Screening for Syphilis: Brief Update for the U.S. Preventive Services Task Force

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Background

Syphilis is a systemic infectious disease caused by sexual or congenital transmission of the bacterium *Treponema pallidum (T. pallidum).* Syphilis causes a variety of symptoms corresponding to stages of infection (primary, secondary, tertiary) and no symptoms during latent stages. Late-stage syphilis includes gummatous, cardiovascular, and neurological complications that can lead to significant disability and premature death. Syphilis is associated with HIV infection. Congenital syphilis results in fetal or perinatal death, as well as disease complications in surviving newborns.

Darkfield examinations and direct fluorescent antibody tests of lesion exudates or tissues are the definitive methods for diagnosing early syphilis; however, these approaches are insensitive and not widely available. A presumptive diagnosis is possible with the use of 2 types of serological tests for syphilis (nontreponemal and treponemal). Reactive nontreponemal tests require confirmation with a treponemal test.

1. Nontreponemal tests (venereal disease research laboratory [VDRL], rapid plasma reagin [RPR]). Sensitivity varies with the levels of antibodies present during the stages of disease and may be 78% to 86% in primary syphilis, 100% during secondary syphilis, and 95% to 98% in latent syphilis.[3] Specificity may be reduced in individuals who have preexisting conditions that produce false-positive reactions. Nontreponemal test titers usually decline or revert to normal after successful treatment, although not in everyone.[4]
2. Treponemal tests (fluorescent treponemal antibody absorbed [FTA-ABS], *T. pallidum* particle agglutination [TP-PA]). The FTA-ABS has a sensitivity of 84% in primary syphilis, and almost 100% in other stages, and a specificity of 96%.[5] Treponemal tests often remain reactive even after successful treatment.

Penicillin G is the recommended drug for treatment of syphilis at all stages. The preparation, dosage, and length of treatment depend on the stage and clinical manifestations of disease.[6] The efficacy of penicillin was well established in clinical practice before the use of randomized controlled trials (RCTs). Doxycycline is recommended if a patient is allergic to penicillin.

Previous USPSTF Recommendation

The USPSTF recommendation published in 1996 stated that routine serological screening for syphilis is recommended for all pregnant women

Systematic Evidence Reviews serve as the basis for U.S. Preventive Services Task Force (USPSTF) recommendations on clinical prevention topics. The USPSTF tailors the scope of these reviews to each topic. The USPSTF determined that a brief, focused evidence review was needed to assist in updating its 1996 recommendations on screening for syphilis.[1]

To assist the USPSTF, the Oregon Evidence-based Practice Center, under contract to the Agency for Healthcare Research and Quality (AHRQ), performed a targeted review of the literature from 1996 to 2003. This brief update and the updated recommendation statement[2] are available through the AHRQ Web site (www.preventiveservices.ahrq.gov), and in print through subscription to the *Guide to Clinical Preventive Services, Third Edition: Periodic Updates.* The subscription costs $60 and can be ordered through the AHRQ Publications Clearinghouse (call 1-800-358-9295, or e-mail ahrqpubs@ahrq.gov). The recommendation is also posted on the Web site of the National Guideline Clearinghouse™ (www.guideline.gov).

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and for persons at increased risk for infection (A recommendation).[1] Clinical considerations included:

- All pregnant women should be tested at their first prenatal visit. For women in high-risk groups, repeat serological testing is recommended in the third trimester and at delivery. Follow-up serological tests should be obtained to document decline initially after treatment. They should be performed using the same nontreponemal test initially used to document infections (eg, VDRL or RPR) to ensure comparability.
- Persons at increased risk because of high-risk sexual activities include commercial sex workers, persons who exchange sex for drugs, those with other sexually transmitted diseases (STDs) including HIV, and contacts of persons with active syphilis. The value of screening for asymptomatic infection in individuals outside these risk groups would depend on both individual risk factors, such as number of sexual partners, and local epidemiology. The optimal frequency for such testing has not been determined and is left to clinical discretion.

