Evidence Synthesis

Number 136

Screening for Syphilis in Nonpregnant Adolescents and Adults: Systematic Review to Update the 2004 U.S. Preventive Services Task Force Recommendation

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No.: HHSA-290-2012-00015-I, Task Order No. 4

Prepared by:
Pacific Northwest Evidence-Based Practice Center
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, OR 97239
www.ohsu.edu/epc

Investigators:
Amy Cantor, MD, MPH
Heidi D. Nelson, MD, MPH
Monica Daeges, BA
Miranda Pappas, MA

AHRQ Publication No. 14-05213-EF-1
June 2016
This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2012-00015-I). The investigators involved have declared no conflicts of interest with objectively conducting this research. The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

The final report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials that are clearly noted in the document. Further reproduction of those copyrighted materials is prohibited without the specific permission of copyright holders.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements

The authors acknowledge Andrew Hamilton, MLS, MS, for conducting literature searches and Spencer Dandy, BS, for assistance with drafting this report at the Oregon Health & Science University. The authors also thank AHRQ Medical Officers Tina Fan, MD, MPH, and Tess Miller, DrPH, as well as current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations.

Suggested Citation

Structured Abstract

**Background:** In 2004, the U.S. Preventive Services Task Force recommended routine screening for syphilis infection in asymptomatic persons at increased risk of infection, and recommended against screening in those not at increased risk.

**Purpose:** To update a prior systematic review on screening for syphilis infection in asymptomatic, nonpregnant adolescents and adults for the U.S. Preventive Services Task Force.

**Data Sources:** Cochrane Central Register of Controlled Trials (to March 2016) and Cochrane Database of Systematic Reviews (to March 2016), MEDLINE (January 2004 to March 2016), and reference lists.

**Study Selection:** English-language trials and observational studies of screening effectiveness, test accuracy, and screening harms.

**Data Extraction:** One investigator abstracted details about study design, patient population, setting, screening method, followup, and results. Two investigators independently applied prespecified criteria to rate study quality. Discrepancies were resolved through consensus.

**Data Synthesis:** Four observational studies conducted outside the United States evaluated detection rates using specific screening intervals among men who have sex with men (MSM) or persons living with HIV. Higher rates of detection were reported for early syphilis in MSM living with HIV (8.1% vs. 3.1%; p=0.001), newly acquired syphilis in MSM living with HIV (7.3 cases [95% CI, 5.2 to 9.9] vs. 2.8 cases [95% CI, 1.8 to 4.0] per 1,000 patient-years; p<0.05); early latent syphilis in MSM (1.7% vs. 0.4%, p=0.008); and early syphilis in higher-risk MSM (53% vs. 16%; p=0.001) when screening every 3 months compared with 6 or 12 months. Three diagnostic accuracy studies found that treponemal or nontreponemal tests are accurate screening tests for syphilis in asymptomatic persons (sensitivity >85% and specificity >91% for nontreponemal and treponemal tests in most studies) but require confirmatory testing. Two studies of the accuracy of reverse sequence testing indicated that using an automated treponemal test for initial screening resulted in a higher rate of false-reactive tests compared with using the Rapid Plasma Reagin test as an initial test in a low prevalence U.S. population (0.6% vs. 0.0%; p=0.03) and a higher prevalence Canadian population (0.26% vs. 0.13%), but both methods also identified additional positive tests that would not have been identified using conventional methods.

**Limitations:** No studies addressed the effectiveness of screening, the effectiveness of risk assessment instruments, or the adverse effects of screening. No studies were specifically conducted in adolescents. Only screening tests and methods cleared by the U.S. Food and Drug Administration for current clinical practice were included to determine diagnostic accuracy.

**Conclusions:** Observational data from four studies demonstrate improved detection of syphilis infection among MSM or men living with HIV who are screened every 3 months compared with 6 or 12 months. Screening with treponemal or nontreponemal tests is accurate for detecting syphilis in asymptomatic persons but requires confirmatory testing. Further research is needed to
understand the impact of screening for syphilis on clinical outcomes; effective screening strategies, including reverse sequence screening, in various patient populations; and harms of screening.
### Table of Contents

**Chapter 1. Introduction**
- Purpose and Previous U.S. Preventive Services Task Force Recommendation ......................................................... 1
- Condition Definition ......................................................................................................................................................... 1
- Prevalence ....................................................................................................................................................................... 2
- Etiology, Natural History, and Burden of Disease ........................................................................................................... 2
- Risk Factors ..................................................................................................................................................................... 2
- Rationale for Screening and Screening Strategies ....................................................................................................... 3
- Interventions and Treatment ........................................................................................................................................ 4
- Current Clinical Practice .............................................................................................................................................. 6
- Recommendations of Other Groups ............................................................................................................................ 6

**Chapter 2. Methods**
- Key Questions and Analytic Framework ........................................................................................................................ 7
  - Key Questions ............................................................................................................................................................... 7
  - Contextual Questions .................................................................................................................................................. 7
- Search Strategies ............................................................................................................................................................. 7
- Study Selection ............................................................................................................................................................... 8
- Data Abstraction and Quality Rating ............................................................................................................................ 9
- Data Synthesis ............................................................................................................................................................... 9
- External Review ............................................................................................................................................................. 9
- Response to Public Comments .................................................................................................................................. 9

**Chapter 3. Results**
- Key Question 1. What Is the Effectiveness of Screening for Syphilis in Reducing Complications of the Disease and Transmission or Acquisition of Other STIs in Asymptomatic, Nonpregnant, Sexually Active Adults and Adolescents? What Is the Effectiveness of Specific Screening Intervals and Screening Among Population Subgroups? .............................................................. 11
  - Summary ..................................................................................................................................................................... 11
  - Evidence .................................................................................................................................................................... 11
- 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? ... 12
- Key Question 3. What Is the Accuracy of Currently Used Screening Tests and Strategies for Detecting Syphilis Infection? .............................................................................................................................................. 13
  - Summary ..................................................................................................................................................................... 13
  - Evidence .................................................................................................................................................................... 13
- Key Question 4. What Are the Harms of Screening? ...................................................................................................... 15
- Contextual Question 1. Which Population Subgroups, Including MSM, Are at Highest Risk for Incident Syphilis Infection? .............................................................................................................................. 16
  - MSM ........................................................................................................................................................................ 16
  - Persons Living With HIV ............................................................................................................................................. 16
  - Young Adult Men .......................................................................................................................................................... 17
  - Racial Minorities .......................................................................................................................................................... 17
  - Sex Workers ............................................................................................................................................................... 17
  - Adults in Correctional Facilities ................................................................................................................................ 18
  - Residents of Specific Regions ..................................................................................................................................... 18
Contextual Question 2. Which Population Subgroups Are at Highest Risk for Syphilis-Related Morbidity and Mortality?............................................................................................................18

Chapter 4. Discussion.............................................................................................................19
  Summary of Review Findings .................................................................................................19
  Limitations ............................................................................................................................20
  Emerging Issues and Next Steps...........................................................................................21
  Relevance for Priority Populations .......................................................................................21
  Future Research ....................................................................................................................21
  Conclusions ..........................................................................................................................22

References ................................................................................................................................23

Figures
  Figure 1. Screening Test Algorithms
  Figure 2. Analytic Framework

Tables
  Table 1. 2014 CDC Case Definitions for Syphilis
  Table 2. Tests for Syphilis
  Table 3. Sensitivity and Specificity of Common Syphilis Tests
  Table 4. Recommendations of Other Groups
  Table 5. Observational Studies of Syphilis and HIV Coinfection
  Table 6. Rates of Primary and Secondary Syphilis Infection by Population Subgroups
  Table 7. Summary of Evidence

Appendixes
  Appendix A. Terminology
  Appendix B. Detailed Methods
    Appendix B1. Search Strategies
    Appendix B2. Inclusion and Exclusion Criteria
    Appendix B3. Literature Flow by Key Question
    Appendix B4. List of Excluded Studies
    Appendix B5. Quality Rating Criteria
    Appendix B6. List of Peer Reviewers
  Appendix C. Evidence and Quality Tables
    Appendix C1. Observational Studies of Screening Intervals for Syphilis and Screening Among Population Subgroups
    Appendix C2. Quality Ratings of Included Cohort Studies
    Appendix C3. Diagnostic Accuracy of Syphilis Testing
    Appendix C4. Quality Ratings of Diagnostic Accuracy Studies
    Appendix C5. Comparison of Traditional and Reverse Algorithms for Syphilis Testing
Chapter 1. Introduction

Purpose and Previous U.S. Preventive Services Task Force Recommendation

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2004 recommendation on screening for syphilis infection in nonpregnant adolescents and adults. It focuses on studies published since the prior USPSTF systematic review of this topic. \(^1\) Appendix A provides a description of terms and abbreviations used in this report.

In 2004, the USPSTF issued an A recommendation to screen for syphilis in all persons at increased risk. \(^2\) Populations at increased risk, based on incidence rates, include men who have sex with men (MSM) and engage in high-risk sexual behavior; commercial sex workers; persons who exchange sex for drugs; and adults in correctional facilities. The USPSTF recommended against routine screening in asymptomatic men and nonpregnant women not at increased risk of infection (D recommendation), and did not find evidence to support an optimal screening interval for persons at increased risk.

Condition Definition

Syphilis is a chronic, systemic, infectious disease caused by sexual or vertical transmission (i.e., acquired during pregnancy or delivery) of the bacterium *Treponema pallidum*. Syphilis causes a variety of symptoms corresponding to stages of infection that can occur in an individual over time. Stages include primary, secondary, early and late latent, and late syphilis. Case definitions for these stages were updated in January 2014 by the Centers for Disease Control and Prevention (CDC) (Table 1). \(^3\)

The clinical manifestation of primary syphilis usually consists of a painless local chancre. Although the chancre usually heals without treatment within a few weeks, the disease quickly becomes systemic. Secondary syphilis may present as rash, fever, headache, malaise, anorexia, diffuse lymphadenopathy, or diminished visual acuity. These symptoms usually resolve without therapy, but some patients experience relapse up to 5 years after the initial episode. \(^4\) Untreated patients with primary syphilis will progress to the secondary stage of syphilis, and untreated patients with secondary syphilis will progress to early latent syphilis. Twenty-five percent of untreated patients in early latent syphilis may experience a relapse back to secondary syphilis. \(^5\)

Latent syphilis occurs when a patient has evidence of infection based on positive serologic tests but is asymptomatic. The updated case definitions distinguish between early and late latent syphilis based on the duration of infection. \(^3\) Early latent syphilis includes infections with evidence that they were acquired within 12 months, while late latent infections have no such evidence. \(^3,4,6\) Late stage syphilis may affect cardiovascular function and can also produce lesions in other organs, especially skin and bones. These can appear from 1 to 30 years after the primary infection. \(^4\) In addition, syphilis can infect the nervous system at any stage and present as a
spectrum of symptoms from none to headache, altered behavior, movement disorders, and dementia.\textsuperscript{7}

**Prevalence**

Early syphilis is defined as an infection present for less than 1 year in duration, and is a reportable infection in the United States because it spreads easily to sexual partners. Data on incidence and prevalence are most often based on cases reported to state health departments and are summarized by the CDC. Reported rates likely underestimate true rates because sexually transmitted infection (STI) screening and case reporting may be low in practice.\textsuperscript{1}

From 2013 to 2014, the total number of syphilis cases in all stages reported to the CDC increased 12.3 percent, from 56,482 to 63,450 cases.\textsuperscript{8} During this period, reported cases of primary and secondary syphilis increased by 15.1 percent, cases of early latent syphilis increased by 14.8 percent, and cases of late and late latent syphilis increased by 7.9 percent. In 2014, the case count (19,999 cases) and rate (6.3 cases per 100,000 persons) of primary and secondary syphilis were the highest reported since 1995.

Increased rates of primary and secondary syphilis infection have occurred primarily among men, increasing from 2013 to 2014 from 10.3 to 11.7 cases per 100,000 men.\textsuperscript{8} Rates among women also increased during this same period from 0.9 to 1.1 cases per 100,000 women.

**Etiology, Natural History, and Burden of Disease**

Nearly all newly acquired syphilis infections occur through sexual transmission, except for cases resulting from vertical transmission. Syphilis infection is characterized by several clinical stages and varying periods of infectivity and can affect any tissue or vascular organ.\textsuperscript{6} Syphilis is transmissible during early stages (primary and secondary syphilis), and requires exposure to open lesions with organisms present or contact of infected secretions with almost any tissue. The efficiency of transmission, or average risk of infection per exposure,\textsuperscript{9} ranges from 15.9 to 30.3 percent based on reports of partner transmission from patients with untreated early syphilis.\textsuperscript{10,11} Vertical transmission can occur during any stage. Syphilis infection is associated with HIV infection and increases risks for acquiring or spreading the HIV virus if exposed.\textsuperscript{8} The presence of syphilis infection in persons living with HIV increases HIV viral load and decreases CD4 cell count, consequently increasing the risk of HIV transmission.\textsuperscript{12-14}

Specific population subgroups are disproportionally affected by syphilis infection. Studies describing prevalence rates for these groups are summarized under Contextual Question 1 in the Results section. The estimated total direct costs of treating adults with syphilis in the United States in 2010 was $39.3 million (range, $19.6 to $58.9 million).\textsuperscript{15}

**Risk Factors**

Several studies and the CDC have reported risk factors that may increase a person’s risk for syphilis infection.\textsuperscript{8,16-18} These include previous syphilis infection, having a partner with a syphilis
infection, current HIV infection, and having more than four sex partners in the preceding year. In addition, increased prevalence rates have been associated with several sociodemographic groups. These include MSM, young adult men, sex workers, adults in correctional facilities, and individuals who are of black race or live in metropolitan areas, particularly in southern and western States. Studies describing prevalence rates for these groups are summarized under Contextual Question 1 in the Results section.

### Rationale for Screening and Screening Strategies

Identification of persons with undiagnosed syphilis infections reduces the severity of complications from untreated disease as well as disease transmission. The availability of accurate screening tests and effective treatment make syphilis screening clinically feasible. Since syphilis has been associated with HIV coinfection, identification of persons infected with syphilis may also reduce rates of HIV infection.

