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Screening for Syphilis Infection in Nonpregnant Adolescents and Adults: A Targeted Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: To systematically update the evidence to support the U.S. Preventive Services Task Force (USPSTF) in reaffirming its 2016 A recommendation for screening for syphilis infection in asymptomatic, nonpregnant adults and adolescents who are at increased risk for syphilis infection. This targeted evidence update includes three key questions (KQ): KQ1) effectiveness of screening for syphilis in reducing complications of the disease and transmission or acquisition of other sexually transmitted infections in asymptomatic, nonpregnant, sexually active adolescents and adults, KQ2) performance of risk assessment instruments or other risk stratification methods for identifying persons at increased risk for syphilis, and KQ3) harms of screening for syphilis infection.

Data Sources: We conducted a literature search of MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2016, to October 28, 2020.

Study Selection: We screened 2,780 abstracts and 40 full-text articles against *a priori* inclusion criteria. We included asymptomatic, nonpregnant adolescents and adults who are not known to have current syphilis infection. We excluded studies conducted exclusively in populations with HIV where screening may be part of disease management, and those studies conducted in low to middle income countries.

Data Analysis: Two investigators independently critically appraised each article that met inclusion criteria using design-specific criteria. One investigator abstracted data into an evidence table and a second investigator checked these data. We provide a narrative synthesis of the newly identified evidence since the prior recommendation by key question.

Results: We included one study for KQ1, one study for KQ2, and one study for KQ3.

KQ1: One fair-quality cohort study (n=117,387) demonstrated that increases in the proportion of men who have sex with men (MSM) screened annually and the mean number of tests per MSM performed annually were associated with a 17 to 22 percent increase in the proportion of early latent syphilis infections identified and a 5 to 19 percent decrease in the proportion of secondary syphilis infections identified, during an 8-year followup period.

KQ2: One fair-quality risk assessment study (n=361) developed and evaluated an online risk calculator for predicting future syphilis among high-risk individuals seeking sexually transmitted infection (STI) testing or treatment. The final model for predicting syphilis incidence within the next three months demonstrated an area under the curve of 0.69 and included the following risk factors: current HIV infection, history of syphilis infection, number of male sex partners in the prior three months, and sex role for anal sex in the prior three months.

KQ3: One fair-quality pre-post study (n=1,097) assessed factors associated with a stressful syphilis testing experience. The results suggest that emotional stress may be a common experience for individuals both pre- and post-testing, although did not compare levels of emotional stress pre- versus post-testing. Factors associated with increased stress experience included history of injected drug use, Black race/ethnicity, less than a high school education, and Single marital status.

Limitations: Our review did not address the test accuracy of screening, although does summarize the test accuracy of traditional versus reverse sequence testing, and rapid point-of-care testing in the Discussion. Our review focused on the interval evidence since the previous USPSTF in 2016, although we provide commentary of the consistency of our findings compared with the prior review's findings in the Discussion. Due to recruitment and settings of included studies conducted outside the U.S., finding from these studies may have limited applicability to screening in a US-based primary care population. No studies were conducted specifically in adolescent populations.

Conclusions: Screening for syphilis in persons at increased risk of infection is currently recommended by the USPSTF and is the standard of care in the United States. The findings of this brief evidence update are consistent with the prior evidence review. Further research on how to best identify those most likely to benefit from screening and the effectiveness of specific screening intervals among different risk populations is still needed.

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Chapter 1. Introduction

Condition Background

Condition Definition

Syphilis is a genital ulcerative disease caused by the bacterium *Treponema pallidum* (*T. pallidum*) that is transmitted through sexual activity.[1] Depending on the stage of infection, syphilis can cause a variety of symptoms and, if left untreated, can lead to significant health complications as well as an increased risk of acquisition or transmission of human immunodeficiency virus (HIV).[1, 2] Case definitions for the stages of syphilis were updated in 2018 by the Centers for Disease Control and Prevention (CDC).[3]

Prevalence and Burden

In 2000 and 2001, the rate of reported primary and secondary syphilis cases in the United States reached a historic low of 2.1 cases per 100,000 population.[4] Since then, syphilis has increased almost every year, rising 11.2 percent from 2018 to 2019.[5] In 2019, 129,813 cases of all stages of syphilis (39.7 cases per 100,000 population) were reported to the CDC,[6] up 75 percent from 2015. Total number of cases included 38,992 cases of primary and secondary syphilis (11.9 cases per 100,000 population).[7] The CDC estimates that, in 2018, the direct medical cost of syphilis in the United States was $174 million.[8]

The Western region of the United States had the highest rate of reported primary and secondary syphilis cases (16.9 cases per 100,000 population) in 2019, followed by the South (12.2 cases per 100,000 population), the Northeast (9.8 cases per 100,000 population), and the Midwest (7.4 cases per 100,000 population).[7] Between 2018 to 2019, the primary and secondary syphilis rate increased 4.2 percent in the Midwest, 10.9 percent in the South, 13.4 percent in the West, and 12.6 percent in the Northeast. Rates also vary by state and within states by county and city/metro area. In 2019, the highest case counts were observed in the state of Nevada and in Los Angeles County, California. The CDC offers up to date rates by states, counties, and city/metro areas online.[9]

Etiology and Natural History

Transmission of syphilis occurs when an infectious lesion (which may or may not be visible) contacts the skin or mucous membrane of an uninfected person. Syphilis can also be transmitted vertically from mother to fetus in utero, or mother to infant during vaginal delivery. Syphilis in pregnancy and congenital syphilis are covered in a separate review and recommendation,[10, 11] and will therefore not be covered by this review. Syphilis is sexually transmissible during the primary and secondary stages of infection.[12] The average risk of transmission after sexual exposure is estimated at 33 percent.[13, 14] The time between the acquisition of syphilis and manifestation of symptoms can range from 10 to 90 days, with an average time of 21 days.[1]

Syphilis is divided into stages according to duration and clinical symptoms (Figure 1). Primary syphilis is characterized by one or more ulcerative lesions (i.e., chancre) that appear at the original site of infection, such as on or inside the genitals, mouth, or rectum.[1] Untreated primary syphilis will move to the secondary stage of infection within one to two months with varying symptoms, which include: skin rash that commonly includes the palms of the hands and the soles of the feet, mucous membrane lesions, swollen lymph nodes, fever, sore throat, patchy hair loss, headaches, weight loss, muscle aches, and fatigue.[1] Like the primary stage, symptoms typically resolve within three to six weeks without therapy. Primary and secondary syphilis symptoms can coincide, particularly for persons living with HIV.[1] Several recent studies suggest syphilis re-infections are more likely to be asymptomatic than initial infection.[15-17]

Untreated secondary syphilis will progress to the latent and possibly tertiary stage of disease.[1] The latent (hidden) stage of syphilis is a period in which there are no visible signs or symptoms of syphilis and can last for years. However, without treatment, the infected person will continue to have syphilis in their body. Tertiary syphilis is rare and develops in approximately one-third of untreated syphilis cases.[18] Tertiary syphilis can appear up to 10 to 30 years after infection was first acquired, can affect multiple organ systems (e.g., nervous system, cardiovascular system, musculoskeletal). At any stage of the infection, syphilis can impact the nervous system (i.e., neurosyphilis) and cause a wide range of symptoms, including difficulty coordinating muscle movement, headaches, altered behavior, sensory deficits, dementia, and paralysis.[19] Among all reported syphilis cases, the prevalence of neurosyphilis from 2009 to 2015 was low (0.84%), but this may be an underestimate of the true burden in the United States.[20] Ocular syphilis can also occur at any stage of infection. Symptoms of ocular syphilis include vision changes, decreased visual acuity, and permanent blindness.[1] A review of ocular syphilis in 8 U.S. jurisdictions found ocular manifestations from syphilis in 0.61 percent of total syphilis cases, increasing from 0.53 percent in 2014 to 0.65 percent in 2015.[21] While syphilis may ultimately be fatal, syphilis related deaths are now rare in the United States.[22] Between 1968 and 2015, there were 6,498 deaths attributed to syphilis. Annual syphilis deaths decreased from 586 in 1968 to 94 in 1984, then leveled off to between 24 to 46 deaths annually since 1998.

Risk Factors

There are known demographic factors, such as sex, age, race, and ethnicity associated with higher risk for syphilis, as is a prior history of syphilis infection (**Table 1**). There are also specific groups of individuals, such as men who have sex with men (MSM) and individuals living with HIV, who are at increased risk for syphilis. These disparities are unlikely to be explained entirely by differences in individual level sexual behavior.[23] More likely, these disparities reflect a combination of factors including social determinants of health (e.g., disparities of income, low educational achievement, unstable housing), differential health insurance coverage or access to quality health care, and funding cuts for sexually transmitted disease programs at the state and local level. For example, areas with greater racial and ethnic disparities of income also tend to be areas with higher STI rates.[24] Differences in sexual network characteristics may also play a role. For example, individuals who live in communities with a greater prevalence of sexually transmitted infections have an increased chance of encountering an infected partner with each sexual encounter than those in lower prevalence settings do.[4, 25]

Demographic Risk Factors

Since 2001, rates of syphilis have increased in both males and females and among all racial and ethnic groups. The 2019 CDC sexually transmitted disease surveillance report highlights significant disparities in rates of syphilis by many demographic factors including sex or gender, age, and race and ethnicity (**Figures 2 and 3**).[4] In 2019, the rate of reported primary and secondary syphilis cases (approximating incidence) among men was much higher than the rate among women (20.1 cases and 3.9 cases per 100,000, respectively) and men accounted for a large majority (83.1%) of cases (**Figure 2**).[4] In men, the rate of primary and secondary syphilis has increased every year since 2000, likely attributable to parallel increases in cases among MSM (see MSM section below). Between 2018 and 2019, the rate among men increased 8.1 percent. In comparison, the primary and secondary syphilis rate among women varied between 0.8 and 1.7 cases per 100,000 females between 2000 to 2013 but has increased significantly since 2013. Although rates of primary and secondary syphilis are lower among women, rates have increased significantly in recent years, increasing 178.6% during 2015 to 2019.[4]

In terms of age-associated risk, the overall rate of reported primary and secondary syphilis cases increased from 2018 to 2019 in all adolescent (15-17 years) and adult age groups.[4] In 2019, the highest rates of reported primary and secondary syphilis cases were observed among persons aged 25 to 29 years (**Figure 2**). Among racial and ethnic groups, the rate of reported primary and secondary syphilis cases was highest among Black adolescents and adults (31.0 cases per 100,000 population), which was 4.7 times the rate among White adolescents and adults (6.6 cases per 100,000 population). The lowest rates were observed in Asian adolescents and adults (4.6 cases per 100,000 population) (**Figure 3**).[4]

Regarding syphilis-related mortality risk, Barragan and colleagues examined all syphilis-related deaths in the United States Multiple Cause of Death dataset for the period 2000 to 2014.[26] A total of 1,829 deaths were attributed to syphilis and 32 percent identified syphilis as the underlying cause of death. Most decedents were men (60%) and either Black (48%) or White (39%). Decedents aged 85 years or older had the highest average mortality rate (0.47 per 100,000 population).

Men Who Have Sex with Men (MSM)

Several recent studies have highlighted the disproportionate rates of syphilis among gay, bisexual, and other men who have sex with men (known collectively as MSM), who are estimated to account for 4 to 6 percent of men in the United States.[27-30] Recently, the CDC used MSM population estimates to produce the first estimates of state-specific rates of primary and secondary syphilis among MSM in the United States.[31] Among 44 states reporting information on the sex of sex partners, the overall rate of primary and secondary syphilis among MSM was 309.0 per 100,000, compared with 17.5 per 100,000 for all men, and 2.9 per 100,000 among men who reported sex with women only. The overall rate of primary and secondary syphilis among MSM was 106.0 times the rate among men who have sex with women (MSW) only and 167.5 times the rate among women. According to the most recent CDC STD Surveillance report, case counts among MSM stabilized between 2018 and 2019. However, MSM are still

disproportionately impacted, accounting for a majority (56.7%) of all male primary and secondary syphilis cases among men in 2019.[4]

Within the broader MSM population, disparities in syphilis rates exist that mirror those in the general population. A recent systematic review of syphilis trend studies published between 2004 and 2015 reported the greatest increases in syphilis infections occurring in MSM between 20 and 29 years old and in racial minority MSM.[28] Similarly, a more recent study by Sullivan and colleagues (2018)[29] utilized state-level surveillance data to estimate syphilis prevalence by race and ethnicity. They reported that rates of syphilis diagnoses were consistently higher for Black MSM than for White MSM in 42 of 44 states (state rate ratio [RR] range = 0.89 [Hawaii] to 17.11 [Alaska]).

Individuals Living With HIV

Individuals living with HIV are at greater risk of contracting syphilis.[28, 31, 32] Some studies have suggested that HIV infection may alter the clinical presentation of syphilis (e.g., greater organ involvement, more rapid progression to neurosyphilis) as well as response to syphilis treatment. Syphilis may also cause a transient increase on HIV viral load during infection.[33] According to the most recent CDC STD surveillance report, cases of primary and secondary syphilis continue to be associated with a high rate of HIV co-infection, particularly among MSM. Among primary and secondary syphilis cases with known HIV status reported in 2018, 41.6 percent of cases among MSM were HIV-positive, compared with 7.9 percent of cases among MSW, and 4.0 percent of cases among women.[31] Because syphilis is known to be associated with HIV coinfection, identification of persons infected with syphilis may also help to reduce rates of HIV infection.

