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Screening for Syphilis Infection in Pregnant Women: A Reaffirmation Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: To systematically update the evidence for three questions to support updating the 2009 USPSTF A recommendation for screening for syphilis in pregnancy: KQ1) effectiveness of screening to reduce the incidence of congenital syphilis or other adverse pregnancy outcomes of syphilis, KQ2) harms of screening in pregnancy, and KQ3) harms of penicillin in pregnancy.

Data Sources: We conducted a literature search of MEDLINE, PubMed Publisher-Supplied Records, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2008 to June 2, 2017.

Study Selection: We screened 453 abstracts and 34 full-text articles against *a priori* inclusion criteria. We included studies conducted in countries categorized as "high" or "very high" on the Human Development Index.

Data Analysis: Two investigators independently critically appraised each article that met inclusion criteria using design-specific criteria. We abstracted and narratively synthesized data from included studies.

Results: We included one study for KQ1, six studies for KQ2, and no studies for KQ3. For KQ1, we included one study reporting longer-term follow-up from a previously included study. This observational study evaluated the implementation of syphilis screening in pregnancy in over 2 million women in China. From 2002 to 2012, screening for syphilis in all pregnant women increased from 89.8 percent to 97.2 percent, and the incidence of congenital syphilis decreased from 109.3 to 9.4 cases per 100,000 live births. For KQ2, we included five studies evaluating the false positives of treponemal tests (i.e., CIA, EIA, and TPPA) and one study evaluating the false negatives of nontreponemal tests (i.e., RPR). These studies found that false positives with EIA or CIA were common (46.5 to 88.2 percent), therefore warranting reflexive testing for all CIA or EIA test positives. One study demonstrated that 2.9 percent of discordant samples (RPR negative/TPPA positive) had a false-negative RPR test due to the prozone phenomenon.

Limitations: Our review was designed to identify evidence that could result in a change in the 2009 USPSTF recommendation and therefore our review does not address the effectiveness of screening or early prenatal care in low- or middle-income countries, the comparative screening accuracy of traditional versus reverse sequence algorithm testing, or the efficacy of penicillin G or alternative antibiotic treatments for the treatment of syphilis.

Conclusions: Screening for syphilis in pregnancy is standard of care in the United States. Our brief evidence update found evidence that is consistent with the understanding that screening for syphilis in pregnancy reduces congenital syphilis and supports the need for reflexive testing to investigate discordant EIA/CIA positive/RPR negative testing in reverse sequence screening algorithms.

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Chapter 1. Introduction

Condition Background

Condition Definition

Syphilis is an infectious disease caused by *Treponema pallidum* (*T. pallidum*) via sexual or vertical transmission. The disease is divided into three clinical stages (i.e., primary, secondary, and tertiary) depending on the duration of the infection and signs/symptoms. Syphilis can also lack any clinical manifestations (i.e., latent infections). Congenital syphilis is the infection of the fetus, which occurs through vertical transmission during pregnancy from the infected mother (i.e., transmitted to the fetus via the placenta). Vertical transmission of syphilis can occur in all stages of syphilis and in every trimester of pregnancy. Congenital syphilis can result in fetal or perinatal death as well as morbidity in surviving newborns.[1]

Disease Incidence and Burden of Disease

While the incidence of primary and secondary syphilis infection in the United States were at historic lows in 2000, new infections have since increased and continue to increase over time. In 2016, the rate of reported primary or secondary syphilis in the United States was 8.7 cases per 100,000 individuals (both men and women), up from 4.5 cases per 100,000 individuals in 2011. In 2016, this rate was 1.9 cases per 100,000 women, with considerable racial/ethnic variation: from 6.3 cases per 100,000 Black women to 0.9 per 100,000 White women and 0.4 cases per 100,000 Asian women (**Table 1**).[2] National rates of syphilis in pregnant women are not available. Likewise, the rates of congenital syphilis have increased over time. 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 1998.[2,3] Again, there was considerable variation in congenital syphilis by race/ethnicity, mirroring the disparities seen in primary and secondary syphilis, from 43.1 cases per 100,000 live births in Black women to 5.3 cases per 100,000 live births in White women in 2016 (**Table 1**).[2] In 2016, rates for both syphilis and congenital syphilis were highest in the South and West, as compared to the Northeast and Midwest regions of the United States (**Table 2**).

Untreated syphilis in pregnancy carries significant risk of infant morbidity and mortality, commonly referred to as adverse pregnancy outcomes of syphilis. These outcomes include stillbirth or fetal loss and premature birth, low birthweight, congenital syphilis, and neonatal death in live-born infants. The risk for fetal infection or congenital syphilis at delivery is related to the stage of untreated syphilis during pregnancy. The highest risk occurs with primary and secondary syphilis, although fetal infection can also occur with latent syphilis, including if low titers in pregnant women.[4] In a 2013 systematic review of six case-control studies on adverse outcomes in pregnancy from untreated maternal syphilis, the estimated absolute difference for pregnant women with untreated syphilis versus those without syphilis was 21 percent for stillbirth or fetal loss, 9 percent for neonatal death, and 5 percent for prematurity or low birthweight. Signs and symptoms of syphilis were found in 15 percent of infants born to

untreated women.[5] Most of these studies were conducted in times and places in which penicillin was not widely available. A 2014 systematic review of 54 observational studies (the majority of which were conducted in China) compared adverse pregnancy outcomes of untreated women with syphilis versus treated women with syphilis versus women without syphilis. The pooled estimate of the incidence of congenital syphilis was 36.0% for untreated women with syphilis and 14.0% for treated women with syphilis. This review also demonstrated dramatically better outcomes in terms of incidence of preterm birth, low birthweight, stillbirth, and neonatal death in women without syphilis and women treated for syphilis, compared with untreated women with syphilis. This review also found that the absolute difference for stillbirth or fetal loss was only slightly less in women treated in the third trimester (17.6 percent) versus untreated women with syphilis (22.7 percent), when compared to women without syphilis.[6]

Around two-thirds of infants with congenital syphilis will be asymptomatic at birth, but most will develop signs in the first several weeks.[7] Forty to 60 percent of infants with congenital syphilis will have one of the following: rash, hemorrhagic rhinitis, lymphadenopathy, hepatosplenomegaly, and skeletal abnormalities.[7]

Screening

Prevention and detection of congenital syphilis depend primarily on the identification of syphilis in pregnant women. Multiple observational studies have demonstrated that the greatest association with reductions in adverse infant and pregnancy outcomes are observed when penicillin is administered early in pregnancy, which supports the rationale for screening for syphilis in the early stages of gestation.[6,8] Repeat screening for syphilis near term (i.e., at the beginning of the third trimester) or at delivery serves primarily to detect congenital cases and allow for early treatment, as opposed to preventing incident cases of congenital syphilis.

Nontreponemal tests measure antibodies not specific to *T. pallidum* and therefore are not specific to syphilis. Nontreponemal tests include rapid plasma reagin (RPR), venereal disease research laboratory (VDRL), and toluidine red unheated serum (TRUST). Nontreponemal tests can be qualitative or quantitative (measure titers). Treponemal tests detect antibodies directed against *T. pallidum* proteins. Treponemal tests include fluorescent treponemal antibody absorbed (FTA-ABS), *T. pallidum* particle agglutination (TPPA), enzyme immunoassays (EIA), chemiluminescence immunoassays (CIA), and microbead immunoassays (MBIA). Treponemal tests are qualitative and generally remain positive after treatment. Serologic laboratory diagnosis of syphilis always requires detection of two types of antibodies: a treponemal test and a quantitative nontreponemal test. Direct detection methods (i.e., darkfield microscopy, PCR, and direct fluorescent antibody test) are used as diagnostic (not screening) tests for symptomatic persons with signs of primary or secondary syphilis and are not widely available.

Two screening protocols are commonly used in pregnant women: 1) the traditional screening algorithm (i.e., nontreponemal testing with reflex to treponemal testing), and 2) the reverse sequence screening algorithm (i.e., treponemal testing with reflex to nontreponemal testing) (**Figure 1**).[9] In the traditional algorithm, because the initial nontreponemal testing can have a high rate of false positives, confirmation with a treponemal test (TPPA preferred) is required. Easier automation with less subjective test results, and lower cost in high-volume settings has

resulted in the adoption of the reverse sequence algorithm in many clinical settings in the United States. Typically, EIA or CIA tests are used at the initial test. These tests cannot distinguish between active, untreated, and old treated infections; so if the initial test is positive, reflexive testing to a quantitative nontreponemal test (RPR preferred) is required. If the tests are discordant (EIA or CIA positive/nontreponemal test negative), a different treponemal test (TPPA preferred) should be performed (ideally on the same specimen) to confirm the results of the initial EIA or CIA test. If the second treponemal test is negative, the initial EIA or CIA positive test may be a false-positive result in low-risk individuals or populations. In pregnant women at high risk for infection with an initial positive EIA/CIA screening test and negative RPR and TPPA, syphilis is possible as the EIA/CIA could be a true positive so either presumptive treatment (if follow-up is unlikely), or a repeat RPR in one month can be considered. If the second treponemal test is positive, women with known previous treatment of syphilis require no further management unless a careful sexual history suggests likelihood of re-exposure. Those with previous inadequate treatment or without a known prior history of treatment should be offered treatment.[4]

Several treponemal-specific point-of-care tests (POCT) are widely available in low- and middle-income countries to expand the range of settings in which early diagnosis and rapid access to treatment can be applied.[9] These POCT (i.e., immunochromatographic strip [ICS] tests, particle agglutination tests [PAT]) are generally not used for antenatal screening for syphilis in the United States.

