Evidence Synthesis

Number 243

Screening for Syphilis Infection during Pregnancy: A Limited Systematic Evidence Review Update for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA-75Q80120D00007, Task Order 758Q0122F32006

Prepared by:
RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center
Research Triangle Park, NC 27709

Investigators:
Gary N. Asher, MD, MPH
Meera Viswanathan, PhD
Afua Takyi, MD, MBS, MPH
Jennifer Cook Middleton, PhD
Claire Baker
Leila C. Kahwati, MD, MPH

AHRQ Publication No. 24-05317-EF-1
May 2025

This report is based on research conducted by the RTI International–University of North Carolina Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (HHSA-75Q80120D00007, Task Order No. 758Q0122F32006). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

The final report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Brandy Peaker, MD, MPH, and Tina Fan, MD, MPH, AHRQ Medical Officers; Tracy Wolff, MD, MPH, Scientific Director, AHRQ U.S. Preventive Services Task Force (USPSTF) Program; current and former members of the USPSTF; expert reviewers Catherine Squire Eppes, MD, MPH, Baylor College of Medicine; Peter Miksovsky, MD, Kaiser Permanente; and Jessica E. P. Williams, MD, Children's National Hospital; Federal partners from the Eunice Kennedy Shriver National Institute of Child Health and Development; National Center for HIV, Viral Hepatitis, STD, and TB Prevention; National Eye Institute; and Office of Research on Women's Health; RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center staff: Christiane E. Voisin, MSLS, research librarian; Roberta Wines, MPH, EPC Project Manager; Jessica Burch, BA, editor; and Alexander Cone, BA, publications specialist.

Suggested Citation

Asher GN, Viswanathan M, Takyi A, Middleton JC, Baker C, Kahwati LC. Screening for Syphilis Infection during Pregnancy: A Limited Systematic Evidence Review Update for the U.S. Preventive Services Task Force. Evidence Synthesis No. 243. AHRQ Publication No. 24-05317-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2025.

Structured Abstract

Purpose: Prior evidence has demonstrated that screening is effective at detecting syphilis and treatment is effective at preventing congenital syphilis and adverse pregnancy outcomes. The purpose of this review is to conduct a limited update of new evidence of the benefits and harms of screening and harms of treatment of syphilis infection during pregnancy for the U.S. Preventive Services Task Force (USPSTF) to update its 2018 recommendation.

Data Sources: Cochrane Library, Ovid MEDLINE, and trial registries from January 1, 2017, through July 25, 2023, with surveillance through March 21, 2025. We also conducted targeted grey literature searches.

Study Selection: Two investigators independently screened abstracts and full-text publications. For evidence on screening benefits and harms, eligible studies included asymptomatic pregnant adolescents or adults, screened using U.S. Food and Drug Administration–approved tests compared with or as the first step within a two-step serologic screening algorithm. Eligible harms of screening included stigma, psychosocial harms, and unnecessary or missed evaluation or treatment that may arise from false-positive or false-negative results arising during two-step screening. Evidence on harms of treatment was restricted to studies of penicillin treatment in pregnancy with syphilis. Eligible treatment harms included allergic reaction, premature labor, Jarisch-Herxheimer (JH) reaction, fetal harms, and other maternal harms. For all key questions, we included studies conducted in countries categorized as "high" or "very high" on the Human Development Index and restricted inclusion to studies conducted in primary care–relevant or primary care–referable settings.

Data Extraction and Analysis: At least one reviewer abstracted predefined data elements into standardized forms, and a second checked the data for accuracy. Two investigators independently assessed the risk of bias for each included study using design-specific criteria. A paucity of studies precluded pooling of results, so studies were synthesized in narrative form.

Results: We found no new studies addressing the effectiveness of screening to reduce congenital syphilis or other adverse outcomes (key question [KQ] 1). Five studies (51,118 participants) addressed the harms of screening (KQ 2), and two studies (130 participants) addressed the harms of treatment (KQ 3). For KQ 2, index test positivity (i.e., the first test in a two-step algorithm) ranged between 1.0 and 4.8 percent, and estimates of false-positive results ranged between 0 and 65 percent, varying by the screening algorithm and index test evaluated. One study of traditional two-step screening (nontreponemal test followed by treponemal test) reported a false-positive rate of 31 percent (11/35). Five studies using a reverse-sequence, two-step screening algorithm (treponemal test followed by nontreponemal test) reported false-positive rates that varied substantially (7% to 65%). One study comparing a treponemal test with a nonstandard composite two-step screening algorithm reported both no false-positive (0/15) and no false-negative (0/301) cases. For KQ 3, one study (N=39) reported JH reaction in 5.1 percent of participants, and one study (N=91) reported 2.5 percent of participants had adverse reactions to standard penicillin provocation or desensitization protocols.

Limitations: Our review was limited to studies published since 2017 and did not include previously reviewed evidence, consistent with a limited review approach to support USPSTF

reaffirmations. Our review did not systematically address the accuracy of screening tests or comparative effectiveness of different screening algorithms, as well as the effectiveness of screening more than once during pregnancy. Syphilis treatment was not included because of its well-established evidence of effectiveness.

Conclusions: Although screening and early treatment for syphilis in pregnancy has been shown to decrease poor maternal and neonatal outcomes, preferred screening algorithms have not been identified. Our limited review found evidence consistent with prior reviews on screening for syphilis in pregnancy that supports the need for two-step serologic screening to reduce false screening results. Although based on small studies, we found estimates of penicillin treatment harms that could be used for bounding of potential harms.

Table of Contents

Figures

Tables

Appendixes

Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this limited systematic evidence review to update its 2018 recommendation on this topic.[1] Limited updates are intended to support reaffirmations of prior "A" or "D" recommendations and focus on new evidence since the prior review. The USPSTF guidance notes "the goal of the search for evidence in a reaffirmation evidence update is to find new and substantial evidence sufficient enough to change the prior recommendation."[2] Accuracy of screening tests to detect syphilis and effectiveness of treatment to prevent congenital syphilis are not included in this review due to their well-established evidence of effectiveness and benefit.

Condition Background

Condition Definition

Syphilis is an infectious disease caused by *Treponema pallidum* (*T. pallidum*)[3] and is primarily transmitted through sexual contact; transplacental transmission (vertical transmission) from mother to fetus; and in rare cases, blood transfusions or organ transplants.[4] Syphilis infection during pregnancy is a particular concern because untreated syphilis is associated with adverse pregnancy outcomes including premature birth, low birth weight, stillbirth, and neonatal death.[5-7] Untreated syphilis infection during pregnancy also puts fetuses at risk for congenital syphilis, [5-7] which is associated with deformed bones, severe anemia, enlarged liver and spleen, jaundice, brain and nerve problems (e.g., permanent vision or hearing loss), meningitis, skin rashes, and death.[7] Syphilis transmission from mother to child is usually caused by vertical transmission or, less commonly, by contact with infected maternal skin lesions during birth.[8] Transmission can occur throughout pregnancy with increasing risk of transmission to the fetus related to maternal syphilis stage; the highest rate of maternal-fetal transmission occurs during secondary syphilis.[9] Early diagnosis in pregnancy is important to be able to initiate treatment as early as possible.[4, 9]

Based on disease stage, syphilis can be asymptomatic or associated with a range of symptoms; because its symptoms can look like many other diseases, syphilis infection may go unrecognized for an extended period.[10] Syphilis has four stages of infection: primary, secondary, latent (early latent or late latent), and tertiary.[11] Primary syphilis usually occurs between 9 to 90 days after infection and usually presents with a single painless ulcer or chancre at the site of inoculation—typically the genitals but also the mouth or anus.[12] Secondary syphilis presents 4 to 10 weeks after the first ulcer or lesion and often presents with a skin rash and/or lesions. Other secondary stage symptoms can include fever, swollen lymph nodes, sore throat, headaches, weight loss, muscle aches, fatigue, alopecia, abdominal pain, and joint swelling.[4, 11, 12] Both primary and secondary stage symptoms will resolve with or without treatment.[11, 12] Early latent syphilis (within the first year of infection, also known as early nonprimary nonsecondary syphilis) or late latent syphilis (more than 1 year after infection and can last for years) both do not have any signs or symptoms[4, 11] and can only be detected through serologic testing.[3] Tertiary syphilis, the rarest

stage of syphilis, can occur 10 to 30 years after untreated or insufficiently treated infection and can result in damage to organ systems and death.[11] Vertical transmission from mother to fetus can occur during all four stages of syphilis, with the highest transmission rates occurring during the earlier stages of the disease,[4] especially when the primary stage chancre is present.[9]

Incidence, Burden, and Risk Factors

Incidence of syphilis in pregnancy is difficult to measure, and available data need to be interpreted in the context of incidence in the overall population. Rates of reported cases of primary and secondary syphilis in the general population in the United States have continued to rise over the past two decades after a historic low of 2.1 cases per 100,000[13] in 2000 to 15.8 cases per 100,000[13] in 2023. Federal surveillance statistics in 2023 reported 209,253 cases in the general population (congenital, primary and secondary, early nonprimary nonsecondary, and unknown duration or late syphilis), of which 3,882 were congenital syphilis cases.[14]

Although absolute syphilis rates are higher in men, a disproportionate burden of the increase in syphilis has occurred in women.[15] Between 2017 and 2021, the rate of change of incidence among women has ranged from 2 to 4 times that of men. For example, in primary and secondary syphilis, the increase in incidence for men was 45.2 percent (from 16.8 cases per 100,000 population to 25.2 cases per 100,000), whereas for women, the increase in incidence was 217 percent (from 2.3 cases per 100,000 to 7.3 cases per 100,000).[16] These patterns—of lower absolute rates but higher relative increases among women—occur for other stages of syphilis as well.

Mirroring increasing incidence among women, rates of congenital syphilis rose from 35.0 cases per 100,000 pregnancies in 2018 to 105.8 per 100,000 in 2023, a percentage change of 302 percent.[13] In 2022, 3,761 congenital syphilis cases were reported through the U.S. Centers for Disease Control and Prevention (CDC) National Notifiable Diseases Surveillance System (NNDSS) (**Figure 1**).[17] National surveillance data among pregnant adolescents and adults indicated that all stages of syphilis had risen by 61 percent between 2012 and 2016 from 1,561 to 2,508 cases. The proportion of these cases attributed to early syphilis (primary, secondary, or early latent syphilis) rose in this time period from 42 to 65 percent, whereas the proportion attributable to late latent syphilis decreased from 65 to 43 percent.[18] Authors noted that the rate of syphilis infections during pregnancy cannot be calculated with accuracy because of a lack of information on total numbers of pregnancies and number of pregnancy terminations or losses attributable to syphilis, but available numbers are likely to undercount true incidence.[18] Importantly, up to 40 percent of pregnancies among persons with early untreated syphilis result in miscarriage, stillbirth, or perinatal death.[19]

Based on data from CDC,[20] the rates of primary and secondary syphilis incidence vary by race/ethnicity and may be associated with social and structural factors influencing health behaviors and access to healthcare.[21] The highest rates occur among American Indians/Alaska Natives (46.7 per 100,000), Black persons (41.9 per 100,000), and Native Hawaiians/Pacific Islanders (33.9 per 100,000). Incidence doubled between 2017 and 2021 among American Indians/Alaska Natives, Native Hawaiians/Pacific Islanders, and multiracial populations. By contrast, the rates remained steady for Asian persons or increased at lower rates for White and Hispanic/Latino persons.

Notably, sharper upticks in incidence occurred during the COVID-19 pandemic (i.e., 2020 and 2021), particularly among American Indians/Alaska Natives, Black persons, and Native Hawaiians/Pacific Islanders. CDC noted the pandemic may have resulted in a complex pattern of changes in health behaviors, healthcare utilization, and public health activities.[22] Social distancing during shelter-in-place orders in March and April 2020, limited resources, and reduced screening may explain lower rates of incidence in March and April 2020.[22] However, case counts later in the year increased substantially, pointing to a possible increase in service utilization to address symptomatic syphilis as healthcare facilities became accessible.[22] Higher rates of transmission because of longer periods of untreated sexually transmitted infections (STIs) may also have played a role, as well as changes in sexual networks due to the pandemic.[22]

Although pandemic-specific issues point to the need for caution in interpreting more recent STI prevalence numbers, the rise in incidence of syphilis predates the pandemic. Several factors may play a role, in addition to the issues arising from or exacerbated by the pandemic. Among pregnant women with reported syphilis cases (all stages) in the United States between 2012 and 2016, history of prior STI (43%) and more than one sexual partner in the 12 months before the diagnosis of syphilis (30%) were the most commonly reported risk factors.[18] Reporting a prior STI, having sex with a known injection drug user, and having sex with a partner known to be a man who has sex with men were statistically significant factors for trends from 2012 through 2016.[18] In a sample of syphilis-infected women in California in 2012 through 2014, common risk factors included more than one male sex partner (29%), sex while intoxicated or high (29%), anonymous sex partners (13%), methamphetamine use (21%), and incarceration in the last 12 months (13%).[23] The same study showed no differences in risk factors among the same women with and without infants with congenital syphilis; however, the study did find differences in screening and adequate treatment. Specifically, 100 percent of syphilis-infected women with infants who did not have congenital syphilis had received screening at or more than 40 days before delivery and received adequate treatment, whereas only 59 percent of syphilis-infected women with infants with congenital syphilis received screening at or more than 40 days before delivery, and only 4 percent received adequate treatment.[23] This finding points to healthcare quality and access, beyond individual risk behavior, as important levers to prevent congenital syphilis. Cases of congenital syphilis are regarded as sentinel health events, indicating the failure of the syphilis control program and the prenatal care system.[3, 24]

Preliminary 2021 data from CDC showed that missed opportunities attributable to having no timely prenatal care or syphilis screening and no adequate maternal treatment have increased from 2017 through 2021, whereas the proportion of congenital syphilis cases attributable to other causes (e.g., timely prenatal care but no syphilis testing, timely syphilis testing but no adequate maternal treatment, late identification of seroconversion during pregnancy) had held steady or decreased (although total numbers had increased in all categories).[25] More recent surveillance statistics use a modified missed opportunities framework that accounts for the receipt of elements of prenatal care and testing in nontraditional venues and frames testing and treatment as part of the prevention cascade.[26] In 2022, the two most significant missed opportunities are attributable to having no or nontimely testing (36.8%) or no or undocumented (11.2%) or inadequate (39.7%) maternal treatment.[17, 26]

A more detailed analysis of missed opportunities to prevent congenital syphilis from 2018 revealed variations by race/ethnicity and region that point to structural differences in access to

care. For example, in the U.S. South, the most commonly missed opportunity was lack of adequate maternal treatment, both overall and among Black and Hispanic persons, whereas for White persons with infants with congenital syphilis, the most commonly missed opportunity was lack of timely prenatal care.[27] Even when providers follow guidelines and health insurance is available, social vulnerabilities such as homelessness and unstable housing or incarceration (sometimes for underlying substance abuse) may prevent pregnant adolescents and adults from accessing care.[28]

Some missed opportunities could potentially be addressed by repeat screening later in pregnancy, after initial screening during the first prenatal visit. Evidence of congenital syphilis after treatment could possibly arise from reinfections or treatment failure. Similarly, evidence of late seroconversion in pregnancy could possibly be identified by repeat screening. Small studies of reinfections during the same pregnancy point to the potential value of repeat screening. In one study of all cases of syphilis reported among pregnant women in Florida in 2018, 19 (7.3%) of 261 pregnant women were reinfected during the same pregnancy.[29] Timely repeat screening (to allow treatment commencement at or more than 30 days before delivery and completion of the regimen as needed for the stage of the disease) could have prevented 6 of 19 infants from contracting congenital syphilis.[29] In another small qualitative study, 6 of 23 pregnant women were infected (4 of 6) or reinfected by partners (2 of 6) after screening.[28] Importantly, repeat screening for behavioral risks alone may be of limited value: 51 percent of syphilis-infected pregnant adolescents and adults cited no risk factors at all.[18] More information on the rate of reinfections during pregnancy could offer relevant contextual information in an updated recommendation statement.

Prevention

Screening

Several observational studies of syphilis in pregnancy have demonstrated improved maternal and neonatal outcomes when infection is detected and treated early in pregnancy,[6, 30] which supports the rationale for screening early in pregnancy at the first prenatal visit.

Serologic screening for syphilis currently involves a two-step process using at least one treponemal and one nontreponemal test. Use of a single serologic test can result in false-negative results during primary infection and false-positive results for those with prior treatment or who never were infected.[3] **Treponemal tests** detect antibodies for *T. pallidum* proteins and include *T. pallidum*-particle agglutination (TP-PA), fluorescent treponemal antibody absorption test (FTA-ABS), enzyme immunoassays (EIA), chemiluminescence immunoassays (CIA), multiplex flow immunoassays (MFI), and microbead immunoassays (MBIA). Treponemal tests are qualitative and typically remain positive after treatment. **Nontreponemal tests** measure antibodies not specific to *T. pallidum* and include rapid plasma reagin (RPR), venereal disease research laboratory (VDRL), and toluidine red unheated serum tests. Nontreponemal tests can be either qualitative or quantitative (i.e., titers). Quantitative nontreponemal tests can be followed over time to assess response to treatment. False-positive nontreponemal test results are associated with multiple factors unrelated to syphilis infection, such as other infections, autoimmune disorders, vaccinations, IV drug use, pregnancy, and older age.[3]

The **traditional screening algorithm** begins with a nontreponemal test followed by reflex treponemal testing for persons with positive nontreponemal test results, due to the high false-positive rates associated with nontreponemal tests, especially in pregnancy. **Reverse-sequence screening** starts with a treponemal test followed by nontreponemal testing for positive treponemal test results. When reverse-sequence test results are discordant (e.g., treponemal test positive, nontreponemal test negative), final diagnostic results are typically resolved with the results of a third test (treponemal). Due to automation and reduced cost in high-volume settings, reverse screening algorithms are increasingly being used across the United States.[31]

Several treponemal point-of-care (POC) tests have been developed, and two have been approved by the U.S. Food and Drug Administration (FDA) at the initial drafting of this report: Syphilis Health Check (SHC) (Diagnostics Direct, LLC, Stone Harbor, NJ) and Dual Path Platform (DPP®) HIV-Syphilis System (Chembio Diagnostic Systems, Inc., Medford, NY). Since the USPSTF reviewed this topic, a third POC test has been FDA approved, the First to Know Syphilis Test (NOWDiagnostics, Springdale, AZ), which is an over-the-counter POC home test.[32] POC testing can be performed in the clinical setting using fingerstick blood samples that do not require laboratory processing, which has the potential to speed diagnosis and initiate early treatment with reduced loss to followup. Pooled sensitivity of prospective studies of the SHC in the general population is estimated at 87.7 percent with pooled specificity of 96.7 percent.[33] For the Chembio DPP® dual assay, sensitivity and specificity among retrospective and prospective studies of a variety of populations ranged from 47 to 99 percent and 99 to 100 percent, respectively.[34]

Treatment

CDC recommends parenteral penicillin G as the only treatment with documented efficacy during pregnancy. Treatment protocols are specific to the stage of syphilis infection with later stage infection requiring longer duration of treatment.[3] Furthermore, persons with penicillin allergy should be desensitized and then treated with penicillin. Although true penicillin allergy may be overreported (5% to 15%), skin testing and graded oral challenge suggest the incidence of true allergy may be as high as 6 percent.[3] Uncommonly, persons treated for syphilis may experience the JH reaction within the first 24 hours of treatment, which can cause fetal distress and induce early labor.[35]

Current Clinical Practice

Currently, CDC,[3, 36] the American College of Obstetricians and Gynecologists (ACOG),[19] the American Academy of Pediatrics (AAP),[19] and American Academy of Family Physicians[37] have strong recommendations to perform universal early prenatal screening for syphilis in pregnancy (Appendix A Table 1). Additionally, CDC and AAP recommend repeat screening in the early third trimester and at delivery in those at increased risk for syphilis infection or when a pregnancy ends in stillbirth (fetal death after 20 weeks' gestation) (Appendix A Table 1). Recently, ACOG updated its syphilis screening recommendations, which were previously aligned with CDC and AAP recommendations, to state repeat screening in the early third trimester and at delivery should be performed universally rather than only in high-risk populations.[38] As of November 2023, 42 U.S. states and the District of Columbia have laws

mandating prenatal syphilis screening. Twenty-one states (42%) require only one test, including for persons at increased risk. Fourteen states mandate additional screening during the third trimester in all pregnancies, and an additional six states require third trimester screening among patients at increased risk. Only six states mandate syphilis screening at delivery, but an additional eight states mandate screening at delivery among high-risk patients. Only four states (8%) require a test at the first prenatal visit and repeat tests in the early third trimester (28 to 32 weeks) and at delivery. Eight states have no laws mandating screening for syphilis in pregnancy.[39]

According to the current perinatal care guidelines by AAP and ACOG,[19] pregnant adolescents and adults with syphilis should be treated with benzathine penicillin G according to the stage of infection because this is the only reliable treatment in pregnancy. Additionally, those treated with penicillin should be monitored for signs of a JH reaction. For treated persons, followup nontreponemal serologic testing is needed to evaluate the effectiveness of the treatment. Pregnant adolescents and adults treated for syphilis should have quantitative nontreponemal serologic tests repeated in the early third trimester (28 to 32 weeks) and at delivery, related to the stage of the disease. The AAP and ACOG also suggest pregnant adolescents and adults at high risk of reinfection or living in areas with a high prevalence of syphilis may receive monthly repeat serological testing for titers. For all pregnancies, any known information on the maternal syphilis status should be recorded in the newborn records and communicated to the newborn medical provider, and the mother's serologic status for syphilis should be determined before the newborn is discharged from the hospital.[19]

Also according to AAP and ACOG guidelines,[19] all infants born to seropositive mothers require a nontreponemal test and thorough physical and diagnostic examination. The diagnostic criteria for evaluating an infant with clinically suspected congenital syphilis include if the mother with a positive treponemal result has one of the following treatment statuses: none, or undocumented; treatment initiated less than 30 days before delivery; or nonpenicillin drug or evidence of reinfection or relapse (increased maternal titers of at least fourfold). Management decisions of an infant depend on 1) maternal treatment before pregnancy, 2) adequate maternal treatment and response during pregnancy, or 3) inadequate maternal treatment or response or reinfection during pregnancy. The preferred treatment for suspected or confirmed congenital syphilis is intravenous (IV) aqueous crystalline penicillin G. All infants with reactive serologic tests for syphilis should have followup examinations and serologic nontreponemal tests every 2 to 3 months until the test becomes nonreactive.[19]

Previous USPSTF Recommendation

In 2018, the USPSTF found that accurate screening algorithms are available to identify syphilis infection, and effective treatment with antibiotics can prevent congenital syphilis and significantly decrease adverse pregnancy outcomes. Additionally, harms associated with screening or treatment were small, leading to an overall substantial net health benefit. Therefore, the USPSTF reaffirmed its previous conclusion that there is convincing evidence that screening for syphilis infection in pregnant women provides substantial benefit and recommended early screening for syphilis infection in all pregnant women (A recommendation).[1]

Chapter 2. Methods

Key Questions and Analytic Framework

The scope and key questions (KQs) were developed by the Evidence-based Practice Center investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers. The analytic framework and KQs that guided the review are shown in **Figure 2**. Three KQs were developed for this review:

1. Does screening for syphilis in pregnant adolescents and adults reduce the incidence of congenital syphilis in newborns?

2. What are the harms of screening for syphilis in pregnant adolescents and adults?

3. What are the harms of treatment of syphilis with penicillin during pregnancy to pregnant adolescents and adults or newborns?

In addition to addressing the KQs, this review also looked for evidence related to one contextual question (CQ) listed below. This CQ was not a part of the systematic literature review, but relevant studies were identified during the literature review process. CQs are intended to provide additional background information. Literature addressing the CQ is summarized in **Appendix A**.