Individuals Using Preexposure Prophylaxis for the Prevention of HIV (PrEP)

The CDC recommends that all adults prescribed PrEP should be screened for syphilis both at initiation of therapy and at semi-annual visits.[34] There is some evidence that the risk of bacterial STIs increases following initiation of HIV PrEP, presumably due to changes in high-risk sexual behaviors, such as decreased condom use.[35] A 2018 systematic review of 17 studies reported an increase in condomless anal sex and bacterial STIs, especially rectal infections, among MSM following PrEP use.[36] However, a 2019 study comparing incidence rates of STIs among PrEP naïve MSM before and after initiating treatment found that while incidence rates of STIs in general increased (IRR 1.71; 95% CI 1.49-1.96, p<.001), there was no significant increase in syphilis infections observed (IRR 1.24; 95% CI 0.87-1.78, p=0.24).[37]

Other High-Risk Populations

Other population subgroups known to be at greater risk of syphilis include sex workers,[32] adults in correctional facilities,[32] United States-bound refugees,[38] and military personnel.[39] The risk of STIs in general are high among individuals who exchange sexual services in exchange for money or goods. However, the prior review found no U.S. based studies published in the prior 10 years reporting information on syphilis prevalence among sex workers.[32] The current review also found no U.S. based studies published in the interim, however recent studies of sex workers

outside the U.S. (e.g., Brazil, China) have reported prevalence of syphilis ranging from 4 to 14 percent.[40, 41]

Individuals living in correctional facilities accounted for 11 percent of all primary and secondary syphilis cases reported to the CDC in 2019.[4] In incarcerated populations, syphilis rates are highest in MSW, followed by women, and then MSM.

Nyangoma and colleagues (2017) reported syphilis screening results for all U.S. bound refugees (age 15 or older) from 2009 through 2013.[38] Among 233,446 refugees, 874 syphilis cases were detected (373 cases per 100,000 refugees). The highest prevalence rates were observed in refugees from Africa (1340 cases per 100,000), followed by East Asia and the Pacific (397 cases per 100,000). Male sex, increasing age, and living in non-refugee camp settings were associated with increased risk of syphilis seropositivity. It is important to note that all U.S. bound refugees aged 15 and older are already required to be screened for syphilis per immigration regulations.

Deiss and colleagues (2016) reported STI incidence rates in N=100,005 military personnel between 1997 and 2011.[39] The syphilis incidence rates (per 100 person-years) for women and men, respectively, were 0.14 and 0.15. In multivariate analyses, factors associated with higher rates of STIs in this population included African American race, younger age, and fewer years of education. In the overall sample, increasing number of years of service was associated with an increased likelihood of an STI diagnosis ($p<0.001$ for trend).[39]

Screening

Screening strategies for syphilis are generally based on risk. Universal screening may be recommended in high prevalence populations, or targeted screening may be recommended based on an individual's risk (see Current Clinical Practice section below). For example, the CDC recommends opt-out screening in correctional facilities based on the local area and institutional prevalence,[19] and the Infectious Diseases Society of America (IDSA) recommends individuals at higher risk for syphilis be tested every 3 to 6 months instead of annually.[42]

Numerous screening tests for syphilis exist (**Table 2**). There are two different categories of serologic (blood antibody) tests based on the type of antigen the antibodies are targeted against. Nontreponemal tests detect antibodies targeted against lipoidal antigens, damaged host cells, and possibly treponemal phospholipids.[43] Treponemal tests detect antibody to *T. pallidum* proteins. Traditionally, screening for syphilis infection is a two-step process that involves an initial nontreponemal test followed by a confirmatory treponemal test (aka "traditional algorithm"). A more recent testing algorithm (aka "reverse sequence syphilis screening" or treponemal test first) was first described by the CDC in 2008[44] and is increasingly being used, especially in high-volume laboratories.[43] Rapid point-of-care (POC) tests are also increasingly being utilized, and are typically treponemal versus non-treponemal.[45] These tests offer results within a short period of time (typically within 5 to 30 minutes), at or near the site of patient care. Both screening strategies are reviewed in more depth as contextual questions (CQ2 and CQ3) in the Discussion section. The syphilis tests commonly used in the U.S. are known to have adequate sensitivity and

specificity, although these performance characteristics vary by the type of test utilized (nontreponemal vs. treponemal) and disease stage (**Table 3**).

While optimal screening intervals are not well established for most populations at risk for syphilis, individuals at higher risk may benefit from more frequent screening. The CDC and IDSA recommend that sexually active MSM and individuals living with HIV be tested at least annually for syphilis.[16,29] Testing every 3 to 6 months is recommended for MSM at elevated risk.[19, 42] While there is some evidence that testing has significantly increased among sexually active HIV-infected adults in the U.S., there is still room for improvement.[46, 47] For example, in California, fewer than two-thirds of Medicare HIV-positive enrollees and fewer than three-quarters of Medicaid HIV-positive enrollees received a syphilis test in 2010.[48] Similarly, from 2013 to 2014, nearly one-third of sexually active HIV-positive MSM were not tested annually, and many MSM at increased risk were not tested at the recommended frequencies.[27]

Treatment Approaches

The effectiveness of penicillin G for the treatment of primary, secondary, and latent syphilis is well established. 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 infection.[19] Penicillin is safe and resistance has not been observed in *T. pallidum*.[12] For penicillin-allergic persons, evidence regarding treatment alternatives (e.g., doxycycline, tetracycline, ceftriaxone, azithromycin) for early syphilis is limited. The CDC cautions that alternative therapies should be used only in conjunction with close clinical and laboratory followup.[19] Potential harms of treatment include adverse drug-related effects, the most severe of which is anaphylaxis. However, true penicillin allergies are rare and the estimated frequency of anaphylaxis is 1-5 per 10,000 cases of penicillin therapy.[49] The Jarisch-Herxheimer reaction is an acute febrile reaction, more commonly among patients with early syphilis, which can occur within the first 24 hours after the initiation of any syphilis treatment.[19]

Previous U.S. Preventive Services Task Force Recommendations and Current Clinical Practice

The USPSTF has had a longstanding A recommendation to screen nonpregnant persons at increased risk as well as all pregnant persons since 1996;[50] these recommendations were most recently updated in 2016 and 2018, respectively.[11, 51-53] In the 2016 recommendation,[51] the USPSTF found overall that screening for syphilis infection in persons who are at increased risk for infection is effective (**A Recommendation**). High-risk groups included MSM, persons living with HIV, and persons living in communities with a high prevalence of infection. The identification of high-risk groups was based on epidemiologic data from the CDC. The USPSTF concluded that accurate screening tests are widely available and effective treatment with antibiotics can help prevent progression to late-stage disease. Furthermore, small harms were associated with treatment, providing an overall substantial health benefit. The USPSTF found no evidence regarding the effectiveness of screening on clinical outcomes. Lastly, no evidence regarding the performance of risk assessment instruments or risk stratification methods for identifying individuals at greater risk of infection, nor harms of screening, were found.

In addition to the USPSTF, other organizations generally recommend routine screening for syphilis in nonpregnant persons at increased risk for infection, although the definitions and criteria for 'at risk' and suggested intervals of screening vary (**Table 4**). The CDC recommends opt-out screening based on local prevalence of early syphilis infection and advises at least annual screening in sexually active MSM with confirmatory testing for individuals with reactive serology.[19] The Public Health Agency of Canada recommends screening for anyone presenting with risk factors for syphilis to prevent complications, transmission, and reinfection.[54] The HIV Medicine Association of the Infectious Diseases Society of America recommends that all patients living with HIV be screened for syphilis on initiation of care and periodically thereafter, depending on risk.[42]

While there is general agreement among professional organizations to screen for syphilis, screening remains suboptimal. Evidence from several studies indicates that 30 to 50 percent of primary care clinicians routinely screen patients for STIs.[55-58] Lower screening may be due to several factors, including reluctance of insurance companies to cover STI screening; stigma and stereotypes associated with STIs and HIV; time constraints of providers to discuss sexual history or assess high-risk behaviors; decreased funding for STI services and subsequent closure of clinics; restrictive policy barriers and state requirements; limited access to resources (e.g., rapid screening tests, patient education resources).[56, 59-61]

Chapter 2. Methods

Purpose and Scope

The USPSTF will use this evidence update to update its 2016 recommendation on screening nonpregnant adults and adolescents for syphilis infection.[32, 51] Topics that represent well-established, evidence-based standards of practice that are within the scope of the USPSTF and remain a USPSTF priority (i.e., the USPSTF has a reason to keep the recommendations active) undergo an updating process known as "reaffirmation."[62] The aim for targeted evidence updates supporting the reaffirmation process is to identify "new and substantial evidence sufficient enough to change the prior recommendation."[62] As such, only specific key questions included in the previous review on screening for syphilis in nonpregnant adults and adolescents were updated in this review. While we did not systematically review the evidence on the diagnostic accuracy of screening in this update, a summary of what is known is presented in the introduction and discussion sections of this report.

Key Questions and Analytic Framework

In consultation with members of the USPSTF, we developed an analytic framework (**Figure 4**) and three Key Questions (KQs) to guide our evidence update.

Key Questions

1. What is the effectiveness of screening for syphilis in reducing complications of the disease and transmission or acquisition of other sexually transmitted infections in asymptomatic, nonpregnant, sexually active adolescents and adults?
    a. What is the effectiveness of specific screening intervals and screening among population subgroups (e.g., based upon demographic characteristics or risk factors)?
2. What is the performance of risk assessment instruments or other risk stratification methods for identifying persons at increased risk for syphilis?
3. What are the harms of screening (e.g., stigma, sequelae of test inaccuracy)?

Contextual Questions

Contextual questions were not systematically reviewed and are not shown in the Analytic Framework. Our findings for these questions are summarized in the Introduction (Chapter 1) and Discussion sections (Chapter 4).

1. Which population subgroups are at highest risk for incident syphilis infection and syphilis-related morbidity and mortality? (Introduction)
2. What are the benefits and tradeoffs of screening with reverse sequence testing (i.e., using a treponemal test for initial screening followed by a nontreponemal test for confirmation)

compared to the traditional sequence testing algorithm (i.e., a nontreponemal test followed by a treponemal test)? (Discussion)
3. What is the clinical test performance of rapid point-of-care antibody tests? (Discussion)

Data Sources and Searches

We conducted a literature search of MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2016, to October 28, 2020. We worked with a research librarian to develop our search strategy, which was peer-reviewed by a second research librarian (**Appendix A**). We supplemented these searches by reviewing reference lists of recent reviews and primary studies. We limited our searches to articles published in English. We managed literature search results using Endnote® version X7 (Thomson Reuters, New York, NY).
A bridge search was conducted from October 29, 2020, to June 3, 2021, and no additional studies meeting inclusion criteria were identified.

Study Selection

We developed specific inclusion criteria to guide study selection (**Appendix A Table 1**). Two reviewers independently reviewed the titles and abstracts of all identified articles using DistillerSR (Evidence Partners, Ottawa, Canada). Two reviewers then independently evaluated the full text of all potentially relevant articles. We resolved differences in the abstract or full-text review by discussion. For all KQs, we included asymptomatic, nonpregnant adolescents and adults who are not known to have current syphilis infection, including persons who are infected with other STIs. However, we excluded studies conducted exclusively in populations for which syphilis screening may be part of disease management, such as persons living with HIV. We included studies conducted in primary care and primary care-referable settings (e.g., school-based clinics, family planning clinics, obstetrics and gynecology clinics, STI clinics, urgent care clinics, emergency departments, community settings, and correctional facilities) in countries categorized as "high" or "very high" on the 2019 Human Development Index.

For evidence on the benefits and harms of screening for syphilis (KQ1 and KQ3, respectively), we included systematic reviews, randomized controlled trials, and nonrandomized studies (NRS) with contemporaneous control groups. Given the paucity of studies (for harms), we broadened our inclusion criteria to also include quasi-experimental studies (e.g., pre-post design). We included studies using any screening strategy. For KQ1, we included studies reporting complications of syphilis infection and transmission or acquisition of STIs, including HIV. Cost-effectiveness studies, cost-related outcomes, and outcomes not directly related to health outcomes (e.g., laboratory studies) were excluded. For KQ3, we selected studies reporting harms from screening (e.g., stigma, sequelae of test inaccuracy). For evidence on the performance of risk assessment instruments or other risk stratification methods for identifying persons at increased risk for syphilis (KQ2), we included systematic reviews and risk prediction studies reporting any measure of discrimination (e.g., area under the curve [AUC], c-statistic) for identification of infection.

Quality Assessment and Data Abstraction

Two reviewers independently assessed the methodological quality of each included study using predefined criteria (**Appendix A Table 2**). We rated articles as good, fair, or poor quality. In general, a good-quality study met all criteria. A fair-quality study did not meet, or it was unclear whether it met, at least one criterion, but also had no known important limitations that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations. We excluded all poor-quality studies from this review. Disagreements were resolved by discussion. One reviewer extracted important study and participant characteristics and outcomes in an Excel spreadsheet, and a second reviewer checked abstracted information for accuracy. We then synthesized the evidence from included studies in a narrative format.

Data Synthesis and Analysis

This targeted update synthesized the evidence published since the USPSTF last considered this topic in 2016. Therefore, the narrative synthesis does not include older evidence previously considered by the USPSTF. Given the limited number of trials for each KQ, we did not conduct any quantitative synthesis. To understand the totality of the evidence for these key questions, we included a summary table comparing the findings of the interval evidence (**Table 5**) to the previous review supporting the 2016 recommendation.

Expert Review and Public Comment

A draft Research Plan for this review was available for public comment from November 19 to December 23, 2020. Comments generally requested clarification on outcomes being considered, population diversity, non-pharmacologic treatments, testing regimen and harms, and inclusion of high-risk populations. Based on comments received, we clarified language of health outcomes in the analytic framework. The remaining comments were either already included in the research plan or beyond the scope of this review. A final research plan was posted on the USPSTF's website on January 28, 2021.

A draft version of this report underwent external peer review from two content experts and invited representatives of Federal partners. All reviewer comments and their disposition will be presented to the USPSTF and revisions in response to comments are reflected in this report. A draft of this report will be posted for public comment on the USPSTF website along with the accompanying USPSTF draft recommendation statement.

