in Adults*, *NEJM* 1992; 326:1060-69 and Larsen et al. *Clin Microbiol Rev* 1995; 8: 1-20)

\*this data can most likely be applied to the TP-PA

#### KEYPOINTS:

- Nontreponemal tests: RPR, VDRL  
Nonspecific, must be confirmed by treponemal test  
Lack of sensitivity in primary syphilis
- Treponemal tests: FTA-ABS, TP-PA  
More specific, fewer false positives  
Often positive for life, so not to be used to assess response to Tx



### C. SEROLOGIC TESTS FOR SYPHILIS AND PREGNANCY

All pregnant women should be tested for syphilis at their first prenatal visit. It should be repeated in the third trimester and at delivery if the patient is at high risk or in communities or populations with a high syphilis prevalence.

Titers may increase slightly when serofast women who were previously adequately treated for syphilis become pregnant. It is generally less than a fourfold increase. Serologic response to treatment is the same as for non pregnant women.

The prozone phenomenon can occur in pregnancy, and request for dilution of sera should be made. No infant should be discharged from the hospital without the serological status of the mother being known.

### D. SEROLOGIC TESTS FOR SYPHILIS AND HIV INFECTION

**The vast majority of HIV infected patients will have nontreponemal and treponemal tests that are consistent with their HIV negative counterparts.**

A significant number of HIV infected patients may, however, have higher nontreponemal test titers than HIV negative patients which may reflect polyclonal activation of the immune system. On the other hand, false negative serologies have been occasionally reported in HIV-infected patients with clinical evidence of syphilis. In these cases, the sera should be evaluated for the prozone phenomenon, and darkfield examination of ulcerative or condylomatous lesions should be performed. If the diagnosis is still in doubt, biopsy of skin rashes or lesions should be considered.

Recent data suggests that HIV positive patients respond less well serologically and titers decline more slowly than the patients without HIV infection (ref # 53) but other studies suggest the response is similar in both groups (ref # 63). Whereas serologically-defined failure may occur in up to 20% of HIV+ patients, clinically-defined failure has been reported but is thought to be much less common. Factors potentially increasing the risk of failure include secondary stage and positive CSF VDRL (ref # 73). Although the nontreponemal test may decline more slowly in HIV-infected individuals, several studies report that seroreversion of the treponemal tests after treatment may be more common in HIV-infected patients, especially those with lower CD4 counts (ref. # 38, #63).

**NOTES:**



## NEW DIAGNOSTIC TECHNIQUES:

### A. ENZYME IMMUNOASSAYS (ELIA) FOR TREPONEMAL ANTIBODIES

The Captia Syphilis-G EIA is an indirect method for the detection of IgG antibodies to *Treponema pallidum*. CDC currently recommends that the test be used as a confirmation test for the diagnosis of syphilis, but it can be used as a screening test in blood banks. May be negative early in infection (2-3 weeks after acquisition) and less sensitive than the FTA-ABS in primary syphilis, but otherwise had comparable sensitivity with the MHA-TP or FTA-ABS (ref #58, 59, 66, 67) for all stages of untreated syphilis. Sensitivity was higher than the VDRL in latent syphilis.

### B. POLYMERASE CHAIN REACTION (PCR)

A multiplex PCR has been developed to test for *H. ducreyi*, HSV and *T. pallidum* in GUD. Limited data suggest that the test is over 90% sensitive for the detection of *T. pallidum* and very specific. However, not commercially available and use limited to epidemiologic typing studies. PCR appears to be sensitive to detect *T. pallidum* in the CSF, but has low specificity. Therefore, use of PCR in the diagnosis of neurosyphilis and its clinical management has not been standardized.

### C. WESTERN BLOT

The Treponemal Western Blot Test is a confirmation test for syphilis. It is not intended to be used for routine confirmation, but is reserved for situations where the clinical picture and other serological test results do not give a clear status of infection. Highest sensitivity and specificity in all stages of syphilis. The use of the IgM Western Blot for the diagnosis of congenital syphilis has not been standardized. May lack specificity. Results alone cannot be used to determine the status of a neonate.