1. To better understand the need for retesting during pregnancy, the USPSTF will review how frequently do pregnant adolescents and adults who initially test negative for syphilis by serologic screening either later test positive for syphilis, give birth to a neonate with congenital syphilis, or have a miscarriage or stillbirth attributed to syphilis? Do these associations vary by populations of interest (demographic characteristics or risk factors)?

Data Sources and Searches

The search strategy was designed and conducted by an experienced systematic review/medical reference librarian with input from the investigators. Another librarian peer reviewed the search strategies using the PRESS Checklist.[40] The Cochrane Library and Ovid MEDLINE® were searched for English-language articles published from January 1, 2017, through July 25, 2023. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, interventions, outcomes, and study designs. **Appendix B** describes the complete search strategies. We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov, Epistemonikos, Google, Google Scholar, Trip Medical, and the World Health Organization's International Clinical Trials Registry Platform. To supplement electronic searches, the reference lists of pertinent review articles and studies that met the inclusion criteria were also reviewed. Studies suggested by peer reviewers or public comment respondents were also reviewed and, if appropriate, incorporated into the final review. Since July 25, 2023, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on March 21, 2025, and no eligible studies

were identified. All literature search results were managed using EndNote™ version 21.2 (Clarivate, Philadelphia, PA).

Study Selection

We developed inclusion and exclusion criteria and selected studies based on the populations, interventions, comparators, outcomes, timing, settings, and study designs briefly described further in this section with input from the USPSTF (**Appendix B**). Titles and abstracts were independently reviewed by two investigators. Those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. The full texts were then independently reviewed by two investigators to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

For studies relevant for KQs specific to the benefits and harms of screening (KQs 1 and 2), we included studies enrolling asymptomatic pregnant adolescents or adults, at any time during pregnancy, who were not known to have syphilis infection. We excluded studies limited to persons known to have syphilis infection, known to have symptoms of syphilis, or who are not pregnant and studies conducted exclusively in populations in which syphilis screening may be part of disease management, such as persons living with HIV. Eligible interventions included two-step screening for syphilis with a nontreponemal and treponemal test (e.g., traditional or reverse-sequence algorithms). For KQ 1, the intervention comparison had to be no screening; alternate screening strategies or studies with no comparators were ineligible. Eligible outcomes included vertical transmission of syphilis (incidence of congenital syphilis) and prevalence of congenital syphilis after implementation of a screening program, stillbirth, and maternal or infant morbidity and mortality.

For KQ 2, we included studies of two-step screening algorithms where initial results were compared with confirmatory results to calculate false-positive and false-negative rates; no other comparator was necessary. Studies comparing different two-step algorithms, or comparing single tests with a two-step algorithm, were both eligible. Only tests that were FDA approved were eligible. Eligible screening harms outcomes included false-positive and false-negative results, stigma, psychosocial harms, and unnecessary evaluation or treatment.

For KQ 3, harms of treatment, we included studies of penicillin treatment in pregnant adolescents and adults with syphilis infection. We excluded studies of penicillin treatment in nonpregnant participants and studies of penicillin treatment for any condition other than syphilis. The eligible intervention was treatment of syphilis with penicillin started during pregnancy. A comparator was not required. Although not part of our inclusion criteria, our search strategy did allow for treatments other than penicillin. Eligible treatment harms outcomes included allergic reaction, premature labor, JH reaction, fetal harms, and other maternal harms.

We included randomized, controlled trials (RCTs); before-after and ecologic studies reporting effect of implementing a widespread screening program with historical or geographic comparator (KQ 1); and systematic reviews and meta-analyses (of eligible study designs). For KQs 2 and 3, we also included cohort studies, case-control studies, diagnostic accuracy studies, and large case series. We only included studies published in English and conducted in countries categorized as

"high" or "very high" on the Human Development Index.[41] For purposes of this limited review update, and to be consistent with prior reviews, eligible study settings were limited to primary care–relevant and primary care–referable settings (e.g., obstetrics/gynecology clinics, prenatal clinics, ambulatory care, family planning clinics, health clinics in correctional facilities, STI clinics).

Quality Assessment and Data Extraction

For newly identified studies, two experienced reviewers independently assessed each study's methodological quality using predefined criteria developed by the USPSTF (**Appendix B**) and informed by tools designed for various study designs (Quality Assessment of Diagnostic Accuracy Studies-2 for screening studies[42] and Risk Of Bias In Non-randomised Studies of Interventions for treatment studies).[43] Disagreements were resolved by discussion and consensus. Only studies rated as having good or fair quality were included in the review. Specific considerations for studies reporting false positives included the retention of study participants. Estimates of false positives from studies that excluded some participants with initial positive tests may be biased. Similarly, studies of false negatives from studies that excluded some participants with initial negative results may be biased. For studies of harms of treatment, key considerations included the potential for bias from selection and attrition.

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. All data extractions were checked by a second investigator for completeness and accuracy.

Data Synthesis and Analysis

This report is a limited systematic review to provide an update of the evidence published since the USPSTF last considered this topic in 2018. Results of studies included in previous evidence reviews are not included in this review. We qualitatively synthesized findings for each KQ by summarizing the characteristics and results of included studies in a narrative format, with accompanying summary tables.

Expert Review and Public Comment

The draft research plan for this topic was posted on the USPSTF website for public comment from December 1, 2022, to January 4, 2023. In response to public comments, the USPSTF updated the wording of the CQ to signify the retesting context more clearly. Additionally, the USPSTF updated the description of eligible settings to "Primary care–relevant and primary care–referable settings…" to indicate the broad inclusion of potentially eligible study recruitment sites. Lastly, the USPSTF updated the analytic framework to specify its interest more clearly in morbidity and mortality outcomes. The final version of the research plan was posted on the USPSTF website on March 2, 2023. The draft evidence review was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers, and minor revisions were made based on comments received, mostly related to clarifying information in the Introduction and Results sections. The draft evidence review was posted for public comment

from November 19, 2024, through December 23, 2024. All comments were reviewed and considered. Most comments related to issues outside the scope of the review, including an evaluation of the comparative benefits of repeat screening compared to one-time screening, inclusion of screening recommendations for other sexually transmitted infections, and inclusion of studies beyond the current inclusion criteria. We updated statistics in the Introduction with newly published data by CDC on syphilis incidence and prevalence.

USPSTF and AHRQ Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and KQs, as well as to resolve issues around scope for the final evidence synthesis.

AHRQ staff provided project oversight, conducted reviews of the draft report, and helped facilitate an external review of the evidence synthesis.

Chapter 3. Results

Literature Search

We screened 1,620 unique records and assessed 111 full-text articles for eligibility (**Figure 3**). We excluded 104 articles for various reasons, as detailed in **Appendix C**, and included seven studies. Details of quality assessments of the included studies are in **Appendix D**.

Results by Key Question

KQ 1. Does Screening for Syphilis in Pregnant Adolescents and Adults Reduce the Incidence of Congenital Syphilis in Newborns?

We found no new studies examining screening for syphilis in pregnancy to reduce the incidence of congenital syphilis.

KQ 2. What Are the Harms of Screening for Syphilis in Pregnant Adolescents and Adults?

Summary

We found five studies (51,118 participants) that reported on harms of screening in pregnancy.[44-48] All five studies reported on false-positive results of the first step in a two-step screening algorithm, and one study also reported on false-negative results. We found no studies addressing other harms of screening for syphilis during pregnancy. One large, fair-quality prospective study evaluated the proportion of false-positive results using RPR as part of the traditional screening algorithm.[44] Three large, fair-quality studies (two prospective[44, 47] and one retrospective[46]) and one good-quality retrospective study[45] evaluated the use of an immunoassay (i.e., ARCHITECT CIA, LIAISON CIA, or BioPlex MFI) as part of a reverse screening algorithm. One moderate-sized, fair-quality prospective study evaluated the use of an immunoassay (Elecsys Immunoassay [IMA]) compared with a nonstandard composite screening algorithm.[48] All of these tests are FDA approved for use in the United States. While all five studies were conducted in the United States, one study also enrolled participants from Argentina.[48] Details describing the study populations (e.g., baseline syphilis risk, gestational age at time of screening, prior syphilis and treatment history) were often unclear or not reported. While all studies appeared to include participants from a variety of racial and ethnic backgrounds (e.g., Asian, Black, White, Hispanic), three studies[45-47] did not report demographic information for their full study cohort, and no study reported Hispanic ethnicity by race (e.g., non-Hispanic Black) (**Table 1**).

Positive index test results (first step in a 2-step algorithm) for syphilis ranged between 1.0 and 4.8 percent across all five studies. False-positive results of the first step of the 2-step screening algorithm ranged between 0 and 65 percent, depending on the 2-step screening algorithm and index test evaluated (**Table 1**). One study reported on false-negative results (0%, Elecsys IMA).[48]

Detailed Evidence

We divide evidence in the paragraphs below by screening algorithm used to determine the false-positive rate of the index test: Traditional, Reverse Sequence, and Composite. Traditional screening algorithms include a nontreponemal test (e.g., RPR) followed by a reflex treponemal test (e.g., immunoassay) only if the nontreponemal test is positive. Reverse-sequence algorithms begin with a treponemal test that is followed by a reflex nontreponemal test only if the treponemal test is positive. For discordant results (i.e., treponemal test positive, nontreponemal test negative), final screening results are determined by the result of a third—treponemal—test. One study used a composite screening algorithm, which is not a typical approach to clinical syphilis screening. The composite algorithm included both a treponemal and nontreponemal test; if either test was positive the screening result was determined by the result of a third—treponemal—test. This approach differs from the standard reverse screening algorithm in that all patients would receive a nontreponemal test regardless of the initial treponemal test results and would receive a third test if the nontreponemal test was positive. Studies of both the traditional and reverse screening algorithms estimated false-positive rates by comparing the initial test results of their two-step protocol (i.e., index test) with the final two-step protocol results, which included the initial test as part of the two-step protocol. One study generated false-positive and false-negative estimates comparing an index test to a separate composite screening algorithm.

Traditional Screening Algorithm

One fair-quality, prospective study evaluated the diagnostic accuracy of the BD Macro-Vue RPR (Becton, Dickinson and Company, Sparkes, MD) using the traditional screening algorithm (i.e., nontreponemal test followed by reflex treponemal if initial test was positive).[44] Pregnant patients from a large healthcare system (N=1,602) were screened at the time of routine prenatal screening. Participants who initially tested positive by RPR (n=35, 2.2%) were confirmed with a qualitative TP-PA (Serodia-TP-PA, Fujirebio Inc., Tokyo, Japan). Reflex TP-PA among those with positive RPR were nonreactive in 11 cases for a false-positive rate of 31 percent (11/35).

Reverse-Sequence Algorithm

Four studies evaluated the accuracy of treponemal tests as part of a reverse screening algorithm. The single study that evaluated the traditional screening algorithm (see above) also retrospectively evaluated the ARCHITECT CIA (ARCHITECT syphilis TP assay, Abbott Diagnostics, Abbott Park, IL) by testing all 1,602 frozen samples with CIA.[44] Samples with initially nonreactive RPR but reactive CIA (i.e., RPR-/CIA+) had confirmatory testing using the TP-PA. Fourteen (1.0%) samples were considered positive following this reverse sequence screening algorithm, and one sample had a negative TP-PA (false-positive rate, 7% [1/14]).

A second prospective study evaluated the ARCHITECT CIA.[47] Pregnant patients (N=9,220) were screened for syphilis in one of ten community-based prenatal clinics within the Dallas County, Texas area. Participants with positive CIA results were referred to a single university medical center in Dallas, Texas for further evaluation and care. Reactive CIA testing was followed by RPR testing, and discordant test results (i.e., CIA+/RPR-) were resolved by confirmatory TP-PA testing. There were 144 (1.6%) positive CIA tests, of which 17 (11.8%) were classified as false positive after TP-PA confirmatory testing.

One good-quality retrospective study evaluated the LIAISON CIA (DiaSorin, Inc., Stillwater, MN).[45] Pregnant patients who delivered either live or stillborn infants at a single university hospital in Baltimore, Maryland (N=4,872) and had positive CIA results received reflex testing with a quantitative RPR (Becton Dickinson, Franklin Lakes, NJ). Discordant results (i.e., CIA+/RPR-) were confirmed with FTA-ABS (ZEUS Scientific, Inc., Branchburg, NJ). There were 60 (1.2%) positive CIA tests, of which 16 (7%) were classified as false positive after FTA-ABS confirmatory testing.

One fair-quality retrospective study evaluated the BioPlex MFI (BioPlex Syphilis Immunoglobulin G [IgG] assay, Bio-Rad Lab, Hercules, California).[46] Pregnant patients with unknown syphilis risk who delivered at a single university hospital in central Ohio (N=35,108) underwent screening with a reverse screening algorithm consisting of an initial MFI IgG test. All positive MFI test results were reflex tested using a quantitative RPR. Discordant test results (i.e., MFI+/RPR-) were resolved with a TP-PA test. There were 384 (1.1%) positive MFI tests at any time during pregnancy or delivery, and 192 (0.5%) screenings had discordant results. Of discordant screening results taken at time of delivery, 83 of 127 (65.4%) had a negative TP-PA and were classified as false-positive screening.

Composite Testing Algorithm

One fair-quality prospective study evaluated the use of the Elecsys IMA (Roche Diagnostics) with a composite testing algorithm that included testing all samples with both the IMMULITE 2000 (IMA) syphilis assay (Siemens Healthcare) and the RPR (Becton, Dickinson and Company) at the same time, regardless of treponemal test results.[48] Discordant results (i.e., IMMULITE IMA+/RPR- or IMMULITE IMA-/RPR+) were resolved by TP-PA (Fujirebio). Positive index tests results (i.e., Elecsys IMA) led to repeat duplicate testing with the same index test and were only finally recorded as positive if at least one of the duplicate tests was positive. Several groups of participants were tested using this algorithm, including 316 pregnant patients of unknown syphilis risk that are reported here. Positive index test results occurred in 15 (4.8%) screenings. There were no reported false-positive (0/15) or false-negative (0/301) results comparing the Elecsys IMA to the composite testing algorithm.

KQ 3. What Are the Harms of Treatment of Syphilis With Penicillin During Pregnancy to Pregnant Adolescents and Adults or Newborns?

Summary

One good-quality study and one fair-quality study reported on the harms of treatment. One reported on the JH reaction[49] and the second on penicillin desensitization.[50] In one study reporting JH reactions, 2 of 39 pregnant patients (5.1%) reported JH reactions.[49] Of these patients, one was treated uneventfully, and another went on to have a stillbirth, but the cause could not be established. In one study on penicillin desensitization, 2 of 91 (2.2%) pregnant patients with a diagnosis of untreated syphilis and a clinical history of an immediate hypersensitivity reaction (IHR) to penicillin were unable to complete treatment and had to be switched to doxycycline.[50] Across all participants, 4 of 91 (4.4%) had an adverse reaction to penicillin (either IHR or delayed reaction). The rates of reactions varied by risk and treatment protocol, with higher rates among high-risk persons receiving oral desensitization (27.3%) than

among high-risk persons receiving IV desensitization (2.5%) or low-risk persons undergoing penicillin provocation (2.5%).

Detailed Evidence

Jarisch-Herxheimer (JH) reaction

JH reactions in the second half of pregnancy can result in fetal heart rate abnormalities, preterm labor, and fetal death. A fair-quality retrospective cohort study reported on JH reactions among patients at greater than 20 weeks gestation hospitalized in Alberta, Canada (2015 to 2020) for treatment of syphilis (26% primary, 10% secondary, and 64% early latent stage).[49] Thirty-seven participants received the standard treatment of two intramuscular benzathine penicillin injections weekly, and two participants with fetal ultrasounds suggestive of congenital syphilis were treated with 10 to 14 days of IV penicillin. The authors noted that no validated scoring system exists for JH reactions; they defined a reaction as having at least one of the following symptoms within 24 hours of penicillin reaction: fever (≥38.0°C); hypotension (systolic blood pressure ≤100 mm Hg); tachycardia (≥110 beats/min); new rash; or patient-reported headache, myalgia, or contractions. The study reported two JH reactions among 39 participants treated for syphilis with penicillin. Of these, one participant (30 weeks gestation) developed fever and headache within 8 hours of treatment, was treated with acetaminophen, and delivered a full-term neonate with no evidence of congenital syphilis. A second participant (28 weeks gestation, noted as having preeclampsia) developed fever, tachycardia, and uterine contractions within 4 hours of treatment, declined supportive measures, and had an unattended out-of-hospital stillbirth at 37 weeks. The authors were not able to determine if the death was related to congenital syphilis.

Penicillin Desensitization

One good-quality prospective Brazilian cohort study, conducted between 2016 and 2019, reported on penicillin desensitization among a group of pregnant patients referred to the Clinical Immunology and Allergy Division of the University of São Paulo School of Medicine with a documented diagnosis of untreated syphilis (all with latent stage disease) and clinical history of IHR to penicillin.[50] The study was designed to test the efficacy and safety of an algorithm to guide re-exposure to penicillin among such patients. The algorithm distinguished between high-risk patients and low-risk patients. High-risk patients were characterized as having at least one of the following: high-risk clinical history [drug-induced IHR in the last 10 years; initial reaction compatible with IHR such as pruritus, urticaria, angioedema, acute hoarseness, rash, flushing, bronchospasm, hypotension, dizziness, blurred vision, and anaphylaxis; no history of tolerated re-exposure to penicillin after the initial reaction], elevated serum tryptase level at the initial reaction, positive skin testing, or positive specific serum immunoglobulin E (IgE). These high-risk patients underwent rapid drug desensitization. Although the study had initially intended for high-risk patients to be randomized to oral vs. IV desensitization, severe breakthrough reactions among patients in the oral group in the early part of the study resulted in a switch to IV desensitization for all later participants.

Low-risk patients had low-risk clinical history, negative skin testing and negative serum IgE, and did not have elevated serum tryptase during the initial reaction. Low-risk patients underwent penicillin provocation. The provocation involved the administration of 1 percent, 9 percent, and

90 percent of the total dose in three steps. If the drug provocation test was negative, the patient was treated with a regular infusion of penicillin.

Of 91 patients, four had an adverse reaction to penicillin (either IHR or delayed reaction) (4.4%). The rates of reaction varied by risk and treatment protocol, with higher rates of reaction among high-risk persons receiving oral desensitization (27.3%) than among high-risk persons receiving IV desensitization (2.5%) or low-risk persons undergoing penicillin provocation (2.5%). The study reported that two (one high-risk and one low-risk) of 91 patients (2.2%) were unable to complete treatment and had to be switched to doxycycline.

Of 51 high-risk patients undergoing desensitization, 11 received oral desensitization, of whom three had IHR (27.3%). Two of these three participants with IHR completed the protocol, but one patient had a severe reaction requiring a switch to doxycycline. The remainder of the 40 high-risk patients received IV desensitization; one had an IHR (2.5%) but completed the protocol.

Of the 40 low-risk patients undergoing penicillin provocation, one person had a delayed reaction (2.5%) 24 hours after the challenge and was switched to doxycycline. The study noted that the person had an uneventful delivery, and the neonate did not have congenital syphilis; delivery and neonatal syphilis outcomes were not reported for other participants.

Chapter 4. Discussion

Summary of Evidence

This limited systematic evidence review update found no new evidence on benefits of screening (KQ 1); limited and heterogeneous findings on the harms of screening (KQ 2), specifically for false positives; and very limited evidence on the harms of treatment (KQ 3). A summary comparing the conclusions of this review with the conclusions of the previous review is provided in **Table 3**. Observational studies from prior reviews demonstrate an association between lower adverse outcomes in pregnant adolescents and adults treated for syphilis compared with those not treated, and universal screening in early pregnancy can prevent congenital syphilis (KQ 1). The findings on harms of screening (KQ 2) are consistent with prior evidence supporting two-step screening algorithms to detect syphilis during pregnancy. We found that false-positive results of several commonly used tests are widely varied with results ranging from 0 to 65 percent. Likewise, from the prior review, false-positive results ranged from 0 to 88 percent. The most commonly evaluated test across both reviews was the ARCHITECT CIA (three studies in the 2018 review,[51-53] two studies in the current review[44, 47]) with false-positive estimates ranging from 7 to 88 percent. Lower false-positive estimates came from the two prospective, U.S.-based studies from the current review, with false-positive estimates of 7 percent and 19 percent.[44, 47] However, even these rates of false-positive testing are unlikely to be acceptable for any single-test screening program. The only study to report a lower false-positive test rate (0%, Elecsys IMA), which also reported a 0 percent false-negative rate, used a composite algorithm for its reference standard, which included TP-PA testing of samples that would not ordinarily be tested in a reverse-sequence screening algorithm (i.e., IMA-/RPR+). The consequences of this testing strategy might reduce false-negative screening results but at the risk of increasing false-positive results. Furthermore, the duplicate testing strategy employed for the index test could increase the number of reported negative tests. Neither of these testing strategies are commonly used for serologic syphilis screening. Evidence from this limited review confirms the concern for false-positive testing with single treponemal or nontreponemal tests, supporting the continued practice of two-step screening algorithms to diagnose syphilis in pregnancy. We did not find studies that evaluated other harms of screening.

Because the diagnosis of syphilis is challenging, requiring at least two serologic tests along with a clinical history and physical exam, several rapid POC tests have been developed, including SHC (Trinity Biotech USA, Inc., Jamestown, NY), which is FDA approved. We found one study that evaluated the accuracy of the SHC in pregnancy,[54] which was excluded due to high risk of bias. Accuracy of the SHC was reported as 95.1 percent sensitive and 92.2 percent specific in 170 stored samples that used a variety of different reference standards and excluded participants (32%) with discordant reference testing results.

Two single-arm cohort studies reported on possible harms of treatment with penicillin.[49, 50] Although the design of these studies precludes causal inference, both studies may aid with bounding potential harms. One study of JH reactions reported a rate of 5.1 percent among pregnant patients in Alberta, Canada with a diagnosis of syphilis who were treated with penicillin.[49] Notably, admission to hospital for treatment of syphilis at or after 20 weeks of

gestation is customary in Alberta. The higher level of monitoring in such settings may result in higher rates of JH reactions being recognized than when patients self-monitor themselves, as is recommended by CDC.[3] Given the small sample size and number of events, as well as issues around surveillance, the evidence is insufficient to judge the risk of harm to the fetus. Another study reported rates of IHR among pregnant patients with a diagnosis of syphilis and a clinical history of IHR to penicillin of 2.5 percent for persons with low-risk history undergoing penicillin provocation testing and 2.5 percent for persons with high-risk history undergoing desensitization using IV penicillin. Persons with high-risk history undergoing oral penicillin desensitization had a higher rate of IHR (27.3%), leading investigators to stop that treatment protocol and complete the study using only an IV-based protocol for high-risk patients.[50]

Alternative Treatments in Pregnancy

We found very few studies that discussed the use of alternative syphilis treatments in pregnancy beyond penicillin. A few studies[50, 55] noted participants with contraindications to penicillin treatment received doxycycline or other treatments, but none provided information on pregnancy or fetal outcomes of those treatments. We found one ongoing trial of amoxicillin and probenecid (detailed below in Ongoing Studies section)[56] and one retrospective cohort study of oral amoxicillin or ampicillin.[55] This study was conducted in Japan from 2010 to 2018[55] and investigated the effectiveness of oral amoxicillin or ampicillin to treat active syphilis in pregnancy. Patients with tertiary or neurosyphilis were excluded. Results from 71 cases were included in the analysis after excluding 51 cases for unknown reasons and an additional nine cases with either unknown outcomes or second trimester abortions. Fifty-nine (83%) participants received amoxicillin and 12 (17%) received ampicillin, 1,500 mg daily, for either a median of 30 days (interquartile range [IQR] 28–64 days; early syphilis, n=26) or 78 days (IQR 51–104 days; late syphilis, n=35), including three participants who also received concurrent probenecid. Of 71 cases, 15 (21%) ended in newborns with congenital syphilis (13 live born, one stillbirth, one miscarriage), including one participant who was co-administered probenecid. Congenital syphilis occurred in 19 percent of pregnancies treated with amoxicillin and 31 percent treated with ampicillin. No cases of congenital syphilis were identified among participants diagnosed with early syphilis. Treatment discontinuation due to adverse events (i.e., skin rash, itching, dizziness) occurred in only three of 80 (3.8%) participants. However, information on overall treatment adherence was not reported.

