JAMA | US Preventive Services Task Force | EVIDENCE REPORT

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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In 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 3 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-screening1.

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 nonrandomized controlled intervention studies and large before-after or ecologic studies reporting the association of implementing a screening program with the incidence of congenital syphilis and other adverse outcomes in pregnant women with syphilis were included. For evidence on the harms of screening (KQ2), studies in pregnant women that reported psychosocial harms, stigma, and screening test inaccuracy (ie, false-positive or false-negative results) were included. For KQ1 and KQ2, studies of screening for syphilis in asymptomatic pregnant women using either traditional or reverse sequence algorithms were selected. Studies of screening tests not currently used in US primary care settings and studies in women living with HIV were excluded. For evidence on the harms of treatment (KQ3), studies of penicillin treatment for syphilis in pregnant women that reported any maternal or neonatal harms were included.

Data Extraction and Quality Assessment

Independent critical appraisal of included trials was conducted by 2 reviewers using predefined criteria (eTable 2 in the Supplement), with disagreements resolved by discussion. Each study was rated as good, fair, or poor quality. A good-quality study met all quality criteria. A fair-quality study failed to meet at least 1 criterion but had no known issue that would invalidate its results. Studies were rated as poor quality if they had major risk of bias. No studies were excluded for poor quality. Important study and participant characteristics and outcomes were abstracted and subsequently checked by a second reviewer for accuracy and completeness.

Data Synthesis and Analysis

Data from 7 studies (reported in 8 publications) were summarized in a narrative format, with an accompanying summary table for KQ2.

Results

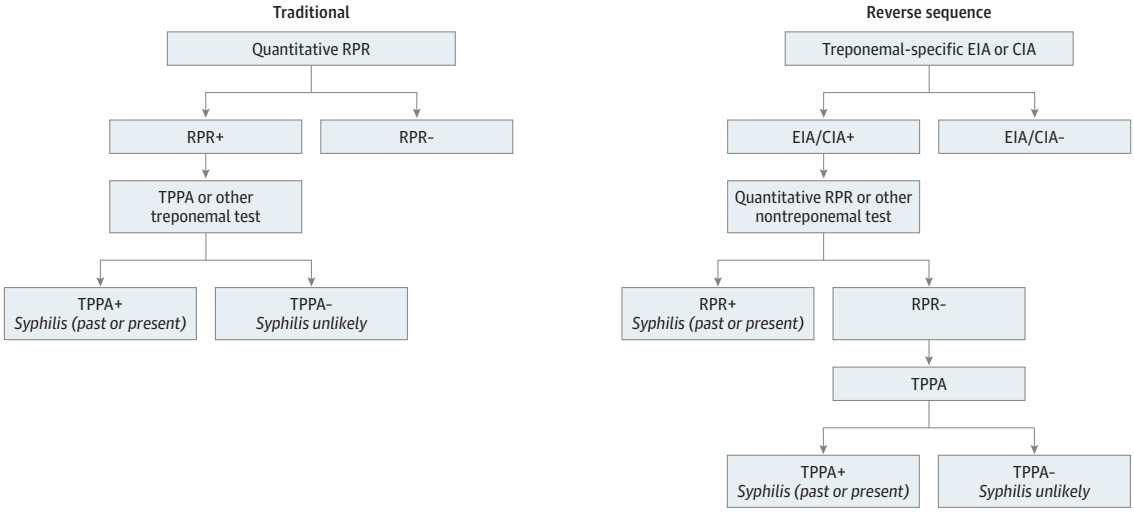
Benefits of Screening

Key Question 1. Does screening for syphilis in pregnant women reduce the incidence of congenital syphilis in newborns?