Treatment

The effectiveness of benzathine penicillin G for the treatment of syphilis is well established. Parenteral long-acting benzathine penicillin G (IM) is the recommended antibiotic for preventing maternal transmission of syphilis to the fetus and treating fetal syphilis infection; therefore, the Centers for Disease Control and Prevention (CDC) recommends that pregnant women should be treated with the benzathine penicillin G regimen appropriate for their stage of infection.[4] Studies suggest the efficacy of benzathine penicillin G to treat maternal infection approximates 100 percent, and about 98 percent for preventing congenital syphilis.[10] The CDC recommends that pregnant women with a known penicillin allergy should be desensitized and treated with penicillin.[4] If penicillin allergy testing is available, it can be performed to confirm the need for desensitization, as approximately 5 percent of pregnant women reporting a penicillin allergy are truly allergic.[11] Antibiotics with efficacy against syphilis (that are not contraindicated in pregnancy) are not currently recommended as alternatives due primarily to the pharmacologic data indicating that these drugs do not cross the placenta to reach the fetus. In addition, there is azithromycin resistance of *T. pallidum* and its efficacy has not been established in pregnant women. Therefore, neither macrolide (azithromycin or erythromycin) is recommended to treat maternal infection or fetal syphilis infections.[4] Although promising, ceftriaxone has very limited evidence of its efficacy for all stages of syphilis and in each trimester of pregnancy and therefore the CDC does not currently recommend it as an alternative.[4,12]

Penicillin is also safe, with rarely documented serious adverse outcomes (e.g., anaphylaxis).[13] The Jarisch-Herxheimer reaction may induce early labor or cause fetal distress in pregnant women.[4] It is an acute febrile reaction that can occur within the first 24 hours after initiation of

any antimicrobial therapy for syphilis in women with high bacterial burdens, although it is more common with penicillin therapy.[12] The reaction is not infrequent during treatment of primary/secondary infections in pregnancy, but is unusual in latent infections and is not a reason to defer treatment. A 2013 systematic review of the safety of penicillin for preventing congenital syphilis found no serious adverse reactions reported among 1,244 pregnant women (5 studies) treated in low- or middle-income countries, albeit from very low-quality evidence.[13]

Previous USPSTF Recommendation and Current Clinical Practice in the United States

The original 1996 A recommendation to screen all pregnant women for syphilis was based on the rationale that existing screening tests are feasible for mass screening and detect syphilis with high accuracy and reliability, available treatments are effective and rarely harmful, and prenatal antibiotic therapy is effective in preventing congenital syphilis when the mother is treated early in pregnancy. In 2004 and again in 2009, the USPSTF reaffirmed this recommendation using brief evidence updates. The CDC, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and American Academy of Family Physicians also recommend screening for syphilis in pregnant women (**Table 3**). Their guidelines explicitly recommend screening as early as possible in pregnancy (i.e., first prenatal visit), with repeat screening in the third trimester and at delivery in women at increased risk for syphilis. In addition, of the 50 U.S. states and the District of Columbia, 45 states have laws mandating prenatal syphilis screening. Sixty-two percent of these states require only one test, and 84 percent specify that the test should be performed at the first prenatal visit.[14]

Despite consistent recommendations and legal mandates, screening for syphilis in pregnancy continues to be suboptimal in certain populations. While administrative data from a survey from 2009 to 2010 suggest that prenatal screening for syphilis in Medicaid and commercially insured women is nearly universal,[15] other studies have found lower screening uptake.[16] For example, in 2013, only 85 percent of a sample of commercially insured women had at least one syphilis test during pregnancy.[17] In addition, recent data suggest that while screening rates for syphilis are generally high, the proportion of those screened earlier in pregnancy remains low (e.g., 80 percent screened before hospital admission for delivery) and varies geographically (e.g., 68 percent in the District of Columbia to 93 percent in Connecticut).[18] Older studies demonstrate differential uptake of screening for syphilis by race/ethnicity;[19,20] however, these disparities appear to be attributable to other factors (e.g., lack of insurance, inadequate access to prenatal care, geography).[21]

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this evidence update to update its 2009 recommendation on screening pregnant women for syphilis infection.[22,23] Topics that represent well-established, evidence-based standards of practice that are within the scope of the USPSTF and remain a USPSTF priority (i.e., the USPSTF has a reason to keep the recommendations active) undergo an updating process known as "reaffirmation".[24] Systematic review methods for reaffirmation evidence updates are described in detail elsewhere.[25] The aim for evidence updates supporting the reaffirmation process is to identify "new and substantial evidence sufficient enough to change the prior recommendation".[24,25] As such, only targeted key questions included in the previous review on screening for syphilis in pregnancy are updated; we did not update the evidence on the effectiveness of treatment of syphilis in pregnancy with penicillin. In consultation with members of the USPSTF, we developed an analytic framework (**Figure 2**) and three Key Questions (KQs) to guide our evidence update.

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

Data Sources and Searches

We conducted a literature search of MEDLINE, PubMed Publisher-Supplied Records, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 2008 to June 2, 2017. We worked with a research librarian to develop our search strategy, which was peer-reviewed by a second research librarian (**Appendix B**). We supplemented these searches by reviewing reference lists of recent reviews and primary studies. We limited our searches to articles published in English. We managed literature search results using Endnote® version X7 (Thomson Reuters, New York, NY).

Study Selection

We developed specific inclusion criteria to guide study selection (**Appendix B Table 1**). Two reviewers independently reviewed the title and abstracts of all identified articles using Abstrackr.[26] Two reviewers then independently evaluated the full text of all potentially relevant articles. We resolved differences in the abstract or full-text review by discussion. For all KQs, we included studies conducted in primary care and primary care-referable settings in countries categorized as "high" or "very high" on the Human Development Index. We excluded editorials, narrative reviews, and case studies.

For evidence on the benefits of screening for syphilis in pregnancy (KQ1), we included randomized or non-randomized controlled trials and large before-after or ecologic studies reporting the effect of implementing a widespread screening program on the incidence of congenital syphilis and other adverse outcomes in pregnant women with syphilis. For evidence on the harms of screening (KQ2), we included studies in pregnant women reporting psychosocial harms, stigma, and screening test inaccuracy (i.e., false-positive or false-negative results). For KQs 1 and 2, we selected studies of screening for syphilis in asymptomatic pregnant women using either traditional or reverse sequence algorithms. We excluded studies of screening tests not currently used in United States primary care settings and studies of women living with HIV. For evidence on the harms of treatment (KQ3), we included studies of penicillin treatment for syphilis in pregnant women that reported any maternal or neonatal harms.

Quality Assessment and Data Abstraction and Synthesis

Two reviewers independently assessed the methodological quality of each included study using predefined criteria (**Appendix B Table 2**); disagreements were resolved by discussion. We extracted important study and participant characteristics and outcomes, and synthesized the evidence from included studies in a narrative format, with an accompanying summary table for KQ2.

Expert Review and Public Comment

A draft Research Plan for this review was available for public comment from June 8 to July 5, 2017. Based on these comments, no substantive changes to the key questions or inclusion criteria were made. The draft version of this report was reviewed by content experts and USPSTF Federal Partners from the CDC. Additionally, a draft of the full report was posted on the USPSTF Web site from February 6, 2018 to March 5, 2018. Based on expert and public comments, revisions were made to update the report and help with clarity of the contextual information (report introduction and discussion); however, no changes made to the results or interpretation of the evidence.

USPSTF Involvement

This reaffirmation evidence update was funded by AHRQ under contract to support the USPSTF. We consulted with USPSTF members at the development of the research plan (i.e., KQs, analytic framework, and inclusion criteria). An AHRQ Medical Officer provided project oversight, reviewed the draft and final versions of the evidence update, and assisted with public comment on the research plan and draft report. The USPSTF and AHRQ had no role in the study selection, quality assessment, or writing of the evidence update.

Chapter 3. Results

Literature Search

Our literature search yielded 453 unique citations. From these citations, we accepted 34 articles for review based on titles and abstracts (**Appendix B Figure 1**). After reviewing the full-text articles and conducting critical appraisal, we included seven studies reported in eight publications. We found one study (two articles) for KQ1, six studies (six articles) for KQ2, and no studies for KQ3. **Appendix C** contains a list of all full-text articles and their reasons for exclusion.

Results of Included Studies

KQ1. Does Screening for Syphilis in Pregnant Women Reduce the Incidence of Congenital Syphilis in Newborns?

We identified only one study that met our inclusion criteria for KQ1.[27] This study was included in the last evidence update to support the 2009 recommendation statement; however, longer-term follow-up has since been published. This fair-quality observational study, which used both a historical and geographical comparator, was designed to evaluate the implementation of free syphilis screening (with follow-up and treatment) for all pregnant women living in the region of Shenzhen, China.[27] All pregnant women from January 2002 to December 2012 in 90 hospitals in Shenzhen (n=2,441,237) were offered syphilis and HIV screening. Screening for syphilis was conducted using a nontreponemal test (TRUST) with reflex to treponemal (TPPA) testing if positive. The diagnosis was based on TRUST and TPPA testing in accordance with then-current CDC treatment guidelines. Women testing positive for syphilis by serology were given follow-up visits and treatment (including health education), and their sexual partner(s) was notified. They were also given the opportunity to terminate their pregnancy. Women who chose to continue their pregnancies were treated with three injections of 2.4 million units IM penicillin G at weekly intervals. For those allergic to penicillin, erythromycin was given or patients were advised to terminate their pregnancy. Infants born to mothers treated for syphilis were screened for congenital syphilis at birth, and all cases of congenital syphilis were treated and followed according to CDC treatment guidelines. Maternal and infant outcomes included syphilis testing coverage and positivity rates in pregnant women, follow-up rates among women with infection, incidence of congenital syphilis, and other adverse pregnancy outcomes.