Repeat Screening in Third Trimester and at Delivery

In 2018, the USPSTF recommended early screening for syphilis in pregnancy (at first presentation for care),[1] and the supporting evidence review found no new evidence examining the effectiveness of repeat screening for syphilis during pregnancy.[57] Other organizations, such as CDC and AAP recommend repeat screening at 28 weeks and again at delivery in populations at high risk for syphilis,[3, 19, 36] which includes those living in high-prevalence areas, history of HIV, history of incarceration, sex in combination with drug use, commercial sex work, history of multiple sexual partners, and homelessness, whereas ACOG recommends universal repeat screening at 28 weeks and at delivery.[38]

Prior evidence reviews supporting the USPSTF recommendations have found limited evidence regarding repeat screening for syphilis in pregnancy. The 2004 evidence review found a single study evaluating mandatory syphilis screening at delivery in upstate New York.[58] Congenital syphilis detection in the 1 year prior and 4 years after implementation demonstrated an increase in infants with positive serology and a decrease in infants with clinical signs of syphilis, suggesting repeat screening identified more cases of congenital syphilis, whereas effective treatment prevented clinical manifestation of the disease.

Although no new studies of repeat screening were identified for the 2018 USPSTF review, two studies were presented in that review that modeled the cost-effectiveness of repeat screening in the third trimester or at delivery. One analysis conducted in the Cleveland, Ohio area concluded the cost of third trimester repeat screening among all pregnancies would be equivalent to the cost of preventing cases of congenital syphilis only if the syphilis prevalence during pregnancy was about 3.5 percent of deliveries, which was about 18-fold greater than the prevalence at the time of that analysis in 2014.[59] That study was based on 113 new cases of syphilis collected over a 17-year period. The second study compared universal syphilis repeat screening in the third trimester with no repeat screening, assuming all pregnant women were initially screened during early pregnancy. Model parameters were based on data from the United States whenever possible, and cost estimates were adjusted to 2014 prices. Results of their model estimated it would take repeat screening of 66,000 pregnant patients to prevent one case of congenital syphilis, 570,000 repeat screenings to prevent one fetal loss, and 950,000 repeat screenings to prevent one neonatal death.[60] Its important to note that rates of reported cases of primary and secondary syphilis in the United States have continued to rise over the past two decades from 2.1 cases per 100,000 (primary and secondary syphilis) in 2000 to 15.8 cases per 100,000 in 2021.[13]

To address the CQ in the current review, we identified three retrospective cohort studies and one national registry that provided information on the number of pregnant adolescents and adults who initially screened negative for syphilis but later screened positive—suggesting late infection—or who screened positive and were adequately treated but continued to have rising nontreponemal titers—suggesting reinfection. Based on the CDC NNDSS database, about 5 percent (197 of 3,761 cases) of congenital syphilis cases in 2022 occurred in pregnancies where initial syphilis screening was negative.[17] Estimates from the cohort studies were derived from state or city health department surveillance data (i.e., Louisiana, Florida, New York City, Arizona). Two of three cohort studies concluded about half of congenital syphilis cases might be prevented with third trimester repeat screening and adequate treatment,[61, 62] whereas the third study estimated about 25 percent of cases might be preventable.[63]

We also identified two recent decision analysis studies that examined cost-effectiveness of universal repeat syphilis screening in late pregnancy. One study was conducted in the United Kingdom,[64] and the second study was conducted using cost and probability estimates from the United States.[65] The U.K. study estimated the incremental cost of universal repeat screening in late pregnancy with universal first-trimester screening.[64] Clinical and cost parameters were derived from U.K. sources whenever possible, and cost estimates were inflated to 2017/2018 prices. The model estimated that universal repeat screening in the United Kingdom would result in 5.5 fewer cases of congenital syphilis among the population of pregnant adolescents and adults (n=725,891), with an incremental increase in costs of £9.9 million, or £1.8 million to

prevent one case of congenital syphilis. Additionally, most of the increased costs were attributable to the additional screening costs.

Hersh, et al created a cost-effectiveness model using clinical parameters based on data from the CDC, U.S. Census Bureau, and U.S. Department of Health and Human Services Vital statistics reports.[65] Cost estimates were inflated to 2017 dollars, and all costs were considered regardless of the payor. Screening accuracy was based on a traditional screening algorithm using an RPR with reflex confirmatory testing of positive RPR using an FTA-ABS. Results indicated that repeat screening would save $52 million and would prevent an additional 140 neonates from being born with congenital syphilis in a theoretical cohort of 3.9 million pregnant adolescents and adults, which is the estimated annual number of U.S. births. Sensitivity analyses demonstrated the model was sensitive to changes in syphilis population prevalence and treatment rates: repeat screening would be cost-effective at a prevalence of 0.34 cases per 100,000 and when at least 12 percent of pregnant adolescents and adults with syphilis were treated and would become the dominant strategy at a prevalence of 1.84 per 100,000 when more than 46 percent were treated. Additional outcomes included fewer stillbirths (n=73), preterm delivery (n=3), neonatal deaths (n=27), as well as cost savings of $14,098 per quality-adjusted life year. In comparing these results to prior cost-effective analyses, the authors noted their cost estimates included long-term neonatal morbidity and mortality, which were not included in prior studies.

Limitations

Our review was intended to support the USPSTF reaffirmation process and therefore only includes evidence published since the prior recommendation in 2018. Our review was limited to identifying evidence that might result in a change to the 2018 USPSTF recommendation on this topic and therefore may not address important questions that a full review would systematically answer, such as the comparative benefit or harms of different screening algorithms, the benefit of repeat syphilis screening beyond the initial prenatal exam, or disparities in the diagnosis and treatment of syphilis. Studies of screening or treatment were limited to only those conducted in countries listed as “high” or “very high” on the Human Development Index. This decision was based upon the populations and systems of care found in these countries compared with the United States. We required studies of screening harms (KQ 2) to evaluate only FDA-approved, currently available screening tests, which excluded some newly developed rapid POC tests. No studies reported baseline syphilis risk of their enrollment population beyond stating they drew from a “high-prevalence” region, and most studies did not provide sufficient information to calculate a syphilis risk for the included study population, so it was not possible to evaluate the effect of syphilis prevalence on harms such as false-positive and false-negative rates. Additionally, because we focused on harms of screening, defined as false-positive and false-negative test results for studies of diagnostic testing (KQ 2), we did not abstract full test accuracy data for pooling with prior review results. Although we did not formally include pharmacologic treatment interventions beyond penicillin, which is currently the only CDC-approved treatment for syphilis in pregnancy, we did allow for discovery of studies of other antibiotics in our search strategy and reported those studies that otherwise met all of our inclusion criteria.

Ongoing Studies

Although there are a variety of ongoing studies of rapid diagnostic tests, including POC tests, we found few ongoing studies of FDA-approved diagnostic tests. We identified a cohort study of the SHC POC test, which is FDA approved. Diagnostic accuracy of the SHC will be established in late pregnancy (24 to 28 weeks) against standard laboratory-based tests in prenatal clinics in California. Although study completion was initially estimated for October 2023, in post-review surveillance, it was discovered that the trial was withdrawn due to insecure funding.[66] We also identified a protocol for a Cochrane review to evaluate the accuracy of POC rapid testing for diagnosis of syphilis infection in pregnant women.[67] The review will include assessments of both treponemal and nontreponemal tests, as well as comparisons between low/middle-income countries and high-income countries.

We identified one ongoing phase I, pharmacokinetic trial of combination amoxicillin and probenecid in healthy pregnant participants. The goal of the trial is to identify an effective dosing strategy to test in future treatment trials of syphilis in pregnancy. The estimated trial completion date is March 2025.[56]

Future Research Needs

It remains unclear if some syphilis screening test strategies are superior to others. While this review and prior reviews have identified studies of single tests of screening accuracy, there is little information comparing the accuracy of traditional and reverse-sequence screening algorithms using different combinations of single tests. Furthermore, there is scant information on the accuracy of single-step screening protocols (e.g., rapid POC tests) in pregnancy compared with gold standard, two-step screening algorithms that have well-defined accuracy.

We found few studies of repeat screening to evaluate the net benefit and cost-effectiveness of repeat screening strategies, including various screening intervals and populations that would benefit most from repeat screening. Although several older cost-effectiveness studies have been previously identified, we found only one new decision analysis study that used U.S.-based parameters. Given the rising syphilis incidence in the United States, as well as the availability of newer screening tests, updated information on probabilities, costs, and utilities of congenital syphilis are needed.

We found no new or ongoing studies of syphilis treatment in pregnancy that were not based on penicillin or its derivatives (e.g., amoxicillin, ampicillin).

Conclusion

Although screening and early treatment for syphilis in pregnancy has been shown to decrease poor maternal and neonatal outcomes, preferred screening algorithms have not been identified. Our limited review found evidence consistent with prior reviews on screening for syphilis in pregnancy that supports the need for two-step serologic screening to reduce false screening

results. Although based on small studies, we found estimates of penicillin treatment harms that could be used for bounding of potential harms.

References

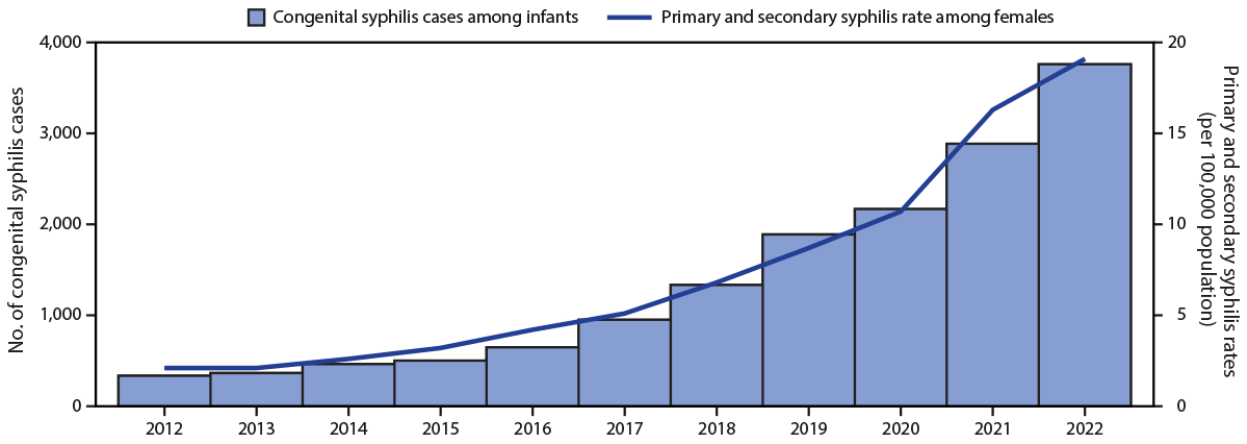
1. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for syphilis infection in pregnant women: US Preventive Services Task Force reaffirmation recommendation statement. *JAMA*. 2018 Sep 4;320(9):911-7. doi: 10.1001/jama.2018.11785. PMID: 30193283.
2. U.S. Preventive Services Task Force. Procedure manual section 4. Evidence review development. Rockville, MD: U.S. Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-section-4-evidence-review-development.
3. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021 Jul 23;70(4):1-187. doi: 10.15585/mmwr.rr7004a1. PMID: 34292926.
4. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. *N Engl J Med*. 2020 Feb 27;382(9):845-54. doi: 10.1056/NEJMra1901593. PMID: 32101666.
5. Gomez GB, Kamb ML, Newman LM, et al. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bull World Health Organ*. 2013 Mar 1;91(3):217-26. doi: 10.2471/BLT.12.107623. PMID: 23476094.
6. Qin J, Yang T, Xiao S, et al. Reported estimates of adverse pregnancy outcomes among women with and without syphilis: a systematic review and meta-analysis. *PLoS One*. 2014;9(7):e102203. doi: 10.1371/journal.pone.0102203. PMID: 25025232.
7. Centers for Disease Control and Prevention. About congenital syphilis. 2025. https://www.cdc.gov/syphilis/about/about-congenital-syphilis.html.
8. Keuning MW, Kamp GA, Schonenberg-Meinema D, et al. Congenital syphilis, the great imitator-case report and review. *Lancet Infect Dis*. 2020 Jul;20(7):e173-e9. doi: 10.1016/S1473-3099(20)30268-1. PMID: 32502432.
9. Cooper JM, Sanchez PJ. Congenital syphilis. *Semin Perinatol*. 2018 Apr;42(3):176-84. doi: 10.1053/j.semperi.2018.02.005. PMID: 29627075.
10. Marks M, Mabey DC. The introduction of syphilis point of care tests in resource limited settings. *Expert Rev Mol Diagn*. 2017 Apr;17(4):321-5. doi: 10.1080/14737159.2017.1303379. PMID: 28266230.
11. Centers for Disease Control and Prevention. About syphilis. 2025. https://www.cdc.gov/syphilis/about/index.html.
12. Tuddenham S, Hamill MM, Ghanem KG. Diagnosis and treatment of sexually transmitted infections: a review. *JAMA*. 2022 Jan 11;327(2):161-72. doi: 10.1001/jama.2021.23487. PMID: 35015033.
13. Centers for Disease Control and Prevention. NCHHSTP AtlasPlus. 2024. https://www.cdc.gov/nchhstp/about/atlasplus.html.
14. Centers for Disease Control and Prevention. Sexually transmitted infections surveillance, 2023: Table 3. total syphilis* — reported cases and rates of reported cases by state/territory and region in alphabetical order, United States. 2024. https://www.cdc.gov/sti-statistics/data-vis/table-syph-total-state-abc.html.
15. Centers for Disease Control and Prevention. Sexually Transmitted Infections Surveillance, 2023: Table 13. Primary and Secondary Syphilis — Reported Cases and Rates of Reported Cases by Age Group and Sex, United States. 2024. https://www.cdc.gov/sti-statistics/data-vis/table-syph-ps-agesex.html.
16. Centers for Disease Control and Prevention. Sexually transmitted infections surveillance, 2023: National overview of STIs in 2023. 2024. https://www.cdc.gov/sti-statistics/annual/summary.html.
17. McDonald R, O'Callaghan K, Torrone E, et al. Vital signs: missed opportunities for preventing congenital syphilis - United States, 2022. *MMWR: Morbidity & Mortality Weekly Report*. 2023 Nov 17;72(46):1269-74. doi: 10.15585/mmwr.mm7246e1. PMID: 37971936.
18. Trivedi S, Williams C, Torrone E, Kidd S. National trends and reported risk factors among pregnant women with syphilis in the United States, 2012-2016. *Obstet Gynecol*. 2019 Jan;133(1):27-32. doi: 10.1097/AOG.0000000000003000. PMID: 30531570.
19. AAP Committee on Fetus and Newborn, ACOG Committee on Obstetric Practice. Guidelines for perinatal care. Eighth ed: AAP Books; 2017.
20. Centers for Disease Control and Prevention. Sexually transmitted infections surveillance, 2023: Table 15. primary and secondary syphilis — rates of reported cases* by race/Hispanic ethnicity, age group, and sex, United States. 2024. https://www.cdc.gov/sti-statistics/data-vis/table-syph-ps-rates-caseagesex.html.
21. Martin EG, Ansari B, Rosenberg ES, et al. Variation in patterns of racial and ethnic disparities in primary and secondary syphilis diagnosis rates among heterosexually active women by region and age group in the

United States. *Sex Transm Dis*. 2022 May 1;49(5):330-7. doi: 10.1097/OLQ.0000000000001607. PMID: 35121717.
22. Centers for Disease Control and Prevention. Impact of COVID-19 on STIs. 2024. https://www.cdc.gov/sti-statistics/about/impact-of-covid-19.html.
23. Biswas HH, Chew Ng RA, Murray EL, et al. Characteristics associated with delivery of an infant with congenital syphilis and missed opportunities for prevention—California, 2012 to 2014. *Sex Transm Dis*. 2018 Jul;45(7):435-41. doi: 10.1097/OLQ.0000000000000782. PMID: 29465666.
24. Zenker PN, Berman SM. Congenital syphilis: reporting and reality. *Am J Public Health*. 1990 Mar;80(3):271-2. doi: 10.2105/ajph.80.3.271. PMID: 2305902.
25. Centers for Disease Control and Prevention. Sexually transmitted infections surveillance, 2023. 2024. https://www.cdc.gov/sti-statistics/annual/index.html.
26. O'Callaghan KP, Johnson Jones ML, McDonald R, et al. The congenital Syphilis Prevention Cascade: reimagining a missed prevention opportunities framework for effective intervention. *Sex Transm Dis*. 2024 Jan 1;51(1):8-10. doi: 10.1097/OLQ.0000000000001892. PMID: 37921849.
27. Kimball A, Torrone E, Miele K, et al. Missed opportunities for prevention of congenital syphilis - United States, 2018. *MMWR: Morbidity & Mortality Weekly Report*. 2020 Jun 5;69(22):661-5. doi: 10.15585/mmwr.mm6922a1. PMID: 32497029.
28. DiOrio D, Kroeger K, Ross A. Social vulnerability in congenital syphilis case mothers: qualitative assessment of cases in Indiana, 2014 to 2016. *Sex Transm Dis*. 2018 Jul;45(7):447-51. doi: 10.1097/OLQ.0000000000000783. PMID: 29465662.
29. Matthias J, Sanon R, Bowen VB, et al. Syphilitic reinfections during the same pregnancy—Florida, 2018. *Sex Transm Dis*. 2021 May 1;48(5):e52-e5. doi: 10.1097/OLQ.0000000000001298. PMID: 32956239.
30. 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. doi: 10.1371/journal.pone.0056713. PMID: 23468875.
31. Ortiz DA, Shukla MR, Loeffelholz MJ. The traditional or reverse algorithm for diagnosis of syphilis: pros and cons. *Clin Infect Dis*. 2020 Jun 24;71(Suppl 1):S43-S51. doi: 10.1093/cid/ciaa307. PMID: 32578864.
32. NOWDiagnostics Inc. NOWDx test for the diagnosis of syphilis. https://clinicaltrials.gov/study/NCT05063344; 2021.
33. Bristow CC, Klausner JD, Tran A. Clinical test performance of a rapid point-of-care syphilis treponemal antibody test: a systematic review and meta-analysis. *Clin Infect Dis*. 2020 Jun 24;71(Suppl 1):S52-S7. doi: 10.1093/cid/ciaa350. PMID: 32578863.
34. Gliddon HD, Peeling RW, Kamb ML, et al. A systematic review and meta-analysis of studies evaluating the performance and operational characteristics of dual point-of-care tests for HIV and syphilis. *Sex Transm Infect*. 2017 Dec;93(S4):S3-S15. doi: 10.1136/sextrans-2016-053069. PMID: 28747410.
35. Butler T. The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. *Am J Trop Med Hyg*. 2017 Jan 11;96(1):46-52. doi: 10.4269/ajtmh.16-0434. PMID: 28077740.
36. Centers for Disease Control and Prevention. Syphilis during pregnancy. 2021. https://www.cdc.gov/std/treatment-guidelines/syphilis-pregnancy.htm.
37. U.S. Preventive Services Task Force. Screening for syphilis in pregnant women: recommendation statement. *American family physician*. 2019;99(8). PMID: 30990298.
38. American College of Obstetricians and Gynecologists. Screening for syphilis in pregnancy: updated ACOG recommendation. 2024. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2024/04/screening-for-syphilis-in-pregnancy.
39. Centers for Disease Control and Prevention. State prenatal syphilis screenings laws and regulations. 2024. https://www.cdc.gov/syphilis/hcp/prenatal-screening-laws/.
40. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016 Jul;75:40-6. doi: 10.1016/j.jclinepi.2016.01.021. PMID: 27005575.
41. UNDP (United Nations Development Programme). Human development report 2021-22: uncertain times, unsettled lives: shaping our future in a transforming world. New York. 2022. https://hdr.undp.org/content/human-development-report-2021-22
42. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011 Oct 18;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009. PMID: 22007046.

43. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354.
44. Adhikari EH, Frame IJ, Hill E, et al. Abbott ARCHITECT syphilis TP chemiluminescent immunoassay accurately diagnoses past or current syphilis in pregnancy. *Am J Perinatol*. 2020 Jan;37(1):112-8. doi: 10.1055/s-0039-3400994. PMID: 31905408.
45. Chen MW, Akinboyo IC, Sue PK, et al. Evaluating congenital syphilis in a reverse sequence testing environment. *J Perinatol*. 2019 Jul;39(7):956-63. doi: 10.1038/s41372-019-0387-9. PMID: 31076626.
46. Williams JEP, Bazan JA, Turner AN, et al. Reverse sequence syphilis screening and discordant results in pregnancy. *J Pediatr*. 2020 Apr;219:263-6 e1. doi: 10.1016/j.jpeds.2019.11.035. PMID: 32093931.
47. Zofkie AC, Seasely AR, Gaffney D, et al. Syphilis immunoassay signal strength correlates with active infection in pregnant women. *Am J Perinatol*. 2020 Jun;37(7):671-8. doi: 10.1055/s-0039-3402748. PMID: 31910464.
48. Christenson RH, Lessig M, Miles G, et al. Evaluation of the Elecsys syphilis immunoassay for detection of syphilis in populations at risk of disease in the US and Argentina. *J Appl Lab Med*. 2018 Jul 1;3(1):89-99. doi: 10.1373/jalm.2017.024943. PMID: 33626825.
49. Macumber S, Singh AE, Gratrix J, et al. Retrospective cohort study of the incidence and outcomes of Jarisch-Herxheimer reactions after treatment of infectious syphilis in late pregnancy. *Sex Transm Dis*. 2022 Oct 1;49(10):e107-e9. doi: 10.1097/OLQ.0000000000001610. PMID: 35093982.
50. Garcia JFB, Aun MV, Motta AA, et al. Algorithm to guide re-exposure to penicillin in allergic pregnant women with syphilis: efficacy and safety. *World Allergy Organ J*. 2021 Jun;14(6):100549. doi: 10.1016/j.waojou.2021.100549. PMID: 34093957.
51. 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 Feb;99(2):119-24. PMID: 27249890.
52. 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. doi: 10.3109/23744235.2015.1044465. PMID: 26313112.
53. 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 Aug;49(8):1375-7. doi: 10.1515/CCLM.2011.643. PMID: 21619473.
54. Pereira LE, McCormick J, Dorji T, et al. Laboratory evaluation of a commercially available rapid syphilis test. *J Clin Microbiol*. 2018 Oct;56(10):e00832-18. doi: 10.1128/JCM.00832-18. PMID: 30021825.
55. Nishijima T, Kawana K, Fukasawa I, et al. Effectiveness and tolerability of oral amoxicillin in pregnant women with active syphilis, Japan, 2010-2018. *Emerg Infect Dis*. 2020 Jun;26(6):1192-200. doi: 10.3201/eid2606.191300. PMID: 32441638.
56. University of Alabama at Birmingham. Phase 1 study of the pharmacokinetics of high dose amoxicillin with and without probenecid in pregnant women [Trial registry record; Clinical trial protocol]. https://clinicaltrials.gov/study/NCT05309928; 2022.
57. Lin JS, Eder M, Bean S. Screening for syphilis infection in pregnant women: a reaffirmation evidence update for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality. Report No. 18-05238-EF-1. Rockville, MD. 2018. https://www.ncbi.nlm.nih.gov/books/NBK525910/
58. 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 May;4(3):50-6. doi: 10.1097/00124784-199805000-00006. PMID: 10186742.
59. 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 Mar;210(3):267 e1-5. doi: 10.1016/j.ajog.2013.12.012. PMID: 24333235.
60. Albright CM, Emerson JB, Werner EF, Hughes BL. Third-trimester prenatal syphilis screening: a cost-effectiveness analysis. *Obstet Gynecol*. 2015 Sep;126(3):479-85. doi: 10.1097/AOG.0000000000000997. PMID: 26244531.
61. Matthias JM, Rahman MM, Newman DR, Peterman TA. Effectiveness of prenatal screening and treatment to prevent congenital syphilis, Louisiana and Florida, 2013-2014. *Sex Transm Dis*. 2017 Aug;44(8):498-502. doi: 10.1097/OLQ.0000000000000638. PMID: 28703731.
62. Slutsker JS, Hennessy RR, Schillinger JA. Factors contributing to congenital syphilis cases - New York City, 2010-2016. *MMWR: Morbidity & Mortality Weekly Report*. 2018 Oct 5;67(39):1088-93. doi: 10.15585/mmwr.mm6739a3. PMID: 30286056.

