US Preventive Services Task Force | EVIDENCE REPORT

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.

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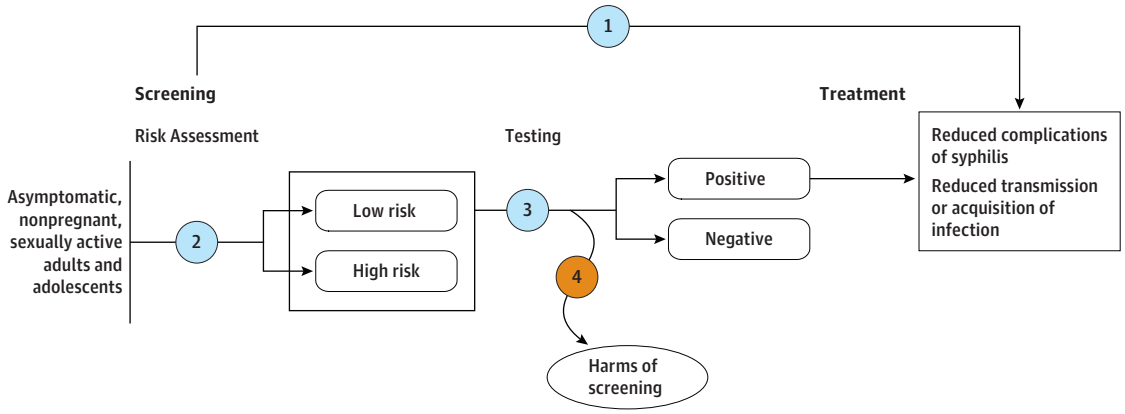
Figure 1. Analytic Framework



Key questions

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?

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

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

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

Contextual questions

A Which population subgroups, including men who have sex with men, are at highest risk for incident syphilis infection?

B Which population subgroups are at highest risk for syphilis-related morbidity and mortality?

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.[1] Syphilis infection is associated with HIV infection and increases the risk for acquiring or spreading HIV.[2] Antibiotics are effective for treating and curing syphilis.[1,3,4]

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.[2,5-7] 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.[2,8,9] Men who have sex with men accounted for 61% of all primary and secondary syphilis cases reported in 2014.[2]

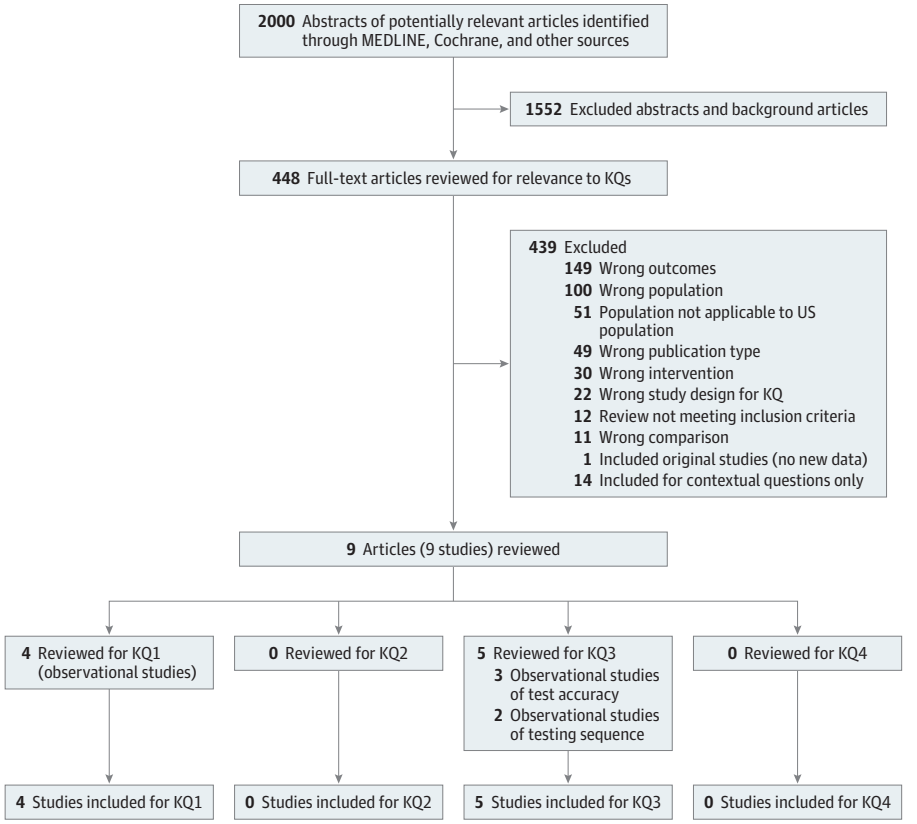
In 2004, the US Preventive Services Task Force (USPSTF) recommended routine screening for syphilis in asymptomatic men and nonpregnant women at increased risk of infection (A recommendation) and recommended against routine screening for those not at increased risk (D recommendation).[10] Studies were 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).[11] 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[12] in collaboration with the USPSTF and Agency for Healthcare Research and Quality, investigators determined the scope and KQs using established methods[13] (**Figure 1**). The final research plan[14] was posted on the USPSTF website before conducting the review.