From 2002 to 2012, 8,455 of the 2,441,237 pregnant women screened tested positive for syphilis.[27] The timing of screening pregnant women was not reported; however, the mean gestational week of treatment was 26.5 weeks (SD 11.2 weeks, range 3 to 43 weeks). The trend over the 10 years of observation of the timing of screening and/or treatment was not reported (e.g., if screening and/or treatment occurred earlier in pregnancy in later years). From 2002 to 2012, screening for syphilis in all pregnant women increased from 89.8 percent to 97.2 percent, 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 percent to 19.2 percent; congenital syphilis declined from 11.7 percent to 3.2 percent; and stillbirth or fetal loss declined from 19.0 percent to 3.3 percent. While this study does not include a true historical comparator (i.e., a time point before implementation of the screening program) since 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. No further details of national incidence data were reported (i.e., unclear if national data excludes Shenzhen). From 2002 to 2012, the incidence of congenital syphilis in China increased from 5.9 to 97.4 cases per 100,000 live births in China, 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 the limitations with both the historical and geographical comparisons, this study provides observational evidence that screening for, coupled with treatment of, syphilis in pregnancy is associated with a decrease in congenital syphilis and adverse outcomes in pregnancy.

KQ2. What Are the Harms of Screening for Syphilis in Pregnant Women?

We found five studies in pregnant women that reported on false positives of treponemal tests,[28-32] one of which also reported on false negatives,[32] and one study that reported on false negatives of non-treponemal testing (**Table 4**).[33] We found no studies addressing other potential harms of screening for syphilis in pregnant women. Four large, fair-quality retrospective studies evaluated the proportion of false positives using CIA (ARCHITECT or LIAISON) or EIA (Captia Syph-G) in screening pregnant women for syphilis.[28-31] All of these tests are cleared for use in the United States by the FDA. Two of these studies were conducted in the United States.[30] Three of these studies used reflex testing with RPR and TPPA,[28,30,31] and one study used reflex testing with TPPA and an immunoblot for confirmation of discordant samples (CIA positive/TPPA negative).[29] Details on the study populations (e.g., age, race/ethnicity, risk, gestational age at time of screening) were generally not reported. These studies found that false positives with EIA or CIA were common (46.5-88.2 percent), therefore warranting reflexive testing for all CIA or EIA test positives. None of the studies reported confidence intervals for false positives. As well, none performed follow-up testing on CIA or EIA negative tests and therefore could not determine false negatives.

One fair-quality prospective study evaluated the diagnostic accuracy of CIA (ARCHITECT and LIAISON) and TPPA in 318 pregnant women using reflex testing with FTA-Abs and an immunoblot for confirmation of discordant samples (CIA or TPPA positive/FTA-Abs negative).[32] This study had only one test positive for CIA testing and two test positives for TPPA testing and therefore could not provide robust estimates of false positives. This study found no false negatives for any of the three tests.

One fair-quality retrospective study evaluated the prozone phenomenon using RPR testing.[33] The prozone phenomenon occurs when undiluted serum containing a high titer of nonspecific antibody (as may occur in secondary syphilis) produces a false negative due to a large quantity of antibodies occupying all the antigen sites (preventing flocculation).[9] This study repeated RPR

testing in discordant samples (RPR negative/TPPA positive) using diluted serum, and found that 2.9 percent of discordant samples had a false-negative RPR test due to the prozone phenomenon.

KQ3. What Are the Harms of Treatment of Syphilis With Penicillin During Pregnancy to Pregnant Women or Newborns?

We found no studies directly examining the harms of penicillin when used in pregnancy. We found no studies that addressed the risk of the Jarisch-Herxheimer reaction or serious adverse events in women with a history of penicillin allergy.

Chapter 4. Discussion

Summary of Evidence

Our brief evidence update findings support the understanding that screening for syphilis early in pregnancy reduces congenital syphilis and the need for reflexive testing to investigate initial EIA/CIA positive testing in reverse sequence screening (**Table 5**). Screening for syphilis in pregnancy at the first prenatal visit to prevent congenital syphilis is standard of care and legally mandated in most places in the United States. Observational evidence not included in this review supports the effectiveness of identification and treatment of syphilis in pregnancy to avoid adverse outcomes of pregnancy, and specifically support identification and treatment as early as possible in pregnancy (as opposed to in the third trimester or at delivery).[5,8,27] Our update includes longer-term follow-up from an observational study evaluating the implementation of syphilis screening in over 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 utilizing both treponemal and nontreponemal tests in combination are feasible for mass screening and provide a presumptive laboratory diagnosis of syphilis with high accuracy and reliability. Due to the false-positive test results with initial treponemal testing (i.e., CIA or EIA) and a negative RPR and TPPA 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 over or under diagnosis 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 is negative and the prozone phenomenon has been ruled out, supporting the rationale for treponemal reflexive testing. Penicillin G is effective and safe. 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, we lack good-quality evidence in pregnant women.[13] 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.

Repeat Testing in Third Trimester and at Delivery

The CDC and the joint guidelines from the American Academy of Pediatrics and American College of Obstetricians and Gynecologists both recommend repeat screening in the third trimester (at 28-32 weeks) and at delivery in selected women at increased risk for syphilis (**Table 3**). Only 17 states have mandatory third trimester testing, 12 of which require the test in all women and 5 in women at high risk.[14] Women at increased risk for infection of syphilis include those living with human immunodeficiency virus, those who are incarcerated or exchange sex for drugs, and those living in a geographic area with high rates of syphilis.[34] Other risk factors can include those diagnosed with a sexually transmitted infection in pregnancy (not limited to syphilis), those with multiple partners, those with substance use disorders, and those with limited prenatal care.[2,4,35]

One study by Coles and colleagues, which was included in a prior evidence update to support the 2004 USPSTF recommendation on screening for syphilis in pregnancy, evaluated the impact of implementing mandatory syphilis screening at the time of delivery, comparing congenital syphilis detected during the 4 years after implementation to the 1 year before.[36] This study in upstate New York demonstrated a decrease in the proportion of infants with clinical manifestations of syphilis and an increase in the proportion of infants with positive serology (from increased testing) but without symptoms. This suggests that early detection of the infection led to effective treatment prior to clinical manifestation of disease.

We found no new studies that examined the effectiveness of repeated testing in the third trimester and/or at delivery. Two recent cost-effectiveness analyses modeled the benefit of repeat screening for syphilis in the third trimester. One analysis concluded that an approximate 18-fold increase in syphilis prevalence (about 3.5 percent of deliveries) would be required for the cost of rescreening all women in the third trimester to be equivalent to the money saved by detecting maternal seroconversion and preventing resultant cases of congenital syphilis.[37] In this study, 113 new cases of syphilis occurred during a 17 year period (193 cases per 100,000 deliveries) in the Cleveland, Ohio metropolitan area. Among these cases there were 17 detected seroconversions in pregnancy, and 7 of these women had repeat testing in the third trimester of pregnancy. A chart review of the 10 women who could have potentially benefitted by implementing universal repeat testing in the third trimester or at delivery found that their newborns were asymptomatic at birth and received a 10-day hospital course of penicillin with no adverse events or unexpected sequelae due to or following treatment. In addition, the authors state that each of these 10 women had specific risk factors which could/should have led to repeat testing (i.e., illicit drug use, incarceration, infection with other sexually transmitted infection, and limited prenatal care). The other analysis evaluated universal syphilis rescreening in the third trimester versus no rescreening;[38] this model assumed 100 percent of women had screening for syphilis early in pregnancy and a 0.012 percent seroconversion in pregnancy (seroconversion in the previously described study in a high-risk prenatal population in the Cleveland area[37]). This study demonstrated that approximately 66,000 pregnant women would need to be rescreened to prevent one case of congenital syphilis, approximately 570,000 rescreened to prevent one fetal loss, and approximately 950,000 rescreened to prevent one neonatal death from maternal syphilis.

Limitations

Our review was intended to support the USPSTF reaffirmation process and thus includes only the interval evidence accrued since the last recommendation in 2009. Our review was scoped to identify evidence that could result in a change in this recommendation and therefore has some notable exclusions listed here. It did not include studies addressing the effectiveness of screening or early prenatal care in low- or middle-income countries, as these studies were less applicable to prenatal care in the United States. Likewise, our review did not include the benefits and harms of point-of-care rapid syphilis testing in these settings. Our review did not address the comparative screening accuracy of traditional versus reverse sequence algorithm testing; however, at the time of drafting this report, we were unaware of any studies comparing these two testing algorithms in prenatal care. The benefit of penicillin G for the treatment of syphilis is well established, so new

evidence for this question was not included. Because our review was primarily focused on screening, we did not address the efficacy of alternative antibiotic treatments (e.g., ceftriaxone) in pregnant women (with or without penicillin allergies).

