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.

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

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

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

Figures

Tables

Appendixes

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.[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.[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.[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.[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.[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,[9] ranges from 15.9 to 30.3 percent based on reports of partner transmission from patients with untreated early syphilis.[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.[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.[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).[15]

Risk Factors

Several studies and the CDC have reported risk factors that may increase a person's risk for syphilis infection.[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.[16,17] 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.[19-21] 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.[6] The availability of accurate screening tests and effective treatment make syphilis screening clinically feasible.[22] Since syphilis has been associated with HIV coinfection, identification of persons infected with syphilis may also reduce rates of HIV infection.[22]

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.[23]

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])[24] 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**).[1] 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.[25] 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**).[25]

Several new screening tests are currently being studied, including the immunochromatographic strip,[33] line immunoassay, and rapid syphilis tests.[1] 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.[27] 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.[34] 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.[6] 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.[1] 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.[6]

Interventions and Treatment

Antibiotics are effective for treating and curing syphilis infection.[3,35,36] 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.[6] Close followup is necessary to ensure treatment success.[37] 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.[19]

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.[6,38,39] 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.[40] Azithromycin administered as a single 2-g oral dose can be effective for treating early syphilis.[41-43] However, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been documented in several geographical areas in the United States.[44-46] 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[44] and in pregnant women due to concerns about therapeutic efficacy.[47] Close followup of patients receiving alternative therapies is essential.[6]

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.[48] 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.[6] 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.[6] 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.[49]

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.[3] 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.[50] 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.[54,55] Based on evidence gaps identified from the prior review,[1] 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.[1] 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[55] 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.[55] 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 Australia[56,58,59] and one fair-quality observational study from the United Kingdom[57] evaluated detection rates of syphilis using specific screening intervals among MSM or HIV-positive populations (**Appendixes 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 HIV[56,57] 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.[56] The detection rate of asymptomatic syphilis infections was significantly higher for 3-month versus annual screening (8.1% vs. 3.1%; 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 (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.[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; $p<0.05$).[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.[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%; 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.[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%]; 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%]; 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%).[60] 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.[61] 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.[62] 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.[28,63] 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.[63] 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.[28] 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**).[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,[60,61] and one study compared the treponemal TPPA test with VDRL testing followed by FTA-ABS.[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).[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%).[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).[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.[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, 60.0 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.

Contextual Question 1. Which Population Subgroups, Including MSM, Are at Highest Risk for Incident Syphilis Infection?

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.[8] 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.[8] 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.[8]

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**).[64] 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**).[67] Four other observational studies enrolled predominately MSM living with HIV and tested them for syphilis.[17,65,66,68] 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**).[68] 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).[68] 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]).[65]

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.[8] 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.[69] 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.[8]

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.[8] 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.[19]

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.[19] 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

about syphilis risk factors or prevalence among sex workers.

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.[70] Another study reported seroprevalence rates of 11 percent among women tested in jails compared with 3 percent among women tested in hospital delivery rooms.[71] In some locations, a high proportion of early syphilis cases are reported from correctional facilities.[72] 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.[19]

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).[8] 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).[8]

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.[2] 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).[56-59] 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),[56] 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),[57] early latent syphilis (1.7% vs. 0.4%; p=0.008),[58] and early syphilis among higher-risk MSM (53% vs. 16%; p=0.001).[59] 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).[60-62] 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%).[60] 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.[61] 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.[62] 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

populations, and developing countries.

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.[28,63] 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.[73] 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**).[24]

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.[24,34] 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

1. Nelson HD, Glass N, Huffman L, et al. Screening for syphilis: brief update for the US Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality. 2004.
2. Calonge N, U. S. Preventive Services Task Force. Screening for syphilis infection: recommendation statement.[Erratum appears in Ann Fam Med. 2004 Sep-Oct;2(5):517]. Ann Fam Med. 2004;2(4):362-5.
3. Centers for Disease Control and Prevention. STD Surveillance Case Definitions. Available at: http://www.cdc.gov/std/stats/CaseDefinitions-2014.pdf. Accessed February 27, 2015.
4. Hicks C. Diagnostic testing for syphilis. Available at: http://www.uptodate.com/contents/diagnostic-testing-for-syphilis. Accessed January 14, 2015.
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.
6. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 2015;64(RR-03):1-137.
7. Shah BB, Lang AE. Acquired neurosyphilis presenting as movement disorders. Mov Disord. 2012;27(6):690-5.
8. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2014. Atlanta, GA: Department of Health and Human Services. 2015. Available at: http://www.cdc.gov/std/stats14/surv-2014-print.pdf. Accessed March 9, 2016.
9. Beranard Roizman. Infectious Diseases in an Age of Change: The Impact of Human Ecology and Behavior on Disease Transmission. Washington, DC: The National Academies Press; 1995.
10. Moore MB, Jr., Price EV, Knox JM, et al. EPIDEMIOLOGIC TREATMENT OF CONTACTS TO INFECTIOUS SYPHILIS. Public health reports (Washington, DC : 1974). 1963;78:966-70.
11. Schroeter AL, Turner RH, Lucas JB, et al. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. JAMA. 1971;218(5):711-3.
12. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. Aids. 2004;18(15):2075-9.
13. Kofoed K, Gerstoft J, Mathiesen LR, et al. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load, and treatment response. Sex Transm Dis. 2006;33(3):143-8.
14. Palacios R, Jimenez-Onate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. J Acquir Immune Defic Syndr. 2007;44(3):356-9.
15. Owusu-Edusei K, Jr., Chesson HW, Gift TL, et al. The estimated direct medical cost of selected sexually transmitted infections in the United States, 2008. Sex Transm Dis. 2013;40(3):197-201.

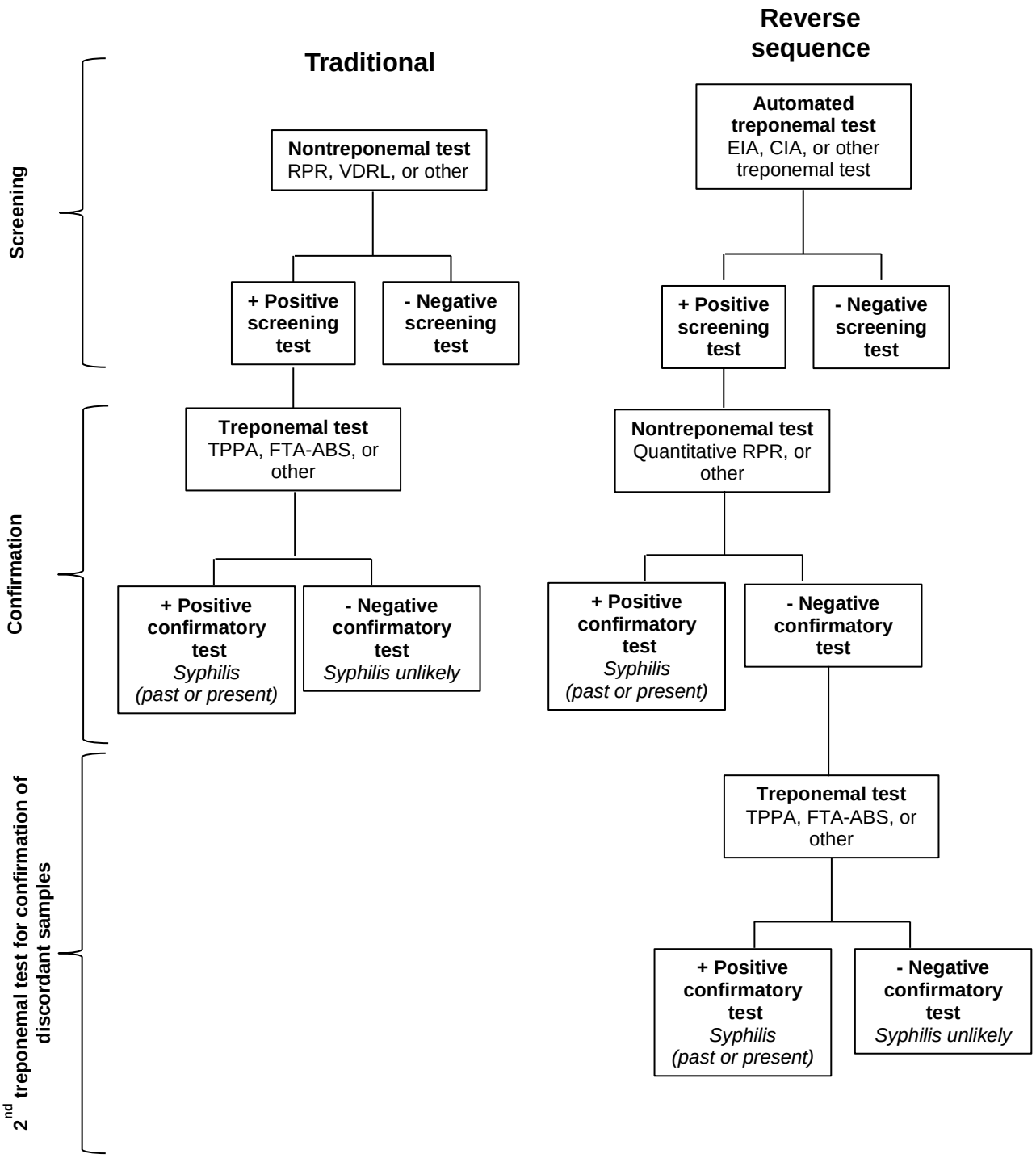
16. Van Wagoner NJ, Harbison HS, Drewry J, et al. Characteristics of women reporting multiple recent sex partners presenting to a sexually transmitted disease clinic for care. Sex Transm Dis. 2011;38(3):210-5.
17. Mayer KH, Bush T, Henry K, et al. Ongoing sexually transmitted disease acquisition and risk-taking behavior among US HIV-infected patients in primary care: implications for prevention interventions. Sex Transm Dis. 2012;39(1):1-7.
18. Brodsky JL, Samuel MC, Mohle-Boetani JC, et al. Syphilis outbreak at a California men's prison, 2007-2008: propagation by lapses in clinical management, case management, and public health surveillance. J Correct Health Care. 2013;19(1):54-64.
19. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2011. Atlanta, GA: Department of Health and Human Services. 2012. Available at: http://www.cdc.gov/std/stats11/Surv2011.pdf. Accessed January 14, 2015.
20. Weinstock H, Berman S, Cates W, Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. Perspect Sex Reprod Health. 2004;36(1):6-10.
21. Marx R, Aral SO, Rolfs RT, et al. Crack, sex, and STD. Sex Transm Dis. 1991;18(2):92-101.
22. Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydial infection. MMWR Recomm Rep. 2008;57(Rr-9):1-83; quiz CE1-4.
23. Blank S, McDonnell DD, Rubin SR, et al. New approaches to syphilis control. Finding opportunities for syphilis treatment and congenital syphilis prevention in a women's correctional setting. Sex Transm Dis. 1997;24(4):218-26.
24. Centers for Disease C, Prevention. Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60(5):133-7.
25. Ratnam S. The laboratory diagnosis of syphilis. The Canadian journal of infectious diseases & medical microbiology = Journal canadien des maladies infectieuses et de la microbiologie medicale / AMMI Canada. 2005;16(1):45-51.
26. American Association for Clinical Chemistry. Syphilis Tests. Available at: http://labtestsonline.org/understanding/analytes/syphilis/tab/test. Accessed June 22, 2015.
27. U.S. Food and Drug Administration. FDA grants CLIA waiver expanding the availability of rapid screening test for syphilis. FDA News Release. U.S. department of Health and Human Services. Available at: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm426843.htm. Accessed May 6, 2015.
28. Binnicker MJ, Jespersen DJ, Rollins LO. Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012;50(1):148-50.
29. Diagnostics Direct LLC. 510(k) Substantial Equivalence Determination Decision Summary #K102400. Available at: http://www.accessdata.fda.gov/cdrh_docs/reviews/k102400.pdf. Accessed May 19, 2015.
30. Sena AC, White BL, Sparling PF. Novel Treponema pallidum serologic tests: a paradigm shift in syphilis screening for the 21st century. Clin Infect Dis. 2010;51(6):700-8.
31. Marangoni A, Sambri V, Accardo S, et al. Evaluation of LIAISON Treponema Screen, a novel recombinant antigen-based chemiluminescence immunoassay for laboratory diagnosis of syphilis. Clin Diagn Lab Immunol. 2005;12(10):1231-4.

32. Binnicker MJ, Jespersen DJ, Rollins LO. Treponema-specific tests for serodiagnosis of syphilis: comparative evaluation of seven assays. J Clin Microbiol. 2011;49(4):1313-7.
33. Tucker JD, Bu J, Brown LB, et al. Accelerating worldwide syphilis screening through rapid testing: a systematic review. Lancet Infect Dis. 2010;10(6):381-6.
34. Park IU, Chow JM, Bolan G, et al. Screening for syphilis with the treponemal immunoassay: analysis of discordant serology results and implications for clinical management. J Infect Dis. 2011;204(9):1297-304.
35. Mahoney JF, Arnold RC, Harris A. Penicillin Treatment of Early Syphilis-A Preliminary Report. American journal of public health and the nation's health. 1943;33(12):1387-91.
36. Douglas JM, Jr. Penicillin treatment of syphilis: clearing away the shadow on the land. JAMA. 2009;301(7):769-71.
37. Mattei PL, Beachkofsky TM, Gilson RT, et al. Syphilis: a reemerging infection. Am Fam Physician. 2012;86(5):433-40.
38. Ghanem KG, Erbelding EJ, Cheng WW, et al. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. Clin Infect Dis. 2006;42(6):e45-9.
39. Wong T, Singh AE, De P. Primary syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. Am J Med. 2008;121(10):903-8.
40. Hook EW, 3rd, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. J Infect Dis. 1988;158(4):881-4.
41. Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. N Engl J Med. 2005;353(12):1236-44.
42. Hook EW, 3rd, Martin DH, Stephens J, et al. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. Sex Transm Dis. 2002;29(8):486-90.
43. Hook EW, 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. J Infect Dis. 2010;201(11):1729-35.
44. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in Treponema pallidum in the United States and Ireland. N Engl J Med. 2004;351(2):154-8.
45. Mitchell SJ, Engelman J, Kent CK, et al. Azithromycin-resistant syphilis infection: San Francisco, California, 2000-2004. Clin Infect Dis. 2006;42(3):337-45.
46. Su J, Hook E, Kenney K. Prevalence of the 23S rRNA point mutation in Treponema pallidum in the United States and Associated Factors, 2006--2008. 18th International Society for Sexually Transmitted Diseases Research,# OS1. 11.03. London, England: June. 2009
47. Ballard RC, Berman SM, Fenton KA. Azithromycin versus penicillin for early syphilis. The New England journal of medicine. 2006;354(2):203-5; author reply -5.
48. Ghanem KG, Erbelding EJ, Wiener ZS, et al. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics. Sex Transm Infect. 2007;83(2):97-101.
49. Beltran VM, Harrison KM, Hall HI, et al. Collection of social determinant of health measures in U.S. national surveillance systems for HIV, viral hepatitis, STDs, and TB. Public Health Rep. 2011;126 Suppl 3:41-53.
50. Tao G, Irwin KL. Receipt of HIV and STD testing services during routine general medical or gynecological examinations: variations by patient sexual risk behaviors. Sex Transm Dis. 2008;35(2):167-71.

51. Physicians AAoF. Syphilis. Available at: http://www.aafp.org/patient-care/clinical-recommendations/all/syphilis.html. Accessed June 22, 2015.
52. Burstein G, Jacobs A, Kissin D, et al. Changes in the 2010 STD Treatment Guidelines: What Adolescent Health Care Providers Should Know. American Congress of Obstetricians and Gynecologists. Washington, DC. Available at: https://www2.aap.org/sections/adolescenthealth/pdfs/STD%20Article%20Feb%202011.pdf. Accessed June 22, 2015.
53. Services USDoHaH. Guide for HIV/Aids Clinical Care. HRSA. Available at: http://hab.hrsa.gov/deliverhivaidscare/2014guide.pdf. Accessed June 22, 2015.
54. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35.
55. U.S. Preventive Services Task Force. *Procedure Manual*. . Available at: http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual. Accessed November 6, 2015.
56. Bissessor M, Fairley CK, Leslie D, et al. Frequent screening for syphilis as part of HIV monitoring increases the detection of early asymptomatic syphilis among HIV-positive homosexual men. J Acquir Immune Defic Syndr. 2010;55(2):211-6.
57. Cohen CE, Winston A, Asboe D, et al. Increasing detection of asymptomatic syphilis in HIV patients. Sex Transm Infect. 2005;81(3):217-9.
58. Zou H, Fairley CK, Guy R, et al. Automated, computer generated reminders and increased detection of gonorrhoea, chlamydia and syphilis in men who have sex with men. PLoS One. 2013;8(4):e61972.
59. Bissessor M, Fairley CK, Leslie D, et al. Use of a computer alert increases detection of early, asymptomatic syphilis among higher-risk men who have sex with men. Clin Infect Dis. 2011;53(1):57-8.
60. Wong EH, Klausner JD, Caguin-Grygiel G, et al. Evaluation of an IgM/IgG sensitive enzyme immunoassay and the utility of index values for the screening of syphilis infection in a high-risk population. Sex Transm Dis. 2011;38(6):528-32.
61. Tsang RS, Martin IE, Lau A, et al. Serological diagnosis of syphilis: comparison of the Trep-Chek IgG enzyme immunoassay with other screening and confirmatory tests. FEMS Immunol Med Microbiol. 2007;51(1):118-24.
62. Juarez-Figueroa L, Uribe-Salas F, Garcia-Cisneros S, et al. Evaluation of a rapid strip and a particle agglutination tests for syphilis diagnosis. Diagn Microbiol Infect Dis. 2007;59(2):123-6.
63. Mishra S, Boily MC, Ng V, et al. The laboratory impact of changing syphilis screening from the rapid-plasma reagin to a treponemal enzyme immunoassay: a case-study from the Greater Toronto Area. Sex Transm Dis. 2011;38(3):190-6.
64. Horberg MA, Ranatunga DK, Quesenberry CP, et al. Syphilis epidemiology and clinical outcomes in HIV-infected and HIV-uninfected patients in Kaiser Permanente Northern California. Sex Transm Dis. 2010;37(1):53-8.
65. Baffi CW, Aban I, Willig JH, et al. New syphilis cases and concurrent STI screening in a southeastern U.S. HIV clinic: a call to action. AIDS Patient Care STDS. 2010;24(1):23-9.
66. Hoover KW, Butler M, Workowski K, et al. STD screening of HIV-infected MSM in HIV clinics. Sex Transm Dis. 2010;37(12):771-6.