One fair-quality observational study, which used both historical and geographic comparators, was designed to evaluate the implementation of free syphilis screening (with follow-up and treatment) among all pregnant women living in the region of Shenzhen, China.[12] This study was included in the last evidence update to support the 2009 recommendation statement; however, results from longer-term follow-up have since been published. All pregnant women from January 2002 to December 2012 in 90 hospitals in Shenzhen (n = 2 441 237) were offered syphilis and HIV screening. A nontreponemal test was used to screen for syphilis, with reflex to treponemal testing if the test result was positive. Women testing positive for syphilis by serology were given follow-up visits and treatment (including health education), partner notification, and the opportunity to terminate their pregnancy. Women who chose to continue their pregnancies were treated with 3 injections of penicillin G (2.4 million units intramuscularly) at weekly intervals.

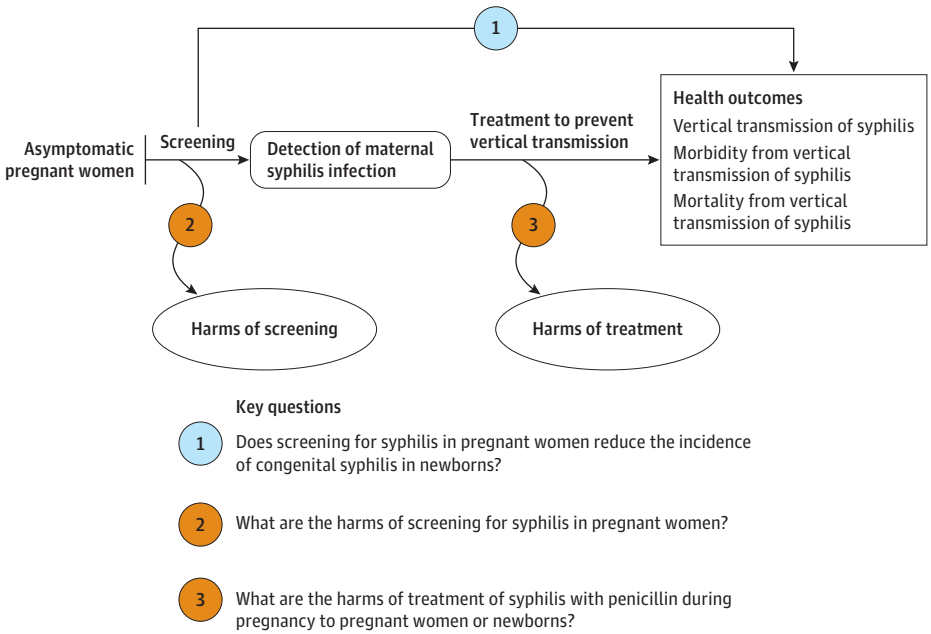
From 2002 to 2012, 8455 of the 2 441 237 pregnant women screened tested positive for syphilis.[12] The timing of screening pregnant women was not reported; however, the mean gestational week in which treatment occurred was 26.5 weeks (SD, 11.2 weeks; range, 3-43 weeks). The trend over the 10 years of observation of

Figure 1. Syphilis Serologic Screening Algorithms



CIA indicates chemiluminescent immunoassay; EIA, enzyme immunoassay; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination.