Figure 2. Literature Search Flow Diagram



Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Other sources include systematic reviews, relevant studies, and reference lists.

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**[15-19]). 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.

Table 1. Sensitivity and Specificity of Commonly Used Syphilis Tests[15-19a]

Syphilis Screening Test	Sensitivity by Stage of Untreated Syphilis, % (Range)[b]					Specificity, % (Range)[b]
	Mixed	Primary	Secondary	Latent	Tertiary	
Nontreponemal						
VDRL[c]		78 (74-87)	100	96 (88-100)	71 (37-94)	98 (96-99)
RPR[c]		86 (77-99)	100	98 (95-100)	73	98 (93-99)
TRUST[c]		85 (77-86)	100	98 (95-100)		99 (98-99)
USR[c]		80 (72-88)	100	95 (88-100)		99
Treponemal						
FTA-ABS[c]		84 (70-100)	100	100	96	97 (84-100)
TPPA[c]		88 (86-100)	100	97 (97-100)	94	96 (95-100)
Enzyme immunoassay		(77-100)	(85-100)	(64-100)	NA	(99-100)
Trep-Check	95.9[d]					98.5[d]
Trep-Sure	96.9[d]					95.4[d]
Chemiluminescence immunoassay		98	100	100	100	99
LIAISON[e]	99.2					99.9
Multiplex flow immunoassay						
BioPlex 2200; Syphilis IgG	96.9[d]					98.0[d]
Syphilis Health Check	95.6,[f] 98.5[g]					90.5,[f] 97.4[g]

Abbreviations: FTA-ABS, fluorescent treponemal antibody absorption; NA, not applicable; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination; TRUST, toluidine red unheated serum test; USR, unheated serum reagin; VDRL, Venereal Disease Research Laboratory.

[a] This is not a comprehensive list of tests available in the United States.

[b] Sensitivity and specificity of tests are also dependent on the disease prevalence in the population tested and may vary considerably by manufacturer or the standard used as a comparison.

[c] Unknown reference standard.

[d] When compared with FTA-ABS test results.

[e] When compared with results from Western blotting.

[f] When compared with nontreponemal test results.

[g] When compared with treponemal test results.

