Screening for Syphilis

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE  Screening for syphilis infection is currently recommended for high-risk individuals, including those with previous syphilis infection, an infected sexual partner, HIV infection, or more than 4 sex partners in the preceding year.

OBJECTIVE  To update a 2004 systematic review of studies of syphilis screening effectiveness, test accuracy, and screening harms in nonpregnant adults and adolescents.

DATA SOURCES  Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews through October 2015 and Ovid MEDLINE (January 2004 to October 2015), with updated search through March 2016.

STUDY SELECTION  English-language trials and observational studies of screening effectiveness, test accuracy, and screening harms in nonpregnant adults and adolescents.

DATA EXTRACTION AND SYNTHESIS  One investigator abstracted data, a second checked data for accuracy, and 2 investigators independently assessed study quality using predefined criteria.

MAIN OUTCOMES AND MEASURES  Transmission of disease, including HIV; complications of syphilis; diagnostic accuracy; and harms of screening.

RESULTS  No evidence was identified regarding the effectiveness of screening on clinical outcomes or the effectiveness of risk assessment instruments; the harms of screening; or the effectiveness of screening in average-risk, nonpregnant adolescents or adults or high-risk individuals other than men who have sex with men (MSM) or men who are HIV positive. Four non-US studies indicated higher rates of syphilis detection with screening every 3 months vs 6 or 12 months for early syphilis in HIV-positive men or MSM. For example, there was an increased proportion of asymptomatic, higher-risk MSM in Australia (n = 6789 consultations) receiving a diagnosis of early syphilis when tested every 3 months vs annually (53% vs 16%, P = .001), but no difference among low-risk MSM. Treponemal and nontreponemal tests were accurate in asymptomatic individuals (sensitivity >85%, specificity >91%) in 3 studies but required confirmatory testing. Reverse sequence testing with an initial automated treponemal test yielded more false reactive test results than with rapid plasma reagin in 2 studies, one with a low-prevalence US population (0.6% vs 0.0%, P = .03) and another in a higher-prevalence Canadian population (0.26% vs 0.13%).

CONCLUSIONS AND RELEVANCE  Screening HIV-positive men or MSM for syphilis every 3 months is associated with improved syphilis detection. Treponemal or nontreponemal tests are accurate screening tests but require confirmation. Research is needed on the effect of screening on clinical outcomes; effective screening strategies, including reverse sequence screening, in various patient populations; and harms of screening.

Syphilis is a chronic, systemic, infectious disease caused by sexual or vertical transmission of the bacterium *Treponema pallidum*. Symptoms correspond to stages of infection including primary, secondary, early- and late-latent, and late syphilis. Vertical transmission occurs during any stage, while sexual transmission occurs during early stages and requires exposure to open lesions or infected secretions. The Centers for Disease Control and Prevention (CDC) updated case definitions in 2014. Syphilis infection is associated with HIV infection and increases the risk for acquiring or spreading HIV. Antibiotics are effective for treating and curing syphilis.

Individuals with previous syphilis infection, an infected sexual partner, current HIV infection, or more than 4 sex partners in the preceding year are at increased risk of acquiring syphilis. Higher prevalence rates are associated with sociodemographic groups including men who have sex with men (MSM), young adult men, sex workers, adults in correctional facilities, and individuals who are black or live in metropolitan areas in the southern and western United States. Men who have sex with men accounted for 61% of all primary and secondary syphilis cases reported in 2014.

In 2004, the US Preventive Services Task Force (USPSTF) recommended routine screening for syphilis in asymptomatic men and nonpregnant women at increased risk of infection (A recommendation) and recommended against routine screening for those not at increased risk (D recommendation). Studies were not available to determine optimal screening intervals. In this systematic review and evidence update, we examine studies from US-relevant populations on the effectiveness of routine screening, accuracy of screening tests and strategies, and potential harms of screening.