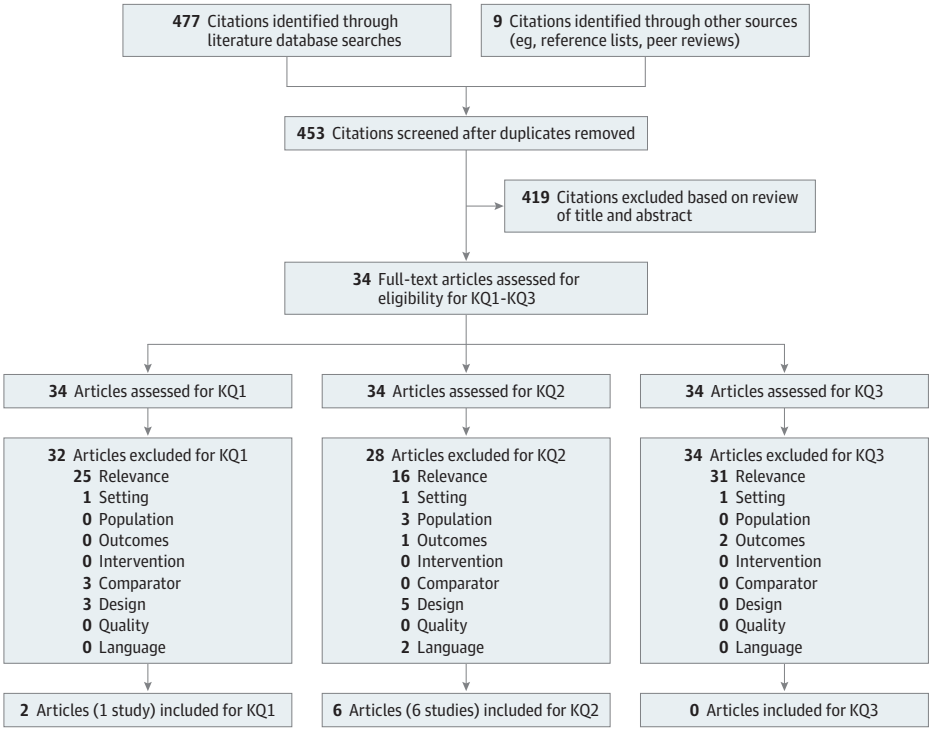
Figure 2. Analytic Framework



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.[11]

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

Figure 3. Literature Search Flow Diagram



KQ indicates key question.

(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 prospective study evaluated the diagnostic accuracy of CIA and the *T pallidum* particle agglutination assay (TPPA) in 318 pregnant women.[17] This study had only 1 positive result from CIA testing and 2 positive results from TPPA testing and therefore could not provide robust estimates of false-positives. This study found no false-negatives for any test.

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

Source (Country)	Patient Selection (No. of Pregnant Women Screened)	Study Design (Years)	Test Evaluated	Cutoff	Testing Strategy	No. of Positive or Negative Results/Total No. of Tests (%)	No. of False-Positive or False-Negative Results/Total No. of Positive or Negative Results (%)	Quality
Reported Harm: False-Positive Results								
Treponemal-specific CIA								
Boonchaoy et al,[13] 2016 (Thailand)	Pregnant women only (11 640)	Retrospective (2011-2013)	ARCHITECT[a]	S/CO value ≥1.00	Reflex testing with RPR and TPPA	65/11 640 (0.56)	35/65 (53.8)	Fair
Wang et al,[14] 2016 (China)	General population, including pregnant women (9600)	Retrospective (2013)	ARCHITECT[a]	S/CO value >1.00	Reflex testing with TPPA; immunoblot used for confirmation of discordant samples	34/9600 (0.35)	30/34 (88.2)	Fair
Mmeje et al,[15] 2015 (United States)	Pregnant women only (NR[b])	Retrospective (2007-2010)	LIAISON[c]	NR	Reflex testing with RPR and TPPA	NR	156/194[d] (80.4)	Fair
Wellinghausen and Dietenberger,[17] 2011 (Gemany)	General population, including pregnant women (318)	Prospective (2010)	ARCHITECT[a]	Index ≥1.0	Reflex testing with FTA-ABS; immunoblot used for confirmation of discordant samples	0/318 (0)	NA	Fair
			LIAISON[c]	Index ≥0.9	Reflex testing with FTA-ABS; immunoblot used for confirmation of discordant samples	1/318 (0.31)	0/1 (0)	
Treponemal-specific EIA								
Henrich and Yawetz,[16] 2011 (United States)	General population, including pregnant women (NR[e])	Retrospective (2004-2007)	Syphilis-G[f]	NR	Reflex testing with RPR and TPPA	NR	20/43[g] (46.5)	Fair
TPPA								
Wellinghausen and Dietenberger,[17] 2011 (Germany)	General population, including pregnant women (318)	Prospective (2010)	TPPA	Titer ≥1:80	Reflex testing with FTA-ABS; recombinant IgG and IgM immunoblot used for confirmation of discordant samples	2/318 (0.63)	1/2 (50)	Fair

(continued)

Table 1. Harms of Screening for Syphilis in Pregnant Women (continued)

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

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.