Screening strategies include universal or targeted screening in high-prevalence areas. Most guidelines currently recommend targeted screening based on a person’s risk for infection. A study conducted in an area of high syphilis incidence demonstrated that screening for and treatment of syphilis among female inmates reduced syphilis in the general community, suggesting that targeted screening of high-risk groups may impact general population infection rates.

Syphilis testing is particularly complicated because there is no gold standard, and testing is almost always testing for antibody, not infection. Traditionally, screening for syphilis infection is a two-step process that involves an initial nontreponemal test (Venereal Disease Research Laboratory [VDRL] or Rapid Plasma Reagin [RPR]) followed by a confirmatory treponemal test (fluorescent treponemal antibody absorbed [FTA-ABS] or \( T. pallidum \) particle agglutination [TPPA]) (Table 2). Sensitivity of the RPR and VDRL tests are estimated to be 78 to 86 percent for detecting primary syphilis infection and 100 percent for detecting secondary infection (Table 3). Specificity ranges from 85 to 99 percent and may be reduced in persons who have preexisting conditions that produce false-positive results (i.e., collagen vascular disease, pregnancy, intravenous drug use, advanced malignancy, tuberculosis, malaria, and viral and rickettsia diseases). The FTA-ABS test has a reported sensitivity of 84 percent for detecting primary syphilis infection and almost 100 percent sensitivity for detecting syphilis infection in other stages, and a specificity of 97 percent. The TPPA test has a reported sensitivity of 88 percent for primary syphilis and 94 to 100 percent in the later stages, with a specificity of 96 percent (Table 3).

Several new screening tests are currently being studied, including the immunochromatographic strip, line immunoassay, and rapid syphilis tests. Recently, the U.S. Food and Drug Administration (FDA) granted a waiver under the Clinical Laboratory Improvements Amendment allowing the distribution of a rapid screening test, the Syphilis Health Check™ test (Diagnostics Direct, LLC, Cape May, NJ), to nontraditional laboratory sites in the United States and the administration of the test by untrained operators. This test allows initial screening results from whole blood obtained from a finger stick within 12 minutes, though positive results need to
be followed up with additional serology. New experimental diagnostic approaches, including using the B-cell-attracting chemokine (C-X-C motif) ligand 13 as a cerebrospinal fluid (CSF) marker, may help identify suspected neurosyphilis cases. Nontreponemal screening tests followed by treponemal confirmatory tests continue to be the standard algorithm; however, interpreting false-negative and false-positive test results can be challenging due to prozone phenomena or serofast reactions (Appendix A).

In addition, variations in the sequence of testing have been proposed to reduce the time and labor involved with syphilis screening (Figure 1). The reverse sequence screening algorithm employs treponemal tests that allow automation, such as the enzyme immunoassay (EIA) or multiplex flow immunoassay (MFI), as initial screening tests, followed by supplemental nontreponemal tests for reactive specimens. Discordant samples (positive by the treponemal screening test, but negative by the nontreponemal supplemental test) should be tested by an additional treponemal test, preferably one that utilizes different antigens to confirm the original positive screen. When using the reverse screening approach, the positive predictive value of the treponemal screening test may be lower in populations with low prevalence of syphilis. Notably, reverse sequence screening identifies previously treated syphilis infections in addition to untreated or incompletely treated syphilis.

The yield of screening using a two-step process (RPR followed by confirmatory FTA-ABS) can be estimated using test characteristics and the incidence of syphilis infection in a given population. For example, in the general population (assuming a prevalence of 5 cases per 100,000 persons, an RPR sensitivity of 91% and specificity of 95%, and FTA-ABS sensitivity of 92% and specificity of 96%), more than 24,000 persons would need to be screened to detect a single case of syphilis. In a high-risk population of incarcerated women (assuming a prevalence of 12%, an RPR sensitivity of 91% and specificity of 95%, and FTA-ABS sensitivity of 92% and specificity of 96%), 10 women would need to be screened to detect a single case of syphilis.

**Interventions and Treatment**

Antibiotics are effective for treating and curing syphilis infection. Penicillin G, administered through injection, is the preferred drug for treating all stages of syphilis. The preparation used (i.e., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and symptoms of the disease. Selection of the appropriate penicillin preparation is important, because *T. pallidum* can reside in sequestered sites (e.g., the central nervous system and aqueous humor) that are poorly accessed by some forms of penicillin. Nearly all the recommendations for the treatment of syphilis are based on clinical trials and observational studies, and almost 50 years of clinical experience that support the efficacy of penicillin. Close followup is necessary to ensure treatment success. Patients with penicillin allergies whose compliance with therapy or followup cannot be ensured can be desensitized and treated with benzathine penicillin. Skin testing for penicillin allergy might be useful in some circumstances in which the reagents and expertise are available to perform the test adequately.

Data to support the use of alternatives to penicillin in the treatment of early syphilis are limited.
However, several therapies might be effective in nonpregnant, penicillin-allergic patients who have primary or secondary syphilis, including doxycycline and tetracycline. Compliance is likely to be better with doxycycline than tetracycline because tetracycline can cause gastrointestinal side effects. Limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone can be effective for treating early syphilis, although the optimal dose and duration of ceftriaxone therapy have not been defined. Azithromycin administered as a single 2-g oral dose can be effective for treating early syphilis. However, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been documented in several geographical areas in the United States. As such, azithromycin should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin is not recommended in MSM due to macrolide resistance patterns and in pregnant women due to concerns about therapeutic efficacy. Close followup of patients receiving alternative therapies is essential.

Assessing response to treatment can be difficult, and definitive criteria for cure or failure have not been established. In addition, nontreponemal test titers might decline more slowly for persons who had previous syphilis infections. Clinical and serologic evaluations should be performed 6 and 12 months after treatment, and more frequent evaluations might be necessary if followup is uncertain and in specific subpopulations. For example, it is recommended that followup occurs at 3, 6, 9, 12, and 24 months after persons living with HIV are treated for primary or secondary syphilis. Patients with persistent signs or symptoms of recurrence with a sustained fourfold increase in nontreponemal test titer (i.e., compared with the maximum or baseline titer at the time of treatment) could have failed treatment or experienced reinfection. These patients should be retreated and reevaluated for HIV infection. Because treatment failure usually cannot be reliably distinguished from reinfection with *T. pallidum*, a CSF analysis should be performed.

Central nervous system involvement can occur during any stage of syphilis. However, CSF laboratory abnormalities are common with early syphilis, even in the absence of clinical neurological findings. If clinical evidence of neurologic involvement is observed (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis), a CSF examination should be performed. Patients who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, and optic neuritis) should be treated with the recommended regimen for neurosyphilis; those with eye disease should be managed in collaboration with an ophthalmologist. A CSF examination should be performed for all patients with syphilitic eye disease to identify those with abnormalities. Patients found to have abnormal CSF test results should be provided followup CSF examinations to assess treatment response.

Harms of treatment include adverse drug-related effects, the most severe of which is anaphylaxis. The Jarisch-Herxheimer reaction is an acute febrile reaction usually occurring within the first 24 hours after the initiation of any therapy for syphilis and is often accompanied by headache, myalgia, fever, and other symptoms. Most commonly, this reaction occurs in patients with early syphilis and can be managed with antipyretics.
Current Clinical Practice

Clinical practice may not follow screening guidelines. A review of the health care claims of 4,296 male and female patients presenting for general medical or gynecological examinations from 2000 to 2003 found that almost none had diagnostic codes for HIV, syphilis, chlamydial, or gonococcal infection, regardless of their high-risk sexual behavior status, although the high-risk sexual behavior code was generally underutilized. Limited use of the high-risk sexual behaviors code may reflect reluctance by patients to report these behaviors, a reluctance by providers to bill for or discuss these behaviors, or a genuinely lower rate of high-risk sexual behaviors in the analyzed population compared with general or high-risk populations. However, even among patients claiming high-risk sexual behaviors, only 25 to 39 percent were tested for syphilis infection.

Recommendations of Other Groups

The CDC recommends universal screening based on local prevalence of early syphilis infection and advises at least annual screening in sexually active MSM. Recommendations of the American Academy of Family Physicians closely follow the USPSTF guidelines for screening in persons at increased risk, while the American Congress of Obstetricians and Gynecologists and the U.S. Department of Health and Human Services’ HIV/AIDS program mirror the CDC guidelines. The Department of Health and Human Services further recommends more frequent testing for MSM who have multiple partners, and the Infectious Diseases Society of America recommends initial screening in persons with new HIV diagnoses and periodic, risk-based screening in persons living with HIV thereafter. Recommendations from the CDC and other professional groups are summarized in Table 4.
Chapter 2. Methods

Key Questions and Analytic Framework

This systematic review followed a standard protocol consistent with the Agency for Healthcare Research and Quality (AHRQ) methods for systematic reviews. Based on evidence gaps identified from the prior review, in collaboration with the USPSTF and AHRQ, investigators determined the scope and Key Questions of the report. In addition, two contextual questions were requested by the USPSTF. Contextual questions address topics important to the USPSTF recommendations, but are reviewed by summarizing evidence from key informative studies rather than by using systematic review methodology. Key Questions and contextual questions are listed below. Investigators created an analytic framework incorporating the Key Questions and outlining the patient populations, interventions, outcomes, and potential adverse effects (Figure 2). The target population includes asymptomatic, sexually active men and nonpregnant women, including adolescents. All Key Questions include studies of high- and low-risk populations unless otherwise specified. A research plan was externally reviewed and modified.

Key Questions

1. What is the effectiveness of screening for syphilis in reducing complications of the disease and transmission or acquisition of other STIs 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 (e.g., sequence of tests) for detecting syphilis infection?
4. What are the harms of screening (e.g., labeling and false-positive or false-negative results)?

Contextual Questions

1. Which population subgroups, including MSM, are at highest risk for incident syphilis infection?
2. Which population subgroups are at highest risk for syphilis-related morbidity and mortality?

Search Strategies

This review includes studies published since the prior (2004) USPSTF review of this topic. The Cochrane Central Register of Controlled Trials (to March 11, 2016), Cochrane Database of Systematic Reviews (to March 11, 2016), and Ovid MEDLINE (January 2004 to March 11, 2016) were searched for relevant studies and systematic reviews. Search strategies are described in Appendix B1. Investigators also manually reviewed reference lists of relevant articles.
Study Selection

Two reviewers independently evaluated each study to determine its inclusion eligibility based on predetermined inclusion and exclusion criteria developed for each Key Question (Appendix B2). In addition, abstracts were selected for full-text review if they included asymptomatic, sexually active men and women, including adolescents, and were applicable to clinical settings and practices in the United States. Applicability was determined by the clinical relevance of participants and health care services and the use of screening tests that are currently available and cleared by the FDA for clinical use in the United States. Non-English–language articles and studies published as abstracts were not included.

Studies of screening effectiveness (Key Question 1) were included if they provided direct evidence of the effectiveness of screening for syphilis, comparing health outcomes of screened versus unscreened asymptomatic individuals. Relevant outcomes included reduced complications of syphilis infection and reduced transmission or acquisition of STIs. Only randomized, controlled trials (RCTs), controlled observational studies, and ecological studies were included to evaluate the effectiveness of screening. Studies were included if they described the study population (number screened, sex, age range, setting, and absence of symptoms), features of the screening program (duration, type of strategy, and followup), and outcome measures. Inclusion criteria for effectiveness studies were less restrictive than criteria for diagnostic accuracy studies regarding the screening methods because the main comparison concerned outcomes related to the overall approach of screening versus not screening, the intervals of screening, and screening strategies among specific population subgroups, not the individual tests themselves.

Indirectly, the effectiveness and accuracy of different screening approaches and tests for identifying syphilis can be ascertained as a step toward the prevention of serious health outcomes, given foundational evidence on the effectiveness of treatment and the known morbidity and mortality of syphilis infections. Links in the chain of indirect evidence include the accuracy of screening for identifying individuals with syphilis, the effectiveness of interventions for reducing the incidence of complications, the association between improvements in intermediate outcomes and clinical health outcomes, and harms associated with screening. Implicit in the indirect chain of evidence is that to understand benefits and harms of screening, it is necessary, but not sufficient, to show that individuals with syphilis can be identified. It is also necessary to show that there are effective treatments for those identified. Not all of the indirect links are included in this update because some of the links, such as treatment efficacy, are already considered established.

Studies of the effectiveness of risk assessment instruments or other risk stratification methods (Key Question 2) were included if they evaluated clinic tools or methods to identify populations or individuals at high risk of syphilis infection. Studies of diagnostic accuracy (Key Question 3) were included if they evaluated the performance of diagnostic tests in asymptomatic persons using technologies and methods that have been cleared by the FDA and are available for clinical practice in the United States. These inclusion criteria reflect the scope of the USPSTF recommendations regarding technologies and medications. Based on these criteria, specimens obtained in nonclinical settings and most point of care or in-house tests were excluded. Included studies used credible reference standards, described the study population (number screened, sex,
age range, setting, and absence of symptoms), defined positive screening test results, and reported performance characteristics (sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio) or provided data to calculate them.

For studies of harms of screening (Key Question 4), searches focused on trials or studies that compared the harms of screening (labeling, false-negative and false-positive diagnoses and related harms, including psychosocial harms) with an unscreened population.

The selection of studies is summarized in the literature flow diagram (Appendix B3). Appendix B4 lists studies excluded at the full-text level, with reasons for exclusion.

**Data Abstraction and Quality Rating**

A single investigator abstracted details about study design, patient population, comparison groups, setting, screening method, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. By using prespecified criteria developed by the USPSTF for RCTs, cohort studies, and diagnostic accuracy studies, two investigators independently rated the quality of studies (good, fair, or poor) and resolved discrepancies by consensus (Appendix B5).

**Data Synthesis**

Two independent reviewers assessed the internal validity (quality) of the body of evidence for the new studies for each Key Question using methods developed by the USPSTF, based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence. Statistical meta-analysis was not performed because of methodological limitations of the studies 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, Key Questions, and inclusion criteria limited aggregate synthesis with the updated evidence.

**External Review**

The draft report was reviewed by content experts, USPSTF members, AHRQ Medical Officers, and collaborative partners (Appendix B6).