Recommendations were based on the rationale that existing screening tests are feasible for mass screening and detect syphilis with high accuracy and reliability, available treatments are effective and rarely harmful, and prenatal antibiotic therapy is effective in preventing congenital syphilis when the mother is treated early in pregnancy.

Methods

MEDLINE® was searched from 1996 to September 2003 (Appendix 1). References cited by expert reviewers were also included. Captured titles and/or abstracts were downloaded and imported into the EndNote® program to create a library. Titles and/or abstracts were dual-reviewed for inclusion or exclusion. Full-text articles were retrieved and reviewed using specific inclusion and exclusion criteria (Appendix 2).

Results

Five hundred and twenty-seven abstracts and titles were identified from the MEDLINE search; 89 full-text articles were retrieved for additional review: 71 from the MEDLINE search and 18 from experts and reference lists. In addition, a systematic review of antenatal screening in the U.K. was reviewed for this update.[7]

1. Is there new direct evidence that screening for syphilis reduces morbidity or mortality, the prevalence of congenital syphilis in neonates, or disease transmission?

A study evaluating the impact of mandatory universal serological testing in pregnant women and/or newborns at delivery was conducted in upstate New York.[8] All infants born after 22 weeks' gestation, including those that were nonviable, were tested at delivery using either umbilical cord or maternal blood specimens. All positive test results were reported within 24 hours, and each case was evaluated by reviewing medical records, laboratory reports, and interviews with physicians. After initiation of this program, there was a decrease in the proportion of infants with clinical manifestations of syphilis, and an increase in the proportion of infants with positive serologies but no symptoms ($P = 0.002$), suggesting improvement in detecting early cases that could be treated before the development of clinical disease.

2. Can high-risk groups and individuals be reliably identified?

No studies defined a set of risk factors and used them to guide selective screening for syphilis. Individual risks can be estimated to some extent by use of population prevalence data. Data on incidence and prevalence are most often based on cases reported to state health departments and summarized by the Centers for Disease Control and Prevention (CDC).[6] Reported rates likely underestimate true rates because STD screening and case reporting may be low in practice. A random sample of 7,300 physicians found that only 56% of respondents always reported syphilis to the health department when detected.[9]

Differences in reported rates by race and ethnicity may be magnified by differences in public and private sector reporting practices. In many

communities, the prevalence of reactive serology may not accurately reflect infectious syphilis because of unavailability of confirmatory tests.[6] Also, nationally reported data do not allow for analysis of trends among important subpopulations because information on sexual behavior, sexual partners, and risk factors for syphilis are not routinely collected or reported nationally.[10]

According to CDC data, rates of primary and secondary syphilis reported in the U.S. decreased during the 1990s, and in 2000 syphilis reporting rates were the lowest since reporting began.[6] In 2001, the number of cases reported increased by 2.1% from 2000 rates (to 6,103 reported cases) and was the first increase since 1990. This increase was evident only in men and was associated with outbreaks confined to several urban areas among men who have sex with men. These outbreaks were also associated with high rates of HIV co-infection and reported high-risk sexual behavior. From 2000 to 2001, the number of reported cases declined by 19.5% for women.

Rates for types of syphilis varied; reports of early-latent syphilis decreased by 8.1% between 2000 and 2001, while late and late-latent syphilis increased by 8.9%. The rate of congenital syphilis decreased by 20.7% between 2000 and 2001, from 14.0 to 11.1 cases per 100,000 live births; this decrease reflects the ongoing decline of rates among women.

