JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Syphilis Infection in Nonpregnant Adolescents and Adults
US Preventive Services Task Force Reaffirmation Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Syphilis is a sexually transmitted infection that can progress through different stages (primary, secondary, latent, and tertiary) and cause serious health problems if left untreated. Reported cases of primary and secondary syphilis in the US increased from a record low of 2.1 cases per 100 000 population in 2000 and 2001 to 11.9 cases per 100 000 population in 2019. Men account for the majority of cases (83% of primary and secondary syphilis cases in 2019), and rates among women nearly tripled from 2015 to 2019.

OBJECTIVE To reaffirm its 2016 recommendation, the US Preventive Services Task Force (USPSTF) commissioned a reaffirmation evidence update focusing on targeted key questions evaluating the performance of risk assessment tools and the benefits and harms of screening for syphilis in nonpregnant adolescents and adults.

POPULATION Asymptomatic, nonpregnant adolescents and adults who have ever been sexually active and are at increased risk for syphilis infection.

EVIDENCE ASSESSMENT Using a reaffirmation process, the USPSTF concludes with high certainty that there is a substantial net benefit of screening for syphilis infection in nonpregnant persons who are at increased risk for infection.

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

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Group Information: A complete list of the members of the US Preventive Services Task Force appears at the end of this article.

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Summary of Recommendation

Population	Recommendation	Grade
Asymptomatic, nonpregnant adolescents and adults who are at increased risk for syphilis infection	The USPSTF recommends screening for syphilis infection in persons who are at increased risk for infection.	A

See the Practice Considerations section for information on increased risk. USPSTF indicates US Preventive Services Task Force.

See the Summary of Recommendation figure.

Importance

Syphilis is a sexually transmitted infection (STI) that can progress through different stages (primary, secondary, latent, and tertiary) and cause serious health problems if left untreated.[1] Tertiary syphilis, which occurs in approximately one-third of latent syphilis cases, can affect multiple organ systems.[2] Syphilis can attack the nervous system (neurosyphilis) and visual system (ocular syphilis) at any stage of disease, resulting in movement disorders, sensory deficits, dementia, paralysis, visual changes, or blindness.[1] Syphilis infection also increases the risk for acquiring or transmitting HIV infection.[1,3]

Primary and secondary syphilis are the most infectious stages of the disease. Reported cases of primary and secondary syphilis in the US increased from a record low of 2.1 cases per 100 000 population in 2000 and 2001 to 11.9 cases per 100 000 population in 2019. Men account for the majority of cases (83% of primary and secondary syphilis cases in 2019), and rates among women nearly tripled from 2015 to 2019. Men who have sex with men are disproportionately affected, accounting for a majority (57%) of all primary and secondary syphilis cases

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Table. Summary of USPSTF Rationale

Rationale	Assessment
Detection	The USPSTF found convincing evidence that screening test algorithms with high sensitivity and specificity are available to accurately detect syphilis infection.
Benefits of early detection and intervention and treatment	The USPSTF found convincing evidence that screening for syphilis and subsequent treatment of persons with syphilis 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 intervention and treatment	• The USPSTF found limited 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 and unnecessary anxiety to the patient. • The harms of antibiotic treatment are well established, and the magnitude of these harms is no greater than small.
USPSTF assessment	Using a reaffirmation process, 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.

Abbreviation: USPSTF, US Preventive Services Task Force.

among men in 2019.[4] The overall rate of primary and secondary syphilis among men who have sex with men was 106 times the rate among men who only have sex with women and 168 times the rate among women.[5] Primary and secondary syphilis rates are highest among Black adolescents and adults, nearly 5 times the rate among White adolescents and adults. Elevated rates have also been reported in Hispanic adolescents and adults, Native American/Alaska Native adolescents and adults, and Native Hawaiian/Pacific Islander adolescents and adults.[4] These disparities are primarily driven by social conditions such as poverty, low education levels, and poor access to quality health care, which disproportionately affect communities of color and make it harder to maintain sexual health. Differences in sexual network characteristics also play a role in disparities. Sexually active people may be more likely to become infected in communities with higher STI rates.[6-10]

Syphilis infection can be passed from a pregnant person to the fetus, causing neonatal morbidity and mortality.[1] The USPSTF addresses screening for syphilis in pregnant persons in a separate recommendation statement.[11]