USPSTF and AHRQ Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and key questions and to resolve issues around scope for the final evidence synthesis. AHRQ staff provided oversight for the project, coordinated

systematic review, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Chapter 3. Results

Literature Search

Our literature search yielded 2,780 unique citations. From these citations, we accepted 40 articles for review based on titles and abstracts (**Appendix A Figure 1**). After reviewing the full-text articles and conducting critical appraisal, we included three studies reported in five publications: one study for KQ1 (1 article)[63], one study for KQ2 (2 articles)[64, 65], and one study for KQ3 (2 articles)[66, 67] (**Appendix B**). **Appendix C** contains a list of all full-text articles and their reasons for exclusion.

Key Question 1. What Is the Effectiveness of Screening for Syphilis in Reducing Complications of the Disease and Transmission or Acquisition of Other Sexually Transmitted Infections in Asymptomatic, Nonpregnant, Sexually Active Adolescents and Adults?

One fair-quality cohort study[63] examined trends in syphilis testing and detection of early syphilis among sexually active MSM attending a national sentinel network of 46 publicly funded sexual health clinics participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS). This study demonstrated that screening in MSM was associated with greater detection of early asymptomatic syphilis and a decrease in secondary syphilis, suggesting that screening is likely to have interrupted the progression of syphilis. The study did not report loss to followup data (i.e., retention of participants during the study period) and did not statistically adjust for potential confounding variables (e.g., number of partners or high-risk sexual behaviors). Furthermore, the study was conducted outside the U.S. and the population was limited to MSM, which may limit the applicability of findings to U.S. primary care settings that serve a broader population.

Between 2007 and 2014, 359,313 clinic visits (N=117,387) were identified and included in the trend analyses. The median age of the population was 33 years (range 25-52 years). Most patients identified as White, with only 2 percent identifying as Aboriginal and/or Torres Strait Islander. Most patients (68%) were HIV-negative MSM. Syphilis screening throughout the study period was based on *T. pallidum* immunoassays using a reverse sequence screening algorithm. Diagnoses were made by clinicians at the clinics based on Australian Department of Health definitions. If a patient had previously been treated for syphilis, a rise in rapid plasma reagin (RPR) titer was considered evidence of repeat infection.

During the 8-year followup period, the proportion of men tested for syphilis annually increased significantly in both HIV-negative (N=97,895) and HIV-positive men (N=19,492); 48 percent to 91 percent and 42 percent to 77 percent, respectively ($p_{trend} < 0.0001$). The mean number of tests also increased significantly from 1.3 to 1.6 tests per man per year in HIV-negative ($p_{trend} <$

.0001) and from 1.6 to 2.3 in HIV-positive ($p_{trend} < 0.0001$) men, resulting in detection of 2,799 (3%) syphilis cases in HIV-negative men and 1,032 (5%) syphilis cases in HIV-positive men during the study period. More importantly, the proportion of *early latent infections* detected increased from 27 percent to 44 percent in HIV-negative men and 23 percent to 45 percent in HIV-positive men ($p_{trend} < 0.0001$), while the proportion of *secondary infections* detected decreased from 24 percent to 19 percent ($p_{trend} = 0.03$) and 45 percent to 26 percent ($p_{trend} = 0.0003$) in HIV-positive and negative men, respectively. The authors concluded, "increases in syphilis screening were associated with increased detection of asymptomatic infectious syphilis for both HIV-positive and HIV-negative MSM nationally, suggesting interruption of syphilis progression."

No studies reported on any of the other outcomes in KQ1 (i.e., acquisition or transmission of other STIs or other complications such as tertiary syphilis or neurosyphilis). No studies meeting our inclusion criteria directly addressed the effectiveness of specific screening intervals in included populations (KQ1a); however, two studies addressing this question in individuals living with HIV are reviewed in the Discussion (Chapter 4).

Key Question 2. What Is the Performance of Risk Assessment Instruments or Other Risk Stratification Methods for Identifying Persons at Increased Risk for Syphilis?

One fair-quality study[64] developed an online risk calculator[68] for predicting future syphilis among high-risk individuals seeking STI testing or treatment in Lima, Peru. The online risk calculator has several potential benefits including allowing individuals to conduct their own self-assessment of risk factors, promotion of health care seeking (e.g., STI testing) for those at higher risk, as well as a tool for counselors to facilitate discussion of specific risk factors with their patients. The study was rated fair quality for excluding participants with no followup data from the model and not using a priori cut points to determine the best predictive model. This study was also conducted outside the U.S., the population was limited to individuals seeking testing or treatment for syphilis, and the variables included in the model would require a detailed clinical and sexual history, potentially limiting the applicability of findings to a U.S.-based primary care population.

The study utilized data from a longitudinal cohort study of MSM and transgender women who were followed quarterly between 2013 and 2016.[65] Among N=361 participants, 78 percent were MSM, 22 percent were transgender women, 36 percent had a history of syphilis, and 35 percent were HIV-infected at baseline. The mean age of participants was 29 years old. Syphilis incidence was 19.9 cases per 100-person years (95% CI, 16.3–24.3). HIV infection (RR 2.22; 95% CI, 1.54 – 3.21) and history of syphilis infection (RR 2.23; 95% 1.62 – 3.64) were significantly associated with incident infection.[64] The predictive model was developed on 70 percent of the dataset and validated on the remaining 30 percent.

Of the six candidate models explored, the final predictive model for syphilis incidence (in the next three months) demonstrated an area under the curve of 0.69 and included the following risk factors: current HIV infection, history of syphilis infection, number of male sex partners in the prior three months, and sex role for anal sex (i.e., receptive versus insertive) in the prior three months. Risk factors that were excluded from the final prediction model included age, use of antiretroviral therapy, condom use for receptive anal intercourse in prior 3 months, and transgender identity.

Key Question 3. What Are the Harms of Screening (e.g., Stigma, Sequelae of Test Inaccuracy)?

One fair-quality, pre-post design study examined factors associated with emotional stress related to POC rapid testing for HIV, hepatitis C, and syphilis.[66] The study findings suggest that emotional stress may be a common experience for individuals both pre- and post-testing, particularly those at high risk. Further, certain demographic and behavioral factors such as age, race, level of education, marital status, and injection drug use may increase the likelihood that an individual will experience stress. The study did not report loss to followup data and limited participation to individuals with specific risk factors which may not be more broadly applicable to other populations being screened for syphilis.

Participants considered to be in high-risk groups were recruited for testing at a behavioral research center in California.[67] Behavioral risk groups were defined as injection drug users (22% of study population); women having at least two sexual partners in the past two years or other high risk sexual behavior (e.g., sex trading; 39%); MSM or men who have sex with men and women (MSMW) (37%); or transgender individuals (1%). Participants were presented with a menu of rapid POC tests and then completed a study-designed "rapid test experience" questionnaire which assessed emotional stress both prior to and after the specimen collection. Specifically, participants were asked to respond to the following yes/no statements: "The idea of getting more than one test was stressful" (pre-test) and "Getting the results of the rapid test was stressful" (post-test). Participants were given the results of the POC tests as soon as they were available (1–40 minutes, depending upon the test used).

Between 2011 and 2013, a total of 1,097 individuals completed STI testing. The study population had a mean age of 39 years (SD=12.7; range 15-77 years), was 44 percent female, and 1 percent transgender. Racial and ethnic groups were reported as: Black participants (35%); Hispanic participants (26%); White participants (26%); Asian, Hawaiian/Pacific Islander, Native American, and multiracial participants (12% combined). Chi-square analyses indicated that the following factors predicted stress at pre-test: injection drug use behavioral risk group (χ^2=12.34, p<.01); Black race and ethnicity (χ^2=12.92, p<0.01); or less than a high school education (χ^2=10.55, p<0.01). Factors that predicted stress at post-test included having less than high school education (χ^2=9.72, p<0.01) or Single marital status (χ^2=17.65, p<0.01). Unfortunately, the study did not report (and cannot infer) the main comparison of interest, that is, changes in stress from pre- to post-testing.

Chapter 4. Discussion

Summary of Evidence

Screening for syphilis in persons at increased risk of infection (based on sociodemographic and behavioral risk factors) is currently the standard of practice in the U.S. While definitions of "at risk" vary across different recommending bodies, the USPSTF described at risk in 2016 as follows: "Men who have sex with men and persons living with HIV have the highest risk for syphilis infection. Other factors that are also associated with increased prevalence rates include a history of incarceration or commercial sex work, geography, race/ethnicity, and being a male younger than 29 years." Overall, risk factors identified in this evidence update were consistent with this definition. Specifically, the most recent CDC STD Surveillance report, and other literature reviewed indicates the following risk factors for syphilis: geography (Western and Southern United States), gender or sex (men or male), age (25 to 29 years in both males and females), race/ethnicity (minority status, other than Asian American), or a member of a high-risk population such as MSM, individuals living with HIV, sex workers, adults in correctional facilities, U.S.-bound refugees, and military personnel. In 2019, the highest rates of syphilis infection were observed in males aged 25 to 29 (58 per 100,000), followed by males aged 30 to 34 (51 per 100,000), and males 20 to 24 (45 per 100,000).

The USPSTF will use this evidence update to update its 2016 recommendation on screening nonpregnant adults and adolescents for syphilis infection.[51] We found very little interval evidence and overall, the evidence was consistent with previous reviews (**Table 5**).

The 2016 review found no studies that directly addressed the effectiveness of syphilis screening. In this update, we found one fair-quality cohort study (n=117,387) that demonstrated that increases in both the proportion of MSM screened annually, and the mean number of tests per MSM performed annually, were associated with a 17 to 22 percent increase in the proportion of early latent syphilis infections identified and a 5 to 19 percent decrease in the proportion of secondary syphilis infections identified, during an 8-year followup period, suggesting an interruption in syphilis progression.[63]

The prior evidence review found no studies evaluating the performance of risk assessment. In this update, one fair-quality risk assessment (n=361) study developed an online risk calculator for predicting future syphilis among high-risk individuals seeking STI testing or treatment.[64] The final model for predicting syphilis incidence within the next three months demonstrated an area under the curve of 0.69 and included the following risk factors: current HIV infection, history of syphilis infection, number of male sex partners in the prior three months, and sex role for anal sex in the prior three months.

The prior evidence review also found no studies assessing the harms of screening for syphilis. In this update, one fair-quality pre-post study (n=1,097) assessed factors associated with a stressful syphilis testing experience, although it did not compare levels of emotional stress pre- versus post-testing.[66] The results suggest that emotional stress may be a common experience for individuals both pre- and post-testing. Factors associated with increased stress experience

included history of injected drug use, Black race, less than a high school education, and single marital status.

While this evidence update did not address screening test accuracy, we do provide a high-level summary of what is known on screening intervals in individuals living with HIV, traditional versus reverse sequence testing algorithms (CQ2) and rapid POC testing (CQ3) in the sections that follow.

Screening Intervals in Individuals Living With HIV

The 2016 review included four non-U.S. observational studies which found that higher rates of earlier detection of syphilis were reported when screening every 3 months compared with 6 or 12 months in MSM or HIV-positive populations.[32] In this update, we found no studies that met our inclusion criteria for KQ1a, but we identified two studies conducted in the U.S. that addressed intervals of screening in HIV-positive populations. Both studies found that increased testing frequency (e.g., every 3 months in one study and every 3 to 6 months in the other) was associated with earlier detection of syphilis and identification of a significant number of cases that would not have otherwise been detected until the next annual examination.[69, 70]

Traditional and Reverse Sequence Testing Algorithms

Modifications in the sequence of syphilis testing have been suggested to reduce time and labor required for screening, and to increase the sensitivity of testing at certain stages of syphilis (**Figure 5, Table 3**). The traditional algorithm utilizes a nontreponemal test as the initial screen and reactive samples are confirmed with a treponemal test. In comparison, the reverse algorithm uses a treponemal test as the initial screen and reactive samples are followed by a nontreponemal test. With the latter approach, contradictory results between the initial treponemal screen and the nontreponemal test are resolved with a second confirmatory treponemal test, preferably one that detects different antigens than the initial screen.[71] A 2015 survey of the College of American Pathologists found that approximately 80 percent of laboratories perform the traditional algorithm, and 20 percent perform the reverse algorithm, when a single algorithm is offered at their facility.[72]

A 2020 narrative review by Ortiz and colleagues addressed the pros and cons of using the traditional or reverse algorithm for diagnosis of syphilis by summarizing 69 relevant articles published between 2000 and 2016.[71] Deciding factors in determining appropriate use of traditional versus reverse sequence testing include the volume of testing, test-accuracy, the patient population being tested (i.e., high- versus low-risk), and cost-effectiveness.[71, 73] Most nontreponemal tests are manual assays (and therefore more time consuming), so many high-volume laboratories have opted to utilize the reverse algorithm with automated treponemal immunoassays as the initial screen. However, automated nontreponemal tests, such as the automated rapid plasma region (RPR) test are now available. The automated RPR demonstrates lower sensitivity than the conventional RPR test, but higher seroconversion after treatment. Therefore, the automated RPR may be more suitable for monitoring treatment response rather than screening.[74]

Previous studies have attempted to compare the traditional and reverse algorithm, but generally lack direct comparison because a nontreponemal and treponemal screen were not run simultaneously.[71, 73] Ortiz and colleagues found only one study that directly compared the two algorithms by prospectively testing 1000 patient samples with both algorithms.[75] In this study, the reverse algorithm produced six false-positive results, whereas the traditional algorithm produced none. Other studies have demonstrated that the reverse algorithm has a higher false positive rate than the traditional algorithm, but the traditional algorithm may miss cases of latent syphilis.[76, 77, 78]

Patient risk of syphilis is another consideration when determining whether the traditional or reverse algorithm should be used.[71] Screening with a nontreponemal test in the traditional algorithm can detect cases of active syphilis in any stage (**Table 3**), but reports have shown decreased sensitivity of these tests for detecting cases of primary and possibly latent syphilis. For this reason, the reverse algorithm may be more appropriate for use in settings that test higher-risk patients (e.g., STI clinics or other settings serving high-prevalence populations), where patients may be at greater risk for primary and latent syphilis that is more likely to be missed by the traditional algorithm.