High Prevalence Groups

Urban area outbreaks among men who have sex with men, associated with high rates of HIV co-infection and high-risk sexual behavior.[6,10] Following a 10-year decline, reported cases of primary and secondary syphilis in New York City doubled from 117 in the year 2000 to 282 in 2001. This increase was reported as having occurred primarily among men who have sex with men.[11] The rising rate of syphilis in this group of men was reported in other U.S. cities as well, including Seattle, Chicago, San Francisco, Los Angeles, and Miami.[11]

High rates of HIV co-infection were documented in each of these outbreaks, ranging from 20% to 73%.[11] In a study of men who have sex with men and have early syphilis, an HIV co-infection rate of approximately one-half was detected.[12] An analysis of 30 studies from 1985 to 1998, to assess HIV prevalence in U.S. patients with syphilis, reported a median HIV seroprevalence rate of 15.7% overall (women 12.4%, men 27.5%).[13] Among homosexual men, seroprevalence rates ranged from 64.3% to 90.0%.

Those who live in southern U.S. states. Although rates of reported syphilis decreased in the South from 2000 to 2001, the South continues to have a higher rate of syphilis (3.4 cases per 1,000) than any other region in the U.S., accounting for 56% of reported cases.[6]

African Americans. Although rates for African Americans declined 9.9% from 2000 to 2001, 62% of all reported cases were in African Americans, representing a rate 16 times greater than that reported in whites.

Persons in adult correctional facilities. Rates for incarcerated individuals vary by sex, with median rates of 8.7% among women (range 2.1%–22.2%) and 2.7% among men (range 0.3%–10.7%).[6] A study of syphilis screening in people who were arrested reported higher rates of syphilis among women charged with prostitution than for other crimes.[14] Another study reported seroprevalence rates of 11% for women tested in jails, compared with 3% among women tested in delivery rooms.[15]

Commercial sex workers, persons who exchange sex for drugs. Although these are known risk factors for syphilis infection, no new information was found about this group.

3. Is there new information on screening tests and methods?

Immunochromatographic strip (ICS). The ICS test for syphilis is intended to provide rapid serological testing for syphilis in non-laboratory settings to guide clinical decision-making. A prototype was tested in a blinded fashion on 353 sera from 157 patients to compare its performance to standard RPR and FTA-ABS tests.[16] ICS tests were interpreted and classified independently by 2 observers. The ICS test was found to be more sensitive than the RPR test, giving positive test results for a number of treated syphilis patients who

had non-reactive RPR tests but reactive FTA-ABS tests. The ICS was also non-reactive for 22 patients with biologically false-positive sera. ICS test reactivity did not appear to correlate with RPR titers.

Line immunoassay (LIA). The INNO-LIA syphilis, a multi-parameter LIA, is a new confirmatory test for treponemal antibodies. In a study of this test, 289 seronegative sera, 219 positive sera, and 23 sera with an indeterminate serological status for syphilis were analyzed.[17] All sera were classified as positive, negative, or indeterminate based on consensual diagnosis from conventional serology (*T. pallidum* hemagglutination assay [TPHA], FTA-ABS, VDRL), and results were compared with those from the INNO-LIA syphilis. The sensitivity and specificity of LIA were 100% and 99.3%, respectively. The LIA gave a significantly higher number of correct results than did the TPHA or FTA-ABS ($P = 0.021$; $P < 0.0001$, respectively).

Enzyme-linked immunosorbent assay (ELISA). The performance of an ELISA technique for detection of syphilis antibodies was evaluated in 441 samples.[18] The sensitivity and specificity of ELISA were 100% and 93% compared to TPHA, and 99.4% and 100% compared to the FTA-ABS test. ELISA showed 100% sensitivity compared to the FTA-ABS test for primary and secondary syphilis, 100% for latent syphilis, and 97.9% for patients treated with past syphilis.

RPR card and rapid syphilis test (RST). These tests were designed to screen for syphilis in clinical settings. This study compared results of clinic RPR and RST tests with standard laboratory RPR and TPHA tests in over 1,300 women presenting to clinics in Africa.[19] The clinic RPR test was 77.5% sensitive and 94.1% specific; the RST was 75% sensitive and 95.2% specific. The RST was easier to use and interpret.