USPSTF Assessment of Magnitude of Net Benefit

Reaffirmation

In 2016, the US Preventive Services Task Force (USPSTF) reviewed the evidence for screening for syphilis infection in nonpregnant adolescents and adults and issued an A recommendation for persons who are at increased risk.[12] The USPSTF has decided to use a reaffirmation deliberation process to update this recommendation. The USPSTF uses the reaffirmation process for well-established, evidence-based standards of practice in current primary care practice for which only a very high level of evidence would justify a change in the grade of the recommendation.[13] In its deliberation of the evidence, the USPSTF considers whether the new evidence is of sufficient strength and quality to change its previous conclusions about the evidence.

Using a reaffirmation process, the USPSTF concludes with high certainty that there is a **substantial net benefit** of screening for syphilis infection in nonpregnant persons who are at increased risk for infection.

See the **Table** for more information on the USPSTF recommendation rationale and assessment and the eFigure in the Supplement for information on the recommendation grade. See the **Figure** for a summary of the recommendation for clinicians. For more details on the methods the USPSTF uses to determine the net benefit, see the USPSTF Procedure Manual.[13]

Practice Considerations

Patient Population Under Consideration

This recommendation applies to asymptomatic, nonpregnant adolescents and adults who have ever been sexually active and are at increased risk for syphilis infection.

In this recommendation statement, sex and gender as well as race and ethnicity terminology are based on how study participants were reported in reviewed studies. This recommendation is inclusive of all persons at increased risk for syphilis.

Assessment of Risk

The USPSTF recommends screening for syphilis in persons who are at increased risk for infection. When deciding which persons to screen for syphilis, clinicians should consider the prevalence of infection in the communities they serve, as well as other sociodemographic and behavioral factors that may be associated with increased risk of syphilis infection. For example, prevalence of syphilis is higher in men, men who have sex with men, persons with HIV infection, young adults, and persons with a history of incarceration, sex work, or military service.[9,10] A substantial percentage of heterosexual syphilis transmission occurs among persons who use illicit drugs, particularly methamphetamine.[14,15] Diagnosis of another STI may signal that a person is having condomless sex, which increases their risk of syphilis infection.[16] Higher infection rates in persons of some racial and ethnic groups have been reported and are primarily a reflection of a combination of factors, including social determinants of health (eg, disparities of income, low educational achievement, and unstable housing),[6] differential health insurance coverage or access to quality health care,[6] and differences in sexual network characteristics (eg, individuals living in communities with a high prevalence of STIs have an increased chance of encountering an infected partner).[7] Local prevalence

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Figure. Clinician Summary of USPSTF Recommendation: Screening for Syphilis Infection in Nonpregnant Adolescents and Adults