67. Mayer KH, Wang L, Koblin B, et al. Concomitant socioeconomic, behavioral, and biological factors associated with the disproportionate HIV infection burden among Black men who have sex with men in 6 U.S. cities. PLoS One. 2014;9(1):e87298.
68. Yang B, Hallmark CJ, Huang JS, et al. Characteristics and risk of syphilis diagnosis among HIV-infected male cohort: a population-based study in Houston, Texas. Sex Transm Dis. 2013;40(12):957-63.
69. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2013. Atlanta, GA: Department of Health and Human Services. 2014. Available at: http://www.cdc.gov/std/stats13/surv2013-print.pdf. Accessed April 3, 2015.
70. Kahn RH, Peterman TA, Arno J, et al. Identifying likely syphilis transmitters: implications for control and evaluation. Sex Transm Dis. 2006;33(10):630-5.
71. Finelli L, Farley TP, Gibson JJ, et al. Prevalence monitoring in syphilis surveillance: results from a multicenter research program. Sex Transm Dis. 2002;29(12):769-74.
72. Kahn RH, Voigt RF, Swint E, et al. Early syphilis in the United States identified in corrections facilities, 1999-2002. Sex Transm Dis. 2004;31(6):360-4.
73. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. Clin Microbiol Rev. 1995;8(1):1-21.
74. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(5):651-681.

Figure 1. Screening Test Algorithms



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

Adapted from: Centers for Disease and Prevention. Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006-2010. *MMWR Morb Mortal Wkly Rep*. 2011;60(5):133-7.

Figure 2. Analytic Framework

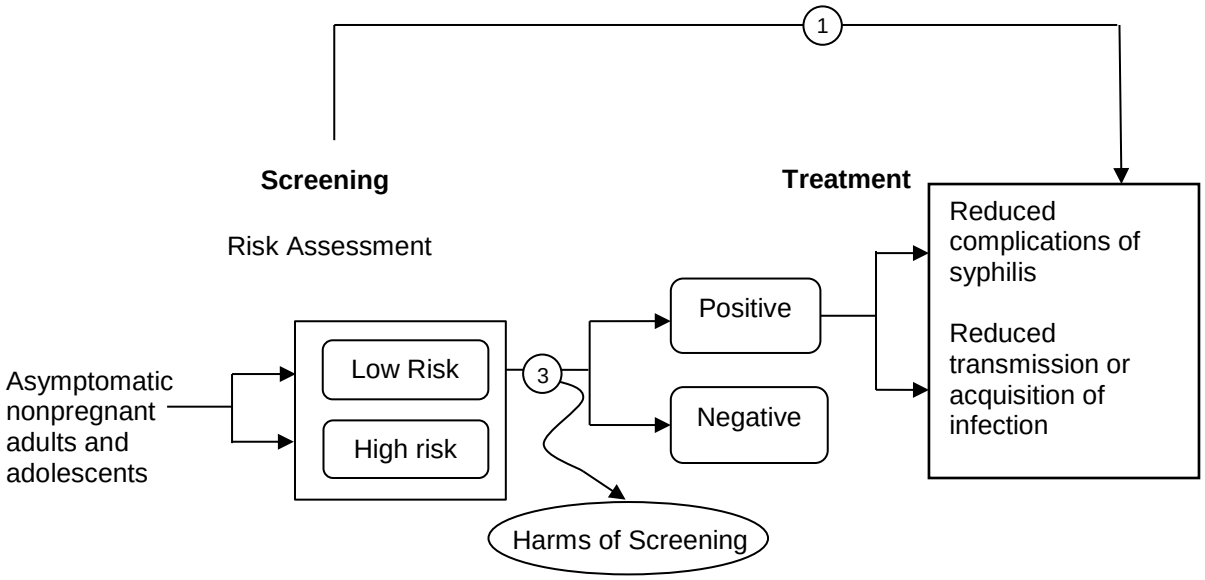


Table 1. 2014 CDC Case Definitions for Syphilis[3]

Stage	Clinical Symptoms	Diagnostic Criteria
Syphilis, primary	One or more ulcerative lesions (e.g., chancre), which might differ considerably in clinical appearance.	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 *T. pallidum* in clinical specimens by darkfield microscopy or by PCR or equivalent direct molecular methods may be present.
Syphilis, secondary	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.	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 *T. pallidum* in clinical specimens by darkfield microscopy or by PCR or equivalent direct molecular methods may be present.
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 1. 2014 CDC Case Definitions for Syphilis[3]

Stage	Clinical Symptoms	Diagnostic Criteria
Syphilis, late 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 >12 months previously.	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)
Syphilis, late, with clinical manifestations (including late benign syphilis and cardiovascular syphilis)	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 >12 months ago, should be reported as "late syphilis."	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 *T. pallidum* in late lesions by special stains or equivalent methods, or by PCR or equivalent direct molecular methods may be present.
Neurosyphilis (can occur at any stage)	Infection of the central nervous system with *T. pallidum*, as evidenced by manifestations such as syphilitic meningitis, meningovascular syphilis, optical involvement (including interstitial keratitis and uveitis), general paresis (including dementia), and tabes dorsalis.	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.

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 reagin; TPPA=*T. pallidum* particle agglutination; VDRL=Venereal Disease Research Laboratory.

Table 2. Tests for Syphilis[26–28]

Test	Use	Characteristics
Antibody tests		
Nontreponemal Antibody Tests: Venereal Disease Research Laboratory (VDRL), rapid plasma reagin (RPR)	To evaluate disease activity; guide treatment; VDRL used to detect neurosyphilis	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.
Treponemal Antibody Tests: Fluorescent treponemal antibody absorbed (FTA-ABS), *T. pallidum* particle agglutination (TPPA), enzyme immunoassay (EIA), chemiluminescence immunoassay (CIA), multiplex flow immunoassay (MFI), Syphilis Health Check	Screen or confirm a positive nontreponemal antibody test	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.
Direct detection methods (less common)		
Microscopic or darkfield exam: Sample from chancre is placed on a slide and examined with a special microscope	Diagnose syphilis in primary stage	Syphilis is diagnosed if bacteria are seen.
Polymerase chain reaction (PCR)	Detects genetic material of bacteria in chancre, blood, or cerebrospinal fluid	Positive test result indicates presence of *T. pallidum* nucleic acid

Table 3. Sensitivity and Specificity of Commonly Used Syphilis Tests*[25,29–32]

Syphilis screening test	Mixed	Sensitivity by stage of untreated syphilis, % (range)†				Specificity % (range)†
		Primary	Secondary	Latent	Tertiary	
Nontreponemal						
VDRL‡		78 (74-87)	100	96 (88-100)	71 (37-94)	98 (96-99)
RPR‡		86 (77-99)	100	98 (95-100)	73	98 (93-99)
TRUST‡		85 (77-86)	100	98 (95-100)		99 (98-99)
USR‡		80 (72-88)	100	95 (88-100)		99
Treponemal						
FTA-ABS‡		84 (70-100)	100	100	96	97 (84-100)
TPPA‡		88 (86-100)	100	97 (97-100)	94	96 (95-100)
EIA: Trep-Chek Trep-Sure	 95.9§ 96.9§	(77-100)	(85-100)	(64-100)	NA	(99-100) 98.5§ 95.4§
CIA: LIAISONǁ	 99.2	98	100	100	100	99 99.9
MFI: BioPlex 2200 Syphilis IgG	96.9§					98.0§
Syphilis Health Check	95.6¶, 98.5**					90.5¶, 97.4**

* 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

Organization	Recommendation/Clinical Guidance
Centers for Disease Control and Prevention[6]	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.
American Academy of Family Physicians[51]	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.
American Congress of Obstetricians and Gynecologists[52]	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.
U.S. Department of Health and Human Services HIV/AIDS Program[53]	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.
Infectious Diseases Society of America, HIV Medicine Association[74]	All patients with HIV should be screened for syphilis upon initiation of care and periodically thereafter, depending on risk.

Abbreviations: MSM=men who have sex with men; STI=sexually transmitted infection; USPSTF=U.S. Preventive Services Task Force.

Table 5. Observational Studies of Syphilis and HIV Coinfection

Study, Location	Population	Setting	Results
CDC, 2015 (data from 2013-2014)[8]	Diagnosis: Syphilis N: 19,999 Male: 91% MSM: 61% Race: 36% black, 34% white, 20% Hispanic	All U.S. hospitals and clinics reporting STIs	Proportion coinfected with HIV: MSM: 51.2% MSW: 10.7% Females: 5.9%
Baffi, 2010 (data from 2004-2007)[65]	Diagnosis: HIV N: 1,544 Male: 76% MSM: 57% Race: 49% black, 49% white	University of Alabama HIV/AIDS clinic	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)
Hoover, 2010 (data from 2004-2006)[66]	Diagnosis: HIV N: 1,334 Male: 100% MSM: 100% Race: 36% white, 28% Hispanic, 18% black	8 large HIV clinics in 6 U.S. states	Proportion coinfected with syphilis: Documented confirmed diagnosis: 1.7% Presumptive syphilis diagnosis: 1.1%
Horberg, 2010 (data from 1995-2005)[64]	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%	Kaiser Permanente Northern California database to identify patients with incident syphilis	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%
Mayer, 2012 (data from 2004-2006)[17] SUN study	Diagnosis: HIV N: 557 Male: 79% MSM: 66% Race: 61% white, 26% black, 10% Hispanic	7 HIV clinics in 4 U.S. cities	Proportion coinfected with syphilis: MSM: 1% MSW: 0% Women: 0%
Mayer, 2014 (data from 2009-2010)[67]	Not based on diagnosis, but enrolled patients screening for STIs N: 1,553 Male: 100% MSM: 100% Race: 100% black	HIV Prevention Trials Network in 6 U.S. cities	Proportion coinfected with HIV: Newly diagnosed with HIV: 11% Previously diagnosed with HIV: 4%
Yang, 2013 (data from 2008-2012)[68]	Diagnosis: HIV N: 3,170 Male: 100% MSM: 58% Race: 45% black, 29% white, 25% Hispanic	Enhanced HIV/AIDS Reporting System in Houston, Texas	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. >40 years Blacks: 1.59 (95% CI, 1.11 to 2.26) vs. whites

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*

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

Table 6. Rates of Primary and Secondary Syphilis Infection by Population Subgroups*

Subgroup	Male	Female
Northeast	10.7	0.5
District of Columbia	34.6	1.5
New York (New York City)	17.6 (17.3)	0.5 (0.5)
Maryland (Baltimore)	13.9 (18.0)	1.6 (2.9)
Midwest	7.9	0.9
Illinois (Chicago)	12.4 (15.7)	1.2 (1.6)
Michigan (Detroit)	8.0 (14.1)	0.6 (1.0)
Missouri (Kansas City)	10.7 (19.5)	1.1 (02.2)

*Rates per 100,000 population; taken from the Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2014. Atlanta, GA: Department of Health and Human Services. 2015. Available at: http://www.cdc.gov/std/stats14/surv-2014-print.pdf.

Table 7. Summary of Evidence

Main findings from prior USPSTF reviews	Number/type of studies in update	Overall quality*	Limitations	Consistency	Applicability	Summary of findings
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?						
No studies met inclusion criteria.	4 observational studies of MSM and HIV-positive males	Fair	No studies of screening effectiveness; no studies of screening intervals in other populations.	Consistent	Studies conducted in Europe and Australia in MSM and HIV+MSM; studies included high-prevalence populations	4 non-U.S. studies on the effectiveness of screening for syphilis among MSM or HIV- infected men found that detection rates increased with routine screening every 3 months compared with annual screening. More cases of infection were detected for early syphilis in HIV-positive MSM (8.1% vs. 3.1%; p=0.001), newly acquired syphilis in HIV-positive MSM (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 (16% vs. 53%; p=0.001) when screening occurred every 3 months compared with 6- or 12-month screening intervals.
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	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: sSensitivity 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	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/]
5 3 or 4

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 - Cochrane Database of Systematic Reviews
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$)).mp. [mp=title, abstract, full text, keywords, caption text]
7 (fals$ 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 - 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

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 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$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 [exp "Sensitivity and Specificity"/]
5 [exp Diagnostic Errors/]
6 (diagnos$ 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:
---

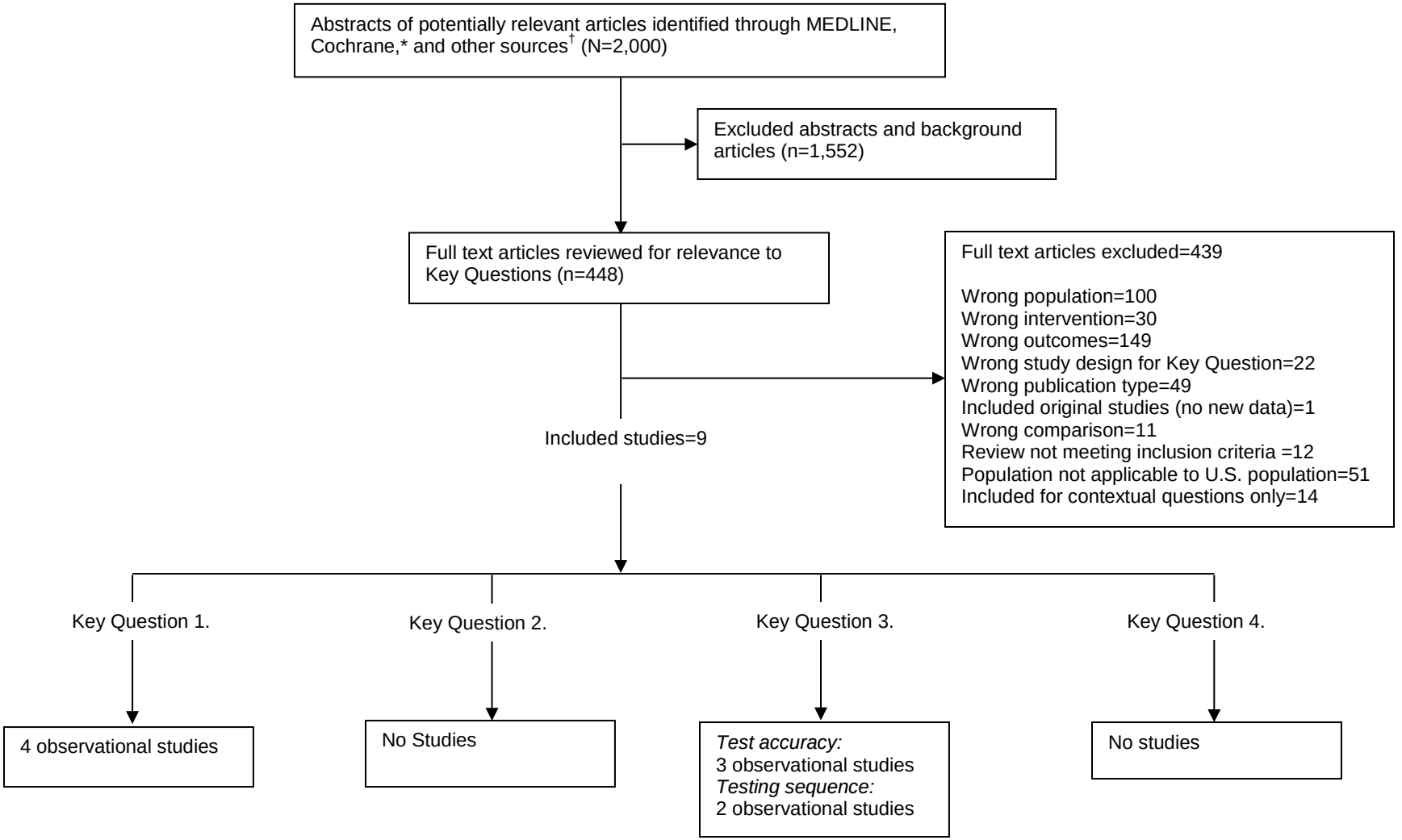
1 syphil$.mp.
2 treponema pallidum.mp.
3 1 or 2
4 exp "Sensitivity and Specificity"/
5 exp Diagnostic Errors/
6 (diagnos$ adj3 (mistak$ or error$ or erroneous$)).mp. [mp=title, text, subject heading word]
7 (fals$ adj3 (positiv$ or negativ$)).mp.
8 (accura$ or inaccura$ or (predict$ adj5 (value$ or able 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		
KQs 1, 4	Screening effectiveness including effectiveness of different screening intervals	
KQs 2	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		
KQs 1, 4	No screening or alternate screening strategy or methods	No comparison
KQ 2	True disease status	No comparison
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)	No comparison
Outcomes		
KQ 1	Reduction in: Complications of syphilis (e.g., neurosyphilis, symptomatic neurosyphilis, tertiary syphilis, congenital syphilis) Disease transmission, including HIV transmission Other clinical outcomes, rates of infection and other similar measures of infection	Outcomes that are not directly related to health outcomes (e.g., laboratory studies)
KQ 2	Detection of infection	
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	Observational studies without comparison groups, case reports
Harms	RCTs, observational studies including cross-sectional studies and ecological studies	Case studies

Abbreviations: FDA=U.S. Food and Drug Administration; KQ=key question; RCT=randomized, controlled trial; STI=sexually transmitted infection.