**Methods**

**Scope of the Review**

Detailed methods and background are available in the full evidence report (http://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-review156/syphilis-infection-in-nonpregnant-adults-and-adolescents). The full report provides additional details about key questions (KQs) lacking evidence and contextual questions, with prevalence data on population subgroups at highest risk for syphilis infection, including MSM. Based on evidence gaps identified from the 2004 review in collaboration with the USPSTF and Agency for Healthcare Research and Quality, investigators determined the scope and KQs using established methods (Figure 1). The final research plan was posted on the USPSTF website before conducting the review.
Data Sources and Searches
A research librarian searched the Cochrane Central Register of Controlled Trials through October 2015, Cochrane Database of Systematic Reviews through October 2015, and Ovid MEDLINE January 2004 to October 2015 for relevant studies and systematic reviews and manually reviewed reference lists. In March 2016, an additional search revealed no new major studies affecting the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The search strategies are listed in the eMethods in the Supplement.

Study Selection
Two investigators independently reviewed 2000 titles and abstracts and 448 full-text articles against prespecified inclusion criteria (Figure 2). Discrepancies were resolved through consensus. Non–English-language articles and studies published as abstracts were not included.

The target population included asymptomatic, sexually active men and women, including adolescents. Populations at increased risk, based on incidence rates, include MSM, individuals who engage in high-risk sexual behavior, commercial sex workers, individuals who exchange sex for drugs, individuals who are HIV positive, and adults in correctional facilities.

Key questions evaluated the effectiveness of screening in reducing syphilis complications and transmission; effectiveness of risk assessment methods; accuracy of diagnostic tests and strategies; and harms related to screening, including false-positive and false-negative diagnoses, and related adverse effects. We included randomized clinical trials, controlled observational studies, and ecological studies to evaluate screening effectiveness; diagnostic accuracy studies to determine accuracy of screening tests and strategies; and studies of various designs to assess harms.

Traditionally, screening for syphilis infection is a 2-step process involving an initial nontreponemal test followed by a confirmatory treponemal test (Table 1). Diagnostic accuracy studies meeting eligibility criteria used credible reference standards, described the study population, defined positive screening test results, and reported performance characteristics (eg, sensitivity, specificity) or provided data to calculate them. Studies of testing strategies were also included because variations in the sequence of testing have been proposed to reduce the time and labor involved with syphilis screening. Studies of harms were included that compared screened vs unscreened populations.

Studies applicable to clinical settings and practices in the United States were emphasized based on the clinical relevance of participants and health care services and the use of screening tests that are currently available and cleared by the US Food and Drug Administration (FDA) for clinical use (eTable 1 in the Supplement). Therefore, tests of specimens obtained in nonclinical settings and most point-of-care or in-house tests were excluded. These inclusion criteria reflect the scope of the USPSTF recommendations regarding technologies and medications.
Data Extraction and Quality Assessment
One investigator abstracted details about study design, patient population, setting, screening method, analysis, follow-up, and results, and a second investigator confirmed the data. Using predefined criteria developed by the USPSTF13 (eTable 2 in the Supplement), 2 investigators independently rated the quality of studies (good, fair, poor) and resolved discrepancies through consensus. See eTable 3 and eTable 4 in the Supplement for the quality ratings of individual studies.

Data Synthesis and Analysis
Studies were qualitatively synthesized based on methods developed by the USPSTF.13 Statistical meta-analysis was not performed because of methodological limitations and heterogeneity in study designs, interventions, populations, and other factors. Studies included in prior reviews were reviewed for consistency with current results; however, lack of studies and differences in scope, KQs, and inclusion criteria limited aggregate synthesis with the updated evidence.

The aggregate internal validity (quality) of the body of evidence was assessed for each key question using methods developed by the USPSTF (Table 2) based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence.

Results
This article focuses only on new evidence since the prior review and omits coverage of the KQs that had no evidence (KQs 2 and 4). Studies were not available to address several KQs, including the effectiveness of screening in reducing syphilis complications and transmission, effectiveness of risk assessment methods, and harms related to screening. No studies were conducted specifically in adolescent populations.

Effectiveness of Screening
Key Question 1. What is the effectiveness of screening for syphilis in reducing complications of the disease and transmission or acquisition of other sexually transmitted infections in asymptomatic, nonpregnant, sexually active adults and adolescents? What is the effectiveness of specific screening intervals and screening among population subgroups?