Conclusion

The prevention and early treatment of congenital syphilis is dependent on screening for syphilis in early pregnancy. Our brief evidence update includes one long-term follow-up of an observational study that supports a larger body of evidence that screening for syphilis in pregnancy reduces congenital syphilis. Syphilis in pregnancy is easily identified with recommended screening protocols and effectively treated with penicillin G. Our update includes several diagnostic accuracy studies that confirm the occurrence of false-positive results with treponemal-specific testing in pregnancy, supporting the need for reflexive testing to investigate discordant EIA/CIA positive/RPR negative testing in reverse sequence screening algorithms. We found no studies addressing serious harms of screening for or treatment of syphilis in pregnancy; specifically, we found no studies evaluating the harms of penicillin G in pregnant women with a documented allergy to penicillin.

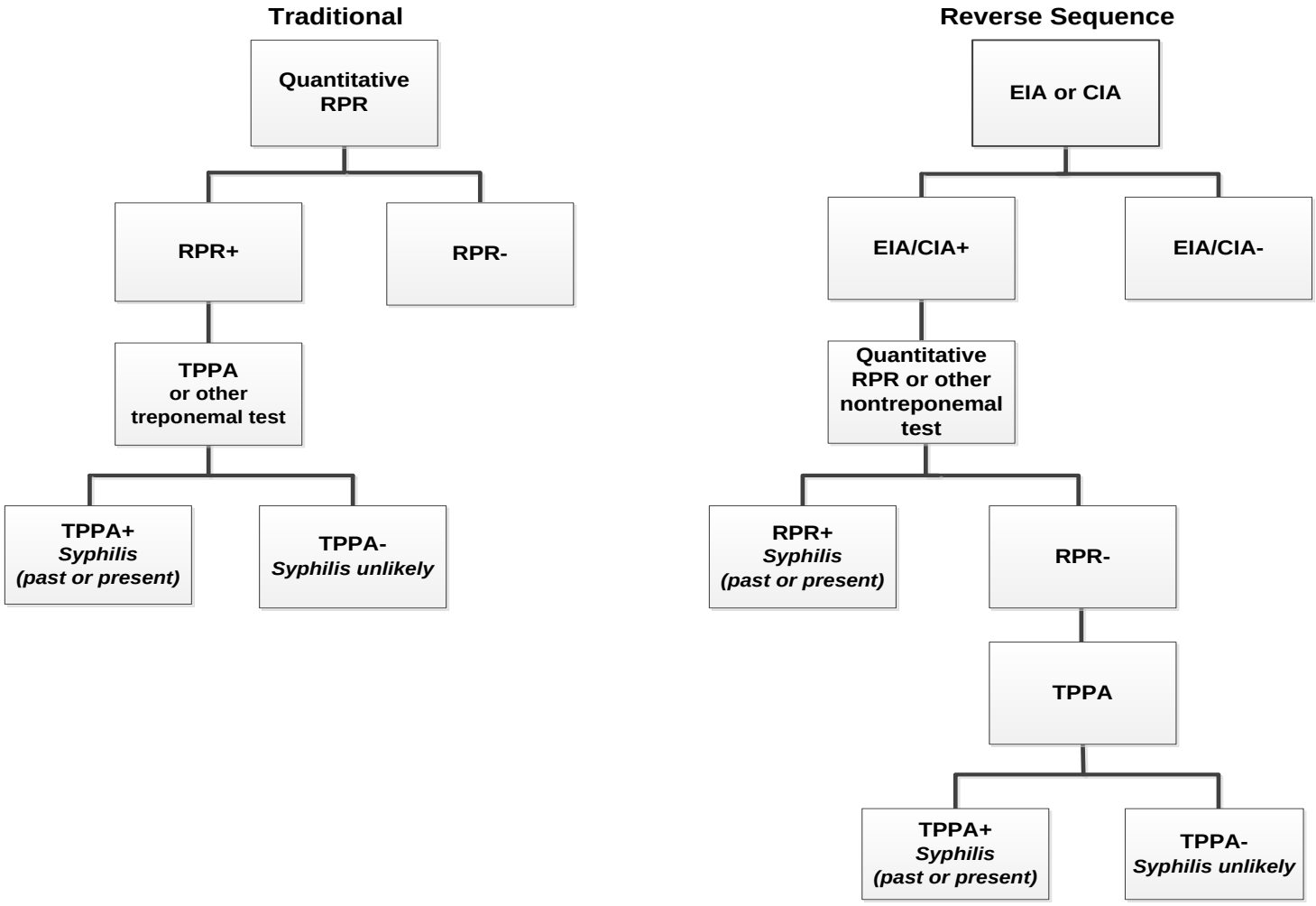
References

1. Cooper JM, Sanchez PJ. Congenital syphilis. *Semin Perinatol*. 2018;42(3):176-184.
2. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2016*. Atlanta: U.S. Department of Health and Human Services;2017.
3. Bowen V, Su J, Torrone E, Kidd S, Weinstock H. Increase in incidence of congenital syphilis - United States, 2012-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(44):1241-1245.
4. Centers for Disease Control and Prevention (CDC). Sexually Transmitted Diseases Treatment Guidelines, 2015. 2015;64:137.
5. Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bulletin of the World Health Organization*. 2013;91(3):217-226.
6. Qin J, Yang T, Xiao S, Tan H, Feng T, Fu H. Reported estimates of adverse pregnancy outcomes among women with and without syphilis: a systematic review and meta-analysis. *PloS one*. 2014;9(7):e102203.
7. Kingston M, French P, Higgins S, et al. UK national guidelines on the management of syphilis 2015. *International journal of STD & AIDS*. 2016;27(6):421-446.
8. Hawkes SJ, Gomez GB, Broutet N. Early antenatal care: does it make a difference to outcomes of pregnancy associated with syphilis? A systematic review and meta-analysis. *PloS one*. 2013;8(2):e56713.
9. Morshed MG, Singh AE. Recent trends in the serologic diagnosis of syphilis. *Clinical and Vaccine Immunology*. 2015;22(2):137-147.
10. Alexander JM, Sheffield JS, Sanchez PJ, Mayfield J, Wendel GD, Jr. Efficacy of treatment for syphilis in pregnancy. *Obstetrics and gynecology*. 1999;93(1):5-8.
11. Macy E. Penicillin skin testing in pregnant women with a history of penicillin allergy and group B streptococcus colonization. *Ann Allergy Asthma Immunol*. 2006;97(2):164-168.
12. Rac MW, Revell PA, Eppes CS. Syphilis during pregnancy: a preventable threat to maternal-fetal health. *Am J Obstet Gynecol*. 2017;216(4):352-363.
13. Galvao TF, Silva MT, Serruya SJ, et al. Safety of benzathine penicillin for preventing congenital syphilis: a systematic review. *PloS one*. 2013;8(2):e56463.
14. Warren HP, Cramer R, Kidd S, Leichliter J. State Prenatal Syphilis Screening Policies in the United States, 2016 *Matern Child Health J*. 2018.
15. Ross CE, Tao G, Patton M, Hoover KW. Screening for human immunodeficiency virus and other sexually transmitted diseases among U.S. women with prenatal care. *Obstetrics & Gynecology*. 2015;125(5):1211-1216.
16. Schrag SJ, Arnold KE, Mohle-Boetani JC, et al. Prenatal screening for infectious diseases and opportunities for prevention. *Obstetrics and gynecology*. 2003;102(4):753-760.
17. Neblett Fanfair R, Tao G, Owusu-Edusei K, Gift TL, Bernstein KT. Suboptimal Prenatal Syphilis Testing Among Commercially Insured Women in the United States, 2013. *Sexually transmitted diseases*. 2017;44(4):219-221.
18. Koumans EH, Rosen J, van Dyke MK, et al. Prevention of mother-to-child transmission of infections during pregnancy: implementation of recommended interventions, United States, 2003-2004. *Am J Obstet Gynecol*. 2012;206(2):158.e151-158.e111.

19. Adams EK, Gavin NI, Raskind-Hood C, Tao G. Explaining racial differences in prenatal care initiation and syphilis screening among Medicaid-covered pregnant women. *J Health Care Poor Underserved*. 2009;20(1):177-193.
20. Fowler CI, Gavin NI, Adams EK, Tao G, Chireau M. Racial and ethnic disparities in prenatal syphilis screening among women with Medicaid-covered deliveries in Florida. *Matern Child Health J*. 2008;12(3):378-393.
21. Sheikh LA, Sarnquist C, Grieb EM, Sullivan B, Maldonado YA. Prenatal screening for infectious diseases: an analysis of disparities and adherence to policy in California. *Matern Child Health J*. 2009;13(2):260-267.
22. U.S. Preventive Services Task Force (USPSTF). Screening for Syphilis Infection in Pregnancy: U.S. Preventive Services Task Force Reaffirmation Recommendation Statement *Annals of Internal Medicine* Vol 1502009.
23. Wolff T, Shelton E, Sessions C, Miller T. Screening for syphilis infection in pregnant women: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. *Annals of Internal Medicine*. 2009;150(10):710-716.
24. U.S. Preventive Services Task Force. *U.S. Preventive Services Task Force Procedure Manual*. Rockville, MD: U.S. Preventive Services Task Force; Dec 2015.
25. Patnode C, Eder M, Walsh E, Viswanathan M, Lin J. The Use of Rapid Review Methods for the U.S. Preventive Services Task Force. *American Journal of Preventive Medicine*. In press.
26. Wallace BC, Small K, Brodley CE, Lau J, Trikalinos TA. Deploying an interactive machine learning system in an evidence-based practice center: abstrackr. *Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium*. 2012:819-824.
27. Qin JB, Feng TJ, Yang TB, et al. Synthesized prevention and control of one decade for mother-to-child transmission of syphilis and determinants associated with congenital syphilis and adverse pregnancy outcomes in Shenzhen, South China. *Eur J Clin Microbiol Infect Dis*. 2014;33(12):2183-2198.
28. Boonchaoy A, Wongchampa P, Hirankarn N, Chaithongwongwatthana S. Performance of Chemiluminescent Microparticle Immunoassay in Screening for Syphilis in Pregnant Women from Low-Prevalence, Resource-Limited Setting. *J Med Assoc Thai*. 2016;99(2):119-124.
29. Wang KD, Xu DJ, Su JR. Preferable procedure for the screening of syphilis in clinical laboratories in China. *Infect Dis (Lond)*. 2016;48(1):26-31.
30. Mmeje O, Chow JM, Davidson L, Shieh J, Schapiro JM, Park IU. Discordant Syphilis Immunoassays in Pregnancy: Perinatal Outcomes and Implications for Clinical Management. *Clinical Infectious Diseases*. 2015;61(7):1049-1053.
31. Henrich TJ, Yawetz S. Impact of age, gender, and pregnancy on syphilis screening using the Captia Syphilis-G assay. *Sexually transmitted diseases*. 2011;38(12):1126-1130.
32. Wellinghausen N, Dietenberger H. Evaluation of two automated chemiluminescence immunoassays, the LIAISON Treponema Screen and the ARCHITECT Syphilis TP, and the Treponema pallidum particle agglutination test for laboratory diagnosis of syphilis. *Clin Chem Lab Med*. 2011;49(8):1375-1377.
33. Liu LL, Lin LR, Tong ML, et al. Incidence and risk factors for the prozone phenomenon in serologic testing for syphilis in a large cohort. *Clinical Infectious Diseases*. 2014;59(3):384-389.