## 1.5 INDICATIONS FOR CSF EVALUATION

- Any time clinical signs and symptoms of CNS and/or ophthalmic and otologic involvement are present (these can occur in early syphilis).
- Treatment failure.
- In syphilis of > 1 year duration or unknown duration if HIV Infection.
- Evidence of active tertiary syphilis (gummas, aortitis, iritis).

### NOTES:



## 1.6 TREATMENT FOR SYPHILIS

Penicillin levels of 0.03 IU/ml or 0.018 µg/ml are felt to be cidal for *T. pallidum*.

Consult the CDC 1998 Guidelines for Treatment of STDs for complete information.



**CDC RECOMMENDED TREATMENT FOR PRIMARY, SECONDARY AND EARLY LATENT (<1 YEAR'S DURATION) SYPHILIS**

### Non Allergic Adults

**Benzathine penicillin G 2.4 million units IM once.**

### Penicillin Allergic, Non Pregnant Adults

**Doxycycline 100 mg orally two times a day x 14 days**

or

**Tetracycline 500 mg orally four times a day x 14 days**

If compliance can be assured, a regimen of erythromycin 500 mg po qid for 14 days can be used as alternate, but it is less effective than the above recommended regimens. Overall, these regimens are less than optimal and efforts should be made to determine if history/records support true penicillin allergy.



**RECOMMENDED TREATMENT FOR EARLY LATENT SYPHILIS (<1 YEAR'S DURATION)**

### Non Allergic Adults

**Benzathine penicillin G, 2.4 million units IM in a single dose**

### Penicillin Allergic, Non Pregnant Adults

**Doxycycline 100 mg orally two times a day x 14 days**

or

**Tetracycline 500 mg orally four times a day x 14 days**

The Jarisch-Herxheimer reaction is an acute febrile reaction- often accompanied by headache, myalgia, and other symptoms- that might occur within the first 24 hours of any therapy for syphilis. Patients should be advised of this possible adverse reaction. The

**NOTES:**



Jarisch-Herxheimer reaction often occurs among patients who have early syphilis. Antipyretics may be recommended, but no proven methods prevent this reaction.



**RECOMMENDED TREATMENT FOR LATE LATENT SYPHILIS  
( > 1 YEAR'S DURATION ) OR SYPHILIS OF UNKNOWN DURATION**

**Non Allergic Adults**

**Benzathine penicillin G 2.4 million units IM weekly x 3 consecutive weeks**

Rule out tertiary disease in all patients with latent syphilis (neurosyphilis, aortitis, gummas, iritis) by history and clinical examination.

**Penicillin Allergic, Non Pregnant Adults Although not included in the guideline, some experts recommend that** the following medications should be given only after a lumbar puncture has been performed to rule out neurosyphilis.

**Doxycycline 100 mg orally two times a day x 28 days**

or

**Tetracycline 500 mg orally four times a day x 28 days**

If compliance can be assured, a regimen of erythromycin 500 mg po qid for 14 days can be used to alternate, but it is less effective than the above regimens. However, these regimens are less than optimal and efforts should be made to determine if history/records support true penicillin allergy.



**RECOMMENDED TREATMENT FOR NEUROSYPHILIS & OCULAR INFECTION**

**Non Allergic Adults**

**Aqueous Crystalline Penicillin G 18-24 million units IV daily, administered as 3-4 million units every 4 hours, for 10-14 days**

or (alternate regimen)

**Aqueous Procaine Penicillin 2.4 million units IM daily, plus  
Probenecid 500 mg PO QID, both x 10-14 days**

The durations of the recommended regimens for neurosyphilis are shorter than that of the regimen used for late syphilis in the absence of neurosyphilis. Therefore, some experts administer benzathine penicillin, 2.4 million units IM after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy. Some experts administer three doses one week apart.