**Response to Public Comment**

A draft version of the evidence review was posted for public comment on the USPSTF Web site from December 15, 2015 to January 18, 2016. Comments from three contributors were directly relevant to the systematic review, while comments from other contributors concerned the
recommendation statement. Comments were minor and only required that the CDC information be updated with current data.
Chapter 3. Results

Key Question 1. What Is the Effectiveness of Screening for Syphilis in Reducing Complications of the Disease and Transmission or Acquisition of Other STIs in Asymptomatic, Nonpregnant, Sexually Active Adults and Adolescents? What Is the Effectiveness of Specific Screening Intervals and Screening Among Population Subgroups?

Summary

No studies directly compared the effectiveness of syphilis screening in screened versus unscreened populations of nonpregnant adolescents or adults. Four observational studies evaluated detection rates using specific screening intervals in MSM or HIV-positive populations outside the United States. No studies evaluated detection rates or screening intervals in other population subgroups. A study of MSM living with HIV in Australia found that detection of asymptomatic early syphilis was higher among those screened every 3 months compared with those screened annually (8.1% vs. 3.1%; p=0.001).56 A study of patients living with HIV in London found that routine screening every 3 months detected more patients with newly acquired syphilis compared with screening every 6 months or more (7.3 cases [95% CI, 5.2 to 9.9] per 1,000 patient-years vs. 2.8 cases [95% CI, 1.8 to 4.0] per 1,000 patient-years; p<0.05).57 Another Australian study of MSM who received automated reminders for syphilis testing demonstrated higher testing rates among men choosing 3-month reminders versus controls receiving yearly testing (67.0% vs. 39.9%; p<0.0001) and higher detection rates of early latent syphilis compared with controls (1.7% vs. 0.4%; p=0.008).58 A related Australian study that implemented a system-based intervention focusing on computer reminders directed at clinicians of high-risk patients demonstrated an increased proportion of higher-risk MSM who received a diagnosis of early syphilis and who were asymptomatic when tested every 3 months versus annually (53% vs. 16%; p=0.001), but no difference among low-risk patients.59

The prior reviews for the USPSTF did not include studies meeting inclusion criteria for this Key Question.

Evidence

Three fair-quality observational studies from the same health center in Australia56,58,59 and one fair-quality observational study from the United Kingdom57 evaluated detection rates of syphilis using specific screening intervals among MSM or HIV-positive populations (Appendices C1 and C2). All four studies were conducted in MSM or men living with HIV, limiting generalizability to other populations. There were no studies in adolescents or other population subgroups, and three studies were conducted at one clinical site in Australia. Two studies of men living with HIV56,57 tested for syphilis as part of HIV disease monitoring rather than screening,
potentially limiting applicability.

A pre-post intervention study conducted among 1,031 MSM attending a public STI clinic in Australia used a historic control group to compare the effect of implementing more frequent syphilis screening (every 3 months) with annual screening as part of disease monitoring in MSM living with HIV.\textsuperscript{56} The detection rate of asymptomatic syphilis infections was significantly higher for 3-month versus annual screening (8.1\% vs. 3.1\%; \textit{p}=0.001). The proportion of MSM living with HIV with early syphilis who were asymptomatic at the time of diagnosis was 21 percent (3 of 14 patients) before the intervention versus 85 percent (41 of 48 patients) after the intervention (\textit{p}=0.006).

An observational study conducted in London among 2,389 MSM attending an outpatient HIV clinic compared detection rates for routine syphilis screening as part of HIV care with detection rates during the year before routine screening was implemented.\textsuperscript{57} Routine screening every 3 months detected more patients with newly acquired syphilis compared with screening every 6 months or more (7.3 cases [95\% CI, 5.2 to 9.9] per 1,000 patient-years vs. 2.8 cases [95\% CI, 1.8 to 4.0] per 1,000 patient-years; \textit{p}<0.05).\textsuperscript{57}

A third Australian study, conducted at the same health center as the others, used a controlled observational design to evaluate the impact of computer-generated reminders on the rates of syphilis testing among 4,514 MSM who elected to receive a reminder every 3, 6, or 12 months.\textsuperscript{58} Men receiving reminders every 3 months had a statistically significantly higher detection rate of early syphilis during the 12-month observation period compared with concurrent controls who were not offered reminders (3.2\% vs. 1.5\%; \textit{p}=0.025).

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 6,789 consultations) to test higher-risk patients improved the rate of syphilis testing and diagnosis.\textsuperscript{59} 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 asymptomatic higher-risk men receiving diagnoses of early syphilis who were tested every 3 months versus annually (31/58 [53\%] vs. 5/31 [16\%]; \textit{p}=0.001). There were no statistically significant changes in the proportion of syphilis diagnoses in asymptomatic lower-risk men who were tested every 3 months versus annually (3/16 [19\%] vs. 1/10 [10\%]; \textit{p}=0.60).

**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?**

No studies evaluated risk assessment instruments or risk stratification methods for identifying individuals at increased risk for syphilis. The prior reviews also did not identify studies evaluating risk instruments or methods.
Key Question 3. What Is the Accuracy of Currently Used Screening Tests and Strategies for Detecting Syphilis Infection?

Summary

Three fair-quality observational studies of diagnostic accuracy evaluated treponemal and nontreponemal tests. A U.S. study conducted in a high-prevalence STI clinic (39.7% positive test rate) compared a treponemal EIA screening test (Trep-Sure™ EIA; Trinity Biotech, Jamestown, NY) with a traditional nontreponemal VDRL test as an initial screening examination, and used a TPPA assay as a confirmatory test. Screening with the Trep-Sure EIA in conjunction with a confirmatory TPPA test was slightly less sensitive than the VDRL test (98.0% vs. 98.6%) but more specific (98.6% vs. 91.1%). A Canadian study also reported results of the diagnostic accuracy of treponemal EIA tests (Trep-Chek immunoglobulin G [IgG] EIA; Phoenix Biotech Corp., Toronto, Canada) in a sample of specimens with a 5.6 percent positive test rate using conventional testing methods. Use of the Trep-Chek IgG EIA as a screening test followed by a confirmatory test resulted in a sensitivity of 85.3 percent and a specificity of 95.6 percent compared with standard testing protocols. A third 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 percent specificity but lower sensitivity (87.1%) compared with the standard. Population demographics were not well characterized in any of the three studies.

Two observational studies from the United States and Canada compared traditional screening strategies with reverse screening strategies. A retrospective cohort study in Canada compared results using RPR or EIA screening as an initial test in a metropolitan area with a known high prevalence of syphilis. This study demonstrated an increase in the rate of confirmed positive tests using EIA as the initial screen compared with RPR screening (1.98% vs. 0.45%). A prospective cohort study in a low-prevalence U.S. population compared MFI followed by RPR screening and TPPA confirmation testing with conventional RPR screening followed by TPPA. Fifteen samples reacted when screened with MFI compared with four samples that reacted with RPR (1.5% vs. 0.4%; p=0.01). In both studies, initial screening using an automated treponemal test resulted in a higher rate of false-positives at the screening stage than when RPR testing was used for initial screening, but both methods also identified additional positive tests that would not have been identified using conventional methods.

The prior reviews mostly included studies of diagnostic accuracy conducted in populations and settings not applicable to this review.

Evidence

Screening Tests

Three fair-quality observational studies from Mexico, Canada, and the United States reported the
diagnostic accuracy of syphilis screening tests (Appendixes C3 and C4).\textsuperscript{60-62} These studies were limited by minimal demographic information and small sample sizes (N=198 to 674). Two studies compared treponemal EIA tests as a screening assay when followed by a second confirmatory test,\textsuperscript{60,61} and one study compared the treponemal TPPA test with VDRL testing followed by FTA-ABS.\textsuperscript{62} The prior reviews mostly included studies of diagnostic accuracy conducted in populations and settings not applicable to this review (symptomatic persons, pregnant women, or patients in developing countries).\textsuperscript{1} Other methodological differences included studies lacking comparison groups or testing performed on stored serum samples.

A cross-sectional U.S. study of remnant sera collected from the San Francisco municipal sexually transmitted disease clinic compared a treponemal EIA screening test 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 sera from patients of unspecified age groups presenting to an STI clinic with a reported syphilis prevalence of 9.4 percent and high rates of patients living with HIV (16.6%) and MSM (69.3%).\textsuperscript{60} The samples used in this study reflected higher syphilis prevalence than in the general population at the clinic, with a positive test rate of 39.7 percent after both the screening and confirmatory tests were completed. In this population, screening with the EIA test 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%).

A study from Canada tested EIA as a screening test followed by confirmatory tests (TPPA, FTA-ABS, line immunoassay) in serum specimens submitted to a reference laboratory for confirmation or further evaluation. Of these specimens, 5.6 percent tested positive for syphilis when screened using conventional screening tests (RPR and VDRL).\textsuperscript{61} Use of the Trep-Chek EIA as a screening test followed by confirmatory testing resulted in a sensitivity of 85.3 percent and a specificity of 95.6 percent compared with samples screened with conventional tests (RPR, VDRL, TPPA, and FTA-ABS). This study is 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 who provided samples submitted for testing.

A cohort study compared the diagnostic accuracy of the treponemal TPPA test with VDRL testing followed by FTA-ABS in a population of 198 female sex workers (15.7% prevalence, ages not specified) at an STI clinic in Mexico.\textsuperscript{62} The study reported 100 percent specificity but lower sensitivity (87.1%) for the samples from the STI clinic compared with standard VDRL testing.

**Screening Strategies**

Two fair-quality observational studies compared traditional screening strategies with reverse screening strategies (Appendixes C4 and C5). In both studies, initial screening using an automated treponemal test resulted in a higher rate of false-positives at the screening stage than when RPR testing was used for screening. Both studies also identified additional positive tests that would not have been identified using conventional methods. Methodological limitations included minimal demographic information or 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 higher-prevalence metropolitan area (incidence rate ratio of 1.69 to 1.80 relative to surrounding suburban areas) using RPR or EIA as the initial screening test on samples submitted for syphilis serology.63 Samples were considered positive after undergoing a confirmatory test.

Results indicated an increase in the detection rate of positive tests when using EIA as the initial screen versus RPR (1.98% vs. 0.46% confirmed positive). Notably, 69.6 percent of all confirmed positives during the EIA screening period were associated with a negative RPR test. The proportion of confirmed positive EIA tests with a negative RPR test result was higher when samples were limited to those from asymptomatic patients (74.7% [95% CI, 73.6 to 75.8]), patients with no risk factors for syphilis (71.5% [95% CI, 70.4 to 72.5]), or intravenous drug users (69.9% [95% CI, 66.3 to 73.3]); and slightly lower for MSM (69% [95% CI, 66.9 to 71.0]) and MSM who are also intravenous drug users (68% [95% CI, 66.0 to 75.4]). Statistical analysis of the test performance indicated that the increase in syphilis detection during the EIA screening period was not only the result of increased prevalence in the community at the time of testing.

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 the BioPlex® 2200 Syphilis IgG (MFI) (Bio-Rad Laboratories, Inc., Hercules, CA). For the reverse sequence, initial MFI testing was followed by RPR testing and TPPA confirmation testing and conventional RPR screening was followed by confirmatory TPPA.28 When screened with MFI, 15 samples were reactive by reverse screening compared with four samples that reacted with RPR or traditional screening (1.5% vs. 0.4%; p=0.01). All four samples that tested positive with the RPR test were confirmed positive by TPPA and were also positive with MFI or reverse screening. Further review revealed that three of 11 samples not detected by RPR represented previously treated syphilis infection, six were interpreted as false-positive screening results based on negative TPPA results and alternative diagnosis, and two cases of probable latent syphilis were identified and treated. Based on these results, reverse screening yielded a higher false-positive rate than traditional testing (0.6% vs. 0%; p=0.03) but two patients with possible latent syphilis that were undetected by RPR were identified using the reverse screening algorithm.

**Key Question 4. What Are the Harms of Screening?**

Consistent with prior reviews, there were no studies addressing the harms of screening for syphilis.
MSM

According to the CDC, the rate of primary and secondary syphilis infection has been increasing in MSM since 2000, with this group accounting for 61 percent of all primary and secondary cases reported in 2014. Of these cases, 37.6 percent were white men, 31.8 percent were black men, 21.8 percent were Hispanic men, and 8.8 percent were men of other races.

Persons Living With HIV

In the United States in 2014, 51.2 percent of MSM with syphilis infections also had HIV infections, compared with 10.7 percent of men who have sex with women, and 5.9 percent of women in general across all racial/ethnic groups. The proportion of MSM who presented to STI Surveillance Network clinics with primary and secondary syphilis infections who were also infected with HIV ranged from 9.1 percent in Los Angeles to 53.2 percent in Baltimore.

An observational study (n=4,256) of patient data from the Kaiser Permanente system in northern California from 1995 to 2005 reported similar results, with HIV coinfection occurring in 57.9 percent of primary syphilis cases, 32.4 percent of secondary syphilis cases, and 9.1 percent of tertiary cases (Table 5). This study also reported that MSM represented 81 percent of those who were coinfected with syphilis and HIV. The adjusted rate ratio of a syphilis infection among HIV-infected cases was 86.0 (95% CI, 78.6 to 94.1), and the rate of syphilis among the HIV-infected population was 12.4 per 1,000 population compared with 0.2 per 1,000 population in the group without HIV infection.

Another observational study conducted among black MSM in six U.S. cities enrolled patients attending an STI clinic for screening (n=1,553). Eleven percent of diagnosed syphilis cases were also newly diagnosed HIV cases and 4 percent were previously diagnosed with HIV (Table 5). Four other observational studies enrolled predominately MSM living with HIV and tested them for syphilis. All of the studies reported that less than 7 percent (range, 0% to 6.3%) of the HIV-infected population was also coinfected with syphilis.