No studies directly compared the effectiveness of syphilis screening in screened vs unscreened populations of nonpregnant adolescents or adults. Four studies evaluated the effectiveness of specific screening intervals and screening among 2 population subgroups, MSM and men who are HIV positive. Three fair-quality observational studies from the same health center in Australia20-22 and 1 fair-quality observational study from the United Kingdom23 evaluated detection rates of syphilis using specific screening intervals (Table 3). All 4 studies were conducted with MSM or HIV-positive men; 2 studies of HIV-positive men20,23 concerned testing for syphilis as part of HIV disease monitoring rather than screening.

A pre-post intervention study of 1031 HIV-positive MSM attending a public sexually transmitted infection (STI) clinic in Australia found a higher detection rate of asymptomatic early syphilis among those screened every 3 months compared with those screened annually (8.1% vs 3.1%, P = .001).20 The proportion of HIV-positive MSM...
Table 2. Summary of Evidence

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Main Findings From Prior USPSTF Reviews</th>
<th>Studies Identified for Update</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of Findings</th>
<th>Overall Quality*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key question 1: Effectiveness of screening in reducing complications and transmission*</td>
<td>No studies</td>
<td>4 observational studies of MSM and HIV-positive males</td>
<td>No studies of screening effectiveness; No studies of screening intervals in other populations</td>
<td>Consistent</td>
<td>Studies conducted in Europe and Australia in MSM and HIV-positive MSM; studies included high-prevalence populations</td>
<td>Four non-US studies on the effectiveness of screening for syphilis among MSM or HIV-infected men found that detection rates increased with routine screening every 3 mo compared with annual screening. More cases of infection were detected for cases of early syphilis in HIV-positive MSM (8.1% vs 3.1%, P = .001), newly acquired syphilis in HIV-positive MSM (7.3 cases [95% CI, 5.2-9.9] vs 2.8 cases [95% CI, 1.8-4.0] per 1000 patient-years; P &lt; .05); early-latent syphilis in MSM (1.7% vs 0.4%, P = .008); and early syphilis in higher-risk MSM (16% vs 53%, P = .001) when screening occurred every 3 mo compared with 6 or 12 mo.</td>
<td>Fair</td>
</tr>
<tr>
<td>Key question 2: Effectiveness of risk assessment</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
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<tr>
<td>Key question 3: Screening accuracy*</td>
<td>Included studies conducted in populations and settings not applicable to this update; descriptive information on new screening tests and methods also mentioned</td>
<td>5 observational studies (3 test accuracy, 2 testing sequence)</td>
<td>Not all tests currently used for screening in the United States were included. Unclear sampling methods and interpretation of tests. Some studies had technical shortcomings.</td>
<td>Consistent</td>
<td>Limited; 1/3 studies from United States in STI clinic with high prevalence of MSM and HIV. Two studies of testing sequence conducted in Mexico and Canada. Studies included high-prevalence populations.</td>
<td>Three observational studies of treponemal and nontreponemal tests found that screening tests for syphilis are accurate (sensitivity, 85.3%-98%; specificity, 91%-100% for both). Two studies of reverse sequence testing accuracy found a higher rate of false reactive tests with automated treponemal tests as initial screening compared with RPR in a low-prevalence US population (0.6% vs 0.0%, P &lt; .03) and in a higher-prevalence Canadian population (0.26% vs 0.13%). Both methods identified additional positive tests not identified using conventional methods.</td>
<td>Fair</td>
</tr>
<tr>
<td>Key question 4: Screening harms*</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
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</tbody>
</table>

Abbreviations: MSM, men who have sex with men; RPR, rapid plasma reagin; STI, sexually transmitted infection; USPSTF, US Preventive Services Task Force.
* Based on new evidence identified for the update plus previously reviewed evidence.
* Key question 1: What is the effectiveness of screening for syphilis in reducing complications of the disease and transmission or acquisition of other sexually transmitted infections in asymptomatic, nonpregnant, sexually active adults and adolescents? What is the effectiveness of specific screening intervals and screening among population subgroups?

Key question 2: What is the effectiveness of risk assessment instruments or other risk stratification methods for identifying individuals who are at increased risk for syphilis?