**NOTES:**



Despite the use of this treatment regimen, patients with ocular infection should have a lumbar puncture (LP) performed to rule out neurosyphilis, as those patients with positive LP results would require follow-up LPs to assess adequacy of treatment.

### Penicillin Allergic Adults

**Penicillin with the above regimen is the only recommended treatment.** Patients should ideally be skin tested with both the major **and** minor penicillin determinants. Experts estimate that testing with only the major determinant and penicillin G (commercially available) detect 90% to 97% of the currently allergic patients. Testing without the minor determinants would miss 3% to 10% of allergic patients. If the full battery of skin-test reagents, including the minor determinants, is not available, the patient should be skin tested using penicilloyl (the major determinant, Pre-Pen) and penicillin G. Those with positive tests should be desensitized. Some experts consider that persons with negative tests to major determinants should be regarded as probably allergic, and be desensitized (since in 3% to 10% could be allergic only to the minor determinants). Others suggest that those with negative tests to major determinants can be test-dosed gradually with oral penicillin in a monitored setting in which treatment for anaphylactic reaction is possible.



### RECOMMENDED TREATMENT FOR SYPHILIS DURING PREGNANCY

**Penicillin remains the drug of choice in treating syphilis during pregnancy.**  
Erythromycin is not recommended because it does not reliably cure an infected fetus.

**Treatment should include the penicillin regimen appropriate for the stage of the syphilis as noted in the previous section.** Recent data demonstrates that such regimens are 98.2% successful for treatment of all stages of syphilis during pregnancy. However, the same study showed that a single dose of benzathine penicillin was significantly less effective in preventing congenital syphilis (94.6%,  $p=0.03$ ) among infants of women with secondary syphilis (see ref #69). For patients with primary, secondary, or early syphilis, the more aggressive regimen of benzathine penicillin 2.4 million units IM x 2 weeks should be considered.

### Penicillin allergic pregnant patients:

There is no alternate treatment for syphilis during pregnancy. Pregnant women with syphilis who have a history of allergy to penicillin should be treated with penicillin after desensitization. Skin testing may be helpful (see penicillin allergic adults box).

### NOTES:



The **Jarisch-Herxheimer Reaction** (self limited reaction to anti-treponemal therapy characterized by chills, fever and malaise) may result in premature labor or fetal distress if it occurs in the second half of the pregnancy. Stillbirth is a rare complication, and concern for this complication should not delay treatment. A recent study demonstrated that a Jarish-Herxheimer reaction occurred in 40% of treated syphilitic pregnancies, over half of whom experienced uterine contractions or fetal heart decelerations. In that study, the contractions were self-limited (less than 24 hours), and did not lead to any deliveries or fetal deaths, but patients should be instructed to contact their provider for prolonged contractions or decrease in fetal movement after treatment.



#### RECOMMENDED TREATMENT FOR CONGENITAL SYPHILIS

Refer to the complete 1998 CDC Treatment Guidelines for complete information (see general ref #3).



#### RECOMMENDED TREATMENT FOR SYPHILIS IN HIV INFECTED PERSONS

**The recommended treatment regimen for each stage of syphilis is the same for HIV infected and non infected persons**

Treatment failures with currently recommended regimens for syphilis have been reported in HIV infected patients. In addition, other reports suggest that HIV infected patients with early syphilis are at increased risk of neurologic complications. Thus, many experts recommend more aggressive therapy (such as three doses of penicillin benzathine 2.4 million units IM three weeks apart for early syphilis). However, a recent randomized clinical trial suggests that the magnitude of these risks is probably small, and no treatment regimen other than the ones recommended have been proven to more effective. **Therefore, close follow-up is warranted for all HIV infected persons treated for syphilis.**

The Jarisch-Herxheimer reaction is reported more frequently in HIV infected persons following treatment for early syphilis (26% vs 12%).

