US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Syphilis Infection in Nonpregnant Adults and Adolescents

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force (USPSTF)

IMPORTANCE In 2014, 19 999 cases of syphilis were reported in the United States. Left untreated, syphilis can progress to late-stage disease in about 15% of persons who are infected. Late-stage syphilis can lead to development of inflammatory lesions throughout the body, which can lead to cardiovascular or organ dysfunction. Syphilis infection also increases the risk for acquiring or transmitting HIV infection.

OBJECTIVE To update the 2004 US Preventive Services Task Force (USPSTF) recommendation on screening for syphilis infection in nonpregnant adults. Screening for syphilis in pregnant women was updated in a separate recommendation statement in 2009 (A recommendation).

EVIDENCE REVIEW The USPSTF reviewed the evidence on screening for syphilis infection in asymptomatic, nonpregnant adults and adolescents, including patients coinfected with other sexually transmitted infections (such as HIV).

FINDINGS The USPSTF found convincing evidence that screening for syphilis infection in asymptomatic, nonpregnant persons at increased risk for infection provides substantial benefit. Accurate screening tests are available to identify syphilis infection in populations at increased risk. Effective treatment with antibiotics can prevent progression to late-stage disease, with small associated harms, providing an overall substantial health benefit.

CONCLUSIONS AND RECOMMENDATION The USPSTF recommends screening for syphilis infection in persons who are at increased risk for infection. (A recommendation)

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The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendation and Evidence

The USPSTF recommends screening for syphilis infection in persons who are at increased risk for infection. (A recommendation) (**Figure 1**)

See the Clinical Considerations section later in this article for information on risk factors for infection.

Rationale

Importance

The number of cases of primary and secondary syphilis have been increasing since 2000. In 2014, 19 999 cases (6.3 cases per 100 000 persons) of primary and secondary syphilis were reported in the United States.[1] Left untreated, syphilis can progress to late-stage disease in approximately 15% of persons who are infected.[2] Consequences of late-stage syphilis include development of inflammatory lesions throughout the body (eg, aortitis, gummatous lesions, and osteitis), which can lead to cardiovascular or organ dysfunction. Syphilis infection of the central nervous system (neurosyphilis) can occur at any stage of disease and can result in blindness, paresis, tabes dorsalis, and dementia. Syphilis infection also increases the risk for acquiring or transmitting HIV infection.

The USPSTF addresses screening for syphilis in pregnant women in a separate recommendation statement.[3]

Figure 1. US Preventive Services Task Force Grades and Levels of Certainty

What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies. inconsistency of findings across individual studies. limited generalizability of findings to routine primary care practice. lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the limited number or size of studies. important flaws in study design or methods. inconsistency of findings across individual studies. gaps in the chain of evidence. findings not generalizable to routine primary care practice. lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.
The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.	

Detection

There are numerous screening tests for syphilis. Most common is a combination of nontreponemal and treponemal antibody tests. The USPSTF found convincing evidence that screening algorithms with high sensitivity and specificity are available to accurately detect syphilis.

Benefits of Early Detection and Treatment

The USPSTF found convincing evidence that treatment with antibiotics can lead to substantial health benefits in nonpregnant persons who are at increased risk for syphilis infection by curing syphilis infection, preventing manifestations of late-stage disease, and preventing sexual transmission to others.

Harms of Early Detection and Treatment

The USPSTF found no direct evidence on the harms of screening for syphilis in nonpregnant persons who are at increased risk for infection. Potential harms of screening include false-positive results that require clinical evaluation, unnecessary anxiety to the patient, and the potential stigma of having a sexually transmitted infection. The harms of antibiotic treatment are well established, and the magnitude of these harms is no greater than small.

USPSTF Assessment

The USPSTF concludes with high certainty that the net benefit of screening for syphilis infection in nonpregnant persons who are at increased risk for infection is substantial.