Appendix B3. Literature Flow by Key Question



* 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

Adolf R, Bercht F, Aronis ML, et al. Prevalence and risk factors associated with syphilis in a cohort of HIV positive individuals in Brazil. *AIDS Care*. 2012;24:252-8.
Exclusion: Population not applicable to U.S. population

Agmon-Levin N, Elbirt D, Asher I, et al. Syphilis and HIV co-infection in an Israeli HIV clinic: incidence and outcome. *Int J STD AIDS*. 2010;21(4):249-52.
Exclusion: Population not applicable to U.S. population

Aktas G, Young H, Moyes A, et al. Evaluation of the serodia *Treponema pallidum* particle agglutination, the Murex Syphilis ICE and the Enzywell TP tests for serodiagnosis of syphilis. *Int J STD AIDS*. 2005;16(4):294-8.
Exclusion: Wrong population

Aktas G, Young H, Moyes A, et al. Evaluation of the fluorescent treponemal antibody absorption test for detection of antibodies (immunoglobulins G and M) to *Treponema pallidum* in serologic diagnosis of syphilis. *Int J STD AIDS*. 2007;18(4):255-60.
Exclusion: Wrong population

Alim A, Artan MO, Baykan Z, et al. Seroprevalence of hepatitis B and C viruses, HIV, and syphilis infections among engaged couples. *Saudi Med J*. 2009;30(4):541-5.
Exclusion: Wrong outcomes

Allen K, Guy R, Leslie D, et al. The rise of infectious syphilis in Victoria and the impact of enhanced clinical testing. *Aust N Z J Public Health*. 2008;32(1):38-42.
Exclusion: Wrong outcomes

American Association for Clinical Chemistry. Syphilis Tests. Available at: http://labtestsonline.org/understanding/analytes/syphilis/tab/test. Accessed June 22, 2015.
Exclusion: custom 7

Amin AK, Manuel RJ, Ison CA, et al. Audit of laboratory diagnostic methods for syphilis in England and Wales. *Sex Transm Infect*. 2009;85(2):88-91.
Exclusion: Wrong outcomes

Araujo CL, Shimizu HE, Sousa AI, et al. Incidence of congenital syphilis in Brazil and its relationship with the Family Health Strategy. *Rev Saude Publica*. 2012;46(3):479-86.
Exclusion: Wrong population

Armed Forces Health Surveillance Center. Sexually transmitted infections, active component, U.S. Armed Forces, 2000-2012. *MSMR*. 2013;20(2):5-10.
Exclusion: Wrong outcomes

Armstrong H, Fernando I. An audit of partner notification for syphilis and HIV. *Int J STD AIDS*. 2012;23(11):825-6.
Exclusion: Wrong study design for Key Question

Arnold CA, Limketkai BN, Illei PB, et al. Syphilitic and lymphogranuloma venereum (LGV) proctocolitis: clues to a frequently missed diagnosis. *Am J Surg Pathol*. 2013;37(1):38-46.
Exclusion: Wrong outcomes

Arora C, Mishra B, Malik JS. Study of STD pattern and its associated risk factors--a hospital study. *J Commun Dis*. 2006;38(1):70-3.
Exclusion: Wrong outcomes

Artz L, Macaluso M, Meinzen-Derr J, et al. A randomized trial of clinician-delivered interventions promoting barrier contraception for sexually transmitted disease prevention. *Sex Transm Dis*. 2005;32(11):672-9.
Exclusion: Wrong intervention

Arumainayagam J, Pallan MJ, Buckley E, et al. Syphilis outbreak in Walsall, UK: lessons for control and prevention. *Int J STD AIDS*. 2007;18(1):55-7.
Exclusion: Wrong outcomes

Augenbraun M, French A, Glesby M, et al. Hepatitis C virus infection and biological false-positive syphilis tests. *Sex Transm Infect*. 2010;86(2):97-8.
Exclusion: Wrong outcomes

Aung WW, Thant M, Wai KT, et al. Sexually transmitted infections among male highway coach drivers in Myanmar. *Southeast Asian J Trop Med Public Health*. 2013;44(3):436-47.
Exclusion: Wrong outcomes

Azariah S. An audit of patients treated for syphilis at Auckland Sexual Health Service. *N Z Med J*. 2010;123(1315):55-64.
Exclusion: Wrong outcomes

Azariah S, Perkins N. Prevalence of sexually transmitted infections in men who have sex with men presenting to Auckland Sexual Health Service. *N Z Med J*. 2010;123(1322):46-54.
Exclusion: Wrong study design for Key Question

Appendix B4. List of Excluded Studies

Azariah S, Perkins N, Austin P, et al. Increase in incidence of infectious syphilis in Auckland, New Zealand: results from an enhanced surveillance survey. *Sex Health*. 2008;5(3):303-4.
Exclusion: Wrong outcomes

Baffi CW, Aban I, Willig JH, et al. New syphilis cases and concurrent STI screening in a southeastern U.S. HIV clinic: a call to action. *AIDS Patient Care STDS*. 2010;24(1):23-9.
Exclusion: Included for contextual questions only

Baguley SD, Horner PJ, Maple PA, et al. An oral fluid test for syphilis. *Int J STD AIDS*. 2005;16(4):299-301.
Exclusion: Wrong population

Balba GP, Kumar PN, James AN, et al. Ocular syphilis in HIV-positive patients receiving highly active antiretroviral therapy. *Am J Med*. 2006;119(5):448.e21-5.
Exclusion: Wrong outcomes

Behrhof W, Springer E, Brauninger W, et al. PCR testing for *Treponema pallidum* in paraffin-embedded skin biopsy specimens: test design and impact on the diagnosis of syphilis. *J Clin Pathol*. 2008;61(3):390-5.
Exclusion: Wrong intervention

Beltrami JF, Williams S, Valentine J. STD screening and treatment during jail intake: the National Syphilis Elimination perspective. *Sex Transm Dis.* 2007;34(2):120-1.
Exclusion: Wrong publication type

Benson PA, Hergenroeder AC. Bacterial sexually transmitted infections in gay, lesbian, and bisexual adolescents: medical and public health perspectives. *Semin Pediatr Infect Dis*. 2005;16(3):181-91.
Exclusion: Wrong publication type

Benzaken AS, Bazzo ML, Galban E, et al. External quality assurance with dried tube specimens (DTS) for point-of-care syphilis and HIV tests: experience in an indigenous populations screening programme in the Brazilian Amazon. *Sex Transm Infect*. 2014;90(1):14-8.
Exclusion: Wrong outcomes

Benzaken AS, Galban Garcia E, Sardinha JC, et al. Rapid tests for diagnosing syphilis: validation in an STD clinic in the Amazon Region, Brazil. *Cad Saude Publica*. 2007;23(Suppl 3):S456-64.
Exclusion: Wrong intervention

Benzaken AS, Sabido M, Galban EG, et al. Field evaluation of the performance and testing costs of a rapid point-of-care test for syphilis in a red-light district of Manaus, Brazil. *Sex Transm Infect*. 2008;84(4):297-302.
Exclusion: Wrong intervention

Beraud G, Pierre-Francois S, Theodose R, et al. Anicteric cholestasis among HIV infected patients with syphilis. *Scand J Infect Dis*. 2009;41(6-7):524-7.
Exclusion: Wrong outcomes

Bibi I, Devrajani BR, Shah SZ, et al. Frequency of syphilis in female sex workers at red light area of Hyderabad, Pakistan. *J Pak Med Assoc*. 2010;60(5):353-6.
Exclusion: Wrong outcomes

Binnicker MJ, Yao JD, Cockerill FR 3rd. Non-treponemal serologic tests: a supplemental, not confirmatory testing approach. *Clin Infect Dis*. 2011;52(2):274-5; author reply 5-6.
Exclusion: Wrong publication type

Blank S, Gallagher K, Washburn K, et al. Reaching out to boys at bars: utilizing community partnerships to employ a wellness strategy for syphilis control among men who have sex with men in New York City. *Sex Transm Dis.* 2005;32(10 Suppl):S65-72.
Exclusion: Wrong outcomes

Blank S, McDonnell DD, Rubin SR, et al. New approaches to syphilis control. Finding opportunities for syphilis treatment and congenital syphilis prevention in a women's correctional setting. *Sex Transm Dis.* 1997;24(4):218-26.
Exclusion: Wrong publication type

Borelli S, Monn A, Meyer J, et al. Evaluation of a particle gel immunoassay as a screening test for syphilis. *Infection*. 2009;37(1):26-8.
Exclusion: Wrong intervention

Borghi J, Gorter A, Sandiford P, et al. The cost-effectiveness of a competitive voucher scheme to reduce sexually transmitted infections in high-risk groups in Nicaragua. *Health Policy Plan*. 2005;20(4):222-31.
Exclusion: Wrong outcomes

Bosshard PP. Usefulness of IgM-specific enzyme immunoassays for serodiagnosis of syphilis: comparative evaluation of three different assays. *J Infect*. 2013;67(1):35-42.
Exclusion: Wrong population

Appendix B4. List of Excluded Studies

Botham SJ, Ressler KA, Bourne C, et al. Epidemic infectious syphilis in inner Sydney--strengthening enhanced surveillance. *Aust N Z J Public Health*. 2006;30(6):529-33.
Exclusion: Wrong outcomes

Bourne C, Knight V, Guy R, et al. Short message service reminder intervention doubles sexually transmitted infection/HIV re-testing rates among men who have sex with men. *Sex Transm Infect*. 2011;87(3):229-31.
Exclusion: Wrong outcomes

Bowden FJ, O'Keefe EJ, Primrose R, et al. Sexually transmitted infections, blood-borne viruses and risk behaviour in an Australian senior high school population--the SHLiRP study. *Sex Health*. 2005;2(4):229-36.
Exclusion: Wrong outcomes

Bradshaw CS, Pierce LI, Tabrizi SN, et al. Screening injecting drug users for sexually transmitted infections and blood borne viruses using street outreach and self collected sampling. *Sex Transm Infect*. 2005;81(1):53-8.
Exclusion: Wrong outcomes

Branger J, van der Meer JT, van Ketel RJ, et al. High incidence of asymptomatic syphilis in HIV-infected MSM justifies routine screening. *Sex Transm Dis.* 2009;36(2):84-5.
Exclusion: Included for contextual questions only

Brewer DD. Case-finding effectiveness of partner notification and cluster investigation for sexually transmitted diseases/HIV. *Sex Transm Dis.* 2005;32(2):78-83.
Exclusion: Wrong study design for Key Question

Brewer TH, Peterman TA, Newman DR, et al. Reinfections during the Florida syphilis epidemic, 2000-2008. *Sex Transm Dis.* 2011;38(1):12-7.
Exclusion: Wrong outcomes

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

Brosh-Nissimov T, Mor Z, Avramovich E, et al. Syphilis outbreak among men who have sex with men, Tel Aviv, Israel, 2008-2009. *Isr Med Assoc J*. 2012;14(3):152-6.
Exclusion: Wrong outcomes

Buchacz K, Klausner JD, Kerndt PR, et al. HIV incidence among men diagnosed with early syphilis in Atlanta, San Francisco, and Los Angeles, 2004 to 2005. *J Acquir Immune Defic Syndr*. 2008;47(2):234-40.
Exclusion: Wrong outcomes

Buchacz KA, Siller JE, Bandy DW, et al. HIV and syphilis testing among men who have sex with men attending sex clubs and adult bookstores--San Francisco, 2003. *J Acquir Immune Defic Syndr*. 2004;37(2):1324-6.
Exclusion: Wrong publication type

Buffet M, Grange PA, Gerhardt P, et al. Diagnosing *Treponema pallidum* in secondary syphilis by PCR and immunohistochemistry. *J Invest Dermatol*. 2007;127(10):2345-50.
Exclusion: Wrong population

Burchell AN, Allen VG, Gardner SL, et al. High incidence of diagnosis with syphilis co-infection among men who have sex with men in an HIV cohort in Ontario, Canada. *BMC Infect Dis.* 2015;15:356.
Exclusion: Wrong study design for Key Question

Burchell AN, Allen VG, Moravan V, et al. Patterns of syphilis testing in a large cohort of HIV patients in Ontario, Canada, 2000-2009. *BMC Infect Dis*. 2013;13:246.
Exclusion: Wrong outcomes

Burke R, Rhodes J. Lessons learned on the implementation of jail syphilis screening in Nashville, Davidson County Jail, 1999-2005. *Sex Transm Dis.* 2009;36(2 Suppl):S14-6.
Exclusion: Wrong outcomes

Busse C, Navid MH, Strubel A, et al. Evaluation of a new recombinant antigen-based Virotech *Treponema pallidum* screen ELISA for diagnosis of syphilis. *Clin Lab*. 2013;59(5-6):523-9.
Exclusion: Wrong population

Cade JE, Boozer CH, Leigh JE. Seropositivity of the rapid plasma reagin (RPR) test in a dental school patient population: a retrospective study. *J Public Health Dent*. 2003;63(1):61-3.
Exclusion: Wrong outcomes

Cai R, Tan JG, Chen L, et al. Prevalence and risk factors of syphilis infection among female sex workers in Shenzhen, China: an observational study (2009-2012). *Trop Med Int Health*. 2013;18(12):1531-8.
Exclusion: Population not applicable to U.S.

population

Callander D, Baker D, Chen M, et al. Including syphilis testing as part of standard HIV management checks and improved syphilis screening in primary care. *Sex Transm Dis.* 2013;40(4):338-40.
Exclusion: Wrong outcomes

Callegari FM, Pinto-Neto LF, Medeiros CJ, et al. Syphilis and HIV co-infection in patients who attend an AIDS outpatient clinic in Vitoria, Brazil. *AIDS Behav*. 2014;18(Suppl 1):S104-9.
Exclusion: Population not applicable to U.S. population

Campos LN, Guimaraes MD, Carmo RA, et al. HIV, syphilis, and hepatitis B and C prevalence among patients with mental illness: a review of the literature. *Cad Saude Publica*. 2008;24(Suppl 4):s607-20.
Exclusion: Review not meeting inclusion criteria

Campos PE, Buffardi AL, Carcamo CP, et al. Reaching the unreachable: providing STI control services to female sex workers via mobile team outreach. *PLoS One*. 2013;8(11):e81041.
Exclusion: Population not applicable to U.S. population

Campos PE, Buffardi AL, Chiappe M, et al. Utility of the Determine Syphilis TP rapid test in commercial sex venues in Peru. *Sex Transm Infect*. 2006;82(Suppl 5):v22-5.
Exclusion: Wrong intervention

Cao Z, Xu J, Zhang H, et al. Risk factors for syphilis among married men who have sex with men in China. *Sex Transm Dis.* 2014;41(2):98-102.
Exclusion: Population not applicable to U.S. population

Carcamo CP, Campos PE, Garcia PJ, et al. Prevalences of sexually transmitted infections in young adults and female sex workers in Peru: a national population-based survey. *Lancet Infect Dis*. 2012;12(10):765-73.
Exclusion: Population not applicable to U.S. population

Castro AR, Esfandiari J, Kumar S, et al. Novel point-of-care test for simultaneous detection of nontreponemal and treponemal antibodies in patients with syphilis. *J Clin Microbiol*. 2010;48(12):4615-9.
Exclusion: Wrong population

Castro R, Lopes A, da Luz Martins Pereira F. Evaluation of an immunochromatographic point-of-care test for the simultaneous detection of nontreponemal and treponemal antibodies in patients with syphilis. *Sex Transm Dis.* 2014;41(8):467-9.
Exclusion: Wrong population

Castro R, Prieto ES, Aguas MJ, et al. Evaluation of the *Treponema pallidum* particle agglutination technique (TP.PA) in the diagnosis of neurosyphilis. *J Clin Lab Anal*. 2006;20(6):233-8.
Exclusion: Wrong population

Castro R, Prieto ES, da Luz Martins Pereira F. Nontreponemal tests in the diagnosis of neurosyphilis: an evaluation of the Venereal Disease Research Laboratory (VDRL) and the rapid plasma reagin (RPR) tests. *J Clin Lab Anal*. 2008;22(4):257-61.
Exclusion: Wrong population

Causer LM, Kaldor JM, Fairley CK, et al. A laboratory-based evaluation of four rapid point-of-care tests for syphilis. *PLoS One*. 2014;9(3):e91504.
Exclusion: Wrong population

Centers for Disease Control and Prevention. Primary and secondary syphilis--Jefferson County, Alabama, 2002-2007. *MMWR Morb Mortal Wkly Rep*. 2009;58(17):463-7.
Exclusion: Wrong study design for Key Question

Centers for Disease Control and Prevention. Syphilis outbreak among American Indians--Arizona, 2007-2009. *MMWR Morb Mortal Wkly Rep*. 2010;59(6):158-61.
Exclusion: Wrong outcomes

Centers for Disease Control and Prevention. STD surveillance case definitions. Available at: http://www.cdc.gov/std/stats/CaseDefinitions-2014.pdf. Accessed February 27, 2015.
Exclusion: custom 7

Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2011. Atlanta, GA: Department of Health and Human Services; 2012. http://www.cdc.gov/std/stats11/Surv2011.pdf. Accessed January 14, 2015.
Exclusion: Custom 7

Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2013. Atlanta, GA: Department of Health and Human Services; 2014. http://www.cdc.gov/std/stats13/surv2013-print.pdf. Accessed April 3, 2015.

