McMaster University | Health Forum

Rapid evidence synthesis appendices

Effects of prenatal screening strategies for prevention, diagnosis, and treatment of syphilis during pregnancy

27 February 2025

[MHF product code: RES 126]

Appendices

Appendix 1: Methodological details

Background to the rapid evidence synthesis

This rapid evidence synthesis mobilizes both global and local research evidence about a question submitted to the McMaster Health Forum's Rapid Response program. Whenever possible, the rapid evidence synthesis summarizes evidence drawn from existing evidence syntheses and from single research studies in areas not covered by existing evidence syntheses and/or if existing evidence syntheses are old or the science is moving fast. A systematic review is a summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select, and appraise research studies, and to synthesize data from the included studies. The rapid evidence synthesis does not contain recommendations, which would have required the authors to make judgments based on their personal values and preferences.

The Forum produces timely and demand-driven contextualized evidence syntheses such as this one that address pressing health and social system issues faced by decision-makers (see our website for more details and examples). This includes evidence syntheses produced within:

- days (e.g., rapid evidence profiles or living evidence profiles)
- weeks (e.g., rapid syntheses that at a minimum include a policy analysis of the best-available evidence, which can be requested in a 10-, 30-, 60-, or 90-business-day timeframe)
- months (e.g., full evidence syntheses or living evidence syntheses with updates and enhancements over time)

This rapid evidence synthesis was prepared using four steps:

1) submission of a question from a policymaker or stakeholder (in this case, Public Health Agency of Canada)
2) identifying, selecting, appraising, and synthesizing relevant research evidence about the question
3) drafting the rapid evidence synthesis in such a way as to present concisely and in accessible language the research evidence
4) finalizing the rapid evidence synthesis based on the input of at least two merit reviewers.

Identification, selection, quality appraisal, and synthesis of evidence

For this rapid evidence synthesis, we searched Medline and Embase via OVID, Health Systems Evidence, and HealthEvidence.org for:

1) evidence syntheses
2) protocols for evidence syntheses that are underway
3) single studies.

In Health Systems Evidence and HealthEvidence.org, we searched for evidence syntheses using key words “syphilis screening.” The detailed search strategy for Medline and Embase via OVID are attached below. We focused on evidence published between 1 January 2010 and 20 January 2025.

Database:
Embase <1974 to 2025 January 17>
Ovid MEDLINE(R) ALL <1946 to January 17, 2025>

#	Query
1	exp "syphilis"/ or "early syphilis".ti,ab,kw. or "lues".ti,ab,kw. or "syphilitic disorder".ti,ab,kw. or "venereal syphilis".ti,ab,kw.
2	Syphilis, Congenital/
3	syphilis.ti,ab,kw.
4	"treponema pallidum".ti,ab.
5	1 or 2 or 3 or 4
6	mass screening/
7	screen$.ti,ab.
8	6 or 7
9	5 and 8
10	Syphilis Serodiagnosis/
11	((nontreponemal or treponemal) adj (test$ or immunoassay$)).ti,ab.
12	venereal disease research laboratory.ti,ab.
13	VDRL.ti,ab.
14	Rapid plasma reagin.ti,ab.
15	Fluorescent treponemal antibody absorbed.ti,ab.
16	Treponema pallidum particle agglutination.ti,ab.
17	10 or 11 or 12 or 13 or 14 or 15 or 16
18	9 or 17
19	Pregnancy/
20	Pregnancy Trimester, First/
21	Pregnancy Trimester, Second/
22	Pregnancy Trimester, Third/
23	Pregnant women/
24	Prenatal Care/
25	Prenatal Diagnosis/
26	Pregnancy Outcome/
27	Pregnancy Complications, Infectious/
28	Infectious Disease Transmission, Vertical/
29	(pregnan$ or prenatal or pre natal or perinatal or peri natal or antenatal or ante natal or antepartum or ante partum).ti,ab.
30	((vertical or maternal or mother or fetomaternal) adj3 transmission).ti,ab.
31	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	18 and 31
33	limit 32 to yr="2010 -Current"
34	remove duplicates from 33