63. Sykes KJ, Scranton RA, Villarroel L, et al. Using surveillance data to respond to an outbreak of congenital syphilis in Arizona through third-trimester screening policies, 2017-2018. *Public Health Rep*. 2021 Jan/Feb;136(1):61-9. doi: 10.1177/0033354920967350. PMID: 33211993.
64. Huntington S, Weston G, Seedat F, et al. Repeat screening for syphilis in pregnancy as an alternative screening strategy in the UK: a cost-effectiveness analysis. *BMJ Open*. 2020 Nov 19;10(11):e038505. doi: 10.1136/bmjopen-2020-038505. PMID: 33444184.
65. Hersh AR, Megli CJ, Caughey AB. Repeat screening for syphilis in the third trimester of pregnancy: a cost-effectiveness analysis. *Obstet Gynecol*. 2018 Sep;132(3):699-707. doi: 10.1097/AOG.0000000000002795. PMID: 30095767.
66. Stanford University, Santa Clara Valley Medical Center. Point-of-care testing for congenital syphilis in mothers and newborns. https://clinicaltrials.gov/study/NCT03814096; 2019.
67. Amaya-Guio J, Grillo-Ardila CF, Angel-Müller E, et al. Point of care rapid test for diagnosis of syphilis infection in pregnant women. *Cochrane Database of Systematic Reviews*. 2018;2018(5). doi: 10.1002/14651858.Cd013037. PMID: PMC013037.
68. National Institute for Health and Care Excellence. Antenatal care. NICE Guideline. 2021. https://www.nice.org.uk/guidance/ng201.
69. Centers for Disease Control and Prevention. Challenges preventing HIV, viral hepatitis, and syphilis during pregnancy. 2024. https://www.cdc.gov/pregnancy-hiv-std-tb-hepatitis/challenges/.
70. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force procedure manual. 2023. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual.
71. O'Connor NP, Burke PC, Worley S, et al. Outcomes after positive syphilis screening. *Pediatrics*. 2022 Sep 1;150(3):e2022056457. doi: 10.1542/peds.2022-056457. PMID: 36000336.

Figure 1. Reported Number of Cases of Congenital Syphilis Among Infants, by Year of Birth, and Rates* of Reported Cases of Primary and Secondary Syphilis† Among Females Aged 15–44 Years, by Year—United States, 2012–2022



* Cases per 100,000 population.

† Primary and secondary syphilis case data for all U.S. territories and freely associated states and outlying areas were not available for all years; therefore, rates presented include only the 50 states and the District of Columbia.

Source: McDonald R, O'Callaghan K, Torrone E, et al. Vital signs: missed opportunities for preventing congenital syphilis - United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2023 Nov 17;72(46):1269-74. doi: 10.15585/mmwr.mm7246e1. PMID: 37971936.[17]

Figure 2. Analytic Framework

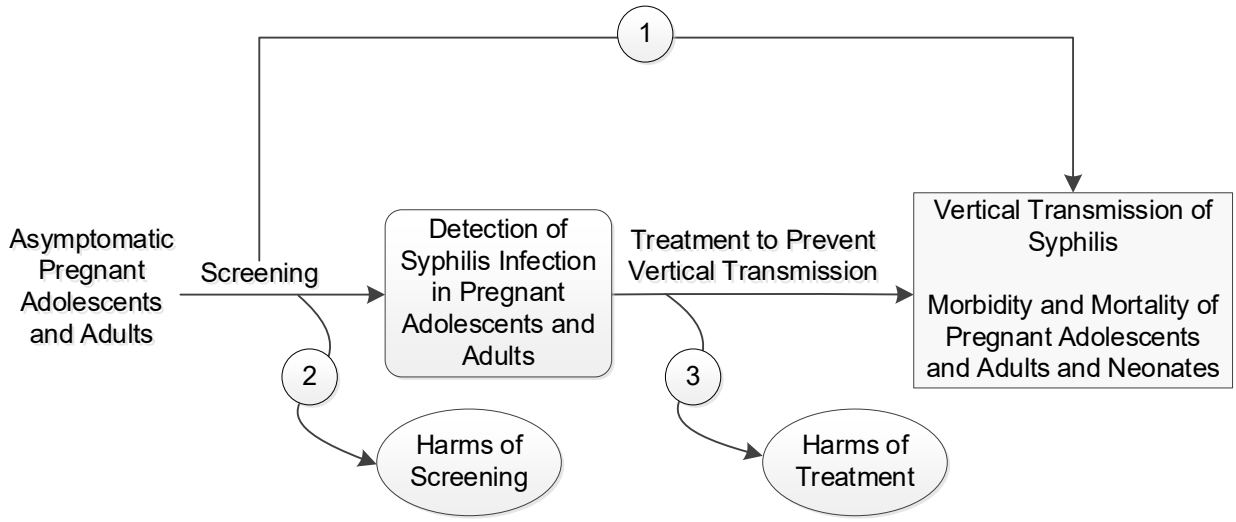
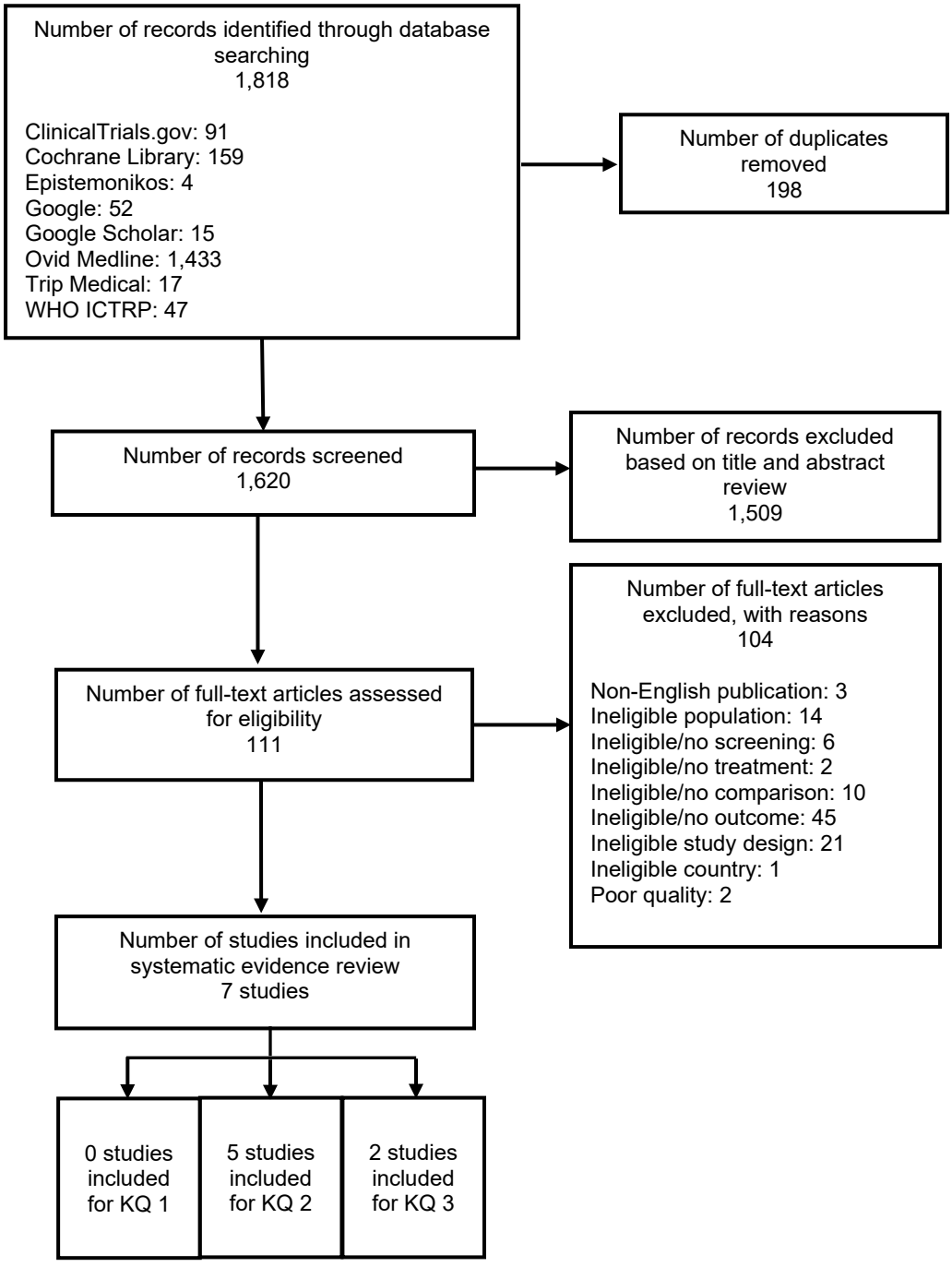


Figure 3. Summary of Evidence Search and Selection



Abbreviations: KQ=key question; WHO ICTRP=World Health Organization International Clinical Trials Registry Platform.

Table 1. Characteristics of Included Harms of Screening Studies (KQ 2)

First Author, Year	Quality Rating Study Design	Country Year(s) Patient Selection	Race/Ethncity N (%)*	Pregnant Patients Screened (N)	Test Evaluated Positive Cutoff	Reference Testing Strategy	Index Test Positivity (%)	Harms
Traditional screening algorithm								
Adhikari, 2020[44]	Fair Prospective Cohort	United States 2017 Pregnant patients with high syphilis prevalence from a large healthcare system in Texas	Asian: 44 (3%) Black: 282 (18%) White: 76 (5%) Hispanic: 1,197 (75%) Other: 3 (0.2%)	1,602	BD Macro-Vue RPR NR	Reflex TP-PA	35/1,602 (2.2%)	FP: 11/35 (31%)
Reverse screening algorithm								
Adhikari, 2020[44]	Fair Prospective Cohort	United States 2017 Pregnant patients with high syphilis prevalence from a large healthcare system in Texas	Asian: 44 (3%) Black: 282 (18%) White: 76 (5%) Hispanic: 1,197 (75%) Other: 3 (0.2%)	1,602	ARCHITECT CIA S/CO value ≥1.0	Reflex RPR with TP-PA for discordant results	14/1,602 (1.0%)	FP: 1/14 (7%)
Chen, 2019[45†]	Good Retrospective Cohort	United States 2011-2014 All patients who delivered live or stillborn infants with positive CIA serology at a university hospital in Baltimore, MD	Black: 40(67%) White: 12 (20%) Other: 8 (13%)	4,872	LIAISON CIA NR	Reflex RPR with FTA-ABS for discordant results	60/4,872 (1.2%)	FP: 16/60 (26.7%)
Williams, 2020[46‡]	Fair Retrospective Cohort	United States 2011-2018 Pregnant patients with unknown syphilis risk who delivered at a university hospital in central Ohio	Black: 64 (50%) White: 37 (29%) Hispanic: 8 (6%) Other: 18 (14%)	35,108	BioPlex MFI NR	Reflex RPR with TP-PA for discordant results	384/35,108[§] (1.1%)	FP: 83/127[‖] (65.4%)
Zofkie, 2020[47¶]	Fair Prospective Cohort	United States 2018-2019 Pregnant patients with unknown syphilis risk who delivered at a large healthcare system in Dallas, TX	Black: 83 (58%) White: 5 (3%) Hispanic: 5 (3%) Other: 1 (1%)	9,220	ARCHITECT CIA S/CO value >1.0	Reflex RPR with TP-PA for discordant results	144/9,220 (1.6%)	FP: 17/144 (11.8%)

Table 1. Characteristics of Included Harms of Screening Studies (KQ 2)

First Author, Year	Quality Rating Study Design	Country Year(s) Patient Selection	Race/Ethncity N (%)*	Pregnant Patients Screened (N)	Test Evaluated Positive Cutoff	Reference Testing Strategy	Index Test Positivity (%)	Harms
Composite screening algorithm								
Christenson, 2018[48#]	Fair Prospective Cohort	United States and Argentina NR Pregnant patients with unknown syphilis risk	Asian: 4 (1%) Black: 22 (7%) White: 285 (90%) Other: 5 (2%)	316	Elecsys IMA S/CO value ≥1.0	IMMULITE 2000 and RPR with TP-PA for discordant results**	15/316 (4.8%)	FP: 0/15 (0%) FN: 0/301 (0%)

* Hispanic category included without differentiating by race (e.g., Black Hispanic versus non-Black Hispanic) in all studies that report this category.

† Race data available only for the 60 (1%) participants with positive CIA results.

ǂ Race data available only for the 127 (0.4%) participants with discordant test results.

§ 384 MFI positive tests at any time during pregnancy.

ǁ 192/384 positive MFI tests were discordant (MFI+/RPR-); 127 pregnancies had discordant results *at time of delivery*.

¶ Race data available only for the 144 (2%) participants with positive CIA results.

Race data reported for all 316 pregnant participants.

** All participants tested with both Immulite and RPR.

Abbreviations: CIA=chemiluminescence immunoassay; FN=false negative; FP=false positive; FTA-ABS=fluorescent treponemal antibody absorption test; IMA=immunoassay; MFI=multiplex flow immunoassay; NR=not reported; RPR=rapid plasma reagin; S/CO=sample/cutoff; TP-PA=*Treponema pallidum*-particle agglutination.

Table 2. Characteristics of Included Harms of Treatment Studies (KQ 3)

First Author, Year Study Design Quality Rating	N	Age	Gestational Age	Recruitment Setting	Race/Ethnicity	Syphilis Status	Treatment Sensitivity	Testing Scheme	Treatment Scheme
Garcia, 2021[50] Prospective Single-arm Cohort Good	91 pregnant patients	Mean years (range): 25.1 (14–42)	Mean weeks (range): 19.8 (5–38)	Clinical Immunology and Allergy Division of the University of São Paulo School of Medicine, Brazil; a reference center that manages patients with drug-induced IHR	NR	Latent syphilis confirmed by laboratory tests and a clinical history of IHR to penicillin	Anaphylaxis as the initial IHR: 46.2% of total population Positive intradermal test: 7.7% of total population	NR	Low-risk patients (low clinical history, no elevated serum tryptase, negative skin testing, negative serum sIgE) underwent drug provocation; if negative, they were treated with pencillin, and if positive, pencillin desensitization was undertaken. High-risk patients (2 of 3 criteria: drug-induced IHR in the last 10 years; initial reaction compatible with IHR; no history of tolerated re-exposure to penicillins after the initial reaction) or elevated serum tryptase during the initial reaction underwernt penicillin desensitization.
Macumber, 2022[49] Retrospective Single-arm Cohort Fair	39 pregnant patients	Median years (IQR): 27 (21–30)	Median weeks (IQR): 27 (23–30)	Women admitted as part of usual care for 24 hours of fetal monitoring after syphilis treatment in the Edmonton zone of Alberta, Canada, and included in the Communicable Disease and Outbreak Management Database	Ethnicity n (%): First Nation: 23 (59.0) Metis: 5 (12.8) White: 5 (12.8) Other: 6 (15.4)	Infectious syphilis stage n (%): Primary: 10 (25.6) Secondary: 4 (10.3) Early latent: 25 (64.1)	NR	Reverse sequence in first trimester and again at delivery: treponemal-specific EIA; positive EIA followed by RPR and TP-PA	39 cases of syphilis treated at ≥20 weeks' gestation: 37 cases treated with benzathine penicillin and two cases with fetal ultrasound findings suggestive of congenital syphilis treated with 10–14 days of intravenous penicillin G.

Abbreviations: EIA=enzyme immunoassay; IHR=immediate hypersensitivity reaction; IQR=interquartile range; sIgE=serum immunoglobulin E; N/n=number; NR=not reported; RPR=rapid plasma reagin; TP-PA=*Treponema pallidum*-particle agglutination.

Table 3. Summary of Evidence

Key Question (KQ)	Rationale and Foundational Evidence	Limitations of Foundational Evidence	Prior Evidence (2018)	New Evidence: N of Studies (Study Designs); N of Participants	New Evidence Findings	Limitations of New Evidence	Consistency of New Evidence With Foundational Evidence
KQ 1. Benefits of Screening	Observational studies demonstrate an association between lower adverse outcomes in pregnant patients treated for syphilis compared with those not treated. Universal screening in early pregnancy can prevent congenital syphilis.	Observational data using historical and geographic comparators. Unclear applicability of study body, which comes from studies out of China.	One observational study evaluating the implementation of screening for syphilis in more than 2 million pregnant women in Shenzhen, China demonstrated an 11-fold decrease in congenital syphilis over 10 years.	None	No new studies identified that evaluated benefits of screening pregnant adolescents and adults for syphilis.	NA	NA
KQ 2. Harms of Screening	Two-step screening algorithms (traditional and reverse sequence) can detect syphilis in pregnancy with high accuracy and reliability. No severe adverse outcomes.	Most accuracy studies only report on the test accuracy of the initial treponemal or nontreponemal test and not the accuracy of the screening algorithm.	Five studies demonstrated that false 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.	5 studies (single-arm cohorts)[44-48]; 51,118 participants	False-positive results ranged between 0 and 65%, depending on the screening algorithm and index test evaluated; one study reported on false-negative results (0%).	The range of estimates is based on a variety of different screening tests.	Two-step screening algorithms should be used to screen for syphilis in pregnancy because false-positive results of single tests are common.

Table 3. Summary of Evidence

Key Question (KQ)	Rationale and Foundational Evidence	Limitations of Foundational Evidence	Prior Evidence (2018)	New Evidence: N of Studies (Study Designs); N of Participants	New Evidence Findings	Limitations of New Evidence	Consistency of New Evidence With Foundational Evidence
KQ 3. Harms of Treatment	Parenteral penicillin G is accepted as safe and effective for treatment of syphilis in pregnancy.	Studies of other treatments are lacking.	None	2 studies (single-arm cohorts); 39 participants on study of JH reactions,[49] 91 participants on penicillin desensitization[50]	JH reactions: 2/39 (5.1%); of these, one went on to have a stillbirth, but the presence of congenital syphilis could not be established, and other diagnoses could not be ruled out.[49] Overall IHR: 2/91 (4.4%)[50] IHR among high-risk persons receiving oral desensitization: 3/11 (27.3%)[50] IHR among high-risk persons receiving intravenous desensitization: 1/40 (2.5%)[50] IHR among low-risk persons undergoing penicillin provocation: 1/40 (2.5%)[50] Incomplete penicillin therapy (switched to doxycycline): 2/91 (2.2%)[50]	Included study designs do not permit causal inference but offer ranges of estimates for bounding of harms.	New studies offer evidence for bounding of harms.

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

Appendix A Table 1. Syphilis Infection Screening and Treatment Recommendations of Others

Organization, Year, Country	Definition of Screening/Treatment Population	Screening Test(s)	Recommendation
American Academy of Family Physicians, 2019, United States[37]	First prenatal visit	Nontreponemal tests commonly used for initial screening: VDRL and RPR Confirmatory tests: FTA-ABS and TP-PA Alternative reverse sequence: Enzyme-linked, chemiluminescence or multiplex flow immunoassay first, followed by VDRL or RPR	Screen all pregnant women for syphilis infection at earliest prenatal visit (derived from USPSTF 2018 recommendation).
American Academy of Pediatrics and American College of Obstetricians and Gynecologists,* 2017, United States[19]	First prenatal visit Additional screening in early third trimester at 28 weeks and delivery in women at high risk* for syphilis or who live in communities of high syphilis morbidity and after exposure to an infected partner Stillbirth (fetal death after 20 weeks' gestation)	Nontreponemal tests: VDRL/RPR before confirmatory treponemal testing for diagnosis of syphilis with active/positive result Alternative reverse sequence: Automated treponemal test first Both nontreponemal and treponemal positive screening test must be confirmed with complementary confirmatory test.	Screen all pregnant women for syphilis infection at earliest prenatal visit and rescreen in the third trimester and at delivery in selected persons at increased risk for syphilis.*
Centers for Disease Control and Prevention, 2021, United States[3, 36]	First prenatal visit Additional screening twice in third trimester at 28 weeks and delivery in women at high risk for syphilis or who live in communities of high syphilis morbidity Stillbirth (fetal death after 20 weeks' gestation)	Serologic test: Manual nontreponemal by traditional screening algorithm or treponemal by reverse sequence Serologic screening and treatment (if test reactive) at the time of pregnancy are confirmed if access to prenatal care is not optimal.	Screen all pregnant women for syphilis infection at earliest prenatal visit and rescreen in the third trimester and at delivery in selected persons at increased risk for syphilis.
National Institute for Health and Care Excellence, 2021, United Kingdom[68]	Early stage in antenatal care	Not specified	Screening for syphilis infection should be offered to all pregnant women.

* Since the initial completion of this draft report, the American College of Obstetricians and Gynecologists has revised its screening recommendations from a risk-based to a universal strategy for repeat screening in the third trimester and at birth.[38]

Abbreviations: FTA-ABS=fluorescent treponemal antibody absorbed; RPR=rapid plasma reagin; TP-PA=*Treponema pallidum*-particle agglutination; USPSTF=U.S. Preventive Services Task Force; VDRL=Venereal Disease Research Laboratory.

Contextual Question

CQ. To better understand the need for retesting during pregnancy, the USPSTF will review how frequently do pregnant adolescents and adults who initially test negative for syphilis by serologic screening either later test positive for syphilis, give birth to a neonate with congenital syphilis, or have a miscarriage or stillbirth attributed to syphilis? Do these associations vary by populations of interest (demographic characteristics or risk factors)?

Early and accurate screening for syphilis during pregnancy to prevent adverse pregnancy outcomes of syphilis, including miscarriages, stillbirth, or congenital syphilis, is still a challenge.[69] Studies have shown gaps in first-trimester screening and failure to rescreen in the third trimester. Cases of syphilis-related stillbirth, miscarriage, and congenital syphilis are disproportionate among racial and ethnic groups and other populations at risk.[16] Although the prior review summarized these disparities and the importance of early prenatal screening, it did not examine possible differences in pregnancy outcomes among pregnant adolescents and adults who initially tested negative for syphilis and, during third trimester repeat screening, tested positive. The following is a summary of the current evidence on pregnant adolescents and adults who initially test negative for syphilis and later test positive or have a miscarriage or stillbirth. Evidence for the CQ is summarized in **Appendix A Table 2**.