Tests for central nervous system (CNS) syphilis infection in infants. A study evaluated methods of diagnosing CNS syphilis infection in 148 infants born to mothers with syphilis by comparing the results of rabbit-infectivity tests of the cerebrospinal fluid (CSF) with clinical, radiographic, and conventional laboratory evaluations (IgM immunoblotting of serum and cerebrospinal fluid; polymerase-chain-reaction [PCR] assay testing of serum or blood and CSF; and rabbit-infectivity testing of serum or blood).[20] Although most cases were identified by physical examination, conventional laboratory tests, and radiographic studies, CNS infection was best predicted by IgM immunoblotting of serum or PCR assay of serum or blood.

Placenta histopathology. A retrospective cohort analysis evaluated how placental pathology may contribute to the diagnosis of congenital syphilis in infants.[21] In this study, all pregnant women (with untreated syphilis) with placental evaluations who presented at a major metropolitan hospital labor and delivery unit were identified. Thirty-three stillborn fetuses (49%) and 18 live-born infants (27%) with congenital syphilis, 15 uninfected live-born infants (22%), and 1 uninfected stillborn fetus were diagnosed using study criteria. A continuum of histological findings in the placentas was related to the clinical spectrum of congenital syphilis. Performing histological evaluations of placentas, in addition to conventional diagnostic evaluations, improved the detection rate for congenital syphilis from 67% to 89% in live-born infants, and from 91% to 97% in stillborn fetuses.

Umbilical cord blood. Several studies mentioned the use of umbilical cord blood at delivery to screen for syphilis; however, none compared this with other methods of testing.

On-site testing with immediate results. The World Health Organization (WHO) Antenatal Trial Research Group conducted an RCT of clinics in 4 countries (Argentina, Cuba, Saudi Arabia, Thailand) to compare 2 models of care and describe the epidemiology of syphilis in pregnancy.[22] Of the 24,526 women recruited for the study, 12,568 were assigned into an intervention arm that provided on-site syphilis testing and immediate results among other services, and 11,958 were assigned into a usual-care arm that provided results 2 weeks after testing. Significantly more cases of syphilis were detected at the first prenatal visit and treated in clinics randomized to the intervention arm than the usual-care arm (1.0% vs 0.7%; $P = 0.03$).

In a clustered RCT among 7 pairs of primary health care clinics with over 7,000 women in South Africa, providing on-site testing for syphilis reduced treatment delays by an average of 16 days, but did not improve treatment rates or reduce perinatal mortality compared with usual laboratory-based testing.[23]

When to screen in pregnancy. Current recommendations for women in high-risk groups call for screening at the first prenatal visit, again during the third trimester (28 weeks), and at delivery.[1,6] New studies support this approach and point out missed opportunities in prenatal screening. However, there is a lack of data about how to identify high-risk groups.

Surveillance data collected for over 6 years in the U.S. indicated a case fatality ratio (stillborns and deaths/all causes) of 6.4%.[24] Untreated, inadequately treated, or undocumented treatment of syphilis during pregnancy accounted for 87% of reported cases. There was an inverse relationship between the number of prenatal care visits and risk for fatal outcomes. Among deaths, 52% of deliveries occurred by 30 weeks' gestation, supporting screening and treatment early in pregnancy. A study based in Georgia indicated that among cases of congenital syphilis, opportunities for earlier maternal screening, treatment, or diagnosis were missed in 60% of cases receiving timely prenatal care, and there was an inverse relationship between cases and number of prenatal care visits.[25] A study of the prevalence of congenital syphilis in an urban area of a low-incidence state indicated that only 56% of probable cases were evaluated adequately and 69% of them treated.[26]

Another surveillance study compared women who received antenatal treatment for syphilis and delivered infants with congenital syphilis with women who were treated and delivered non-infected infants.[27] High VDRL titers at treatment and delivery, earlier maternal stage of syphilis, shorter intervals from treatment to delivery, and delivery of an infant at 36 weeks' or less gestation were associated with an infected neonate despite maternal treatment.

