Screening for Syphilis Infection in Pregnant Women
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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**IMPORTANCE** The incidence of syphilis and congenital syphilis in the United States has increased after reaching historic lows in the early 2000s.

**OBJECTIVE** To systematically review literature on the effectiveness and harms of screening for syphilis in pregnancy and the harms of penicillin treatment in pregnancy to inform the US Preventive Services Task Force.

**DATA SOURCES** MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant English-language literature, published from January 1, 2008, to June 2, 2017. Ongoing surveillance was conducted through November 22, 2017.

**STUDY SELECTION** Studies conducted in countries categorized as “high” or “very high” on the Human Development Index that explicitly addressed 1 of 3 a priori-defined key questions.

**DATA EXTRACTION AND SYNTHESIS** Independent critical appraisal and data abstraction by 2 reviewers. Data from included studies were narratively synthesized without pooling data.

**MAIN OUTCOMES AND MEASURES** Incidence of congenital syphilis; any harms of screening or penicillin treatment in pregnancy.

**RESULTS** Seven studies in 8 publications were included. One observational study evaluated the implementation of syphilis screening in pregnancy in 2,441,237 women in China. From 2002 to 2012, screening for syphilis in all pregnant women increased from 89.8% to 97.2%, and the incidence of congenital syphilis decreased from 109.3 to 9.4 cases per 100,000 live births. Five studies (n = 21,795) evaluated the false-positive findings of treponemal tests and 1 study (n = 318) evaluated the false-negative findings of nontreponemal tests. These studies found that false-positives with treponemal-specific enzyme or chemiluminescent immunoassays were common (46.5%-88.2%), therefore warranting reflexive (automatic confirmatory) testing for all positive test findings. One study (n = 318) found no false-negatives with treponemal tests, and 1 study (n = 139) demonstrated the prozone phenomenon (false-negative response from high antibody titer) with rapid plasma reagin screening using undiluted samples (2.9%). No studies were identified for harms of penicillin in pregnancy.

**CONCLUSIONS AND RELEVANCE** Screening for syphilis infection in pregnant women is associated with reduced incidence of congenital syphilis, and available evidence supports the need for reflexive testing for positive test results.
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n the United States, the rate of reported congenital syphilis was 15.7 cases per 100 000 live births in 2016, the highest rate reported since 2001.1,2 Congenital syphilis is an infectious disease caused by the vertical transmission of Treponema pallidum; thus, prevention and detection of congenital syphilis depend on the identification of syphilis in pregnant women. Two screening protocols are commonly used: the traditional screening algorithm (ie, nontreponemal testing with reflex to treponemal testing) and the reverse sequence screening algorithm (ie, treponemal testing with reflex to nontreponemal testing) (Figure 1).3,4 Untreated syphilis in pregnancy carries significant risk for stillbirth or fetal loss, premature birth, low birthweight, congenital syphilis, and neonatal death.5,6 Parenteral benzathine penicillin G is the only recommended antibiotic for preventing maternal transmission of syphilis to the fetus and treating fetal syphilis infection.7 This evidence review was completed to inform the US Preventive Services Task Force (USPSTF) in the update to its 2009 “A” recommendation to screen all pregnant women for syphilis.8,9

Methods

Scope of Review

Because this topic represents well-established, evidence-based standards of practice, the USPSTF commissioned a targeted review using an updating process known as “reaffirmation,” which aims to identify “new and substantial evidence sufficient enough to change the prior recommendation.”10,11 As such, only the interval evidence for targeted key questions from the previous systematic review is included. After members of the USPSTF were consulted, an analytic framework and 5 key questions (KQs) were developed to guide the evidence update (Figure 2). Detailed methods and results, including evidence to address the effect of repeat testing for syphilis in the third trimester, at delivery, or both, are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/syphilis-infection-in-pregnancy-screening).

Data Sources and Searches

MEDLINE, PubMed (publisher-supplied references only), and the Cochrane Central Register of Controlled Trials were searched from January 1, 2008, to June 2, 2017 (eMethods in the Supplement). In addition to these searches, reference lists of existing reviews and primary studies were scanned. Searches were limited to articles published in English. Active surveillance via article alerts and targeted searches of high-impact factor journals to identify major studies published in the interim was conducted through November 22, 2017.

