Letters

RESEARCH LETTER

EVIDENCE REPORT

Screening for Syphilis Infection During Pregnancy: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Prior evidence has demonstrated that screening in pregnancy is effective at detecting syphilis and that treatment is effective at preventing congenital syphilis and adverse pregnancy outcomes. The purpose of this review was to conduct a limited update of the evidence for the benefits and harms of screening and harms of treatment of syphilis during pregnancy for the US Preventive Services Task Force to reaffirm its 2018 recommendation.[1,2]

Editorial

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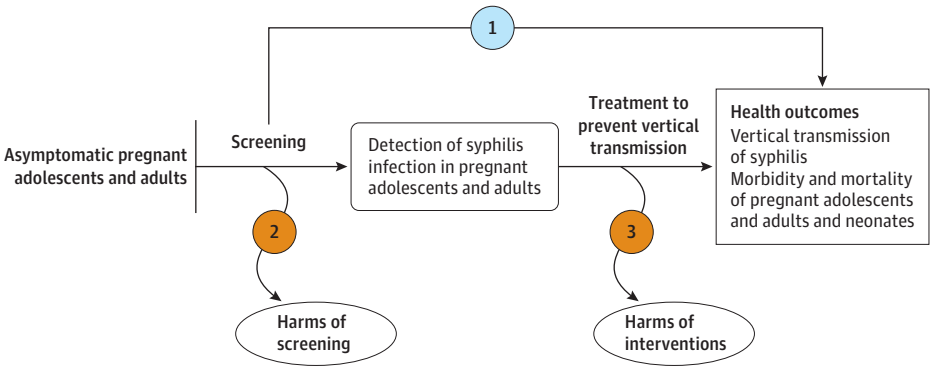
Methods | An analytic framework and 3 key questions (KQs) guided the update (**Figure**). A literature search of Cochrane Library, Ovid MEDLINE, and trial registries was conducted from January 1, 2017, through July 25, 2023, with surveillance through March 21, 2025. Two investigators independently screened abstracts and articles and rated study quality using predefined criteria. Detailed methods and results are available in the full evidence review.[4] The review also reported on a contextual question regarding the need for repeat screening during pregnancy; this question was not evaluated systematically.

For evidence on screening, eligible studies included asymptomatic pregnant adolescents and adults, screened using US Food and Drug Administration–approved tests that compared different 2-step serologic screening algorithms or compared single tests with a 2-step algorithm. Screening benefits included reduction in congenital syphilis and neonatal or maternal morbidity and mortality. Eligible screening harms included false-positive or false-negative results and psychosocial harms. The evidence review on harms of treatment was restricted to studies of syphilis treatment during pregnancy using penicillin. Eligible treatment harms included allergic reaction, premature labor, Jarisch-Herxheimer reaction, fetal harms, and other maternal harms.

Results | We found no new studies addressing the effectiveness of screening to reduce congenital syphilis or other adverse pregnancy outcomes (KQ1). Five new studies (51 118 participants) addressed the harms of screening (KQ2), and 2 studies (130 participants) addressed the harms of treatment (KQ3). A summary of the evidence is presented in the **Table**.

For screening harms, index test positivity across the 5 studies ranged between 1.0% and 4.8% and estimates of false-positive results ranged between 0% and 65%, varying by the index test evaluated and to which algorithm the index test was compared. One fair-quality, prospective study of traditional 2-step screening (nontreponemal test followed by treponemal

Figure. Analytic Framework and Key Questions: Screening for Syphilis Infection During Pregnancy



Key questions

1. Does screening for syphilis in pregnant adolescents and adults reduce the incidence of congenital syphilis in newborns?
2. What are the harms of screening for syphilis in pregnant adolescents and adults?
3. What are the harms of treatment of syphilis with penicillin during pregnancy to pregnant adolescents and adults or newborns?

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.[3]