Appendix B4. List of Excluded Studies

Exclusion: Custom 7

Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2014. Atlanta, GA: Department of Health and Human Services; 2015. http://www.cdc.gov/std/stats14/surv-2014-print.pdf. Accessed March 9, 2016.
Exclusion: Custom 7

Champenois K, Cousien A, Ndiaye B, et al. Risk factors for syphilis infection in men who have sex with men: results of a case-control study in Lille, France. *Sex Transm Infect*. 2013;89(2):128-32.
Exclusion: Wrong outcomes

Chang CC, Leslie DE, Spelman D, et al. Symptomatic and asymptomatic early neurosyphilis in HIV-infected men who have sex with men: a retrospective case series from 2000 to 2007. *Sex Health*. 2011;8(2):207-13.
Exclusion: Wrong population

Chauhan M, Serisha B, Sankar KN, et al. Audit of the use of benzathine penicillin, post-treatment syphilis serology and partner notification of patients with early infectious syphilis. *Int J STD AIDS*. 2006;17(3):200-2.
Exclusion: Wrong study design for Key Question

Chen JL, Bovee MC, Kerndt PR. Sexually transmitted diseases surveillance among incarcerated men who have sex with men--an opportunity for HIV prevention. *AIDS Educ Prev*. 2003;15(1 Suppl A):117-26.
Exclusion: Wrong outcomes

Chen XS, Wang QQ, Yin YP, et al. Prevalence of syphilis infection in different tiers of female sex workers in China: implications for surveillance and interventions. *BMC Infect Dis*. 2012;12:84.
Exclusion: Population not applicable to U.S. population

Cheung KK, Montgomery D, Benjamins LJ. Prevalence of sexually transmitted infections among adolescents entering Child Protective Services. *J Pediatr Adolesc Gynecol*. 2015;28(5):324-6.
Exclusion: Wrong study design for Key Question

Choe PG, Song JS, Song KH, et al. Usefulness of routine lumbar puncture in non-HIV patients with latent syphilis of unknown duration. *Sex Transm Infect*. 2010;86(1):39-40.
Exclusion: Wrong intervention

Choi KH, Ning Z, Gregorich SE, et al. The influence of social and sexual networks in the spread of HIV and syphilis among men who have sex with men in Shanghai, China. *J Acquir Immune Defic Syndr*. 2007;45(1):77-84.
Exclusion: Population not applicable to U.S. population

Chow EP, Wilson DP, Zhang L. HIV and syphilis co-infection increasing among men who have sex with men in China: a systematic review and meta-analysis. *PLoS One*. 2011;6(8):e22768.
Exclusion: Wrong outcomes

Ciesielski C, Kahn RH, Taylor M, et al. Control of syphilis outbreaks in men who have sex with men: the role of screening in nonmedical settings. *Sex Transm Dis*. 2005;32(10 Suppl):S37-42.
Exclusion: Wrong outcomes

Clement ME, Hicks CB. RPR and the serologic diagnosis of syphilis. *JAMA*. 2014;312(18):1922-3.
Exclusion: Wrong study design for Key Question

Cohen CE, Winston A, Asboe D, et al. Screening for syphilis in HIV-positive men who have sex with men (MSM). *Int J STD AIDS*. 2006;17(2):142.
Exclusion: Wrong publication type

Cohen RS, Xiong SC, Sakamoto P. Retrospective review of serological testing of potential human milk donors. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(2):F118-20.
Exclusion: Wrong outcomes

Cohen SE, Chew Ng RA, Katz KA, et al. Repeat syphilis among men who have sex with men in California, 2002-2006: implications for syphilis elimination efforts. *Am J Public Health*. 2012;102(1):e1-8.
Exclusion: Wrong population

Cohen SE, Klausner JD, Engelman J, et al. Syphilis in the modern era: an update for physicians. *Infect Dis Clin North Am*. 2013;27(4):705-22.
Exclusion: Wrong publication type

Colletti JE, Giudice EL. Syphilis screening in a high-risk, inner-city adolescent population. *Am J Emerg Med*. 2005;23(2):225-6.
Exclusion: Wrong population

Cornish N. A new reflex testing algorithm for syphilis screening. *MLO Med Lab Obs*. 2011;43(6):40-1.
Exclusion: Wrong publication type

Appendix B4. List of Excluded Studies

Couture MC, Soto JC, Akom E, et al. Clients of female sex workers in Gonaives and St-Marc, Haiti: characteristics, sexually transmitted infection prevalence and risk factors. *Sex Transm Dis.* 2008;35(10):849-55.
Exclusion: Population not applicable to U.S. population

Cowan S. Syphilis in Denmark--outbreak among MSM in Copenhagen, 2003-2004. *Euro Surveill.* 2004;9(12):25-7.
Exclusion: Wrong study design for Key Question

Coyne KM, Banks A, Heggie C, et al. Sexual health of adults working in pornographic films. *Int J STD AIDS.* 2009;20(7):508-9.
Exclusion: Wrong outcomes

Creegan L, Bauer HM, Samuel MC, et al. An evaluation of the relative sensitivities of the Venereal Disease Research Laboratory test and the *Treponema pallidum* particle agglutination test among patients diagnosed with primary syphilis. *Sex Transm Dis.* 2007;34(12):1016-8.
Exclusion: Wrong population

Cronin M, Domegan L, Thornton L, et al. The epidemiology of infectious syphilis in the Republic of Ireland. *Euro Surveill.* 2004;9(12):14-7.
Exclusion: Wrong outcomes

Cunningham SD, Olthoff G, Burnett P, et al. Evidence of heterosexual bridging among syphilis-positive men who have sex with men. *Sex Transm Infect.* 2006;82(6):444-5.
Exclusion: Wrong outcomes

Dai S, Chi P, Lin Y, et al. Improved reverse screening algorithm for *Treponema pallidum* antibody using signal-to-cutoff ratios from chemiluminescence microparticle immunoassay. *Sex Transm Dis.* 2014;41(1):29-34.
Exclusion: Wrong population

Davies SC, Madjid B, Pardohudoyo S, et al. Prevalence of sexually transmissible infections (STI) among male patients with STI in Denpasar and Makassar, Indonesia: are symptoms of urethritis sufficient to guide syndromic treatment? *Sex Health.* 2007;4(3):213-5.
Exclusion: Population not applicable to U.S. population

de Larranaga G, Trombetta L, Wingeyer SP, et al. False positive reactions in confirmatory tests for syphilis in presence of antiphospholipid antibodies: misdiagnosis with prognostic and social consequences. *Dermatol Online J.* 2006;12(4):22.
Exclusion: Wrong study design for Key Question

Debattista J, Dwyer J, Anderson R, et al. Screening for syphilis among men who have sex with men in various clinical settings. *Sex Transm Infect.* 2004;80(6):505-8.
Exclusion: Wrong population

Dhairyawan R, Creighton S, Sivyour L, et al. Testing the fathers: carrying out HIV and STI tests on partners of pregnant women. *Sex Transm Infect.* 2012;88(3):184-6.
Exclusion: Wrong comparison

Diagnostics Direct LLC. 510(k) Substantial equivalence determination decision summary #K102400. http://www.accessdata.fda.gov/cdrh_docs/reviews/k102400.pdf. Accessed May 19, 2015.
Exclusion: custom 7

Diaz T, Almeida MG, Georg I, et al. Evaluation of the Determine Rapid Syphilis TP assay using sera. *Clin Diagn Lab Immunol.* 2004;11(1):98-101.
Exclusion: Wrong population

Dissemination CfRa. The efficacy of clinic-based interventions aimed at increasing screening for bacterial sexually transmitted infections among men who have sex with men: a systematic review (Provisional abstract). Database of Abstracts of Reviews of Effects. 2014(4).
Exclusion: Wrong publication type

Dlamini NR, Phili R, Connolly C. Evaluation of rapid syphilis tests in KwaZulu-Natal. *J Clin Lab Anal.* 2014;28(1):77-81.
Exclusion: Wrong population

Dodge B, Reece M, Herbenick D, et al. Relations between sexually transmitted infection diagnosis and sexual compulsivity in a community-based sample of men who have sex with men. *Sex Transm Infect.* 2008;84(4):324-7.
Exclusion: Wrong outcomes

Donkers A, Levy HR, Letens-van Vliet A. Syphilis detection using the Siemens ADVIA Centaur syphilis treponemal assay. *Clin Chim Acta.* 2014;433:84-7.
Exclusion: Wrong population

Dorigo-Zetsma JW, Belewu D, Meless H, et al. Performance of routine syphilis serology in the Ethiopian cohort on HIV/AIDS. *Sex Transm Infect.* 2004;80(2):96-9.

Appendix B4. List of Excluded Studies

Exclusion: Population not applicable to U.S. population

Enders M, Hunjet A, Gleich M, et al. Performance evaluation of the Elecsys syphilis assay for the detection of total antibodies to *Treponema pallidum*. *Clin Vaccine Immunol*. 2015;22(1):17-26.
Exclusion: Wrong population

Engelgau MM, Woernle CH, Rolfs RT, et al. Control of epidemic early syphilis: the results of an intervention campaign using social networks. *Sex Transm Dis.* 1995;22(4):203-9.
Exclusion: Wrong intervention

Fairley CK, Law M, Chen MY. Eradicating syphilis, hepatitis C and HIV in MSM through frequent testing strategies. *Curr Opin Infect Dis.* 2014;27(1):56-61.
Exclusion: Review not meeting inclusion criteria

Farhi D, Zizi N, Grange P, et al. The epidemiological and clinical presentation of syphilis in a venereal disease centre in Paris, France. A cohort study of 284 consecutive cases over the period 2000-2007. *Eur J Dermatol*. 2009;19(5):484-9.
Exclusion: Wrong outcomes

Farley TA, Cohen DA, Kahn RH, et al. The acceptability and behavioral effects of antibiotic prophylaxis for syphilis prevention. *Sex Transm Dis.* 2003;30(11):844-9.
Exclusion: Wrong intervention

Fernandes FR, Zanini PB, Rezende GR, et al. Syphilis infection, sexual practices and bisexual behaviour among men who have sex with men and transgender women: a cross-sectional study. *Sex Transm Infect*. 2015;91(2):142-9.
Exclusion: Population not applicable to U.S. population

Finelli L, Farley TP, Gibson JJ, et al. Prevalence monitoring in syphilis surveillance: results from a multicenter research program. *Sex Transm Dis.* 2002;29(12):769-74.
Exclusion: Included for contextual questions only

Fisher DG, Reynolds GL, Creekmur B, et al. Reliability and criterion-related validity of self-report of syphilis. *Sex Transm Dis.* 2007;34(6):389-91.
Exclusion: Wrong outcomes

Forbes KM, Davis P, Sarner L. Introduction of a nurse-led sexual health service for HIV-positive men. *Int J STD AIDS*. 2009;20(1):54-5.
Exclusion: Wrong comparison

Gayet-Ageron A, Lautenschlager S, Ninet B, et al. Sensitivity, specificity and likelihood ratios of PCR in the diagnosis of syphilis: a systematic review and meta-analysis. *Sex Transm Infect*. 2013;89(3):251-6.
Exclusion: Wrong population

Gayet-Ageron AS, Lautenschlager S, Ferry T, et al. Use of *Treponema pallidum* PCR in testing of ulcers for diagnosis of primary syphilis. *Emerg Infect Dis*. 2015;21(1):127-9.
Exclusion: Wrong population

Geusau A, Kittler H, Hein U, et al. Biological false-positive tests comprise a high proportion of Venereal Disease Research Laboratory reactions in an analysis of 300,000 sera. *Int J STD AIDS*. 2005;16(11):722-6.
Exclusion: Wrong population

Ghanem KG, Erbelding EJ, Wiener ZS, et al. Serological response to syphilis treatment in HIV-positive and HIV-negative patients attending sexually transmitted diseases clinics. *Sex Transm Infect*. 2007;83(2):97-101.
Exclusion: Wrong population

Ghanem KG, Moore RD, Rompalo AM, et al. Antiretroviral therapy is associated with reduced serologic failure rates for syphilis among HIV-infected patients. *Clin Infect Dis*. 2008;47(2):258-65.
Exclusion: Wrong outcomes

Ghanem KG, Moore RD, Rompalo AM, et al. Lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms. *Clin Infect Dis*. 2009;48(6):816-21.
Exclusion: Wrong population

Gianino MM, Dal Conte I, Sciole K, et al. Performance and costs of a rapid syphilis test in an urban population at high risk for sexually transmitted infections. *J Prev Med Hyg*. 2007;48(4):118-22.
Exclusion: Wrong intervention

Gift TL, Hogben M. Emergency department sexually transmitted disease and human immunodeficiency virus screening: findings from a national survey. *Acad Emerg Med*. 2006;13(9):993-6.
Exclusion: Wrong outcomes

Appendix B4. List of Excluded Studies

Glatz M, Juricevic N, Altwegg M, et al. A multicenter prospective trial to asses a new real-time polymerase chain reaction for detection of *Treponema pallidum*, herpes simplex-1/2 and *Haemophilus ducreyi* in genital, anal and oropharyngeal ulcers. *Clin Microbiol Infect*. 2014;20(12):O1020-7.
Exclusion: Wrong intervention

Goel N, Sharma M, Gupta N, et al. Rapid immunochromatographic test for syphilis. *Indian J Med Microbiol*. 2005;23(2):142-3.
Exclusion: Wrong population

Goh BT. Syphilis in adults. *Sex Transm Infect*. 2005;81(6):448-52.
Exclusion: Wrong publication type

Gomez E, Jespersen DJ, Harring JA, et al. Evaluation of the Bio-Rad BioPlex 2200 syphilis multiplex flow immunoassay for the detection of IgM- and IgG-class antitreponemal antibodies. *Clin Vaccine Immunol*. 2010;17(6):966-8.
Exclusion: Wrong population

Goswami ND, Stout JE, Miller WC, et al. The footprint of old syphilis: using a reverse screening algorithm for syphilis testing in a U.S. Geographic Information Systems-Based Community Outreach Program. *Sex Transm Dis.* 2013;40(11):839-41.
Exclusion: Wrong comparison

Grange PA, Gressier L, Dion PL, et al. Evaluation of a PCR test for detection of *Treponema pallidum* in swabs and blood. *J Clin Microbiol*. 2012;50(3):546-52.
Exclusion: Wrong population

Gratrix J, Plitt S, Lee BE, et al. Impact of reverse sequence syphilis screening on new diagnoses of late latent syphilis in Edmonton, Canada. *Sex Transm Dis.* 2012;39(7):528-30.
Exclusion: Wrong outcomes

Gratzer B, Pohl D, Hotton AL. Evaluation of diagnostic serological results in cases of suspected primary syphilis infection. *Sex Transm Dis.* 2014;41(5):285-9.
Exclusion: Wrong population

Gray RT, Hoare A, Prestage GP, et al. Frequent testing of highly sexually active gay men is required to control syphilis. *Sex Transm Dis.* 2010;37(5):298-305.
Exclusion: Wrong study design for Key Question

Grewal R, Allen VG, Tan DH, et al. Enhanced syphilis screening among HIV-positive men: evaluation of a clinic-based intervention. *Can J Infect Dis Med Microbiol*. 2015;26(Suppl B):90B.
Exclusion: Wrong population

Guarner J, Jost H, Pillay A, et al. Evaluation of treponemal serum tests performed on cerebrospinal fluid for diagnosis of neurosyphilis. *Am J Clin Pathol*. 2015;143(4):479-84.
Exclusion: Wrong population

Guimaraes Nebenzahl H, Lopes A, Castro R, et al. Prevalence of human immunodeficiency virus, hepatitis C virus, hepatitis B virus and syphilis among individuals attending anonymous testing for HIV in Luanda, Angola. *S Afr Med J*. 2013;103(3):186-8.
Exclusion: Population not applicable to U.S. population

Guinard J, Prazuck T, Pere H, et al. Usefulness in clinical practice of a point-of-care rapid test for simultaneous detection of nontreponemal and *Treponema pallidum*-specific antibodies in patients suffering from documented syphilis. *Int J STD AIDS*. 2013;24(12):944-50.
Exclusion: Wrong population

Gupta SM, Bala M, Muralidhar S, et al. Evaluation of test results of microbiology laboratories of North India for standard tests for syphilis under an external quality assurance scheme. *Eur J Clin Microbiol Infect Dis*. 2009;28(5):461-8.
Exclusion: Wrong population

Gupte S, Daly C, Agarwal V, et al. Introduction of rapid tests for large-scale syphilis screening among female, male, and transgender sex workers in Mumbai, India. *Sex Transm Dis.* 2011;38(6):499-502.
Exclusion: Wrong outcomes

Guy R, El-Hayek C, Fairley CK, et al. Opt-out and opt-in testing increases syphilis screening of HIV-positive men who have sex with men in Australia. *PLoS One*. 2013;8(8):e71436.
Exclusion: Wrong outcomes

Guy R, Wand H, Holt M, et al. High annual syphilis testing rates among gay men in Australia, but insufficient retesting. *Sex Transm Dis.* 2012;39(4):268-75.
Exclusion: Wrong outcomes

Appendix B4. List of Excluded Studies

Halling VW, Jones MF, Bestrom JE, et al. Clinical comparison of the *Treponema pallidum* CAPTIA syphilis-G enzyme immunoassay with the fluorescent treponemal antibody absorption immunoglobulin G assay for syphilis testing. *J Clin Microbiol*. 1999;37(10):3233-4.
Exclusion: Wrong population

Hammett TM. Sexually transmitted diseases and incarceration. *Curr Opin Infect Dis*. 2009;22(1):77-81.
Exclusion: Review not meeting inclusion criteria

Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. *Sex Transm Dis.* 2012;39(4):291-7.
Exclusion: Review not meeting inclusion criteria

Heffelfinger JD, Swint EB, Berman SM, et al. Trends in primary and secondary syphilis among men who have sex with men in the United States. *Am J Public Health*. 2007;97(6):1076-83.
Exclusion: Wrong outcomes

Heijman TL, Van der Bij AK, De Vries HJ, et al. Effectiveness of a risk-based visitor-prioritizing system at a sexually transmitted infection outpatient clinic. *Sex Transm Dis.* 2007;34(7):508-12.
Exclusion: Wrong comparison

Heiligenberg M, Rijnders B, Schim van der Loeff MF, et al. High prevalence of sexually transmitted infections in HIV-infected men during routine outpatient visits in the Netherlands. *Sex Transm Dis.* 2012;39(1):8-15.
Exclusion: Wrong outcomes

Heiligenberg M, van der Loeff MF, de Vries HJ, et al. Low prevalence of asymptomatic sexually transmitted infections in HIV-infected heterosexuals visiting an HIV clinic in the Netherlands. *AIDS*. 2012;26(5):646-9.
Exclusion: Wrong outcomes

Herremans M, Notermans DW, Mommers M, et al. Comparison of a *Treponema pallidum* IgM immunoblot with a 19S fluorescent treponemal antibody absorption test for the diagnosis of congenital syphilis. *Diagn Microbiol Infect Dis*. 2007;59(1):61-6.
Exclusion: Wrong population

Herring A, Ballard R, Mabey D, et al. Evaluation of rapid diagnostic tests: syphilis. *Nat Rev Microbiol*. 2006;4(12 Suppl):S33-40.
Exclusion: Wrong publication type

Heymans R, van der Helm JJ, de Vries HJ, et al. Clinical value of *Treponema pallidum* real-time PCR for diagnosis of syphilis. *J Clin Microbiol*. 2010;48(2):497-502.
Exclusion: Wrong population

Hladun O, Grau A, Esteban E, et al. Results from screening immigrants of low-income countries: data from a public primary health care. *J Travel Med*. 2014;21(2):92-8.
Exclusion: Wrong outcomes

Ho EL, Tantalo LC, Jones T, et al. Point-of-care treponemal tests for neurosyphilis diagnosis. *Sex Transm Dis.* 2015;42(1):48-52.
Exclusion: Wrong intervention

Hoang MP, High WA, Molberg KH. Secondary syphilis: a histologic and immunohistochemical evaluation. *J Cutan Pathol*. 2004;31(9):595-9.
Exclusion: Wrong population

Holman KM, Carr JA, Baddley JW, et al. Sexual history taking and sexually transmitted infection screening in patients initiating erectile dysfunction medication therapy. *Sex Transm Dis.* 2013;40(11):836-8.
Exclusion: Wrong outcomes

Hook EW 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. *J Infect Dis*. 2010;201(11):1729-35.
Exclusion: Wrong outcomes

Hoover KW, Butler M, Workowski K, et al. STD screening of HIV-infected MSM in HIV clinics. *Sex Transm Dis.* 2010;37(12):771-6.
Exclusion: Included for contextual questions only

Horberg MA, Ranatunga DK, Quesenberry CP, et al. Syphilis epidemiology and clinical outcomes in HIV-infected and HIV-uninfected patients in Kaiser Permanente Northern California. *Sex Transm Dis.* 2010;37(1):53-8.
Exclusion: Included for contextual questions only

Appendix B4. List of Excluded Studies

Hotton AL, Gratzer B, Pohl D, et al. Factors associated with repeat syphilis testing at a large urban LGBT health clinic: Chicago, IL 2002-2008. *Sex Transm Dis.* 2011;38(3):205-9.
Exclusion: Wrong outcomes