Study Selection

Two reviewers independently reviewed 453 unique citations and 34 full-text articles against a priori inclusion criteria (Figure 3; eTable 1 in the Supplement). For all KQs, studies conducted in countries categorized as “high” or “very high” on the Human Development Index were included. For evidence on the benefits of screening for syphilis in pregnancy (KQ1), randomized or non-randomized controlled intervention studies and large before-after or ecologic studies reporting the association of implement-
the timing of screening, treatment, or both (eg, if screening, treatment, or both occurred earlier in pregnancy in later years) was not reported. From 2002 to 2012, screening for syphilis in all pregnant women increased from 89.8% to 97.2%, and the incidence of congenital syphilis decreased from 109.3 to 9.4 cases per 100,000 live births. During this same period, in pregnant women infected with syphilis, the incidence of all adverse outcomes declined from 42.7% to 19.2%; incidence of congenital syphilis declined from 11.7% to 3.2%; and incidence of stillbirth or fetal loss declined from 19.0% to 3.3%. Although this study does not include an historical comparator (ie, a time point before implementation of the screening program) because the screening program was initiated in 2001 and screening commenced in 2002, the authors also report the incidence of congenital syphilis in Shenzhen compared with the national incidence. From 2002 to 2012, the incidence of congenital syphilis in China increased from 5.9 to 97.4 cases per 100,000 live births, while incidence of congenital syphilis specifically in Shenzhen decreased from 109.3 to 9.4 cases per 100,000 live births. No P values are reported for any of these comparisons or trends of outcomes. Despite methodological limitations (with both the historical and geographic comparisons) and concerns about applicability to US practice
timing of screening; treatment options, including termination of pregnancy and use of erythromycin for women with penicillin allergies), this study provides observational evidence that screening for, coupled with treatment of, syphilis in pregnancy is associated with a decrease in incidence of congenital syphilis.

Harms of Screening
Key Question 2. What are the harms of screening for syphilis in pregnant women?

Five new studies (n = 21,795) that reported on false-positive results of treponemal tests were identified,13-17 1 of which also reported on false-negative results,17 along with 1 new study (n = 318) that reported on false-negative results of nontreponemal testing (Table 1).18 No studies were found that addressed the diagnostic inaccuracy of the entire screening algorithm or other potential harms of screening for syphilis in pregnant women. Four large, fair-quality retrospective studies evaluated the proportion of false-positive results using treponemal-specific enzyme immunoassays (EIAs) or chemiluminescent immunoassays (CIAs) in screening pregnant women for syphilis.13-16 These studies found that false-positives with EIA or CIA were common (46.5 to 88.2%), therefore warranting reflexive (automatic confirmatory) testing for all positive CIA or EIA test results. None of the studies reported confidence intervals for false-positives.

One fair-quality retrospective study (n = 139) evaluated the prozone phenomenon using rapid plasma reagin (RPR) testing.18 The prozone phenomenon occurs when undiluted serum containing a high titer of nonspecific antibody (as may occur in secondary syphilis) produces a false-negative result attributable to a large quantity of antibodies occupying all the antigen sites (preventing flocculation).3 This study repeated RPR testing in discordant samples (RPR-negative/TPPA-positive) using diluted serum and found that 2.9% of discordant samples had a false-negative RPR result attributable to the prozone phenomenon.

Harms of Treatment
Key Question 3. What are the harms of treatment of syphilis with penicillin during pregnancy to pregnant women or newborns?

No studies directly examining the harms of penicillin in pregnancy and meeting the inclusion criteria were identified. In particular, no studies were found that addressed the risk of the Jarisch-Herxheimer reaction or serious adverse events in women with a history of penicillin allergy.

Discussion

The findings of this brief evidence review support the understanding that screening for syphilis early in pregnancy reduces congenital syphilis and also support the need for reflexive testing to investigate initial positive EIA/CIA test results in reverse sequence screening (Table 2). Screening for syphilis at the first prenatal visit to prevent congenital syphilis is standard of care and legally mandated in most US states.19 Observational evidence not
# Table 1. Harms of Screening for Syphilis in Pregnant Women