34. U. S. Preventive Services Task Force. Screening for Syphilis Infection in Nonpregnant Adults and Adolescents: US Preventive Services Task Force Recommendation Statement. *Jama*. 2016;315(21):2321-2327.
35. AAP Committee on Fetus and Newborn and ACOG Committee on Obstetric Practice. *Guidelines for Perinatal Care, 8th Edition*. 2017.
36. Coles FB, Muse AG, Hipp SS. Impact of a mandatory syphilis delivery test on reported cases of congenital syphilis in Upstate New York. *J Public Health Manag Pract*. 1998;4(3):50-56.
37. Shiber L, Todia WJ. Cost and clinical utility of repeated syphilis screening in the third trimester in a high-risk population. *Am J Obstet Gynecol*. 2014;210(3):267.e261-265.
38. Albright CM, Emerson JB, Werner EF, Hughes BL. Third-Trimester Prenatal Syphilis Screening: A Cost-Effectiveness Analysis. *Obstetrics & Gynecology*. 2015;126(3):479-485.
39. American Academy of Family Physicians. Clinical Preventive Service Recommendation: Syphilis, Pregnant Women. 2009; http://www.aafp.org/patient-care/clinical-recommendations/all/syphilis.html Accessed 09/21/2017.
40. Akkerman D, Cleland L, Croft G, et al. Routine Prenatal Care. *Institute for Clinical Systems Improvement*. 2012.
41. National Institute for Care and Excellence (NICE). *Antenatal care for uncomplicated pregnancies*. London (UK): National lnstitute for Health and Care Excellence2008.

Figure 1. Syphilis Serologic Screening Algorithms*



*Adapted from: Centers for Disease Control and Prevention (CDC). Discordant results from reverse sequence syphilis screening – five laboratories, United States, 2006-2010. *MMWR Morb Mortal Wkly Rep*. 2011;60(5):133-7.

Figure 2. Analytic Framework

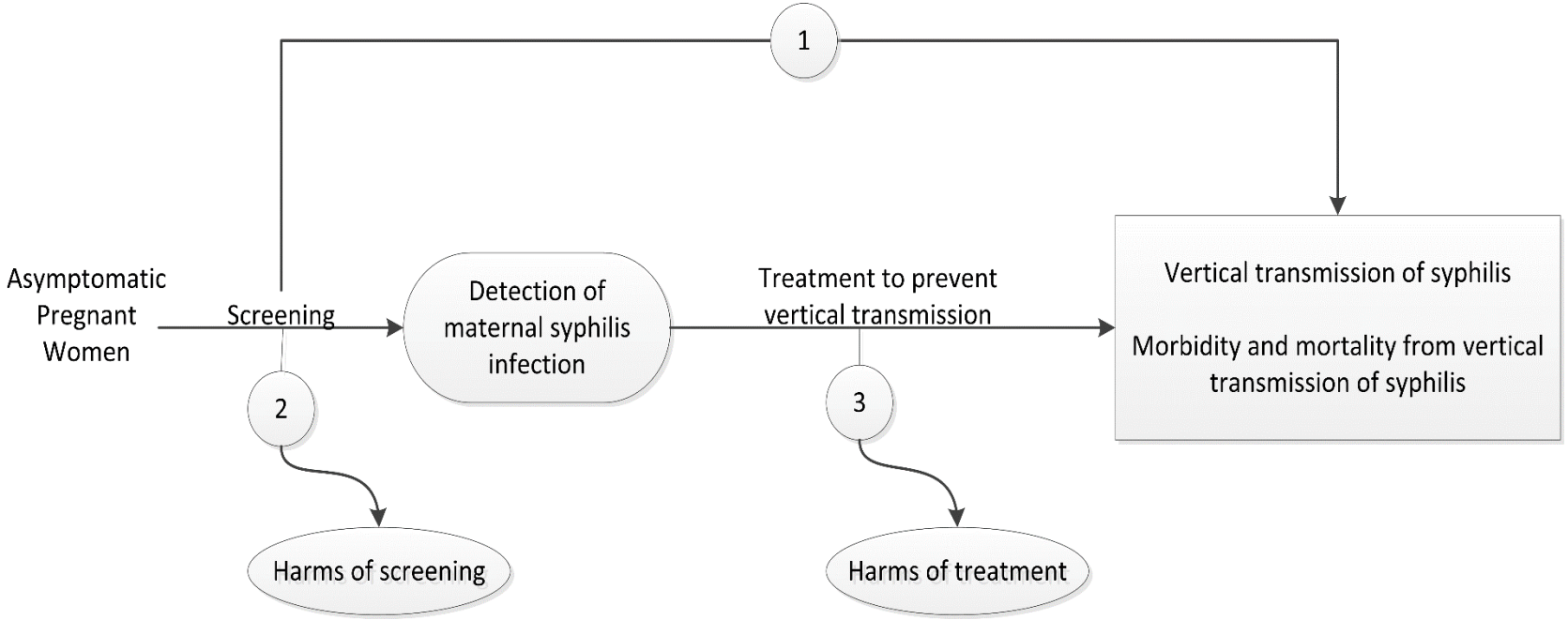


Table 1. Rates of Reported Syphilis Cases by Race/Ethnicity and Age Group, United States, 2016[2]

Age	White	Black	Asian	Native Hawaiian/Other Pacific Islander	American Indian/Alaska Native	Hispanic	Total
Primary and Secondary Syphilis Among Women, Rates per 100,000 Population							
15-19	1.1	13.6	0.4	10.2	3.4	2.2	3.3
20-24	3.0	21.9	1.3	8.7	8.2	6.0	6.7
25-29	3.0	18.2	0.8	0.0	14.4	4.8	5.6
30-34	2.6	11.3	0.9	0.0	12.2	4.9	4.3
35-39	2.1	7.3	1.2	14.4	8.1	2.5	3.0
40-44	1.3	3.8	0.7	0.0	4.1	2.0	1.9
All ages	0.9	6.3	0.4	2.5	3.7	1.9	1.9
Congenital Syphilis, Rates per 100,000 Live Births							
	5.3	43.1	NA	NA	31.6	20.5	15.7

Table 2. Rates of Reported Syphilis Cases by Region, United States, 2016[2]

Northeast	Midwest	South	West	Total
Primary and Secondary Syphilis Among Women, Rates per 100,000 Population				
0.9	1.2	2.2	2.7	1.9
Congenital Syphilis, Rates per 100,000 Live Births				
5.4	8.4	17.8	25.6	15.7

Table 3. Recommendations for Screening for Syphilis in Pregnancy

Organization Year	Recommendation	Screening Test(s)	Screening Interval
U.S. Preventive Services Task Force[22] 2009	Screen all pregnant women for syphilis infection (A recommendation)	Nontreponemal tests commonly used for initial screening: Venereal Disease Research Laboratory (VDRL) Rapid plasma reagin (RPR) Confirmatory tests: Fluorescent treponemal antibody absorbed (FTA-ABS) *Treponema pallidum* particle agglutination (TPPA)	First prenatal visit
American Academy of Family Physicians[39] 2009	Screen all pregnant women for syphilis infection (derived from USPSTF recommendation)	Nontreponemal tests commonly used for initial screening: Venereal Disease Research Laboratory (VDRL) Rapid plasma reagin (RPR) Confirmatory tests: Fluorescent treponemal antibody absorbed (FTA-ABS) *Treponema pallidum* particle agglutination (TPPA)	First prenatal visit
Centers for Disease Control and Prevention[4] 2015	Screen all pregnant women for syphilis infection	Serologic test RPR at the time pregnancy is confirmed if access to prenatal care is not optimal	First prenatal visit Additional screening early in third trimester (≈28 weeks' gestation) and at delivery for women at high risk for syphilis or who live in areas of high syphilis morbidity
Institute for Clinical Systems Improvement[40] 2012	Screen all pregnant women for syphilis infection	Serologic test (RPR or VDRL) Treponemal tests should not be used as initial screening tests in asymptomatic patients due to increased expense and the persistent positive test in previously treated patients	First prenatal visit Preconception visit for all high-risk women
American Academy of Pediatrics and American College of Obstetricians and Gynecologists[35] 2017	Screen all pregnant women for syphilis infection	Nontreponemal test (VDRL/RPR) followed by treponemal test to confirm the diagnosis of syphilis in persons with a reactive VDRL/RDR result	First prenatal visit/as early as possible Additional screening early in third trimester (28 to 32 weeks' gestation), at delivery, and after exposure to an infected partner for communities and populations with a high prevalence
National Institute for Health and Care Excellence[41] 2008	Screening for syphilis infection should be offered to all pregnant women	Not specified, but notes that enzyme immunoassay (EIA) tests are being used more frequently in the United Kingdom.	At an early stage in antenatal care