Each source for these documents is assigned to one team member who conducts hand searches (when a source contains a smaller number of documents) or keyword searches to identify potentially relevant documents. A final inclusion assessment is performed both by the person who did the initial screening and the lead author of the rapid evidence synthesis, with disagreements resolved by consensus or with the input of a third reviewer on the team. The team uses a dedicated virtual channel to discuss and iteratively refine inclusion/exclusion criteria throughout the

process, which provides a running list of considerations that all members can consult during the first stages of assessment.
For each evidence synthesis we included, we documented key findings, living status, methodological quality (using AMSTAR), last year the literature was searched (as an indicator of how recently it was conducted), availability of GRADE profile, and equity considerations using PROGRESS PLUS.

Two reviewers independently appraise the methodological quality of evidence syntheses that are deemed to be highly relevant using the first version of the AMSTAR tool. Two reviewers independently appraise each synthesis, and disagreements are resolved by consensus with a third reviewer if needed. AMSTAR rates overall methodological quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. High-quality evidence syntheses are those with scores of eight or higher out of a possible 11, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. It is important to note that the AMSTAR tool was developed to assess evidence syntheses focused on clinical interventions, so not all criteria apply to those pertaining to health-system arrangements or implementation strategies. Furthermore, we apply the AMSTAR criteria to evidence syntheses addressing all types of questions, not just those addressing questions about effectiveness, and some of these evidence syntheses addressing other types of questions are syntheses of qualitative studies. While AMSTAR does not account for some of the key attributes of syntheses of qualitative studies, such as whether and how citizens and subject-matter experts were involved, researchers' competency, and how reflexivity was approached, it remains the best general quality-assessment tool of which we're aware. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, an evidence synthesis that scores 8/8 is generally of comparable quality to another scoring 11/11; both ratings are considered 'high scores.' A high score signals that readers of the evidence synthesis can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the evidence synthesis should be discarded, merely that less confidence can be placed in its findings and that it needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1): S8.)

For primary research (if included), we documented the dimension of the organizing framework with which it aligns, publication date, jurisdiction studied, methods used, a description of the sample and intervention, declarative title and key findings, and equity considerations using PROGRESS PLUS. We then used this extracted information to develop a synthesis of the key findings from the included syntheses and primary studies. We used ROBINS-I to assess risk of bias of each included primary study.

During this process we include published, pre-print, and grey literature. We do not exclude documents based on the language of a document. However, we are not able to extract key findings from documents that are written in languages other than Chinese, English, French, Portuguese, or Spanish. We provide any documents that do not have content available in these languages in an appendix containing documents excluded at the final stages of reviewing. We excluded documents that did not directly address the research questions and the relevant organizing framework. All of the information provided in the appendix tables was taken into account by the authors in describing the findings in the rapid evidence synthesis.

Appendix 2: A summary of the highly relevant single studies on effect of prenatal screening strategies for prevention, diagnosis, and treatment of syphilis during pregnancy

Table 2.1 Descriptive characteristics of included highly relevant study on effect of prenatal screening strategies