We identified three retrospective cohort studies and one national registry relevant to this question. In a U.S. national sample, approximately 5 percent of cases of congenital syphilis occurred in pregnancies that initially screened negative for syphilis.[17] Two of three cohort studies concluded about half of congenital syphilis cases might be prevented with third trimester repeat screening and adequate treatment,[61, 62] whereas the third study estimated about 25 percent of cases might be preventable.[63]

One retrospective cohort study assessed maternal and congenital syphilis cases among women from Louisiana and Florida, two states with high syphilis morbidity.[61] All cases of women of childbearing age who were diagnosed with syphilis from both states were investigated to determine if they were pregnant. All syphilis cases who were classified as pregnant from January 2013 through December 2014 were included. Among reported syphilis infections during pregnancy (N=710), 155 (21.8%) cases of congenital syphilis were identified. Early screening (i.e., during first two trimesters) was conducted in 589 (83%) of these pregnancies, of which 76 tested negative at this early screening. Of the 76 negative early screenings, 41 had repeat screening during the third trimester, with 36 (47.4%) positive screens and five (6.6%) negative screens; 35 (46.1%) had no repeat screening. Among the 36 cases of positive repeat screenings, 30 were prevented from developing congenital syphilis; all 40 infants born to those with either negative repeat screening results or no repeat screening were diagnosed with congenital syphilis. Additionally, among 513 pregnancies that did test positive during early screening, 13 (2.5%) were determined to become reinfected during pregnancy. Lastly, of 27 congenital syphilis cases that didn't have early syphilis screening, 9 (30%) had negative third trimester syphilis screening with seroconversion at or around time of delivery. Across both states, the majority of syphilis

cases occurred in persons who identified as non-Hispanic Black (68%). In Florida, a higher percentage of persons with syphilis identified as Hispanic (20%) compared with Louisiana (3%). In Florida, 33 percent of pregnancies with syphilis occurred in foreign-born persons (data not collected for Louisiana). Early syphilis was associated with about half of the congenital syphilis cases, while the rest of the cases were associated with the latent stage of syphilis (20% with high RPR titer ≥1:32; 30% with medium/low RPR titer).

A retrospective cohort study (N=578) was conducted by the New York City (NYC) Department of Health and Mental Hygiene to evaluate congenital syphilis cases among pregnant adolescents and adults in NYC.[62] Between 2010 and 2016, a total of 578 syphilis cases among pregnant adolescents and adults were reported, including 68 (11.8%) congenital syphilis cases. Among the 68 congenital syphilis cases, 43 (63.2%) of the pregnancies underwent syphilis screening at least 45 days prior to delivery, and 22 (51.2%) of those screens were negative; all 22 had positive screening results within 30 days of or at delivery, suggesting syphilis infection had been acquired shortly before delivery. Another 15 congenital syphilis cases occurred among pregnant adolescents and adults who were adequately screened and treated yet had rising serologic titers, suggestive of reinfection. Although demographic data were not reported for all pregnancies, among those with an infant with congenital syphilis (n=68), the vast majority occurred in pregnant adolescents and adults who identified as either non-Hispanic Black (42.7%) or Hispanic (35.3%); most pregnant adolescents and adults were either in their 20s (50.0%) or 30s (35.3%); a little more than half (55.4%) were foreign-born; and the majority reported no prior history of STI (60.3%) and no STI during pregnancy (91.2%).

The Arizona Department of Health Services (ADHS) conducted a retrospective cohort study to identify missed opportunities for congenital syphilis prevention through third trimester syphilis screening.[63] From January 2017 through June 2018, they identified 205 pregnant adolescents and adults who had positive syphilis screening results using ADHS surveillance data. Of those pregnancies, 57 (27.8%) infants were born with congenital syphilis. In 14 (24.6%) congenital syphilis cases, the mother had negative early syphilis screening, and in five (8.8%) cases, the mother was reinfected after appropriate screening and treatment. From the 57 congenital syphilis cases, 35 pregnant adolescents and adults (61.4%) were diagnosed with either primary, secondary, or early-stage syphilis; 15 (26.3%) had late latent syphilis with a high titer (>1:16) on a nontreponemal test. No additional demographic data were reported.

One U.S. national registry of notifiable infectious diseases was used to estimate the number of cases of congenital syphilis cases in 2022, including the number of cases that occurred after initial negative prenatal syphilis screening.[17] CDC NNDSS receives infectious disease reports from all 50 states, the District of Columbia, and U.S. territories. Cases of congenital syphilis that occur in the United States that meet the 2018 Council of State and Territorial Epidemiologists congenital syphilis case definition are reported to the NNDSS. In 2022, 3,761 cases of congenital syphilis were reported to the NNDSS. In 197 (5.2%) of these cases, syphilis was diagnosed late in pregnancy (<30 days prior to delivery) after an earlier negative screening result. Most of these cases were in Black or African American women (n=80), Hispanic or Latino women (n=56), and White women (n=39). Across these higher-frequency groups, the proportion of late identification of seroconversion ranged from 3.8 percent in White women to 7.1 percent in Black or African American women.

Appendix A. Table 2. Incidence of Positive Syphilis Test, Miscarriage, Neonate With Congenital Syphilis, or Stillbirth After an Initial Negative Test Among Pregnant Adolescents and Adults

First Author, Year Study Design Country	Population (N)	Ascertainment of Positive Syphilis Test, Miscarriage, Congenital Syphilis, or Stillbirth	Proportion With Positive Syphilis Test After Initial Negative Test (N)
Matthias, 2017[61] Retrospective Cohort United States	Pregnant women with positive syphilis screening from Louisiana and Florida (710)	Serologic test reports from each state's STD surveillance system	47.4% (36/76) screened positive after at least one initial negative screening; 83% (30/36) did not develop congenital syphilis after appropriate treatment
Slutsker, 2018[62] Retrospective Cohort United States	Pregnant women ages 15-44 years with positive syphilis screening from New York City (578)	Serologic test reports within DOHMH surveillance and case management registry	51.2% (22/43) of congenital syphilis cases had a negative screening result at least 45 days prior to delivery; 34.9% (15/43) had positive screening and adequate treatment but tested positive within 30 days of or at delivery
Sykes, 2021[63] Retrospective Cohort United States	Pregnant women of reproductive age (13-45 years) with positive syphilis screening in Arizona (205)	Electronic medical records, vital statistics data, and medical records review	24.6% (14/57) of congenital syphilis cases had negative initial syphilis screen; 8.8% (5/57) of congenital syphilis cases were due to a reinfected mother after appropriate treatment
McDonald, 2023[17] National Registry United States	Pregnant females (ages 15-44 years) who delivered neonates with congenital syphilis (3,761)	Reported to the NNDSS based on standardized case definitions	Among 3,761 cases of congenital syphilis, 197 (5.2%) cases occured in pregnancies with an initial negative early screening result

Abbreviations: DOHMH=Department of Health and Mental Hygiene; EHR=electronic health records; ICD-9-CM=*International Classification of Diseases, Ninth Revision, Clinical Modification*; ICD-10-CM=*International Classification of Diseases, Tenth Revision, Clinical Modification*; NNDSS=National Notifiable Diseases Surveillance System; STD=sexually transmitted disease.

Appendix B1. Original Search Strategies

Ovid MEDLINE®, Screening Search, 1/11/2023

Search Number	Query	Results
1	Syphilis/ or Syphilis, Congenital/ or syphil*.ti,ab.	37042
2	Treponema Pallidum/ or ("treponema pallidum" or "t. pallidum").ti,ab.	6496
3	or/1-2	38848
4	Mass Screening/ or Maternal Serum Screening Tests/ or (assay$1 or immunoassay$1 or immuno-assay$1 or screen* or test*).ti,ab. Or di.fs.	7489855
5	Syphilis Serodiagnosis/ or Fluorescent Treponemal Antibody-Absorption Test/	5408
6	((nontreponemal or non-treponemal or treponema or treponemal) adj3 (test$3 or assay$1 or immunoassay* or immuno-assay*)).ti,ab.	1634
7	("Venereal disease research laboratory" or VDRL).ti,ab.	1610
8	("Toluidine red unheated serum" or Tolul* or TRUST).ti,ab.	45642
9	("Rapid plasma reagin" or RPR or reagin).ti,ab.	2444
10	("Fluorescent treponemal antibody absorption" or fluorescen* or FTA-ABS or IgM-FTA-ABS).ti,ab.	531010
11	("Treponema pallidum particle agglutination" or "t. pallidum particle agglutination" or TPPA or agglutination).ti,ab.	22165
12	("treponema pallidum hemagglutination assay" or haemagglutination or hemagglutination or TPHA or MHA-TP or AMHA-TP).ti,ab.	22130
13	("enzyme immunoassay*" or "enzyme-linked immunosorbent" or EIA or ELISA or enzyme).ti,ab.	980895
14	(CIA or CMIA or MBIA or ((chemiluminescen* or enzyme or microbead) adj3 (assay* or immunoassay* or immuno-assay* or test*)) or chemiluminescen*).ti,ab.	180692
15	(positiv* or "reverse sequence" or seroconver* or sero-conv* or serodiagnos* or sero-diagnos* or seronegativ* or sero-negativ* or seropositiv* or sero-positiv* or (serologic* adj2 (screen* or diagnos*))).ti,ab.	2174136
16	or/4-15	9745733
17	Pregnancy/ or Pregnancy Trimester, First/ or Pregnancy Trimester, Second/ or Pregnancy Trimester, Third/ or Pregnant Women/ or Prenatal Care/ or Prenatal Diagnosis/ or Pregnancy Outcome/ or Pregnancy Complications, Infectious/ or Infectious Disease Transmission, Vertical/	985024
18	(antenatal* or ante-natal* or antepartum or ante-partum or congenital* or delivery or gestation* or perinatal* or peri-natal* or peripartum or peri-partum or pregnan* or prenatal* or pre-natal* or prepartum or pre-partum or trimester$1).ti,ab.	1469491
19	((fetomaternal* or foetomaternal* or feto-maternal* or foeto-maternal* or mother-to-child or MTC or maternal* or mother$1 or vertical*) adj3 (transmission$1 or transmitted)).ti,ab.	19823
20	or/17-19	1865677
21	and/3,16,20	3484
22	21	3484
23	limit 22 to (english language and yr="2008 -Current")	1430
24	23 not ((exp Animals/ not Humans/) or (animal model* or bitch$2 or bovine or canine or capra or cat or cats or cattle or cow$1 or dog$1 or equine or ewe$1 or feline or goat$1 or hamster$1 or horse$1 or invertebrate$1 or macaque$1 or mare$1 or mice or monkey$1 or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate$1 or rabbit$1 or rat$1 or rattus or rhesus or rodent* or sheep or simian or sow$1 or vertebrate$1 or whale* or zebrafish).ti.)	1420
25	24 not (case report or news).pt.	1415
26	limit 25 to yr="2017 -Current"	783

Appendix B1. Original Search Strategies

Ovid MEDLINE®, Treatment Search, 1/11/2023

Search Number	Query	Results
1	Syphilis/ or Syphilis, Congenital/ or syphil*.ti,ab.	37042
2	Treponema Pallidum/ or ("treponema pallidum" or "t. pallidum").ti,ab.	6496
3	or/1-2	38848
4	exp Anti-Bacterial Agents/ or Ampicillin/ or Amoxicillin/ or Azlocillin/ or Carbenicillin/ or Carfecillin/ or Ceftriaxone/ or Doxycycline/ or exp Erythromycin/ or Mezlocillin/ or Minocycline/ or Penicillin G Benzathine/ or Penicillin G/ or Penicillin G Procaine/ or Piperacillin/ or Pivampicillin/ or Sulbenicillin/ or Talampicillin/ or Tetracycline/ or (dt or th).fs.	5012373
5	(antibiotic* or anti-biot* or ampicillin or amoxicillin or azlocillin or benzathine or benzylpenicillin or carbenicillin or carfecillin or ceftriaxone or doxycycline or erythromycin or mezlocillin or minocycline or penicillin or piperacillin or pivampicillin or procaine or sulbenicillin or talampicillin or tetracycline or manag* or outcome or treat*).ti,ab.	8310911
6	or/4-5	10394296
7	Pregnancy/ or exp Pregnancy Complications/ or Pregnancy Outcome/ or Pregnancy Trimester, First/ or Pregnancy Trimester, Second/ or Pregnancy Trimester, Third/ or Pregnant Women/ or Prenatal Care/ or Postpartum Period/	1014955
8	(antenatal* or ante-natal* or antepartum or ante-partum or birth* or childbirth or deliver* or gestation* or perinatal* or peri-natal* or peripartum or peri-partum or postnatal* or post-natal* or postpartum or post-partum or pregnan* or prenatal* or pre-natal* or prepartum or pre-partum or puerper* or trimester$1).ti,ab.	1754353
9	Infectious Disease Transmission, Vertical/ or Maternal-Fetal Exchange/	48349
10	((fetomaternal* or foetomaternal* or feto-maternal* or foeto-maternal* or mother* or MTC or maternal* or mother$1 or vertical*) adj3 (infect* or transmission$1 or transmitted)).ti,ab.	28946
11	Embryo, Mammalian/ or embryo*.ti,ab.	403010
12	Fetus/ or (fetus* or foetus* or fetal or foetal).ti,ab.	363177
13	Infant/ or Infant, Newborn/ or Infant, Low Birth Weight/ or Infant, Small for Gestational Age/ or Infant, Very Low Birth Weight/ or Infant, Extremely Low Birth Weight/ or Infant, Premature/ or Infant, Extremely Premature/ or (infant* or neonat* or newborn*).ti,ab.	1527793
14	Abnormalities, Drug-Induced/ or Congenital Abnormalities/ or congenital.hw. or (ab or ae or cn or mo or pc).fs. or (abnormal* or adverse or anomal* or congenital* or defect* or delay* or deformit* or disab* or malform*).ti,ab.	6274589
15	Maternal Mortality/ or ((maternal or parturient*) adj2 (death* or morbid* or mortal*)).ti,ab.	27627
16	Abortion, Spontaneous/ or Abortion, Threatened/ or Embryo Loss/ or Stillbirth/ or (miscarriag* or ((spontaneous* or threaten*) adj2 abortion*) or stillborn or stillbirth*).ti,ab.	59585
17	Fetal Mortality/ or Infant Mortality/ or Perinatal Mortality/ or ((baby or babies or infant* or neonat* or neo-nat* or newborn* or new-born*) adj2 (death* or morbid* or mortal*)).ti,ab.	66562
18	or/7-17	8810279
19	and/3,6,18	5089
20	limit 19 to yr="2017 -Current"	1096
21	20 not ((exp Animals/ not Humans/) or (animal model* or bitch$2 or bovine or canine or capra or cat or cats or cattle or cow$1 or dog$1 or equine or ewe$1 or feline or goat$1 or hamster$1 or horse$1 or invertebrate$1 or macaque$1 or mare$1 or mice or monkey$1 or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate$1 or rabbit$1 or rat$1 or rattus or rhesus or rodent* or sheep or simian or sow$1 or vertebrate$1 or zebrafish).ti.)	1087
22	21 not ((case reports or news).pt. or (case report or boy or girl or man or mother or patient or woman).ti.)	861

Appendix B1. Original Search Strategies

Cochrane Library, Wiley, Screening Search, 1/11/2023

ID	Search	Hits
#1	[mh Syphilis] OR [mh "Syphilis, Congenital"] OR syphil*:ti,ab	782
#2	[mh "Treponema Pallidum"] OR "treponema pallidum":ti,ab OR "t. pallidum":ti,ab	90
#3	#1 OR #2	814
#4	[mh "Mass Screening"] OR [mh "Maternal Serum Screening Tests"] OR assay*:ti,ab OR immunoassay*:ti,ab OR immuno-assay*:ti,ab OR screen*:ti,ab OR test*:ti,ab OR [mh /DI]	506421
#5	[mh "Syphilis Serodiagnosis"] OR [mh "Fluorescent Treponemal Antibody-Absorption Test"]	24
#6	((nontreponemal:ti,ab OR non-treponemal:ti,ab OR treponema:ti,ab OR treponemal:ti,ab) NEAR/3 (test*:ti,ab OR assay*:ti,ab OR immunoassay*:ti,ab OR immuno-assay*:ti,ab))	35
#7	"Venereal disease research laboratory":ti,ab OR VDRL:ti,ab	51
#8	"Toluidine red unheated serum":ti,ab OR Tolul*:ti,ab OR TRUST:ti,ab	3611
#9	"Rapid plasma reagin":ti,ab OR RPR:ti,ab OR reagin:ti,ab	178
#10	"Fluorescent treponemal antibody absorption":ti,ab OR fluorescen*:ti,ab OR FTA-ABS:ti,ab OR IgM-FTA-ABS:ti,ab	4450
#11	"Treponema pallidum particle agglutination":ti,ab OR "t. pallidum particle agglutination":ti,ab OR TPPA:ti,ab OR agglutination:ti,ab	273
#12	"treponema pallidum hemagglutination assay":ti,ab OR haemagglutination:ti,ab OR hemagglutination:ti,ab OR TPHA:ti,ab OR MHA-TP:ti,ab OR AMHA-TP:ti,ab	1192
#13	("enzyme" NEXT immunoassay*):ti,ab OR "enzyme-linked immunosorbent":ti,ab OR EIA:ti,ab OR ELISA:ti,ab OR enzyme:ti,ab	29298
#14	(CIA:ti,ab OR CMIA:ti,ab OR MBIA:ti,ab OR ((chemiluminescen*:ti,ab OR enzyme:ti,ab OR microbead:ti,ab) NEAR/3 (assay*:ti,ab OR immunoassay*:ti,ab OR immuno-assay*:ti,ab OR test*:ti,ab)) OR chemiluminescen*:ti,ab)	6259
#15	(positiv*:ti,ab OR "reverse sequence":ti,ab OR seroconver*:ti,ab OR sero-conv*:ti,ab OR serodiagnos*:ti,ab OR sero-diagnos*:ti,ab OR seronegativ*:ti,ab OR sero-negativ*:ti,ab OR seropositiv*:ti,ab OR sero-positiv*:ti,ab OR (serologic*:ti,ab NEAR/2 (screen*:ti,ab OR diagnos*:ti,ab)))	159107
#16	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	616337
#17	[mh Pregnancy] OR [mh "Pregnancy Trimester, First"] OR [mh "Pregnancy Trimester, Second"] OR [mh "Pregnancy Trimester, Third"] OR [mh "Pregnant Women"] OR [mh "Prenatal Care"] OR [mh "Prenatal Diagnosis"] OR [mh "Pregnancy Outcome"] OR [mh "Pregnancy Complications, Infectious"] OR [mh "Infectious Disease Transmission, Vertical"]	25327
#18	(antenatal*:ti,ab OR ante-natal*:ti,ab OR antepartum:ti,ab OR ante-partum:ti,ab OR congenital*:ti,ab OR delivery:ti,ab OR gestation*:ti,ab OR perinatal*:ti,ab OR peri-natal*:ti,ab OR peripartum:ti,ab OR peri-partum:ti,ab OR pregnan*:ti,ab OR prenatal*:ti,ab OR pre-natal*:ti,ab OR prepartum:ti,ab OR pre-partum:ti,ab OR trimester*:ti,ab)	120963
#19	((fetomaternal*:ti,ab OR foetomaternal*:ti,ab OR feto-maternal*:ti,ab OR foeto-maternal*:ti,ab OR mother-to-child:ti,ab OR MTC:ti,ab OR maternal*:ti,ab OR mother*:ti,ab OR vertical*:ti,ab) NEAR/3 (transmission*:ti,ab OR transmitted:ti,ab))	1017
#20	#17 OR #18 OR #19	126440
#21	#3 AND #16 AND #20	162
#22	#21 NOT ("case report":pt OR)	162
#23	#22 Limited to results published 2017-2023	93

Appendix B1. Original Search Strategies

Cochrane Library, Wiley, Treatment Search, 1/11/2023

ID	Search	Hits
#1	[mh Syphilis] OR [mh "Syphilis, Congenital"] OR syphil*:ti,ab	782
#2	[mh "Treponema Pallidum"] OR "treponema pallidum":ti,ab OR "t. pallidum":ti,ab	90
#3	#1 OR #2	814
#4	[mh "Anti-Bacterial Agents"] OR [mh Ampicillin] OR [mh Amoxicillin] OR [mh Azlocillin] OR [mh Carbenicillin] OR [mh Carfecillin] OR [mh Ceftriaxone] OR [mh Doxycycline] OR [mh Erythromycin] OR [mh Mezlocillin] OR [mh Minocycline] OR [mh "Penicillin G Benzathine"] OR [mh "Penicillin G"] OR [mh "Penicillin G Procaine"] OR [mh Piperacillin] OR [mh Pivampicillin] OR [mh Sulbenicillin] OR [mh Talampicillin] OR [mh Tetracycline] OR ([mh /dt] OR [mh /th])	322007
#5	antibiotic*:ti,ab OR anti-biot*:ti,ab OR ampicillin:ti,ab OR amoxicillin:ti,ab OR azlocillin:ti,ab OR benzathine:ti,ab OR benzylpenicillin:ti,ab OR carbenicillin:ti,ab OR carfecillin:ti,ab OR ceftriaxone:ti,ab OR doxycycline:ti,ab OR erythromycin:ti,ab OR mezlocillin:ti,ab OR minocycline:ti,ab OR penicillin:ti,ab OR piperacillin:ti,ab OR pivampicillin:ti,ab OR procaine:ti,ab OR sulbenicillin:ti,ab OR talampicillin:ti,ab OR tetracycline:ti,ab OR manag*:ti,ab OR outcome:ti,ab OR treat*:ti,ab	1158963
#6	#4 OR #5	1228548
#7	[mh Pregnancy] OR [mh "Pregnancy Complications"] OR [mh "Pregnancy Outcome"] OR [mh "Pregnancy Trimester, First"] OR [mh "Pregnancy Trimester, Second"] OR [mh "Pregnancy Trimester, Third"] OR [mh "Pregnant Women"] OR [mh "Prenatal Care"] OR [mh "Postpartum Period"]	29294
#8	antenatal*:ti,ab OR ante-natal*:ti,ab OR antepartum:ti,ab OR ante-partum:ti,ab OR birth*:ti,ab OR childbirth:ti,ab OR deliver*:ti,ab OR gestation*:ti,ab OR perinatal*:ti,ab OR peri-natal*:ti,ab OR peripartum:ti,ab OR peri-partum:ti,ab OR postnatal*:ti,ab OR post-natal*:ti,ab OR postpartum:ti,ab OR post-partum:ti,ab OR pregnan*:ti,ab OR prenatal*:ti,ab OR pre-natal*:ti,ab OR prepartum:ti,ab OR pre-partum:ti,ab OR puerper*:ti,ab OR trimester*:ti,ab	171337
#9	[mh "Infectious Disease Transmission, Vertical"] OR [mh "Maternal-Fetal Exchange"]	920
#10	((fetomaternal*:ti,ab OR foetomaternal*:ti,ab OR feto-maternal*:ti,ab OR foeto-maternal*:ti,ab OR mother*:ti,ab OR MTC:ti,ab OR maternal*:ti,ab OR mother*:ti,ab OR vertical*:ti,ab) NEAR/3 (infect*:ti,ab OR transmission*:ti,ab OR transmitted:ti,ab))	1790
#11	[mh "Embryo, Mammalian"] OR embryo*:ti,ab	8704
#12	[mh Fetus] OR fetus*:ti,ab OR foetus*:ti,ab OR fetal:ti,ab OR foetal:ti,ab	15170
#13	[mh Infant] OR [mh "Infant, Newborn"] OR [mh "Infant, Low Birth Weight"] OR [mh "Infant, Small for Gestational Age"] OR [mh "Infant, Very Low Birth Weight"] OR [mh "Infant, Extremely Low Birth Weight"] OR [mh "Infant, Premature"] OR [mh "Infant, Extremely Premature"] OR (infant*:ti,ab OR neonat*:ti,ab OR newborn*:ti,ab)	77771
#14	[mh "Abnormalities, Drug-Induced"] OR [mh "Congenital Abnormalities"] OR [mh /ab] OR [mh /ae] OR [mh /cn] OR [mh /mo] OR [mh /pc] OR abnormal*:ti,ab OR adverse:ti,ab OR anomal*:ti,ab OR congenital*:ti,ab,kw OR defect*:ti,ab OR delay*:ti,ab OR deformit*:ti,ab OR disab*:ti,ab OR malform*:ti,ab	499922
#15	[mh "Maternal Mortality"] OR ((maternal:ti,ab OR parturient*:ti,ab) NEAR/2 (death*:ti,ab OR morbid*:ti,ab OR mortal*:ti,ab))	1981
#16	[mh "Abortion, Spontaneous"] OR [mh "Abortion, Threatened"] OR [mh "Embryo Loss"] OR [mh Stillbirth] OR (miscarriag*:ti,ab OR ((spontaneous*:ti,ab OR threaten*:ti,ab) NEAR/2 abortion*:ti,ab) OR stillborn:ti,ab OR stillbirth*:ti,ab)	4806
#17	[mh "Fetal Mortality"] OR [mh "Infant Mortality"] OR [mh "Perinatal Mortality"] OR ((baby:ti,ab OR babies:ti,ab OR infant*:ti,ab OR neonat*:ti,ab OR neo-nat*:ti,ab OR newborn*:ti,ab OR new-born*:ti,ab) NEAR/2 (death*:ti,ab OR morbid*:ti,ab OR mortal*:ti,ab))	4692
#18	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	648577
#19	#3 AND #6 AND #18	298
#20	#19 NOT ("case reports":pt OR news:pt OR "case report":ti OR boy:ti OR girl:ti OR man:ti OR mother:ti OR patient:ti OR woman:ti)	239
#21	#20 limited to publication dates 2017-2023	111

Grey Literature

ClinicalTrials.gov, 3/9/2023

ClinicalTrials.gov suggested the following search, which will cover all KQs and the CQ:

66 studies found for: Syphilis OR EXPAND[Concept] "Treponema Pallidum" OR EXPAND[Concept] "t. pallidum" | Last update posted from January 1, 2017, to March 9, 2023.