What does the USPSTF recommend?	**Screen for syphilis in persons at increased risk for infection.** **Grade: A**
To whom does this recommendation apply?	• Adolescents and adults who have ever been sexually active and are at increased risk for syphilis infection. • It does not apply to pregnant persons, who are discussed in a separate recommendation statement. • It does not apply to persons who have signs or symptoms of syphilis.
What's new?	This recommendation is consistent with the 2016 USPSTF recommendation. The USPSTF continues to recommend screening for syphilis in nonpregnant persons who are at increased risk for infection.
How to implement this recommendation?	**Assess risk:** • Risk of syphilis is higher in men who have sex with men; persons with HIV infection or other sexually transmitted infections; persons who use illicit drugs; and persons with a history of incarceration, sex work, or military service. • However, clinicians should be aware of how common syphilis infection is in their community and assess patient's individual risk. **Screen and confirm:** Options for testing include: • *Traditional screening algorithm:* Screen with an initial nontreponemal test (eg, Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] test). If positive, confirm with a treponemal antibody detection test (eg, *Treponema pallidum* particle agglutination [TP-PA] test). • *Reverse sequence algorithm:* Screen with an initial automated treponemal test (eg, enzyme-linked or chemiluminescence immunoassay). If positive, confirm with a nontreponemal test. **Screening interval:** • Although evidence on optimal screening intervals is limited for the general population, men who have sex with men or persons with HIV infection may benefit from screening at least annually or more frequently (eg, every 3 to 6 months) if they continue to be at high risk.
What additional information should clinicians know about this recommendation?	• Primary and secondary syphilis rates are higher in Black, Hispanic, Native American/Alaska Native, and Native Hawaiian/Pacific Islander persons. These disparities are primarily driven by social determinants of health such as differences in income level, education level, and access to coverage and care, which make it harder to maintain sexual health. • Differences in sexual network characteristics also play a role in disparities. Sexually active people may be more likely to become infected in communities with higher sexually transmitted infection rates.
Why is this recommendation and topic important?	• After reaching a record low in 2000, rates of syphilis have been increasing over the past 20 years. • Without treatment, syphilis can damage the brain, nerves, eyes, and cardiovascular system. • Screening and follow-up treatment can cure syphilis and prevent complications.
What are other relevant USPSTF recommendations?	• Screening for syphilis infection in pregnant women • Behavioral counseling for sexually transmitted infections These recommendations and screening recommendations for other sexually transmitted infections are available at https://www.uspreventiveservicestaskforce.org/uspstf/
What are additional tools and resources?	The Centers for Disease Control and Prevention provide fact sheets, treatment guidelines, and surveillance data for syphilis at https://www.cdc.gov/std
Where to read the full recommendation statement?	Visit the USPSTF website (https://www.uspreventiveservicestaskforce.org/uspstf/) or the *JAMA* website (https://jamanetwork.com/collections/44068/united-states-preventive-services-task-force) to read the full recommendation statement. This includes more details on the rationale of the recommendation, including benefits and harms; supporting evidence; and recommendations of others.

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.

USPSTF indicates US Preventive Services Task Force.

rates may change over time, so clinicians should be aware of the latest data and trends for their specific population and geographic area, which are available through their state and local health departments and Centers for Disease Control and Prevention (CDC) surveillance.[9,10,17]

Although direct evidence on screening in 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.[9,10] Therefore, screening in this population may result in high false-positive rates and overtreatment.

Screening Tests

Current syphilis screening tests rely on detection of antibodies rather than direct detection of the organism that causes syphilis, *Treponema pallidum*. A *traditional screening algorithm* is a 2-step process involving an initial nontreponemal test (eg, Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] test) followed by a confirmatory treponemal antibody detection test (eg, *T pallidum* particle agglutination [TP-PA] test).[18] A more recently developed *reverse sequence algorithm* uses an automated treponemal test (eg, enzyme-linked or chemiluminescence immunoassay) for the initial screening, followed by a nontreponemal test for reactive samples.[18] Discordant results in the reverse sequence

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are resolved with a second confirmatory treponemal test, preferably testing for different antigens than the initial test.[9] Most laboratories perform traditional screening[19]; however, the automated processes used in reverse sequence may be appropriate for high-volume laboratories or areas where populations may be at higher risk for late-stage latent disease that traditional screening may miss.[20]

Rapid point-of-care (POC) testing for antibodies to *T pallidum* can provide quick on-site results (typically within 5 to 30 minutes); however, initial real-world data show sensitivity may be low.[21]

Screening Intervals

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 with HIV infection may benefit from screening at least annually or more frequently (eg, every 3 to 6 months) if they continue to be at high risk.[9,10,16]

Treatment

The effectiveness of parenteral penicillin G for the treatment of primary, secondary, and latent syphilis is well established. Dosage and the length of treatment depend on the stage and symptoms of the infection. Clinicians are encouraged to refer to the CDC's STI Treatment Guidelines for the most up-to-date treatment guidance.[16]

Implementation

The USPSTF did not review evidence on screening for syphilis in persons with HIV infection or taking HIV preexposure prophylaxis if screening was part of disease management. The CDC provides recommendations for these circumstances and other specific groups. The CDC also describes management and follow-up considerations, including interventions to decrease transmission and reinfection.[16]

Additional Tools and Resources

The CDC provides fact sheets, treatment guidelines, and national and state surveillance data for syphilis (https://www.cdc.gov/std). It also provides guidance for clinicians on providing quality STI clinical services (https://www.cdc.gov/mmwr/volumes/68/rr/rr6805a1.htm).

The National Academies of Sciences, Engineering, and Medicine provides a comprehensive systems-based approach for prevention and control of STIs (https://nap.nationalacademies.org/catalog/25955/sexually-transmitted-infections-adopting-a-sexual-health-paradigm).