<table>
<thead>
<tr>
<th>Source (Country)</th>
<th>Patient Selection (No. of Pregnant Women Screened)</th>
<th>Study Design (Years)</th>
<th>Test Evaluated</th>
<th>Cutoff</th>
<th>Testing Strategy</th>
<th>No. of Positive or Negative Results/Total No. of Tests (%)</th>
<th>No. of False-Positive or False-Negative Results/Total No. of Positive or Negative Results (%)</th>
<th>Quality</th>
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<tbody>
<tr>
<td><strong>Reported Harm: False-Positive Results</strong></td>
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<tr>
<td>Treponemal-specific CIA</td>
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<td></td>
<td>ARCHITECT*</td>
<td>S/CO value ≥1.00 Reflex testing with RPR and TPPA</td>
<td>65/11 640 (0.56)</td>
<td>35/65 (5.3) Fair</td>
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<tr>
<td>Boonchaoy et al, 2016 (Thailand)</td>
<td>Pregnant women only (11 640)</td>
<td>Retrospective (2011-2013)</td>
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<tr>
<td>Wang et al, 2016 (China)</td>
<td>General population, including pregnant women (9600)</td>
<td>Retrospective (2013)</td>
<td></td>
<td>ARCHITECT*</td>
<td>S/CO value &gt;1.00 Reflex testing with TPPA; immunoblot used for confirmation of discordant samples</td>
<td>34/9600 (0.35)</td>
<td>30/34 (0.0) Fair</td>
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<tr>
<td>Mmeje et al, 2015 (United States)</td>
<td>Pregnant women only (NR)</td>
<td>Retrospective (2007-2010)</td>
<td>LIAISONc</td>
<td>NR</td>
<td>Reflex testing with RPR and TPPA</td>
<td>NR 156/194 (0.80)</td>
<td>Fair</td>
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<tr>
<td>Wellinghausen and Dietenberger, 2011 (Germany)</td>
<td>General population, including pregnant women (318)</td>
<td>Prospective (2010)</td>
<td>ARCHITECT*</td>
<td>Index ≥1.0</td>
<td>Reflex testing with FTA-ABS; immunoblot used for confirmation of discordant samples</td>
<td>0/318 (0)</td>
<td>NA Fair</td>
<td></td>
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<tr>
<td>Henrich and Yawetz, 2011 (United States)</td>
<td>General population, including pregnant women (NR)</td>
<td>Retrospective (2004-2007)</td>
<td>Syphilis-Gf</td>
<td>NR</td>
<td>Reflex testing with RPR and TPPA</td>
<td>NR 20/43 (0.46)</td>
<td>Fair</td>
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<td>TTPA</td>
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<td>TTPA</td>
<td>Titer ≥1.80</td>
<td>Reflex testing with FTA-ABS; recombinant IgG and IgM immunoblot used for confirmation of discordant samples</td>
<td>2/318 (0.63)</td>
<td>1/2 (0.50) Fair</td>
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<tr>
<td>Wellinghausen and Dietenberger, 2011 (Germany)</td>
<td>General population, including pregnant women (318)</td>
<td>Prospective (2010)</td>
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### Table 1. Harms of Screening for Syphilis in Pregnant Women (continued)

<table>
<thead>
<tr>
<th>Source (Country)</th>
<th>Patient Selection (No. of Pregnant Women Screened)</th>
<th>Study Design (Years)</th>
<th>Test Evaluated</th>
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<th>Testing Strategy</th>
<th>No. of Positive or Negative Results/Total No. of Tests (%)</th>
<th>No. of False-Positive or False-Negative Results/Total No. of Positive or Negative Results (%)</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Reported Harm: False-Negative Results</td>
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<td>RPR</td>
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<tr>
<td>Liu et al,18 2014 (China)</td>
<td>General population, including pregnant women (NR)</td>
<td>Retrospective (2010-2013)</td>
<td>RPR</td>
<td>RPR: Reactive at dilution of 1:1</td>
<td>TPPA: Titer ≥1:80</td>
<td>RPR test repeated for RPR−, TPPA+ samples using serum diluted to 1:32</td>
<td>Reflex testing of TPPA+ samples with CIA</td>
<td>NR 4/139 (2.9) (prozone phenomenon)</td>
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<td>TPPA</td>
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<td>Treknonemal-specific CIA</td>
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<td>Wellinghausen and Dietenberger,17 2011 (Germany)</td>
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<td>Prospective (2010)</td>
<td>ARCHITECTa</td>
<td>Index ≥1.0; Reflex testing with FTA-ABS; immunoblot used for confirmation of discordant samples</td>
<td>0/318 (0)</td>
<td>0/317 (0)</td>
<td>Fair</td>
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<td></td>
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<td></td>
<td>LIAISONc</td>
<td>Index ≥0.9 Reflex testing with FTA-ABS; immunoblot used for confirmation of discordant samples</td>
<td>1/318 (0.31)</td>
<td>0/317 (0)</td>
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<td></td>
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<td></td>
<td>TPPA</td>
<td>Titer ≥1:80 Reflex testing with FTA-ABS; recombinant IgG and IgM immunoblot used for confirmation of discordant samples</td>
<td>2/318 (0.63)</td>
<td>0/316 (0)</td>
<td>Fair</td>
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</tbody>
</table>

Abbreviations: CIA, chemiluminescent immunoassay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption test; NA, not applicable; NR, not reported; RPR, rapid plasma reagin; S/CO, ratio of optical density value of samples to cutoff; TPPA, Treponema pallidum particle agglutination.

* The ARCHITECT Syphilis TP Assay (Abbott) is a chemiluminescent microparticle immunoassay for the qualitative detection of antibodies (IgG and IgM) directed against Treponema pallidum in human serum and plasma.

+ The LIAISON Treponema Assay (DiaSorin) uses CIA technology for the qualitative determination of total antibodies directed against *T. pallidum* in human serum.