Testing laboratories are continually challenged to increase output at a reduced cost. Therefore, test cost is another important consideration when choosing an algorithm. However, data supporting the cost-effectiveness of either algorithm are limited.[71] In two cost-analysis studies included in the Ortiz review, the reverse algorithm was found to result in more unnecessary treatment than the traditional algorithm, attributed largely due to the substantially higher number of confirmatory tests required for the reverse algorithm.[57, 58] Both studies concluded that the number of syphilis cases detected and treated was essentially similar when performing either algorithm in low- and high-prevalence settings.

Ortiz and colleagues concluded that, considering all these factors, the traditional algorithm may be more appropriate for smaller laboratories with lower volumes of testing, because manual nontreponemal screening assays are usually less expensive and have limited effect on workflow. Alternatively, the reverse algorithm may be more suitable for either larger laboratories where automated testing processes can improve workflow and efficiency, or for smaller laboratories serving higher-risk populations. The CDC offers additional guidance if reverse sequence screening is used.[79] Specifically, if reverse sequence screening results are discordant (i.e., the treponemal test is positive but the nontreponemal test is negative), the laboratory should perform a different treponemal test (preferably one based on different antigens) to confirm the results of the initial treponemal test.[19]

Rapid Point-of-Care Testing

Conventional testing for syphilis is clinic-based, although developments over the past several years have enabled decentralized testing and thus greater access to testing in at-risk populations. These developments include self-testing, dried blood spots (self-collection but not self-testing), and rapid POC testing.[80] In this section we focus on rapid POC testing, which involves conducting syphilis testing with results given within a short time (typically within 5 to 30 minutes), at or near the site of patient care. The World Health Organization has developed a

published set of criteria, known as the ASSURED criteria, to guide the development of POC tests.[81] These criteria include that the POC test is affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable (accessible) to end users.

A number of POC tests for syphilis or HIV/syphilis are commercially available; the majority detect antibodies specific to *T. pallidum,* and these can be used as screening tests (**Table 6**).[82-84] However, to date, only two of these tests have been cleared by the U.S. Food and Drug Administration (FDA) for use in the U.S., Syphilis Health Check (Trinity Biotech USA, Inc.) and DPP HIV-Syphilis Assay (Chembio Diagnostics, Inc). Syphilis Health Check is a qualitative test for antibodies to *T. pallidum* by whole blood (fingerstick), serum, or plasma, in about 10 minutes.[83] DPP HIV-Syphilis is a dual test that combines testing for antibodies to HIV 1/2 and *T. pallidum* by whole blood (fingerstick), serum, or plasma, in about 15 minutes.[85] A 2018 survey of U.S. local health departments found that a majority had clinics in their jurisdiction that provided STI services; approximately one-fifth of these offered POC testing for syphilis.[86]

A 2020 systematic review by Bristow and colleagues evaluated the performance of the Syphilis Health Check.[45] In total, this review included 15 studies, both published test evaluations and studies submitted to the FDA and for a Clinical Laboratory Improvement Amendments waiver application. All but one was conducted in the U.S. Reference standards varied by study, but typically some combination of enzyme immunoassay, rapid plasma reagin, *T. pallidum* hemagglutination assay, or *T. pallidum* particle agglutination assay tests were used. This review found that the pooled sensitivity from the laboratory evaluations (n = 5) was 98.5 percent (95% CI, 92.1–100%), while pooled specificity was 95.9 percent (95% CI, 81.5–100.0%). The pooled sensitivity for prospective studies (n = 10) was 87.7 percent (95% CI, 71.8–97.2%), while pooled specificity was 96.7 percent (95% CI, 91.9–99.2%). However, in two of these prospective studies the sensitivity was only 50 percent. Using nontreponemal supplemental testing, the sensitivity improved from 87.7 percent to a pooled sensitivity of 97.0 percent (95% CI, 94.8–98.6%). Review authors note that higher sensitivity in laboratory evaluations may be due in part to these studies included more rigorous training and oversight while the other studies described in the literature did not mention methods around quality monitoring. In addition, laboratory evaluations for the FDA used sera for testing while other studies used whole-blood specimen. Nonetheless, this meta-analysis suggests that overall Syphilis Health Check had reasonable test performance; however further studies to investigate factors contributing to lower sensitivity in real world practice (i.e., outside traditional laboratory evaluations) are warranted. The sensitivity and specificity to detect syphilis using other commercially available POC testing for antibodies to *T. pallidum* or dual HIV/syphilis POC testing, including DPP HIV-Syphilis Assay, in more resource-poor settings appear to be similar to those found for Syphilis Health Check.[82, 84, 87] However, there does appear to be variation of test performance by setting and test manufacturer. Of note, while the accuracy for syphilis in dual HIV/syphilis POC testing appears consistent with single POC tests for syphilis, the test accuracy for syphilis in these tests is lower than for detection of HIV.

Limitations and Future Research Needs

Limitations of this review include that we only included English-language articles, studies conducted in very high- and high-income countries, studies of asymptomatic patients, and

studies conducted in settings and with tests applicable to current practice in the U.S. These exclusions were designed to improve clinical relevance of the findings for the USPSTF but may have excluded some research in the field. We also excluded studies limited to populations in which syphilis screening may be part of disease management, such as persons living with HIV. Only one fair-quality study was identified for each key question and two of the three studies were conducted outside the U.S. Given the racial disparities in the U.S. in syphilis rates, studies conducted in majority white populations (such as the study conducted in Australia) may not be generalizable to the U.S. context. Furthermore, two of the three studies involved participants who were seeking STI testing or treatment and therefore not conventional "screening" studies.

Screening tests for syphilis demonstrate adequate sensitivity and specificity, but the sequence of tests may result in different diagnostic accuracy depending on the population prevalence of the disease and the stage of disease. The 2016 Syphilis Summit sponsored by the CDC provided an opportunity for clinicians and researchers to discuss gaps in existing knowledge and technologies.[88] Major gaps identified relevant to this evidence update included the need to optimize existing diagnostic tests, to improve the availability and FDA approval of nucleic acid amplification tests for primary and secondary syphilis, and to develop effective new blood tests for diagnosis of active (vs. treated) syphilis infection.

Novel approaches to improve the convenience, acceptability, and confidentiality of syphilis screening are emerging in the literature and in clinical practice. Examples include rapid POC testing, offering STI screening services in community pharmacies, Internet-accessed STI (e-STI) testing or allowing individuals to collect their own specimen and send it to a laboratory of their choice.[89-91] To date, only two POC tests have been FDA-cleared for use in the U.S., the Syphilis Health Check (Trinity Biotech USA, Inc.) and the DPP HIV-Syphilis Assay (Chembio Diagnostics, Inc). A 2020 systematic review and meta-analysis suggested that the Syphilis Health Check had good test performance overall.[92] However, studies to investigate factors contributing to lower sensitivity in real world practice (i.e., outside traditional laboratory evaluations) are still needed. A 2019 systematic review and meta-analysis found that programs offering self-collection of samples in Australia, Denmark, and the U.S. increased overall uptake of STI testing services nearly three-fold and case identification by approximately two-fold, while previous literature has demonstrated that self-collected samples for STIs are as accurate as clinician-collected methods.[89] It is important to note that although these novel approaches seem promising, they may be better suited for non-blood specimen collection (i.e., urine, vaginal flush, or vaginal swab). More research is needed to determine if these novel approaches can be applied effectively to syphilis screening. We identified two ongoing studies that may help address these questions (**Appendix D, Table 1**).

Research is lacking on the effectiveness of specific screening intervals among high-risk populations (other than individuals living with HIV) and on effective risk assessment instruments or other risk stratification methods for identifying persons at increased risk of syphilis. While we know key risk factors and groups, assessing risk status currently requires a thorough clinical and sexual history. Development of externally validated risk assessment tools that do not rely so heavily on a detailed sex history may be helpful in implementing systematic screening of at-risk individuals. Finally, neither the 2016 review nor this evidence update identified studies specifically conducted in adolescent populations.

Conclusions

Screening for syphilis in persons at increased risk of infection is currently recommended by the USPSTF and is the standard of care in the U.S. The findings of this brief evidence update are consistent with the prior evidence review, however, there is limited data from U.S. settings and therefore a need for additional studies that are more generalizable to the U.S. population. Further research on novel testing approaches, how to best identify those most likely to benefit from screening, and the effectiveness of specific screening intervals among different risk populations is still needed.

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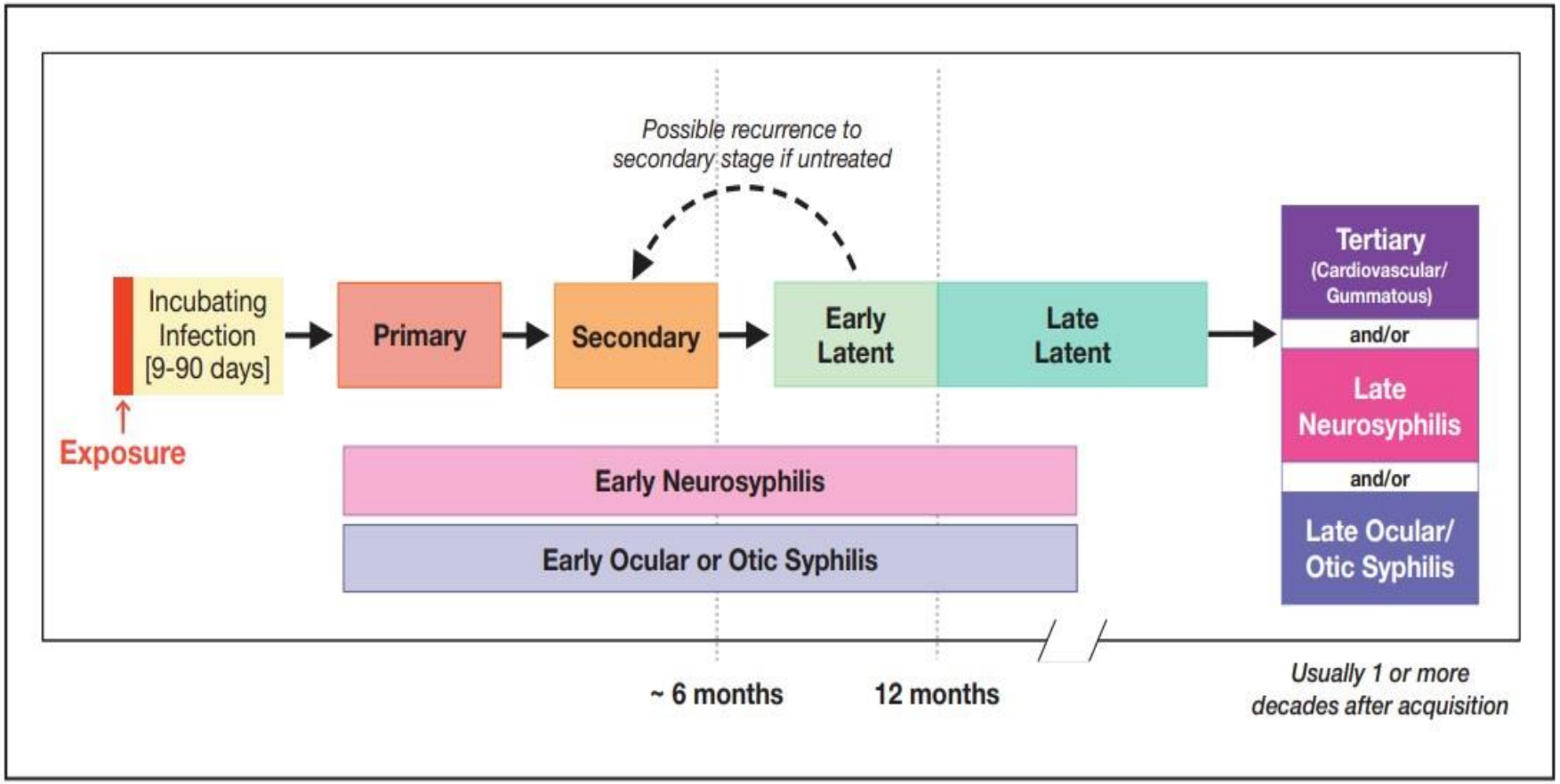
Figure 1. Stages of Syphilis*



***** From: https://emorymedicine.wordpress.com/2021/01/15/krakow-conference-what-are-the-different-stages-of-syphilis

Figure 2. Rates of Primary and Secondary Syphilis by Age and Sex in the United States, 2019