Key question 3: What is the accuracy of currently used screening tests and strategies (eg, sequence of tests) for detecting syphilis infection?

Key question 4: What are the harms of screening (eg, labeling and false-positive or false-negative results)?

An Australian observational study evaluated the association of computer-generated reminders with the rates of syphilis testing among 4514 MSM who elected to receive a reminder every 3, 6, or 12 months.21 There was a higher detection rate for early syphilis among MSM receiving reminders every 3 months during the 12-month observation period compared with concurrent controls who were not offered reminders (3.2% vs 1.5%, P = .03). Using a system-based approach to testing, a study conducted at the same Australian health center evaluated whether a computer alert for physicians of MSM in 6789 consultations to test higher-

with early syphilis who were asymptomatic at the time of diagnosis was 21% (3/14 patients) before vs 85% (41/48 patients) after the intervention (P = .006). An observational study of 2389 patients with HIV infection in London (72% MSM) compared detection rates for routine syphilis screening as part of HIV care with rates during the year before routine screening was implemented.23 Routine screening every 3 months detected more patients with newly acquired syphilis compared with screening every 6 months or more (7.3 cases per 1000 patient-years [95% CI, 5.2-9.9] vs 2.8 cases per 1000 patient-years [95% CI, 1.8-4.0], P < .05).23
diagnosed with early syphilis or who were asymptomatic. Results indicated an increased proportion of higher-risk men receiving diagnoses of early syphilis who were asymptomatic at the time of diagnosis in the intervention group tested every 3 months vs annually (31/58 [53%] vs 5/31 [16%]; P = .001). There were no statistically significant changes in the proportion of syphilis diagnoses in asymptomatic lower-risk men who were tested every 3 months vs annually (3/16 [19%] vs 1/10 [10%]; P = .60).

**Diagnostic Accuracy of Currently Used Screening Tests and Strategies**

**Key Question 3.** What is the accuracy of currently used screening tests and strategies (eg, sequence of tests) for detecting syphilis infection?

**Test Accuracy**

Three fair-quality observational studies of diagnostic accuracy evaluated treponemal and nontreponemal tests (Table 4). Two of the studies compared treponemal enzyme immunoassay (EIA) tests as a screening assay when followed by a second confirmatory test.24,25 and the other study compared the treponemal T pallidum particle agglutination (TPPA) test with Venereal Disease Research Laboratory (VDRL) testing followed by fluorescent treponemal antibody absorption (FTA-ABS).26 These studies were limited by their lack of demographic information and small sample sizes (n = 198-674).

A cross-sectional study conducted in a high-prevalence STI clinic in San Francisco compared a treponemal EIA screening test (Trep-Sure EIA) with a traditional nontreponemal VDRL test as an initial screening examination and used a TPPA assay as a confirmatory test. Tests were run on remnant serum samples from patients of unspecified age groups presenting to an STI clinic with a reported syphilis prevalence of 9.4% and high rates of HIV-positive patients (16.6%) and MSM (69.3%).24 The samples used in this study reflected higher syphilis prevalence than the general population at the clinic, with a positive test rate of 39.7% after the screening and confirmatory tests were completed. In this population, screening with the EIA in conjunction with a confirmatory TPPA test was slightly less sensitive than when the VDRL was used as the screening test (98.0% vs 98.6%) but was more specific (98.6% vs 91.1%).24

A Canadian study also reported results of the diagnostic accuracy of treponemal EIA tests (Trep-Check IgG EIA) in a sample of...
compared with standard VDRL testing.26 of female sex workers (15.7% prevalence) at an STI clinic and TPPA test with VDRL testing followed by FTA-ABS in a population patients in samples submitted for testing. A cohort study from tested, and the lack of demographic data specifying the ages of control wells for the EIA, the small number of positive cases the conventional tests rapid plasma reagin (RPR), VDRL, TPPA, and a specificity of 95.6% compared with samples obtained with followed by a confirmatory test resulted in a sensitivity of 85.3% higher rate of false-positive results at the screening stage than mated treponemal test as the initial screening test resulted in a strategies (25). Use of the Trep-Check IgG EIA as a screening test specimens with a 5.6% positive test rate using conventional test-ation methods.25 Use of the Trep-Check IgG EIA as a screening test followed by a confirmatory test resulted in a sensitivity of 85.3% and a specificity of 95.6% compared with samples obtained with the conventional tests rapid plasma reagin (RPR), VDRL, TPPA, and FTA-ABS. This study was limited by the lack of no-antigen control wells for the EIA, the small number of positive cases tested, and the lack of demographic data specifying the ages of patients in samples submitted for testing. A cohort study from Mexico compared the diagnostic accuracy of the treponemal TPPA test with VDRL testing followed by FTA-ABS in a population of female sex workers (15.7% prevalence) at an STI clinic and reported 100% specificity but a lower sensitivity (87.1%) when compared with standard VDRL testing.26