Huang Q, Lan X, Tong T, et al. Dot-immunogold filtration assay as a screening test for syphilis. *J Clin Microbiol*. 1996;34(8):2011-3.
Exclusion: Wrong population

Huang YF, Nelson KE, Lin YT, et al. Syphilis among men who have sex with men (MSM) in Taiwan: its association with HIV prevalence, awareness of HIV status, and use of antiretroviral therapy. *AIDS Behav*. 2013;17(4):1406-14.
Exclusion: Population not applicable to U.S. population

Hussain T, Kulshreshtha KK, Sinha S, et al. HIV, HBV, HCV, and syphilis co-infections among patients attending the STD clinics of district hospitals in Northern India. *Int J Infect Dis*. 2006;10(5):358-63.
Exclusion: Population not applicable to U.S. population

Imrie J, Lambert N, Mercer CH, et al. Refocusing health promotion for syphilis prevention: results of a case-control study of men who have sex with men on England's south coast. *Sex Transm Infect*. 2006;82(1):80-3.
Exclusion: Wrong outcomes

Issa BA, Fadeyi A, Durotoye IA, et al. Sero-prevalence of syphilis among patients with mental illness: comparison with blood donors. *West Afr J Med*. 2013;32(3):210-5.
Exclusion: Wrong population

Ivens D, Patel M. Incidence and presentation of early syphilis diagnosed in HIV-positive gay men attending a central London outpatients' department. *Int J STD AIDS*. 2005;16(3):201-2.
Exclusion: Wrong comparison

Jafari Y, Peeling RW, Shivkumar S, et al. Are *Treponema pallidum* specific rapid and point-of-care tests for syphilis accurate enough for screening in resource limited settings? Evidence from a meta-analysis. *PLoS One*. 2013;8(2):e54695.
Exclusion: Review not meeting inclusion criteria

Javanbakht M, Murphy R, Harawa NT, et al. Sexually transmitted infections and HIV prevalence among incarcerated men who have sex with men, 2000-2005. *Sex Transm Dis.* 2009;36(2 Suppl):S17-21.
Exclusion: Wrong outcomes

Jayaraman GC, Read RR, Singh A. Characteristics of individuals with male-to-male and heterosexually acquired infectious syphilis during an outbreak in Calgary, Alberta, Canada. *Sex Transm Dis.* 2003;30(4):315-9.
Exclusion: Wrong outcomes

Jin F, Prestage GP, Kippax SC, et al. Epidemic syphilis among homosexually active men in Sydney. *Med J Aust*. 2005;183(4):179-83.
Exclusion: Wrong outcomes

Jin F, Prestage GP, Zablotska I, et al. High incidence of syphilis in HIV-positive homosexual men: data from two community-based cohort studies. *Sex Health*. 2009;6(4):281-4.
Exclusion: Wrong outcomes

Jin F, Prestage GP, Zablotska I, et al. High rates of sexually transmitted infections in HIV positive homosexual men: data from two community based cohorts. *Sex Transm Infect*. 2007;83(5):397-9.
Exclusion: Wrong outcomes

Johnson BK. Sexually transmitted infections and older adults. *J Gerontol Nurs*. 2013;39(11):53-60.
Exclusion: Review not meeting inclusion criteria

Jozkowski K, Rosenberger JG, Schick V, et al. Relations between circumcision status, sexually transmitted infection history, and HIV serostatus among a national sample of men who have sex with men in the United States. *AIDS Patient Care STDS*. 2010;24(8):465-70.
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

Kahle E, Zhang Q, Golden M, et al. Trends in evaluation for sexually transmitted infections among HIV-infected people, King County, Washington. *Sex Transm Dis.* 2007;34(12):940-6.
Exclusion: Wrong comparison

Appendix B4. List of Excluded Studies

Kahn RH, Moseley KE, Thilges JN, et al. Community-based screening and treatment for STDs: results from a mobile clinic initiative. *Sex Transm Dis.* 2003;30(8):654-8.
Exclusion: Wrong outcomes

Kahn RH, Peterman TA, Arno J, et al. Identifying likely syphilis transmitters: implications for control and evaluation. *Sex Transm Dis.* 2006;33(10):630-5.
Exclusion: Included for contextual questions only

Kahn RH, Voigt RF, Swint E, et al. Early syphilis in the United States identified in corrections facilities, 1999-2002. *Sex Transm Dis.* 2004;31(6):360-4.
Exclusion: Included for contextual questions only

Katz KA, Lee MA, Gray T, et al. Repeat syphilis among men who have sex with men--San Diego County, 2004-2009. *Sex Transm Dis.* 2011;38(4):349-52.
Exclusion: Wrong outcomes

Katz KA, Raymond HF, Bernstein KT, et al. Knowledge, attitudes, and practices regarding syphilis screening among men who have sex with men in San Francisco. *Sex Transm Dis.* 2013;40(4):318-22.
Exclusion: Wrong outcomes

Katz LM. A test that won't die: the serologic test for syphilis. *Transfusion*. 2009;49(4):617-9.
Exclusion: Wrong publication type

Kay NS, Peeling RW, Mabey DC. State of the art syphilis diagnostics: rapid point-of-care tests. *Expert Rev Anti Infect Ther*. 2014;12(1):63-73.
Exclusion: Wrong publication type

Kazi AM, Shah SA, Jenkins CA, et al. Risk factors and prevalence of tuberculosis, human immunodeficiency virus, syphilis, hepatitis B virus, and hepatitis C virus among prisoners in Pakistan. *Int J Infect Dis*. 2010;14(Suppl 3):e60-6.
Exclusion: Population not applicable to U.S. population

Keiser O, Martinez de Tejada B, Wunder D, et al. Frequency of gynecologic follow-up and cervical cancer screening in the Swiss HIV cohort study. *J Acquir Immune Defic Syndr*. 2006;43(5):550-5.
Exclusion: Wrong outcomes

Kerani RP, Handsfield HH, Stenger MS, et al. Rising rates of syphilis in the era of syphilis elimination. *Sex Transm Dis.* 2007;34(3):154-61.
Exclusion: Wrong outcomes

Kim J, Kim WH, Cho C, et al. [Evaluation of automated architect syphilis TP as a diagnostic laboratory screening test for syphilis]. *Korean J Lab Med*. 2008;28(6):475-82.
Exclusion: Wrong population

Kim YJ, Cho SY, Kim MJ, et al. Investigation of concordance in two automated rapid plasma reagin assays and conventional manual card method. *Clin Lab*. 2015;61(7):861-3.
Exclusion: Wrong publication type

Kim YS, Lee J, Lee HK, et al. [Comparison of quantitative results among two automated rapid plasma reagin (RPR) assays and a manual RPR test]. *Korean J Lab Med*. 2009;29(4):331-7.
Exclusion: Wrong population

Kitahata MM, Dillingham PW, Chaiyakunapruk N, et al. Electronic human immunodeficiency virus (HIV) clinical reminder system improves adherence to practice guidelines among the University of Washington HIV Study Cohort. *Clin Infect Dis*. 2003;36(6):803-11.
Exclusion: Wrong outcomes

Kizito D, Woodburn PW, Kesande B, et al. Uptake of HIV and syphilis testing of pregnant women and their male partners in a programme for prevention of mother-to-child HIV transmission in Uganda. *Trop Med Int Health*. 2008;13(5):680-2.
Exclusion: Wrong population

Klausner JD. Frequency of syphilis testing in HIV-infected patients: more and more often. *Sex Transm Dis.* 2009;36(2):86-7.
Exclusion: Wrong publication type

Klausner JD, Kent CK, Wong W, et al. The public health response to epidemic syphilis, San Francisco, 1999-2004. *Sex Transm Dis.* 2005;32(10 Suppl):S11-8.
Exclusion: Wrong study design for Key Question

Knight CS, Crum MA, Hardy RW. Evaluation of the LIAISON chemiluminescence immunoassay for diagnosis of syphilis. *Clin Vaccine Immunol*. 2007;14(6):710-3.
Exclusion: Wrong population

Ko NY, Liu HY, Lee HC, et al. One-year follow-up of relapse to risky behaviors and incidence of syphilis among patients enrolled in the HIV case management program. *AIDS Behav*. 2011;15(5):1067-74.
Exclusion: Population not applicable to U.S. population

Appendix B4. List of Excluded Studies

Koek AG, Bruisten SM, Dierdorp M, et al. Specific and sensitive diagnosis of syphilis using a real-time PCR for *Treponema pallidum*. *Clin Microbiol Infect*. 2006;12(12):1233-6.
Exclusion: Wrong population

Koekenbier RH, Davidovich U, van Leent EJ, et al. Online-mediated syphilis testing: feasibility, efficacy, and usage. *Sex Transm Dis.* 2008;35(8):764-9.
Exclusion: Wrong outcomes

Kotnik V, Jordan K, Stopinsek S, et al. Intrathecal antitreponemal antibody synthesis determination using the INNO-LIA syphilis score. *Acta Dermatovenerol Alp Pannonica Adriat*. 2007;16(4):135-41.
Exclusion: Wrong outcomes

Kourbatova EV, Akovbyan VA, Chesson HW, et al. Assessment of the routine, occupation-based gonorrhea and syphilis screening program in Moscow, Russia: an analysis of sexually transmitted infection prevalence and cost-effectiveness. *Sex Transm Dis.* 2008;35(5):453-60.
Exclusion: Wrong outcomes

Kudo T, Kido A, Nishiyama Y, et al. Whole-blood counting immunoassay as a short-turnaround test for detection of hepatitis B surface antigen, anti-hepatitis C virus antibodies, and anti-*Treponema pallidum* antibodies. *J Clin Microbiol*. 2004;42(9):4250-2.
Exclusion: Wrong outcomes

Kunkel J, Schurmann D, Pleyer U, et al. Ocular syphilis--indicator of previously unknown HIV-infection. *J Infect*. 2009;58(1):32-6.
Exclusion: Wrong population

Lam TK, Lau HY, Lee YP, et al. Comparative evaluation of the INNO-LIA syphilis score and the MarDx *Treponema pallidum* immunoglobulin G Marblot test assays for the serological diagnosis of syphilis. *Int J STD AIDS*. 2010;21(2):110-3.
Exclusion: Wrong population

Lam TK, Lau HY, Lee YP, et al. Use of the INNO-LIA syphilis score assay in the resolution of discordant positive screening enzyme immunoassay results for the serological diagnosis of syphilis. *Int J STD AIDS*. 2014;25(1):52-6.
Exclusion: Wrong intervention

Lambert NL, Fisher M, Imrie J, et al. Community based syphilis screening: feasibility, acceptability, and effectiveness in case finding. *Sex Transm Infect*. 2005;81(3):213-6.
Exclusion: Wrong outcomes

Lee JH, Lim CS, Lee MG, et al. Comparison of an automated rapid plasma reagin (RPR) test with the conventional RPR card test in syphilis testing. *BMJ Open*. 2014;4(12):e005664.
Exclusion: Wrong publication type

Lee K, Park H, Roh EY, et al. Characterization of sera with discordant results from reverse sequence screening for syphilis. *Biomed Res Int*. 2013;2013:269347.
Exclusion: Wrong population

Leslie DE, Azzato F, Karapanagiotidis T, et al. Development of a real-time PCR assay to detect *Treponema pallidum* in clinical specimens and assessment of the assay's performance by comparison with serological testing. *J Clin Microbiol*. 2007;45(1):93-6.
Exclusion: Wrong population

Leuridan E, Wouters K, Stalpaert M, et al. Male sex workers in Antwerp, Belgium: a descriptive study. *Int J STD AIDS*. 2005;16(11):744-8.
Exclusion: Population not applicable to U.S. population

Lewis FM, Schillinger JA, Taylor M, et al. Needle in a haystack: the yield of syphilis outreach screening at 5 US sites--2000 to 2007. *J Public Health Manag Pract*. 2011;17(6):513-21.
Exclusion: Wrong outcomes

Li D, Jia Y, Ruan Y, et al. Correlates of incident infections for HIV, syphilis, and hepatitis B virus in a cohort of men who have sex with men in Beijing. *AIDS Patient Care STDS*. 2010;24(9):595-602.
Exclusion: Population not applicable to U.S. population

Li J, Chen XS, Merli MG, et al. Systematic differences in risk behaviors and syphilis prevalence across types of female sex workers: a preliminary study in Liuzhou, China. *Sex Transm Dis.* 2012;39(3):195-200.
Exclusion: Population not applicable to U.S. population

Li J, Zheng HY, Wang LN, et al. Clinical evaluation of four recombinant *Treponema pallidum* antigen-based rapid diagnostic tests for syphilis. *J Eur Acad Dermatol Venereol*. 2009;23(6):648-50.
Exclusion: Wrong population

Appendix B4. List of Excluded Studies

Lim RB, Tan MT, Young B, et al. Risk factors and time-trends of cytomegalovirus (CMV), syphilis, toxoplasmosis and viral hepatitis infection and seroprevalence in human immunodeficiency virus (HIV) infected patients. *Ann Acad Med Singapore*. 2013;42(12):667-73.
Exclusion: Population not applicable to U.S. population

Lin LR, Fu ZG, Dan B, et al. Development of a colloidal gold-immunochromatography assay to detect immunoglobulin G antibodies to *Treponema pallidum* with TPN17 and TPN47. *Diagn Microbiol Infect Dis*. 2010;68(3):193-200.
Exclusion: Wrong population

Lin LR, Tong ML, Fu ZG, et al. Evaluation of a colloidal gold immunochromatography assay in the detection of *Treponema pallidum* specific IgM antibody in syphilis serofast reaction patients: a serologic marker for the relapse and infection of syphilis. *Diagn Microbiol Infect Dis*. 2011;70(1):10-6.
Exclusion: Wrong population

Lipinsky D, Schreiber L, Kopel V, et al. Validation of reverse sequence screening for syphilis. *J Clin Microbiol*. 2012;50(4):1501.
Exclusion: Wrong publication type

Liu C, Ou Q, Chen H, et al. The diagnostic value and performance evaluation of five serological tests for the detection of *Treponema pallidum*. *J Clin Lab Anal*. 2014;28(3):204-9.
Exclusion: Wrong comparison

Liu F, Liu LL, Guo XJ, et al. Characterization of the classical biological false-positive reaction in the serological test for syphilis in the modern era. *Int Immunopharmacol*. 2014;20(2):331-6.
Exclusion: Wrong outcomes

Liu LL, Zheng WH, Tong ML, et al. Ischemic stroke as a primary symptom of neurosyphilis among HIV-negative emergency patients. *J Neurol Sci*. 2012;317(1-2):35-9.
Exclusion: Wrong population

Ljubojevic S, Lipozencic J. Sexually transmitted infections and adolescence. *Acta Dermatovenerol Croat*. 2010;18(4):305-10.
Exclusion: Review not meeting inclusion criteria

Loeffelholz MJ, Binnicker MJ. It is time to use treponema-specific antibody screening tests for diagnosis of syphilis. *J Clin Microbiol*. 2012;50(1):2-6.
Exclusion: Wrong publication type

Loeffelholz MJ, Wen T, Patel JA. Analysis of BioPlex syphilis IgG quantitative results in different patient populations. *Clin Vaccine Immunol*. 2011;18(11):2005-6.
Exclusion: Wrong population

Long CM, Klausner JD, Leon S, et al. Syphilis treatment and HIV infection in a population-based study of persons at high risk for sexually transmitted disease/HIV infection in Lima, Peru. *Sex Transm Dis*. 2006;33(3):151-5.
Exclusion: Wrong outcomes

Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med*. 2004;351(2):154-8.
Exclusion: Wrong outcomes

Lynn WA, Lightman S. Syphilis and HIV: a dangerous combination. *Lancet Infect Dis*. 2004;4(7):456-66.
Exclusion: Wrong publication type

Mabey D, Peeling RW, Ballard R, et al. Prospective, multi-centre clinic-based evaluation of four rapid diagnostic tests for syphilis. *Sex Transm Infect*. 2006;82(Suppl 5):v13-6.
Exclusion: Wrong population

Macnow T, Hum RS, Soren K. Screening for syphilis in adolescents: how useful is it? *Clin Pediatr (Phila)*. 2014;53(8):800-3.
Exclusion: Wrong population

MacPherson DW, Gushulak BD. Syphilis in immigrants and the Canadian immigration medical examination. *J Immigr Minor Health*. 2008;10(1):1-6.
Exclusion: Wrong study design for Key Question

Manavi K, Bhaduri S, Tariq A, et al. Audit on the success of partner notification for sexually transmitted infections in the West Midlands. *Int J STD AIDS*. 2008;19(12):856-8.
Exclusion: Wrong intervention

Appendix B4. List of Excluded Studies

Manavi K, Luo PL, McMillan A. The three-year positivity rate of sexually transmitted infections among a group of HIV-infected men attending the Department of Genitourinary Medicine, Edinburgh, UK. *Int J STD AIDS*. 2005;16(11):730-2.
Exclusion: Wrong outcomes

Manavi K, Williams G, Newton R. The uptake of HIV and syphilis testing in a nurse-delivered service during Gay Pride events. *Int J STD AIDS*. 2012;23(12):887-9.
Exclusion: Wrong outcomes

Manavi K, Young H, McMillan A. The sensitivity of syphilis assays in detecting different stages of early syphilis. *Int J STD AIDS*. 2006;17(11):768-71.
Exclusion: Wrong study design for Key Question

Manzardo C, Trevino B, Gomez i Prat J, et al. Communicable diseases in the immigrant population attended to in a tropical medicine unit: epidemiological aspects and public health issues. *Travel Med Infect Dis*. 2008;6(1-2):4-11.
Exclusion: Wrong outcomes

Maple PA, Simms I, Kafatos G, et al. Application of a noninvasive oral fluid test for detection of treponemal IgG in a predominantly HIV-infected population. *Eur J Clin Microbiol Infect Dis*. 2006;25(12):743-9.
Exclusion: Wrong intervention

Marangoni A, Moroni A, Accardo S, et al. Laboratory diagnosis of syphilis with automated immunoassays. *J Clin Lab Anal*. 2009;23(1):1-6.
Exclusion: Wrong population

Marangoni A, Nardini P, Foschi C, et al. Evaluation of the BioPlex 2200 syphilis system as a first-line method of reverse-sequence screening for syphilis diagnosis. *Clin Vaccine Immunol*. 2013;20(7):1084-8.
Exclusion: Wrong population

Marangoni A, Sambri V, Accardo S, et al. Evaluation of LIAISON Treponema Screen, a novel recombinant antigen-based chemiluminescence immunoassay for laboratory diagnosis of syphilis. *Clin Diagn Lab Immunol*. 2005;12(10):1231-4.
Exclusion: Wrong population