Figure 2. Screening for Syphilis Infection in Nonpregnant Adults and Adolescents: Clinical Summary

Population	Asymptomatic, nonpregnant adults and adolescents at increased risk for syphilis infection
Recommendation	Screen for syphilis infection. Grade: A

Risk Assessment	Men who have sex with men and persons living with HIV have the highest risk for syphilis infection. Other factors that are also associated with increased prevalence rates include a history of incarceration or commercial sex work, geography, race/ethnicity, and being a male younger than 29 years.
Screening Tests	There are numerous screening tests for syphilis. The most common is a combination of nontreponemal and treponemal antibody tests.
Treatment and Interventions	Syphilis infection is treated with parenteral penicillin G benzathine. Dosage and route may vary depending on the stage of disease and patient characteristics.
Balance of Benefits and Harms	The USPSTF concludes with high certainty that the net benefit of screening for syphilis infection in nonpregnant persons at increased risk for infection is substantial.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on screening for syphilis in pregnant women, as well as screening for HIV, gonorrhea, and chlamydia in sexually active adolescents and adults and behavioral counseling interventions to prevent sexually transmitted infections. These recommendations are available on the USPSTF website (http://www.uspreventiveservicestaskforce.org).

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to http://www.uspreventiveservicestaskforce.org.

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JAMA

Clinical Considerations

Patient Population Under Consideration

This recommendation applies to asymptomatic, nonpregnant adults and adolescents who are at increased risk for syphilis infection (**Figure 2**). Screening for syphilis in nonpregnant populations is an important public health approach to preventing the sexual transmission of syphilis and subsequent vertical transmission of congenital syphilis.

Assessment of Risk

The USPSTF recommends screening for syphilis in persons who are at increased risk for infection. Based on 2014 surveillance data,[1] men who have sex with men (MSM) and men and women living with HIV have the highest risk for syphilis infection; 61.1% of cases of primary and secondary syphilis occurred among MSM, and approximately one-half of all MSM diagnosed with syphilis were also coinfected with HIV. One study found that rates of syphilis coinfection were 5 times higher in MSM living with HIV compared with men living with HIV who do not have sex with men.[4] Based on older study data from northern California, the adjusted relative risk for syphilis infection in persons living with HIV (vs those without HIV) was 86.0 (95% CI, 78.6-94.1); 97% of those living with HIV and with incident syphilis were male.[5]

When deciding which other persons to screen for syphilis, clinicians should be aware of the prevalence of infection in the communities they serve, as well as other sociodemographic factors that may be associated with increased risk of syphilis infection. Factors associated with increased prevalence that clinicians should consider include history of incarceration, history of commercial sex work, certain racial/ethnic groups, and being a male younger than 29 years, as well as regional variations that are well described. Men accounted for 90.8% of all cases of primary and secondary syphilis in 2014. Men aged 20 to 29 years had the highest prevalence rate, nearly 3 times higher than that in the average US male population.[1] Syphilis prevalence rates are also higher in certain racial/ethnic groups (among both men and women); in 2014, prevalence rates of primary and secondary syphilis were 18.9 cases per 100 000 black individuals, 7.6 cases per 100 000 Hispanic individuals, 7.6 cases per 100 000 American Indian/Alaska Native individuals, 6.5 cases per 100 000 Native Hawaiian/Pacific Islander individuals, 3.5 cases per 100 000 white individuals, and 2.8 cases per 100 000 Asian individuals.[1] The southern United States comprises the largest proportion of syphilis cases (41%); however, the case rate is currently highest in the western United States (7.9 cases per 100 000 persons). Metropolitan areas in general have increased prevalence rates of syphilis.[1] Risk factors for syphilis often do not present independently and may frequently overlap. In addition, local prevalence rates may change over time, so clinicians should be aware of the latest data and trends for their specific population and geographic area.

Although direct evidence on screening among nonpregnant persons who are not at increased risk for syphilis infection is lacking, based on the established test performance characteristics of current screening tests and the low prevalence rate of syphilis in this population, the yield of screening is likely low. Therefore, screening in this population may result in high false-positive rates and overtreatment.

Screening Tests

Current screening tests for syphilis rely on detection of antibodies rather than direct detection of the organism. Screening for syphilis infection is a 2-step process involving an initial nontreponemal test (Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] test) followed by a confirmatory treponemal antibody detection test (fluorescent treponemal antibody absorption [FTA-ABS] or *Treponema pallidum* particle agglutination [TP-PA] test). A reverse sequence screening algorithm has been developed in which an automated treponemal test (such as enzyme-linked, chemiluminescence, or multiplex flow immunoassays) is performed first, followed by a nontreponemal test. If the test results are discordant in the reverse sequence algorithm, a second treponemal test (preferably using a different treponemal antibody) is performed.[6] There is limited evidence on the accuracy of screening using the reverse sequence algorithm. Findings from 2 studies suggest that using a reverse sequence algorithm may detect additional cases of syphilis missed by the usual algorithm.[7] However, the clinical significance of these additional cases is unclear, and more studies are needed to better understand the implications of using a reverse sequence algorithm for screening in a primary care setting. Newer screening technologies that include rapid syphilis tests are also currently emerging. These tests have the potential to be performed in nontraditional and nonclinical settings; however, more evidence is needed on the effectiveness of these tests as part of a screening program in a primary care setting.