Table. Summary of Evidence: Screening for Syphilis Infection During Pregnancy

Rationale and foundational evidence	Limitations of foundational evidence	Prior evidence (2018)	New evidence: No. of studies (study design); No. of participants	New evidence findings	Limitations of new evidence	Consistency of new evidence with foundational evidence
KQ1: Benefits of screening						
Observational studies demonstrate an association between fewer adverse outcomes in pregnant women treated for syphilis compared with those not treated Universal screening in early pregnancy can prevent congenital syphilis	Observational data using historical and geographic comparators Unclear applicability of study body, which comes from studies conducted in China	One observational study evaluating the implementation of screening for syphilis in more than 2 million pregnant women in Shenzhen, China, demonstrated an 11-fold decrease in congenital syphilis over 10 y	None	No new studies identified that evaluated benefits of screening pregnant adolescents and adults for syphilis	NA	NA
KQ2: Harms of screening						
Two-step screening algorithms (traditional and reverse-sequence) can detect syphilis in pregnancy with high accuracy and reliability No severe adverse outcomes	Most accuracy studies only report on the test accuracy of the initial treponemal or nontreponemal test and not the accuracy of the screening algorithm	Five studies demonstrated that false-positive results with CIA or EIA in pregnancy are common One study demonstrated that undiluted serum with high titers of nontreponemal antibodies can result in false-negative RPR test results	5 Studies (single-group cohorts); 51 118 participants	False-positive results ranged between 0% and 65%, depending on the screening algorithm and index test evaluated; 1 study reported on false-negative results (0%)	The range of estimates is based on a variety of different screening tests	Two-step screening algorithms should be used to screen for syphilis in pregnancy because false-positive results from single tests are common
KQ3: Harms of treatment						
Parenteral penicillin G is accepted as safe and effective for treatment of syphilis in pregnancy	Studies of other treatments in pregnant persons are lacking	None	2 Studies (single-group cohorts); 39 participants in study of JH reactions, 91 participants in study of penicillin desensitization	JH reactions: 2/39 (5.1%); of these, 1 went on to have a stillbirth, but the presence of congenital syphilis could not be established, and other diagnoses could not be ruled out Overall IHR: 2/91 (4.4%) IHR among high-risk persons receiving oral desensitization: 3/11 (27.3%) IHR among high-risk persons receiving intravenous desensitization: 1/40 (2.5%) IHR among low-risk persons undergoing penicillin provocation: 1/40 (2.5%) Incomplete penicillin therapy (switched to doxycycline): 2/91 (2.2%)	Included study designs do not permit causal inference but offer ranges of estimates for bounding of harms	New studies offer evidence for bounding of harms

Abbreviations: CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; IHR, immediate hypersensitivity reaction; JH, Jarisch-Herxheimer; NA, not applicable; RPR, rapid plasma reagin.

test) reported a false-positive rate of 31% (11/35) for the initial nontreponemal test compared with the treponemal test. Five studies using a reverse-sequence, 2-step screening algorithm (treponemal test followed by nontreponemal test) reported false-positive rates that varied substantially (7%-65%). Three of those studies, all fair quality, were conducted prospectively, and 2 studies, 1 fair quality and 1 good quality, were conducted retrospectively. One study comparing a treponemal test with a nonstandard, composite 2-step screening algorithm reported no false-positives (0/15) and no false-negatives (0/301).

For treatment harms, 1 fair-quality study (n = 39) reported Jarisch-Herxheimer reaction in 5.1% of participants, and 1 good-quality study (n = 91) reported that 2.5% of participants had adverse reactions to standard penicillin provocation or desensitization protocols.

For the contextual question on repeat screening, we identified 3 retrospective cohort studies and 1 national registry. In a US national sample, approximately 5% of congenital syphilis cases occurred in pregnancies that initially screened negative for syphilis. Two of 3 cohort studies concluded that about one-half of congenital syphilis cases might be prevented with third-trimester repeat screening and adequate treatment, whereas the third study estimated that about one-fourth of cases might be preventable.

Discussion | Although screening and early treatment for syphilis in pregnancy decreases adverse maternal and neonatal outcomes, optimal screening algorithms have not been identified. This limited review found evidence consistent with prior reviews on screening for syphilis in pregnancy that supports the need for 2-step serologic screening to reduce inaccurate screening results. Although based on small studies, we found estimates of penicillin treatment harms that could be used for bounding of potential harms. This review did not systematically address the accuracy of screening tests or comparative effectiveness of different screening algorithms, nor did it address the effectiveness of screening more than once during pregnancy. More information is needed regarding third-trimester repeat screening.

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Author Contributions: Dr Asher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
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Additional Information: A draft version of the full evidence review underwent external peer review from 3 content experts (Catherine Squire Eppes, MD, MPH, Baylor College of Medicine; Peter Miksovsky, MD, Kaiser Permanente; and Jessica E. P. Williams, MD, Children's National Hospital) and 5 individuals from 4 federal partner organizations (*Eunice Kennedy Shriver* National Institute of Child Health and Development; National Center for HIV, Viral Hepatitis, STD, and Tuberculosis Prevention; National Eye Institute; and Office of Research on Women's Health). Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review. The USPSTF members and peer reviewers did not receive financial compensation for their contributions.

Editorial Disclaimer: This evidence review 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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