**NOTES:**

## 1.7 FOLLOW-UP

Nontreponemal tests are used for follow-up. The same nontreponemal test should be used each time. Variation in titers occurs when comparing the VDRL and the RPR (the RPR gives in general higher titers than the VDRL). The rate of decline of serology titers after adequate therapy and the rate of seroreversion after treatment of early syphilis is dependent on the duration of the disease, whether it was a repeat infection, and the level of the initial titer.

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### PRIMARY AND SECONDARY SYPHILIS

#### A. HIV NEGATIVE (OR STATUS UNKNOWN)

- ä Reexamine serologically and clinically at 6 and 12 months after therapy. More frequent and earlier reevaluations may be performed.
- ä Consider reinfection or treatment failure if signs and symptoms persist or fourfold increase in titers occur ⇒ assess for HIV infection ⇒ perform CSF exam if reinfection ruled out ⇒ retreat with 2.4 million units of IM benzathine penicillin weekly x 3 if no evidence of neurosyphilis.
- ä If titers fail to decrease fourfold after 6 months ⇒ assess for HIV infection ⇒ at minimum, additional follow-up every 6 months for up to 2 years or every 3 months if HIV infected ⇒ retreatment recommended if follow-up cannot be assured ⇒ some experts recommend CSF exam if titers fail to decline fourfold after 6 months.

#### B. HIV POSITIVE

- ä Reexamine serologically and clinically at 3, 6, 9, 12, and 24 months after treatment.
- ä Some experts recommend CSF exam 6 months after therapy (unproven benefit).
- ä CSF exam if treatment failure suspected (persistent signs and symptoms, fourfold increase in titers) or failure of titers to decrease fourfold after 6 to 12 months ⇒ retreat with 2.4 million units IM of benzathine penicillin x 3 if no neurosyphilis per CSF exam.

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#### KEY POINTS:

- **Penicillin** is the **only** recommended treatment for syphilis during **pregnancy**.
- Pregnant women infected with syphilis who are allergic to penicillin should be desensitized under observation in the hospital and treated with penicillin.

## LATENT SYPHILIS

### A. HIV NEGATIVE (OR STATUS UNKNOWN)

- ä VDRL or RPR at 6 months, 12 and 24 months
- ä A titer of >1:32 should fall 4-fold within 12-24 months
- ä Titers are often low, and a fourfold decrease may not occur (serofast)
- ä If titers increase fourfold, signs and symptoms of syphilis reappear or initially high titers (>1:32) fail to decline fourfold within 12 to 24 months ⇒ r/o neurosyphilis and retreat.

### B. HIV POSITIVE

- ä Reexamine serologically and clinically at 6, 12, 18 and 24 months after therapy.
- ä If titers fail to decrease fourfold between 12 and 24 months, clinical symptoms develop, or titers rise fourfold ⇒ perform LP ⇒ treat according to CSF results.

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## NEUROSYPHILIS

- ä If initial pleocytosis is present, CSF examination every 6 months until cell count is normal.
- ä If CSF cell count has not decreased after 6 months or if CSF is not entirely normal after 2 years (negative VDRL and normal protein level), consider retreatment.

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## PREGNANCY

- ä All pregnant patients are to be screened for syphilis at the first prenatal visit.
- ä VDRL or RPR repeated in the third trimester and at delivery
- ä Repeat monthly if high risk of reinfection or in areas with a high prevalence of syphilis
- ä Expect same response as non pregnant
- ä Assess and retreat as described above

### KEY POINTS:

#### RECOMMENDED FOLLOW-UP AFTER TREATMENT OF SYPHILIS (NON PREGNANT HIV NEGATIVE PATIENTS)

##### Primary and Secondary Syphilis

- VDRL or RPR at 6 and 12 months
- Fourfold drop in titers generally expected after 6 months

##### Latent Syphilis

- VDRL or RPR at 6, 12 and 24 months
- a titer of >1:32 should fall 4-fold within 12-24 months