A large observational study (n=3,170) reporting the highest proportion of HIV coinfection among MSM was a population study of men from Houston, Texas (Table 5). This study conducted additional analyses on the risk of syphilis associated with HIV infection and reported high hazard ratios (HRs) for MSM (5.24 [95% CI, 3.41 to 8.05] vs. nonMSM), males ages 13 to 19 years (4.06 [95% CI, 2.18 to 7.55] vs. age >40 years), and black men (1.59 [95% CI, 1.11 to 2.26] vs. white men). Another study conducted at an HIV clinic in Alabama also reported a high odds ratio (OR) of syphilis infection for black individuals and other races (2.26 [95% CI, 1.12 to 4.59] vs. white individuals) and a lower OR with each 10 years of increasing age (0.62 [95% CI, 0.44 to 0.87]).
**Young Adult Men**

Rates of syphilis infection among men ages 20 to 24 years have increased each consecutive year since 2002, from 5.2 to 31.1 cases per 100,000 in 2014. Rates have also increased among men ages 25 to 29 years since 2008, from 16.9 to 34.0 cases per 100,000. In addition to MSM, the rate of primary and secondary syphilis infection has been increasing among men ages 20 to 24 years and 25 to 29 years by 60.1 percent and 65.7 percent, respectively, from 2008 to 2013. This is a shift from 2006, when the rate was highest in men ages 35 to 39 years. Rates of all syphilis infections increased for all age groups between the ages of 15 and 64 years in 2014; 11.6 percent for ages 15 to 19 years, 13.1 percent for ages 20 to 24 years, 23.4 percent for ages 25 to 29 years, 18.3 percent for ages 30 to 34 years, 13.0 percent for ages 35 to 39 years, 3.7 percent for ages 40 to 44 years, 13.3 percent for ages 45 to 54 years, and 21.1 percent for ages 55 to 64 years.

**Racial Minorities**

While the rate for primary and secondary syphilis infection has decreased for black individuals overall, the rate among black males ages 20 to 29 years remains the highest reported for all subgroups (106.3 to 121.3 cases per 100,000), with black males ages 30 to 39 years having the second highest prevalence for all subgroups (44.4 to 72.4 cases per 100,000). Young Native Hawaiian/Pacific Islander men ages 20 to 29 years also had high rates of primary and secondary syphilis infection in 2014 (21.0 to 44.8 cases per 100,000). There are wide racial/ethnic disparities among young men ages 20 to 24 years and 25 to 29 years, with the rate of primary and secondary syphilis cases 8.5 and 7.9 times higher in black men, 3.5 and 1.4 times higher in Native Hawaiian/Pacific Islander men, and 2.6 and 2.2 times higher in Hispanic men compared with white men. The disparity is also present in males ages 15 to 19 years, with black males having 12.5 times higher rates of primary and secondary syphilis infection than white males and 2.7 times higher than Hispanic males. For black females ages 15 to 19 years, the rate of primary and secondary syphilis infection was 14.7 times higher than for white females and 6.0 times higher than for Hispanic females. Table 6 provides additional details on prevalence rates by subgroup.

From 2010 to 2014, the rate of primary and secondary syphilis infection increased for all races, and between 2013 and 2014 the rate increased the most among American Indian/Alaska Native individuals (68.8%) and those who identified as multiple races (47.3%). During 2013 and 2014, rates increased for all groups, except Native Hawaiian/Pacific Islander individuals. In 2014, 38.1 percent of all primary and secondary cases of syphilis reported to the CDC were among black individuals and 34.0 percent were among white individuals.

**Sex Workers**

The risk of STIs in general is high among persons who exchange sexual activity for income, employment, or nonmonetary items, such as food, drugs, and shelter. Sex workers frequently encounter barriers to seeking care or reducing risk for STIs because of other social factors, such as poverty. Although sex workers have been previously identified as a group at higher risk for syphilis, there were no U.S.-based studies published in the last 10 years reporting information...
Adults in Correctional Facilities

A study of syphilis screening in arrested individuals reported higher rates of syphilis infection among women charged with prostitution than for other crimes. Another study reported seroprevalence rates of 11 percent among women tested in jails compared with 3 percent among women tested in hospital delivery rooms. In some locations, a high proportion of early syphilis cases are reported from correctional facilities. In 2011, reports of primary and secondary syphilis cases from correctional facilities accounted for 6 percent of primary and secondary syphilis cases among men, 3 percent among women, and 1 percent among MSM.

Residents of Specific Regions

The rate of primary and secondary syphilis infection in 2014 for the 50 most populous metropolitan statistical areas was 8.7 cases per 100,000 population; which was a 13.0 percent increase since 2013, and exceeded the overall rate for the United States (6.3 cases per 100,000 population). The southern states continue to have the highest number of reported cases (40.6% of all reported cases); however, the rate in the West (7.9 cases per 100,000 population) continued to exceed the rate in the South (6.9 cases per 100,000 population).

Contextual Question 2. Which Population Subgroups Are at Highest Risk for Syphilis-Related Morbidity and Mortality?

No studies were identified that address morbidity and mortality among population subgroups.
Chapter 4. Discussion

Summary of Review Findings

Targeted screening for syphilis in persons at increased risk of infection based on sociodemographic factors is currently recommended by the USPSTF and other groups and is the standard of practice in the United States. Routine screening in asymptomatic persons not at increased risk for syphilis infection is not recommended. Previous recommendations were based on various levels of evidence indicating that screening provides earlier identification and treatment of infections and reduces adverse health outcomes and transmission.

A summary of evidence for this update is provided in Table 7. No new studies were identified that determined the effectiveness of screening or described the harms of screening, consistent with results of prior reviews. However, four observational studies evaluated detection rates using specific screening intervals in MSM or HIV-positive populations (Key Question 1). Results from these studies indicated that testing for syphilis every 3 months identified more new cases of infection in MSM or men living with HIV compared with screening every 6 or 12 months. Detection rates were higher for early syphilis (8.1% vs. 3.1%; p=0.001), newly acquired syphilis (7.3 cases [95% CI, 5.2 to 9.9] vs. 2.8 cases [95% CI, 1.8 to 4.0] per 1,000 patient-years; p<0.05), early latent syphilis (1.7% vs. 0.4%; p=0.008), and early syphilis among higher-risk MSM (53% vs. 16%; p=0.001). These studies were all conducted outside the United States and are limited by their study designs, sample sizes, and clinical applicability to U.S. populations and other high-risk population subgroups. Importantly, the generalizability of these studies may be limited to MSM or men living with HIV as no studies on other population subgroups were identified. No studies were conducted specifically in adolescent populations.

No new studies meeting inclusion criteria evaluated risk assessment instruments or risk stratification methods for identifying persons at increased risk for syphilis (Key Question 2). The prior reviews also did not identify studies evaluating risk instruments or risk stratification methods for nonpregnant adults.

Three studies of the diagnostic accuracy of screening tests met inclusion criteria (Key Question 3). One U.S. study found that screening with the Trep-Sure EIA followed by a confirmatory TPPA test in a higher prevalence population was slightly less sensitive than the traditional nontreponemal VDRL test (98.0% vs. 98.6%) but more specific (98.6% vs. 91.1%). In a lower prevalence population in Canada, screening with the Trep-Chek IgG EIA test followed by a confirmatory test had 85.3 percent sensitivity and 95.6 percent specificity compared with standard testing protocols. A study in a high prevalence population of sex workers in Mexico compared treponemal TPPA testing with VDRL testing followed by FTA-ABS and reported 100 percent specificity but 87.1 percent sensitivity compared with standard testing. These results are fairly consistent with the known sensitivities of the tests currently cleared by the FDA for syphilis testing (Table 3). However, limitations of these studies include minimal demographic information of populations tested and limited applicability to the general U.S. population. The prior reviews included studies of diagnostic accuracy conducted in populations and settings not applicable to this review, including pregnant women, stored serum samples, symptomatic
Two studies of reverse sequence testing conducted in both high and low prevalence populations used an automated treponemal test as the initial screening test. Rates of false-positive tests 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 screening (nontreponemal testing 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 longstanding untreated infections. There are limited data on reverse testing algorithms, which also require a nontreponemal test to gauge disease activity. The CDC recommends using a third treponemal test based on different antigens (TPPA or FTA-ABS) to confirm the original treponemal results when employing the reverse sequence screening algorithm (Figure 1).

We identified two reports of test performance using reverse sequence screening that lacked comparison groups and were not included in this systematic review. These may offer additional context for this newly employed testing strategy, and they report similar outcomes as the two studies included in this review. A report by the CDC demonstrated a higher percentage of discrepant serology in low prevalence populations than in high prevalence populations (60.6% vs. 50.6%) using reverse sequence testing. Additionally, the percentage of tests with nonreactive confirmatory treponemal tests was greater in the low prevalence population than the high prevalence population. There was also a higher percentage of samples that were RPR negative but positive on both treponemal tests in the high prevalence population (43.6% vs. 35.8%). These samples may represent false-positives, early primary syphilis in an individual who has not developed nontreponemal antibodies, or a previous treated or untreated infection with seroversion of nontreponemal antibodies. Currently, there is no evidence to direct the management of patients with discrepant serology (e.g., positive enzyme/chemiluminescence immunoassay and negative RPR/positive TPPA). As with any diagnostic test, the diagnostic accuracy of reverse sequence screening appears to be affected by the population prevalence or risk of syphilis in the population being tested.

**Limitations**

Limitations of this review include using only English-language articles, which could result in language bias, though we did not identify non-English-language studies otherwise meeting inclusion criteria in our searches. We only included studies with asymptomatic participants and settings and tests applicable to current practice in the United States to improve clinical relevance for the USPSTF, excluding some research in the field. For example, limiting the review to tests cleared by the FDA excludes studies of many rapid tests. This is especially important for screening in asymptomatic MSM and other high-risk populations, including HIV-positive populations. Diagnostic accuracy studies did not provide details on patient demographics other than risk groups, potentially limiting applicability. Studies were lacking for many Key Questions, and the number, quality, and applicability of studies varied widely. Also, the available...
screening studies focused on detection rates in MSM and HIV-positive populations in Australia and the United Kingdom, while other populations are also relevant to screening. The studies of screening in men living with HIV were included because the line between screening and disease management in the context of HIV care is a blurry one, yet the reintegration of patients with HIV into primary care is increasingly common. The included studies evaluated the effect of more frequent screening in a population considered higher risk for asymptomatic infection. As such, the generalizability of these studies may be limited.

Emerging Issues and Next Steps

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. While there may be a role for automated EIA-based screening, the clinical impact 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 utilized 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 persons at increased risk.

Relevance for Priority Populations

Specific population subgroups at increased risk for infection are the most relevant to include in studies of syphilis screening. Expanding the field of testing types, including rapid tests, and further validation or evaluation of test sequence, has the potential to improve disease detection, particularly among priority populations. For example, the availability of rapid tests in high-risk populations or high-risk settings (HIV clinics, STI clinics, and MSM) may provide additional opportunities for point of care testing. The availability of automated tests, as employed by reverse sequence testing, may provide additional opportunity for screening populations at risk when confirmatory testing is available.

Future Research

Research is lacking on the effectiveness of screening for syphilis in asymptomatic, nonpregnant, sexually active adolescents and adults without risk factors. Studies evaluating the effectiveness of different screening strategies for identifying persons at increased risk of infection, cotesting for concurrent STIs, and different screening intervals are needed to inform practice guidelines.

Risk assessment instruments could help narrow the field of targeted testing, and risk stratification methods could help improve screening efforts. Future studies of risk assessment could compare the effectiveness of screening versus not screening in populations with different levels of risk and the effectiveness of risk assessment instruments and validated prediction tools for identifying
persons at increased risk for syphilis. Studies of diagnostic accuracy could include effectiveness of test strategies, including the sequence of tests. Future research should be directed at the direct comparison of the performance of various treponemal tests (EIA, chemiluminescence immunoassay, TPPA, FTA-ABS, 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 serology with nonreactive confirmatory treponemal tests and study the utility of certain tests in diagnosing early primary syphilis.

Conclusions

Only four new studies evaluating detection rates of syphilis using specific screening intervals in MSM or HIV-positive populations, three studies of the diagnostic accuracy of screening tests, and two studies of the accuracy of testing sequence met inclusion criteria. No studies evaluated the effectiveness of screening for syphilis, the effectiveness of risk assessment instruments or risk stratification methods, or the adverse effects of screening. There were no studies of adolescent populations. Results from four observational studies indicate that screening for syphilis in MSM or men living with HIV every 3 months may improve detection of early syphilis, newly acquired syphilis, early latent syphilis, and early syphilis among higher-risk MSM. Screening with treponemal or nontreponemal tests is accurate for diagnosing syphilis in asymptomatic persons (sensitivity >85% and specificity >91% for nontreponemal and treponemal tests in most studies) but requires confirmatory testing. Further research is needed to understand the impact of screening for syphilis on clinical outcomes; effective screening strategies, including reverse sequence screening, in various patient populations; and harms of screening.
References

5. Gjestland T. The Oslo study of untreated syphilis; an epidemiologic investigation of the natural course of the syphilitic infection based upon a re-study of the Boeck-Bruusgaard material. Acta Derm Venereol Suppl (Stockh). 1955;35(Suppl 34):3-368; Annex I-LVI.


Abbreviations: CIA=chemiluminescence immunoassay; EIA=enzyme immunoassay; FTA-ABS=fluorescent treponemal antibody absorption; RPR=rapid plasma reagin; TPPA=*Treponema pallidium* partical agglutination test; VDRL=Venereal Disease Research Laboratories.

