

# Letters

## RESEARCH LETTER

### EVIDENCE REPORT

#### Screening for Syphilis Infection in Nonpregnant Adults and Adolescents: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Syphilis is a sexually transmitted infection (STI) caused by the bacterium *Treponema pallidum*. In 2019, the reported incidence of syphilis was 39.7 cases per 100 000 population, increasing 75% from 2015.<sup>1</sup>

In 2016, the US Preventive Services Task Force (USPSTF) recommended screening for syphilis infection in asymptomatic, nonpregnant adults and adolescents at increased risk for syphilis infection (A recommendation).<sup>2</sup> High-risk groups included men who have sex with men (MSM), persons living with HIV, and persons living in communities with a high prevalence of infection. This targeted evidence update was conducted

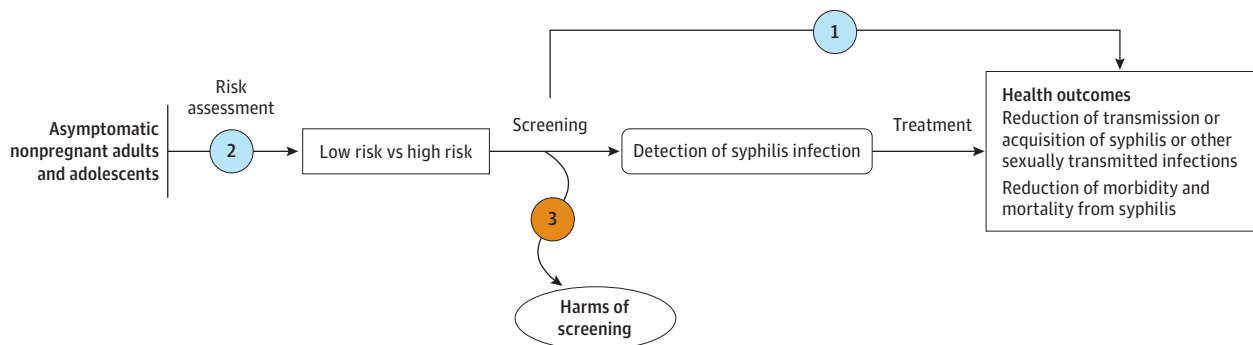
to inform the USPSTF for an updated recommendation statement and focused solely on the new evidence since the 2016 recommendation.

**Methods** | An analytic framework and 3 key questions (KQs) guided the evidence update (Figure). Detailed methods are available in the full evidence report.<sup>3</sup> A literature search of MEDLINE and the Cochrane Central Register of Controlled Trials was conducted from January 1, 2016, to June 3, 2021. Ongoing surveillance in targeted publications was conducted through April 6, 2022. We included studies of asymptomatic, nonpregnant adolescents and adults who were not known to have current syphilis infection. We excluded studies conducted exclusively in populations with HIV and studies conducted in low- to middle-income countries. Two investigators independently evaluated articles for inclusion criteria and quality.

**Results** | A summary of the evidence is presented in the Table. A total of 2780 titles and abstracts and 40 full-text articles were screened. One fair-quality cohort study (n = 117 387) addressed the association between screening for syphilis and complications of the disease (KQ1).<sup>4</sup> Chow et al reported that the proportion of MSM screened annually and the mean

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Figure. Analytic Framework: Screening for Syphilis Infection in Nonpregnant Adults and Adolescents



#### 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 (eg, based on 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 (eg, stigma, sequelae of test inaccuracy)?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service.

The questions are depicted by linkages that relate to interventions and outcomes. Further details are available from the USPSTF Procedure Manual (<https://www.uspreventiveservicestaskforce.org/uspstf/procedure-manual>).