## 1.8 PARTNER MANAGEMENT

### PARTNER(S) REQUIRING EVALUATION

- ä Exposed to patients with **primary syphilis** within the preceding **90 days** plus duration of symptoms
- ä Exposed to patients with **secondary syphilis** within the preceding **6 months** plus duration of symptoms
- ä Exposed to patients with **early latent syphilis** within the preceding **12 months**
- ä Exposed to patients with syphilis of **unknown duration with a high titer (>1:32)** within the preceding 12 months
- ä **Long term** sexual partners of patients with **late syphilis**

### PARTNER MANAGEMENT

- ä Persons exposed to primary, secondary, early latent syphilis, or latent syphilis of unknown duration with high titers (>1:32) **within the preceding 90 days should be tested for syphilis and treated presumptively** ( single dose of 2.4 million units of Benzathine penicillin)\*, as they may be seronegative when seen initially.
- ä Persons exposed to primary, secondary, early latent syphilis, or latent syphilis of unknown duration with high titers (>1:32) and exposed **> 90 days** before the examination **should be tested** and treated presumptively if the test is not available immediately and follow-up is uncertain.
- ä Long term sexual partners of persons with late syphilis and late latent syphilis should be evaluated clinically and serologically and treated based on the findings of the evaluation.

\*for patients who are allergic to penicillin doxycycline 100 mg twice a day orally for 7 days or azithromycin 1 gm single dose orally may be efficacious for treatment of incubating syphilis (ref #71, 74).

#### KEY POINTS:

#### RECOMMENDED FOLLOW-UP AFTER TREATMENT OF SYPHILIS: (CONT.)

##### Pregnancy

VDRL or RPR in the third trimester and at delivery, monthly if at high risk of reinfection or area of high prevalence of syphilis. Response should be the same as for non-pregnant persons.

##### HIV infection

VDRL or RPR at 3, 6, 19, 12 and 24 months for primary and secondary syphilis, and 6, 12, 18 and 24 months for latent syphilis.

Expect a fourfold decrease within 6 to 12 months for primary and secondary syphilis, and within 12 to 24 months for latent syphilis.

## 1.9 PREVENTION

- ã Abstinence.
- ã Sex with noninfected partners.
- ã Barriers such as condoms are relatively ineffective because they do not protect against all body secretions. Nevertheless, they should be employed as part of an overall educational program stressing sex with uninfected partners and monogamy.
- ã If there is a question of exposure, rapid evaluation by field and medical staff will help prevent the spread of syphilis.

## 1.10 REVIEW QUESTIONS

1. A pregnant patient (16 weeks) with an RPR of 1:8 and a positive MHA-TP, and no history of prior syphilis, reports a severe allergic reaction to penicillin. How would you manage this patient?

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2. A 27 year old male presents with a rash, malaise and myalgias. He reports multiple unprotected sexual contacts. The RPR is negative. What would be your next step in investigating this patient?

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**NOTES:**



# 1.11 FIGURES

Source: Division of STD Prevention. Sexually Transmitted Disease Surveillance, 1996. USDHHS, PHS. Atlanta: Centers for Disease Control and Prevention, September 1997, pp. 23, 24, 25, 27.