Screening Strategies
Two observational studies from the United States and Canada compared traditional screening strategies with reverse screening strategies (Table 5).27,28 In both studies, screening using an automated treponemal test as the initial screening test resulted in a higher rate of false-positive results at the screening stage than occurred when RPR testing was used for screening. Both studies also identified additional positive results that would not have been identified using conventional methods. Methodological limita-tions for both studies include minimal demographic information and unclear descriptions of sampling methods.

A large (n = 3,092,938 samples) retrospective time-series study in Canada evaluated a reverse screening algorithm by com-paring laboratory results from a high-prevalence metropolitan area (incidence rate ratio of 1.69-1.80 relative to surrounding sub-urban areas) using RPR or EIA as the initial screening tests on samples submitted for syphilis serology.27 Samples were considered positive after undergoing a confirmatory test. Using EIA as the initial test resulted in an increased detection rate of positive results when compared with screening with RPR (1.98% confirmed positive vs 0.46%). Of all confirmed positive results during the EIA screening period, 69.6% were associated with a negative RPR test result. The proportion of confirmed positive EIA results with a negative RPR result was higher when samples were limited to those from asymptomatic patients (74.7%; 95% CI, 73.6%-75.8%), patients with no risk factors for syphilis (71.5%; 95% CI, 70.4%-72.5%), or intravenous drug users (69.9%; 95% CI, 66.3%-73.3%) and slightly lower for MSM (69%; 95% CI, 66.9%-71.0%) and MSM who were also intravenous drug users (68%; 95% CI, 60.0%-75.4%).

A prospective cohort study from the United States (n = 1,000 samples) directly compared reverse and traditional syphilis screening algorithms in a low-prevalence population using a
Table 5. Comparison of Traditional and Reverse Algorithms for Syphilis Testing (Key Question 3)*

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Reverse Screening Algorithm</th>
<th>Traditional Screening Algorithm</th>
<th>Definition of a Positive Screening Examination</th>
<th>Country and Setting</th>
<th>Population (Proportion With Condition)</th>
<th>Results From Traditional Screening Algorithm</th>
<th>Results From Reverse Screening Algorithm</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra et al, 27 2011</td>
<td>Total</td>
<td>August 2005-July 2008</td>
<td>August 1998-July 2005</td>
<td>Screen-positive samples defined as reactive RPR or positive/indeterminate EIA on &gt;1 duplicate tests of sample; confirmed positive if a treponemal test (TPPA, FTA-ABS, or microhemagglutination assay) was positive</td>
<td>Canada, laboratory</td>
<td>Samples submitted for syphilis screening from testing centers in the greater Toronto area between August 1998 and July 2008 were included unless they were repeat submissions after an initial positive result for a patient or samples submitted as blood donor screening (0.46% of RPR screening samples) (1.98% of EIA screening samples)</td>
<td>0.59% of samples screened positive, and 0.46% of samples were confirmed positive</td>
<td>2.24% of samples screened positive; 1.98% of samples confirmed positive. 69.6% of all confirmed positives were RPR negative. After EIA implementation, the monthly rate of confirmed positive results increased from 3.2 to 13.5 per 100 000 population (P &lt; .001).</td>
<td>Screening with EIA resulted in an increased diagnosis of syphilis, which would not have been detected under screening with RPR. 74.7% (95% CI, 73.6%-75.8%) of asymptomatic samples screened using EIA as a screening test were RPR negative. Proportion of confirmed positive tests during EIA screening that were RPR negative in patients with risk factors: MSM, 69.0% Intravenous drug users, 69.9% MSM and intravenous drug users, 68.0%</td>
</tr>
<tr>
<td>Binnicker et al, 28 2012</td>
<td>1000</td>
<td>MFI followed by RPR and TPPA for positive samples. If MFI and RPR positive, the titer of the serum sample was determined to an end point.</td>
<td>RPR screening followed by TPPA</td>
<td>Reverse algorithm: MFI+/RPR or TPPA+ Traditional algorithm: RPR+/TPPA+</td>
<td>United States, laboratory</td>
<td>Low-prevalence patient population (NR)</td>
<td>Four of 1000 (0.4%) samples tested positive by RPR and were confirmed by TPPA. These samples represented 1 case of newly diagnosed neurosyphilis, and 3 patients whose serum samples were submitted to monitor response to therapy.</td>
<td>Fifteen of 1000 (1.5%) samples tested positive by MFI screening; 11/15 samples would not have been detected by traditional screening. After record review, 3 patients had a history of previously treated syphilis, 6 patients were interpreted as falsely reactive screening results based on alternative diagnosis and/or negative TPPA results, and 2 patients were diagnosed with possible latent syphilis.</td>
<td>Reverse screening in a low-prevalence population results in a higher false reactive rate as compared with traditional testing (0.6% vs 0.0%, P = .03); however, reverse screening detected 2 patients with possible latent syphilis whose cases were not detected by the traditional screening algorithm.</td>
</tr>
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</table>