Table 4. Harms of Screening for Syphilis in Pregnant Women

Author, Year	Quality Study Design	Country Years Patient Selection	N Pregnant Women Screened	Test Evaluated Cutoff	Testing Strategy	Test Positivity (%)	Harm
Reported Harm: False-Positive Results							
Chemiluminescent Immunoassay (CIA)							
Boonchaoy, 2016[28]	Fair Retrospective	Thailand 2011–2013 Pregnant women only	11,640	ARCHITECT S/CO value ≥1.00	Reflex testing with RPR and TPPA	65/11,640 (0.56%)	35/65 (53.8%) false positives
Wang, 2016[29]	Fair Retrospective	China 2013 General population, including pregnant women	9,600	ARCHITECT S/CO value >1.00	Reflex testing with TPPA; immunoblot used for confirmation of discordant samples	34/9,600 (0.35%)	30/34 (88.2%) false positives
Mmeje, 2015[30]	Fair Retrospective	US 2007–2010 Pregnant women only	NR*	LIAISON NR	Reflex testing with RPR and TPPA	NR	156/194† (80.4%) false positives
Wellinghausen, 2011[32]	Fair Prospective	Germany 2010 General population, including pregnant women	318	ARCHITECT, LIAISON ARCHITECT: Index ≥1.0; LIAISON: Index ≥0.9	Reflex testing with FTA-Abs; immunoblot used for confirmation of discordant samples	ARCHITECT: 0/318 (0%) LIAISON: 1/318 (0.31%)	ARCHITECT: NA LIAISON: 0/1 (0%) false positives
Enzyme Immunoassay (EIA)							
Henrich, 2011[31]	Fair Retrospective	US 2004–2007 General population, including pregnant women	NR‡	Captia Syph-G NR	Reflex testing with RPR and TPPA	NR	20/43§ (46.5%) false positives
Treponema pallidum particle agglutination (TPPA)							
Wellinghausen, 2011[32]	Fair Prospective	Germany 2010 General population, including pregnant women	318	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%) false positives

Table 4. Harms of Screening for Syphilis in Pregnant Women

Author, Year	Quality Study Design	Country Years Patient Selection	N Pregnant Women Screened	Test Evaluated Cutoff	Testing Strategy	Test Positivity (%)	Harm
Reported Harm: False-Negative Results							
Rapid Plasma Reagin (RPR)							
Liu, 2014[33]	Fair Retrospective	China 2010–2013 General population, including pregnant women	NR	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%) false negatives (prozone phenomenon)
Chemiluminescent Immunoassay (CIA)							
Wellinghausen, 2011[32]	Fair Prospective	Germany 2010 General population, including pregnant women	318	ARCHITECT, LIAISON ARCHITECT: Index ≥1.0; LIAISON: Index ≥0.9	Reflex testing with FTA-Abs; immunoblot used for confirmation of discordant samples	ARCHITECT: 0/318 (0%) LIAISON: 1/318 (0.31%)	ARCHITECT: 0/317 (0%) false negatives LIAISON: 0/317 (0%) false negatives
Treponema pallidum particle agglutination (TPPA)							
Wellinghausen, 2011[32]	Fair Prospective	Germany 2010 General population, including pregnant women	318	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%) false negatives

*All pregnant women tested with reverse sequence algorithm at Kaiser Permanente Northern California.
†194 women with CIA+, RPR- serology.
‡All pregnant women screened with IgG EIA at first prenatal visit.
§43 pregnant women with positive EIA.

Abbreviations: S/CO = sample/cutoff; RPR = rapid plasma reagin; TPPA = *Treponema pallidum* particle agglutination; WB = Western blotting; NR = not reported; CIA = chemiluminescent immunoassay; FTA-ABS = fluorescent treponemal antibody absorption test; Ig = immunoglobulin; NA = not applicable; EIA = enzyme immunoassay.

Table 5. 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 more than 2 million pregnant women in Shenzhen, China demonstrated an 11-fold decrease in congenital syphilis over 10 years. **Treatment:** Not readdressed.	Included observational study has significant methodologic limitations (i.e., with the use of historical and geographic comparators), as well as significant concerns around external validity of findings (e.g., national data from China suggest a syphilis epidemic). The magnitude of benefit in U.S. 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 positives 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. **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 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 positives are common in pregnancy (as well as cannot distinguish between old and current infection).

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

Appendix A. Abbreviations

AAFP = American Academy of Family Physicians
AAP = American Academy of Pediatrics
ACOG = American College of Obstetricians and Gynecologists
AHRQ = Agency for Healthcare Research and Quality
CENTRAL = Cochrane Central Register of Controlled Trials
CDC = Centers for Disease Control and Prevention
CIA = chemiluminescence immunoassay
EIA = enzyme immunoassay
FDA = U.S. Food and Drug Administration
FTA-ABS = fluorescent treponemal antibody absorbed test
GRADE = Grading of Recommendations Assessment, Development, and Evaluation
HIV = human immunodeficiency virus
ICS = immunochromatographic strip tests
IM = intramuscular
KQ = key question
MBIA = microbead immunoassay
MTC = mother-to-child
PAT = particle agglutination test
PCR = polymerase chain reaction
POCT = point-of-care test
RPR = rapid plasma reagin
STD = sexually transmitted disease
STI = sexually transmitted infection
T. pallidum = *Treponema pallidum*
TPPA = *Treponema pallidum* article agglutination
TRUST = toluidine red unheated serum test
USPSTF = U.S. Preventive Services Task Force
VDRL = Venereal Disease Research Laboratory

Literature Search Strategies

Screening

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

---

1 Syphilis/
2 Syphilis, Congenital/
3 syphilis.ti,ab.
4 treponema pallidum.ti,ab.
5 or/1-4
6 Mass screening/
7 screen$.ti,ab.
8 6 or 7
9 5 and 8
10 Syphilis Serodiagnosis/
11 ((nontreponemal or treponemal) adj (test$ or immunoassay$)).ti,ab.
12 venereal disease research laboratory.ti,ab.
13 VDRL.ti,ab.
14 Rapid plasma reagin.ti,ab.
15 Fluorescent treponemal antibody absorbed.ti,ab.
16 Treponema pallidum particle agglutination.ti,ab.
17 or/10-16
18 9 or 17
19 Pregnancy/
20 Pregnancy Trimester, First/
21 Pregnancy Trimester, Second/
22 Pregnancy Trimester, Third/
23 Pregnant women/
24 Prenatal Care/
25 Prenatal Diagnosis/
26 Pregnancy Outcome/
27 Pregnancy Complications, Infectious/
28 Infectious Disease Transmission, Vertical/
29 (pregnan$ or prenatal or pre natal or perinatal or peri natal or antenatal or ante natal or antepartum or ante partum).ti,ab.
30 ((vertical or maternal or mother or fetomaternal) adj3 transmission).ti,ab.
31 or/19-30
32 18 and 31
33 limit 32 to (english language and yr="2008 -Current")

34 remove duplicates from 33

Treatment

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

---

1 Syphilis/
2 Syphilis, Congenital/
3 syphilis.ti,ab.
4 treponema pallidum.ti,ab.
5 or/1-4
6 exp Anti-Bacterial Agents/
7 (antibiotic$ or Penicillin or Benzylpenicillin or Amoxicillin or Ampicillin or Carbenicillin or Sulbenicillin).ti,ab.
8 6 or 7
9 Pregnancy/
10 Pregnancy Trimester, First/
11 Pregnancy Trimester, Second/
12 Pregnancy Trimester, Third/
13 Pregnant women/
14 Prenatal Care/
15 Pregnancy Outcome/
16 (pregnan$ or prenatal or pre natal or perinatal or peri natal or antenatal or ante natal or antepartum or ante partum).ti,ab.
17 Infant/
18 Infant, newborn/
19 Fetus/
20 (fetal or foetal or fetus$ or foetus$ or neonat$ or infant$ or newborn$).ti,ab.
21 exp Pregnancy Complications/
22 Infectious Disease Transmission, Vertical/
23 ((vertical or maternal or mother or fetomaternal) adj3 transmission).ti,ab.
24 Congenital Abnormalities/
25 Abnormalities, Drug-Induced/
26 fetal mortality/
27 infant mortality/
28 perinatal mortality/
29 maternal mortality/
30 or/9-29
31 5 and 8 and 30

32 limit 31 to (english language and yr="2008 -Current")
33 remove duplicates from 32

Pubmed, publisher-supplied [search run on 6.2.2017]