(Also searched for Treponemal infections)

Saved all 66 to EndNote.

World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) Advanced Search, 3/9/2023

Condition box:

Syphilis OR "Treponema Pallidum" OR "t. pallidum" OR “Treponemal infections”

Recruitment status: ALL

Date of registration is from January 1, 2017, through March 9, 2023.

56 trials found, all saved to EndNote. Reviewed manual duplicate detection and removed 18 for a total of 38.

Google Scholar Advanced Search in Durham, North Carolina, 3/9/2023

pregnan* AND (Syphilis OR "Treponema Pallidum" OR "t. pallidum" OR “Treponemal infections”)

Limited to articles between 2017 and 2023.

Approximately 17,600 results.

Sorted by relevance and saved first 50 records. Imported to published lit library to remove duplicates; 15 unique saved and imported to EndNote library for grey literature.

Google Advanced Search in Durham, North Carolina, 3/9/2023

pregnan* Syphilis OR "Treponema Pallidum" OR "t. pallidum" OR “Treponemal OR infections” -prevalence site:.gov

Searched English pages.

January 1, 2017, to March 9, 2023.

About 97,300 results (0.55 seconds); saved first ~50 links.

Browsed National Institute of Allergy and Infectious Diseases (NIAID) Website, 3/9/2023: Sexually Transmitted Diseases | National Institutes of Health: NIAID

Nothing relevant found.

Epistemonikos Advanced Search for Broad Syntheses/Systematic Reviews, 3/9/2023:

(title:(pregnan* AND (Syphilis OR "Treponema Pallidum" OR "t. pallidum" OR "Treponemal infections")) OR abstract:(pregnan* AND (Syphilis OR "Treponema Pallidum" OR "t. pallidum" OR "Treponemal infections"))) AND (screen* OR treat* OR intervention* OR harm* or Adverse*) NOT prevalence

Limited to published and added to Epistemonikos between January 1, 2017, and March 9, 2023.

Nine results; imported four that were not already in the published literature results into the grey literature library.

Trip Medical Database Search, 3/9/2023:

For ongoing systematic reviews, and guidelines.

Searched in population: pregnan* AND (syphilis OR "treponema pallidum" OR "t. pallidum" OR "treponemal infections") from_date: 2017

12 results for ongoing systematic reviews.

Six results (five saved) for guidelines.

Ovid MEDLINE®, Screening Search, 7/25/2023

Search Number	Query	Results
1	Syphilis/ or Syphilis, Congenital/ or syphil*.ti,ab.	37505
2	Treponema Pallidum/ or ("treponema pallidum" or "t. pallidum").ti,ab.	6567
3	or/1-2	39327
4	Mass Screening/ or Maternal Serum Screening Tests/ or (assay$1 or immunoassay$1 or immuno-assay$1 or screen* or test*).ti,ab. or di.fs.	7623871
5	Syphilis Serodiagnosis/ or Fluorescent Treponemal Antibody-Absorption Test/	5425
6	((nontreponemal or non-treponemal or treponema or treponemal) adj3 (test$3 or assay$1 or immunoassay* or immuno-assay*)).ti,ab.	1651
7	("Venereal disease research laboratory" or VDRL).ti,ab.	1627
8	("Toluidine red unheated serum" or Tolul* or TRUST).ti,ab.	47042
9	("Rapid plasma reagin" or RPR or reagin).ti,ab.	2491
10	("Fluorescent treponemal antibody absorption" or fluorescen* or FTA-ABS or IgM-FTA-ABS).ti,ab.	539903
11	("Treponema pallidum particle agglutination" or "t. pallidum particle agglutination" or TPPA or agglutination).ti,ab.	22339
12	("treponema pallidum hemagglutination assay" or haemagglutination or hemagglutination or TPHA or MHA-TP or AMHA-TP).ti,ab.	22237
13	("enzyme immunoassay*" or "enzyme-linked immunosorbent" or EIA or ELISA or enzyme).ti,ab.	993184
14	(CIA or CMIA or MBIA or ((chemiluminescen* or enzyme or microbead) adj3 (assay* or immunoassay* or immuno-assay* or test*)) or chemiluminescen*).ti,ab.	183381
15	(positiv* or "reverse sequence" or seroconver* or sero-conv* or serodiagnos* or sero-diagnos* or seronegativ* or sero-negativ* or seropositiv* or sero-positiv* or (serologic* adj2 (screen* or diagnos*))).ti,ab.	2221095
16	or/4-15	9919457
17	Pregnancy/ or Pregnancy Trimester, First/ or Pregnancy Trimester, Second/ or Pregnancy Trimester, Third/ or Pregnant Women/ or Prenatal Care/ or Prenatal Diagnosis/ or Pregnancy Outcome/ or Pregnancy Complications, Infectious/ or Infectious Disease Transmission, Vertical/	1001108
18	(antenatal* or ante-natal* or antepartum or ante-partum or congenital* or delivery or gestation* or perinatal* or peri-natal* or peripartum or peri-partum or pregnan* or prenatal* or pre-natal* or prepartum or pre-partum or trimester$1).ti,ab.	1493038
19	((fetomaternal* or foetomaternal* or feto-maternal* or foeto-maternal* or mother-to-child or MTC or maternal* or mother$1 or vertical*) adj3 (transmission$1 or transmitted)).ti,ab.	20078
20	or/17-19	1892174
21	and/3,16,20	3526
22	21	3526
23	limit 22 to (english language and yr="2008 -Current")	1472
24	23 not ((exp Animals/ not Humans/) or (animal model* or bitch$2 or bovine or canine or capra or cat or cats or cattle or cow$1 or dog$1 or equine or ewe$1 or feline or goat$1 or hamster$1 or horse$1 or invertebrate$1 or macaque$1 or mare$1 or mice or monkey$1 or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate$1 or rabbit$1 or rat$1 or rattus or rhesus or rodent* or sheep or simian or sow$1 or vertebrate$1 or whale* or zebrafish).ti.)	1463
25	24 not (case report or news).pt.	1458
26	limit 25 to dt=20220711-20230725	129

Ovid MEDLINE®, Treatment Search, 7/25/2023

Search Number	Query	Results
1	Syphilis/ or Syphilis, Congenital/ or syphil*.ti,ab.	37505
2	Treponema Pallidum/ or ("treponema pallidum" or "t. pallidum").ti,ab.	6567
3	or/1-2	39327
4	Mass Screening/ or Maternal Serum Screening Tests/ or (assay$1 or immunoassay$1 or immuno-assay$1 or screen* or test*).ti,ab. or di.fs.	7623871
5	Syphilis Serodiagnosis/ or Fluorescent Treponemal Antibody-Absorption Test/	5425
6	((nontreponemal or non-treponemal or treponema or treponemal) adj3 (test$3 or assay$1 or immunoassay* or immuno-assay*)).ti,ab.	1651
7	("Venereal disease research laboratory" or VDRL).ti,ab.	1627
8	("Toluidine red unheated serum" or Tolul* or TRUST).ti,ab.	47042
9	("Rapid plasma reagin" or RPR or reagin).ti,ab.	2491
10	("Fluorescent treponemal antibody absorption" or fluorescen* or FTA-ABS or IgM-FTA-ABS).ti,ab.	539903
11	("Treponema pallidum particle agglutination" or "t. pallidum particle agglutination" or TPPA or agglutination).ti,ab.	22339
12	("treponema pallidum hemagglutination assay" or haemagglutination or hemagglutination or TPHA or MHA-TP or AMHA-TP).ti,ab.	22237
13	("enzyme immunoassay*" or "enzyme-linked immunosorbent" or EIA or ELISA or enzyme).ti,ab.	993184
14	(CIA or CMIA or MBIA or ((chemiluminescen* or enzyme or microbead) adj3 (assay* or immunoassay* or immuno-assay* or test*)) or chemiluminescen*).ti,ab.	183381
15	(positiv* or "reverse sequence" or seroconver* or sero-conv* or serodiagnos* or sero-diagnos* or seronegativ* or sero-negativ* or seropositiv* or sero-positiv* or (serologic* adj2 (screen* or diagnos*))).ti,ab.	2221095
16	or/4-15	9919457
17	Pregnancy/ or Pregnancy Trimester, First/ or Pregnancy Trimester, Second/ or Pregnancy Trimester, Third/ or Pregnant Women/ or Prenatal Care/ or Prenatal Diagnosis/ or Pregnancy Outcome/ or Pregnancy Complications, Infectious/ or Infectious Disease Transmission, Vertical/	1001108
18	(antenatal* or ante-natal* or antepartum or ante-partum or congenital* or delivery or gestation* or perinatal* or peri-natal* or peripartum or peri-partum or pregnan* or prenatal* or pre-natal* or prepartum or pre-partum or trimester$1).ti,ab.	1493038
19	((fetomaternal* or foetomaternal* or feto-maternal* or foeto-maternal* or mother-to-child or MTC or maternal* or mother$1 or vertical*) adj3 (transmission$1 or transmitted)).ti,ab.	20078
20	or/17-19	1892174
21	and/3,16,20	3526
22	21	3526
23	limit 22 to (english language and yr="2008 -Current")	1472
24	23 not ((exp Animals/ not Humans/) or (animal model* or bitch$2 or bovine or canine or capra or cat or cats or cattle or cow$1 or dog$1 or equine or ewe$1 or feline or goat$1 or hamster$1 or horse$1 or invertebrate$1 or macaque$1 or mare$1 or mice or monkey$1 or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate$1 or rabbit$1 or rat$1 or rattus or rhesus or rodent* or sheep or simian or sow$1 or vertebrate$1 or whale* or zebrafish).ti.)	1463
25	24 not (case report or news).pt.	1458
26	limit 25 to dt=20220711-20230725	129
27	Syphilis/ or Syphilis, Congenital/ or syphil*.ti,ab.	37505
28	Treponema Pallidum/ or ("treponema pallidum" or "t. pallidum").ti,ab.	6567
29	or/27-28	39327
30	exp Anti-Bacterial Agents/ or Ampicillin/ or Amoxicillin/ or Azlocillin/ or Carbenicillin/ or Carfecillin/ or Ceftriaxone/ or Doxycycline/ or exp Erythromycin/ or Mezlocillin/ or Minocycline/ or Penicillin G Benzathine/ or Penicillin G/ or Penicillin G Procaine/ or Piperacillin/ or Pivampicillin/ or Sulbenicillin/ or Talampicillin/ or Tetracycline/ or (dt or th).fs.	5094673

Search Number	Query	Results
31	(antibiotic* or anti-biot* or ampicillin or amoxicillin or azlocillin or benzathine or benzylpenicillin or carbenicillin or carfecillin or ceftriaxone or doxycycline or erythromycin or mezlocillin or minocycline or penicillin or piperacillin or pivampicillin or procaine or sulbenicillin or talampicillin or tetracycline or manag* or outcome or treat*).ti,ab.	8471358
32	or/30-31	10577104
33	Pregnancy/ or exp Pregnancy Complications/ or Pregnancy Outcome/ or Pregnancy Trimester, First/ or Pregnancy Trimester, Second/ or Pregnancy Trimester, Third/ or Pregnant Women/ or Prenatal Care/ or Postpartum Period/	1031779
34	(antenatal* or ante-natal* or antepartum or ante-partum or birth* or childbirth or deliver* or gestation* or perinatal* or peri-natal* or peripartum or peri-partum or postnatal* or post-natal* or postpartum or post-partum or pregnan* or prenatal* or pre-natal* or prepartum or pre-partum or puerper* or trimester$1).ti,ab.	1784484
35	Infectious Disease Transmission, Vertical/ or Maternal-Fetal Exchange/	48602
36	((fetomaternal* or foetomaternal* or feto-maternal* or foeto-maternal* or mother* or MTC or maternal* or mother$1 or vertical*) adj3 (infect* or transmission$1 or transmitted)).ti,ab.	29322
37	Embryo, Mammalian/ or embryo*.ti,ab.	407547
38	Fetus/ or (fetus* or foetus* or fetal or foetal).ti,ab.	366610
39	Infant/ or Infant, Newborn/ or Infant, Low Birth Weight/ or Infant, Small for Gestational Age/ or Infant, Very Low Birth Weight/ or Infant, Extremely Low Birth Weight/ or Infant, Premature/ or Infant, Extremely Premature/ or (infant* or neonat* or newborn*).ti,ab.	1539378
40	Abnormalities, Drug-Induced/ or Congenital Abnormalities/ or congenital.hw. or (ab or ae or cn or mo or pc).fs. or (abnormal* or adverse or anomal* or congenital* or defect* or delay* or deformit* or disab* or malform*).ti,ab.	6358919
41	Maternal Mortality/ or ((maternal or parturient*) adj2 (death* or morbid* or mortal*)).ti,ab.	28176
42	Abortion, Spontaneous/ or Abortion, Threatened/ or Embryo Loss/ or Stillbirth/ or (miscarriag* or ((spontaneous* or threaten*) adj2 abortion*) or stillborn or stillbirth*).ti,ab.	60489
43	Fetal Mortality/ or Infant Mortality/ or Perinatal Mortality/ or ((baby or babies or infant* or neonat* or neo-nat* or newborn* or new-born*) adj2 (death* or morbid* or mortal*)).ti,ab.	67242
44	or/33-43	8925241
45	and/29,32,44	5164
46	limit 45 to yr="2018 -Current"	1045
47	46 not ((exp Animals/ not Humans/) or (animal model* or bitch$2 or bovine or canine or capra or cat or cats or cattle or cow$1 or dog$1 or equine or ewe$1 or feline or goat$1 or hamster$1 or horse$1 or invertebrate$1 or macaque$1 or mare$1 or mice or monkey$1 or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate$1 or rabbit$1 or rat$1 or rattus or rhesus or rodent* or sheep or simian or sow$1 or vertebrate$1 or zebrafish).ti.)	1036
48	47 not ((case reports or news).pt. or (case report or boy or girl or man or mother or patient or woman).ti.)	808
49	limit 48 to dt=20220711-20230725	152

Cochrane Library, Wiley, Screening Search, 7/25/2023

ID	Search	Hits
#1	[mh Syphilis] OR [mh "Syphilis, Congenital"] OR syphil*:ti,ab	827
#2	[mh "Treponema Pallidum"] OR "treponema pallidum":ti,ab OR "t. pallidum":ti,ab	99
#3	#1 OR #2	863
#4	[mh "Mass Screening"] OR [mh "Maternal Serum Screening Tests"] OR assay*:ti,ab OR immunoassay*:ti,ab OR immuno-assay*:ti,ab OR screen*:ti,ab OR test*:ti,ab OR [mh /DI]	537702
#5	[mh "Syphilis Serodiagnosis"] OR [mh "Fluorescent Treponemal Antibody-Absorption Test"]	27
#6	((nontreponemal:ti,ab OR non-treponemal:ti,ab OR treponema:ti,ab OR treponemal:ti,ab) NEAR/3 (test*:ti,ab OR assay*:ti,ab OR immunoassay*:ti,ab OR immuno-assay*:ti,ab))	36
#7	"Venereal disease research laboratory":ti,ab OR VDRL:ti,ab	57
#8	"Toluidine red unheated serum":ti,ab OR Tolul*:ti,ab OR TRUST:ti,ab	3810
#9	"Rapid plasma reagin":ti,ab OR RPR:ti,ab OR reagin:ti,ab	185
#10	"Fluorescent treponemal antibody absorption":ti,ab OR fluorescen*:ti,ab OR FTA-ABS:ti,ab OR IgM-FTA-ABS:ti,ab	4592
#11	"Treponema pallidum particle agglutination":ti,ab OR "t. pallidum particle agglutination":ti,ab OR TPPA:ti,ab OR agglutination:ti,ab	279
#12	"treponema pallidum hemagglutination assay":ti,ab OR haemagglutination:ti,ab OR hemagglutination:ti,ab OR TPHA:ti,ab OR MHA-TP:ti,ab OR AMHA-TP:ti,ab	1215
#13	("enzyme" NEXT immunoassay*):ti,ab OR "enzyme-linked immunosorbent":ti,ab OR EIA:ti,ab OR ELISA:ti,ab OR enzyme:ti,ab	30090
#14	(CIA:ti,ab OR CMIA:ti,ab OR MBIA:ti,ab OR ((chemiluminescen*:ti,ab OR enzyme:ti,ab OR microbead:ti,ab) NEAR/3 (assay*:ti,ab OR immunoassay*:ti,ab OR immuno-assay*:ti,ab OR test*:ti,ab)) OR chemiluminescen*:ti,ab)	6379
#15	(positiv*:ti,ab OR "reverse sequence":ti,ab OR seroconver*:ti,ab OR sero-conv*:ti,ab OR serodiagnos*:ti,ab OR sero-diagnos*:ti,ab OR seronegativ*:ti,ab OR sero-negativ*:ti,ab OR seropositiv*:ti,ab OR sero-positiv*:ti,ab OR (serologic*:ti,ab NEAR/2 (screen*:ti,ab OR diagnos*:ti,ab)))	166203
#16	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	651060
#17	[mh Pregnancy] OR [mh "Pregnancy Trimester, First"] OR [mh "Pregnancy Trimester, Second"] OR [mh "Pregnancy Trimester, Third"] OR [mh "Pregnant Women"] OR [mh "Prenatal Care"] OR [mh "Prenatal Diagnosis"] OR [mh "Pregnancy Outcome"] OR [mh "Pregnancy Complications, Infectious"] OR [mh "Infectious Disease Transmission, Vertical"]	31659
#18	(antenatal*:ti,ab OR ante-natal*:ti,ab OR antepartum:ti,ab OR ante-partum:ti,ab OR congenital*:ti,ab OR delivery:ti,ab OR gestation*:ti,ab OR perinatal*:ti,ab OR peri-natal*:ti,ab OR peripartum:ti,ab OR peri-partum:ti,ab OR pregnan*:ti,ab OR prenatal*:ti,ab OR pre-natal*:ti,ab OR prepartum:ti,ab OR pre-partum:ti,ab OR trimester*:ti,ab)	127028
#19	((fetomaternal*:ti,ab OR foetomaternal*:ti,ab OR feto-maternal*:ti,ab OR foeto-maternal*:ti,ab OR mother-to-child:ti,ab OR MTC:ti,ab OR maternal*:ti,ab OR mother*:ti,ab OR vertical*:ti,ab) NEAR/3 (transmission*:ti,ab OR transmitted:ti,ab))	1046
#20	#17 OR #18 OR #19	133667
#21	#3 AND #16 AND #20	175
#22	#21 NOT ("case report":pt OR news:pt)	175

Cochrane Library, Wiley, Treatment Search, 7/25/2023

ID	Search	Hits
#1	[mh Syphilis] OR [mh "Syphilis, Congenital"] OR syphil*:ti,ab	827
#2	[mh "Treponema Pallidum"] OR "treponema pallidum":ti,ab OR "t. pallidum":ti,ab	99
#3	#1 OR #2	863
#4	[mh "Anti-Bacterial Agents"] OR [mh Ampicillin] OR [mh Amoxicillin] OR [mh Azlocillin] OR [mh Carbenicillin] OR [mh Carfecillin] OR [mh Ceftriaxone] OR [mh Doxycycline] OR [mh Erythromycin] OR [mh Mezlocillin] OR [mh Minocycline] OR [mh "Penicillin G Benzathine"] OR [mh "Penicillin G"] OR [mh "Penicillin G Procaine"] OR [mh Piperacillin] OR [mh Pivampicillin] OR [mh Sulbenicillin] OR [mh Talampicillin] OR [mh Tetracycline] OR ([mh /dt] OR [mh /th])	388600
#5	antibiotic*:ti,ab OR anti-biot*:ti,ab OR ampicillin:ti,ab OR amoxicillin:ti,ab OR azlocillin:ti,ab OR benzathine:ti,ab OR benzylpenicillin:ti,ab OR carbenicillin:ti,ab OR carfecillin:ti,ab OR ceftriaxone:ti,ab OR doxycycline:ti,ab OR erythromycin:ti,ab OR mezlocillin:ti,ab OR minocycline:ti,ab OR penicillin:ti,ab OR piperacillin:ti,ab OR pivampicillin:ti,ab OR procaine:ti,ab OR sulbenicillin:ti,ab OR talampicillin:ti,ab OR tetracycline:ti,ab OR manag*:ti,ab OR outcome:ti,ab OR treat*:ti,ab	1210601
#6	#4 OR #5	1297776
#7	[mh Pregnancy] OR [mh "Pregnancy Complications"] OR [mh "Pregnancy Outcome"] OR [mh "Pregnancy Trimester, First"] OR [mh "Pregnancy Trimester, Second"] OR [mh "Pregnancy Trimester, Third"] OR [mh "Pregnant Women"] OR [mh "Prenatal Care"] OR [mh "Postpartum Period"]	36294
#8	antenatal*:ti,ab OR ante-natal*:ti,ab OR antepartum:ti,ab OR ante-partum:ti,ab OR birth*:ti,ab OR childbirth:ti,ab OR deliver*:ti,ab OR gestation*:ti,ab OR perinatal*:ti,ab OR peri-natal*:ti,ab OR peripartum:ti,ab OR peri-partum:ti,ab OR postnatal*:ti,ab OR post-natal*:ti,ab OR postpartum:ti,ab OR post-partum:ti,ab OR pregnan*:ti,ab OR prenatal*:ti,ab OR pre-natal*:ti,ab OR prepartum:ti,ab OR pre-partum:ti,ab OR puerper*:ti,ab OR trimester*:ti,ab	180043
#9	[mh "Infectious Disease Transmission, Vertical"] OR [mh "Maternal-Fetal Exchange"]	1087
#10	((fetomaternal*:ti,ab OR foetomaternal*:ti,ab OR feto-maternal*:ti,ab OR foeto-maternal*:ti,ab OR mother*:ti,ab OR MTC:ti,ab OR maternal*:ti,ab OR mother*:ti,ab OR vertical*:ti,ab) NEAR/3 (infect*:ti,ab OR transmission*:ti,ab OR transmitted:ti,ab))	1860
#11	[mh "Embryo, Mammalian"] OR embryo*:ti,ab	9074
#12	[mh Fetus] OR fetus*:ti,ab OR foetus*:ti,ab OR fetal:ti,ab OR foetal:ti,ab	16005
#13	[mh Infant] OR [mh "Infant, Newborn"] OR [mh "Infant, Low Birth Weight"] OR [mh "Infant, Small for Gestational Age"] OR [mh "Infant, Very Low Birth Weight"] OR [mh "Infant, Extremely Low Birth Weight"] OR [mh "Infant, Premature"] OR [mh "Infant, Extremely Premature"] OR (infant*:ti,ab OR neonat*:ti,ab OR newborn*:ti,ab)	82485
#14	[mh "Abnormalities, Drug-Induced"] OR [mh "Congenital Abnormalities"] OR [mh /ab] OR [mh /ae] OR [mh /cn] OR [mh /mo] OR [mh /pc] OR abnormal*:ti,ab OR adverse:ti,ab OR anomal*:ti,ab OR congenital*:ti,ab,kw OR defect*:ti,ab OR delay*:ti,ab OR deformit*:ti,ab OR disab*:ti,ab OR malform*:ti,ab	541333
#15	[mh "Maternal Mortality"] OR ((maternal:ti,ab OR parturient*:ti,ab) NEAR/2 (death*:ti,ab OR morbid*:ti,ab OR mortal*:ti,ab))	2094
#16	[mh "Abortion, Spontaneous"] OR [mh "Abortion, Threatened"] OR [mh "Embryo Loss"] OR [mh Stillbirth] OR (miscarriag*:ti,ab OR ((spontaneous*:ti,ab OR threaten*:ti,ab) NEAR/2 abortion*:ti,ab) OR stillborn:ti,ab OR stillbirth*:ti,ab)	5102
#17	[mh "Fetal Mortality"] OR [mh "Infant Mortality"] OR [mh "Perinatal Mortality"] OR ((baby:ti,ab OR babies:ti,ab OR infant*:ti,ab OR neonat*:ti,ab OR neo-nat*:ti,ab OR newborn*:ti,ab OR new-born*:ti,ab) NEAR/2 (death*:ti,ab OR morbid*:ti,ab OR mortal*:ti,ab))	4972
#18	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	696321
#19	#3 AND #6 AND #18	333
#20	#19 NOT ("case reports":pt OR news:pt OR "case report":ti OR boy:ti OR girl:ti OR man:ti OR mother:ti OR patient:ti OR woman:ti)	267

Grey Literature

ClinicalTrials.gov, 7/25/2023

30 Studies found for: Syphilis OR EXPAND[Concept] "Treponema Pallidum" OR EXPAND[Concept] "t. pallidum" | Last update posted from July 11, 2022, to July 25, 2023

Also searched for treponemal infections.

