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Syphilis Screening for Adolescents and Adults

Rapid Review

CADTH

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Abbreviations

MSM	men who have sex with men
USPSTF	US Preventive Services Task Force

Key Messages

- The literature search did not identify any studies with relevant evidence on the clinical utility of syphilis screening using risk-based approaches versus population-wide approaches for adolescents and adults.
- One overview of systematic reviews of variable methodological quality did not identify any systematic reviews on the clinical utility of syphilis screening comparing risk-based assessment to routine population-based screening in people at low risk of syphilis.

Context and Policy Issues

Syphilis is a sexually transmitted infection caused by *Treponema pallidum* bacterium.[1] In 2018, WHO estimated that there were 7.1 million new syphilis infections globally.[2] In Canada, syphilis is the third most-reported notifiable sexually transmitted infection. The national rate of infectious syphilis has risen from 6.7 per 100,000 population in 2014[3] to 24.1 per 100,000 in 2020.[4] Nine provincial or territorial outbreaks of syphilis infection were declared in Canada as of November 2020.[3] These increased rates have been associated with behavioural risks such as lapses in safe sex practice, increased recreational sexual encounters, and substance use.[5]

Screening for syphilis can prevent adverse health outcomes and reduce transmission.[1] The Public Health Agency of Canada currently recommends that anyone with risk factors for syphilis should be screened.[6] Risk factors for syphilis include unprotected sexual activity, especially in men who have sex with men (MSM); sexual contact with an identified case of syphilis; sexual contact with an individual from a country or region with an elevated prevalence of syphilis; individuals previously tested positive for syphilis, HIV, or other sexually transmitted bloodborne infection; born to a person with syphilis during pregnancy; and being a member of a vulnerable population.[7]

In 2016, the US Preventive Services Task Force (USPSTF) also recommended screening people at increased risk for syphilis, including people living in communities with a high prevalence, people with HIV, MSM who engage in high-risk sexual behaviour, commercial sex workers, people who exchange sex for drugs, and adults in prisons.[8,9] An update to the 2016 USPSTF recommendation for risk-based screening is underway and not yet available.

An alternative to risk-based syphilis screening is a population-wide approach, in which screening is systematically offered to everyone in a target group, regardless of individual risk factors.[10] It is important to consider the clinical utility of this screening approach given that syphilis incidence has risen over time and there are epidemics across Canada, with a greater number of outbreaks in the larger population and not solely in high-risk groups. For example, syphilis rates increased in both heterosexual men and women from 2011 to 2020, and the magnitude of the increase was greater in women, especially in women of reproductive age (15 years to 49 years) from 2016 to 2020.[4] In 2004, the USPSTF recommended against routine screening in asymptomatic men and nonpregnant women not at increased risk of syphilis infection.[11] However, in 2016, USPSTF found convincing evidence that screening for syphilis in asymptomatic, nonpregnant persons at increased risk for infection was effective and provided substantial benefit.[12] Mathematical modelling projections also suggest that testing every 3 months at 100% annual coverage or every 6 months at 52% annual screening could reduce syphilis transmission at the population level.[13,14]

This Rapid Response report aims to review the clinical utility of syphilis screening using risk-based screening approaches for adolescents and adults compared with population-wide approaches.

Research Question

What is the clinical utility of syphilis screening using risk-based approaches versus population-wide approaches for adolescents and adults?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were syphilis, screening, syphilis tests, and risk assessment. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons; and randomized controlled trials, controlled clinical trials, or any other type of clinical trial.

If possible, retrieval was limited to the human population. The search was completed on May 18, 2022, and limited to English-language documents published after January 1, 2012.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before 2012. It was also planned that systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews would be excluded, and primary studies captured in 1 or more included systematic reviews would be excluded. However, because no potentially relevant studies were identified, none of these criteria were applied.

Critical Appraisal of Individual Studies

The included publication was critically appraised by 1 reviewer using the A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[15] instrument for systematic reviews. Summary

scores were not calculated for the included study; rather, the strengths and limitations of the included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 1,032 citations were identified in the literature search. Following screening of titles and abstracts, 1,005 citations were excluded and 27 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 31 potentially relevant articles, 30 publications were excluded for various reasons, and 1 overview of systematic reviews (overview or reviews)[16] met the inclusion criteria and was included in this report. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA)[17] flow chart of the study selection.