[a] 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.

[b] All pregnant women tested with reverse sequence algorithm at Kaiser Permanente Northern California.

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

[d] One hundred ninety-four women with CIA-positive, RPR-negative serology results.

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

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

[g] Forty-three pregnant women with positive EIA results.

Table 2. Snapshot of the Evidence

Rationale and Foundational Evidence	New Evidence Findings	Limitations of New Evidence	Consistency of New Evidence With Foundational Evidence and Current Understanding
Benefits			
Screening: Observational studies demonstrate the association of lower adverse outcomes of pregnancy in women with syphilis infection treated in pregnancy vs those not treated Treatment: Parenteral penicillin G is highly effective in treating maternal syphilis and preventing congenital syphilis	Screening: One observational study evaluating the implementation of screening for syphilis in >2 million pregnant women in Shenzhen, China, demonstrated an 11-fold decrease in congenital syphilis over 10 y[12] Treatment: Not readdressed	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) The magnitude of benefit in US practice will depend on underlying rates of syphilis in local practice settings	Included observational study is consistent with the understanding that universal screening for syphilis early in pregnancy can prevent congenital syphilis
Harms			
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 Treatment: Parenteral penicillin G is generally accepted as safe; however, evidence is limited in pregnant women	Screening: Five studies demonstrated that false-positive results with CIA or EIA in pregnancy are common.[13-17] One study demonstrated that undiluted serum with high titers of nontreponemal antibodies can result in false-negative RPR testing results[18] Treatment: No new studies examining harms of treatment in pregnant women were identified	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 Different CIA and EIA tests may have varying test (in)accuracy	Included studies confirm that CIA and EIA should be used in combination with reflexive testing to screen for syphilis because false- positive results are common in pregnancy (as well as cannot distinguish between old and current infection)

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

included in this review supports the effectiveness of identification and treatment of syphilis in pregnancy to avoid adverse outcomes of pregnancy and specifically supports identification and treatment as early as possible in pregnancy (as opposed to in the third trimester or at delivery).[5,12,20]

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 the incidence of congenital syphilis over 10 years. Screening for syphilis using treponemal and nontreponemal tests in combination is feasible for mass screening and provides a presumptive laboratory diagnosis of syphilis with high accuracy and reliability. Because of the false-positive test results with initial treponemal testing (ie, CIA or EIA) and a negative RPR and TPPA result in low-risk patients or low-prevalence populations, clinician education on the reverse sequencing algorithm and interpretation and limitations of syphilis serologic test results in general is critical to avoid overdiagnosis or underdiagnosis and treatment errors. Evidence from this review confirms concern for false-positives with treponemal-specific screening tests in low-risk pregnant females when the RPR result is negative and the prozone phenomenon has been ruled out, supporting the rationale for treponemal reflexive testing. Penicillin G is generally accepted to be effective and safe for use in pregnancy. Observational data support the effectiveness of benzathine penicillin G in preventing congenital syphilis when the mother is treated early in pregnancy, and serious harms are uncommon[5,6]; however, good-quality evidence in pregnant women is lacking.[21] The Jarisch-Herxheimer reaction, 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.

Limitations

This review was intended to support the USPSTF reaffirmation process and thus includes only the interval evidence accrued since the last recommendation in 2009. The review was scoped to identify evidence that could result in a change in this recommendation and therefore has some notable exclusions. First, it did not include studies addressing the effectiveness of screening or early prenatal care in low- or middle-income countries, because these studies were less applicable to prenatal care in the United States. Second, the review did not address the comparative screening accuracy of traditional vs reverse sequence algorithm testing; however, to our knowledge, no studies have compared these 2 testing algorithms in prenatal care. Third, the benefit of penicillin G for the treatment of syphilis is well established, so new evidence for this question was not included. Fourth, because the review was primarily focused on screening, it did not address the efficacy of alternative antibiotic treatments (eg, ceftriaxone) in pregnant women (with or without penicillin allergies).

Conclusions

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.

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.

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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.

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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*.

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