**Table. 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**

Evidence summary in 2016	New evidence findings	Limitations of new evidence	Consistency of new evidence with prior evidence findings
<b>KQ1: Effectiveness of screening</b>			
No studies directly compared the effectiveness of syphilis screening in screened vs unscreened populations of nonpregnant adolescents or adults	One fair-quality <sup>a</sup> 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-y follow-up period <sup>4</sup>	Risk of bias: Did not report data on loss to follow-up; potential confounding of variables  Applicability: Conducted in MSM, including 31% HIV-positive MSM, attending publicly funded sexual health clinics in Australia	NA (no studies identified in the prior review)
<b>KQ1a: Effectiveness of screening intervals</b>			
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 = .001), newly acquired syphilis in MSM living with HIV (7.3 cases vs 2.8 cases per 1000 patient-years; P < .05); early latent syphilis in MSM (1.7% vs 0.4%; P = .008); and early syphilis in higher-risk MSM (53% vs 16%; P = .001) when screening every 3 mo vs 6 or 12 mo	No studies met inclusion criteria for this evidence update	NA (no new studies identified in the current review)	NA (no new studies identified in the current review)
<b>KQ2: Performance of risk assessment instruments or other risk stratification methods</b>			
No studies evaluated the performance of risk assessment	One fair-quality <sup>a</sup> 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 3 mo demonstrated an AUC of 69% and included the risk factors current HIV infection, history of syphilis infection, number of male sex partners in the prior 3 mo, and sex role for anal sex in the prior 3 mo <sup>5</sup>	Risk of bias: Participants with no follow-up 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	NA (no studies identified in the prior review)
<b>KQ3: Harms of screening</b>			
No studies directly assessed the harms of screening for syphilis	One fair-quality <sup>a</sup> pre-post US study (n = 1097) 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 pretest and posttest  Factors associated with increased stress experience included history of injection drug use, Black race, less than a high school education, and single marital status <sup>6</sup>	Risk of bias: Did not report data on loss to follow-up, although loss to follow-up was likely minimal because pretest and posttest data were collected at same study visit  Applicability: Conducted at a behavioral research center in the US, 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 pretest and posttest	NA (no studies identified in the prior review)

Abbreviations: AUC, area under the curve; 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; USPSTF, US Preventive Services Task Force.

Questions around the diagnostic accuracy were not addressed in this review.

<sup>a</sup> Two reviewers independently assessed the methodological quality of each included study using predefined criteria appropriate to the study design (ie, CHARMS checklist, National Heart, Lung, and Blood Institute [NHLBI] tool for

observational and cross-sectional studies, NHLBI tool for pre-post studies). Articles were rated 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 1 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. All poor-quality studies were excluded from this review. Disagreements were resolved by discussion.

number of tests per MSM performed annually increased between 2007 and 2014. In addition, in HIV-negative MSM, a 17% increase (from 27% of total syphilis diagnoses in 2007 to 44% in 2014) in the proportion of early latent syphilis

infections was identified, as well as a 5% decrease (from 24% of total diagnoses in 2007 to 19% in 2014) in the proportion of secondary syphilis infections, suggesting an interruption of disease progression. Similar although more

pronounced trends were found among HIV-positive MSM. No studies reported on other outcomes of interest, such as acquisition or transmission of other STIs or complications of tertiary syphilis or neurosyphilis.

One fair-quality study (n = 361) addressed the performance of risk assessment methods (KQ2).<sup>5</sup> Allan-Blitz et al developed and evaluated an online risk calculator for predicting future syphilis among high-risk individuals (eg, individuals living with HIV or who have a history of syphilis infection) seeking STI testing or treatment. The final model for predicting syphilis incidence within the next 3 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, and receptive sex role in anal sex in the past 3 months.

One fair-quality study (n = 1097) addressed potential harms of screening for syphilis (KQ3).<sup>6</sup> Reynolds et al examined factors associated with emotional stress just before and after syphilis testing. Factors that were associated with stress at pretest were injection drug use, Black race, and less than a high school education. Factors associated with stress at posttest included less than a high school education and single marital status. The results suggested that emotional stress may be a common experience for individuals, although the study did not directly compare changes in levels of emotional stress pretest vs posttest.

**Discussion** | The findings of this targeted evidence update are generally consistent with those from the prior systematic review that supported the USPSTF 2016 statement recommending screening for syphilis in at-risk adolescents and adults. Limitations of this review include that only studies in English, conducted in very high-income and high-income countries, and conducted in settings and with tests applicable to current practice in the US were included. Further research on novel screening approaches, how to best identify persons most likely to benefit from screening, and the effectiveness of specific screening intervals among different risk populations is still needed.

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

**Concept and design:** Henninger, Lin.

**Acquisition, analysis, or interpretation of data:** Henninger, Bean.

**Drafting of the manuscript:** Henninger, Bean.

**Critical revision of the manuscript for important intellectual content:** Lin.

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**Supervision:** Henninger, Lin.

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**Role of the Funder/Sponsor:** Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

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**Additional Information:** A draft version of this evidence report underwent external peer review from 2 content experts (Kahlil Ghanem, MD, PhD, Johns Hopkins University; Elitza Theel, PhD, Mayo Clinic) and 4 federal partners (Centers for Disease Control and Prevention, US Food and Drug Administration, National Institute of Allergy and Infectious Diseases, and Eunice Kennedy Shriver National Institute of Child Health and Human Development). Comments were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

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

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