The Community Preventive Services Task Force has issued several recommendations on the prevention of HIV/AIDS, other STIs, and teen pregnancy. The Community Guide discusses interventions that have been efficacious in school settings and for men who have sex with men (https://www.thecommunityguide.org/topic/hiv-stis-and-teen-pregnancy).

Other Related USPSTF Recommendations

The USPSTF has issued a separate recommendation for screening for syphilis infection in pregnant persons[11] as well as screening recommendations for other STIs, including hepatitis B,[22] hepatitis C,[23] genital herpes,[24] HIV,[25] and chlamydia and gonorrhea.[26] The USPSTF has also issued a recommendation on behavioral counseling for all sexually active adolescents and for adults who are at increased risk for STIs.[27]

Reaffirmation of Previous USPSTF Recommendation

This recommendation is a reaffirmation of the USPSTF 2016 recommendation statement. In 2016, the USPSTF reviewed the evidence for syphilis screening in nonpregnant adolescents and adults and found convincing evidence that the benefits of screening substantially outweighed the harms (A recommendation).[12] In the current update, the USPSTF found no new substantial evidence that could change its recommendation and, therefore, reaffirms its recommendation to screen for syphilis in nonpregnant adolescents and adults who are at increased risk of infection.

Supporting Evidence

Scope of Review

To reaffirm its recommendation, the USPSTF commissioned a reaffirmation evidence update. The aim of evidence updates that support the reaffirmation process is to identify if there is new and substantial evidence sufficient enough to change the prior recommendation.[13] The reaffirmation update focuses on targeted key questions evaluating the performance of risk assessment tools and the benefits and harms of screening for syphilis in nonpregnant adolescents and adults. The review also included a more limited literature search comparing testing algorithms and the accuracy of rapid POC tests. Because the USPSTF previously determined that treatments for these infections are effective and well established, this review did not include a review of treatments.

Accuracy of Screening Tests and Risk Assessment

Test accuracy can vary based on disease stage. A literature review showed the sensitivity of commonly used nontreponemal tests, such as RPR and VDRL, ranged from 61% to 78% for detecting primary and late latent syphilis. Sensitivity of these nontreponemal tests for detecting secondary and early latent syphilis ranged from 85% to 100%. Sensitivity of preferred treponemal tests ranged from 82% to 100% across the spectrum of disease. Specificity of preferred treponemal tests for detecting primary syphilis ranged from 94% to 100%.[9,10]

There is limited evidence directly comparing the traditional and reverse sequence algorithms. A recent 2020 narrative study reviewed 69 articles summarizing the pros and cons of the 2 algorithms. Findings showed that the nontreponemal test in the traditional algorithm may have decreased sensitivity for detecting primary and latent syphilis. The automated tests used in the reverse sequence algorithm allows for faster processing but may have higher false-positive rates than the traditional algorithm. The study concluded that the traditional algorithm may be more appropriate for smaller laboratories with lower volumes of testing because performing manual nontreponemal screening assays would not significantly affect workflow. Alternatively, the reverse algorithm may be more suitable for either larger laboratories where automated

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testing processes can improve workflow and efficiency or for smaller laboratories serving higher-risk populations.[20]

A 2020 systematic review evaluated rapid POC test performance in laboratory and real-world settings. The study found that the pooled sensitivity from the laboratory evaluations (n = 5) was 98.5% (95% CI, 92.1%-100%), while pooled specificity was 95.9% (95% CI, 81.5%-100.0%). The pooled sensitivity for prospective studies (n = 10) was 87.7% (95% CI, 71.8%-97.2%), while pooled specificity was 96.7% (95% CI, 91.9%-99.2%). However, in 2 of these prospective studies, the sensitivity was only 50%. Differences in testing protocols, training, and specimen collection (eg, sera vs whole-blood samples) are potential factors explaining the inconsistency in test performance between laboratory and real-world POC testing.[21]

The USPSTF reviewed 1 fair-quality study (n = 361) that evaluated an online calculator for predicting syphilis within the next 3 months in high-risk individuals seeking STI testing or treatment in Peru. The model with the greatest area under the curve (0.69) included the risk factors current HIV infection, history of syphilis infection, number of male sex partners in past 3 months, and sex role for anal sex (receptive or insertive) in the prior 3 months.[28]