# One hundred ninety-four women with CIA-positive, RPR-negative serology results.

All pregnant women screened with IgG EIA at first prenatal visit.

Syphilis (*T. pallidum*)-G (CAPTIA) is an EIA for the qualitative detection of IgG antibodies to *T. pallidum* in serum specimens.

* Forty-three pregnant women with positive EIA results.
Table 2. Snapshot of the Evidence

<table>
<thead>
<tr>
<th>Rationale and Foundational Evidence</th>
<th>New Evidence Findings</th>
<th>Limitations of New Evidence</th>
<th>Consistency of New Evidence With Foundational Evidence and Current Understanding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td>Screening: Observational studies demonstrate the association of lower adverse outcomes of pregnancy in women with syphilis infection treated in pregnancy vs those not treated</td>
<td>Screening: One observational study evaluating the implementation of screening for syphilis in &gt;2 million pregnant women in Shenzhen, China, demonstrated an 11-fold decrease in congenital syphilis over 10 y</td>
<td>Included observational study has significant methodologic limitations (ie, with the use of historical and geographic comparators), as well as significant concerns around external validity of findings (eg, national data from China suggest a syphilis epidemic)</td>
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<tr>
<td></td>
<td>Treatment: Parenteral penicillin G is highly effective in treating maternal syphilis and preventing congenital syphilis</td>
<td>Treatment: Not readdressed</td>
<td>The magnitude of benefit in US practice will depend on underlying rates of syphilis in local practice settings</td>
</tr>
<tr>
<td>Harms</td>
<td>Screening: No severe adverse outcomes, as screening only requires blood testing (widely available) and these tests (treponemal and nontreponemal) in combination detect syphilis with high accuracy and reliability</td>
<td>Screening: 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 testing results</td>
<td>Included diagnostic accuracy studies only report on the test inaccuracy of initial treponemal or nontreponemal test and not the inaccuracy of the entire testing sequence</td>
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<td></td>
<td>Treatment: Parenteral penicillin G is generally accepted as safe; however, evidence is limited in pregnant women</td>
<td>Treatment: No new studies examining harms of treatment in pregnant women were identified</td>
<td>Different CIA and EIA tests may have varying test (in)accuracy</td>
</tr>
</tbody>
</table>

Abbreviations: CIA, chemiluminescent immunoassay; EIA, enzyme immunoassay; RPR, rapid plasma reagin.

This update includes longer-term follow-up from an observational study evaluating the implementation of syphilis screening in more than 2 million pregnant women in Shenzhen, China, demonstrating an approximate 11-fold decrease in congenital syphilis over 10 y. Screening for syphilis using rapid serologic tests in conjunction with confirmation testing provides presumptive laboratory diagnosis of syphilis with high provides presumptive laboratory diagnosis of syphilis with high accuracy and reliability, which can induce early labor or cause fetal distress in pregnant women, albeit rarely, is more common in primary and secondary syphilis during pregnancy and cannot be mitigated with a different choice of antibiotic treatments (eg, ceftriaxone) in pregnant women with or without penicillin allergies.

This review was intended to support the USPSTF reaffirmation process. However, this review did not address the efficacy of alternative antibiotic treatments (eg, ceftriaxone) in pregnant women with or without penicillin allergies.

This review includes a meta-analysis of six studies examining harms of treatment in pregnant women. Included in this review supports the effectiveness of identification and treatment of syphilis infection in pregnant women, avoiding adverse outcomes of pregnancy and specifically supports identification and treatment of syphilis as early as possible in pregnancy. This review did not address the efficacy of alternative antibiotic treatments (eg, ceftriaxone) in pregnant women with or without penicillin allergies.
ARTICLE INFORMATION

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Author Contributions: Dr Lin 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: Lin, Eder.

Drafting of the manuscript: All authors.

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

Obtained funding: Lin.

Administrative, technical, or material support: Eder, Bean.

Supervision: Lin.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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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 findings. 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.

Additional Contributions: We gratefully acknowledge the following individuals for their contributions to this project: Smyth Lai, MLS, Katherine Essick, BS, and Shannon Robalino, MLS (Kaiser Permanente Center for Health Research); Peter Mikosyevsky, MD (Northwest Permanente); Tina Fan, MD, MPH (AHRQ); and current and former members of the USPSTF who contributed to topic deliberations. USPSTF members, peer reviewers, and federal partner reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of this evidence report underwent external peer review from 5 content experts (Robert Phillips Heine, MD, Duke University School of Medicine; Jeanne S. Sheffield, MD, Johns Hopkins School of Medicine; and 3 individuals from the US Centers for Disease Control and Prevention). Comments from reviewers 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.

REFERENCES