Figure 2. Analytic Framework

Reduced complications of syphilis
Reduced transmission or acquisition of infection

Screening
Risk Assessment
Asymptomatic nonpregnant adults and adolescents

Treatment
Positive
Negative

Low Risk
High risk

Harms of Screening
Table 1. 2014 CDC Case Definitions for Syphilis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Symptoms</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis, primary</td>
<td>One or more ulcerative lesions (e.g., chancre), which might differ considerably in clinical appearance.</td>
<td>Meets the clinical description of primary syphilis with a reactive serologic test (nontreponemal: VDRL, RPR, or equivalent serologic methods; treponemal: FTA-ABS, TPPA, EIA, CIA, or equivalent serologic methods). These treponemal tests supersede older testing technologies, including MHA-TP. Although not required for diagnosis, demonstration of <em>T. pallidum</em> in clinical specimens by darkfield microscopy or by PCR or equivalent direct molecular methods may be present.</td>
</tr>
<tr>
<td>Syphilis, secondary</td>
<td>Localized or diffuse mucocutaneous lesions (e.g., rash, such as nonpruritic macular, maculopapular, papular, or pustular lesions), often with generalized lymphadenopathy. Other symptoms include mucous patches, condyloma lata, and alopecia. The primary ulcerative lesion may still be present.</td>
<td>Meets the clinical description of secondary syphilis with a nontreponemal (VDRL, RPR, or equivalent serologic methods) titer ≥4 AND a reactive treponemal test (FTA-ABS, TPPA, EIA, CIA, or equivalent serologic methods). Although not required for diagnosis, demonstration of <em>T. pallidum</em> in clinical specimens by darkfield microscopy or by PCR or equivalent direct molecular methods may be present.</td>
</tr>
</tbody>
</table>
| Syphilis, early latent | A subcategory of latent syphilis (a stage of infection caused by *T. pallidum* in which organisms persist in the body of the infected individual without causing symptoms or signs) when initial infection has occurred within the previous 12 months. | No clinical signs or symptoms of syphilis, but has one of the following:  
• No past diagnosis of syphilis, AND a reactive nontreponemal test (e.g., VDRL, RPR, or equivalent serologic methods), AND a reactive treponemal test (e.g., FTA-ABS, TPPA, EIA, CIA, or equivalent serologic methods)  
OR  
• A current nontreponemal test titer demonstrating fourfold or greater increase from the last nontreponemal test titer  
AND  
• Evidence of having acquired the infection within the previous 12 months based on one or more of the following:  
  o Documented seroconversion or fourfold or greater increase in titer of a nontreponemal test during the previous 12 months  
  o Documented seroconversion of a treponemal test during the previous 12 months  
  o A history of symptoms consistent with primary or secondary syphilis during the previous 12 months  
  o A history of sexual exposure to a partner within the previous 12 months who had primary, secondary, or early latent syphilis (documented independently as duration <12 months)  
  o Only sexual contact was within the last 12 months (sexual debut) |
<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Symptoms</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis, late latent</td>
<td>A subcategory of latent syphilis (a stage of infection caused by <em>T. pallidum</em> in which organisms persist in the body of the infected individual without causing symptoms or signs) when initial infection has occurred &gt;12 months previously.</td>
<td>No clinical signs or symptoms of syphilis, but has one of the following: • No past diagnosis of syphilis, AND a reactive nontreponemal test (e.g., VDRL, RPR, or equivalent serologic methods), AND a reactive treponemal test (e.g., FTA-ABS, TPPA, EIA, CIA, or equivalent serologic methods) OR • A past history of syphilis therapy and a current nontreponemal test titer demonstrating fourfold or greater increase from the last nontreponemal test titer AND • No evidence of having acquired the disease within the previous 12 months (see Syphilis, early latent)</td>
</tr>
<tr>
<td>Syphilis, late, with clinical manifestations (including late benign syphilis and cardiovascular syphilis)</td>
<td>Inflammatory lesions of the cardiovascular system (e.g., aortitis, coronary vessel disease), skin (e.g., gummatous lesions), bone (e.g., osteitis) or other tissue. Rarely, other structures (e.g., the upper and lower respiratory tracts, mouth, eye, abdominal organs, reproductive organs, lymph nodes, and skeletal muscle) may be involved. Late syphilis usually becomes clinically manifest only after a period of 15–30 years of untreated infection. If only neurologic manifestations of syphilis (e.g., tabes dorsalis, dementia) are present and infection occurred &gt;12 months ago, should be reported as “late syphilis.”</td>
<td>Characteristic abnormalities or lesions of the cardiovascular system (e.g., aortitis, coronary vessel disease), skin (e.g., gummatous lesions), bone (e.g., osteitis), or other tissue AND a reactive treponemal test (e.g., FTA-ABS, TPPA, EIA, CIA, or equivalent serologic methods), in the absence of other known causes of these abnormalities. CSF abnormalities and clinical symptoms or signs consistent with neurologic manifestations of syphilis might be present. Although not required for diagnosis, demonstration of <em>T. pallidum</em> in late lesions by special stains or equivalent methods, or by PCR or equivalent direct molecular methods may be present.</td>
</tr>
<tr>
<td>Neurosyphilis (can occur at any stage)</td>
<td>Infection of the central nervous system with <em>T. pallidum</em>, as evidenced by manifestations such as syphilitic meningitis, meningoencephalitis syphilis, optical involvement (including interstitial keratitis and uveitis), general paresis (including dementia), and tabes dorsalis.</td>
<td>A reactive VDRL in CSF and 1) a reactive serologic test for syphilis (treponemal or nontreponemal) OR 2) if the VDRL test in CSF is negative, a reactive serologic test for syphilis (treponemal or nontreponemal) AND both an elevated CSF protein (or leukocyte count) AND clinical symptoms or signs consistent with neurosyphilis, without other known causes for these abnormalities.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CDC=Centers for Disease Control and Prevention; CIA=chemiluminescence immunoassay; CSF=cerebrospinal fluid; EIA=enzyme immunoassay; FTA-ABS=fluorescent treponemal antibody absorption assay; MHA-TP= microhemagglutination assay for antibody to *T. pallidum*; PCR=polymerase chain reaction; RPR=rapid plasma reagent; TPPA=*T. pallidum* particle agglutination; VDRL=Venereal Disease Research Laboratory.
<table>
<thead>
<tr>
<th>Test</th>
<th>Use</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibody tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Nontreponemal Antibody Tests:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venereal Disease Research Laboratory (VDRL), rapid plasma reagin (RPR)</td>
<td>To evaluate disease activity; guide treatment; VDRL used to detect neurosyphilis</td>
<td>Highly sensitive; positive results must be confirmed with treponemal antibody test because it can be positive in other conditions. Nontreponemal antibodies generally disappear with treatment after 3 years.</td>
</tr>
<tr>
<td><em>Treponemal Antibody Tests:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorescent treponemal antibody absorbed (FTA-ABS), <em>T. pallidum</em> particle agglutination (TPPA), enzyme immunoassay (EIA), chemiluminescence immunoassay (CIA), multiplex flow immunoassay (MFI), Syphilis Health Check</td>
<td>Screen or confirm a positive nontreponemal antibody test</td>
<td>Highly specific; positive results must be followed by nontreponemal antibody test to differentiate between active and past infection. Treponemal antibodies remain positive for life, even after treatment.</td>
</tr>
<tr>
<td><strong>Direct detection methods (less common)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic or darkfield exam:</td>
<td>Diagnose syphilis in primary stage</td>
<td>Syphilis is diagnosed if bacteria are seen.</td>
</tr>
<tr>
<td>Sample from chancre is placed on a slide and examined with a special microscope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymerase chain reaction (PCR)</td>
<td>Detects genetic material of bacteria in chancre, blood, or cerebrospinal fluid</td>
<td>Positive test result indicates presence of <em>T. pallidum</em> nucleic acid</td>
</tr>
</tbody>
</table>

Screening for Syphilis Infection 32 Pacific Northwest EPC
Table 3. Sensitivity and Specificity of Commonly Used Syphilis Tests*25,29–32

<table>
<thead>
<tr>
<th>Syphilis screening test</th>
<th>Sensitivity by stage of untreated syphilis, % (range)†</th>
<th>Specificity % (range)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary</td>
<td>Secondary</td>
</tr>
<tr>
<td>Nontreponemal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDRL‡</td>
<td>78 (74-87)</td>
<td>100</td>
</tr>
<tr>
<td>RPR‡</td>
<td>86 (77-99)</td>
<td>100</td>
</tr>
<tr>
<td>TRUST‡</td>
<td>85 (77-86)</td>
<td>100</td>
</tr>
<tr>
<td>USR‡</td>
<td>80 (72-88)</td>
<td>100</td>
</tr>
<tr>
<td>Treponemal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTA-ABS‡</td>
<td>84 (70-100)</td>
<td>100</td>
</tr>
<tr>
<td>TPPA‡</td>
<td>88 (86-100)</td>
<td>100</td>
</tr>
<tr>
<td>EIA:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trep-Chek</td>
<td>95.9§</td>
<td>(77-100)</td>
</tr>
<tr>
<td>Trep-Sure</td>
<td>96.9§</td>
<td>(77-100)</td>
</tr>
<tr>
<td>CIA:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIAISONǁ</td>
<td>99.2</td>
<td>98</td>
</tr>
<tr>
<td>MFI:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BioPlex 2200 Syphilis IgG</td>
<td>96.9§</td>
<td>(77-100)</td>
</tr>
<tr>
<td>Syphilis Health Check</td>
<td>95.6¶</td>
<td>98.5**</td>
</tr>
</tbody>
</table>

* This is not a comprehensive list of tests available in the United States.
† Sensitivity and specificity of tests also depends on the disease prevalence in the population tested, and may vary considerably by manufacturer or the standard used as a comparison.
‡ Unknown reference standard.
§ When compared with FTA-ABS test results.
ǁ When compared with results from western blotting.
¶ When compared with nontreponemal test results.
** When compared with treponemal test results.

Abbreviations: CIA=chemiluminescence immunoassay; EIA=enzyme immunoassay; FTA-ABS=fluorescent treponemal antibody absorption; IgG=immunoglobulin G; MFI=multiplex flow immunoassay; 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.
Table 4. Recommendations of Other Groups

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation/Clinical Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers for Disease Control and Prevention&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Recommends at least annual screening in sexually active MSM using syphilis serology and confirmatory testing for those with reactive screening tests; screening in correctional facilities on the basis of local area and institutional prevalence of early infectious syphilis. HIV-infected individuals should be screened at least annually; more frequent screening may be appropriate based on individual risk behaviors and local epidemiology.</td>
</tr>
<tr>
<td>American Academy of Family Physicians&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Strongly recommends that clinicians screen individuals at increased risk for syphilis infection. Refers to the USPSTF syphilis screening recommendations to define those at risk, which include MSM and individuals engaging in high-risk sexual behavior like commercial sex workers or individuals who exchange sex for drugs, as well as adults in correctional facilities. Recommends against routine screening of asymptomatic individuals who are not at increased risk for syphilis infection.</td>
</tr>
<tr>
<td>American Congress of Obstetricians and Gynecologists&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Screening recommendations should be based on local area and syphilis prevalence within correctional facilities since individuals entering correctional facilities have high STI rates. Since syphilis transmission (likely through oral sex) between female sex partners can occur, providers should consider screening all females for syphilis, regardless of reported same-sex behavior.</td>
</tr>
<tr>
<td>U.S. Department of Health and Human Services HIV/AIDS Program&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Sexually active persons with HIV who are at risk of acquiring syphilis should be screened at least annually. MSM with multiple partners should be tested every 3 to 6 months.</td>
</tr>
<tr>
<td>Infectious Diseases Society of America, HIV Medicine Association&lt;sup&gt;74&lt;/sup&gt;</td>
<td>All patients with HIV should be screened for syphilis upon initiation of care and periodically thereafter, depending on risk.</td>
</tr>
</tbody>
</table>

**Abbreviations**: MSM=men who have sex with men; STI=sexually transmitted infection; USPSTF=U.S. Preventive Services Task Force.
<table>
<thead>
<tr>
<th>Study, Location</th>
<th>Population</th>
<th>Setting</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC, 2015 (data from 2013-2014)</td>
<td>Diagnosis: Syphilis N: 19,999 Male: 91% MSM: 61% Race: 36% black, 34% white, 20% Hispanic</td>
<td>All U.S. hospitals and clinics reporting STIs</td>
<td>Proportion coinfected with HIV: MSM: 51.2% MSW: 10.7% Females: 5.9%</td>
</tr>
<tr>
<td>Baffi, 2010 (data from 2004-2007)</td>
<td>Diagnosis: HIV N: 1,544 Male: 76% MSM: 57% Race: 49% black, 49% white</td>
<td>University of Alabama HIV/AIDS clinic</td>
<td>Proportion diagnosed with HIV and coinfected with syphilis: 2.6% Adjusted OR of syphilis diagnosis among HIV-infected patients: Black/other race: 2.26 (95% CI, 1.12 to 4.59) Increasing age by 10 years: 0.62 (95% CI, 0.44 to 0.87)</td>
</tr>
<tr>
<td>Hoover, 2010 (data from 2004-2006)</td>
<td>Diagnosis: HIV N: 1,334 Male: 100% MSM: 100% Race: 36% white, 28% Hispanic, 18% black</td>
<td>8 large HIV clinics in 6 U.S. states</td>
<td>Proportion coinfected with syphilis: Documented confirmed diagnosis: 1.7% Presumptive syphilis diagnosis: 1.1%</td>
</tr>
<tr>
<td>Horberg, 2010 (data from 1995-2005)</td>
<td>Diagnosis: Syphilis N: 4,246 HIV infected vs. HIV uninfected: Male: 97% vs. 50% MSM: not reported Black: 23% vs. 37% White: 49% vs. 27%</td>
<td>Kaiser Permanente Northern California database to identify patients with incident syphilis</td>
<td>Rate of syphilis: HIV infected: 12.4/1,000 person-years HIV uninfected: 0.2/1,000 person-years Adjusted RR of syphilis infection: HIV infected: 86.0 (95% CI, 78.6 to 94.1) Proportion coinfected with HIV: Primary cases: 57.9% Secondary cases: 32.4% Tertiary cases: 9.1% MSM: 81%</td>
</tr>
<tr>
<td>Mayer, 2012 (data from 2004-2006) SUN study</td>
<td>Diagnosis: HIV N: 557 Male: 79% MSM: 66% Race: 61% white, 26% black, 10% Hispanic</td>
<td>7 HIV clinics in 4 U.S. cities</td>
<td>Proportion coinfected with syphilis: MSM: 1% MSW: 0% Women: 0%</td>
</tr>
<tr>
<td>Mayer, 2014 (data from 2009-2010)</td>
<td>Not based on diagnosis, but enrolled patients screening for STIs N: 1,553 Male: 100% MSM: 100% Race: 100% black</td>
<td>HIV Prevention Trials Network in 6 U.S. cities</td>
<td>Proportion coinfected with HIV: Newly diagnosed with HIV: 11% Previously diagnosed with HIV: 4%</td>
</tr>
<tr>
<td>Yang, 2013 (data from 2008-2012)</td>
<td>Diagnosis: HIV N: 3,170 Male: 100% MSM: 58% Race: 45% black, 29% white, 25% Hispanic</td>
<td>Enhanced HIV/AIDS Reporting System in Houston, Texas</td>
<td>Proportion coinfected with syphilis: 6.3% Adjusted HRs of syphilis diagnosis: MSM: 5.24 (95% CI, 3.41 to 8.05) vs. nonMSM Ages 13-19 years: 4.06 (95% CI, 2.18 to 7.55) vs. &gt;40 years Blacks: 1.59 (95% CI, 1.11 to 2.26) vs. whites</td>
</tr>
</tbody>
</table>