The 2022 evidence synthesis update by the USPSTF on the effectiveness of syphilis screening in nonpregnant adolescents and adults[9] was screened and excluded because it did not meet the selection criteria for this report.[9] The key questions guiding the USPSTF evidence review[9] included the effectiveness and harms of screening, and it provided no relevant evidence about the clinical utility of syphilis screening using risk-based approaches versus population-wide approaches for adolescents and adults. The review[9] included 1 cohort study on the effectiveness of annual syphilis screening of MSM and 1 before-and-after study assessing the factors associated with a stressful syphilis testing experience.

Additional references of potential interest are provided in Appendix 4.

Summary of Study Characteristics

One overview of reviews,[16] published in 2015, was included. It was written by authors in Canada, based on a research question focusing on screening adult patients (16 years of age and older) at low risk for syphilis.[16] The other selection criteria included risk-based screening

Table 1: Selection Criteria

Criteria	Description
Population	Adolescents and adults
Intervention	Risk-based screening (based on clinician assessment and opinion) for syphilis with serologic testing using traditional or reverse sequence algorithms
Comparator	Population-wide screening, at any time interval (e.g., 3 months, 6 months, 12 months), for syphilis with serologic testing using traditional or reverse sequence algorithms
Outcomes	Clinical utility (e.g., incidence of syphilis [infectious or non-infectious], neurosyphilis, or congenital syphilis, proportion of participants who receive unnecessary or inadequate treatment [e.g., due to false-positive or false-negative test results], participant acceptability, safety [e.g., adverse events, psychosocial harms])
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

(intervention) and routine population screening (control) at community clinics (setting), with identification of syphilis as outcome. Eligible study designs were synthesized evidence studies and guidelines. Evidence-based guidelines are not relevant for this report and will not be described. The authors did not search for primary studies. The authors searched multiple databases for synthesized studies published between 2005 and July 10, 2015. The overview of reviews did not identify any relevant synthesized evidence studies for inclusion.[16]

Additional details regarding the characteristics of included systematic review are provided in Appendix 2.

Summary of Critical Appraisal

The overview of reviews[16] was assessed with a focus on the comprehensiveness and quality of search strategies, study selection and inclusion criteria to understand whether it may have missed key studies. It was not evaluated for the quality of reporting and evidence assessment.

The overview of reviews[16] demonstrated both strengths and limitations. The research objective and eligibility criteria were made clear, which is important for framing and establishing the aim and research question of a review. The search covered multiple bibliographic databases. Screening and selection were conducted by 2 reviewers, which is an important feature of a well-conducted systematic review because it helps to minimize the risk of bias due to preferential study selection and reduces the potential for error. However, the authors of the overview of reviews[16] did not report if they developed a review protocol in advance of conducting the study, which is important to ensure transparency and reproducibility of the review and to assess deviations that could introduce bias. Also, there were no searches of the grey literature, study registries (e.g., PROSPERO), and the reference lists of included systematic reviews for potentially relevant studies not captured by the database searches.

Details regarding the strengths and limitations of the included publication are provided in Appendix 3.

Summary of Findings

Clinical Utility of Syphilis Screening

No relevant evidence regarding syphilis screening using risk-based approaches versus population-wide approaches for adolescents and adults was identified; therefore, no summary can be provided.

Limitations

This report is limited by the quantity of evidence. One overview of reviews[16] on risk-based screening versus population-wide routine screening was included. However, the search strategy of this review[16] was restricted to synthesized evidence of "low-risk" and "non–high-risk" adults and did not identify studies relevant for this report. The overview of reviews[16] did not include any studies; thus, it did not contribute evidence to this report.

Based on the findings of this report, there appears to be a lack of published systematic reviews and primary clinical studies regarding the clinical utility of risk-based screening compared to population-wide screening for syphilis in adolescents and adults.

Conclusions and Implications for Decision- or Policy-Making

This report included 1 overview of reviews[16] that met the pre-specified inclusion criteria in Table 1. However, the overview of reviews[16] did not contribute any evidence to answer the research question of interest to this report because it did not include any studies. Therefore, a conclusion could not be drawn regarding the clinical utility of syphilis screening in adolescents and adults using risk-based versus population-wide approaches.

In view of the limited comparative evidence regarding the clinical utility of risk-based versus population-based syphilis screening approaches in the clinical literature, there is a need for further research examining these 2 different approaches to inform decision-makers on the best approach for syphilis screening in Canada.