Benefits of Early Detection and Treatment

The USPSTF reviewed 1 fair-quality Australian cohort study (n = 117 387) examining trends in syphilis testing and detection among sexually active men who have sex with men (68% HIV-negative). During an 8-year follow-up period, the proportion of men tested for syphilis annually increased significantly among both HIV-negative (n = 97 895) and HIV-positive (n = 19 492) men (48% to 91% in HIV-negative men and 42% to 77% in HIV-positive men; P <.001 for trend). Syphilis was detected in 2799 HIV-negative men (3%) and 1032 HIV-positive men (5%). The proportion of early latent infections detected increased from 27% to 44% in HIV-negative men and from 23% to 45% in HIV-positive men (P < .001 for trend), while the proportion of secondary infections decreased from 24% to 19% (P = .03 for trend) and from 45% to 26% (P < .001 for trend) in HIV-positive and negative men, respectively. This study demonstrated that screening in men who have sex with men was associated with greater detection of early asymptomatic syphilis and a decrease in secondary syphilis, suggesting that screening is likely to have interrupted the progression of syphilis.[29]

No studies reported the effectiveness of screening on acquisition or transmission of other STIs or other complications such as tertiary syphilis or neurosyphilis. No studies directly addressed effective screening intervals in the included populations.

The effectiveness of penicillin G for the treatment of primary, secondary, and latent syphilis is well established and was not reviewed for this recommendation update.[16]

Harms of Screening and Treatment

The USPSTF reviewed 1 fair-quality, pre-post design study (n = 1097) examining emotional stress associated with rapid POC STI testing. Participants considered to be in high-risk groups completed a questionnaire assessing emotional stress prior to and after testing for HIV, hepatitis C, and syphilis. Factors associated with increased stress included history of injection drug use, Black race, less than a high school education, and single marital status. The study did not compare changes in the levels of emotional stress pretesting vs posttesting.[30]

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from February 15 to March 14, 2022. The USPSTF clarified factors driving disparities in syphilis prevalence among certain populations in the Importance and Practice Considerations sections. The USPSTF clarified preferred screening tests by the CDC as well as test performance of different screening tests in the Practice Considerations and Supporting Evidence sections. Additional risk behaviors were added to the Practice Considerations section to further help identify persons who would benefit from screening. Last, the USPSTF clarified harms in the Table.

Research Needs and Gaps

Studies are needed that provide more information on the following.

- Validated risk assessment tools, feasible for use in primary care, that will more accurately identify populations at increased risk of infection who would benefit most from screening.
- Direct evidence evaluating the benefits and harms of screening for syphilis in adolescents.
- Factors driving demographic, geographic, and occupational health disparities and effective prevention strategies that may improve health inequities.
- Optimal screening intervals for all high-risk populations.
- Effectiveness of rapid POC testing in real-world settings compared with laboratory-based testing.

Recommendations of Others

The CDC recommends at least annual screening for syphilis in sexually active men who have sex with men, with confirmatory testing for individuals with reactive serology. The CDC recommends that persons with HIV infection who are sexually active be screened at the first HIV evaluation and at least annually thereafter. Men who have sex with men and persons with HIV infection may benefit from more frequent screening (eg, every 3 to 6 months) based on individual risk behaviors and local epidemiology. The CDC also recommends opt-out syphilis screening in correctional facilities based on the local area and institutional prevalence.[16] The American College of Obstetricians and Gynecologists does not recommend routine screening for syphilis in persons who are not pregnant.[31] The HIV Medicine Association (part of the Infectious Diseases Society of America) recommends that all patients with HIV infection be screened for syphilis on initiation of care and periodically thereafter, depending on risk.[32] The recommendation of the American Academy of Family Physicians is similar to the USPSTF guidelines for screening for syphilis in persons at increased risk.[33,34]

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Additional Information: 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. Published by JAMA®—Journal of the American Medical Association under arrangement with the Agency for Healthcare Research and Quality (AHRQ). ©2022 AMA and United States Government, as represented by the Secretary of the Department of Health and Human Services (HHS), by assignment from the members of the United States Preventive Services Task Force (USPSTF). All rights reserved.

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