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 USPSTF[13] (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 Australia[20-22] and 1 fair-quality observational study from the United Kingdom[23] 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 men[20,23] 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

Key Question	Main Findings From Prior USPSTF Reviews	Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
Key question 1: Effectiveness of screening in reducing complications and transmission[b]	No studies	4 observational studies of MSM and HIV-positive males	No studies of screening effectiveness No studies of screening intervals in other populations	Consistent	Studies conducted in Europe and Australia in MSM and HIV-positive MSM; studies included high-prevalence populations	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* < .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.	Fair
Key question 2: Effectiveness of risk assessment[c]	No studies	No studies	No studies	No studies	No studies	No studies	No studies
Key question 3: Screening accuracy[d]	Included studies conducted in populations and settings not applicable to this update; descriptive information on new screening tests and methods also mentioned	5 observational studies (3 test accuracy, 2 testing sequence)	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.	Consistent	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.	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* = .03) and in a higher-prevalence Canadian population (0.26% vs 0.13%). Both methods identified additional positive tests not identified using conventional methods.	Fair
Key question 4: Screening harms[e]	No studies	No studies	No studies	No studies	No studies	No studies	No studies

Abbreviations: MSM, men who have sex with men; RPR, rapid plasma reagin; STI, sexually transmitted infection; USPSTF, US Preventive Services Task Force.

[a] Based on new evidence identified for the update plus previously reviewed evidence.

[b] 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?

[c] 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?

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

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

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]

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-

Table 3. Observational Studies of Screening Intervals for Syphilis and Screening Among Population Subgroups (Key Question 1)[a]

Source	No. of Participants	Population	Interventions	Duration of Intervention	Outcomes
Bissessor et al,[20] 2010	1301	MSM attending a public STI clinic in Australia, offering HIV care to 20% of men in the region	Routine syphilis screening every 3 mo as part of HIV monitoring vs annual screening (control)	1 y	Proportion of HIV-positive MSM attending the HIV clinic diagnosed with early syphilis: Screened: 8.1% (48/587) Control: 3.1% (14/444) *P* = .001
					Proportion of asymptomatic with early syphilis: Screened: 85% (41/48) Control: 21% (3/14) *P* = .006
Cohen, et al,[23] 2005	2389	HIV patients in the United Kingdom with newly positive syphilis serology, asymptomatic at the time of screening	Routine syphilis screening every 3 mo vs annual screening (control)	1 y	Event rate of early asymptomatic infection, per 1000 patient-years: Screened: 7.3 (CI, 5.2-9.9) Controls: 2.8 (CI, 1.8-4.0) *P* < .05
Zou et al,[21] 2013	4514	MSM attending public STI clinic in Australia, opting to receive clinical reminders	Three-, 6-, or 12-mo clinical reminders vs control	18 mo	No. (%) of MSM diagnosed with syphilis at least once: Early syphilis: 3 mo: 19 (3.2), *P* = .03 6 mo: 5 (1.9), *P* = .68 3, 6, or 12 mo: 25 (2.8), *P* = .06 Control: 15 (1.5) Early-latent syphilis: 3 mo: 10 (1.7), *P* = .008 6 mo: 2 (0.8), *P* = .47 3, 6, or 12 mo: 12 (1.4), *P* = .03 Control: 4 (0.4)
					No. (%) of all tests positive in subsequent visits: Early syphilis: 3 mo: 22 (3.0), *P* = .53 6 mo: 5 (2.5), *P* = .98 3, 6, or 12 mo: 28 (3.0), *P* = .57 Control: 15 (2.5)
Bissessor et al,[22] 2011	6789	Consultations with MSM attending public STI clinic in Australia, offering HIV care to 20% of men in the region	A computer alert system aimed at clinicians to screen higher-risk MSM (>10 partners in 12 mo) for syphilis every 3 mo vs annually (control)	1 y	Proportion of higher-risk MSM diagnosed with early syphilis who are asymptomatic: Screened: 53% (31/58) Control: 16% (5/31) *P* = .001
					Proportion of lower-risk MSM diagnosed with early syphilis who are asymptomatic: Screened: 19% (3/16) Control: 10% (1/10) No difference, *P* = .60

Abbreviations: MSM, men who have sex with men; STI, sexually transmitted infection.