Marcus JL, Katz KA, Bernstein KT, et al. Syphilis testing behavior following diagnosis with early syphilis among men who have sex with men--San Francisco, 2005-2008. *Sex Transm Dis.* 2011;38(1):24-9.
Exclusion: Wrong outcomes

Marcus U, Bremer V, Hamouda O. Syphilis surveillance and trends of the syphilis epidemic in Germany since the mid-90s. *Euro Surveill*. 2004;9(12):11-4.
Exclusion: Wrong publication type

Marques NM, Margalho R, Melo MJ, et al. Seroepidemiological survey of transmissible infectious diseases in a Portuguese prison establishment. *Braz J Infect Dis*. 2011;15(3):272-5.
Exclusion: Wrong outcomes

Marra CM, Tantalo LC, Maxwell CL, et al. Alternative cerebrospinal fluid tests to diagnose neurosyphilis in HIV-infected individuals. *Neurology*. 2004;63(1):85-8.
Exclusion: Wrong population

Marra CM, Tantalo LC, Maxwell CL, et al. The rapid plasma reagin test cannot replace the Venereal Disease Research Laboratory test for neurosyphilis diagnosis. *Sex Transm Dis.* 2012;39(6):453-7.
Exclusion: Wrong population

Marrazzo J. Sexually transmitted diseases in the HIV care setting: what's really going on down there? *Top HIV Med*. 2004;12(2):57-60.
Exclusion: Wrong publication type

Martin IE, Lau A, Sawatzky P, et al. Serological diagnosis of syphilis: enzyme-linked immunosorbent assay to measure antibodies to individual recombinant *Treponema pallidum* antigens. *J Immunoassay Immunochem*. 2008;29(2):143-51.
Exclusion: Wrong population

Martin JA, Mak DB. Changing faces: a review of infectious disease screening of refugees by the Migrant Health Unit, Western Australia in 2003 and 2004. *Med J Aust*. 2006;185(11-12):607-10.
Exclusion: Wrong outcomes

Matteelli A, Schlagenhauf P, Carvalho AC, et al. Travel-associated sexually transmitted infections: an observational cross-sectional study of the GeoSentinel surveillance database. *Lancet Infect Dis*. 2013;13(3):205-13.
Exclusion: Wrong outcomes

Mattei PL, Beachkofsky TM, Gilson RT, et al. Syphilis: a reemerging infection. *Am Fam Physician*. 2012;86(5):433-40.
Exclusion: Wrong publication type

Appendix B4. List of Excluded Studies

Mayer KH. Sexually transmitted diseases in men who have sex with men. *Clin Infect Dis.* 2011;53(Suppl 3):S79-83.
Exclusion: Review not meeting inclusion criteria

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

Mayer KH, Ducharme R, Zaller ND, et al. Unprotected sex, underestimated risk, undiagnosed HIV and sexually transmitted diseases among men who have sex with men accessing testing services in a New England bathhouse. *J Acquir Immune Defic Syndr*. 2012;59(2):194-8.
Exclusion: Wrong outcomes

Mayer KH, Wang L, Koblin B, et al. Concomitant socioeconomic, behavioral, and biological factors associated with the disproportionate HIV infection burden among black men who have sex with men in 6 U.S. cities. *PLoS One*. 2014;9(1):e87298.
Exclusion: Included for contextual questions only

McLean CA, Kohl K, Baker MA, et al. The syphilis reactor grid: help or hindrance for syphilis surveillance? *Sex Transm Dis.* 2003;30(8):650-3.
Exclusion: Wrong outcomes

McMillan A, Young H. Qualitative and quantitative aspects of the serological diagnosis of early syphilis. *Int J STD AIDS*. 2008;19(9):620-4.
Exclusion: Wrong population

Medhi GK, Mahanta J, Kermode M, et al. Factors associated with history of drug use among female sex workers (FSW) in a high HIV prevalence state of India. *BMC Public Health*. 2012;12:273.
Exclusion: Wrong outcomes

Mejia A, Bautista CT, Leal L, et al. Syphilis infection among female sex workers in Colombia. *J Immigr Minor Health*. 2009;11(2):92-8.
Exclusion: Wrong outcomes

Miller M, Liao Y, Wagner M, et al. HIV, the clustering of sexually transmitted infections, and sex risk among African American women who use drugs. *Sex Transm Dis.* 2008;35(7):696-702.
Exclusion: Wrong outcomes

Mimiaga MJ, Helms DJ, Reisner SL, et al. Gonococcal, chlamydia, and syphilis infection positivity among MSM attending a large primary care clinic, Boston, 2003 to 2004. *Sex Transm Dis.* 2009;36(8):507-11.
Exclusion: Wrong outcomes

Mimiaga MJ, Reisner SL, Vanderwarker R, et al. Polysubstance use and HIV/STD risk behavior among Massachusetts men who have sex with men accessing Department of Public Health mobile van services: implications for intervention development. *AIDS Patient Care STDS*. 2008;22(9):745-51.
Exclusion: Wrong outcomes

Miranda AE, Figueiredo NC, Pinto VM, et al. Risk factors for syphilis in young women attending a family health program in Vitoria, Brazil. *An Bras Dermatol*. 2012;87(1):76-83.
Exclusion: Population not applicable to U.S. population

Mishra S, Naik B, Venugopal B, et al. Syphilis screening among female sex workers in Bangalore, India: comparison of point-of-care testing and traditional serological approaches. *Sex Transm Infect*. 2010;86(3):193-8.
Exclusion: Wrong intervention

Mitchell SJ, Engelman J, Kent CK, et al. Azithromycin-resistant syphilis infection: San Francisco, California, 2000-2004. *Clin Infect Dis*. 2006;42(3):337-45.
Exclusion: Wrong outcomes

Mo X, Jin Y, Yang Y, et al. Evaluation of a new chemiluminescence immunoassay for diagnosis of syphilis. *Eur J Med Res*. 2010;15(2):66-9.
Exclusion: Wrong population

Moore MB Jr, Price EV, Knox JM, et al. Epidemiologic treatment of contacts to infectious syphilis. Public health reports (Washington, DC: 1974). 1963;78:966-70.
Exclusion: Wrong publication type

Morshed MG. Current trend on syphilis diagnosis: issues and challenges. *Adv Exp Med Biol*. 2014;808:51-64.
Exclusion: Wrong publication type

Appendix B4. List of Excluded Studies

Muller H, Eisendle K, Brauninger W, et al. Comparative analysis of immunohistochemistry, polymerase chain reaction and focus-floating microscopy for the detection of *Treponema pallidum* in mucocutaneous lesions of primary, secondary and tertiary syphilis. *Br J Dermatol*. 2011;165(1):50-60.
Exclusion: Wrong population

Muller I, Brade V, Hagedorn HJ, et al. Is serological testing a reliable tool in laboratory diagnosis of syphilis? Meta-analysis of eight external quality control surveys performed by the German infection serology proficiency testing program. *J Clin Microbiol*. 2006;44(4):1335-41.
Exclusion: Wrong intervention

Mullick S, Broutet N, Htun Y, et al. Controlling congenital syphilis in the era of HIV/AIDS. *Bull World Health Organ*. 2004;82(6):431-2.
Exclusion: Wrong publication type

Munday PE, Allan A, Hearne S, et al. The role of the nurse in screening asymptomatic male and female patients in a sexual health clinic. *Int J STD AIDS*. 2005;16(4):281-3.
Exclusion: Wrong outcomes

Mustikawati DE, Morineau G, Nurhayati, et al. Sexual risk taking, sexually transmitted infections and HIV prevalence among four "high-risk" occupational groups of Indonesian men. *Sex Transm Infect*. 2009;85(5):391-6.
Exclusion: Population not applicable to U.S. population

Muzny CA, Sunesara IR, Martin DH, et al. Sexually transmitted infections and risk behaviors among African American women who have sex with women: does sex with men make a difference? *Sex Transm Dis*. 2011;38(12):1118-25.
Exclusion: Wrong outcomes

Naaber P, Makoid E, Aus A, et al. Evaluation of ID-PaGIA syphilis antibody test. *Indian J Dermatol Venereol Leprol*. 2009;75(5):492-4.
Exclusion: Wrong population

Nessa K, Alam A, Chawdhury FA, et al. Field evaluation of simple rapid tests in the diagnosis of syphilis. *Int J STD AIDS*. 2008;19(5):316-20.
Exclusion: Population not applicable to U.S. population

Nessa K, Waris SA, Alam A, et al. Sexually transmitted infections among brothel-based sex workers in Bangladesh: high prevalence of asymptomatic infection. *Sex Transm Dis*. 2005;32(1):13-9.
Exclusion: Wrong outcomes

Noh J, Ko HH, Yun Y, et al. [Evaluation of performance and false positivity of Mediace RPR test that uses a chemistry autoanalyzer]. *Korean J Lab Med*. 2008;28(4):312-8.
Exclusion: Wrong population

Nyamwamu LB, Gicheru MM, Sharma RR, et al. Evaluation of the immunochromatographic strip test for the rapid diagnosis of antenatal syphilis in women in Eldoret, Kenya. *J Nanjing Med Univ*. 2009;23(5):317-21.
Exclusion: Wrong population

O'Connor EA, Lin JS, Burda BU, et al. Behavioral sexual risk-reduction counseling in primary care to prevent sexually transmitted infections: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2014;161(12):874-83.
Exclusion: Wrong outcomes

Ortega KL, Rezende NP, Magalhaes MH. Diagnosing secondary syphilis in a patient with HIV. *Br J Oral Maxillofac Surg*. 2009;47(2):169-70.
Exclusion: Wrong study design for Key Question

Owusu-Edusei K Jr, Koski KA, Ballard RC. The tale of two serologic tests to screen for syphilis--treponemal and nontreponemal: does the order matter? *Sex Transm Dis*. 2011;38(5):448-56.
Exclusion: Wrong study design for Key Question

Owusu-Edusei K Jr, Peterman TA, Ballard RC. Serologic testing for syphilis in the United States: a cost-effectiveness analysis of two screening algorithms. *Sex Transm Dis*. 2011;38(1):1-7.
Exclusion: Wrong outcomes

Oxman GL, Doyle L. A comparison of the case-finding effectiveness and average costs of screening and partner notification. *Sex Transm Dis*. 1996;23(1):51-7.
Exclusion: Wrong outcomes

Palmer HM, Higgins SP, Herring AJ, et al. Use of PCR in the diagnosis of early syphilis in the United Kingdom. *Sex Transm Infect*. 2003;79(6):479-83.
Exclusion: Wrong population

Appendix B4. List of Excluded Studies

Park IU, Chow JM, Bolan G, et al. Screening for syphilis with the treponemal immunoassay: analysis of discordant serology results and implications for clinical management. *J Infect Dis.* 2011;204(9):1297-304.
Exclusion: Wrong comparison

Park Y, Park Y, Joo SY, et al. Evaluation of a fully automated treponemal test and comparison with conventional VDRL and FTA-ABS tests. *Am J Clin Pathol*. 2011;136(5):705-10.
Exclusion: Wrong population

Parthasarathy MR, Narayanan P, Das A, et al. Integrating syphilis screening in a large-scale HIV prevention program for key populations: the Avahan experience from India. *J Infect Dev Ctries.* 2013;7(6):484-8.
Exclusion: Wrong outcomes

Pathela P, Braunstein SL, Schillinger JA, et al. Men who have sex with men have a 140-fold higher risk for newly diagnosed HIV and syphilis compared with heterosexual men in New York City. *J Acquir Immune Defic Syndr*. 2011;58(4):408-16.
Exclusion: Wrong outcomes

Patterson D, Vilensky JA, Robertson WM, et al. Treatment and diagnostic accuracy of neurosyphilis at Boston City Hospital's Neurological Unit, 1930-1979. *J Neurol Sci*. 2012;314(1-2):1-4.
Exclusion: Wrong outcomes

Paz-Bailey G, Teran S, Levine W, et al. Syphilis outbreak among Hispanic immigrants in Decatur, Alabama: association with commercial sex. *Sex Transm Dis.* 2004;31(1):20-5.
Exclusion: Wrong outcomes

Peate I. Syphilis: clinical presentation, diagnosis and treatment. *Nurs Stand*. 2007;22(10):48-55.
Exclusion: Wrong publication type

Peeling RW, Mabey DC. Syphilis. *Nat Rev Microbiol*. 2004;2(6):448-9.
Exclusion: Wrong publication type

Perry M, Iveson H, White J. Assessment of the performance of a rapid point of care syphilis test in a London genitourinary medicine clinic. *Int J STD AIDS.* 2014;25(13):967-8.
Exclusion: Wrong publication type

Person AK, Blain ML, Jiang H, et al. Text messaging for enhancement of testing and treatment for tuberculosis, human immunodeficiency virus, and syphilis: a survey of attitudes toward cellular phones and healthcare. *Telemed J E Health*. 2011;17(3):189-95.
Exclusion: Wrong outcomes

Peterman TA, Furness BW. The resurgence of syphilis among men who have sex with men. *Curr Opin Infect Dis.* 2007;20(1):54-9.
Exclusion: Review not meeting inclusion criteria

Peterman TA, Heffelfinger JD, Swint EB, et al. The changing epidemiology of syphilis. *Sex Transm Dis.* 2005;32(10 Suppl):S4-10.
Exclusion: Review not meeting inclusion criteria

Peterman TA, Su J, Bernstein KT, et al. Syphilis in the United States: on the rise? *Expert Rev Anti Infect Ther*. 2015;13(2):161-8.
Exclusion: Wrong publication type

Phipps W, Kent CK, Kohn R, et al. Risk factors for repeat syphilis in men who have sex with men, San Francisco. *Sex Transm Dis.* 2009;36(6):331-5.
Exclusion: Wrong outcomes

Phipps W, Stanley H, Kohn R, et al. Syphilis, chlamydia, and gonorrhea screening in HIV-infected patients in primary care, San Francisco, California, 2003. *AIDS Patient Care STDS.* 2005;19(8):495-8.
Exclusion: Wrong outcomes

American Academy of Family Physicians. Syphilis. http://www.aafp.org/patient-care/clinical-recommendations/all/syphilis.html. Accessed June 22, 2015.
Exclusion: custom 7

Pintye J, Baeten JM, Manhart LE, et al. Association between male circumcision and incidence of syphilis in men and women: a prospective study in HIV-1 serodiscordant heterosexual African couples. *Lancet Glob Health*. 2014;2(11):e664-e71.
Exclusion: Population not applicable to U.S. population

Pittrof R, McLellan J. Test Not Talk screening for asymptomatic men. *Int J STD AIDS.* 2007;18(4):274-5.
Exclusion: Wrong study design for Key Question

Appendix B4. List of Excluded Studies

Plant A, Javanbakht M, Montoya JA, et al. Check Yourself: a social marketing campaign to increase syphilis screening in Los Angeles County. *Sex Transm Dis.* 2014;41(1):50-7.
Exclusion: Wrong outcomes

Platt L, Rhodes T, Judd A, et al. Effects of sex work on the prevalence of syphilis among injection drug users in 3 Russian cities. *Am J Public Health*. 2007;97(3):478-85.
Exclusion: Population not applicable to U.S. population

Platteau T, Wouters K, Apers L, et al. Voluntary outreach counselling and testing for HIV and STI among men who have sex with men in Antwerp. *Acta Clin Belg*. 2012;67(3):172-6.
Exclusion: Wrong outcomes

Pope V. Use of treponemal tests to screen for syphilis. *Infect Med*. 2004;21(8):399-402.
Exclusion: Wrong publication type

Qin JB, Feng TJ, Yang TB, et al. Maternal and paternal factors associated with congenital syphilis in Shenzhen, China: a prospective cohort study. *Eur J Clin Microbiol Infect Dis.* 2014;33(2):221-32.
Exclusion: Wrong outcomes

Quaglio G, Lugoboni F, Pattaro C, et al. Patients in long-term maintenance therapy for drug use in Italy: analysis of some parameters of social integration and serological status for infectious diseases in a cohort of 1091 patients. *BMC Public Health.* 2006;6:216.
Exclusion: Wrong outcomes

Qyra ST, Basho M, Bani R, et al. Behavioral risk factors and prevalence of HIV and other STIs among female sex workers in Tirana, Albania. *New Microbiol*. 2011;34(1):105-8.
Exclusion: Population not applicable to U.S. population

Rajapure V, Tirwa R, Poudyal H, et al. Prevalence and risk factors associated with sexually transmitted diseases (STDs) in Sikkim. *J Community Health*. 2013;38(1):156-62.
Exclusion: Population not applicable to U.S. population

Rajaram SP, Banandur P, Thammattoor UK, et al. Two cross-sectional studies in south India assessing the effect of an HIV prevention programme for female sex workers on reducing syphilis among their clients. *Sex Transm Infect.* 2014;90(7):556-62.
Exclusion: Wrong outcomes

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

Reynolds GL, Fisher DG, Napper LE, et al. Results from a multiple morbidities testing program offering rapid HIV testing bundled with hepatitis and sexually transmitted infection testing. *Public Health Rep*. 2008;123(Suppl 3):63-9.
Exclusion: Wrong outcomes

Reynolds SJ, Shepherd ME, Risbud AR, et al. Male circumcision and risk of HIV-1 and other sexually transmitted infections in India. *Lancet.* 2004;363(9414):1039-40.
Exclusion: Population not applicable to U.S. population

Reynolds SL, Kapadia AS, Leonard L, et al. Examining the direct costs and effectiveness of syphilis detection by selective screening and partner notification. *J Public Health Med*. 2001;23(4):339-45.
Exclusion: Wrong outcomes

Ribeiro D, Rezende EF, Pinto VM, et al. Prevalence of and risk factors for syphilis in Brazilian armed forces conscripts. *Sex Transm Infect.* 2012;88(1):32-4.
Exclusion: Population not applicable to U.S. population

Riedner G, Hoffmann O, Rusizoka M, et al. Decline in sexually transmitted infection prevalence and HIV incidence in female barworkers attending prevention and care services in Mbeya Region, Tanzania. *AIDS*. 2006;20(4):609-15.
Exclusion: Wrong outcomes

Rieg G, Lewis RJ, Miller LG, et al. Asymptomatic sexually transmitted infections in HIV-infected men who have sex with men: prevalence, incidence, predictors, and screening strategies. *AIDS Patient Care STDS.* 2008;22(12):947-54.
Exclusion: Wrong comparison

Righarts AA, Simms I, Wallace L, et al. Syphilis surveillance and epidemiology in the United Kingdom. *Euro Surveill.* 2004;9(12):21-5.
Exclusion: Wrong study design for Key Question

Rogstad KE, Simms I, Fenton KA, et al. Screening, diagnosis and management of early syphilis in genitourinary medicine clinics in the UK. *Int J STD AIDS.* 2005;16(5):348-52.
Exclusion: Wrong outcomes