Screening Intervals

The optimal screening frequency for persons who are at increased risk for syphilis infection is not well established. Men who have sex with men or persons living with HIV may benefit from more frequent screening. Initial studies suggest that detection of syphilis infection in MSM or persons living with HIV improves when screening is performed every 3 months compared with annually.[7]

Treatment

In its 2015 guidelines on the treatment of sexually transmitted diseases, the Centers for Disease Control and Prevention (CDC) recommends parenteral penicillin G benzathine for the treatment of syphilis. Dosage and route may vary depending on the stage of disease and patient characteristics. To obtain the most up-to-date information, clinicians are encouraged to access the CDC website.[8]

Additional Approaches to Prevention

Public health agencies and local health departments have a critical role in the prevention and treatment of syphilis. Local health departments are often responsible for investigating incident cases of syphilis and identifying potential contacts who may need further testing or treatment. Primary care clinicians should be aware of applicable local public health laws and reporting requirements for syphilis cases.

Useful Resources

Persons who are at risk for or have been diagnosed with syphilis infection may engage in behavior that increases their risk for other sexually transmitted infections. The USPSTF has made a separate recommendation on screening for syphilis in pregnant women, as well as screening for HIV, gonorrhea, and chlamydia in sexually active adults and adolescents and behavioral counseling interventions to prevent sexually transmitted infections (available at http://www.uspreventiveservicestaskforce.org).

Other Considerations

Implementation

Although testing for syphilis in persons living with HIV may be part of HIV management care provided in a specialty setting, screening for syphilis is often conducted in primary care settings, and primary care clinicians are encouraged to routinely screen their patients who are living with HIV.

Research Needs and Gaps

Studies are needed that directly evaluate the effectiveness of screening for syphilis on related morbidity and mortality in other high-risk populations, in addition to MSM and persons living with HIV, as well as studies that help identify optimal screening intervals. Studies in adolescent populations are particularly needed. In addition, studies that evaluate the effectiveness of risk assessment instruments or other methods to identify persons who are at increased risk and who may benefit from screening are needed. Further, studies on the diagnostic accuracy of reverse sequence screening algorithms in well-defined patient populations are needed, as well as studies on the interpretation and management of discrepant serology results (such as a positive automated treponemal test, negative nontreponemal test, and positive second treponemal test).

Discussion

Burden of Disease

Syphilis is a chronic, systemic infectious disease caused by the bacterium *T pallidum*. Left untreated, syphilis can progress through the following stages: primary, secondary, latent (early and late), and tertiary disease. Syphilis infection of the nervous system (neurosyphilis) can occur at any stage. Although not always present or noticed by patients, manifestations of primary syphilis include ulcers or a single chancre at the infection site. Manifestations of secondary syphilis include rash, mucocutaneous lesions, and lymphadenopathy. Manifestations of tertiary syphilis include inflammatory lesions of the cardiovascular system (eg, aortitis or coronary vessel disease), skin (eg, gummatous lesions), bone (eg, osteitis), or other tissue. Rarely, other structures may be involved. Manifestations of early neurosyphilis include cranial nerve dysfunction, meningitis stroke, acute altered mental status, and auditory or ophthalmic abnormalities; late neurologic manifestations include tabes dorsalis and general paresis and can occur 10 to 30 years after initial infection.[9] Syphilis can be sexually transmitted during the early stages of infection (primary, secondary, and early-latent syphilis); reported transmission rates range from 15.9% to 30.3%.[10,11] Congenital or vertical transmission may occur at any stage. Syphilis infection increases the risk for acquiring or transmitting HIV if exposed[1]; among persons living with HIV, syphilis infection is associated with a subsequent increase in HIV viral load and decrease in CD4 cell counts.[12-14]