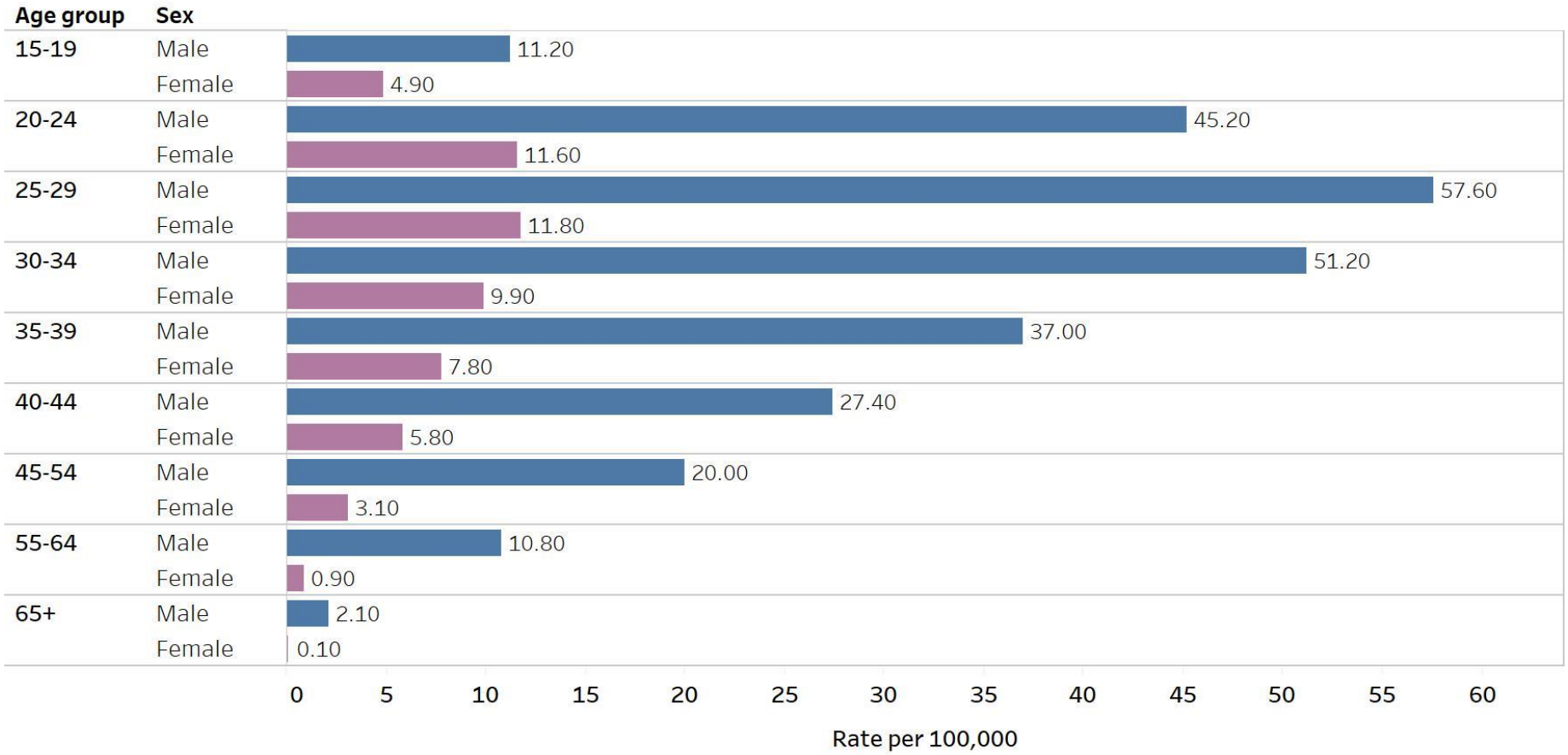


Figure 3. Rates of Primary and Secondary Syphilis by Race and Ethnicity and Age in the United States, 2019

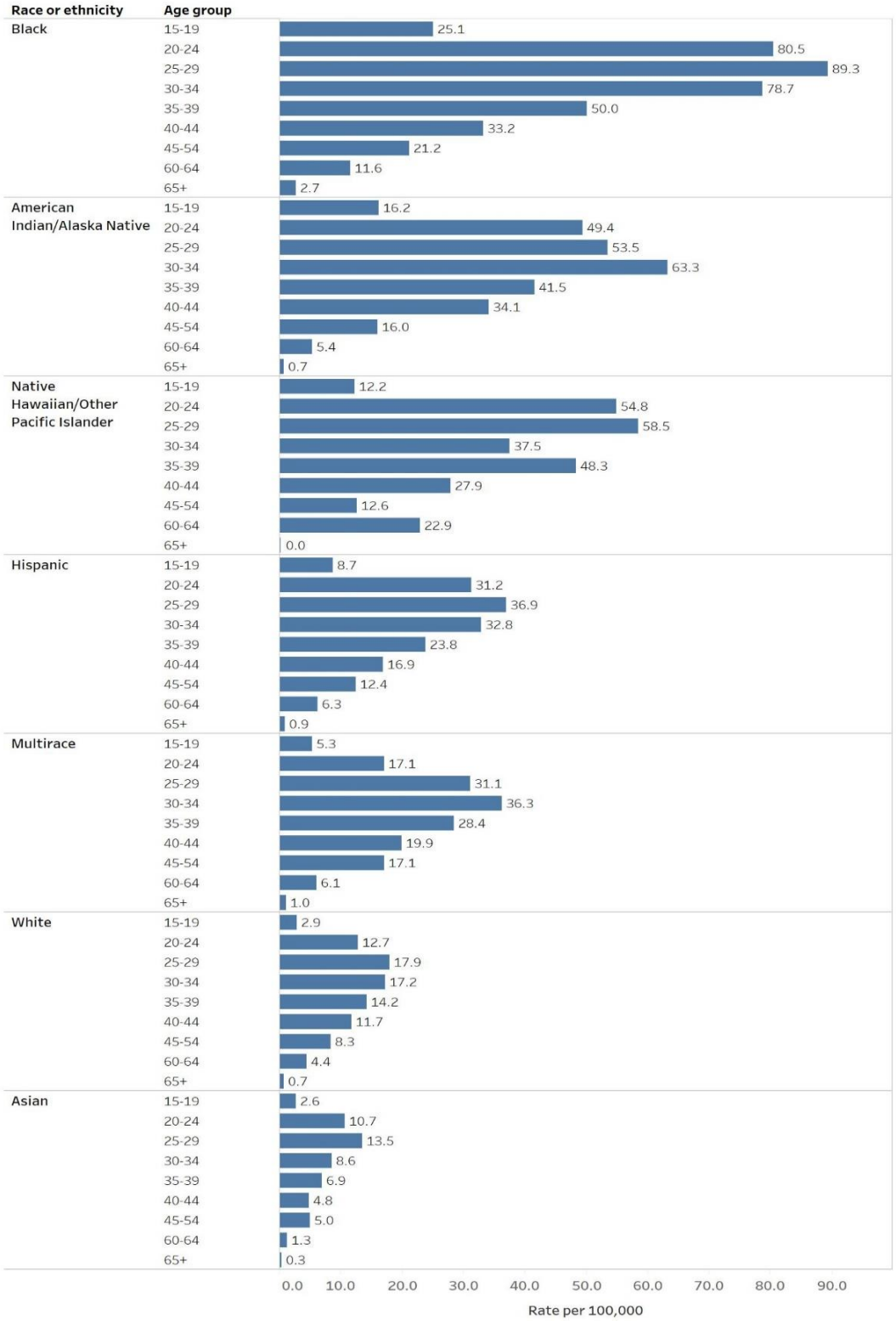


Figure 4. Analytic Framework

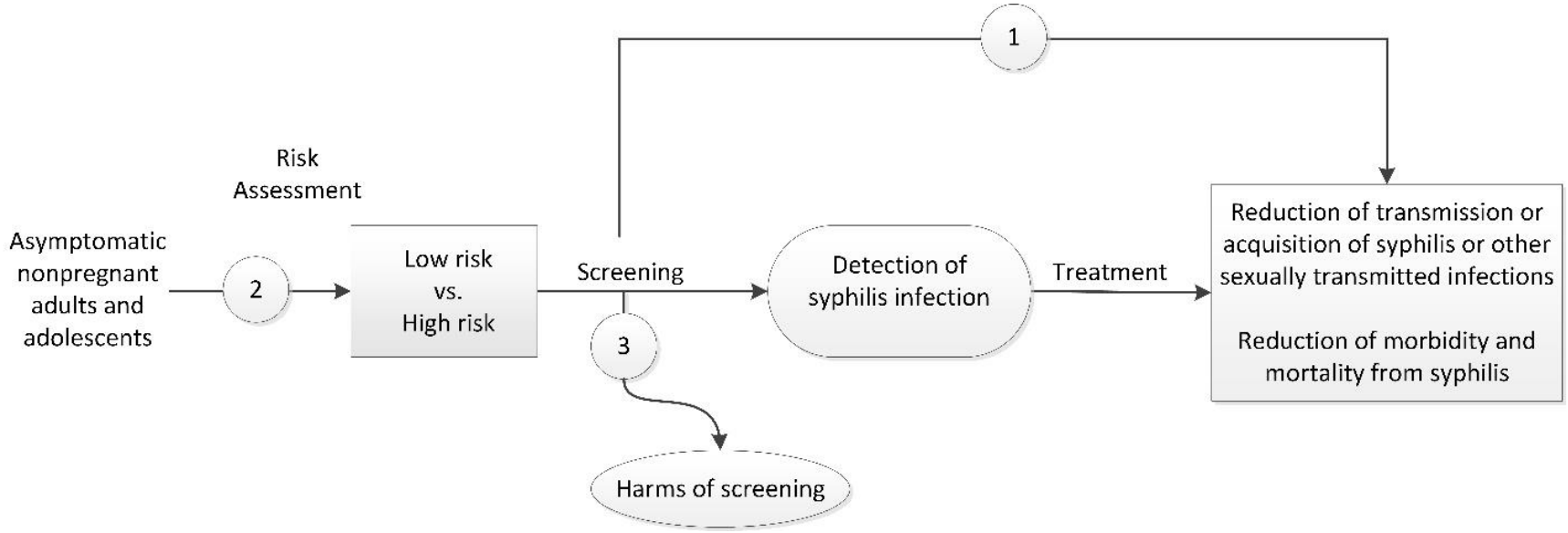
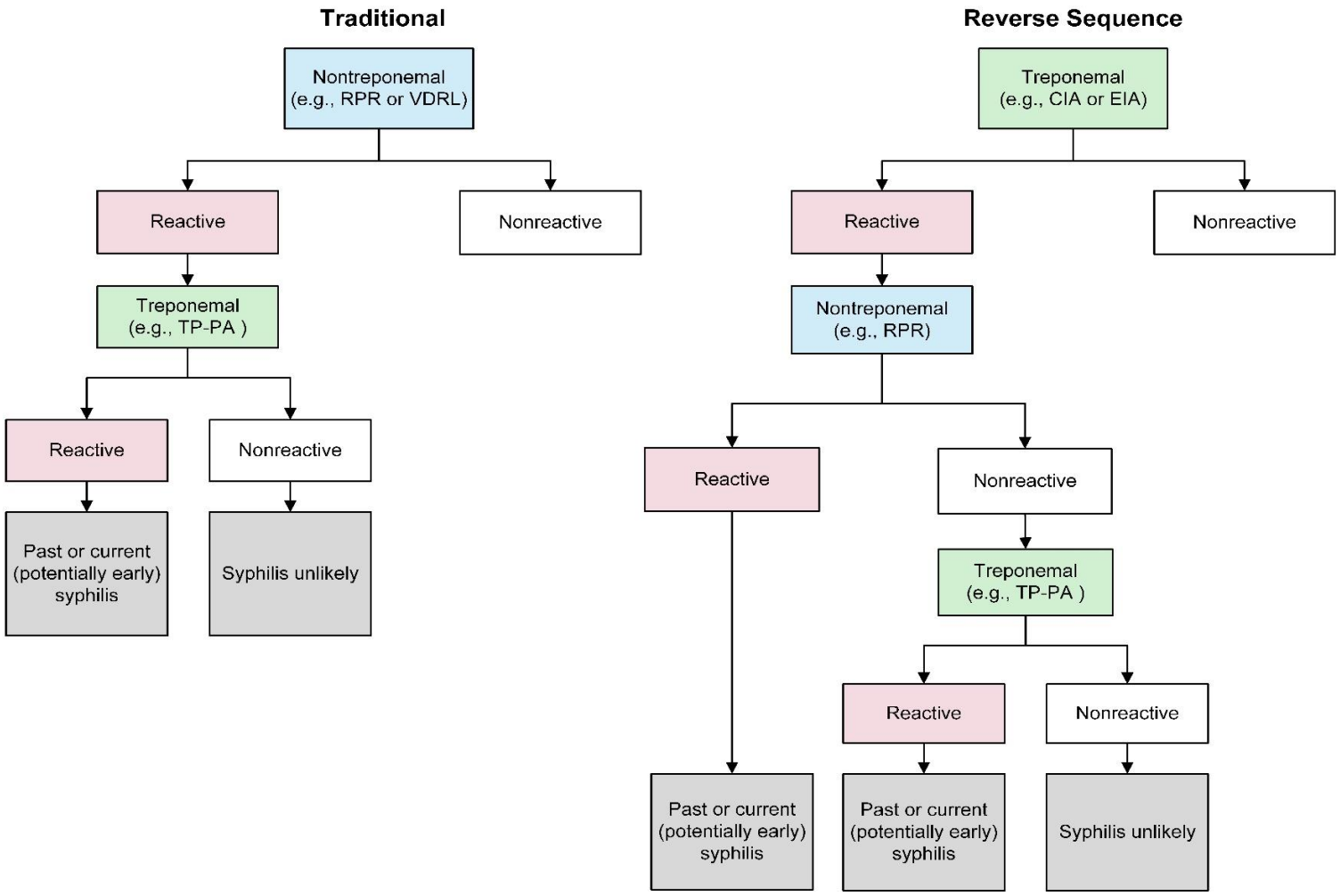


Figure 5. Syphilis Serologic Screening Algorithms*



*Adapted from: Association of Public Health Laboratories. Suggested Reporting Language for Syphilis Serological Testing. https://www.aphl.org/programs/infectious_disease/std/Documents/ID-2020Aug-Syphilis-Reporting-Language.pdf. Accessed April 27, 2021. PMID. None.