**Abbreviations:** CDC=Centers for Disease Control and Prevention; CI=confidence interval; HR=hazard ratio; MSM=men who have sex with men; MSW=men who have sex with women; OR=odds ratio; RR=rate ratio; STI=sexually transmitted infection.
Table 6. Rates of Primary and Secondary Syphilis Infection by Population Subgroups*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(rate per 100,000)</td>
<td>(rate per 100,000)</td>
</tr>
<tr>
<td><strong>Race by age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All races combined; ages combined</td>
<td>11.7</td>
<td>1.1</td>
</tr>
<tr>
<td>15-19</td>
<td>7.0</td>
<td>2.5</td>
</tr>
<tr>
<td>20-24</td>
<td>31.1</td>
<td>4.5</td>
</tr>
<tr>
<td>25-29</td>
<td>34.0</td>
<td>3.4</td>
</tr>
<tr>
<td>30-34</td>
<td>24.7</td>
<td>2.3</td>
</tr>
<tr>
<td>35-39</td>
<td>19.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Black; ages combined</td>
<td>34.5</td>
<td>4.6</td>
</tr>
<tr>
<td>15-19</td>
<td>23.7</td>
<td>10.3</td>
</tr>
<tr>
<td>20-24</td>
<td>106.3</td>
<td>18.8</td>
</tr>
<tr>
<td>25-29</td>
<td>121.3</td>
<td>11.9</td>
</tr>
<tr>
<td>30-34</td>
<td>72.4</td>
<td>16.3</td>
</tr>
<tr>
<td>35-39</td>
<td>44.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Native Hawaiians/Pacific Islander; ages combined</td>
<td>12.0</td>
<td>0.8</td>
</tr>
<tr>
<td>15-19</td>
<td>9.9</td>
<td>0.0</td>
</tr>
<tr>
<td>20-24</td>
<td>44.8</td>
<td>0.0</td>
</tr>
<tr>
<td>25-29</td>
<td>21.0</td>
<td>4.4</td>
</tr>
<tr>
<td>30-34</td>
<td>31.9</td>
<td>0.0</td>
</tr>
<tr>
<td>35-39</td>
<td>10.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Hispanic; ages combined</td>
<td>13.9</td>
<td>1.1</td>
</tr>
<tr>
<td>15-19</td>
<td>8.6</td>
<td>1.7</td>
</tr>
<tr>
<td>20-24</td>
<td>32.0</td>
<td>3.3</td>
</tr>
<tr>
<td>25-29</td>
<td>34.0</td>
<td>3.2</td>
</tr>
<tr>
<td>30-34</td>
<td>25.2</td>
<td>2.1</td>
</tr>
<tr>
<td>35-39</td>
<td>22.8</td>
<td>1.6</td>
</tr>
<tr>
<td>White; ages combined</td>
<td>6.5</td>
<td>0.5</td>
</tr>
<tr>
<td>15-19</td>
<td>1.9</td>
<td>0.7</td>
</tr>
<tr>
<td>20-24</td>
<td>12.5</td>
<td>1.5</td>
</tr>
<tr>
<td>25-29</td>
<td>15.4</td>
<td>1.6</td>
</tr>
<tr>
<td>30-34</td>
<td>14.3</td>
<td>1.2</td>
</tr>
<tr>
<td>35-39</td>
<td>12.2</td>
<td>1.0</td>
</tr>
<tr>
<td>American Indian/Alaskan Native; ages combined</td>
<td>10.5</td>
<td>4.8</td>
</tr>
<tr>
<td>15-19</td>
<td>8.7</td>
<td>13.7</td>
</tr>
<tr>
<td>20-24</td>
<td>24.0</td>
<td>9.8</td>
</tr>
<tr>
<td>25-29</td>
<td>31.1</td>
<td>12.5</td>
</tr>
<tr>
<td>30-34</td>
<td>32.5</td>
<td>6.7</td>
</tr>
<tr>
<td>35-39</td>
<td>17.8</td>
<td>14.4</td>
</tr>
<tr>
<td>Asian; ages combined</td>
<td>5.6</td>
<td>0.2</td>
</tr>
<tr>
<td>15-19</td>
<td>1.7</td>
<td>0.0</td>
</tr>
<tr>
<td>20-24</td>
<td>13.8</td>
<td>0.3</td>
</tr>
<tr>
<td>25-29</td>
<td>15.7</td>
<td>0.4</td>
</tr>
<tr>
<td>30-34</td>
<td>10.7</td>
<td>0.1</td>
</tr>
<tr>
<td>35-39</td>
<td>9.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Multirace; ages combined</td>
<td>9.5</td>
<td>0.5</td>
</tr>
<tr>
<td>15-19</td>
<td>3.2</td>
<td>0.3</td>
</tr>
<tr>
<td>20-24</td>
<td>21.4</td>
<td>1.2</td>
</tr>
<tr>
<td>25-29</td>
<td>26.9</td>
<td>1.5</td>
</tr>
<tr>
<td>30-34</td>
<td>32.1</td>
<td>2.2</td>
</tr>
<tr>
<td>35-39</td>
<td>30.8</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Region of United States, followed by states and cities with the highest rates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire United States</td>
<td>11.7</td>
<td>1.1</td>
</tr>
<tr>
<td>West</td>
<td>14.6</td>
<td>1.2</td>
</tr>
<tr>
<td>California (San Francisco)</td>
<td>18.4 (32.8)</td>
<td>1.7 (1.5)</td>
</tr>
<tr>
<td>Nevada (Las Vegas)</td>
<td>23.8 (29.6)</td>
<td>1.7 (1.7)</td>
</tr>
<tr>
<td>Oregon (Portland)</td>
<td>12.9 (17.2)</td>
<td>1.1 (0.8)</td>
</tr>
<tr>
<td>South</td>
<td>12.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Georgia (Atlanta)</td>
<td>23.3 (35.0)</td>
<td>1.9 (2.0)</td>
</tr>
<tr>
<td>Louisiana (New Orleans)</td>
<td>19.6 (33.7)</td>
<td>5.6 (2.8)</td>
</tr>
<tr>
<td>Florida (Miami-Fort Lauderdale)</td>
<td>16.8 (27.5)</td>
<td>1.4 (1.5)</td>
</tr>
</tbody>
</table>
Table 6. Rates of Primary and Secondary Syphilis Infection by Population Subgroups*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Northeast</td>
<td>10.7</td>
<td>0.5</td>
</tr>
<tr>
<td>District of Columbia</td>
<td>34.6</td>
<td>1.5</td>
</tr>
<tr>
<td>New York (New York City)</td>
<td>17.6 (17.3)</td>
<td>0.5 (0.5)</td>
</tr>
<tr>
<td>Maryland (Baltimore)</td>
<td>13.9 (18.0)</td>
<td>1.6 (2.9)</td>
</tr>
<tr>
<td>Midwest</td>
<td>7.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Illinois (Chicago)</td>
<td>12.4 (15.7)</td>
<td>1.2 (1.6)</td>
</tr>
<tr>
<td>Michigan (Detroit)</td>
<td>8.0 (14.1)</td>
<td>0.6 (1.0)</td>
</tr>
<tr>
<td>Missouri (Kansas City)</td>
<td>10.7 (19.5)</td>
<td>1.1 (2.2)</td>
</tr>
</tbody>
</table>

Table 7. Summary of Evidence

<table>
<thead>
<tr>
<th>Main findings from prior USPSTF reviews</th>
<th>Number/type of studies in update</th>
<th>Overall quality*</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Question 1. What is the effectiveness of screening for syphilis in reducing complications of the disease and transmission or acquisition of other STIs in asymptomatic, nonpregnant, sexually active adults and adolescents? What is the effectiveness of specific screening intervals and screening among population subgroups?</td>
<td>No studies met inclusion criteria.</td>
<td>4 observational studies of MSM and HIV-positive males</td>
<td>Fair</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+MSM; studies included high-prevalence populations</td>
</tr>
</tbody>
</table>

| 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? | No studies met criteria. | No studies | NA | NA | NA | NA |

| Key Question 3. What is the accuracy of currently used screening tests and strategies for detecting syphilis infection? | Included mostly studies of diagnostic accuracy 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) | Fair | Not all tests currently used for screening in the U.S. were included; unclear sampling methods and interpretation of tests; some studies had technical shortcomings. | Consistent | Limited; 1 of 3 studies from the U.S. in STI clinic with high prevalence of MSM and HIV; 2 studies of testing sequence conducted in the U.S. and Canada; studies included high-prevalence populations | 3 observational studies of treponemal and nontreponemal tests found that screening tests for syphilis are accurate: sensitivity 85.3%-98% and specificity 91%-100% for both treponemal and nontreponemal tests. 2 studies of the accuracy of reverse sequence testing found a higher rate of false-positive tests when using an automated treponemal test for initial screening compared with rapid plasma reagin in a low-prevalence U.S. population (0.6% vs. 0.0%; p=0.03), and in a higher prevalence Canadian population (0.26% vs. 0.13%). Both methods identified additional positive tests that would not have been identified using conventional methods. |

| Key Question 4. What are the harms of screening? | No studies identified | No studies | NA | NA | NA | NA |

* “Overall quality” is based on new evidence identified for the update plus previously reviewed evidence.

**Abbreviations:** CI=confidence interval; MSM=men who have sex with men; NA=not applicable; STI=sexually transmitted infection.
Appendix A. Terminology

**Enzyme Immunoassay (EIA):** An assay designed to detect antigens of antibodies by producing an enzyme triggered color change.

**Indeterminate test result:** Test result was not clear.

**Likelihood Ratio:** Positive Likelihood Ratio – ratio between the probability of a positive test result given the presence of the disease and the probability of a positive test result given the absence of the disease; Negative Likelihood Ratio – ratio between the probability of a negative test result given the presence of the disease and the probability of a negative test result given the absence of the disease.

**Men who have sex with men (MSM):** Men who engage in sexual activities with other men, even if they engage in sexual activities with women as well.

**Men who have sex with women (MSW):** Men who engage in sexual activities with women only.

**Predictive Value (PPV):** Positive Predictive Value – the proportion of people with a positive test who have the disease; Negative Predictive Value – proportion of people with a negative test who are free of disease.

**Prozone phenomenon:** False negative due to lack of agglutination with high antibody levels.

**Rapid Plasma Reagin (RPR):** A type of rapid diagnostic test that looks for non-specific antibodies in the blood of a patient.

**Relative Risk (RR):** Ratio of the risk of an event among an exposed population to the risk among the unexposed.

**Sensitivity:** The proportion of truly diseased/infected persons in the screened population who are identified as diseased by the screening test—that is, the true-positive rate.

**Serofast:** Persistent, low-level positive titer after adequate treatment.

**Specificity:** The proportion of truly nondiseased/noninfected persons who are identified as such by the screening test—that is, the true-negative rate.

**Venereal Disease Research Laboratory (VDRL):** A blood test for syphilis developed by the former Venereal Disease Research Laboratory, now the Treponemal Pathogenesis and Immunology Branch of the United States Public Health Service. The test is used to screen for syphilis.
Appendix B1. Search Strategies

Database: Ovid MEDLINE(R) without Revisions
Search Strategy:

1 exp Treponema pallidum/
2 exp Syphilis/ or syphili$.mp.
3 1 or 2
4 exp mass screening/ or screen$.mp.
5 3 and 4
6 limit 5 to english language
7 limit 5 to abstracts
8 6 or 7

Database: Ovid MEDLINE(R) without Revisions
Search Strategy:

1 exp Treponema pallidum/
2 exp Syphilis/ep, et, pc, px, tm
3 1 or 2
4 exp risk/
5 ((assess$ or stratif$ or quantif$ or identif$) adj7 risk$).mp.
6 4 or 5
7 3 and 6

Database: Ovid MEDLINE(R) without Revisions
Search Strategy:

1 exp Treponema pallidum/
2 exp Syphilis/di
3 1 or 2
4 exp "Sensitivity and Specificity"/
5 3 and 4
6 exp Diagnostic Errors/
7 3 and 6
8 5 or 7
9 (fals$ adj3 (positiv$ or negativ$)).mp.
10 3 and 9
11 (accura$ or inaccura$ or (predict$ adj5 (value$ or able or abilit$ or capab$ or effectiv$ or unable or inabilit$ or incapab$ or ineffect$ or correct$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12 3 and 11
13 8 or 10 or 12
Appendix B1. Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:

1 syphil$.mp.
2 treponema pallidum.mp.
3 screen$.mp.
4 exp Mass Screening/
5 3 or 4
6 1 or 2
7 5 and 6

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:

1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 exp Risk/
5 risk$.mp.
6 4 or 5
7 3 and 6

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:

1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 exp "Sensitivity and Specificity"/
5 exp Diagnostic Errors/
6 (diagnos$ adj3 (mistak$ or error$ or erroneous$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 (fals$ adj3 (positiv$ or negativ$)).mp.
8 (accura$ or inaccura$ or (predict$ adj5 (value$ or able or abilit$ or capab$ or effectiv$ or unable or inabilit$ or incapab$ or ineffect$ or correct$))).mp.
9 4 or 5 or 6 or 7 or 8
10 3 and 9

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:

1 syphil$.mp.
2 treponema pallidum.mp.
3 screen$.mp.
4 [exp Mass Screening/]
Appendix B1. Search Strategies

6 1 or 2
7 5 and 6

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:

1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 [exp Risk/]
5 risk$.mp.
6 4 or 5
7 3 and 6

Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:

1 syphil$.mp.
2 treponema pallidum.mp.
3 screen$.mp.
4 [exp Mass Screening/]
5 3 or 4
6 1 or 2
7 5 and 6
Appendix B1. Search Strategies

Database: EBM Reviews - Database of Abstracts of Reviews of Effects
Search Strategy:

1  syphil$.mp.
2  treponema pallidum.mp.
3  1 or 2
4  [exp "Sensitivity and Specificity"/]
5  [exp Diagnostic Errors/]
6  (diagnos$ adj3 (mistak$ or error$ or erroneous$)).mp. [mp=title, full text, keywords]
7  (fals$ adj3 (positiv$ or negativ$)).mp.
8  (accura$ or inaccura$ or (predict$ adj5 (value$ or able or abilit$ or capab$ or effectiv$ or unable or inabilit$ or incapab$ or ineffect$ or correct$))).mp.
9  4 or 5 or 6 or 7 or 8
10  3 and 9

Database: EBM Reviews - NHS Economic Evaluation Database
Search Strategy:

1  syphil$.mp.
2  treponema pallidum.mp.
3  screen$.mp.
4  exp Mass Screening/
5  3 or 4
6  1 or 2
7  5 and 6

Database: EBM Reviews - NHS Economic Evaluation Database
Search Strategy:

1  syphil$.mp.
2  treponema pallidum.mp.
3  1 or 2
4  exp Risk/
5  risk$.mp.
6  4 or 5
7  3 and 6
Appendix B1. Search Strategies

Database: EBM Reviews - NHS Economic Evaluation Database

Search Strategy:

1. syphil$.mp.
2. treponema pallidum.mp.
3. 1 or 2
4. exp "Sensitivity and Specificity"
5. exp Diagnostic Errors/
6. (diagnos$ adj3 (mistak$ or error$ or erroneous$)).mp. [mp=title, text, subject heading word]
7. (fals$ adj3 (positiv$ or negativ$)).mp.
8. (accura$ or inaccura$ or (predict$ adj5 (value$ or able or abilit$ or capab$ or effectiv$ or unable or inabilit$ or incapab$ or ineffect$ or correct$))).mp.
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9
### Appendix B2. Inclusion and Exclusion Criteria

| Include | Exclude |
|---------|
| **Definition of Disease** | Positive for syphilis on any test modality |
| **Populations** | Asymptomatic, nonpregnant adults and adolescents, including those who are coinfected with other STIs, including HIV |
| | Symptomatic patients; neonates, infants, and children; pregnant women; contacts of cases; studies of HIV patients for whom syphilis testing is disease management rather than a screening intervention |
| **Interventions** | Screening effectiveness including effectiveness of different screening intervals |
| KQs 1, 4 | Risk assessment instruments and other risk stratification methods that identify individuals at increased risk for syphilis infection |
| KQs 3 | FDA cleared tests available in the United States that detect syphilis in biological specimens including varying testing strategies (e.g., traditional, reverse sequence) |
| **Comparators** | No screening or alternate screening strategy or methods |
| KQs 1, 4 | No comparison |
| KQ 2 | True disease status |
| KQs 3 | Study-specific comparator or gold standard, as determined by the study itself (e.g., an enzyme-linked immunosorbent assay technique could be evaluated by comparing its sensitivity and specificity with that of MHA-TP and FTA-ABS tests) |
| **Outcomes** | Reduction in: Complications of syphilis (e.g., neurosyphilis, symptomatic neurosyphilis, tertiary syphilis, congenital syphilis) |
| KQ 1 | Disease transmission, including HIV transmission |
| | Other clinical outcomes, rates of infection and other similar measures of infection |
| KQ 2 | Outcomes that are not directly related to health outcomes (e.g., laboratory studies) |
| KQ 3 | Diagnostic accuracy (i.e., measures of the test’s sensitivity, specificity, positive and negative predictive values, and other related measures) |
| KQ 4 | Harms from screening (e.g., labeling, false-negative, false-positive, harms related to false-positive and false negative tests, including psychosocial harms) |
| | Harms related to true positive and true negative tests, including psychosocial harms |
| **Setting** | Primary care and primary care–referable settings (e.g., correctional facilities and community care, such as schools, family planning clinics, obstetrics and gynecology clinics, emergency departments, and STI clinics) |
| **Study Designs** | All KQs | Good-quality systematic reviews |
| Benefits | RCTs, observational studies with comparison groups, including ecological studies |
| Harms | RCTs, observational studies including cross-sectional studies and ecological studies |
| Observational studies without comparison groups, case reports |
| Case studies |

**Abbreviations:** FDA=U.S. Food and Drug Administration; KQ=key question; RCT=randomized, controlled trial; STI=sexually transmitted infection.
Abstracts of potentially relevant articles identified through MEDLINE, Cochrane,* and other sources† (N=2,000)

Excluded abstracts and background articles (n=1,552)

Full text articles reviewed for relevance to Key Questions (n=448)

Full text articles excluded=439
Wrong population=100
Wrong intervention=30
Wrong outcomes=149
Wrong study design for Key Question=22
Wrong publication type=49
Included original studies (no new data)=1
Wrong comparison=11
Review not meeting inclusion criteria =12
Population not applicable to U.S. population=51
Included for contextual questions only=14

Included studies=9

Key Question 1.
4 observational studies

Key Question 2.
No Studies

Key Question 3.
Test accuracy: 3 observational studies
Testing sequence: 2 observational studies

Key Question 4.
No studies

* Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Other sources include reference lists and experts.
Appendix B4. List of Excluded Studies

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong population

**Exclusion:** Wrong population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** custom 7

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Wrong study design for Key Question

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong intervention

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong study design for Key Question
Appendix B4. List of Excluded Studies

**Exclusion:** Wrong outcomes

**Exclusion:** Included for contextual questions only

**Exclusion:** Wrong population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong intervention

**Exclusion:** Wrong publication type

**Exclusion:** Wrong publication type

**Exclusion:** Wrong intervention

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong publication type

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong publication type

**Exclusion:** Wrong intervention

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Included for contextual questions only


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong outcomes


**Exclusion:** Included for contextual questions only


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Population not applicable to U.S.
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong outcomes


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Review not meeting inclusion criteria


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong intervention


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong outcomes


**Exclusion:** custom 7


**Exclusion:** Custom 7

Appendix B4. List of Excluded Studies

**Exclusion:** Custom 7


**Exclusion:** Custom 7


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong outcomes


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong intervention


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong publication type


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong publication type


**Exclusion:** Wrong population


**Exclusion:** Wrong publication type

**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong publication type


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong population

Appendix B4. List of Excluded Studies

Exclusion: Population not applicable to U.S. population


Exclusion: Wrong population


Exclusion: Wrong intervention


Exclusion: Review not meeting inclusion criteria


Exclusion: Wrong outcomes


Exclusion: Wrong intervention


Exclusion: Population not applicable to U.S. population


Exclusion: Included for contextual questions only


Exclusion: Wrong outcomes


Exclusion: Wrong comparison


Exclusion: Wrong population


Exclusion: Wrong population


Exclusion: Wrong population


Exclusion: Wrong population


Exclusion: Wrong outcomes


Exclusion: Wrong population


Exclusion: Wrong intervention


Exclusion: Wrong outcomes
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong intervention


**Exclusion:** Wrong population


**Exclusion:** Wrong publication type


**Exclusion:** Wrong population


**Exclusion:** Wrong comparison


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong population


**Exclusion:** Review not meeting inclusion criteria


**Exclusion:** Review not meeting inclusion criteria


**Exclusion:** Wrong comparison


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong intervention


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Included for contextual questions only


**Exclusion:** Included for contextual questions only
Appendix B4. List of Excluded Studies

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Wrong comparison

**Exclusion:** Review not meeting inclusion criteria

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Review not meeting inclusion criteria

**Exclusion:** Wrong study design for Key Question

Jun L, He-Yi Z. Characteristics of patients with primary and late latent syphilis who were initially non-reactive to the rapid plasma reagin test. *Jpn J Infect Dis.* 2013;66(1):36-40.
**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong comparison
Appendix B4. List of Excluded Studies

**Exclusion:** Wrong outcomes

**Exclusion:** Included for contextual questions only

**Exclusion:** Included for contextual questions only

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong publication type

**Exclusion:** Wrong publication type

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Wrong publication type

**Exclusion:** Wrong population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Wrong publication type

**Exclusion:** Wrong study design for Key Question

**Exclusion:** Wrong publication type

**Exclusion:** Population not applicable to U.S. population
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong intervention


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong publication type


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong outcomes


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong population
Appendix B4. List of Excluded Studies

Exclusion: Population not applicable to U.S. population

Exclusion: Wrong population

Exclusion: Wrong population

Exclusion: Wrong comparison

Exclusion: Wrong comparison

Exclusion: Wrong outcomes

Exclusion: Wrong population

Exclusion: Review not meeting inclusion criteria

Exclusion: Wrong publication type

Exclusion: Wrong population

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong publication type

Exclusion: Wrong population

Exclusion: Wrong population

Exclusion: Wrong study design for Key Question

Exclusion: Wrong intervention
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong population


**Exclusion:** Wrong publication type


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong publication type


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong publication type
Appendix B4. List of Excluded Studies

Exclusion: Review not meeting inclusion criteria

Exclusion: Included for contextual questions only

Exclusion: Wrong outcomes

Exclusion: Included for contextual questions only

Exclusion: Wrong outcomes

Exclusion: Wrong population

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Population not applicable to U.S. population

Exclusion: Wrong intervention

Exclusion: Wrong outcomes

Exclusion: Wrong population

Exclusion: Wrong publication type

Exclusion: Wrong publication type
Appendix B4. List of Excluded Studies

**Exclusion:** Wrong population

**Exclusion:** Wrong intervention

**Exclusion:** Wrong publication type

**Exclusion:** Wrong outcomes

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong intervention

**Exclusion:** Wrong publication type

**Exclusion:** Wrong outcomes

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Wrong population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong study design for Key Question

**Exclusion:** Wrong study design for Key Question

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong comparison


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong publication type


**Exclusion:** Wrong publication type


**Exclusion:** Wrong publication type


**Exclusion:** Wrong outcomes


**Exclusion:** Review not meeting inclusion criteria


**Exclusion:** Review not meeting inclusion criteria


**Exclusion:** Wrong publication type


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong study design for Key Question


**Exclusion:** custom 7


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong study design for Key Question
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong outcomes


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong publication type


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong outcomes


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong publication type


**Exclusion:** Wrong outcomes


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong outcomes


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong comparison


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong outcomes

Rogstad KE, Simms I, Wallace L, et al. Screening for Syphilis Infection 64 Pacific Northwest EPC
Appendix B4. List of Excluded Studies


Exclusion: Wrong intervention


Exclusion: Wrong outcomes


Exclusion: Wrong outcomes


Exclusion: Wrong population


Exclusion: Population not applicable to U.S. population


Exclusion: Wrong outcomes


Exclusion: Population not applicable to U.S. population


Exclusion: Wrong intervention


Exclusion: Wrong outcomes


Exclusion: Wrong outcomes


Exclusion: Wrong outcomes


Exclusion: Wrong outcomes


Exclusion: Wrong publication type


Exclusion: Wrong population


Exclusion: Wrong publication type


Exclusion: Wrong study design for Key Question


Exclusion: Wrong population
Appendix B4. List of Excluded Studies

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong intervention

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong publication type

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Wrong publication type

**Exclusion:** Wrong publication type

**Exclusion:** Review not meeting inclusion criteria

**Exclusion:** Wrong publication type

**Exclusion:** Wrong intervention

**Exclusion:** Wrong population

**Exclusion:** Wrong population

**Exclusion:** Wrong population

**Exclusion:** Wrong population

**Exclusion:** Wrong intervention

**Exclusion:** Wrong outcomes

Singh AE, Wong T, De P. Characteristics of primary and late latent syphilis cases which were initially non-reactive with the rapid plasma reagin as the screening test. *Int J STD AIDS*. 2008;19(7):464-8.
**Exclusion:** Wrong outcomes
Appendix B4. List of Excluded Studies

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong intervention

Exclusion: Wrong publication type

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes

Exclusion: Wrong publication type

Exclusion: Wrong population

Exclusion: Wrong intervention

Exclusion: Wrong outcomes

Exclusion: Wrong intervention

Exclusion: Wrong population
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes

Tankhiwale SS, Naikwade SR. Seroprevalence of syphilis and biologically false positive cases in a tertiary care center. *Indian J Dermatol Venereol Leprol.* 2014;80(4):340-1.