Saved all 30 to EndNote.

WHO ICTRP Advanced search, 7/25/2023

Condition box:

Syphilis OR "Treponema Pallidum" OR "t. pallidum" OR “Treponemal infections”

Recruitment status: ALL

Date of registration is between July 11, 2022, and July 25, 2023.

Nine trials found, all saved to EndNote. Reviewed manual duplicate detection and removed five for a total of four.

Appendix B2. Eligibility Criteria

Category	Include	Exclude
Populations	**KQs 1, 2:** Asymptomatic pregnant adolescents or adults, at any time during pregnancy, who are not known to have syphilis infection **KQ 3:** Studies of penicillin treatment in pregnant adolescents and adults with syphilis infection	**KQs 1, 2:** Persons known to have syphilis infection, have symptoms, or are not pregnant; studies conducted exclusively in populations in which syphilis screening may be part of disease management, such as persons living with HIV **KQ 3:** Studies of penicillin treatment in nonpregnant adolescents and adults; 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:** Syphilis treatment with penicillin outside of pregnancy
Comparisons	**KQ 1:** No screening **KQ 2:** No comparator necessary for studies on psychosocial harms; studies on screening test 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, and maternal or infant morbidity and mortality **KQ 2:** Harms of screening (e.g., false-positive and false-negative results, stigma, and psychosocial harms) **KQ 3:** Harms of treatment of syphilis with penicillin during pregnancy (e.g., allergic reaction, premature labor, Jarisch-Herxheimer reaction, fetal harms, and other maternal harms)	Cost-effectiveness or cost-related outcomes
Setting	Primary care–relevant and primary care–referable settings (e.g., obstetrics/gynecology clinics, prenatal clinics, ambulatory care, family planning clinics, health clinics in correctional facilities, and sexually transmitted infection clinics)	Nonprimary care or nonprimary care–referable settings
Country	Studies conducted in countries categorized as “high” or “very high” on the Human Development Index (as defined by the United Nations Development Programme in 2022)	Studies conducted in countries not categorized as “high” or “very high” on the Human Development Index (as defined by the United Nations Development Programme in 2022)
Study Designs	**KQ 1:** Randomized, controlled trials; before-after and ecologic studies reporting effect of implementing a widespread screening program with historical or geographic comparator; and 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; and systematic reviews and meta-analyses (of included study designs)	Narrative reviews, editorials, and case reports
Publication Language	English	Non-English studies
Quality	Good- or fair-quality studies	Poor-quality studies

Abbreviation: KQ=key question.

Randomized, Controlled Trials and Cohort Studies Criteria

- Initial assembly of comparable groups
- Randomized, controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements that are equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies will be graded "fair" if any or all of the following problems occur without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force procedure manual. Rockville, MD; 2021.[70]

Diagnostic Accuracy Studies Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of Ratings Based on Above Criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has a fatal flaw, such as uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force procedure manual. Rockville, MD; 2021.[70]

Appendix C. Excluded Articles

X1: Non-English Publication
X2: Ineligible Population
X3: Ineligible/No Screening
X4: Ineligible/No Treatment
X5: Ineligible/No Comparison
X6: Ineligible/No Outcome
X7: Ineligible Study Design
X8: Ineligible Country
X9: Poor Quality

1. Akhtar F, Rehman S. Prevention of congenital syphilis through antenatal screenings in Lusaka, Zambia: a systematic review. *Cureus*. 2018 Jan 16;10(1):e2078. doi: 10.7759/cureus.2078. PMID: 29560291. Exclusion Code: X7.

2. Althabe F, Chomba E, Tshefu AK, et al. A multifaceted intervention to improve syphilis screening and treatment in pregnant women in Kinshasa, Democratic Republic of the Congo and in Lusaka, Zambia: a cluster randomised controlled trial. *Lancet Glob Health*. 2019 May;7(5):e655-e63. doi: 10.1016/S2214-109X(19)30075-0. PMID: 30910531. Exclusion Code: X3.

3. Anugulruengkitt S, Yodkitudomying C, Sirisabya A, et al. Gaps in the elimination of congenital syphilis in a tertiary care center in Thailand. *Pediatr Int*. 2020 Mar;62(3):330-6. doi: 10.1111/ped.14132. PMID: 31886919. Exclusion Code: X7.

4. Barbosa de Andrade R, Pirkle CM, Sentell T, et al. Adequacy of prenatal care in Northeast Brazil: pilot data comparing attainment of standard care criteria for first-time adolescent and adult pregnant women. *Int J Womens Health*. 2020;12:1023-31. doi: 10.2147/IJWH.S272743. PMID: 33204175. Exclusion Code: X6.

5. Berrueta M, Cafferata ML, Mwenechanya M, et al. Syphilis screening and treatment in pregnant women in Kinshasa, Democratic Republic of the Congo and in Lusaka, Zambia: a cross-sectional study. *Gates Open Res*. 2017 Dec 8;1:13. doi: 10.12688/gatesopenres.12768.1. PMID: 29355227. Exclusion Code: X7.

6. Bian C, Qin Z, Zhang J, et al. Analysis of adverse pregnancy outcomes of pregnant women with syphilis and maternal-infant serological association in Changzhou, China, 2015-2019. *Stem Cells Int*. 2022;2022:9673850. doi: 10.1155/2022/9673850. PMID: 36106175. Exclusion Code: X6.

7. Biswas HH, Chew Ng RA, Murray EL, et al. Characteristics associated with delivery of an infant with congenital syphilis and missed opportunities for prevention—California, 2012 to 2014. *Sex Transm Dis*. 2018 Jul;45(7):435-41. doi: 10.1097/OLQ.0000000000000782. PMID: 29465666. Exclusion Code: X6.

8. Bowen VB, McDonald R, Grey JA, et al. High congenital syphilis case counts among U.S. infants born in 2020. *N Engl J Med*. 2021 Sep 16;385(12):1144-5. doi: 10.1056/NEJMc2111103. PMID: 34525291. Exclusion Code: X3.

9. Cavalcante PAdM, Pereira RBdL, Castro JGD. Syphilis in pregnancy and congenital syphilis in Palmas, Tocantins State, Brazil, 2007-2014. *Epidemiol Serv Saude*. 2017 Apr-Jun;26(2):255-64. doi: 10.5123/S1679-49742017000200003. PMID: 28492767. Exclusion Code: X6.

10. Caya C, Maheu-Giroux M, Xia Y, et al. Stopping syphilis transmission in Arctic communities through rapid diagnostic testing: the STAR study protocol. *PLoS One*. 2022;17(9):e0273713. doi: 10.1371/journal.pone.0273713. PMID: 36094912. Exclusion Code: X5.

11. Cesar JA, Camerini AV, Paulitsch RG, et al. Non-performance of serological tests for syphilis during prenatal care: prevalence and associated factors. *Rev Bras Epidemiol*. 2020;23:e200012. doi: 10.1590/1980-

549720200012. PMID: 32130400. Exclusion Code: X7.

12. Dalle J, Baumgarten VZ, Ramos MC, et al. Maternal syphilis and accomplishing sexual partner treatment: still a huge gap. *Int J STD AIDS*. 2017 Aug;28(9):876-80. doi: 10.1177/0956462416678710. PMID: 27810981. Exclusion Code: X6.

13. Dalle J, Ramos MC, Jimenez MF, et al. Oral desensitization to penicillin for the treatment of pregnant women with syphilis: a successful program. *Rev Bras Ginecol Obstet*. 2018 Jan;40(1):43-6. doi: 10.1055/s-0037-1606274. PMID: 28859210. Exclusion Code: X4.

14. Delvaux T, Ouk V, Samreth S, et al. Challenges and outcomes of implementing a national syphilis follow-up system for the elimination of congenital syphilis in Cambodia: a mixed-methods study. *BMJ Open*. 2023 Jan 10;13(1):e063261. doi: 10.1136/bmjopen-2022-063261. PMID: 36627153. Exclusion Code: X6.

15. Domingues RMSM, Leal MdC, Pereira APE, et al. Prevalence of syphilis and HIV infection during pregnancy in incarcerated women and the incidence of congenital syphilis in births in prison in Brazil. *Cad Saude Publica*. 2017 Nov 21;33(11):e00183616. doi: 10.1590/0102-311X00183616. PMID: 29166489. Exclusion Code: X6.

16. Dou LX, Wang Q, Wang XY, et al. [Serologic surveillance indicators analysis among syphilis-infected pregnant women in East China]. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2018 Jan 6;52(1):68-72. doi: 10.3760/cma.j.issn.0253-9624.2018.01.013. PMID: 29334711. Exclusion Code: X1.

17. Du L, Li Y, Jin H, et al. Prevent Mother-to-Child Transmission (PMTCT) programs and enhancement of maternal healthcare infrastructure to improve early detection of maternal syphilis in Shanghai, China. *Int J Environ Res Public Health*. 2019 Mar 20;16(6):1002. doi: 10.3390/ijerph16061002. PMID: 30897696. Exclusion Code: X5.

18. Duan C-C, Zhang X-H, Li S-S, et al. Risk factors for stillbirth among pregnant women infected with syphilis in the Zhejiang Province of China, 2010-2016. *Can J Infect Dis Med Microbiol*. 2021;2021:8877962. doi: 10.1155/2021/8877962. PMID: 33603937. Exclusion Code: X6.

19. Dunaway SB, Maxwell CL, Tantalo LC, et al. Neurosyphilis treatment outcomes after intravenous penicillin G versus intramuscular procaine penicillin plus oral probenecid. *Clin Infect Dis*. 2020 Jul 11;71(2):267-73. doi: 10.1093/cid/ciz795. PMID: 31504293. Exclusion Code: X2.

20. Estrada V, Santiago E, Cabezas I, et al. Tolerability of IM penicillin G benzathine diluted or not with local anesthetics, or different gauge needles for syphilis treatment: a randomized clinical trial. *BMC Infect Dis*. 2019 Oct 23;19(1):883. doi: 10.1186/s12879-019-4490-5. PMID: 31646969. Exclusion Code: X2.

21. Fica A, Montiel P, Saavedra S, et al. The resurgence of syphilis among pregnant women in southern Chile. *Rev Med Chil*. 2021 Mar;149(3):348-56. doi: 10.4067/s0034-98872021000300348. PMID: 34479313. Exclusion Code: X7.

22. Furness A, Kalicinsky C, Rosenfield L, et al. Penicillin skin testing, challenge, and desensitization in pregnancy: a systematic review. *J Obstet Gynaecol Can*. 2020 Oct;42(10):1254-61 e3. doi: 10.1016/j.jogc.2019.11.067. PMID: 32005632. Exclusion Code: X7.

23. Garcia-Cisneros S, Herrera-Ortiz A, Olamendi-Portugal M, et al. Re-emergence of syphilis in women of reproductive age and its association with the increase in congenital syphilis in Mexico during 2010-2019: an ecological study. *BMC Infect Dis*. 2021 Sep 23;21(1):992. doi: 10.1186/s12879-021-06680-w. PMID: 34556026. Exclusion Code: X6.

24. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. *N Engl J Med*. 2020 Feb 27;382(9):845-54. doi: 10.1056/NEJMra1901593. PMID: 32101666. Exclusion Code: X7.

25. Gong T, Shao Y, Liu J, et al. Treatment evaluation to improve preventing mother to child transmission among women with syphilis. *Sci Rep*. 2019 Dec 20;9(1):19547. doi: 10.1038/s41598-019-56095-6. PMID: 31862938. Exclusion Code: X6.

26. Gratrix J, Karwacki J, Eagle L, et al. Outcomes of infectious syphilis in pregnant patients and maternal factors associated with congenital syphilis diagnosis, Alberta, 2017-2020. *Can Commun Dis Rep*. 2022 Feb 24;48(2-3):61-7. doi: 10.14745/ccdr.v48i23a02. PMID: 35342367. Exclusion Code: X6.

27. Hadjadj J, Gaube G, Groh M, et al. The clinical spectrum and outcome of uveomeningitis: a comprehensive analysis of 110 cases. *Ocul Immunol Inflamm*. 2022 Aug;30(6):1489-94. doi: 10.1080/09273948.2021.1898000. PMID: 33974484. Exclusion Code: X2.

28. Herbst de Cortina S, Bristow CC, Humphries R, et al. Laboratory evaluation of a smartphone-based electronic reader of rapid dual point-of-care tests for antibodies to human immunodeficiency virus and treponema pallidum infections. *Sex Transm Dis*. 2017 Jul;44(7):412-6. doi: 10.1097/OLQ.0000000000000628. PMID: 28604483. Exclusion Code: X3.

29. Hersh AR, Megli CJ, Caughey AB. Comparing syphilis screening protocols in the third trimester of pregnancy: a cost-effective analysis. *Am J Obstet Gynecol*. 2017;216(1 Supplement 1):S183-S4. PMID: CN-01304048. Exclusion Code: X6.

30. Hersh AR, Megli CJ, Caughey AB. Repeat screening for syphilis in the third trimester of pregnancy: a cost-effectiveness analysis. *Obstet Gynecol*. 2018 Sep;132(3):699-707. doi: 10.1097/AOG.0000000000002795. PMID: 30095767. Exclusion Code: X6.

31. Ho YA, Allen K, Tao G, et al. Provider adherence to syphilis testing guidelines among stillbirth cases. *Sex Transm Dis*. 2020 Oct;47(10):686-90. doi: 10.1097/OLQ.0000000000001230. PMID: 32936603. Exclusion Code: X6.

32. Holden J, Goheen J, Jett-Goheen M, et al. An evaluation of the SD Bioline HIV/syphilis duo test. *Int J STD AIDS*. 2018 Jan;29(1):57-62. doi: 10.1177/0956462417717649. PMID: 28661234. Exclusion Code: X2.

33. Hong F-C, Wu X-B, Yang F, et al. Risk of congenital syphilis (CS) following treatment of maternal syphilis: results of a CS control program in China. *Clin Infect Dis*. 2017 2017/04/27;65(4):588-94. doi: 10.1093/cid/cix371. PMID: 28444157. Exclusion Code: X6.

34. Hu F, Guo S-J, Lu J-J, et al. The effect of different treatment regimens and multiple risk factors on adverse pregnancy outcomes among syphilis-seropositive women in Guangzhou: a retrospective cohort study. *Biomed Res Int*. 2020;2020:7626274. doi: 10.1155/2020/7626274. PMID: 32462016. Exclusion Code: X6.

35. Hui BB, Ward JS, Guy R, et al. Impact of testing strategies to combat a major syphilis outbreak among Australian Aboriginal and Torres Strait Islander Peoples: a mathematical modeling study. *Open Forum Infect Dis*. 2022 May;9(5):ofac119. doi: 10.1093/ofid/ofac119. PMID: 35474757. Exclusion Code: X2.

36. Huntington S, Weston G, Seedat F, et al. Repeat screening for syphilis in pregnancy as an alternative screening strategy in the UK: a cost-effectiveness analysis. *BMJ Open*. 2020 Nov 19;10(11):e038505. doi: 10.1136/bmjopen-2020-038505. PMID: 33444184. Exclusion Code: X6.

37. Ikuta T, Abe S, Suga S, et al. Administration of intravenous benzylpenicillin in 13 infants born to mothers with syphilis infection: A case series. *J Infect Chemother*. 2021 Nov;27(11):1662-4. doi: 10.1016/j.jiac.2021.06.022. PMID: 34246542. Exclusion Code: X2.

38. Jin J. Screening for syphilis in pregnant women. *JAMA*. 2018 Sep 4;320(9):948. doi: 10.1001/jama.2018.12119. PMID: 30193278. Exclusion Code: X7.

39. Johnson KA, Burghardt NO, Snyder RE, et al. Comparing 7-day versus 6-8-day

penicillin treatment intervals among pregnant people with syphilis of late or unknown duration: no difference found in incidence of congenital syphilis. *Open Forum Infect Dis*. 2023 Jun;10(6):ofad300. doi: 10.1093/ofid/ofad300. PMID: 37389226. Exclusion Code: X6.

40. Kasaro MP, Bosomprah S, Taylor MM, et al. Field performance evaluation of dual rapid HIV and syphilis tests in three antenatal care clinics in Zambia. *Int J STD AIDS*. 2019 Mar;30(4):323-8. doi: 10.1177/0956462418800872. PMID: 30472926. Exclusion Code: X7.

41. Kelly M, Hendry S, Norton R. The utility of the syphilis enzyme immunoassay IgM in the diagnosis of congenital syphilis. *Diagn Microbiol Infect Dis*. 2020 Nov;98(3):115152. doi: 10.1016/j.diagmicrobio.2020.115152. PMID: 32866939. Exclusion Code: X6.

42. Kidd S, Bowen VB, Torrone EA, et al. Use of national syphilis surveillance data to develop a congenital syphilis prevention cascade and estimate the number of potential congenital syphilis cases averted. *Sex Transm Dis*. 2018 Sep;45(9S Suppl 1):S23-S8. doi: 10.1097/OLQ.0000000000000838. PMID: 29543623. Exclusion Code: X6.

43. Laktabai J, Mobley VL, Prudhomme-O'Meara W, et al. Associations between antenatal syphilis test results and adverse pregnancy outcomes in western Kenya. *Am J Trop Med Hyg*. 2022 Aug 17;107(2):401-6. doi: 10.4269/ajtmh.22-0083. PMID: 35895406. Exclusion Code: X6.

44. Langendorf C, Lastrucci C, Sanou-Bicaba I, et al. Dual screen and confirm rapid test does not reduce overtreatment of syphilis in pregnant women living in a non-venereal treponematoses endemic region: a field evaluation among antenatal care attendees in Burkina Faso. *Sex Transm Infect*. 2019 Sep;95(6):402-4. doi: 10.1136/sextrans-2018-053722. PMID: 30580325. Exclusion Code: X8.

45. Le Chevalier de Preville M, Alessandri JL, Traversier N, et al. Evaluation of the management of pregnancies and infants at risk for congenital syphilis: La Reunion, 2008 to 2014. *J Perinatol*. 2017 Feb;37(2):116-21. doi: 10.1038/jp.2016.158. PMID: 27711044. Exclusion Code: X6.

46. Li H, Tan J, Luo Z, et al. Standardized treatment and determinants on 9,059 syphilis-infected pregnant women during 2015-2018 in Hunan, China. *Sci Rep*. 2020 Jul 21;10(1):12026. doi: 10.1038/s41598-020-69070-3. PMID: 32694571. Exclusion Code: X6.

47. Li Y, Jiang G. Azithromycin vs penicillin G benzathine for early syphilis: a meta-analysis of randomized controlled trials. *Dermatol Ther*. 2020 Nov;33(6):e14025. doi: 10.1111/dth.14025. PMID: 32677163. Exclusion Code: X2.

48. Li Y, Zhu L, Du L, et al. Effects on preventing mother-to-child transmission of syphilis and associated adverse pregnant outcomes: a longitudinal study from 2001 to 2015 in Shanghai, China. *BMC Infect Dis*. 2017 Sep 18;17(1):626. doi: 10.1186/s12879-017-2721-1. PMID: 28923018. Exclusion Code: X5.

49. Lin JS, Eder M, Bean S. Screening for syphilis infection in pregnant women: a reaffirmation evidence update for the U.S. Preventive Services Task Force Agency for Healthcare Research and Quality. Report No. 18-05238-EF-1. Rockville, MD: 2018. https://www.ncbi.nlm.nih.gov/books/NBK525910/ Exclusion Code: X7.

50. Lin JS, Eder ML, Bean SI. Screening for syphilis infection in pregnant women: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018 Sep 4;320(9):918-25. doi: 10.1001/jama.2018.7769. PMID: 30193282. Exclusion Code: X7.

51. Liu H, Chen N, Yu J, et al. Syphilis-attributable adverse pregnancy outcomes in China: a retrospective cohort analysis of 1187 pregnant women with different syphilis treatment. *BMC Infect Dis*. 2019 Mar 29;19(1):292. doi: 10.1186/s12879-019-3896-4. PMID: 30925908. Exclusion Code: X6.

52. Lodiongo DK, K Bior B, W Dumo G, et al. Field evaluation of SD BIOLINE

HIV/Syphilis Duo assay among pregnant women attending routine antenatal care in Juba, South Sudan. *PLoS One*. 2018;13(10):e0205383. doi: 10.1371/journal.pone.0205383. PMID: 30304043. Exclusion Code: X5.

53. Macedo VCd, Lira PICd, Frias PGd, et al. Risk factors for syphilis in women: case-control study. *Rev Saude Publica*. 2017 Aug 17;51:78. doi: 10.11606/S1518-8787.2017051007066. PMID: 28832758. Exclusion Code: X6.

54. Madan RP. Syphilis screening in pregnant women: Discordant results require careful confirmation. *J Pediatr*. 2020 Apr;219:1-3. doi: 10.1016/j.jpeds.2020.02.028. PMID: 32204795. Exclusion Code: X7.

55. Matthias JM, Rahman MM, Newman DR, et al. Effectiveness of prenatal screening and treatment to prevent congenital syphilis, Louisiana and Florida, 2013-2014. *Sex Transm Dis*. 2017 Aug;44(8):498-502. doi: 10.1097/OLQ.0000000000000638. PMID: 28703731. Exclusion Code: X5.