Author year	Country	Study design	Dates of enrolment	Study population	Settings, number in intervention/ control	Pregnant individuals enrolled, number intervention/ control	Mean gestational age at enrolment/ screening (weeks)	Syphilis at enrolment	Main outcomes	(ROBIN-I)
Qin, 2014	China	Prospective cohort	January 2002 to December 2012	All pregnant individuals visiting hospitals (first antenatal care visit)	Hospitals, 90	2,441,237	Not reported 26.5 (second trimester) (treatment)	Not reported	• Annual screening coverage • Incidence of the following outcomes ○ Congenital syphilis ○ All adverse event ○ Miscarriage ○ Stillbirth or fetal loss	Serious
Wang, 2023	China	Retrospective cohort	2015 to 2020	Pregnant individuals who gave live or stillbirths (first antenatal care visit and time of delivery)	Healthcare institutions and delivery hospitals, number not specified	3,658,266	Within 13 gestational weeks (first trimester)	13,829	• Annual screening coverage • Incidence of perinatal death • Incidence of congenital syphilis • Incidence of other neonatal • Adverse pregnancy outcomes • Maternal syphilis treatment	Moderate
Boodman, 2023	Canada	Conservative cost-avoidance analysis	2021	Pregnant individuals and syphilis-exposed infants (antenatal care)	Hospital, number not specified	Not reported	Three tests, at first and third trimester and delivery	206	• The total cost of expanded syphilis screening	Moderate
Laktabai, 2022	Kenya	Matched case-control cohort study	29 March 2018 to 10	Pregnant individuals	Hospital, 1	151	22 weeks (second trimester)	51	• Prevalence of preterm births,	Moderate

Author year	Country	Study design	Dates of enrolment	Study population	Settings, number in intervention/ control	Pregnant individuals enrolled, number intervention/ control	Mean gestational age at enrolment/ screening (weeks)	Syphilis at enrolment	Main outcomes	(ROBIN-I)
			September 2019	receiving routine antenatal care					• Prevalence of low birthweight	
Adeyinka, 2017	Nigeria	Retrospective	2013 to 2016	Pregnant individuals making first antenatal care visit	Prevention of mother-to-child transmission clinics, number not specified	9,713,724	Not reported	Not reported	• Percentage of new antenatal care attendees • Maternal syphilis • Coverage of syphilis treatment	Serious
Wang, 2018	China	Implementation study	February to July 2015	All pregnant individuals visiting 21 hospitals in China (Yuantan and Funan regions)	Hospitals, number in each not specified	1,787 participants received testing	20.4 weeks (range 8–43 weeks) (Second trimester)	Not reported	• Uptake in syphilis screening	Serious
Ganiyu, 2017	Botswana	Descriptive	2004 to 2008	Pregnant individuals attending antenatal care clinic	15 antenatal clinics	31,221 pregnant individuals	Not reported	Not reported	• Screen coverage for syphilis	Serious
Stafford, 2024	United States	Pre-and post-implementation study	Pre-implementation phase: 1 November 2023 to 29 February 2024 Post-implementation phase: 1 March 2024 to 25 June 2024	Pregnant individuals without prenatal care or with prenatal care but no documented syphilis result in the medical record	Emergency department (ED), University of Texas Health Science Center, not applicable	302 pregnant patients presented to the ED (during the pre-implementation period); 322 pregnant patients presented to the ED (during the post-implementation period)	Not reported	Not applicable	• Syphilis testing rate	Serious

Table 2.2 Descriptive characteristics of included highly relevant single studies on harms of screening for syphilis in pregnant individuals

Author year	Country	Study design	Dates of enrolment	Study population (No. of pregnant individuals screened, Mean gestational age at enrolment (weeks))	Cutoff	Testing strategy	No. of positive or negative results/total No. of test (%)	No. of False-positive or False-negative results/ total No. of positive or negative results (%)	Risk of bias (ROBIN-I)
Shiber, 2014	United States	Retrospective cohort	January 1993 to December 2009	57,642 of patients delivering at hospital had at least one venereal disease research laboratory (VDRL) test (total 122,408 VDRL tests)	Not reported	VDRL test at initial prenatal visit and delivery; average number of VDRL tests per pregnancy was 2.1 If VDRL was positive, an FTA was performed for confirmation Only patients with positive FTA were considered true positives	236/122,408 (0.19)	24/236 (10.2%)	Serious
O'Connor, 2022	United States	Retrospective cohort study	1 June 2014 to 28 February 2021	75,056 patients who received perinatal care	Reverse screening cutoffs for an IgG assay was ≤0.8 nonreactive, 0.9–5.9 weak reactive, and ≥6.0 reactive Reverse screening cutoffs for and IgM and IgG assay was <0.8 nonreactive, 0.9–1.1 weak reactive, and ≥1.1 reactive	Traditional screening using an rapid plasma reagin (RPR) Reverse screening confirmed with an RPR or a *Treponema pallidum* antibody	221 positive tests; number of total tests not reported	183/221 (82.8%)	Moderate
Lagendorf, 2019	Burkina Faso	Prospective	May 2014 to August 2014	242 pregnant individuals, 27 weeks	Not reported	• Used two different rapid diagnostic tests (RDTs): ○ SD Bioline T-RDT ○ DPP Screen and Confirm Assay	91/242 (37.6%) had presumptive active syphilis	• DPP testing did not reduce the number of pregnant individuals who would have been over treated compared with T-RDT (0.0% vs. 2.5%; p = 0.218)	Moderate