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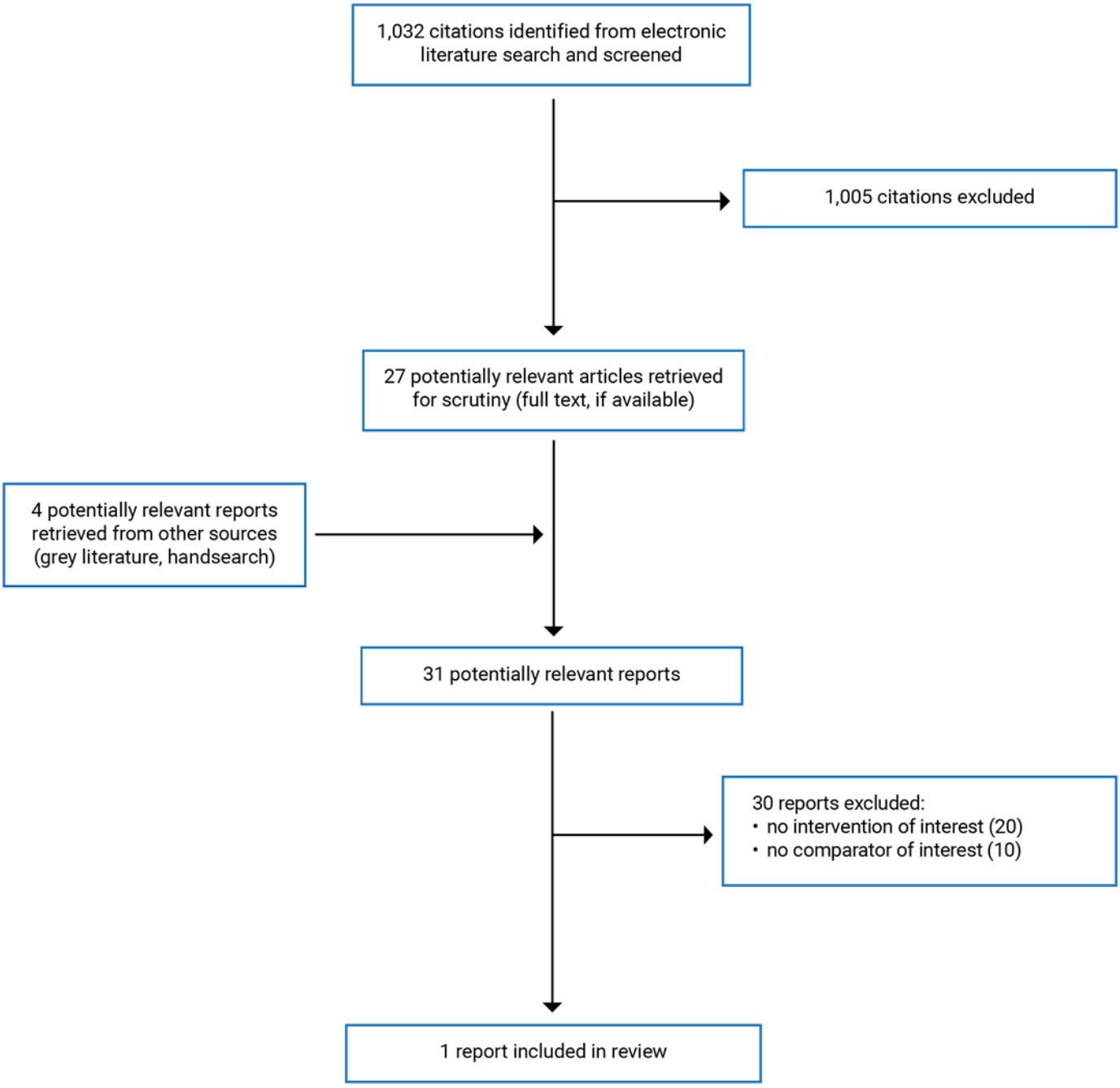
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34. PubMed

Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Review question, numbers of reports included	Inclusion criteria	Intervention and comparator	Clinical outcomes, length of follow-up
Fernane and Fowler 2015[16] Canada **Funding source**: NR	**Review question**: Is it efficacious to screen low-risk clients? No relevant reports were included in the overview of reviews	**Population**: general population ≥ 16 years of age **Settings**: community clinics **Study design:** synthesized research **Date of publication:** 10 years (2005 to 2015)	**Intervention**: Syphilis screening based on risk assessment (excluding prenatal testing, HIV testing, congenital syphilis) **Comparator**: Routine screening of population for syphilis	**Outcome**: Identification of syphilis **Follow-up**: NA

NA = not applicable; NR = not reported.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 3: Strengths and Limitations of Systematic Review Using AMSTAR 2[15]