In 2014, the total number of syphilis cases reported for all stages (including 458 cases of congenital syphilis) and all ages in the United States was 63 450, which is a 12.3% increase from the previous year. The case count (19 999 cases) and case rate (6.3 cases per 100 000 persons) of primary and secondary syphilis were the highest reported since 1994. All but 24 cases occurred in persons 15 years and older. Among men, the rate of primary and secondary syphilis has increased every year since 2000; however, among women, the rate of primary and secondary syphilis has fluctuated between 0.8 and 1.7 cases per 100 000 since 2000. During 2013-2014, the rate among men increased 14.4%, from 10.2 to 11.7 cases per 100 000; among women, the rate increased 22.7%, from 0.9 to 1.1 cases per 100 000.[1] The majority of cases of primary and secondary syphilis still occur among MSM. In 2014, there were 23 541 cases (7.4 cases per 100 000 persons) of late and late-latent syphilis.[1] More recently, the CDC has reported an increase in cases of ocular syphilis, with more than 200 cases reported in 20 states since 2014, the majority of which have been among MSM living with HIV.[15]

Scope of Review

The USPSTF commissioned a systematic review[7,16] of studies published since it previously reviewed the evidence on this topic in 2004.[17] The USPSTF also considered evidence from its previous evidence review. Included studies had to be applicable to the United States, as determined by the similarity of study participants and availability of health care services and screening tests in the study setting. The review focused on screening for syphilis infection in asymptomatic, nonpregnant adults and adolescents, including patients coinfected with other sexually transmitted infections (such as HIV).

Accuracy of Screening Tests

Screening for syphilis is usually a 2-step process. A nontreponemal test (RPR or VDRL) is performed first, followed by a treponemal test (TP-PA or FTA-ABS) if the first nontreponemal test result is positive. Positive results on both tests indicate past or present syphilis infection. Estimated sensitivities of the RPR and VDRL tests are 86% and 78%, respectively, for detecting primary syphilis infection; 100% for detecting secondary syphilis infection; and 98% and 96% for detecting latent syphilis infection, respectively.[7] Specificity ranges from 85% to 99% and may be reduced in persons who have a preexisting condition (ie, collagen vascular disease, pregnancy, intravenous drug use, advanced malignancy, tuberculosis, malaria, or viral and rickettsial diseases) that may produce false-positive results.[7] The TP-PA and FTA-ABS tests have a sensitivity of 88% and 84%, respectively, for detecting primary syphilis infection and almost 100% for detecting other stages and a specificity of 96% to 97%, respectively.[7]

Screening yield using the 2-step process (RPR followed by confirmatory FTA-ABS) can be estimated using test characteristics and the incidence of syphilis infection in a given population. For example, in the general population (assuming prevalence of 5 cases per 100 000 persons, RPR sensitivity of 91% and specificity of 95%, and FTA-ABS sensitivity of 92% and specificity of 96%), more than 24 000 patients would have to be screened to detect a single case of syphilis infection; further, 200 per 100 000 persons screened would have false-positive results. In a high-risk population (assuming prevalence of 12%, RPR sensitivity of 91% and specificity of 95%, and FTA-ABS sensitivity of 92% and specificity of 96%), 10 patients would have to be screened to detect a single case of syphilis infection; almost 2000 per 100 000 persons screened would have false-negative results.[7]

More recently, automated treponemal tests have been developed, including enzyme-linked, chemiluminescence, and multiplex flow immunoassays. Reported sensitivity ranges from 64% to 100% (depending on stage of disease and type of test used), and specificity ranges from 95.4% to 99.9%.[7] These automated treponemal tests are often used in a reverse sequence screening algorithm, in which an automated treponemal test is performed first, followed by a nontreponemal test (quantitative) if the first automated treponemal test result is positive. A positive result on both the automated treponemal and the nontreponemal test indicates past or present syphilis infection. If the result of the automated treponemal test is positive but the nontreponemal test result is negative, a second treponemal test (TP-PA, FTA-ABS, or other) is performed; a positive result on the second treponemal test indicates past or present syphilis infection.[6] The USPSTF reviewed 2 studies that compared a reverse sequence screening algorithm with the traditional 2-step approach to screening.[18,19] One study was conducted in a low-prevalence US population[19] and the other in a high-prevalence metropolitan area in Canada.[18] Although both studies found that more cases were detected using the reverse sequence algorithm, use of the reverse sequence algorithm was associated with a higher false-positive rate. Overall, more studies on the reverse sequence screening algorithm are needed before definitive conclusions can be made on its effectiveness.