Author year	Country	Study design	Dates of enrolment	Study population (No. of pregnant individuals screened, Mean gestational age at enrolment (weeks))	Cutoff	Testing strategy	No. of positive or negative results/total No. of test (%)	No. of False-positive or False-negative results/ total No. of positive or negative results (%)	Risk of bias (ROBIN-I)
								• DPP testing also had a higher proportion of under diagnosis (48.4% vs. 2.2%; p<0.001)	
Boonchaoy, 2016	Thailand	Retrospective descriptive study	February 2011 to January 2013	11,640 pregnant individuals	(S/CO) ≥1.00 was considered reactive	A treponemal test, the chemiluminescent microparticle immunoassay, was used; reactive tests were followed up with rapid plasma reagin and *Treponema pallidum* particle agglutination tests	65/11,640 (0.56%)	35/65 (53.85%)	Serious
Mmeje, 2015	United States	Retrospective analysis	August 2007 to August 2010	Not reported	Not reported	A treponemal test, the chemiluminescent microparticle immunoassay, was used; reactive tests were followed up with rapid plasma reagin and *Treponema pallidum* particle agglutination tests	Not reported	156/194 (80.4%)	Moderate
Laktabai, 2022	Kenya	Matched case-control cohort study	29 March 2018 to 10 September 2019	150 pregnant individuals	Not reported	Both syphilis-only (Wondfo) and HIV-syphilis dual tests (SD Bioline) were used for routine enrolment point-of-care (POC) testing, with quantitative RPR testing performed at enrolment and follow-ups, and Treponema pallidum hemagglutination assays (TPHA) testing conducted at enrolment only – all laboratory testing met ISO 15189 standards	Positive results: 33/150 (22.0%) Negative results: 88/150 (58.7%)	False-positive results: 18/51 (35.3%) False-negative results: 11/99 (11.1%)	Moderate

Appendix 3: Detailed data extractions from evidence syntheses about effect of prenatal screening strategies for prevention, diagnosis, and treatment of syphilis during pregnancy

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations

• Population
  ○ Asymptomatic pregnant individuals
• Outcomes
  ○ Vertical transmission of syphilis (incidence of congenital syphilis)
  ○ Prevalence of congenital syphilis after implementation of a screening program
  ○ Stillbirth
  ○ Harms of screening
	Syphilis screening measures demonstrated positive impacts in reducing adverse outcomes related to syphilis; however, they have varying levels of specificity (1)
	• The purpose of this review was to determine the effects of screening for syphilis in pregnancy
	• The type, frequency, and comparator of screening intervention investigated was not specified
	• In the years 2002 to 2012 the following syphilis related outcomes were observed:
	  ○ syphilis screening coverage increased from 89.8% to 97.2%
	  ○ adverse outcomes decreased from 42.7% to 19.2%
	  ○ incidence of congenital syphilis decreased from 11.7% to 3.2%
	  ○ incidence of stillbirth or fetal loss decreased from 19.0% to 3.3%
	• False positives for syphilis in immunoassays ranging from 46.5% to 88.2% were identified across five studies
		High	No	6/9	2018	Not available	• Gender/sex