Appendix B4. List of Excluded Studies

Rosenman M, Wang J, Dexter P, et al. Computerized reminders for syphilis screening in an urban emergency department. 2003. Annual Symposium Proceedings/AMIA Symposium. 987.
Exclusion: Wrong intervention

Rosenman MB, Kraft SK, Harezlak J, et al. Syphilis testing in association with gonorrhea/chlamydia testing during a syphilis outbreak. *Am J Public Health.* 2004;94(7):1124-6.
Exclusion: Wrong outcomes

Ross MW, Risser J, Peters RJ, et al. Cocaine use and syphilis trends: findings from the arrestee drug abuse monitoring (ADAM) program and syphilis epidemiology in Houston. *Am J Addict.* 2006;15(6):473-7.
Exclusion: Wrong outcomes

Rotty J, Anderson D, Garcia M, et al. Preliminary assessment of *Treponema pallidum*-specific IgM antibody detection and a new rapid point-of-care assay for the diagnosis of syphilis in human immunodeficiency virus-1-infected patients. *Int J STD AIDS.* 2010;21(11):758-64.
Exclusion: Wrong population

Ruan Y, Cao X, Qian HZ, et al. Syphilis among female sex workers in southwestern China: potential for HIV transmission. *Sex Transm Dis.* 2006;33(12):719-23.
Exclusion: Population not applicable to U.S. population

Ruan Y, Jia Y, Zhang X, et al. Incidence of HIV-1, syphilis, hepatitis B, and hepatitis C virus infections and predictors associated with retention in a 12-month follow-up study among men who have sex with men in Beijing, China. *J Acquir Immune Defic Syndr.* 2009;52(5):604-10.
Exclusion: Wrong outcomes

Ruan Y, Luo F, Jia Y, et al. Risk factors for syphilis and prevalence of HIV, hepatitis B and C among men who have sex with men in Beijing, China: implications for HIV prevention. *AIDS Behav.* 2009;13(4):663-70.
Exclusion: Population not applicable to U.S. population

Ruger JP, Abdallah AB, Ng NY, et al. Cost-effectiveness of interventions to prevent HIV and STDs among women: a randomized controlled trial. *AIDS Behav.* 2014;18(10):1913-23.
Exclusion: Wrong intervention

Rust G, Minor P, Jordan N, et al. Do clinicians screen Medicaid patients for syphilis or HIV when they diagnose other sexually transmitted diseases? *Sex Transm Dis.* 2003;30(9):723-7.
Exclusion: Wrong outcomes

Ryder N, Bourne C, Rohrsheim R. Clinical audit: adherence to sexually transmitted infection screening guidelines for men who have sex with men. *Int J STD AIDS.* 2005;16(6):446-9.
Exclusion: Wrong outcomes

Samaranayake A, Chen M, Hocking J, et al. Legislation requiring monthly testing of sex workers with low rates of sexually transmitted infections restricts access to services for higher-risk individuals. *Sex Transm Infect.* 2009;85(7):540-2.
Exclusion: Wrong outcomes

Sanchez J, Campos PE, Courtois B, et al. Prevention of sexually transmitted diseases (STDs) in female sex workers: prospective evaluation of condom promotion and strengthened STD services. *Sex Transm Dis.* 2003;30(4):273-9.
Exclusion: Wrong outcomes

Sasidharanpillai S, Bindu V, Riyaz N, et al. Syphilis among sexually transmitted infections clinic attendees in a tertiary care institution: a retrospective data analysis. *Indian J Dermatol Venereol Leprol.* 2014;80(2):161-2.
Exclusion: Wrong publication type

Sato NS, de Melo CS, Zerbini LC, et al. Assessment of the rapid test based on an immunochromatography technique for detecting anti-*Treponema pallidum* antibodies. *Rev Inst Med Trop Sao Paulo.* 2003;45(6):319-22.
Exclusion: Wrong population

Sato NS, Suzuki T, Ueda T, et al. Recombinant antigen-based immuno-slot blot method for serodiagnosis of syphilis. *Braz J Med Biol Res.* 2004;37(7):949-55.
Exclusion: Wrong publication type

Savage EJ, Hughes G, Ison C, et al. Syphilis and gonorrhoea in men who have sex with men: a European overview. *Euro Surveill.* 2009;14(47).
Exclusion: Wrong study design for Key Question

Schaffzin JK, Koumans EH, Kahn RH, et al. Evaluation of syphilis reactor grids: optimizing impact. *Sex Transm Dis.* 2003;30(9):700-6.
Exclusion: Wrong population

Appendix B4. List of Excluded Studies

Scherbaum N, Baune BT, Mikolajczyk R, et al. Prevalence and risk factors of syphilis infection among drug addicts. *BMC Infect Dis*. 2005;5:33.
Exclusion: Wrong outcomes

Schmidt BL. Evaluation of a new particle gel immunoassay for determination of antibodies against *Treponema pallidum*. *J Clin Microbiol.* 2004;42(6):2833-5.
Exclusion: Wrong intervention

Schmitt K, Bulecza S, George D, et al. Florida's multifaceted response for increases in syphilis among MSM: the Miami-Ft. Lauderdale initiative. *Sex Transm Dis.* 2005;32(10 Suppl):S19-23.
Exclusion: Wrong outcomes

Schroeter AL, Turner RH, Lucas JB, et al. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. *JAMA.* 1971;218(5):711-3.
Exclusion: Wrong publication type

Schumacher CM, Bernstein KT, Zenilman JM, et al. Reassessing a large-scale syphilis epidemic using an estimated infection date. *Sex Transm Dis.* 2005;32(11):659-64.
Exclusion: Wrong outcomes

Scott LJ, Gunson RN, Carman WF, et al. A new multiplex real-time PCR test for HSV1/2 and syphilis: an evaluation of its impact in the laboratory and clinical setting. *Sex Transm Infect.* 2010;86(7):537-9.
Exclusion: Wrong population

Scythes JB, Jones CM. Syphilis in the AIDS era: diagnostic dilemma and therapeutic challenge. *Acta Microbiol Immunol Hung*. 2013;60(2):93-116.
Exclusion: Wrong publication type

Sena A, Wolff M, Behets F, et al. Seroreversion of nontreponemal antibody titers among HIV-negative patients with an appropriate serological response after treatment of early syphilis. *Sex Transm Dis.* 2014;41(9).
Exclusion: Wrong publication type

Shah BB, Lang AE. Acquired neurosyphilis presenting as movement disorders. *Mov Disord*. 2012;27(6):690-5.
Exclusion: Review not meeting inclusion criteria

Sharma M, Wanchu A, Biswal M, et al. Syphilis serology in human immunodeficiency virus patients: a need to redefine the VDRL test cut-off for biological false-positives. *J Med Microbiol.* 2010;59(Pt 1):130-1.
Exclusion: Wrong publication type

Sheng Q, Wang J, Zheng J, et al. Ultrasensitive electrical biosensing of syphilis DNA using target-guided formation of polyaniline based on enzyme-catalyzed polymerization. *Biosens Bioelectron*. 2010;25(9):2071-7.
Exclusion: Wrong intervention

Shields M, Guy RJ, Jeoffreys NJ, et al. A longitudinal evaluation of *Treponema pallidum* PCR testing in early syphilis. *BMC Infect Dis*. 2012;12:353.
Exclusion: Wrong population

Shimanskaya I, Zhurauskaya L, Pankratov O, et al. Evaluation of three serological tests manufactured in Belarus for the diagnosis of syphilis. Acta Derm Venereol. 2011;91(3):299-302.
Exclusion: Wrong population

Shimelis T, Tadesse E. The diagnostic performance evaluation of the SD BIOLINE HIV/syphilis duo rapid test in southern Ethiopia: a cross-sectional study. *BMJ Open*. 2015;5(4):e007371.
Exclusion: Wrong population

Shrestha B. Screening of syphilis in abroad job seeking healthy males. *J Nepal Med Assoc*. 2008;47(172):201-4.
Exclusion: Wrong population

Siedner M, Zapitz V, Ishida M, et al. Performance of rapid syphilis tests in venous and fingerstick whole blood specimens. *Sex Transm Dis.* 2004;31(9):557-60.
Exclusion: Wrong intervention

Silberstein GS, Coles FB, Greenberg A, et al. Effectiveness and cost-benefit of enhancements to a syphilis screening and treatment program at a county jail. *Sex Transm Dis.* 2000;27(9):508-17.
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

Singh S, Bell G, Talbot M. The characterisation of a recent syphilis outbreak in Sheffield, UK, and an evaluation of contact tracing as a method of control. *Sex Transm Infect.* 2007;83(3):193-9.
Exclusion: Wrong outcomes

Skinner JM, Distefano J, Warrington J, et al. Trends in reported syphilis and gonorrhea among HIV-infected people in Arizona: implications for prevention and control. *Public Health Rep*. 2014;129(Suppl 1):85-94.
Exclusion: Wrong outcomes

Smit PW, Mabey D, Changalucha J, et al. The trade-off between accuracy and accessibility of syphilis screening assays. *PLoS One.* 2013;8(9):e75327.
Exclusion: Wrong population

Smit PW, Mabey D, van der Vlis T, et al. The implementation of an external quality assurance method for point-of-care tests for HIV and syphilis in Tanzania. *BMC Infect Dis*. 2013;13:530.
Exclusion: Wrong outcomes

Smit PW, van der Vlis T, Mabey D, et al. The development and validation of dried blood spots for external quality assurance of syphilis serology. *BMC Infect Dis*. 2013;13:102.
Exclusion: Wrong population

Smith BC, Simpson Y, Morshed MG, et al. New proteins for a new perspective on syphilis diagnosis. *J Clin Microbiol.* 2013;51(1):105-11.
Exclusion: Wrong outcomes

Snow AF, Vodstrcil LA, Fairley CK, et al. Introduction of a sexual health practice nurse is associated with increased STI testing of men who have sex with men in primary care. *BMC Infect Dis*. 2013;13:298.
Exclusion: Wrong outcomes

Solomon MM, Mayer KH, Glidden DV, et al. Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. *Clin Infect Dis*. 2014;59(7):1020-6.
Exclusion: Wrong intervention

Soreng K, Mardis C. Syphilis: evolving screening algorithms and role of automated immunoassays. *MLO Med Lab Obs*. 2012;44(6):30, 2.
Exclusion: Wrong publication type

Sosman J, Macgowan R, Margolis A, et al. Sexually transmitted infections and hepatitis in men with a history of incarceration. *Sex Transm Dis.* 2011;38(7):634-9.
Exclusion: Wrong outcomes

Sosman JM, MacGowan RJ, Margolis AD, et al. Screening for sexually transmitted diseases and hepatitis in 18-29-year-old men recently released from prison: feasibility and acceptability. *Int J STD AIDS.* 2005;16(2):117-22.
Exclusion: Wrong outcomes

Spaulding AC, Miller J, Trigg BG, et al. Screening for sexually transmitted diseases in short-term correctional institutions: summary of evidence reviewed for the 2010 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. *Sex Transm Dis.* 2013;40(9):679-84.
Exclusion: Wrong publication type

Stephens SC, Fann CK, Strona FV, et al. Identifying syphilis risk networks through venue attendance in San Francisco. *Sex Transm Dis.* 2014;41(5):333-7.
Exclusion: Wrong population

Strathdee SA, Abramovitz D, Lozada R, et al. Reductions in HIV/STI incidence and sharing of injection equipment among female sex workers who inject drugs: results from a randomized controlled trial. *PLoS One.* 2013;8(6).
Exclusion: Wrong intervention

Su JR, Beltrami JF, Zaidi AA, et al. Primary and secondary syphilis among black and Hispanic men who have sex with men: case report data from 27 states. *Ann Intern Med*. 2011;155(3):145-51.
Exclusion: Wrong outcomes

Sun AH, Mao YF, Hu Y, et al. Sensitive and specific ELISA coated by TpN15-TpN17-TpN47 fusion protein for detection of antibodies to *Treponema pallidum*. *Clin Chem Lab Med.* 2009;47(3):321-6.
Exclusion: Wrong intervention

Suntoke TR, Hardick A, Tobian AA, et al. Evaluation of multiplex real-time PCR for detection of *Haemophilus ducreyi*, *Treponema pallidum*, herpes simplex virus type 1 and 2 in the diagnosis of genital ulcer disease in the Rakai District, Uganda. *Sex Transm Infect.* 2009;85(2):97-101.
Exclusion: Wrong population

Appendix B4. List of Excluded Studies

Tai E, Sanchez T, Lansky A, et al. Self-reported syphilis and gonorrhoea testing among men who have sex with men: national HIV behavioural surveillance system, 2003-5. *Sex Transm Infect.* 2008;84(6):478-82.
Exclusion: Wrong outcomes

Talha E, Juhasz E, Kanizsai S, et al. Molecular detection of *T. pallidum* by PCR in seronegative cases. *Acta Microbiol Immunol Hung*. 2009;56(2):181-9.
Exclusion: Wrong population

Tang J, Zhou L, Gao W, et al. Visual DNA microarrays for simultaneous detection of human immunodeficiency virus type-1 and *Treponema pallidum* coupled with multiplex asymmetric polymerase chain reaction. *Diagn Microbiol Infect Dis*. 2009;65(4):372-8.
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

Tao G, Irwin KL. Receipt of HIV and STD testing services during routine general medical or gynecological examinations: variations by patient sexual risk behaviors. *Sex Transm Dis.* 2008;35(2):167-71.
Exclusion: Wrong outcomes

Tayal S, Ahmed MS, Hanif U. Audit of early syphilis: Teesside experience 2005-2007. *Int J STD AIDS.* 2009;20(9):647-9.
Exclusion: Wrong study design for Key Question

Taylor MM, Hawkins K, Gonzalez A, et al. Use of the serologic testing algorithm for recent HIV seroconversion (STARHS) to identify recently acquired HIV infections in men with early syphilis in Los Angeles County. *J Acquir Immune Defic Syndr*. 2005;38(5):505-8.
Exclusion: Wrong population

Thurnheer MC, Weber R, Toutous-Trellu L, et al. Occurrence, risk factors, diagnosis and treatment of syphilis in the prospective observational Swiss HIV Cohort Study. *AIDS*. 2010;24(12):1907-16.
Exclusion: Wrong outcomes

Tong ML, Lin LR, Liu LL, et al. Analysis of 3 algorithms for syphilis serodiagnosis and implications for clinical management. *Clin Infect Dis*. 2014;58(8):1116-24.
Exclusion: Wrong population

Tucker JD, Bien CH, Peeling RW. Point-of-care testing for sexually transmitted infections: recent advances and implications for disease control. *Curr Opin Infect Dis.* 2013;26(1):73-9.
Exclusion: Wrong publication type

Tucker JD, Bu J, Brown LB, et al. Accelerating worldwide syphilis screening through rapid testing: a systematic review. *Lancet Infect Dis.* 2010;10(6):381-6.
Exclusion: Review not meeting inclusion criteria

Tucker JD, Hawkes SJ, Yin YP, et al. Scaling up syphilis testing in China: implementation beyond the clinic. *Bull World Health Organ*. 2010;88(6):452-7.
Exclusion: Wrong publication type

Tucker JD, Yang LG, Zhu ZJ, et al. Integrated syphilis/HIV screening in China: a qualitative analysis. *BMC Health Serv Res*. 2010;10:58.
Exclusion: Population not applicable to U.S. population

Tuite AR, Fisman DN, Mishra S. Screen more or screen more often? Using mathematical models to inform syphilis control strategies. *BMC Public Health.* 2013;13:606.
Exclusion: Wrong study design for Key Question

Valway S, Jenison S, Keller N, et al. Risk assessment and screening for sexually transmitted infections, HIV, and hepatitis virus among long-distance truck drivers in New Mexico, 2004-2006. *Am J Public Health.* 2009;99(11):2063-8.
Exclusion: Wrong comparison

Van den Bossche D, Florence E, Kenyon C, et al. Vitros 5600 Syphilis TPA assay: evaluation of an automated chemiluminescence assay for detection of *Treponema pallidum* antibodies in a high prevalence setting. *Sex Transm Dis.* 2014;41(11):680-3.
Exclusion: Wrong population

van Dommelen L, Smismans A, Goossens VJ, et al. Evaluation of a rapid one-step immunochromatographic test and two immunoenzymatic assays for the detection of anti-*Treponema pallidum* antibodies. *Sex Transm Infect.* 2008;84(4):292-6.
Exclusion: Wrong population

Appendix B4. List of Excluded Studies

Van Wagoner NJ, Harbison HS, Drewry J, et al. Characteristics of women reporting multiple recent sex partners presenting to a sexually transmitted disease clinic for care. *Sex Transm Dis.* 2011;38(3):210-5.
Exclusion: Included for contextual questions only

Vandepitte J, Bukenya J, Weiss HA, et al. HIV and other sexually transmitted infections in a cohort of women involved in high-risk sexual behavior in Kampala, Uganda. *Sex Transm Dis.* 2011;38(4):316-23.
Exclusion: Population not applicable to U.S. population

Viriyataveekul R, Laodee N, Potprasat S, et al. Comparative evaluation of three different treponemal enzyme immunoassays for syphilis. *J Med Assoc Thai*. 2006;89(6):773-9.
Exclusion: Wrong population

Wagner KD, Pitpitan EV, Chavarin CV, et al. Drug-using male clients of female sex workers who report being paid for sex: HIV/sexually transmitted infection, demographic, and drug use correlates. *Sex Transm Dis.* 2013;40(8):619-23.
Exclusion: Population not applicable to U.S. population

Wang B, Wang QQ, Yin YP, et al. The effect of a structural intervention for syphilis control among 3597 female sex workers: a demonstration study in South China. *J Infect Dis.* 2012;206(6):907-14.
Exclusion: Wrong outcomes

Wang HC, Chen C, Wang LN, et al. The clinical significance comparison of a latex agglutination based syphilis screening test at low antibody titer. *Clin Lab*. 2013;59(11-12):1429-32.
Exclusion: Wrong population

Wang LJ, Lin SK, Chiang SC, et al. Risk factors for HIV, viral hepatitis, and syphilis among heroin users in northern Taiwan. *Subst Use Misuse*. 2013;48(1-2):89-98.
Exclusion: Population not applicable to U.S. population

Wang LN, Yang L, Zheng HY. Clinical evaluation of four recombinant *Treponema pallidum* antigen-based rapid tests in the diagnosis of syphilis. *Chin Med Sci J*. 2007;22(4):250-3.
Exclusion: Wrong intervention