Effectiveness of Early Detection and Treatment

Based on CDC data,[1] MSM and persons living with HIV are at highest risk for syphilis infection. In 2014, the majority of cases (61.1%) of primary and secondary syphilis occurred among MSM, and approximately one-half of all MSM diagnosed with syphilis were also coinfected with HIV. Increased prevalence of syphilis infection was also associated with certain racial/ethnic groups (black, Hispanic, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander individuals had higher prevalence rates than white individuals, ranging from 6.5 to 18.9 vs 3.5 cases per 100 000 persons), geography (southern and western United States and metropolitan areas), and being a male younger than 29 years.[1]

The USPSTF found no recent studies on the direct effectiveness of screening for syphilis in asymptomatic, nonpregnant adults and adolescents to reduce complications or transmission of syphilis infection or acquisition of other sexually transmitted infections. Older clinical trials and observational studies and almost 50 years of clinical experience provide evidence that penicillin is effective in the treatment of syphilis infection.[9] Penicillin G has long been an effective and accepted regimen for the treatment of all stages of syphilis infection, and new trials are focusing on antibiotics that are easier to administer or are alternatives for patients who are allergic to penicillin. Data on these alternative regimens are limited.[9] Given the well-documented risk factors associated with increased prevalence of syphilis infection and the availability of accurate screening tests and treatment, the USPSTF found overall that screening for syphilis infection in persons who are at increased risk for infection is effective.

Potential Harms of Screening and Treatment

No studies directly evaluated the harms of screening. Potential harms of screening include opportunity costs to the clinician and patient (eg, time and resources) and false-positive results that may lead to stress, labeling, and further diagnostic workup. Harms of treatment include rare adverse drug-related effects, such as anaphylaxis due to penicillin allergy and the Jarisch-Herxheimer reaction (febrile reaction with headache, myalgia, and other symptoms), which may occur within the first 24 hours after any syphilis therapy.[9]

Estimate of Magnitude of Net Benefit

Overall, the USPSTF found convincing evidence that screening for syphilis infection in asymptomatic, nonpregnant persons who are at increased risk for infection provides substantial benefit. Accurate screening tests are available to identify syphilis infection in populations at increased risk. Effective treatment with antibiotics can prevent progression to late-stage disease, with small associated harms, providing an overall substantial health benefit.

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from December 15, 2015, to January 18, 2016. A few comments sought clarification on which populations were considered to be at increased risk. The USPSTF added language to the Clinical Considerations section to clarify that men and women living with HIV who are not MSM are considered to be at increased risk for syphilis. In addition, men and women (and not just young men) who have identified sociodemographic risk factors associated with increased prevalence rates of syphilis may be considered at increased risk as well. In response to public comments, the USPSTF provided updated surveillance data from 2014. A few comments also requested additional information on various screening tests. However, these tests are outside the scope of this recommendation for various reasons (eg, diagnostic tests performed in symptomatic patients or newer technologies not yet evaluated for screening in a primary care setting).

Update of Previous USPSTF Recommendation

This recommendation is consistent with and updates the 2004 USPSTF recommendation. The current recommendation statement includes updated information on prevalence and risk factors in the United States and data on newer screening tests and approaches. Screening for syphilis infection in pregnant women is now addressed in a separate recommendation statement.[3]

Recommendations of Others

The CDC recommends at least annual screening for sexually active MSM with confirmatory testing for individuals with reactive serology. Persons living with HIV should be screened at least annually; more frequent screening may be appropriate based on individual risk behaviors and local epidemiology. The CDC also recommends syphilis screening in correctional facilities on the basis of the local area and institutional prevalence.[9] The American Congress of Obstetricians and Gynecologists endorses the CDC's guidelines.[20] The HIV Medicine Association (part of the Infectious Diseases Society of America) recommends that all patients living with HIV be screened for syphilis on initiation of care and periodically thereafter, depending on risk.[21] The American Academy of Family Physicians recommends screening for syphilis infection in persons who are at increased risk for infection.[22]

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