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
• Outcomes
  ○ Congenital syphilis cases
	Antenatal syphilis point-of-care tests (POCTs) significantly improve syphilis detection and same-day treatment rates, reduce congenital syphilis cases, and decrease adverse pregnancy outcomes, including stillbirth and neonatal death, making them a cost-effective and feasible solution for low-resource settings (2)
	• The study systematically reviewed nine modelling studies and two clinical studies (one from Mongolia and other from South Africa) for inclusion regarding the impact of antenatal syphilis POCTs on pregnancy outcomes in low-resource settings, concluding that POCTs significantly improve syphilis detection, treatment rates, and reduce adverse pregnancy outcomes compared to conventional laboratory testing or no screening
	• Treponemal POCT reduced congenital syphilis cases by 93% compared to laboratory testing, highlighting its effectiveness in preventing vertical transmission
	• POCTs meet WHO ASSURED criteria and are particularly suited for low-resource areas, offering affordable, rapid, and reliable diagnostic solutions without requiring extensive technical expertise or equipment
		High	No	6/10	2021	No	• None reported

• Population ○ Asymptomatic pregnant individuals	Rapid testing can improve syphilis screening in pregnant individuals regardless of geographic location or baseline testing in low-income countries (3)	High	No	4/10	2014	Not available	• Gender/sex

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations

• Screening Intervention
  ○ Universal Baseline Screening
  ▪ Point-of-care/rapid testing approaches
  ○ Risk-Based Additional Screening
  ▪ Geographic Risk
	• The purpose of this review was to examine the impact of syphilis screening on pregnant individuals
	• All studies included in this review demonstrated in increase in syphilis screening post the implementation of rapid testing
	• Results were similar across geographic locations and in locations with no prior screening measures
	• Rapid testing helped to improve screening by reducing the level of required resources and was found acceptable by healthcare professionals
	• Healthcare worker training and quality checks can increase implementation of rapid screening
	• Stockouts can limit access to testing						

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
  ▪ Point-of-care/rapid testing approaches
  ○ Risk-Based Additional Screening
  ▪ Geographic Risk
  ○ Screening Frequency Patterns
  ▪ Dual screen (first visit + third trimester)
• Outcomes
  ○ Vertical transmission of syphilis (incidence of congenital syphilis)
  ○ Prevalence of congenital syphilis after implementation
	The efficacy of rapid point-of-care testing for syphilis screening differed in two studies and demonstrates the need to explore testing within the context of age, social constructs, and resource availability (4)
	• The purpose of this review was to assess the effectiveness of antenatal syphilis screening in screening uptake and reducing perinatal mortality
	• Only two studies were included in this review
	• The results of on-site syphilis screening test using rapid treponemal tests versus conventional laboratory tests in Mongolia
	  ○ A 93.5% (95% CI 66.0 to 98.6%) reduction in syphilis was seen post implementation of screening in one study
	  ○ Syphilis was tested at the antenatal visit and third trimester
	  ○ Approximately 99.7% of participants who completed screening returned for a third trimester visit, compared to the 62.1% control (AOR 617.88, 95% CI 13.44–28399.01; P = < 0.001)
	  ○ Screening improved treatment rates in both females and their partners: treatment 98.9%, control 89.6% (AOR 10.44, 95% CI 1.00–108.99; P = 0.05)
	• The results of onsite syphilis test with rapid plasma regain testing versus routine laboratory testing with rapid screening in South Africa
	  ○ Fewer stillbirth deaths were observed in the intervention group (3.3%) versus the control group 5.1% (OR 0.63; 95% CI 0.27–1.48)
	  ○ On-site testing was insignificant to treat maternal syphilis: 11.1% intervention versus 64.1% control (OR 0.82; 95% CI 0.57–1.1)
	  ○ Proportion of females receiving in adequate treatment was similar between groups: 20.2% intervention versus 19.4% control (OR: 1.05; 95% CI 0.69–1.60)
	  ○ This study had technical issues due to limited resources
	• Across studies, adverse events were not adequately reported
		High	No	8/11	2014	Not available	• Gender/sex
							• Place of residence