Strengths	Limitations
Fernane and Fowler (2015)[16]	
• The review question was clearly stated • The inclusion criteria for the review included the population, intervention, comparator group, and outcome • The inclusion and exclusion criteria were clearly described • Multiple databases (EBM Reviews, Global Health, Ovid Healthstar, MEDLINE) were searched • Search strategies were provided, and they were appropriate • Study screening and selection were done by 2 reviewers	• An a priori protocol was not reported for the review • A search of the grey literature was not performed • A search of study registries was not performed • A search of the reference lists or bibliographies of screened studies was not performed • Although reasons for the exclusion of studies were provided, a list of the excluded systematic reviews was not • Authors did not disclose whether they had conflicts of interest related to this review • Authors did not report their funding sources

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2.

Appendix 4: References of Potential Interest

Note that this appendix has not been copy-edited.

Review Articles

Adawiyah RA, Saweri OPM, Boettiger DC, et al. The costs of scaling up HIV and syphilis testing in low- and middle-income countries: a systematic review. *Health Policy Plan*. 2021;36(6):939-954. PubMed

Cantor AG, Pappas M, Daeges M, Nelson HD. Screening for Syphilis: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2016;315(21):2328-2337. PubMed

Henninger MH BS, Lin JS. Screening for Syphilis Infection in Nonpregnant Adolescents and Adults: A Targeted Evidence Update for the U.S. Preventive Services Task Force. Evidence Synthesis No. 218. Rockville (MD): Agency for Healthcare Research and Quality; 2022: https://www.uspreventiveservicestaskforce.org/uspstf/document/draft-evidence-review/syphilis-infection-nonpregnant-adults-adolescents-1 Accessed 24 May 2022.

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Ong JJ, Fu H, Baggaley RC, et al. Missed opportunities for sexually transmitted infections testing for HIV pre-exposure prophylaxis users: a systematic review. *J Int AIDS Soc*. 2021;24(2):e25673. PubMed

Pearce-Smith N. What is the effect of syphilis testing frequency on the incidence of syphilis in men who have sex with men (MSM)? London (UK): Public Health England; 2018: https://ukhsa.koha-ptfs.co.uk/cgi-bin/koha/opac-retrieve-file.pl?id=7ab5fe97bc0c66f48278980b7f3ead48 Accessed 20 May 2022.

Rapid Response Service. Interventions and best practices to address increasing rates of syphilis transmission. Toronto (ON): Ontario HIV Treatment Network; 2022: https://www.ohtn.on.ca/wp-content/uploads/2022/02/RR167_Syphilis-interventions_February152022.pdf Accessed 20 May 2022.

Werner RN, Gaskins M, Nast A, Dressler C. Incidence of sexually transmitted infections in men who have sex with men and who are at substantial risk of HIV infection - A meta-analysis of data from trials and observational studies of HIV pre-exposure prophylaxis. *PLoS ONE*. 2018;13(12):e0208107. PubMed

Randomized Controlled Studies

Burchell AN, Tan DHS, Grewal R, et al. Routinized Syphilis Screening Among Men Living With Human Immunodeficiency Virus: A Stepped Wedge Cluster Randomized Controlled Trial. *Clin Infect Dis*. 2022;74(5):846-853. PubMed

Wang C, Ong JJ, Zhao P, et al. Expanding syphilis test uptake using rapid dual self-testing for syphilis and HIV among men who have sex with men in China: A multiarm randomized controlled trial. *PLoS Med*. 2022;19(3):e1003930 PubMed

Non-Randomized Studies

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):261-268. PubMed

Chen XS. Turning off the tap: sustaining elimination of congenital syphilis through the programme targeting high-risk groups. *J Glob Health*. 2019;9(2):020312. PubMed

Clement ME, Hammouda A, Park LP, et al. Screening Veterans for Syphilis: Implementation of the Reverse Sequence Algorithm. *Clin Infect Dis*. 2017;65(11):1930-1933. PubMed

Cornelisse VJ, Chow EPF, Latimer RL, et al. Getting to the Bottom of It: Sexual Positioning and Stage of Syphilis at Diagnosis, and Implications for Syphilis Screening. *Clin Infect Dis*. 2020;71(2):318-322. PubMed

Harmon JL, Dhaliwal SK, Burghardt NO, et al. Routine Screening in a California Jail: Effect of Local Policy on Identification of Syphilis in a High-Incidence Area, 2016-2017. *Public Health Rep*. 2020;135(1_suppl):57S-64S. PubMed

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Modelling Studies

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