56. Morgan J, Mathew T, Azariah S. Eliminating congenital syphilis from Aotearoa New Zealand. *N Z Med J*. 2021 Oct 22;134(1544):8-12. PMID: 34695089. Exclusion Code: X7.

57. Mori H, Shibata E, Kondo E, et al. The incidence of Jarisch-Herxheimer reactions and associated risk factors in pregnant women and nonpregnant women: a retrospective chart review at a university hospital in Japan. *J Obstet Gynaecol Res*. 2023 May;49(5):1435-42. doi: 10.1111/jog.15583. PMID: 36854284. Exclusion Code: X7.

58. Neblett Fanfair R, Tao G, Owusu-Edusei K, et al. Suboptimal prenatal syphilis testing among commercially insured women in the United States, 2013. *Sex Transm Dis*. 2017 Apr;44(4):219-21. doi: 10.1097/OLQ.0000000000000569. PMID: 28282647. Exclusion Code: X6.

59. Nishijima T, Kawana K, Fukasawa I, et al. Effectiveness and tolerability of oral amoxicillin in pregnant women with active syphilis, Japan, 2010-2018. *Emerg Infect Dis*. 2020 Jun;26(6):1192-200. doi: 10.3201/eid2606.191300. PMID: 32441638. Exclusion Code: X4.

60. Norwitz ER, Hicks CB. Syphilis in pregnancy. *UpToDate*. 2021;19:2021. Exclusion Code: X7.

61. O'Connor NP, Burke PC, Worley S, et al. Outcomes after positive syphilis screening. *Pediatrics*. 2022 Sep 1;150(3):e2022056457. doi: 10.1542/peds.2022-056457. PMID: 36000336. Exclusion Code: X9.

62. Ogundipe OF, Van den Bergh R, Thierry B, et al. Better care for babies: the added value of a modified reverse syphilis testing algorithm for the treatment of congenital syphilis in a maternity hospital in Central African Republic. *BMC Pediatr*. 2019 Aug 15;19(1):284. doi: 10.1186/s12887-019-1622-4. PMID: 31416437. Exclusion Code: X7.

63. Olugbenga I, Taiwo O, Laverty M, et al. Clinic-based evaluation study of the diagnostic accuracy of a dual rapid test for the screening of HIV and syphilis in pregnant women in Nigeria. *PLoS One*. 2018;13(7):e0198698. doi: 10.1371/journal.pone.0198698. PMID: 29990336. Exclusion Code: X5.

64. Patel CG, Huppert JS, Tao G. Provider adherence to syphilis testing recommendations for women delivering a stillbirth. *Sex Transm Dis*. 2017 Nov;44(11):685-90. doi: 10.1097/OLQ.0000000000000656. PMID: 28876321. Exclusion Code: X6.

65. Patwardhan VV, Bhattar S, Bhalla P, et al. Seroprevalence of syphilis by VDRL test and biological false positive reactions in different patient populations: is it alarming? Our experience from a tertiary care center in India. *Indian J Sex Transm Dis AIDS*. 2020 Jan-Jun;41(1):43-6. doi: 10.4103/0253-7184.194317. PMID: 33062981. Exclusion Code: X2.

66. Pereira LE, McCormick J, Dorji T, et al. Laboratory evaluation of a commercially available rapid syphilis test. *J Clin Microbiol*. 2018 Oct;56(10):e00832-18. doi:

10.1128/JCM.00832-18. PMID: 30021825. Exclusion Code: X9.

67. Perez F, Mayaud P. One step in the right direction: improving syphilis screening and treatment in pregnant women in Africa. *Lancet Glob Health*. 2019 May;7(5):e550-e1. doi: 10.1016/S2214-109X(19)30064-6. PMID: 30910530. Exclusion Code: X7.

68. Pham MN, Ho H-E, Desai M. Penicillin desensitization: treatment of syphilis in pregnancy in penicillin-allergic patients. *Ann Allergy Asthma Immunol*. 2017 May;118(5):537-41. doi: 10.1016/j.anai.2017.03.013. PMID: 28477786. Exclusion Code: X7.

69. Pinilla G, Campos L, Duran A, et al. Deteccion de Treponema pallidum subespecie pallidum para el diagnostico de sifilis congenita mediante reaccion en cadena de la polimerasa anidada. *Biomedica*. 2018 Mar 15;38(1):128-35. doi: 10.7705/biomedica.v38i0.3740. PMID: 29676865. Exclusion Code: X1.

70. Plotzker RE, Burghardt NO, Murphy RD, et al. Congenital syphilis prevention in the context of methamphetamine use and homelessness. *Am J Addict*. 2022 May;31(3):210-8. doi: 10.1111/ajad.13265. PMID: 35340101. Exclusion Code: X6.

71. Plotzker RE, Murphy RD, Stoltey JE. Congenital syphilis prevention: strategies, evidence, and future directions. *Sex Transm Dis*. 2018 Sep;45(9S Suppl 1):S29-S37. doi: 10.1097/OLQ.0000000000000846. PMID: 29624562. Exclusion Code: X7.

72. Qiao Y, Wang X, Wang Q, et al. Screening and treatment of syphilis for pregnant women - China, 2011-2018. *China CDC Wkly*. 2020 Jun 26;2(26):476-80. doi: 10.46234/ccdcw2020.123. PMID: 34594683. Exclusion Code: X6.

73. Qin QH, Xie XH, Yao H, et al. [Analysis of adverse pregnancy outcomes and related factors in pregnant women with syphilis infection in Guangxi of China, 2014-2018]. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2019 Dec 6;53(12):1284-9. doi: 10.3760/cma.j.issn.0253-9624.2019.12.015. PMID: 31795587. Exclusion Code: X1.

74. Ribeiro ADdC, Dan CdS, Santos AdS, et al. Neurosyphilis in Brazilian newborns: a health problem that could be avoided. *Rev Inst Med Trop Sao Paulo*. 2020;62:e82. doi: 10.1590/S1678-9946202062082. PMID: 33174978. Exclusion Code: X6.

75. Roberts CP, Raich A, Stafylis C, et al. Alternative treatments for syphilis during pregnancy. *Sex Transm Dis*. 2019 Oct;46(10):637-40. doi: 10.1097/OLQ.0000000000001050. PMID: 31517802. Exclusion Code: X7.

76. Rocha AFB, Araujo MAL, de Oliveira AKD, et al. Follow-up of infants with congenital syphilis during the penicillin shortage period. *J Pediatr (Rio J)*. 2023 May-Jun;99(3):302-8. doi: 10.1016/j.jped.2022.11.011. PMID: 36584977. Exclusion Code: X6.

77. Rocha AFB, Araujo MAL, Taylor MM, et al. Treatment administered to newborns with congenital syphilis during a penicillin shortage in 2015, Fortaleza, Brazil. *BMC Pediatr*. 2021 Apr 8;21(1):166. doi: 10.1186/s12887-021-02619-x. PMID: 33832443. Exclusion Code: X2.

78. Rogozinska E, Kara-Newton L, Zamora JR, et al. On-site test to detect syphilis in pregnancy: a systematic review of test accuracy studies. *BJOG*. 2017 Apr;124(5):734-41. doi: 10.1111/1471-0528.14455. PMID: 28029229. Exclusion Code: X3.

79. Round JM, Plitt SS, Eisenbeis L, et al. Examination of care milestones for preventing congenital syphilis transmission among syphilis-infected pregnant women in Alberta, Canada: 2017-2019. *Sex Transm Dis*. 2022 Jul 1;49(7):477-83. doi: 10.1097/OLQ.0000000000001640. PMID: 35470347. Exclusion Code: X6.

80. Schlueter A, Doshi U, Garg B, et al. Adverse pregnancy outcomes associated with maternal syphilis infection. *J Matern Fetal Neonatal Med*. 2022 Dec;35(25):5828-33. doi: 10.1080/14767058.2021.1895740. PMID: 33678095. Exclusion Code: X5.

81. Simms I, Tookey PA, Goh BT, et al. The incidence of congenital syphilis in the

United Kingdom: February 2010 to January 2015. *BJOG*. 2017 Jan;124(1):72-7. doi: 10.1111/1471-0528.13950. PMID: 26931054. Exclusion Code: X6.

82. Soares DC, Filho LCF, Souza Dos Reis H, et al. Assessment of the accuracy, usability and acceptability of a rapid test for the simultaneous diagnosis of syphilis and HIV infection in a real-life scenario in the Amazon Region, Brazil. *Diagnostics (Basel)*. 2023 Feb 20;13(4)doi: 10.3390/diagnostics13040810. PMID: 36832298. Exclusion Code: X3.

83. Solaimalai D, Rathore S, Beck MM, et al. Enzyme-linked immunosorbent assay (ELISA) versus Venereal Disease Research Laboratory test (VDRL) and rapid plasma reagin test (RPR) for screening of syphilis in pregnant women. *Int J Gynaecol Obstet*. 2020 Jul;150(1):103-7. doi: 10.1002/ijgo.13154. PMID: 32246772. Exclusion Code: X5.

84. Stafylis C, Mehta S, Tellalian D, et al. Clinical trial of cefixime for the treatment of early syphilis-preliminary results. *Sex Transm Dis*. 2020;47(9 SUPPL 2):S47-. PMID: CN-02212786. Exclusion Code: X2.

85. Swayze EJ, Nielsen-Saines K, Segura ER, et al. Failure to recognize low non-treponemal titer syphilis infections in pregnancy may lead to widespread under-treatment. *Int J Infect Dis*. 2021 Mar;104:27-33. doi: 10.1016/j.ijid.2020.12.076. PMID: 33401033. Exclusion Code: X6.

86. Taremwa IM, Twelwanike A, Mwambi B, et al. Laboratory assessment of SD Bioline HIV/Syphilis Duo Kit among pregnant women attending antenatal clinic Mayuge Health Center III, East central Uganda. *BMC Res Notes*. 2019 Apr 25;12(1):238. doi: 10.1186/s13104-019-4272-6. PMID: 31023349. Exclusion Code: X3.

87. Taylor M, Gliddon H, Nurse-Findlay S, et al. Revisiting strategies to eliminate mother-to-child transmission of syphilis. *Lancet Glob Health*. 2018 Jan;6(1):e26-e8. doi: 10.1016/S2214-109X(17)30422-9. PMID: 29241606. Exclusion Code: X7.

88. Thompson LA, Plitt SS, Gratrix J, et al. Prevalence of syphilis coinfection in hepatitis C virus positive prenatal patients from Alberta during a pilot routine screening program. *Can Liver J*. 2023 Feb;6(1):70-5. doi: 10.3138/canlivj-2022-0017. PMID: 36908571. Exclusion Code: X6.

89. Tong H, Heuer A, Walker N. The impact of antibiotic treatment for syphilis, chlamydia, and gonorrhoea during pregnancy on birth outcomes: a systematic review and meta-analysis. *J Glob Health*. 2023 Jun 16;13:04058. doi: 10.7189/jogh.13.04058. PMID: 37325885. Exclusion Code: X6.

90. Townsend CL, Francis K, Peckham CS, et al. Syphilis screening in pregnancy in the United Kingdom, 2010-2011: a national surveillance study. *BJOG*. 2017 Jan;124(1):79-86. doi: 10.1111/1471-0528.14053. PMID: 27219027. Exclusion Code: X6.

91. Tuddenham S, Ghanem KG. Management of adult syphilis: key questions to inform the 2021 Centers for Disease Control and Prevention sexually transmitted infections treatment guidelines. *Clin Infect Dis*. 2022 Apr 13;74(Suppl_2):S127-S33. doi: 10.1093/cid/ciac060. PMID: 35416969. Exclusion Code: X7.

92. Vescovi JS, Schuelter-Trevisol F. Increase of incidence of congenital syphilis in Santa Catarina state between 2007-2017: temporal trend analysis. *Rev Paul Pediatr*. 2020;38:e2018390. doi: 10.1590/1984-0462/2020/38/2018390. PMID: 32667471. Exclusion Code: X6.

93. Walker GJ, Walker D, Molano Franco D, et al. Antibiotic treatment for newborns with congenital syphilis. *Cochrane Database Syst Rev*. 2019 Feb 15;2(2):CD012071. doi: 10.1002/14651858.CD012071.pub2. PMID: 30776081. Exclusion Code: X2.

94. Wan Z, Zhang H, Xu H, et al. Maternal syphilis treatment and pregnancy outcomes: a retrospective study in Jiangxi Province, China. *BMC Pregnancy Childbirth*. 2020 Oct 27;20(1):648. doi: 10.1186/s12884-020-03314-y. PMID: 33109116. Exclusion Code: X6.

95. Warr AJ, Pintye J, Kinuthia J, et al. Sexually transmitted infections during pregnancy and subsequent risk of stillbirth and infant mortality in Kenya: a prospective study. *Sex Transm Infect*. 2019 Feb;95(1):60-6. doi: 10.1136/sextrans-2018-053597. PMID: 30228109. Exclusion Code: X6.

96. Withers K, Bristow C, Nguyen M, et al. A field evaluation of a rapid dual immunoassay for human immunodeficiency virus and syphilis antibodies, Hanoi, Vietnam. *Int J STD AIDS*. 2019 Feb;30(2):173-80. doi: 10.1177/0956462418802685. PMID: 30348065. Exclusion Code: X2.

97. Wu M, Seel M, Britton S, et al. Addressing the crisis of congenital syphilis: Key findings from an evaluation of the management of syphilis in pregnancy and the newborn in South-East Queensland. *Aust N Z J Obstet Gynaecol*. 2022 Feb;62(1):91-7. doi: 10.1111/ajo.13424. PMID: 34463955. Exclusion Code: X6.

98. Wu MX, Moore A, Seel M, et al. Congenital syphilis on the rise: the importance of testing and recognition. *Med J Aust*. 2021 Oct 18;215(8):345-6 e1. doi: 10.5694/mja2.51270. PMID: 34564860. Exclusion Code: X7.

99. Wu Y, Gao J, Qin J, et al. Mother-to-child transmission prevention of human immunodeficiency virus, syphilis and hepatitis B virus. *Women Birth*. 2019 Dec;32(6):570-8. doi: 10.1016/j.wombi.2018.11.004. PMID: 30497906. Exclusion Code: X5.

100. Xia C-S, Yue Z-H, Wang H. Evaluation of three automated Treponema pallidum antibody assays for syphilis screening. *J Infect Chemother*. 2018 Nov;24(11):887-91. doi: 10.1016/j.jiac.2018.07.017. PMID: 30197093. Exclusion Code: X2.

101. Yang X, Zhu X, Wang H, et al. The treatment of syphilis infection in pregnant women and the follow-up investigation and analysis of syphilis infection in children after delivery in Huaian City. *Panminerva Med*. 2022 Dec;64(4):569-71. doi: 10.23736/S0031-0808.21.04294-4. PMID: 33565759. Exclusion Code: X6.

102. Young N, Taegtmeyer M, Aol G, et al. Integrated point-of-care testing (POCT) of HIV, syphilis, malaria and anaemia in antenatal clinics in western Kenya: a longitudinal implementation study. *PLoS One*. 2018;13(7):e0198784. doi: 10.1371/journal.pone.0198784. PMID: 30028852. Exclusion Code: X5.

103. Zhang X, Shahum A, Yang L-G, et al. Outcomes from re-treatment and cerebrospinal fluid analyses in patients with syphilis who had serological nonresponse or lack of seroreversion after initial therapy. *Sex Transm Dis*. 2021 Jun 1;48(6):443-50. doi: 10.1097/OLQ.0000000000001321. PMID: 33093287. Exclusion Code: X2.

104. Zhang X, Yu Y, Yang H, et al. Surveillance of maternal syphilis in China: pregnancy outcomes and determinants of congenital syphilis. *Med Sci Monit*. 2018 Oct 29;24:7727-35. doi: 10.12659/MSM.910216. PMID: 30370903. Exclusion Code: X6.

Appendix D Table 1. Quality Ratings of Harms of Screening Studies (KQ 2)

First Author, Year	Index Test	Reference Standard	Bias Due to Patient Selection	Comments on Patient Selection	Applicability	Comments on Applicability	Bias Due to Index Test	Comments on Index Test	Applicability
Adhikari, 2020[44]	Traditional: RPR Reverse: ARCHITECT CIA	Traditional - BD Macro-Vue RPR + TP-PA Reverse sequence - ARCHITECT syphilis TP assay (Abbott Diagnostics, Abbott Park, IL) + RPR with TP-PA for discordant results	Unclear	Details on risk status and selection of pregnant adolescents and adults were unknown, leading to unclear risk of bias.	Unclear	Details on risk status and selection of pregnant adolescents and adults was unknown, leading to potential for spectrum bias. Catchment area has high syphilis prevalence.	NA	NA	NA
Chen, 2019[45]	LIAISON CIA	LIAISON automated chemiluminescence immunoassay (DiaSorin, Inc., Stillwater, MN). RPR (BectonDickinson, Franklin Lankes, NJ). FTA-ABS (Zeus Sceintific, Inc., Branchburg, NJ)	No	None	Unclear	Details on risk status and selection of pregnant adolescents and adults was unknown, leading to potential for spectrum bias. Inner city Baltimore has high syphilis prevalence.	NA	NA	NA
Christenson, 2018[48]	Elecsys syphilis immunoassay	IMMULITE 2000 syphilis screen assay (Siemens Healthcare), the RPR nontreponemal specific assay (Becton, Dickinson and Company), and the TP-PA Treponema-specific assay (Fujirebio)	Unclear	Details on risk status and selection of pregnant women were unknown, leading to unclear risk of bias.	Unclear	Setting and risk of pregnant adolescents and adults not reported.	Unclear	No information on blinding to reference standard results.	High
O'Connor, 2022[71]	NA	(1) Traditional sequence: RPR with fluorescent treponemal antibody absorption test or a *T. pallidum* antibody; (2) Reverse sequence: syphilis IgG assay (BioPlexTM2200 syphilis IgG, Bio-Rad assay) with enhanced cutoffs ($\leq$0.8 nonreactive, 0.9–5.9 weak reactive, and $\geq$6.0 reactive). In October 2019, reverse screening was introduced using a syphilis IgM and IgG	No	None	High	None	NA	NA	NA

Appendix D Table 1. Quality Ratings of Harms of Screening Studies (KQ 2)

First Author, Year	Index Test	Reference Standard	Bias Due to Patient Selection	Comments on Patient Selection	Applicability	Comments on Applicability	Bias Due to Index Test	Comments on Index Test	Applicability
		assay (Bio-PlexTM2200 syphilis total IgM and IgG Bio-Rad) using the manufacturer's cutoffs (<0.8 nonreactive, 0.9–1.1 weak reactive, and ≥1.1 reactive)							
Pereira, 2018[54]	Syphilis Health Check (SHC) (Trinity Biotech USA, Inc., Jamestown, NY)	Test panel consensus (treponemal and nontreponmal concordant results): TP-PA/EIA/CIA and RPR, details on RPR NR; discordant results excluded	Unclear	None	Unclear	No information on included patients.	No	None	High
Williams, 2020[46]	MFI	MFI for treponemal IgG antibody (BioPlex Syphilis IgG); RPR; TP-PA assay, Bio-Rad Lab, Hercules, California	No	None	Low	Unknown how many and which patients delivered outside their hospital. Excluded those with equivocal or negative retesting results, thereby potentially reducing the numerator for false positives.	NA	NA	NA
Zofkie, 2020[47]	ARCHITECT CIA	ARCHITECT CIA, RPR, and particle agglutination test (TP-PA)	Unclear	Excluded those who didn't deliver at Parkland Hospital (unknown number).	Unclear	Inclusion based on screening in community clinics and delivery in Parkland hospital, unclear how many community clinic patients did not deliver at Parkland and were excluded as a result.	NA	NA	NA

Abbreviations: CIA=chemiluminescent immunoassay; EIA=enzyme immunoassay; IgG=immunoglobulin G; IgM=immunoglobulin M; MFI=multiplex flow immunoassay; NA=not applicable; NR=not reported; RPR=rapid plasma reagin; TP-PA=*Treponema pallidum*-particle agglutination.

Appendix D Table 2. Quality Ratings of Harms of Screening Studies (KQ 2)

First Author, Year	Bias due to Reference Standard	Comments on Reference Standard	Applicability	Comments on Applicability	Bias Due to Flow and Timing	Comments on Flow and Timing	Overall Quality Rating	Comments on Quality Rating
Adhikari, 2020[44]	No	None	High	None	Unclear	TP-PA was performed either as part of traditional algorithm or frozen, then thawed and later tested as part of reverse-sequence algorithm.	Fair	Unclear participant selection; unclear effect of freezing samples.
Chen, 2019[45]	No	None	High	None	No	None	Good	None
Christenson, 2018[48]	Unclear	Blinding not reported. Composite standard.	Unclear	Reference standard algorithm will likely have better accuracy for false-negative results compared with standard practice.	No	None	Fair	Unclear setting and populations; unclear blinding.
O'Connor, 2022[71]	No	None	High	None	Yes	Based on personal correspondence, six participants received RPR alone and were excluded. For traditional algorithm, participants could have receieved FTA (63%), syphilis IgG (24%), or TP-PA (11%).	Poor	Potential for bias from exclusion of persons without confirmatory tests and for use of three different confirmatory tests in the traditional algorithm.*
Pereira, 2018[54]	Yes	Dropping discordant results has the potential to misclassify those with or without the target condition.	Low	Reference procedure does not replicate traditional or reverse-sequence testing.	Yes	None	Poor	Unknown patient population with unknown risk. Unclear how participants were enrolled. Removal of 32% of participants due to discordant results. Multiple freeze/thaw cycles of samples.
Williams, 2020[46]	No	None	High	None	No	None	Fair	Those with equivocal or negative retests at delivery were excluded.
Zofkie, 2020[47]	No	None	Low	Routine prenatal care including syphilis screening at first visit, 32 weeks gestation, and delivery.	No	None	Fair	Unclear how many participants were excluded because they did not deliver at Parkland Hospital.

* Based on email communication with corresponding study author.

Abbreviations: FTA=fluorescent treponemal antibody; RPR=rapid plasma reagin; TP-PA=*Treponema pallidum*-particle agglutination.

Appendix D Table 3. Quality Ratings of Harms of Treatment Studies (KQ 3)

First Author, Year	Bias Due to Confounding	Comments on Confounding	Bias in Selection of Participants into the Study	Comments on Selection of Participants into the Study	Bias in Classification of Intervention	Comments on Classification of Intervention	Bias Due to Deviation from Intended Intervention	Comments on Deviation from Intended Intervention
Garcia, 2021[50]	NA	Single-arm cohort study	Low	None	Low	None	Low	Switched from oral to intravenous desensitization protocol after observing three severe breakthrough reactions with oral protocol.
Macumber, 2022[49]	NA	Single-arm cohort study	Low	None	Low	None	Low	None

Abbreviation: NA=not applicable.

Appendix D Table 4. Quality Ratings of Harms of Treatment Studies (KQ 3)

First Author, Year	Bias Due to Missing Data	Comments on Missing Data	Bias in Measurement of Outcomes	Comments on Measurement of Outcomes	Bias in Selection of the Reported Result	Comments on Selection of the Reported Result	Overall Quality Rating	Comments on Quality Rating
Garcia, 2021[50]	Low	None	Low	None	Low	None	Good	None
Macumber, 2022[49]	Some concerns	Cases were excluded "if the women were not staged as infectious syphilis (primary, secondary, and early latent) or if hospital records were not available." No further details provided.	Some concerns	Potential for bias from lack of blinding of outcome assessors, but because this is retrospective, likely impact is low. Surveillance and outcome measurement could have been different based on penicillin given (37 benzathine penicillin and two intravenous penicillin G).	Low	None	Fair	Potential for bias from missing cases; no information to assess the extent of potential bias.