[a] All studies were rated as fair quality using predefined criteria developed by the US Preventive Services Task Force[13] (eTable 2 in the Supplement).

risk patients improved the rate of syphilis testing and diagnosis.[22] Men who reported 10 or more sexual partners within the prior 12 months were defined as higher risk for syphilis. 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 both 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

Table 4. Diagnostic Accuracy of Syphilis Testing (Key Question 3)[a]

Source	No. of Participants and Screening Test	Definition of a Positive Screening Test	Reference Standards	Country and Setting	Population (Percentage With Condition)	Sensitivity, Specificity, PPV, and NPV (95% CI)[b]	False-Positive and False-Negative Results
Wong et al,[24] 2011	n = 674 Trep-Sure EIA	Samples that tested positive by TPPA confirmation test	VDRL screening with TPPA confirmation	United States, routine syphilis testing	Patients presenting to the San Francisco municipal sexually transmitted disease clinic; population at this clinic is 69.3% MSM, 16.6% HIV positive (39.7%)	Sensitivity: 98.0% (95.8%-99.3%) Specificity: 98.6% (96.9%-99.6%) PPV: 98.4% (96.2%-99.5%) NPV: 98.4% (96.5%-99.4%)	FP: 5/673 FN: 6/673
Tsang et al,[25] 2007	n = 604 Trep-Check IgG EIA	Consensus results were derived from conventional serologic tests, both screening (RPR, VDRL, or EIA) and confirmatory (FTA-ABS, INNO-LIA, or TPPA). Probable past syphilis infection was indicated if samples were negative by screening EIA but positive by confirmatory treponemal assay. Probable active syphilis infection was indicated if samples were positive by both the screening EIA and confirmatory treponemal assay.	RPR, VDRL, or EIA screening with FTA-ABS, INNO-LIA, or TPPA confirmation	Canada, National Microbiology Laboratory	Specimens from local hospitals or provincial public health laboratories submitted for confirmation of local test results or for further evaluation of serologic status (5.6%)	Sensitivity: 85.3% (68.9%-95.1%) Specificity: 95.6% (93.6%-97.1%) PPV: 53.7% (39.6%-67.4%) NPV: 99.1% (97.9%-99.7%)	FP: 25/604 FN: 5/604
Juárez-Figueroa et al,[26] 2007	n = 198 TPPA	Samples that tested positive to VDRL and FTA-ABS were defined as serologically active syphilis	VDRL screening with FTA-ABS confirmation	Mexico, STI clinic	Asymptomatic female sex workers (15.7%)	Sensitivity: 87.1% (70.2%-96.3%) Specificity: 100% (97.6%-100%) PPV: 100% (87.1%-100%) NPV: 97.5% (93.6%-99.3%)	FP: 0 FN: 4/185

Abbreviations: EIA, enzyme immunoassay; FN, false-negative results; FP, false-positive results; FTA-ABS, fluorescent treponemal antibody absorption; INNO-LIA, a multiparameter line immunoassay; MSM, men who have sex with men; NPV, negative predictive value; PPV, positive predictive value; RPR, rapid plasma reagin; STI, sexually transmitted infection; TPPA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory.

[a] All studies were rated as fair quality using predefined criteria developed by the US Preventive Services Task Force[13] (eTable 2 in the Supplement).

[b] Calculated.

specimens with a 5.6% positive test rate using conventional testing 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. Methodologic limitations 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 comparing laboratory results from a high-prevalence metropolitan area (incidence rate ratio of 1.69-1.80 relative to surrounding suburban 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 = 1000 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)[a]