Wang XF, Norris JL, Liu YJ, et al. Health-related attitudes and risk factors for sexually transmitted infections of Chinese women who have sex with women. *Chin Med J*. 2012;125(16):2819-25.
Exclusion: Population not applicable to U.S. population

Wang Y, Gao W, Wang H, et al. Preparation of a visual protein chip for detection of IgG against *Treponema pallidum*. *Mol Biotechnol*. 2005;31(2):121-8.
Exclusion: Wrong intervention

Wei C, Herrick A, Raymond FH, et al. Social marketing interventions to increase HIV/STI testing uptake among men who have sex with men and male-to-female transgender women. *Cochrane Database Syst Rev*. 2013(4).
Exclusion: Wrong outcomes

Weiss HA, Thomas SL, Munabi SK, et al. Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. *Sex Transm Infect.* 2006;82(2):101-9; discussion 10.
Exclusion: Wrong outcomes

Welch RJ, Litwin CM. Evaluation of two immunoblot assays and a Western blot assay for the detection of antisyphilis immunoglobulin G antibodies. *Clin Vaccine Immunol*. 2010;17(1):183-4.
Exclusion: Wrong population

Wellinghausen N, Dietenberger H. Evaluation of two automated chemiluminescence immunoassays, the LIAISON Treponema Screen and the ARCHITECT Syphilis TP, and the *Treponema pallidum* particle agglutination test for laboratory diagnosis of syphilis. *Clin Chem Lab Med.* 2011;49(8):1375-7.
Exclusion: Wrong population

Wenhai L, Jianzhong Z, Cao Y. Detection of *Treponema pallidum* in skin lesions of secondary syphilis and characterization of the inflammatory infiltrate. *Dermatology*. 2004;208(2):94-7.
Exclusion: Wrong population

West B, Walraven G, Morison L, et al. Performance of the rapid plasma reagin and the rapid syphilis screening tests in the diagnosis of syphilis in field conditions in rural Africa. *Sex Transm Infect.* 2002;78(4):282-5.
Exclusion: Wrong intervention

Appendix B4. List of Excluded Studies

Wheeler HL, Agarwal S, Goh BT. Dark ground microscopy and treponemal serological tests in the diagnosis of early syphilis. *Sex Transm Infect.* 2004;80(5):411-4.
Exclusion: Wrong population

White DA, Alter HJ, Irvin NA, et al. Low rate of syphilis screening among high-risk emergency department patients tested for gonorrhea and chlamydia infections. *Sex Transm Dis.* 2012;39(4):286-90.
Exclusion: Wrong outcomes

Wimberly YH, Hogben M. Physicians' STD diagnosis and screening practices in the South. *South Med J*. 2004;97(7):624-30.
Exclusion: Wrong outcomes

Winscott M, Taylor M, Kenney K. Sexually transmitted diseases among American Indians in Arizona: an important public health disparity. *Public Health Rep*. 2010;125(Suppl 4):51-60.
Exclusion: Wrong outcomes

Winston A, Hawkins D, Mandalia S, et al. Is increased surveillance for asymptomatic syphilis in an HIV outpatient department worthwhile? *Sex Transm Infect.* 2003;79(3):257-9.
Exclusion: Wrong outcomes

Wong W, Chaw JK, Kent CK, et al. Risk factors for early syphilis among gay and bisexual men seen in an STD clinic: San Francisco, 2002-2003. *Sex Transm Dis.* 2005;32(7):458-63.
Exclusion: Wrong outcomes

Wong W, Tambis JA, Hernandez MT, et al. Prevalence of sexually transmitted diseases among Latino immigrant day laborers in an urban setting--San Francisco. *Sex Transm Dis.* 2003;30(8):661-3.
Exclusion: Wrong outcomes

Wong WC, Yim YL, Leung TN, et al. Prevalence and risk factors of sexually transmitted infections in female sex workers in Hong Kong. *Hong Kong Med J*. 2012;18(Suppl 3):42-6.
Exclusion: Population not applicable to U.S. population

Wong WC, Yim YL, Lynn H. Sexually transmitted infections among female sex workers in Hong Kong: the role of migration status. *J Travel Med*. 2011;18(1):1-7.
Exclusion: Population not applicable to U.S. population

Woznicova V, Valisova Z. Performance of CAPTIA SelectSyph-G enzyme-linked immunosorbent assay in syphilis testing of a high-risk population: analysis of discordant results. *J Clin Microbiol.* 2007;45(6):1794-7.
Exclusion: Wrong population

Wu J, Huang J, Xu D, et al. Infection status and risk factors of HIV, HBV, HCV, and syphilis among drug users in Guangdong, China--a cross-sectional study. *BMC Public Health.* 2010;10:657.
Exclusion: Population not applicable to U.S. population

Wu Z, Xu J, Liu E, et al. HIV and syphilis prevalence among men who have sex with men: a cross-sectional survey of 61 cities in China. *Clin Infect Dis.* 2013;57(2):298-309.
Exclusion: Wrong outcomes

Xiao Y, Sun J, Li C, et al. Prevalence and correlates of HIV and syphilis infections among men who have sex with men in seven provinces in China with historically low HIV prevalence. *J Acquir Immune Defic Syndr.* 2010;53(Suppl 1):S66-73.
Exclusion: Population not applicable to U.S. population

Xu JJ, Reilly KH, Lu CM, et al. A cross-sectional study of HIV and syphilis infections among male students who have sex with men (MSM) in northeast China: implications for implementing HIV screening and intervention programs. *BMC Public Health.* 2011;11:287.
Exclusion: Wrong outcomes

Yang B, Hallmark CJ, Huang JS, et al. Characteristics and risk of syphilis diagnosis among HIV-infected male cohort: a population-based study in Houston, Texas. *Sex Transm Dis.* 2013;40(12):957-63.
Exclusion: Included for contextual questions only

Yang H, Li D, He R, et al. A novel quantum dots-based point of care test for syphilis. *Nanoscale Res Lett*. 2010;5(5):875-81.
Exclusion: Wrong population

Yang Z, Su J, Peng X, et al. A decline in HIV and syphilis epidemics in Chinese female sex workers (2000-2011): a systematic review and meta-analysis. *PLoS One.* 2013;8(12):e82451.
Exclusion: Population not applicable to U.S. population

Appendix B4. List of Excluded Studies

Yen-Lieberman B, Daniel J, Means C, et al. Identification of false-positive syphilis antibody results using a semiquantitative algorithm. *Clin Vaccine Immunol*. 2011;18(6):1038-40.
Exclusion: Wrong population

Yin YP, Chen XS, Wei WH, et al. A dual point-of-care test shows good performance in simultaneously detecting nontreponemal and treponemal antibodies in patients with syphilis: a multisite evaluation study in China. *Clin Infect Dis.* 2013;56(5):659-65.
Exclusion: Wrong intervention

Yin YP, Wei WH, Wang HC, et al. Performance of serological tests for syphilis in sexually transmitted diseases clinics in Guangxi Autonomous Region, China: implications for syphilis surveillance and control. *Sex Health*. 2009;6(1):5-9.
Exclusion: Population not applicable to U.S. population

Yin YP, Wong SP, Liu MS, et al. Improving strategies for syphilis control in China: selective testing of sexually transmitted disease patients--too little, too late? *Int J STD AIDS.* 2008;19(12):838-42.
Exclusion: Population not applicable to U.S. population

Yoshida M, Chiba A, Kawano S, et al. Comparison of free and anonymous testing for HIV and sexually transmitted infections between the university hospital and health center. *J Infect Chemother.* 2012;18(5):704-8.
Exclusion: Wrong outcomes

Young F. Syphilis: still with us, so watch out! *J Fam Health Care*. 2006;16(3):77-81.
Exclusion: Wrong publication type

Young H, Pryde J, Duncan L, et al. The Architect syphilis assay for antibodies to *Treponema pallidum*: an automated screening assay with high sensitivity in primary syphilis. *Sex Transm Infect.* 2009;85(1):19-23.
Exclusion: Wrong comparison

Zarakolu P, Buchanan I, Tam M, et al. Preliminary evaluation of an immunochromatographic strip test for specific *Treponema pallidum* antibodies. *J Clin Microbiol.* 2002;40(8):3064-5.
Exclusion: Wrong population

Zeng Y, Zhang L, Li T, et al. Risk factors for HIV/syphilis infection and male circumcision practices and preferences among men who have sex with men in China. *Biomed Res Int*. 2014;2014:498987.
Exclusion: Population not applicable to U.S. population

Zhang L, Ding X, Lu R, et al. Predictors of HIV and syphilis among men who have sex with men in a Chinese metropolitan city: comparison of risks among students and non-students. *PLoS One.* 2012;7(5):e37211.
Exclusion: Population not applicable to U.S. population

Zhang L, Liang S, Lu W, et al. HIV, syphilis, and behavioral risk factors among female sex workers before and after implementation of harm reduction programs in a high drug-using area of China. *PLoS One.* 2014;9(1):e84950.
Exclusion: Population not applicable to U.S. population

Zhang L, Qian H, Blevins ML, et al. Internet-based behavioral interventions for preventing HIV infection in men who have sex with men (MSM). *Cochrane Database Syst Rev*. 2012(1).
Exclusion: Wrong publication type

Zhang X, Wang C, Hengwei W, et al. Risk factors of HIV infection and prevalence of co-infections among men who have sex with men in Beijing, China. *AIDS*. 2007;21(Suppl 8):S53-7.
Exclusion: Population not applicable to U.S. population

Zhao YS, Su SI, Lv CX, et al. Seroprevalence of hepatitis C, hepatitis B virus and syphilis in HIV-1 infected patients in Shandong, China. *Int J STD AIDS.* 2012;23(9):639-43.
Exclusion: Wrong outcomes

Zheng J, Wu Z, Poundstone KE, et al. HIV, syphilis infection, and risky sexual behaviors among male university students who have sex with men in Beijing, China: a cross-sectional study. *AIDS Educ Prev*. 2012;24(1):78-88.
Exclusion: Wrong outcomes

Appendix B4. List of Excluded Studies

Zhu L, Gu X, Peng RR, et al. Comparison of the cerebrospinal fluid (CSF) toluidine red unheated serum test and the CSF rapid plasma reagin test with the CSF Venereal Disease Research Laboratory test for diagnosis of neurosyphilis among HIV-negative syphilis patients in China. *J Clin Microbiol.* 2014;52(3):736-40.
Exclusion: Wrong population

Zhuang YH, Tian Y, Chen Y, et al. Evaluation of the Determine Syphilis TP assay for the detection of antibodies against *Treponema pallidum* for the serodiagnosis of syphilis. *Eur J Clin Microbiol Infect Dis.* 2012;31(6):929-35.
Exclusion: Wrong intervention

Zou H, Fairley CK, Guy R, et al. The efficacy of clinic-based interventions aimed at increasing screening for bacterial sexually transmitted infections among men who have sex with men: a systematic review. *Sex Transm Dis.* 2012;39(5):382-7.
Exclusion: Included orriginal studies (no new data)

Zou H, Wu Z, Yu J, et al. Sexual risk behaviors and HIV infection among men who have sex with men who use the internet in Beijing and Urumqi, China. *J Acquir Immune Defic Syndr.* 2010;53(Suppl 1):S81-7.
Exclusion: Population not applicable to U.S. population

Zou S, Notari EP, Fang CT, et al. Current value of serologic test for syphilis as a surrogate marker for blood-borne viral infections among blood donors in the United States. *Transfusion*. 2009;49(4):655-61.
Exclusion: Wrong population

Cohort Studies[1,2]

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[1,2]

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

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

Author, Year	Population, *n*	Interventions	Duration	Attrition	Outcomes	Quality
Bissessor et al, 2010[56] (see text)	1,031 MSM attending a public STI clinic in Australia, offering HIV care to 20% of men in the region	Routine syphilis screening every 3 months as part of HIV monitoring vs. annual screening (control)	1 year	NR	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	Fair
Bissessor et al, 2011[59]	6,789 consultations with MSM attending public STI clinic in Australia, offering HIV care to 20% of men in the region	A computer alert system aimed at clinicians to screen higher risk MSM (>10 partners in 12 months) for syphilis every 3 months vs. annually (control)	1 year	NR	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	Fair
Cohen et al, 2005[57]	2,389 HIV patients in the UK with newly positive syphilis serology, asymptomatic at the time of screening	Routine syphilis screening every 3 months vs. annual screening (control)	1 year	NR	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<0.05	Fair
Zou et al, 2013[58]	4,514 MSM attending public STI clinic in Australia, opting to receive clinical reminders	3, 6, or 12 month clinical reminders vs. control	18 months	NR	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)	Fair

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

Author, Year	KQ?	Did the study attempt to enroll a random sample or consecutive patients meeting inclusion criteria (inception cohort)?	Were the groups comparable at baseline?	Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	Were outcome assessors and/or data analysts blinded to treatment?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality
Bissessor et al, 2010[56]	KQ1	Yes-- consecutive	Yes	Yes	No	No	Unclear	Unclear	Yes	Fair
Bissessor et al, 2011[59]	KQ1	Yes-- consecutive	Yes	Yes	No	No	Unclear	Unclear	Yes	Fair
Cohen et al, 2005[57]	KQ1	Yes-- consecutive	Yes	Yes	No	No	Unclear	Unclear	Yes	Fair
Zou et al, 2013[58]	KQ1	Yes	Yes	Yes	No	No	Yes	Unclear	Yes	Fair

Abbreviation: KQ=key question.

Appendix C3. Diagnostic Accuracy of Syphilis Testing

Study, year	Screening test	Definition of a positive screening test	Reference standard(s)	Country, setting
Juárez-Figueroa et al, 2007[62]	TPPA	Samples that tested positive to VDRL and FTA-ABS were defined as serologically active syphilis	VDRL screening with FTA-ABS confirmation	Mexico STI clinic
Wong et al, 2011[60]	Trep-Sure EIA	Samples that tested positive by TPPA confirmation test	VDRL screening with TPPA confirmation	U.S. Routine syphilis testing
Tsang et al, 2007[61]	Trep-Check IgG EIA	Consensus results were derived from conventional serologic tests, both screening (RPR, VDRL, or EIA) and confirmatory (FTA-ABS, INNO-LIA, or TPPA). Probable past syphilis infection was indicated if samples were negative by screening EIA but positive by confirmatory treponemal assay. Probable active syphilis infection was indicated if samples were positive by both the screening EIA and confirmatory treponemal assay.	RPR, VDRL, or EIA screening with FTA-ABS, INNO-LIA, or TPPA confirmation	Canada National Microbiology Laboratory

Study, year	Population characteristics	Sample size, Proportion with condition	Proportion unexaminable by screening test	Analysis of screening failures
Juárez-Figueroa et al, 2007[62]	Asymptomatic female sex workers	198 31/198 (15.7%) tested positive	False-positive results, defined as VDRL positive with negative FTA-ABS, or previously treated syphilis were not included in the analysis	NR
Wong et al, 2011[60]	Patients presenting to the San Francisco municipal sexually transmitted diseases clinic. Population at this clinic is 69.3% MSM, 16.6% HIV positive.	674 samples 39.7% tested positive for syphilis Clinic has a 9.4% prevalence rate	0/674	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.
Tsang et al, 2007[61]	Specimens from local hospitals or provincial public health laboratories submitted for confirmation of local test results or for further evaluation of serologic status.	34/604 (5.6%)	NA	Discordant test results also examined with INNO-LIA immunoassay.

Study, year	Proportion included in analysis	Sensitivity, Specificity, PPV, NPV (95% CI)	False-positives, False-negatives
Juárez-Figueroa et al, 2007[62]	185/198 (93%)	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%)*	FP: 0 FN: 4/185
Wong et al, 2011[60]	673/674 samples included in analysis. One sample did not have adequate volume for confirmation testing and was excluded.	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%)*	FP: 5/673 FN: 6/673

Appendix C3. Diagnostic Accuracy of Syphilis Testing

Study, year	Proportion included in analysis	Sensitivity, Specificity, PPV, NPV (95% CI)	False-positives, False-negatives
Tsang et al, 2007[61]	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* partical agglutination; TRUST=toluidine red unheated serum test; VDRL=Venereal Disease Research Laboratory.

Appendix C4. Quality Ratings of Diagnostic Accuracy Studies

Study, year	Representative spectrum	Random or consecutive sample	Screening test adequately described	Screening cutoffs predefined	Credible reference standard	Reference standard applied to and analysis includes all patients, or a random subset	Same reference standard applied to all patients	Reference standard and screening examination interpreted independently	High rate of uninterpretable results or non-compliance with screening test	Analysis includes patients with uninterpretable results or non-compliance	Quality score
Binnicker et al, 2012[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes	Fair
Juárez-Figueroa et al, 2007[62]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Fair
Mishra et al, 2011[63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes	Fair
Tsang et al, 2007[61]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Fair
Wong et al, 2011[60]	No	No	Yes	No	Yes	Yes	Yes	Unclear	No	Yes	Fair

Appendix C5. Comparison of Traditional and Reverse Algorithms for Syphilis Testing

Study, year	Reverse screening algorithm	Traditional screening algorithm	Definition of a positive screening exam	Type of study	Country Setting
Mishra et al, 2011[63]	August 2005-July 2008 EIA screening followed by RPR testing and an alternate treponemal confirmatory test.	August 1998-July 2005 RPR screening and confirmatory treponemal test	Screen-positive samples defined as reactive RPR or positive/indeterminate EIA on >1 duplicate tests of sample. Confirmed positive if a treponemal test (TPPA, FTA-ABS, or microhemagglutination assay) was positive.	Retrospective cohort	Canada Laboratory
Binnicker et al, 2012[28]	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.	RPR screening followed by TPPA	**Reverse algorithm:** MFI+/RPR or TPPA+ **Traditional algorithm:** RPR+/TPPA+	Prospective cohort study	U.S. Laboratory

Study, year	Population Characteristics	Sample size Proportion with condition	Analysis of screening failures	Results from traditional screening algorithm
Mishra et al, 2011[63]	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.	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	NR	0.59% of samples screened positive and 0.46% of samples were confirmed positive
Binnicker et al, 2012[28]	Low-prevalence patient population	n=1,000 samples submitted for routine syphilis testing	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.	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.

Study, year	Results from reverse screening algorithm	Outcomes	Quality rating
Mishra et al, 2011[63]	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<0.001).	Screening with EIA resulted in an increased diagnosis of syphilis which would not have been detected under screening with RPR. 74.7% (95% CI, 73.6% 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%	Fair

Appendix C5. Comparison of Traditional and Reverse Algorithms for Syphilis Testing

Study, year	Results from reverse screening algorithm	Outcomes	Quality rating
Binnicker et al, 2012[28]	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.	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.	Fair

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.