**Exclusion:** Wrong publication type


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong population


**Exclusion:** Wrong outcomes


**Exclusion:** Wrong population


**Exclusion:** Wrong publication type


**Exclusion:** Review not meeting inclusion criteria


**Exclusion:** Wrong publication type


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong study design for Key Question


**Exclusion:** Wrong comparison


**Exclusion:** Wrong population


**Exclusion:** Wrong population
Appendix B4. List of Excluded Studies

**Exclusion:** Included for contextual questions only

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong population

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong intervention

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong intervention

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong population

**Exclusion:** Wrong population

**Exclusion:** Wrong population

**Exclusion:** Wrong intervention
Appendix B4. List of Excluded Studies

**Exclusion:** Wrong population

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Wrong outcomes

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong population

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong outcomes

**Exclusion:** Population not applicable to U.S. population

**Exclusion:** Wrong outcomes

**Exclusion:** Included for contextual questions only

**Exclusion:** Wrong population

**Exclusion:** Population not applicable to U.S. population

Screening for Syphilis Infection 70 Pacific Northwest EPC
Appendix B4. List of Excluded Studies

Exclusion: Wrong population

Exclusion: Wrong intervention

Exclusion: Population not applicable to U.S. population

Exclusion: Population not applicable to U.S. population

Exclusion: Wrong outcomes

Exclusion: Wrong publication type

Exclusion: Wrong comparison

Exclusion: Wrong population

Exclusion: Population not applicable to U.S. population

Exclusion: Population not applicable to U.S. population

Exclusion: Population not applicable to U.S. population

Exclusion: Wrong publication type

Exclusion: Population not applicable to U.S. population

Exclusion: Wrong outcomes

Exclusion: Wrong outcomes
Appendix B4. List of Excluded Studies


**Exclusion:** Wrong population


**Exclusion:** Wrong intervention


**Exclusion:** Included original studies (no new data)


**Exclusion:** Population not applicable to U.S. population


**Exclusion:** Wrong population
Appendix B5. Quality Rating Criteria

Cohort Studies

**Criteria:**
- Initial assembly of comparable groups: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies.

**Definition of ratings based on above criteria:**

**Good:** Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

**Fair:** Studies will be graded “fair” if any or all of the following problems occur, without the fatal flaws noted in the “poor” category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

**Poor:** Studies will be graded “poor” if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Diagnostic Accuracy Studies

**Criteria:**
- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test
Appendix B5. Quality Rating Criteria

**Definition of ratings based on above criteria:**

**Good:** Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.

**Fair:** Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a “medium” spectrum of patients.

**Poor:** Has fatal flaw such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.
Appendix B6. List of Peer Reviewers

Expert reviewers

Matthew J. Binnicker, PhD, D(ABMM) Director of Clinical Virology, Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

Khalil Ghanem, MD, PhD Associate Professor of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD

Heidi M. Bauer, MD, MPH, MS Chief, STD Control Branch, California Department of Public Health, Richmond, CA

Jeffrey D. Klausner, MD, MPH Professor of Medicine and Public Health, UCLA, Los Angeles, CA

Federal reviewers

Tom Peterman, MD, MSc Chief, Epidemiology 2 Unit, Division of STD Prevention, CDC, Atlanta, Georgia

Catherine T. Witkop, MD, MPH Chief, Preventive Medicine, Air Force
### Appendix C1. Observational Studies of Screening Intervals for Syphilis and Screening Among Population Subgroups

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Population, n</th>
<th>Interventions</th>
<th>Duration</th>
<th>Attrition</th>
<th>Outcomes</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bissessor et al, 2010&lt;sup&gt;36&lt;/sup&gt; (see text)</td>
<td>1,031 MSM attending a public STI clinic in Australia, offering HIV care to 20% of men in the region</td>
<td>Routine syphilis screening every 3 months as part of HIV monitoring vs. annual screening (control)</td>
<td>1 year</td>
<td>NR</td>
<td>Proportion of HIV+ MSM attending the HIV clinic diagnosed with early syphilis: Screened: 8.1% (48/587) Control: 3.1% (14/444) (p=0.001) Proportion of asymptomatic with early syphilis: Screened: 85% (41/48) Control: 21% (3/14) (p=0.006)</td>
<td>Fair</td>
</tr>
<tr>
<td>Bissessor et al, 2011&lt;sup&gt;59&lt;/sup&gt;</td>
<td>6,789 consultations with MSM attending public STI clinic in Australia, offering HIV care to 20% of men in the region</td>
<td>A computer alert system aimed at clinicians to screen higher risk MSM (&gt;10 partners in 12 months) for syphilis every 3 months vs. annually (control)</td>
<td>1 year</td>
<td>NR</td>
<td>Proportion of higher risk MSM diagnosed with early syphilis that are asymptomatic: Screened: 53% (31/58) Control: 16% (5/31) (p=0.001) Proportion of lower risk MSM diagnosed with early syphilis that are asymptomatic: Screened: 19% (3/16) Control: 10% (1/10) No difference, (p=0.6)</td>
<td>Fair</td>
</tr>
<tr>
<td>Cohen et al, 2005&lt;sup&gt;57&lt;/sup&gt;</td>
<td>2,389 HIV patients in the UK with newly positive syphilis serology, asymptomatic at the time of screening</td>
<td>Routine syphilis screening every 3 months vs. annual screening (control)</td>
<td>1 year</td>
<td>NR</td>
<td>Event rate of early asymptomatic infection, per 1,000 patient-years: Screened: 7.3 (CI, 5.2 to 9.9) Controls: 2.8 (CI, 1.8 to 4.0) (p&lt;0.05)</td>
<td>Fair</td>
</tr>
<tr>
<td>Zou et al, 2013&lt;sup&gt;38&lt;/sup&gt;</td>
<td>4,514 MSM attending public STI clinic in Australia, opting to receive clinical reminders</td>
<td>3, 6, or 12 month clinical reminders vs. control</td>
<td>18 months</td>
<td>NR</td>
<td>Proportion of MSM diagnosed with syphilis at least once, n (%): Early syphilis: 3: 19 (3.2); (p=0.025) 6: 5 (1.9); (p=0.680) 3, 6, or 12: 25 (2.8); (p=0.060) Control: 15 (1.5) Early, latent syphilis: 3: 10 (1.7); (p=0.008) 6: 2 (0.8); (p=0.469) 3, 6, or 12: 12 (1.4); (p=0.028) Control: 4 (0.4) Proportion of all tests positive in subsequent visits, n (%): Early syphilis: 3: 22 (3.0); (p=0.530) 6: 5 (2.5); (p=0.982) 3, 6, or 12: 28 (3.0); (p=0.568) Control: 15 (2.5)</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI=confidence interval; HIV=human immunodeficiency virus; MSM=men who have sex with men; NR=not reported; STI=sexually transmitted infection; UK=United Kingdom.
### Appendix C2. Quality Ratings of Included Cohort Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>KQ?</th>
<th>Did the study attempt to enroll a random sample or consecutive patients meeting inclusion criteria (inception cohort)?</th>
<th>Were the groups comparable at baseline?</th>
<th>Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?</th>
<th>Were outcome assessors and/or data analysts blinded to treatment?</th>
<th>Did the study report attrition?</th>
<th>Did the study perform appropriate statistical analyses on potential confounders?</th>
<th>Is there important differential loss to followup or overall high loss to followup?</th>
<th>Were outcomes prespecified and defined, and ascertained using accurate methods?</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bissessor et al, 2010</td>
<td>KQ1</td>
<td>Yes-- consecutive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Bissessor et al, 2011</td>
<td>KQ1</td>
<td>Yes-- consecutive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Cohen et al, 2005</td>
<td>KQ1</td>
<td>Yes-- consecutive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Zou et al, 2013</td>
<td>KQ1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Abbreviation:** KQ=key question.
### Appendix C3. Diagnostic Accuracy of Syphilis Testing

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Screening test</th>
<th>Definition of a positive screening test</th>
<th>Reference standard(s)</th>
<th>Country, setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juárez-Figueroa et al, 2007&lt;sup&gt;62&lt;/sup&gt;</td>
<td>TPPA</td>
<td>Samples that tested positive to VDRL and FTA-ABS were defined as serologically active syphilis</td>
<td>VDRL screening with FTA-ABS confirmation</td>
<td>Mexico STI clinic</td>
</tr>
<tr>
<td>Wong et al, 2011&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Trep-Sure EIA</td>
<td>Samples that tested positive by TPPA confirmation test</td>
<td>VDRL screening with TPPA confirmation</td>
<td>U.S. Routine syphilis testing</td>
</tr>
<tr>
<td>Tsang et al, 2007&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Trep-Check IgG EIA</td>
<td>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.</td>
<td>RPR, VDRL, or EIA screening with FTA-ABS, INNO-LIA, or TPPA confirmation</td>
<td>Canada National Microbiology Laboratory</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Population characteristics</th>
<th>Proportion with condition</th>
<th>Proportion unexaminable by screening test</th>
<th>Analysis of screening failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juárez-Figueroa et al, 2007&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Asymptomatic female sex workers</td>
<td>198/198 (99.5%) tested positive</td>
<td>False-positives, defined as VDRL positive with negative FTA-ABS, or previously treated syphilis were not included in the analysis</td>
<td>NR</td>
</tr>
<tr>
<td>Wong et al, 2011&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Patients presenting to the San Francisco municipal sexually transmitted diseases clinic. Population at this clinic is 69.3% MSM, 16.6% HIV positive.</td>
<td>674 samples 39.7% tested positive for syphilis Clinic has a 9.4% prevalence rate</td>
<td>0/674</td>
<td>Uncategorized samples confirmed via Western blot and/or EIA for antibodies to specific treponemal antigens. These confirmatory tests are not approved for use in testing patient specimens.</td>
</tr>
<tr>
<td>Tsang et al, 2007&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Specimens from local hospitals or provincial public health laboratories submitted for confirmation of local test results or for further evaluation of serologic status.</td>
<td>34/604 (5.6%)</td>
<td>NA</td>
<td>Discordant test results also examined with INNO-LIA immunoassay.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Proportion included in analysis</th>
<th>Sensitivity, Specificity, PPV, NPV (95% CI)</th>
<th>False-positives, False-negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juárez-Figueroa et al, 2007&lt;sup&gt;62&lt;/sup&gt;</td>
<td>185/198 (93%)</td>
<td>Sensitivity: 87.1% (70.2% to 96.3%)* Specificity: 100% (97.6% to 100%)* PPV: 100% (87.1% to 100%)* NPV: 97.5% (93.6% to 99.3%)*</td>
<td>FP: 0 FN: 4/185</td>
</tr>
<tr>
<td>Wong et al, 2011&lt;sup&gt;60&lt;/sup&gt;</td>
<td>673/674 samples included in analysis. One sample did not have adequate volume for confirmation testing and was excluded.</td>
<td>Sensitivity: 98.0% (95.8% to 99.3%)* Specificity: 98.6% (96.9% to 99.6%)* PPV: 98.4% (96.2% to 99.5%)* NPV: 98.4% (96.5% to 99.4%)*</td>
<td>FP: 5/673 FN: 6/673</td>
</tr>
</tbody>
</table>
## Appendix C3. Diagnostic Accuracy of Syphilis Testing

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Proportion included in analysis</th>
<th>Sensitivity, Specificity, PPV, NPV (95% CI)</th>
<th>False-positives, False-negatives</th>
</tr>
</thead>
</table>
| Tsang et al, 2007 | 100% | Sensitivity: 85.3% (68.9% to 95.1%)*  
Specificity: 95.6% (93.6% to 97.1%)*  
PPV: 53.7% (39.6% to 67.4%)*  
NPV: 99.1% (97.9% to 99.7%)* | FP: 25/604  
FN: 5/604 |

* Calculated.

**Abbreviations:** EIA=enzyme immunoassay; FN=false-negative; FP=false-positive; FTA-ABS=fluorescent treponemal antibody absorption; IgG=immunoglobulin G; MSM=men who have sex with men; NA=not available; NPV=negative predictive value; NR=not relevant; PPV=positive predictive value; RPR=rapid plasma reagin; STI=sexually transmitted infection; TPPA=*Treponema pallidium* partial agglutination; TRUST=toluidine red unheated serum test; VDRL=Venereal Disease Research Laboratory.
### Appendix C4. Quality Ratings of Diagnostic Accuracy Studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Representative spectrum</th>
<th>Random or consecutive sample</th>
<th>Screening test adequately described</th>
<th>Screening cutoffs predefined</th>
<th>Credible reference standard</th>
<th>Reference standard applied to and analysis includes all patients, or a random subset</th>
<th>Same reference standard applied to all patients</th>
<th>Reference standard and screening examination interpreted independently</th>
<th>High rate of uninterpretable results or non-compliance with screening test</th>
<th>Analysis includes patients with uninterpretable results or non-compliance</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binnicker et al, 2012&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Juárez-Figueroa et al, 2007&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Mishra et al, 2011&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Tsang et al, 2007&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Fair</td>
</tr>
<tr>
<td>Wong et al, 2011&lt;sup&gt;49&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Appendix C5. Comparison of Traditional and Reverse Algorithms for Syphilis Testing

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Reverse screening algorithm</th>
<th>Traditional screening algorithm</th>
<th>Definition of a positive screening exam</th>
<th>Type of study</th>
<th>Country Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra et al, 2011&lt;sup&gt;63&lt;/sup&gt;</td>
<td>August 2005-July 2008 EIA screening followed by RPR testing and an alternate treponemal confirmatory test.</td>
<td>August 1998-July 2005 RPR screening and confirmatory treponemal test</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>Retrospective cohort</td>
<td>Canada Laboratory</td>
</tr>
<tr>
<td>Binnicker et al, 2012&lt;sup&gt;28&lt;/sup&gt;</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 endpoint.</td>
<td>RPR screening followed by TPPA</td>
<td>Reverse algorithm: MFI+/RPR or TPPA+ Traditional algorithm: RPR+/TPPA+</td>
<td>Prospective cohort study</td>
<td>U.S. Laboratory</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Population Characteristics</th>
<th>Sample size</th>
<th>Analysis of screening failures</th>
<th>Results from traditional screening algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra et al, 2011&lt;sup&gt;63&lt;/sup&gt;</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.</td>
<td>Total samples: 3,092,938 RPR screening samples: 2,055,913 with 0.46% prevalence EIA screening samples: 1,037,025 with 1.98% prevalence</td>
<td>NR</td>
<td>0.59% of samples screened positive and 0.46% of samples were confirmed positive</td>
</tr>
<tr>
<td>Binnicker et al, 2012&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Low-prevalence patient population</td>
<td>n=1,000 samples submitted for routine syphilis testing</td>
<td>1 patient with an underlying HIV infection was treated for neurosyphilis based on a positive VDRL result from a cerebrospinal fluid sample. Chart reviews were conducted for final clinical interpretation of unclear results.</td>
<td>4/1,000 (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 sera were submitted to monitor response to therapy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Results from reverse screening algorithm</th>
<th>Outcomes</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra et al, 2011&lt;sup&gt;63&lt;/sup&gt;</td>
<td>2.24% of samples screened positive, 1.98% of samples confirmed positive. 69.6% of all confirmed positives were RPR negative. Following EIA implementation, the monthly rate of confirmed positives increased from 3.2 to 13.5 per 100,000 population (p&lt;0.001).</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% to 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 use: 69.9% MSM and intravenous drug use: 68.0%</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Appendix C5. Comparison of Traditional and Reverse Algorithms for Syphilis Testing

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Results from reverse screening algorithm</th>
<th>Outcomes</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binnicker et al, 2012 (^{28})</td>
<td>15/1,000 (1.5%) samples tested positive by MFI screening. 11/15 samples would not have been detected by traditional screening. After chart review, 3 patients had a history of previously treated syphilis, 6 patients were interpreted as false-positive 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-positive rate compared with traditional testing (0.6% vs. 0.0%; p=0.03); however, reverse screening detected 2 patients with possible latent syphilis who were not detected by the traditional screening algorithm.</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Abbreviations:** 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; VDRL= Venereal Disease Research Laboratory.