Search	Query
#6	Search #5 AND ("2008/01/01"[Date - Publication] : "3000"[Date - Publication]) AND English[Language]
#5	Search #4 AND publisher[sb]
#4	Search #1 AND (#2 OR #3)
#3	Search (vertical[tiab] OR maternal[tiab] OR mother[tiab] OR fetomaternal[tiab]) AND transmission[tiab]
#2	Search pregnan*[tiab] OR prenatal[tiab] OR "pre natal"[tiab] OR perinatal[tiab] OR "peri natal"[tiab] OR antenatal[tiab] OR "ante natal"[tiab] OR antepartum[tiab] OR "ante partum"[tiab] OR fetal[tiab] OR foetal[tiab] OR fetus*[tiab] OR foetus*[tiab] OR neonat*[tiab] OR infant*[tiab] OR newborn*[tiab]
#1	Search syphilis[tiab] OR "treponema pallidum"[tiab]

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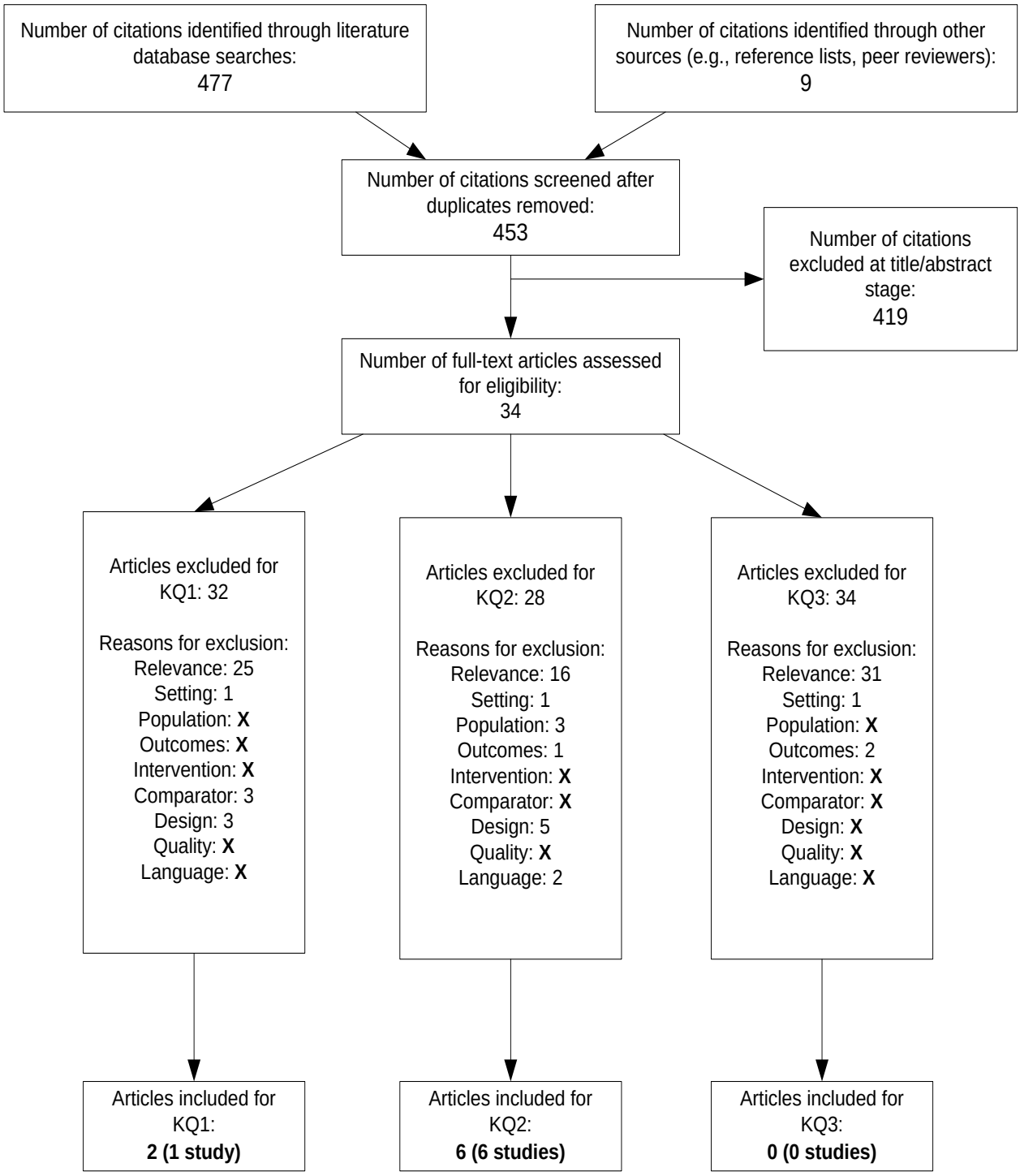
#1 syphilis:ti,ab,kw
#2 "treponema pallidum":ti,ab,kw
#3 #1 or #2
#4 (pregnan* or prenatal or pre natal or perinatal or peri natal or antenatal or ante natal or antepartum or ante partum):ti,ab,kw
#5 (fetal or foetal or fetus* or foetus* or neonat* or infant* or newborn*):ti,ab,kw
#6 ((vertical or maternal or mother or fetomaternal) near/3 transmission):ti,ab,kw
#7 #4 or #5 or #6
#8 #3 and #7 Publication Year from 2008 to 2017 in Trials

Appendix B Figure 1. Literature Flow Diagram



Appendix B Table 1. Inclusion and Exclusion Criteria

Category	Include	Exclude
Populations	**KQs 1, 2:** Asymptomatic pregnant adolescents or adult women, at any time during pregnancy, who are not known to have syphilis infection **KQ 3:** Studies of penicillin treatment in pregnant women with syphilis infection	**KQs 1, 2:** Women who are known to have syphilis infection, have symptoms, or are not pregnant; studies in women living with HIV **KQ 3:** Studies of penicillin treatment in nonpregnant women or men; studies of penicillin treatment for any condition other than syphilis
Interventions	**KQs 1, 2:** Two-step screening for syphilis with a nontreponemal and treponemal test (traditional or reverse sequence algorithms) **KQ 3:** Treatment of syphilis with penicillin started during pregnancy	**KQs 1, 2:** Screening tests not currently used in U.S. primary care settings **KQ 3:** Other types of treatment of syphilis; treatment of syphilis with penicillin outside of pregnancy
Comparisons	**KQ 1:** No screening **KQ 2:** No comparator necessary for studies on psychosocial harms; studies on screening test in accuracy must define their criteria for false-positive and false-negative results **KQ 3:** No comparator necessary	**KQ 1:** Alternate screening strategy or no comparator
Outcomes	**KQ 1:** Vertical transmission of syphilis (incidence of congenital syphilis); prevalence of congenital syphilis after implementation of a screening program; stillbirth; maternal or infant morbidity and mortality **KQ 2:** Harms of screening (e.g., false-positive and false-negative results, stigma, psychosocial harms) **KQ 3:** Harms of treatment of syphilis with penicillin during pregnancy (e.g., allergic reaction, premature labor, Jarish-Herxheimer reaction, fetal harms, other maternal harms)	Cost-effectiveness or cost-related outcomes
Setting	Primary care and primary care–referable settings (e.g., obstetrics/gynecology clinics, prenatal clinics, ambulatory care, family planning clinics, correctional facilities, sexually transmitted infection clinics)	
Country	Studies conducted in countries categorized as "high" or "very high" on the Human Development Index (as defined by the United Nations Development Programme)	
Study design	**KQ 1:** Randomized, controlled trials; before-after and ecologic studies reporting effect of implementing a widespread screening program with historical or geographic comparator; systematic reviews and meta-analyses (of included study designs) **KQs 2, 3:** Randomized, controlled trials; cohort studies; case-control studies; diagnostic accuracy studies; large case series; systematic reviews and meta-analyses (of included study designs)	Narrative reviews, editorials, and case reports
Publication Language	English-language only	Languages other than English
Study quality	Fair- or good-quality studies	Poor-quality studies

Appendix B. Table 2. Quality Assessment Criteria

Study Design	Criteria
Randomized and nonrandomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[1]	• Was there valid random assignment? (NA for non-randomized controlled trials) • Was allocation concealed? • Was eligibility criteria specified? • Were groups similar at baseline? • Were outcome assessors blinded? • Were measurements equal, valid and reliable? • Was there adequate adherence to the intervention? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there acceptable follow up? • Was there evidence of selective reporting of outcomes? • Was there risk of contamination?
Cohort studies, adapted from the Newcastle-Ottawa Scale[2]	• Was the exposed cohort(s) representative of the general population? • Was the non-exposed cohort selected from the same community as exposed cohort? • How was "exposure" ascertained? • Was it demonstrated that the outcome of interest was not present at the start of the study? • Were the cohorts comparable on the basis of the design or analysis? • Were outcome assessors blind? • Was follow up long enough for outcomes to occur? • Was there adequate of follow up of cohorts?
National Heart, Lung, and Blood Institute tool for before-after (pre-post) studies with no control group[3]	• Was the study question or objective clearly stated? • Were eligibility/selection criteria prespecified and clearly described? • Were the participants representative of the general population? • Were all eligible participants enrolled? • Was the sample size sufficiently large? • Was the test/service/intervention clearly described and delivered consistently? • Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently? • Were outcome assessors blind? • Was loss to follow up ≤20% and those lost to follow-up accounted for in analysis? • Did statistical methods examine changes in outcome measures from before to after the intervention? Were p values provided? • Were outcome measures taken multiple times before and after the intervention? • If a group-level intervention, did statistical analysis take into account the use of individual-level data to determine group-level effects?