Abbreviations: *, positive; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption; MFI, multiplex flow immunoassay; MSM, men who have sex with men; NR, not reported; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination.

* Both studies were rated as fair quality using predefined criteria developed by the US Preventive Services Task Force13 (eTable 2 in the Supplement).
Bioplex IgG (multiplex flow immunoassay [MFI]). When screened with MFI, 15 samples reacted compared with 4 samples that reacted with RPR as the initial test (1.5% vs 0.4%, P = .01). All 4 samples that tested positive were positive with both testing methods. Reverse screening yielded a higher false-positive rate than traditional testing (0.6% vs 0%, P = .03), but 2 patients with possible latent syphilis that was undetected by RPR were identified using the reverse screening algorithm.

Discussion

A summary of evidence is provided in Table 2. For men who are HIV positive or MSM, screening every 3 months was associated with increased detection rates at various stages of syphilis infection, based on 4 observational studies from Australia and the United Kingdom. These studies screened MSM or HIV-positive men every 3 months and identified more new cases of infection compared with screening every 6 or 12 months. Detection rates were higher for early syphilis, newly acquired syphilis, and early-latent syphilis. These studies were limited by their nonrandomized study designs, small sizes, and reduced clinical applicability to US populations. Furthermore, confidence intervals, when reported, were wide, reflecting limited power of the studies. Results of these studies may be restricted to MSM or HIV-positive men. No studies were specifically conducted with adolescents or average-risk adults.

Three studies of the diagnostic accuracy of screening tests confirmed that they are accurate for diagnosing syphilis in asymptomatic individuals (sensitivity >85%, specificity >91% for nontreponemal and treponemal tests in most studies) but require supplemental testing. Limitations of studies include lack of demographic information for tested individuals and reduced applicability to the general US population.

Two studies of reverse sequence testing from both high- and low-prevalence populations used an automated treponemal test as the initial screening test. Rates of false-positive results at the screening stage were higher than when RPR was used for initial screening. Both methods identified additional cases of syphilis that would not have been identified using conventional methods. Although traditional sequence screening (nontreponemal tests followed by treponemal testing) is recommended for general screening because it correlates with disease activity, it may have the disadvantage of missing early primary, previously treated, or long-standing untreated infections. There are limited data on reverse testing algorithms, which also require a nontreponemal test to gauge disease activity. The CDC recommends that a third treponemal test based on different antigens (TPPA or FTA-ABS) be used to confirm the original treponemal results when using the reverse sequence screening algorithm.