Abbreviations: CIA = Chemiluminescent immunoassay; EIA = Enzyme-linked immunoassay; RPR = Rapid plasma reagin; TP-PA = Treponema pallidum particle agglutination; VDRL = Venereal Disease Research Laboratory

Table 1. Rates of Syphilis per 100,000 Persons by Population, in the United States

Population	Men and Women (per 100,000)*	Men (per 100,000)*	Women (per 100,000)*
US Population	11.9	20.1	3.9
MSM/MSW	N/A	309.0/2.9	N/A
HIV+/HIV-†	12.4/0.2	NR	NR
Age (years)			
15-29	8.1	11.20	4.90
20-24	28.9	45.20	11.60
25-29	35.3	57.60	11.80
30-34	30.9	51.20	9.90
35-39	22.4	37.00	7.80
40-44	16.6	27.40	5.80
45-54	11.4	20.00	3.10
55-64	5.7	10.80	0.90
65+	1.0	2.10	0.10
Black	31.0	53.5	10.2
Native Hawaiian/PI	23.0	35.9	9.6
AI/AN	21.2	27.1	15.4
Hispanic	13.7	23.4	3.8
White	6.6	11.0	2.3
Asian	4.6	8.9	0.6
Military‡	4.7	4.9	3.7
Correctional Facilities	Accounted for 11% of all primary and secondary syphilis cases reported to the CDC in 2019		
Sex workers§	High risk for STIs in general		

* Rates of Primary and Secondary syphilis from CDC Sexually Transmitted Disease Surveillance, 2019 (published 2021), unless otherwise specified.
† Horberg et al. (2010), as cited in Cantor et al (2016). Includes all stages of syphilis, rates per 1,000 person-years.
‡ Armed Forces Health Surveillance Branch (2021). Includes all stages of syphilis, rates per 10,000 person-years.
§ Cantor et al. (2016).

Abbreviations: AI = American Indian; AN = Alaska Native; HIV = human immunodeficiency virus; MSM = men having sex with men; MSW = men having sex with women; NA = not applicable; NR = not reported; PI = Pacific Islander; PY = person-years; US = United States

Table 2. Serologic Methods for Syphilis Diagnosis*

Test	Manual or Automated	Antibodies
Nontreponemal		
Venereal Disease Research Laboratory (VDRL)	Manual	NR
Rapid plasma reagin (RPR)	Manual or Automated	NR
Toluidine red unheated serum test (TRUST)	Manual	NR
Unheated serum reagin (USR)	Manual	NR
Treponemal		
Fluorescent treponemal antibody absorption (FTA-ABS) †	Manual	IgM/IgG
Treponema pallidum particle agglutination (TP-PA) assay†	Manual	IgM/IgG
Line immunoassay (LIA)‡	Manual/Automated	IgG
Enzyme-linked immunoassay (EIA)	Manual/Automated	IgG or IgM/IgG
Chemiluminescent immunoassay/Chemiluminescent microparticle immunoassay (CIA/CMIA)	Automated	IgG or IgM/IgG
Microbead immunoassay (MBIA)	Automated	IgG or IgM/IgG
Rapid antibody test	Manual	IgG

***** Adapted from: Association of Public Health Laboratories. Suggested Reporting Language for Syphilis Serological Testing. https://www.aphl.org/programs/infectious_disease/std/Documents/ID-2020Aug-Syphilis-Reporting-Language.pdf. Accessed April 27, 2021. PMID: None.
† These methods may be performed on cerebrospinal fluid (CSF) to support a diagnosis of neurosyphilis.
‡ Not cleared by U.S. Food and Drug Administration.

Abbreviations: Ig = immunoglobin; N/A = not applicable

Table 3. Sensitivity and Specificity of Commonly Used Syphilis Tests*

Test type	Test Name	Primary		Secondary		Early Latent		Late Latent or Unknown		Tertiary	
		Sen, % (range)	Spec, % (range)	Sen, % (range)	Spec, % (range)	Sen, % (range)	Spec, % (range)	Sen, % (range)	Spec, % (range)	Sen, % (range)	Spec, % (range)
Nontrep	VDRL[93]	(63-78)	N/A	100	N/A	(85-100)	N/A	64	N/A	(47-64)	N/A
	RPR[93]	(63-76)	N/A	100	N/A	NR	N/A	61	N/A	NR	N/A
	TRUST[94]	85 (77-86)	99 (98-99)	100	NR	98 (95-100)	NR	NR	NR	NR	NR
	USR[94]	80 (72-88)	99	100	NR	95 (88-100)	NR	NR	NR	NR	NR
Trep	FTA-ABS[95]	(78-100)	(87-100)	(93-100)	NR	(94-100)	NR	(84-93)	NR	NR	NR
	TP-PA[95]	(86-100)	100	100	NR	(94-100)	NR	(87-100)	NR	NR	NR
	EIA: Captia Syphilis-G Assay[95]	(82-100)	(98-100)	100	NR	100	NR	(92-100)	NR	NR	NR
	CIA: LIASON[95]	(96-100)	(94-100)	100	NR	98	NR	93	NR	NR	NR

* Selected list of tests available in the United States.

Abbreviations: CIA = Chemiluminescent immunoassay; EIA = Enzyme-linked immunoassay; FTA-ABS= Fluorescent treponemal antibody absorption; MHA-TP = Microhemagglutination assay; N/A = Not applicable; Nontrep = Nontreponemal; NR = Not reported; RPR = rapid plasma reagin; Sen = Sensitivity; Spec = Specificity; TP-PA = Treponema pallidum particle agglutination; Trep = Treponemal; TRUST = Toluidine red unheated serum test; USR = Unheated serum reagin; VDRL = Venereal Disease Research Laboratory

Table 4. Recommendations of Others

Organization, year	Recommendation
Centers for Disease Control and Prevention (CDC), 2021[19]	Recommends at least annual screening for sexually active MSM with confirmatory testing for individuals with reactive serology. MSM at increased risk should be screened every 3 to 6 months. Persons living with HIV who are sexually active should be screened at the first HIV evaluation, and at least annually thereafter; more frequent screening may be appropriate based on individual risk behaviors and local epidemiology. The CDC also recommends opt-out syphilis screening in correctional facilities based on the local area and institutional prevalence. In short-term facilities, screening at entry might be indicated.
American College of Obstetricians and Gynecologists (ACOG), 2021[96]	Does not recommend routine screening for syphilis for women who are not pregnant.
Public Health Agency of Canada, 2020[54]	Recommends screening for anyone presenting with risk factors for syphilis to prevent complications, transmission, and reinfection. Risk factors included unprotected sexual activity, including MSM; sexual contact with a known case of syphilis; sex with someone from a country/region with a high prevalence of syphilis; prior syphilis, HIV infection, or other STI; born to a person diagnosed with infectious syphilis in pregnancy; or member of a vulnerable population.
European Academy of Dermatology and Venereology (EADV), 2020[97]	Recommends routine screening in high-risk groups: all patients who are newly diagnosed with STI; persons with HIV; persons on PrEP; patients with hepatitis B and/or hepatitis C; patients suspected of early neurosyphilis patients who engage in sexual behaviour that places them at higher risk (e.g., MSM, sex workers and all those individuals at higher risk of acquiring STIs). Screening tests should also be offered to all attendees at dermatovenereology or genitourinary medicine/STI clinics.
The American Academy of Family Physicians (AAFP), 2016[98]	Supports the USPSTF clinical preventive service recommendations on this topic.
British Association for Sexual Health and HIV (BASHH), 2016[99]	Recommends screening with confirmatory testing for individuals with positive screening tests. Recommends repeat screening for syphilis 6 and 12 weeks after a single 'high risk' exposure (unprotected oral, anal, or vaginal intercourse with homosexual man, multiple partners, anonymous sex in saunas and other venues, commercial sex worker or sex partner linked with a country where the prevalence of syphilis is known to be high). In individuals at ongoing risk due to frequent 'high risk' exposures as defined above, screening as part of routine sexual health check-ups for all STIs including HIV and others is recommended, usually every three months and informed by sexual history.
The HIV Medicine Association, Infectious Diseases Society of America, 2013[42]	Recommends that all patients living with HIV be screened for syphilis on initiation of care and periodically thereafter, depending on risk. Risk factors that may warrant more frequent testing (i.e., every 3-6 months vs. annually) include having multiple partners, a history of unprotected intercourse, a history of sex in conjunction with illicit drug use, methamphetamine use, or multiple sexual partners who participate in these activities.

Abbreviations: HIV = Human immunodeficiency virus; MSM = Men who have sex with men; PrEP = Pre-exposure prophylaxis; STI = Sexually transmitted infection; USPSTF = United States Preventive Services Task Force

Table 5. Summary of Targeted Evidence Update in the Context of the Prior Systematic Review to Support the 2016 USPSTF Screening for Syphilis in Nonpregnant Adults and Adolescents*

Key Question	Evidence summary in 2016	New evidence findings	Limitations of new evidence	Consistency of new evidence with prior evidence findings
KQ1: Effectiveness of screening	No studies directly compared the effectiveness of syphilis screening in screened versus unscreened populations of nonpregnant adolescents or adults.	One Australian cohort study (n= 117,387) found that increases in both the proportion of MSM tested annually, and the mean number of tests per MSM performed annually, were associated with a 17-22% increase in the proportion of early latent infections identified and a 5-19% decrease in the proportion of secondary infections identified, during an 8-year followup period.	Risk of bias: Did not report loss to followup data; potential confounding of variables. Applicability: Conducted in MSM, including 31% HIV positive MSM, attending publicly funded sexual health clinics in Australia.	N/A (no studies identified in the prior review).
KQ1a: Effectiveness of screening intervals	Four non-US observational studies evaluated detection rates using specific screening intervals in MSM or HIV-positive populations. 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 vs. 2.8 cases 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.	No studies met inclusion criteria for this evidence update, but 2 studies addressed intervals of screening in HIV-positive populations and found that increased testing frequency (e.g., every 3 months in one study and every 3 to 6 months in the other) was associated with earlier detection of syphilis and identification of a significant number of cases that would not have otherwise been detected.	Applicability: Studies limited to HIV positive MSM.	The results of the new evidence were consistent with the previous review.
KQ2: Performance of risk assessment instruments or other risk stratification methods	No studies evaluated the performance of risk assessment.	One risk prediction study (n=361) conducted in Peru developed an online risk calculator for predicting future syphilis among high-risk individuals. The final model for predicting syphilis incidence within the next three months demonstrated an AUC of 69% and included the following risk factors: current HIV infection, history of syphilis infection, number of male sex partners in the prior three months, and sex role for anal sex in the prior three months.	Risk of bias: Participants with no followup data excluded from models. Internal validation only. Applicability: Conducted among high-risk individuals seeking STI treatment in Peru, including 78% MSM, 22% transgender women, 36% with a history of syphilis, and 35% HIV positive.	N/A (no studies identified in the prior review).

Table 5. Summary of Targeted Evidence Update in the Context of the Prior Systematic Review to Support the 2016 USPSTF Screening for Syphilis in Nonpregnant Adults and Adolescents*

Key Question	Evidence summary in 2016	New evidence findings	Limitations of new evidence	Consistency of new evidence with prior evidence findings
KQ3: Harms of screening	No studies directly assessed the harms of screening for syphilis.	One pre-post US study (n=1,097) assessed factors associated with emotional stress related to rapid POC testing for STIs. The results suggest that emotional stress may be a common experience for individuals both pre- and post-testing. Factors associated with increased stress experience included history of injected drug use, Black race/ethnicity, less than a high school education, and Single marital status.	Risk of bias: Did not report loss to followup data, although pre- and post-data collected at same study visit, therefore likely to be minimal. Applicability: Conducted at a behavioral research center in the United States, among high-risk participants (39% women with high-risk sexual behaviors; 37% MSM or MSMW; 22% injection drug users; 1% transgender individuals). Study did not compare changes in stress levels pre- and post-test.	N/A (no studies identified in the prior review).

* Question around the diagnostic accuracy were not addressed in this review.

Abbreviations: AOC = Area Under the Curve; CI = Confidence interval; HIV = Human Immunodeficiency Virus; KQ = Key Question; MSM = men who have sex with men; MSMW = Men who have sex with men and women; NA= Not applicable; POC = Point of care; STI = Sexually transmitted infection; US=United States; USPSTF = United States Preventive Services Task Force; vs = Versus

Table 6. Point-of-Care Tests Currently on the Market With Available Sensitivities and Specificities*

Test	Sample type	Test type	Target	Sensitivity, %	Specificity, %
Qualpro Syphicheck-WB	Whole blood/serum/plasma	Treponemal POC	Treponemal Antibody	64-97.6	98.4-99.7
SD Bioline Syphilis 3.0	Whole blood/serum/plasma	Treponemal POC	Treponemal Antibody	85.7-100	95.5-99.4
Dual Path Platform (DDP®) Syphilis Test (Chemio Diagnostic Systems, Inc)	Whole blood/serum/plasma	Dual Treponemal & Non-Treponemal Syphilis POC	Treponemal Antibody	90.1-98.2	91.2-98.0
			Non-Treponemal Antibody	80.6-98.2	89.4
SD Bioline HIV/Syphilis Duo Rapid Test (Alere/Standard Diagnostics, Inc)	Whole blood/serum/plasma	Combined Syphilis and HIV POC	HIV Antibody	97.9-99.0	99.0-100
			Treponemal Antibody	93.0-99.6	99.1-100
DPP® HIV-Syphilis Assay (Chembio Diagnostic Systems, Inc)	Whole blood/serum/plasma	Combined Syphilis and HIV POC	HIV Antibody	98.9	97.9-99.6
			Treponemal Antibody	95.3	97.0-99.6
Multiplo Rapid TP/HIV Antibody Test (MedMira, Inc)	Whole blood/serum/plasma	Combined Syphilis and HIV POC	HIV Antibody	97.9	94.2-99.5
			Treponemal Antibody	94.1	94.2-99.1

* Adapted from: Marks M, Mabey DC. The introduction of syphilis point of care tests in resource limited settings. Expert Rev Mol Diagn. 2017;17(4):321-5. PMID: 28266230. https://dx.doi.org/10.1080/14737159.2017.1303379

Abbreviations: HIV = Human Immunodeficiency Virus; POC = Point of care

Sex or Gender Terminology

In the absence of specific and detailed information on gender or sex (e.g., cis-man, trans-man), we will use gender terminology (e.g., man, woman) rather than terminology commonly used to describe biological sex birth (i.e., male, female, intersex).