1. U.S. Preventive Services Task Force. *U.S. Preventive Services Task Force Procedure Manual*. Rockville, MD: U.S. Preventive Services Task Force; Dec 2015.
2. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed 9/12/2017.
3. National Heart Lung and Blood Institute. Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group. https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after. Accessed 9/12/2017.

Appendix C. Excluded Studies

1. Study Aim: Not applicable/relevant to key question
E2. Setting: **a.** Not in a high or very high human development index country **b.** Screening and/or intervention not conducted in primary care, primary care-feasible, or widely available for primary care-referral
E3. Population: **a.** Women who are known to have syphilis infection, have symptoms, or are not pregnant; studies in women living with HIV, for whom syphilis testing is considered disease management rather than a screening intervention; results for pregnant women not reported separately (KQ1, KQ2) **b.** Studies of penicillin treatment in nonpregnant women or men; studies of penicillin treatment for any condition other than syphilis (KQ3) **c.** Otherwise out of scope (e.g., selected population not normally seen in primary care)
E4. Outcome: Cost-effectiveness or cost-related outcomes; no relevant outcomes
E5. Intervention **a.** Screening tests not currently used in U.S. primary care settings (KQ1, KQ2) **b.** Other types of treatment of syphilis; treatment of syphilis with penicillin outside of pregnancy (KQ3)
E6. Comparator: Alternate screening strategy or no comparator (KQ1)
E7. Study Design: Narrative reviews, editorials, case reports, systematic review checked for relevant studies; studies that use pregnant women as controls
E8. Study Quality: Poor
E9. Publication type: Abstract only, Non-English publication, main results published prior to review start date

1. Bala M, Toor A, Malhotra M, et al. Evaluation of the usefulness of Treponema pallidum hemagglutination test in the diagnosis of syphilis in weak reactive Venereal Disease Research Laboratory sera. Indian J Sex Transm Dis. 2012;33(2):102-6. PMID: 23188934. **KQ1E2a, KQ2E2a, KQ3E2a.**
2. Blencowe H, Cousens S, Kamb M, et al. Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality. BMC Public Health. 2011;11 Suppl 3:S9. PMID: 21501460. **KQ1E7, KQ2E1, KQ3E1.**
3. Bosshard PP. Usefulness of IgM-specific enzyme immunoassays for serodiagnosis of syphilis: comparative evaluation of three different assays. J Infect. 2013;67(1):35-42. PMID: 23542782. **KQ1E1, KQ2E7, KQ3E1.**
4. Buffolano W, Agnese M, Pizzuti R. Secular trend on congenital infections: insights from Campania region register for perinatal infection, southern Italy. Journal of Maternal-Fetal & Neonatal Medicine. 2011;24 Suppl 1:94-6. PMID: 21942602. **KQ1E1, KQ2E1, KQ3E1.**
5. Busse C, Navid MH, Strubel A, et al. Evaluation of a new recombinant antigen-based Virotech Treponema pallidum screen ELISA for diagnosis of syphilis. Clin Lab. 2013;59(5-6):523-9. PMID: 23865350. **KQ1E1, KQ3E1, KQ2E3a.**
6. Cerda R, Perez F, Domingues RM, et al. Prenatal Transmission of Syphilis and Human Immunodeficiency Virus in Brazil: Achieving Regional Targets for Elimination. Open forum infect. 2015;2(2):ofv073. PMID: 26180825. **KQ1E1, KQ2E1, KQ3E1.**
7. de Jongh T, Gurol-Urganci I, Allen E, et al. Integration of antenatal care services with health programmes: Systematic review. International journal of gynaecology and obstetrics. 2016;131:E363-e4. PMID: None. **KQ1E7, KQ2E1, KQ3E1.**
8. Donkers A, Levy HR, Letens-van Vliet A. Syphilis detection using the Siemens ADVIA Centaur Syphilis treponemal assay. Clin Chim Acta. 2014;433:84-7. PMID: 24513542. **KQ1E1, KQ3E1, KQ2E3a**
9. Enders M, Hunjet A, Gleich M, et al. Performance evaluation of the Elecsys syphilis assay for the detection of total antibodies to Treponema pallidum. Clin Vaccine Immunol. 2015;22(1):17-26. PMID: 25355799. **KQ1E1, KQ3E1, KQ2E3a.**
10. Gu WM, Yang Y, Wang QZ, et al. Comparing the performance of traditional non-treponemal tests on syphilis and non-syphilis serum samples. International journal of STD & AIDS. 2013;24(12):919-25. PMID: 23970626. **KQ1E1, KQ3E1, KQ2E7.**

11. Hawkes S, Matin N, Broutet N, et al. Effectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis. Lancet Infect Dis. 2011;11(9):684-91. PMID: 21683653. **KQ1E7, KQ2E1, KQ3E1.**
12. Hong FC, Wu XB, Yang F, et al. Risk of congenital syphilis following treatment of maternal syphilis: results of a congenital syphilis control program in China. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2017. PMID: 28444157. **KQ1E1, KQ2E1, KQ3E4.**
13. Knight CS, Crum MA, Hardy RW. Evaluation of the LIAISON chemiluminescence immunoassay for diagnosis of syphilis. Clin Vaccine Immunol. 2007;14(6):710-3. PMID: 17460119. **KQ1E1**, **KQ2E9, KQ3E1.**
14. Lee JH, Lim CS, Lee MG, et al. Evaluation of a Rapid Immunochromatographic Treponemal Antibody Test Comparing the Treponema Pallidum Particle Agglutination Assay. J Clin Lab Anal. 2015;29(5):383-6. PMID: 25385043. **KQ1E1, KQ3E1, KQ2E7.**
15. Liu JB, Hong FC, Pan P, et al. A risk model for congenital syphilis in infants born to mothers with syphilis treated in gestation: a prospective cohort study. Sexually transmitted infections. 2010;86(4):292-6. PMID: 20460262. **KQ1E1, KQ2E1, KQ3E1.**
16. Marangoni A, Moroni A, Accardo S, et al. Laboratory diagnosis of syphilis with automated immunoassays. J Clin Lab Anal. 2009;23(1):1-6. PMID: 19140205. **KQ1E1, KQ2E7, KQ3E1.**
17. Marangoni A, Moroni A, Tridapalli E, et al. Antenatal syphilis serology in pregnant women and follow-up of their infants in northern Italy. Clin Microbiol Infect. 2008;14(11):1065-8. PMID: 18834451. **KQ1E1, KQ2E1, KQ3E1.**
18. Marangoni A, Nardini P, Foschi C, et al. Evaluation of the BioPlex 2200 syphilis system as a first-line method of reverse-sequence screening for syphilis diagnosis. Clin Vaccine Immunol. 2013;20(7):1084-8. PMID: 23697575. **KQ1E1, KQ3E1, KQ2E7.**
19. McGettrick P, Ferguson W, Jackson V, et al. Syphilis serology in pregnancy: an eight-year study (2005-2012) in a large teaching maternity hospital in Dublin, Ireland. International journal of STD & AIDS. 2016;27(3):226-30. PMID: 25829517. **KQ1E1, KQ2E1, KQ3E1.**
20. Munkhuu B, Liabsuetrakul T, Chongsuvivatwong V, et al. One-stop service for antenatal syphilis screening and prevention of congenital syphilis in Ulaanbaatar, Mongolia: a cluster randomized trial. Sexually transmitted diseases. 2009;36(11):714-20. PMID: 19773681. **KQ1E6, KQ2E4, KQ3E4.**
21. Oliveira LR, Costa Mda C, Barreto FR, et al. Evaluation of preventative and control measures for congenital syphilis in State of Mato Grosso. Rev Soc Bras Med Trop. 2014;47(3):334-40. PMID: 25075485. **KQ1E1, KQ2E1, KQ3E1.**
22. Op de Coul EL, Hahne S, van Weert YW, et al. Antenatal screening for HIV, hepatitis B and syphilis in the Netherlands is effective. BMC infectious diseases. 2011;11:185. PMID: 21718466. **KQ1E6, KQ2E1, KQ3E1.**
23. Qin JB, Feng TJ, Yang TB, et al. Maternal and paternal factors associated with congenital syphilis in Shenzhen, China: a prospective cohort study. Eur J Clin Microbiol Infect Dis. 2014;33(2):221-32. PMID: 23948753. **KQ1E1, KQ2E1, KQ3E1.**
24. Sia VM, Romero C, Sia DC, et al. Epidemiology of congenital syphilis in a South Bronx population: a follow-up study. J Perinat Med. 2011;39(1):71-5. PMID: 20979448. **KQ1E6, KQ2E1, KQ3E1.**
25. Tao C, Wang L, Hao X, et al. Evaluation of the elecsys syphilis assay for the detection of treponema pallidum in routine samples from the Chinese population compared with local market competitors. Vox Sanguinis Conference: 34th International Congress of the International Society of Blood Transfusion United Arab Emirates Conference Start: 20160903 Conference End: 20160908. 2016;111:174. PMID: None. **KQ1E1, KQ3E1, KQ2E9.**
26. Zhu L, Qin M, Du L, et al. Maternal and congenital syphilis in Shanghai, China, 2002 to 2006. Int J Infect Dis. 2010;14 Suppl 3:e45-8. PMID: 20137991. **KQ1E1, KQ2E1, KQ3E1.**