Studies were lacking for several key questions, including the effectiveness of screening in reducing syphilis complications and transmission, effectiveness of risk assessment methods, and harms related to screening. The number, quality, and applicability of studies varied widely, and no studies were conducted specifically with adolescent populations. Also, the available screening studies focused on detection rates in MSM and HIV-positive patients, while other populations relevant to screening were not studied. Studies of testing during routine surveillance of HIV-positive patients were included because the distinction between screening and disease management in the context of HIV care is not always clear, and the reintegration of HIV patients into primary care is increasingly common.

Limitations of this systematic review include using only English-language articles, which could result in language bias, although there were no non-English-language studies that met inclusion criteria. Publication bias could not be assessed because of the small numbers of studies. The inclusion criteria for diagnostic accuracy studies specified asymptomatic participants and settings and tests applicable to current practice in the United States to improve clinical relevance for the USPSTF, which excluded some research in the field. For example, limiting the review to FDA-cleared tests excluded studies of many rapid tests that are becoming increasingly important for screening in asymptomatic MSM, HIV-positive patients, and other high-risk populations.

Screening tests for syphilis are accurate; however, the sequence of tests may result in different diagnostic accuracy depending on the population prevalence of the disease. Test sensitivity may also vary depending on the stage of the disease. Although there may be a role for automated EIA-based screening, the clinical effect of altering syphilis testing algorithms is poorly understood, and positive results may confer a diagnosis of prior or latent infection requiring additional testing. More studies of reverse sequence screening could provide support for limited applications of this approach when used appropriately in certain populations. Consideration of rapid testing may provide evidence for FDA clearance of this technique and increase testing access and acceptability, potentially expanding screening strategies and encouraging point-of-care screening among individuals at increased risk.

Additional research on syphilis screening is needed to directly compare the effectiveness of different screening strategies for identifying individuals at increased risk of infection, co-testing for concurrent STIs, and different screening intervals among various patient populations. Research is needed on risk assessment instruments that could narrow the field of targeted testing and risk stratification methods to improve screening efforts. More studies on diagnostic accuracy should directly compare the performance of various treponemal tests (EIA, CIA, TPPA, FTA-ABS test, and microbead immunoassay) and their use in well-defined patient populations whose clinical history and syphilis risk are known. New studies of diagnostic accuracy would characterize discordant sera with nonreactive confirmatory treponemal tests and study the utility of certain tests in diagnosing early primary syphilis. Further research is needed to understand the effect of screening for syphilis on clinical outcomes; effective screening strategies, including reverse sequence screening, in various patient populations; harms of screening.

Conclusions

Screening MSM or HIV-positive men for syphilis every 3 months is associated with improved syphilis detection in these groups. Treponemal or nontreponemal tests are accurate screening tests but require confirmation. Research is needed on the effect of screening on clinical outcomes; effective screening strategies, including reverse sequence screening, in various patient populations; and harms of screening.
Evidence Report: Screening for Syphilis

US Preventive Services Task Force
Clinical Review & Evaluation

ARTICLE INFORMATION

Author Contributions: Dr Cantor had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cantor, Pappas, Nelson.

Acquisition, analysis, or interpretation of data: Cantor, Pappas, Daeger, Nelson.

Drafting of the manuscript: Cantor, Pappas, Daeger, Nelson.

Critical revision of the manuscript for important intellectual content: Cantor, Nelson.

Administrative, technical, or material support: Pappas, Daeger.

Study supervision: Cantor, Nelson.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the USPSTF.

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We gratefully acknowledge the following individuals for their contributions to this project: the AHRQ staff; the USPSTF; and Evidence-based Practice Center staff members Spencer Dandy, BS, and Andrew Hamilton, MLS, MS. None received compensation for their role in the study.

Additional Information: A draft version of this evidence report underwent external peer review from 4 content experts (Heidi M. Bauer, MS, MPH, MD; California Department of Public Health; Matthew J. Binnicker, PhD, Mayo Clinic; Khalil Ghanem, MD, PhD, Johns Hopkins University School of Medicine; and Jeffrey D. Klausner, MD, MPH, University of California, Los Angeles) and 2 federal partners: Centers for Disease Control and Prevention and the Military Health System. Comments were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to JAMA.

REFERENCES


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