4. What are the harms and costs of screening?

A study of the relationship stability of sexual partners found that 33% of partnerships dissolved after one partner was notified by a disease intervention specialist that the other partner had syphilis.[28] However, partnerships in which notification was not completed had a significantly higher rate of ending in this study (55%; $P < 0.05$). When multiple factors were analyzed to determine associations with the dissolution of the partnership, duration of partnership, but not disease status, was reported as a significant factor.

Two studies relating to cost were identified. One study focused on cost-effectiveness for detecting syphilis using either selective versus partner notification. When prophylactic treatment of sexual contacts was not considered, selective screening proved to be more cost-effective, while partner notification was more cost-effective if prophylactic treatment was taken into consideration.[29] A cost-effectiveness analysis in the U.K. evaluated possible screening-strategy options of an antenatal syphilis screening program. It concluded that the current universal antenatal screening program was more feasible and cost-effective than other screening options.[30]

5. Is there new information on the effectiveness of treatment?

Penicillin G. Penicillin G has long been an effective regimen for all stages of syphilis, and new trials focus on antibiotics that are easier to administer or are alternatives for penicillin-allergic individuals.

Azithromycin. Several small studies support the use of oral azithromycin for early-stage syphilis, although the studies use different doses and measure different outcomes. A study of the treatment of individuals exposed to a sexual partner with early-stage syphilis compared outcomes of a group given a single-dose of oral azithromycin with a group given a single benzathine penicillin G injection.[31] None of the patients in either group developed syphilis. A U.S. RCT[32] and a study conducted outside the U.S.[33] compared azithromycin and penicillin treatments in patients with early-stage syphilis and indicated similar serological and clinical responses in both groups. A non-comparative trial

of azithromycin in patients with primary, secondary, and early-latent syphilis reported serological non-reactivity in 86% after treatment.[34] Single dose oral azithromycin was used for high-risk individuals in a targeted mass treatment program during a syphilis outbreak in Vancouver, B.C. during 2000.[35] Cases dropped significantly during the 6 months following the intervention; however, a rebound occurred later that was attributed to reinfection.

Ceftriaxone. Although ceftriaxone has been considered an alternative to penicillin since the late 1980s, there is a lack of well-designed trials to support this. Nonetheless, it has been reported that ceftriaxone is used clinically for treating syphilis in the U.S.[36]

Value of augmented therapy. A multicenter RCT assessed 2 treatments for early syphilis: both groups received 2.4 million units of penicillin G benzathine and one group received an additional 10-day course of amoxicillin and probenecid.[37] The serological and clinical responses of patients with and without HIV infection were studied during 1 year of follow-up and found to be similar between both treatment groups.

Treatment in pregnancy. Little evidence is available to guide treatment in pregnancy. The CDC recommends using the penicillin regimen appropriate for the stage of syphilis, despite the lack of evidence to determine whether the specific recommended regimens are optimal for pregnancy.[6] The approach for women who are penicillin-allergic is to undergo desensitization because the alternative, doxycycline, is contraindicated in pregnancy. Although there is interest in using azithromycin and ceftriaxone in pregnant women, no clinical trials exist, and the only studies available concern pharmocokinetics.[38] Erythromycin is used for penicillin-allergic pregnant women in the U.K.[7]

6. What are the harms and costs of treatment?

No studies were identified that specifically described the harms and costs of treatment. Harms include drug-related effects including anaphylaxis from penicillin allergy. The Jarisch-Herxheimer reaction (febrile reaction with headache, myalgia, and other symptoms) could occur within the first 24 hours after any treatment for syphilis.

See Table 1 for a summary of the new evidence.