FIGURE 1. SYPHILIS – REPORTED CASES BY STAGES OF ILLNESS: UNITED STATES, 1941 - 1999

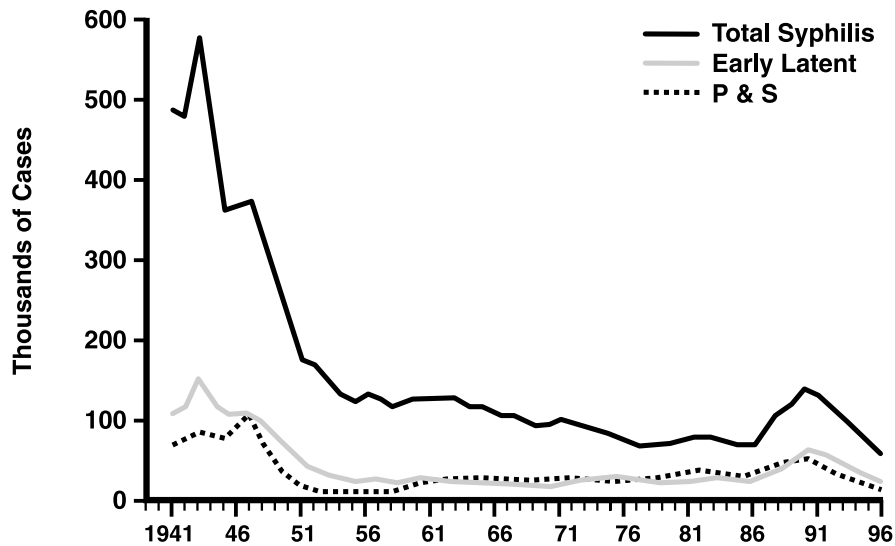
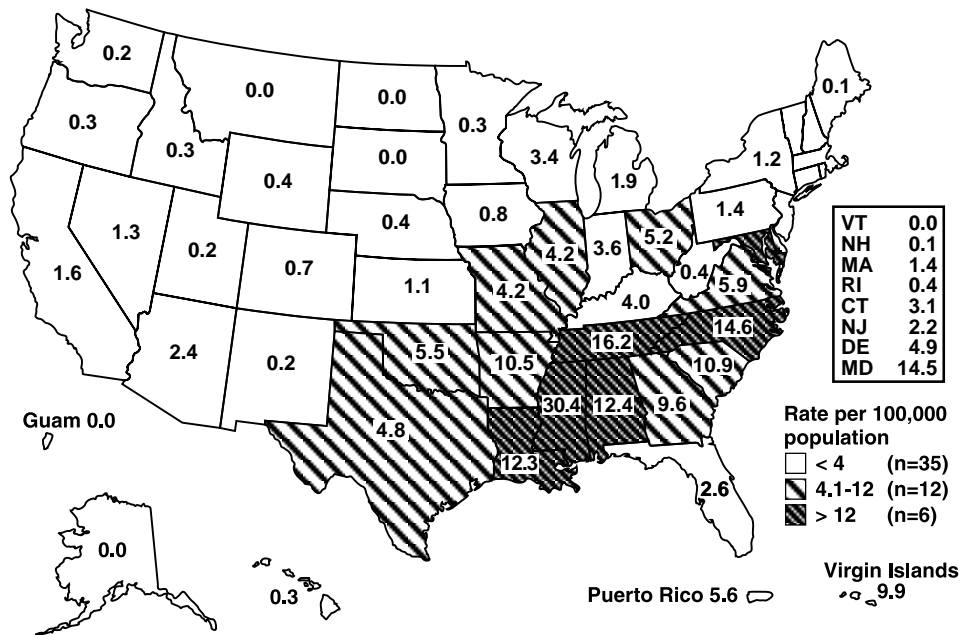
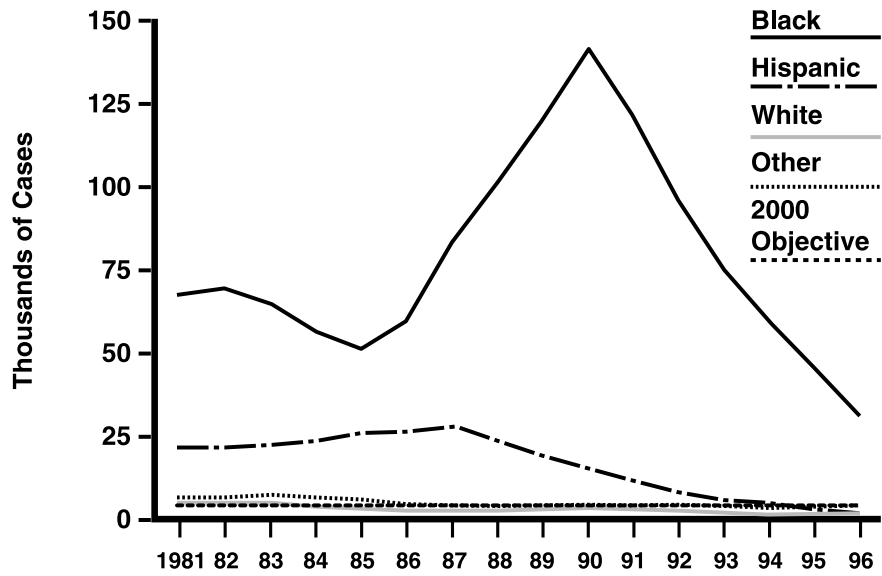