Source	No.	Reverse Screening Algorithm	Traditional Screening Algorithm	Definition of a Positive Screening Examination	Type of Study	Country and Setting	Population (Proportion With Condition)	Results From Traditional Screening Algorithm	Results From Reverse Screening Algorithm	Outcomes
Mishra et al,[27] 2011	Total samples: 3 092 938 RPR screening samples: 2 055 913 EIA screening samples: 1 037 025	August 2005-July 2008 EIA screening followed by RPR testing and an alternate treponemal confirmatory test	August 1998-July 2005 RPR screening and confirmatory treponemal test	Screen-positive samples defined as reactive RPR or positive/indeterminate EIA on >1 duplicate tests of sample; confirmed positive if a treponemal test (TPPA, FTA-ABS, or microhemagglutination assay) was positive	Retrospective cohort	Canada, laboratory	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)	0.59% of samples screened positive, and 0.46% of samples were confirmed positive	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 ($P < .001$).	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%
Binnicker et al,[28] 2012	1000	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.	RPR screening followed by TPPA	Reverse algorithm: MFI+/RPR or TPPA+ Traditional algorithm: RPR+/TPPA+	Prospective cohort study	United States, laboratory	Low-prevalence patient population (NR)	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.	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.	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.

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.

[a] Both studies were rated as fair quality using predefined criteria developed by the US Preventive Services Task Force[13] (eTable 2 in the Supplement).

Bioplex IgG (multiplex flow immunoassay [MFI]).[28] 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.[20-23] Detection rates were higher for early syphilis,[20,22] newly acquired syphilis,[23] and early-latent syphilis.[21] 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[24-26] 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.[27,28] 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.[29] 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.[30]

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; and 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.

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, Daeges, Nelson.
Drafting of the manuscript: Cantor, Pappas, Daeges, Nelson.
Critical revision of the manuscript for important intellectual content: Cantor, Nelson.
Administrative, technical, or material support: Pappas, Daeges.
Study supervision: Cantor, Nelson.

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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

1. STD surveillance case definitions. Centers for Disease Control and Prevention. http://www.cdc.gov/std/stats/CaseDefinitions-2014.pdf. Accessed February 27, 2015.

2. 2014 Sexually transmitted diseases surveillance. Centers for Disease Control and Prevention. http://www.cdc.gov/std/stats14/. Accessed May 6, 2016.

3. Mahoney JF, Arnold RC, Harris A. Penicillin treatment of early syphilis: a preliminary report. *Am J Public Health Nations Health*. 1943;33(12):1387-1391.

4. Douglas JM Jr. Penicillin treatment of syphilis: clearing away the shadow on the land. *JAMA*. 2009;301(7):769-771.

5. Van Wagoner NJ, Harbison HS, Drewry J, Turnipseed E, Hook EW III. Characteristics of women reporting multiple recent sex partners presenting to a sexually transmitted disease clinic for care. *Sex Transm Dis*. 2011;38(3):210-215.

6. Mayer KH, Bush T, Henry K, et al; SUN Investigators. Ongoing sexually transmitted disease acquisition and risk-taking behavior among US HIV-infected patients in primary care: implications for prevention interventions. *Sex Transm Dis*. 2012;39(1):1-7.

7. Brodsky JL, Samuel MC, Mohle-Boetani JC, et al. Syphilis outbreak at a California men's prison, 2007-2008: propagation by lapses in clinical management, case management, and public health surveillance. *J Correct Health Care*. 2013;19(1):54-64.

8. Weinstock H, Berman S, Cates W Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. *Perspect Sex Reprod Health*. 2004;36(1):6-10.

9. Marx R, Aral SO, Rolfs RT, Sterk CE, Kahn JG. Crack, sex, and STD. *Sex Transm Dis*. 1991;18(2):92-101.

10. Calonge N; US Preventive Services Task Force. Screening for syphilis infection: recommendation statement [published correction in *Ann Fam Med*. 2004;2(5):517]. *Ann Fam Med*. 2004;2(4):362-365.

11. Cantor A, Nelson HD, Daeges M, Pappas M. *Screening for Syphilis in Nonpregnant Adolescents and Adults: Systematic Review to Update the 2004 US Preventive Services Task Force Recommendation: Evidence Synthesis No. 136*. Rockville, MD: Agency for Healthcare Research and Quality; 2016. AHRQ publication 14-05213-EF-1.