Key:
/ = MeSH subject heading
$ = truncation
ti = word in title
ab = word in abstract
pt = publication type
* = truncation
kw = keyword

MEDLINE
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 27, 2020>
Search Strategy:
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1 exp Syphilis/ (27880)
2 syphil$.ti,ab. (28063)
3 (treponema or t pallidum).ti,ab. (7358)
4 or/1-3 (41337)
5 Mass screening/ (104596)
6 screen$.ti,ab. (765399)
7 5 or 6 (794718)
8 4 and 7 [syphilis and screening] (3634)
9 exp Syphilis Serodiagnosis/ or exp Syphilis/di [Diagnosis] (11330)
10 ((nontreponemal or treponemal or syphilis or t pallidum) adj (test$ or immunoassay$ or EIA or enzyme or igg or igm)).ti,ab. (1035)
11 venereal disease research laboratory.ti,ab. (517)
12 VDRL.ti,ab. (1320)
13 Rapid plasma reagin.ti,ab. (838)
14 Fluorescent treponemal antibody absorbed.ti,ab. (48)
15 Treponema pallidum particle agglutination.ti,ab. (188)
16 (Trep-sure or trep-check).ti,ab. (11)
17 BioPlex 2200 Syphilis.ti,ab. (9)
18 toluidine red unheated serum test.ti,ab. (36)
19 or/9-18 [syphilis tests] (12800)
20 risk/ or risk assessment/ (388064)
21 ((assess$ or stratif$ or quantif$ or identif$ or instrument$ or tool$ or scale$) adj7 risk$).ti,ab. (382368)
22 20 or 21 (689946)
23 4 and 22 [syphilis and risk assessment] (979)
24 exp "Sensitivity and Specificity"/ (590633)
25 exp Diagnostic Errors/ (117202)
26 (fals$ adj3 (positiv$ or negativ$)).ti,ab. (80226)

27 (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$))).ti,ab. (1003036)
28 "Reproducibility of Results"/ (403093)
29 Reference Values/ (160408)
30 Reference Standards/ (42526)
31 specificit$.ti,ab. (494997)
32 sensitiv$.ti,ab. (1408099)
33 miss rate$.ti,ab. (513)
34 error rate$.ti,ab. (14702)
35 detection rate$.ti,ab. (24566)
36 diagnostic yield$.ti,ab. (9670)
37 likelihood ratio$.ti,ab. (15900)
38 diagnostic odds ratio$.ti,ab. (2472)
39 odds ratio/ and di.fs. (18449)
40 ROC curve$.ti,ab. (35422)
41 missed case$.ti,ab. (454)
42 (overdetect$ or over detect$).ti,ab. (264)
43 (Labelling or labelled or stigma).ti,ab. (131213)
44 or/24-43 (3305671)
45 4 and 44 [context Qs] (3708)
46 8 or 19 or 23 or 45 (16602)
47 limit 46 to (english language and yr="2016 -Current") (2122)

Cochrane Central Register of Controlled Clinical Trials (CENTRAL)
Date Run: 28/10/2020 16:55:21

ID Search Hits
#1 Syphil*:ti,ab,kw 689
#2 (treponema or "t pallidum"):ti,ab,kw 269
#3 ("venereal disease research laboratory" or VDRL or "Rapid plasma regain" or "Fluorescent treponemal antibody absorbed" or "Treponema pallidum particle agglutination" or "Trep sure" or "trep check" or "BioPlex 2200 Syphilis" or "toluidine red unheated serum test"):ti,ab,kw 41
#4 ((nontreponemal or treponemal or syphilis or "t pallidum") NEAR (test$ or immunoassay* or EIA or enzyme or igg or igm)):ti,ab,kw 198
#5 #1 or #2 or #3 or #4 with Publication Year from 2016 to present, in Trials 323

Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Populations	Asymptomatic, nonpregnant adolescents and adults who are not known to have current syphilis infection, including persons who are infected with other STIs	Symptomatic patients; neonates, infants, and children; pregnant persons; other populations in which syphilis screening may be part of disease management, such as persons living with HIV
Interventions	**KQs 1, 3:** Two-step screening for syphilis with a nontreponemal and treponemal test (traditional or reverse sequence algorithm), including different screening intervals **KQ 2:** Risk assessment instruments and other risk stratification methods that identify persons at increased risk for syphilis infection	**KQs 1, 3:** Screening tests not currently used in U.S. primary care settings
Comparisons	**KQs 1, 3:** No screening **KQ 2:** Reference standard (identification or diagnosis of infection)	**KQs 1, 3:** No comparator or alternate screening test/algorithm
Outcomes	**KQ 1:** Complications of syphilis infection and transmission or acquisition of STIs, including HIV **KQ 2:** Any measure of discrimination (e.g., AUC, c-statistic) for identification of infection **KQ 3:** Harms from screening (e.g., stigma, sequelae of test inaccuracy)	**KQ 1:** Outcomes that are not directly related to health outcomes (e.g., laboratory studies); cost-effectiveness or cost-related outcomes
Setting	Primary care and primary care–relevant settings (e.g., school-based clinics, family planning clinics, obstetrics and gynecology clinics, STI clinics, urgent care clinics, emergency departments, community settings, and correctional facilities)	
Study Design	**All KQs:** Good-quality systematic reviews **KQs 1, 3:** Randomized, controlled trials; observational studies with contemporaneous control groups **KQ 2:** Risk prediction studies	**KQs 1, 3:** Observational studies without comparison groups or historical comparators; narrative reviews; editorials; case reports
Study Quality	Good- and fair-quality	Poor-quality
Language	English	Non-English studies
Country	Studies conducted in countries categorized as “High” or Very High” on the 2019 Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries categorized as less than “High” or “Very High” on the 2019 Human Development Index

Abbreviations: AUC = Area under the curve; c = Concordance; HIV = human immunodeficiency virus; KQ = Key question; STI = Sexually transmitted infection; U.S. = United States.

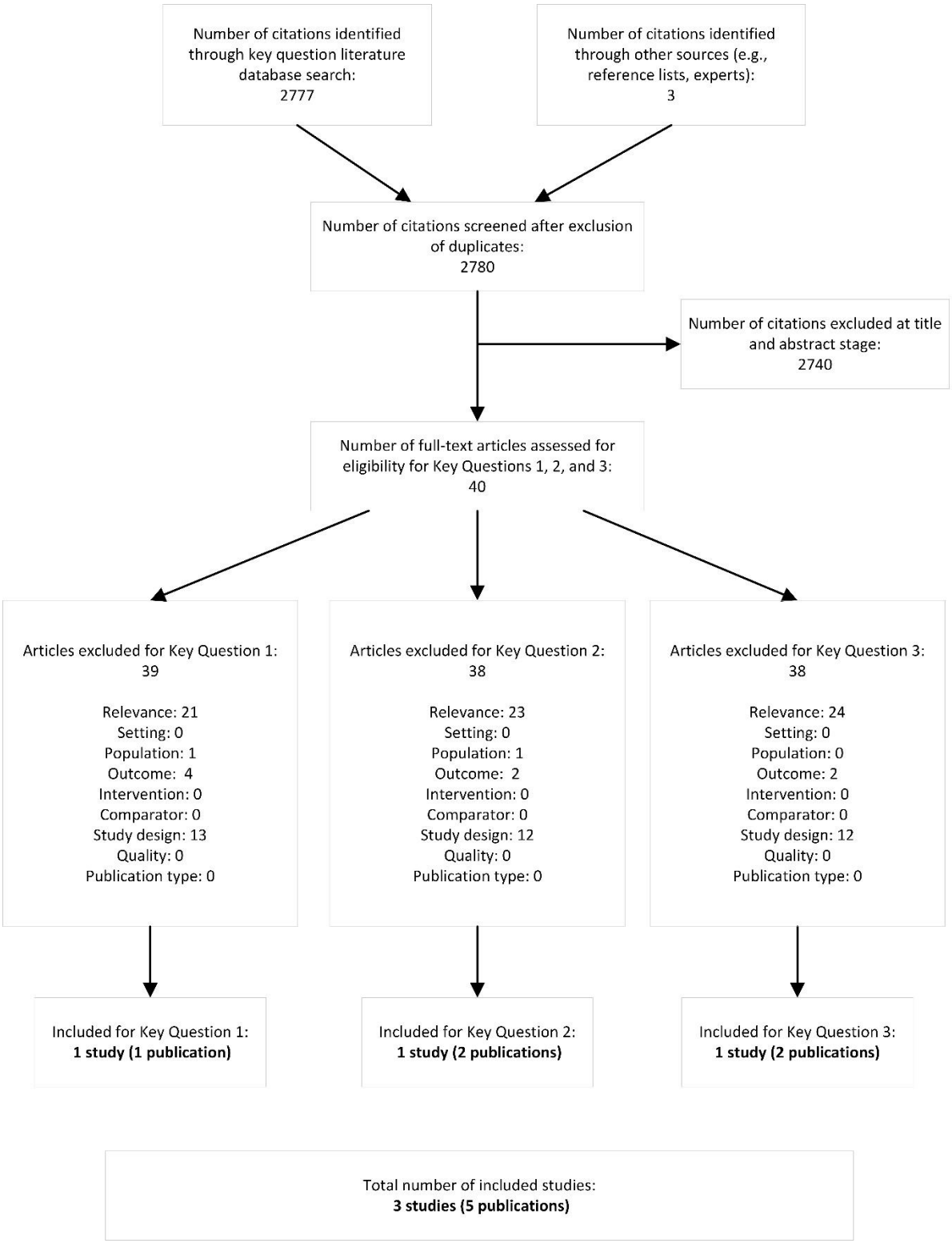
Appendix A Table 2. Quality Assessment Criteria

Study Design	Criteria
Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) Checklist[100]	• Does study sample adequately represent population of interest (participant eligibility and recruitment)? • Was there selective inclusion of participants in the model based on data availability? • If participants are from a treatment RCT, is treatment accounted for? • Is a definition and method for measurement of the outcome reported? • Was the same outcome definition (and method for measurement) used in all patients? • Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)? • Is a definition and method for measurement of candidate predictors reported? • Were predictors assessed blinded for each other? • How was the predictor of interest handled in the modelling? • How was missing data handled? • Were both calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and discrimination (C-statistic, D-statistic, log-rank) measures reported? • Were confidence intervals reported? • Were a priori cut points used for classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement [NRI])?
National Heart, Lung, and Blood Institute tool for Observational cohort and cross-sectional studies[101]	• Study objective clearly stated? • Was the study population clearly specified and defined? • Was the participation rate of eligible persons at least 50%? • Were all the subjects selected or recruited from the same or similar populations (including the same time period)? • Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? • Was a sample size justification, power description, or variance and effect estimates provided? • For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? • Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? • For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? • Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? • Was the exposure(s) assessed more than once over time? • Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? • Were the outcome assessors blinded to the exposure status of participants? • Was loss to follow-up after baseline 20% or less?

Appendix A Table 2. Quality Assessment Criteria

Study Design	Criteria
	• Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
National Heart, Lung, and Blood Institute tool for before-after (pre-post) studies with no control group[102]	• Was the study question or objective clearly stated? • Were eligibility/selection criteria prespecified and clearly described? • Were the participants representative of the general population? • Were all eligible participants enrolled? • Was the sample size sufficiently large? • Was the test/service/intervention clearly described and delivered consistently? • Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently? • Were outcome assessors blind? • Was loss to followup ≤20% and those lost to follow-up accounted for in analysis? • Did statistical methods examine changes in outcome measures from before to after the intervention? Were p values provided? • Were outcome measures taken multiple times before and after the intervention? • If a group-level intervention, did statistical analysis take into account the use of individual-level data to determine group-level effects?