FIGURE 2. PRIMARY AND SECONDARY SYPHILIS – RATES BY STATE: UNITED STATES AND OUTLYING AREAS, 1999



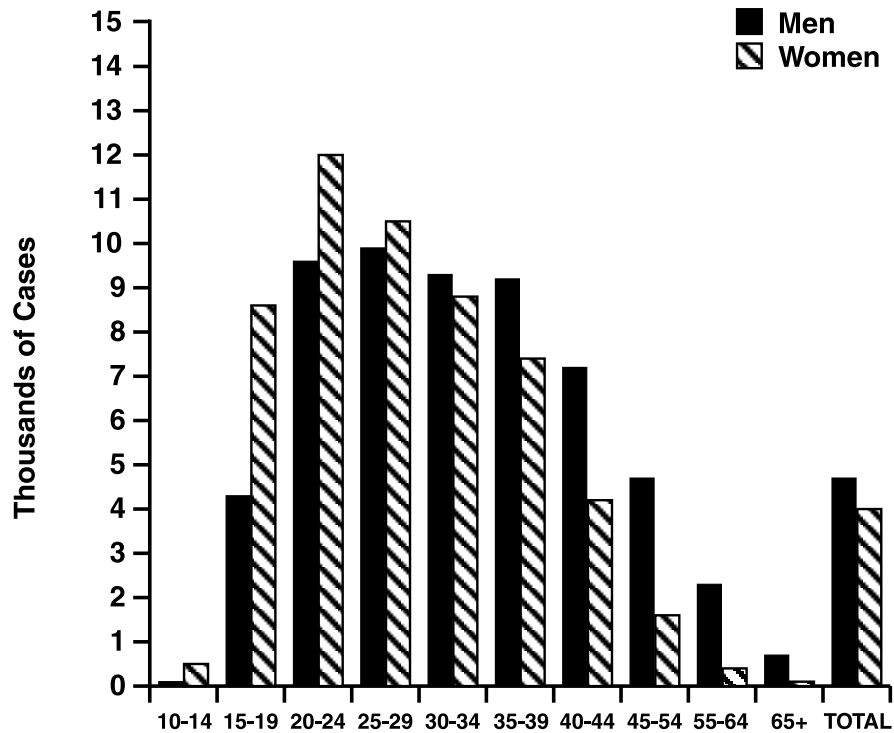
Note: The total rate of primary and secondary syphilis for the United States and outlying areas (including Guam, Puerto Rico and Virgin Islands) was 2.5 per 100,000 population. The Healthy People Year 2000 Objective was 4.0 per 100,000 population.

**FIGURE 3. PRIMARY AND SECONDARY SYPHILIS — RATES BY RACE AND ETHNICITY: UNITED STATES, 1981 - 1999 AND THE HEALTHY PEOPLE YEAR 2000 OBJECTIVE**



Note: "Other" includes Asian/Pacific Islander and American Indian/Alaskan Native populations.

**FIGURE 4. PRIMARY AND SECONDARY SYPHILIS — AGE AND GENDER SPECIFIC RATES: UNITED STATES, 1999**



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