Conclusions

Screening for syphilis previously received an "A" recommendation from the USPSTF for pregnant women and individuals considered to be at high risk. The evidence for this recommendation was based on prevalence rates for individuals in risk groups, performance of screening tests, and clinical observations of treatment. New studies do not contradict this evidence.

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Table 1. Summary of New Evidence

Key Question	New Evidence
1. Is there new direct evidence that screening for syphilis reduces morbidity or mortality, the prevalence of congenital syphilis in neonates, or disease transmission?	After initiation of a mandatory screening program, there was a decrease in the proportion of infants with clinical manifestations of syphilis and an increase in the proportion of infants with positive serologies, but no symptoms suggesting improvement in detecting early cases.
2. Can high-risk groups and individuals be reliably identified?	No studies evaluated this question directly. New incidence and prevalence data indicate rising rates among men who have sex with men and declining rates among other demographic groups.
3. Is there new information on screening tests and methods?	New tests are being developed, particularly those related to on-site testing or improved testing in newborns.
4. What are the harms and costs of screening?	A cost study in the U.K. supports continued universal testing during pregnancy.
5. Is there new information on the effectiveness of treatment?	A number of small studies on alternative treatments such as oral azithromycin have been published and indicate comparable outcomes to penicillin treatment. These alternatives are not included in recent treatment recommendations of the CDC.
6. What are the harms and costs of treatment?	No new studies identified.

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Appendix 1
Search Strategies

Database: MEDLINE®
Dates: 1996 to September 2003

Syphilis Trials

1 syphilis.mp. or exp SYPHILIS/ (2504)
2 treponema pallidum.mp. (536)
3 1 or 2 (2682)
4 limit 3 to (human and English language and yr=2002–2003) (370)
5 limit 4 to (clinical trial or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or review) (54)
6 4 not 5 (316)
7 from 5 keep 1–54 (54)

Syphilis Not Trials

1 syphilis.mp. or exp SYPHILIS/ (2504)
2 treponema pallidum.mp. (536)
3 1 or 2 (2682)
4 limit 3 to (human and English language and yr=2002–2003) (370)
5 limit 4 to (clinical trial or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or review) (54)
6 4 not 5 (316)
7 from 5 keep 1–54 (54)
8 from 6 keep 1–316 (316)

Syphilis in Newborns

1 syphilis.mp. or exp SYPHILIS/ (2523)
2 treponema pallidum.mp. (539)
3 1 or 2 (2703)
4 limit 3 to (human and English language and all infant <birth to 23 months> and yr=1996–2002 and (clinical trial or guideline or meta analysis or multicenter study or practice guideline or review)) (33)
5 from 4 keep 1–33 (33)

Syphilis in Pregnancy

1 syphilis.mp. or exp SYPHILIS/ (2523)
2 treponema pallidum.mp. (539)
3 1 or 2 (2703)
4 exp Mass Screening/ or screen$.mp. (96999)
5 exp pregnancy/ or exp pregnancy complications/ or exp infant/ or fetus.mp. or fetal.mp. or disease transmission, vertical/ (252912)
6 3 and 4 and 5 (148)
7 limit 6 to (human and English language and yr=1996–2002) (124)
8 from 7 keep 1–124 (124)

Appendix 2
Inclusion and Exclusion Criteria for Articles

Code	Include or Exclude	Reason
1	Include	RCT of screening
2	Include	High-risk group or individuals (unselected pop, relevant to primary care)
3	Include	Harms of screening (unselected pop, relevant to primary care)
4	Include	Harms of treatment (unselected pop, relevant to primary care)
5	Include	Health outcomes, prevalence of congenital syphilis
6	Exclude	No valid comparison group
7	Exclude	Not an unselected pop, not relevant to primary care
8	Exclude	Not an RCT
9	Exclude	No health outcomes described
10	Exclude	Not relevant to key question
11	Pending	Relevant background information
12	Pending	Relationship between syphilis and HIV

RCT, randomized controlled trial; pop, population.

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