Appendix A Figure 1. Literature Flow Diagram



Appendix B. Included Studies List

Key Question 1

Chow EPF, Callander D, Fairley CK, et al. Increased Syphilis Testing of Men Who Have Sex With Men: Greater Detection of Asymptomatic Early Syphilis and Relative Reduction in Secondary Syphilis. Clin Infect Dis. 2017;65(3):389-95. PMID: 28419198. https://dx.doi.org/10.1093/cid/cix326

Key Question 2

Allan-Blitz LT, Konda KA, Vargas SK, et al. The development of an online risk calculator for the prediction of future syphilis among a high-risk cohort of men who have sex with men and transgender women in Lima, Peru. Sex Health. 2018;15(3):261-8. PMID: 30021680. https://dx.doi.org/10.1071/SH17118

Kojima N, Park H, Konda KA, et al. The PICASSO Cohort: baseline characteristics of a cohort of men who have sex with men and male-to-female transgender women at high risk for syphilis infection in Lima, Peru. BMC Infect Dis. 2017;17(1):255. https://dx.doi.org/10.1186/s12879-017-2332-x

Key Question 3

Reynolds GL, Fisher DG, Brocato J, et al. Stressful point-of-care rapid testing for human immunodeficiency virus, hepatitis C virus, and syphilis. Int J STD AIDS. 2017;28(10):975-84. PMID: 28632469. https://dx.doi.org/10.1177/0956462416684460

Hess KL, Fisher DG, Reynolds GL. Sensitivity and specificity of point-of-care rapid combination syphilis-HIV-HCV tests. PLoS ONE. 2014;9(11):e112190. PMID: 25375138. https://dx.doi.org/10.1371/journal.pone.0112190

Appendix C. Excluded Studies List

Exclusion Code	Definition
E1	**Study Aim:** Not applicable/relevant to key question
E2a	**Setting:** Not in a high or very high human development index country*
E2b	**Setting:** Screening and/or intervention is not conducted in primary care-relevant settings
E3a	**Population:** Symptomatic patients; neonates, infants, and children; pregnant persons; other populations in which syphilis screening may be part of disease management, such as persons living with HIV
E4	**Outcome**: Outcomes that are not directly related to health outcomes (e.g., laboratory studies); cost-effectiveness or cost-related outcomes
E5	**Intervention (KQ1, KQ3):** Screening tests not currently used in U.S. primary care settings
E6	**Comparator (KQ1, KQ3):** No comparator or alternate screening test/algorithm
E7	**Study design:** Narrative reviews, editorials, and case reports
E8	**Study Quality:** Poor
E9	**Publication type:** Abstract-only, Non-English publication, main results published prior to review start date

Reference	Code
An, Q, Bernstein, KT, et al. Sexually transmitted infection screening and diagnosis among adolescent men who have sex with men, three US cities, 2015. Int J STD AIDS. 31(1): 53-61. 2020. PMID: 31842696. https://dx.doi.org/10.1177/0956462419870223	KQ1E1 KQ2E1 KQ3E1
Anonymous, Syphilis. Nature Reviews. Disease Primers. 3(): 17076. 2017. PMID: 29022573. https://dx.doi.org/10.1038/nrdp.2017.76	KQ1E7 KQ2E7 KQ3E7
Bao, Y, Medland, NA, et al. Predicting the diagnosis of HIV and sexually transmitted infections among men who have sex with men using machine learning approaches. J Infect. 82(1): 48-59. 2021. PMID: 33189772. https://dx.doi.org/10.1016/j.jinf.2020.11.007	KQ1E1 KQ2E1 KQ3E1
Bernstein, KT, Chow, JM, et al. Bacterial Sexually Transmitted Disease Screening Outside the Clinic--Implications for the Modern Sexually Transmitted Disease Program. Sex Transm Dis. 43(2 Suppl 1): S42-52. 2016. PMID: 26779687. https://dx.doi.org/10.1097/OLQ.0000000000000343	KQ1E1 KQ2E1 KQ3E1
Casey, G. Sexually transmissable infections. Nursing New Zealand (Wellington). 23(4): 20-24. 2017. PMID: 30549796.	KQ1E7 KQ2E7 KQ3E7
Cha, S, Matthias, JM, et al. Reactor Grids for Prioritizing Syphilis Investigations: Are Primary Syphilis Cases Being Missed?. Sex Transm Dis. 45(10): 648-654. 2018. PMID: 29528995.	KQ1E1 KQ2E1 KQ3E1

Reference	Code
https://dx.doi.org/10.1097/OLQ.0000000000000833	
Chesson, HW, Kidd, S, et al. The Cost-Effectiveness of Syphilis Screening Among Men Who Have Sex With Men: An Exploratory Modeling Analysis. Sex Transm Dis. 43(7): 429-32. 2016. PMID: 27322043. https://dx.doi.org/10.1097/OLQ.0000000000000461	KQ1E4 KQ2E4 KQ3E4
Coll, J, Videla, S, et al. Early detection of HIV infection and of asymptomatic sexually transmitted infections among men who have sex with men. Clinical Microbiology & Infection. 24(5): 540-545. 2018. PMID: 28843621. https://dx.doi.org/10.1016/j.cmi.2017.08.012	KQ1E4 KQ2E1 KQ3E1
Eickhoff, CA, Decker, CF. Syphilis. Dis Mon. 62(8): 280-6. 2016. PMID: 27091635. https://dx.doi.org/https://dx.doi.org/10.1016/j.disamonth.2016.03.012	KQ1E7 KQ2E7 KQ3E7
Elder, HR, Gruber, S, et al. Can Machine Learning Help Identify Patients at Risk for Recurrent Sexually Transmitted Infections?. Sex Transm Dis. 17(): 17. 2020. PMID: 32810028. https://dx.doi.org/10.1097/OLQ.0000000000001264	KQ1E1 KQ2E3 KQ3E1

Appendix C. Excluded Studies List

Reference	Code
Fan, T, Rogers, A. Screening for Syphilis Infection in Nonpregnant Adults and Adolescents. Am Fam Physician. 96(6): 393-394. 2017. PMID: 28925643.	KQ1E7 KQ2E7 KQ3E7
Ghanem, KG, Ram, S, et al. The Modern Epidemic of Syphilis. N Engl J Med. 382(9): 845-854. 2020. PMID: 32101666. https://dx.doi.org/10.1056/NEJMra1901593	KQ1E7 KQ2E7 KQ3E7
Guy RJ, Kong F, Goller J, et al. A new national Chlamydia Sentinel Surveillance System in Australia: evaluation of the first stage of implementation. Commun Dis Intell Q Rep. 2010;34(3):319-28. PMID: 21090187.	KQ1E1 KQ2E1 KQ3E1
Klausner, JD. The Evidence That Increased Syphilis Testing Controls Syphilis Is Compelling: What Is Needed to Act?. Clin Infect Dis. 65(3): 396-397. 2017. PMID: 28419214. https://dx.doi.org/10.1093/cid/cix329	KQ1E7 KQ2E7 KQ3E7
Larios Venegas, A, Melbourne, HM, et al. Enhancing the Routine Screening Infrastructure to Address a Syphilis Epidemic in Miami-Dade County. Sex Transm Dis. 47(5S Suppl 1): S61-S65. 2020. PMID: 32004258. https://dx.doi.org/10.1097/OLQ.0000000000001133	KQ1E4 KQ2E4 KQ3E4
Low, N. From testing to screening for STIs. Sex Transm Infect. 93(1): 75. 2017. PMID: 28100762. https://dx.doi.org/10.1136/sextrans-2016-053001	KQ1E7 KQ2E7 KQ3E7
Marcus, U, Mirandola, M, et al. Changes in the prevalence of self-reported sexually transmitted bacterial infections from 2010 and 2017 in two large European samples of men having sex with men-is it time to re-evaluate STI-screening as a control strategy?. PLoS ONE [Electronic Resource]. 16(3): e0248582. 2021. PMID: 33720969. https://dx.doi.org/10.1371/journal.pone.0248582	KQ1E1 KQ2E1 KQ3E1
Merson, JR, Shehu, M. Syphilis. JAAPA. 32(5): 59-60. 2019. PMID: 31033717. https://dx.doi.org/10.1097/01.JAA.0000554749.77547.b1	KQ1E7 KQ2E7 KQ3E7
Ndeikoundam Ngangro, N, Viriot, D, et al. Bacterial sexually transmitted infections in France: recent trends and patients' characteristics in 2016. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin. 24(5): . 2019. PMID: 30722812. https://dx.doi.org/10.2807/1560-7917.ES.2019.24.5.1800038	KQ1E1 KQ2E1 KQ3E1
Nguyen, MP, Sembajwe, S, et al. Impacts of Sexually Transmitted Disease/HIV Outreach Sites on the Effectiveness of Detecting New Infections in Baltimore City, 2015 to 2018. Sex Transm Dis. 48(1): 1-4. 2021. PMID: 32826481. https://dx.doi.org/10.1097/OLQ.0000000000001262	KQ1E1 KQ2E1 KQ3E1
O'Byrne, P, MacPherson, P. Syphilis. BMJ. 365(): l4159. 2019. PMID: 31253629. https://dx.doi.org/10.1136/bmj.l4159	KQ1E7 KQ2E7 KQ3E7
Ong, JJ, Fu, H, et al. Missed opportunities for sexually transmitted infections testing for HIV pre-exposure prophylaxis users: a systematic review. J Int AIDS Soc. 24(2): e25673. 2021. PMID: 33605081. https://dx.doi.org/10.1002/jia2.25673	KQ1E1 KQ2E1 KQ3E1
Parra-Rodriguez, L, Imran, S, et al. Screening for hiv and syphilis co-infection in patients with gonorrhea and/or chlamydia in the emergency departments of two chicago safety-net hospitals. Sex Transm Dis. 47(9 suppl 2): S135-s136. 2020.	KQ1E1 KQ2E1 KQ3E1
Peel, J, Chow, EPF, et al. Clinical presentation of incident syphilis among men who have sex with men taking HIV Pre-Exposure Prophylaxis in Melbourne, Australia. Clin Infect Dis. 01(): 01. 2021. PMID: 33522575. https://dx.doi.org/10.1093/cid/ciab052	KQ1E3 KQ2E1 KQ3E1
Schmidt, AJ, Rasi, M, et al. The Swiss STAR trial - an evaluation of target groups for sexually transmitted infection screening in the sub-sample of men. Swiss Med Wkly. 150(): w20392. 2020. PMID: 33382077. https://dx.doi.org/10.4414/smw.2020.20392	KQ1E1 KQ2E1 KQ3E1

Appendix C. Excluded Studies List

Reference	Code
Schumacher, C, Wu, L, et al. Sexually Transmitted Infection Screening Among Gay, Bisexual, and Other Men Who Have Sex With Men Prescribed Pre-exposure Prophylaxis in Baltimore City, Maryland. Clin Infect Dis. 71(10): 2637-2644. 2020. PMID: 31761944. https://dx.doi.org/10.1093/cid/ciz1145	KQ1E1 KQ2E1 KQ3E1
Stanford, KA, Hazra, A, et al. Routine Opt-out Syphilis Screening in the Emergency Department: A Public Health Imperative. Acad Emerg Med. 27(5): 437-438. 2020. PMID: 31802561. https://dx.doi.org/10.1111/acem.13897	KQ1E7 KQ2E7 KQ3E7
Stockton, JM. Assessment for sexually transmitted infections in men who have sex with men attending a nurse-run HIV preexposure prophylaxis clinic. J Am Assoc Nurse Pract. 18(): 18. 2021. PMID: 33625163. https://dx.doi.org/10.1097/JXX.0000000000000569	KQ1E1 KQ2E1 KQ3E1
Suijkerbuijk, AWM, Over, EAB, et al. Consequences of restricted STI testing for young heterosexuals in the Netherlands on test costs and QALY losses. Health Policy (New York). 122(2): 198-203. 2018. PMID: 29246657. https://dx.doi.org/10.1016/j.healthpol.2017.12.001	KQ1E1 KQ2E1 KQ3E1
Sullivan, PS. Practical Considerations for Implementing a New Syphilis Action Plan. Sex Transm Dis. 45(9S Suppl 1): S78-S79. 2018. PMID: 29485538. https://dx.doi.org/10.1097/OLQ.0000000000000826	KQ1E7 KQ2E7 KQ3E7
Taine, S, Norcross, C, et al. Changing face of the syphilis epidemic in men who have sex with men. Sex Transm Infect. 94(7): 501. 2018. PMID: 30082332. https://dx.doi.org/10.1136/sextrans-2018-053749	KQ1E7 KQ2E7 KQ3E7
Vernazza, PL, Rasi, M, et al. The Swiss STAR trial - an evaluation of target groups for sexually transmitted infection screening in the sub-sample of women. Swiss Med Wkly. 150(): w20393. 2020. PMID: 33382076. https://dx.doi.org/10.4414/smw.2020.20393	KQ1E1 KQ2E1 KQ3E1
Wanni, NHO, Dossary, RA, et al. Seropositivity of syphilis among individuals screened in a tertiary hospital in the Eastern Province of Saudi Arabia. Ann Saudi Med. 41(1): 8-13. 2021. PMID: 33550909. https://dx.doi.org/10.5144/0256-4947.2021.8	KQ1E1 KQ2E1 KQ3E1
Wilson, E, Free, C, et al. Internet-accessed sexually transmitted infection (e-STI) testing and results service: A randomised, single-blind, controlled trial. PLoS Medicine / Public Library of Science. 14(12): e1002479. 2017. PMID: 29281628. https://dx.doi.org/10.1371/journal.pmed.1002479	KQ1E4 KQ2E1 KQ3E1
Wood, H, Gudka, S. Pharmacist-led screening in sexually transmitted infections: current perspectives. Integrated Pharmacy Research & Practice. 7(): 67-82. 2018. PMID: 29942790. https://dx.doi.org/10.2147/IPRP.S140426	KQ1E7 KQ2E1 KQ3E1

Appendix D Table 1. Ongoing Screening Studies

Study reference/ trial identifier Primary Investigator	Study name	Location	Estimated N	Intervention Description	Relevant Outcomes	Status* Estimated Completion
ChiCTR1900022409 Weibin Cheng and Cheng Wang	Promoting routine syphilis screening among men who have sex with men in China	China	444	High-risk MSM will be recruited online and randomized in a 1:1:1 ratio to (1) standard syphilis self-testing arm; (2) a self-testing arm program enhanced with crowdsourcing and a lottery-based incentive, and (3) a standard of care (control). Participants in each arm will be followed-up at three and 6 months through WeChat (a social media app like Facebook messenger). Confirmation of syphilis self-test use will be determined by requiring participants to submit a photo of the used test kit to study staff via secure data messaging.	Proportion of participants who tested for syphilis in the past 3 months, number of newly identified syphilis infections, linkage to syphilis clinical care after self-testing	NR (Preliminary data published) July 2020
NCT04514848 Ameeta Singh, BMBS (UK), MSc, FRCPC	Dual Syphilis and HIV Point of Care Testing (POCT) to Improve Access to Testing Among Inner City, Remote, Rural and Hard to Reach Populations in Alberta	Canada	1500	Individuals at risk for syphilis and HIV (e.g., gay and bisexual men, indigenous communities experiencing a resurgence of syphilis, persons who inject drugs, etc.) will undergo testing with both POCT and standard laboratory testing. Individuals testing positive for syphilis or HIV on the POCT will be informed that this is a preliminary positive and standard testing will be done. Individuals testing positive for syphilis on POCT may be offered treatment at the time of testing.	Diagnostic accuracy of the Multiplo TP/HIV test and the INSTI Multiplex HIV-1/HIV-2/Syphilis Antibody Test in field settings	Recruiting December 31, 2021