12. Nelson HD, Glass N, Huffman L, et al. *Screening for Syphilis: Brief Update for the US Preventive Services Task Force*. Rockville, MD: Agency for Healthcare Research and Quality; 2004.

13. Procedure manual. US Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes. Accessed May 16, 2015.

14. Final research plan: syphilis infection in nonpregnant adolescents and adults: screening. US Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/Page/Document/final-research-plan95/syphilis-infection-in-nonpregnant-adults-and-adolescents. Accessed November 11, 2015.

15. 510(k) Substantial equivalence determination decision summary No. K102400: Diagnostics Direct LLC. US Food and Drug Administration. http://www.accessdata.fda.gov/cdrh_docs/reviews/k102400.pdf. Accessed May 19, 2015.

16. Seña AC, White BL, Sparling PF. Novel *Treponema pallidum* serologic tests: a paradigm shift in syphilis screening for the 21st century. *Clin Infect Dis*. 2010;51(6):700-708.

17. Marangoni A, Sambri V, Accardo S, et al. Evaluation of LIAISON Treponema Screen, a novel recombinant antigen-based chemiluminescence immunoassay for laboratory diagnosis of syphilis. *Clin Diagn Lab Immunol*. 2005;12(10):1231-1234.

18. Binnicker MJ, Jespersen DJ, Rollins LO. Treponema-specific tests for serodiagnosis of syphilis: comparative evaluation of seven assays. *J Clin Microbiol*. 2011;49(4):1313-1317.

19. Ratnam S. The laboratory diagnosis of syphilis. *Can J Infect Dis Med Microbiol*. 2005;16(1):45-51.

20. Bissessor M, Fairley CK, Leslie D, Howley K, Chen MY. Frequent screening for syphilis as part of HIV monitoring increases the detection of early asymptomatic syphilis among HIV-positive homosexual men. *J Acquir Immune Defic Syndr*. 2010;55(2):211-216.

21. Zou H, Fairley CK, Guy R, et al. Automated, computer generated reminders and increased detection of gonorrhoea, chlamydia and syphilis in men who have sex with men. *PLoS One*. 2013;8(4):e61972.

22. Bissessor M, Fairley CK, Leslie D, Chen MY. Use of a computer alert increases detection of early, asymptomatic syphilis among higher-risk men who have sex with men. *Clin Infect Dis*. 2011;53(1):57-58.

23. Cohen CE, Winston A, Asboe D, et al. Increasing detection of asymptomatic syphilis in HIV patients. *Sex Transm Infect*. 2005;81(3):217-219.

24. Wong EH, Klausner JD, Caguin-Grygiel G, et al. Evaluation of an IgM/IgG sensitive enzyme immunoassay and the utility of index values for the screening of syphilis infection in a high-risk population. *Sex Transm Dis*. 2011;38(6):528-532.

25. Tsang RS, Martin IE, Lau A, Sawatzky P. Serological diagnosis of syphilis: comparison of the Trep-Chek IgG enzyme immunoassay with other screening and confirmatory tests. *FEMS Immunol Med Microbiol*. 2007;51(1):118-124.

26. Juárez-Figueroa L, Uribe-Salas F, García-Cisneros S, Olamendi-Portugal M, Conde-Glez CJ. Evaluation of a rapid strip and a particle agglutination tests for syphilis diagnosis. *Diagn Microbiol Infect Dis*. 2007;59(2):123-126.

27. Mishra S, Boily MC, Ng V, et al. The laboratory impact of changing syphilis screening from the rapid-plasma reagin to a treponemal enzyme immunoassay: a case-study from the Greater Toronto Area. *Sex Transm Dis*. 2011;38(3):190-196.

28. Binnicker MJ, Jespersen DJ, Rollins LO. Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. *J Clin Microbiol*. 2012;50(1):148-150.

29. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev*. 1995;8(1):1-21.

30. Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening: five laboratories, United States, 2006-2010. *MMWR Morb Mortal Wkly Rep*. 2011;60(5):133-137.