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
of a screening program	• Differences across studies could be because participants were different in age at baseline and the results were in two countries with differences in social constructs and resources available in clinic						

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Screening Frequency Patterns
  ▪ Single screen (first visit only)
• Outcomes
  ○ Vertical transmission of syphilis (incidence of congenital syphilis)
	The timing of antenatal syphilis screening makes a significant difference in the risk of pregnant individuals and their infants having an adverse outcome according to evidence that showed a higher prevalence of adverse pregnancy and congenital syphilis outcomes in pregnant individuals who were screened and treated in the third trimester compared to the first and second trimesters (5)
	• This review assessed the impact of screening and treating females in their first and second trimesters of pregnancy compared to later in the third trimester of pregnancy
	• In the five studies identified that were relevant to the research question, the prevalence of any adverse pregnancy outcome was higher among females screened and treated in their third trimester compared to females in their first and second trimesters, resulting in an odds ratio of 2.24
	• The risk of congenital syphilis was particularly significant when comparing these two groups (odds ratio of 2.92)
	• These results support the approach to encourage pregnant individuals to be screened for syphilis within the first two trimesters of their pregnancy to reduce the risk of preventable adverse outcomes
		High	No	4/11	November 2010	No	• None

• Screening Intervention
  ○ Universal Baseline Screening
  ▪ Point-of-care/rapid testing approaches
	Antenatal syphilis screening lowers stillbirth and perinatal death rates by 50%; expanding screening programs requires identifying effective interventions, securing health financing, and advocating for policy support to eliminate this preventable disease (6)
	• Examined the effectiveness of screening interventions to prevent congenital syphilis and other adverse pregnancy outcomes
	• The review included 10 studies of interventions to improve the outcomes of antenatal syphilis screening by assessing the effects of introducing point-of-care testing and same-day treatment
	• Interventions were linked to reduced perinatal death (95% CI 0.26–0.82) and stillbirth (95% CI 0.19–0.93)
	• All studies measuring congenital syphilis incidence showed a decline, though results were heterogeneous
		High	No	7/11	2009	No	• None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations

• Outcomes
  ○ Stillbirth
  ○ Maternal or infant morbidity and mortality
	At least 2.4 MU penicillin given at least 28 days prior to delivery is effective in the treatment of syphilis in pregnant individuals to prevent congenital syphilis, with greatest effect when given early in pregnancy (before 24–28 weeks) (7)
	• Examined the effect of detection and treatment of active syphilis in pregnancy with at least 2.4 MU benzathine penicillin (or equivalent) on syphilis-related stillbirths and neonatal mortality
	• Prenatal detection of maternal syphilis and treatment with at least 2.4 million units of penicillin is estimated to reduce congenital syphilis incidence by 97%
	• Treatment with penicillin is associated with an 82% reduction in stillbirth, a 64% reduction in preterm delivery and an 80% reduction in neonatal deaths
		High	No	8/11	2009	No	• None reported

• Outcomes
  ○ Stillbirth
  ○ Maternal or infant morbidity and mortality
	The strongest evidence for stillbirth reduction was linked to effective prevention and treatment of syphilis, with a potential impact from malaria treatment (8)
	• Examined the impact of interventions targeting various important infections during pregnancy on stillbirth or perinatal mortality
	• A review of 25 studies found that syphilis detection and treatment during pregnancy reduced stillbirths by 80%
	• Malaria prevention interventions (intermittent preventive treatment and insecticide-treated mosquito nets) reduced stillbirths by 22%, though the results were not statistically significant
		High	No	7/11	2010	No	• None reported

• Screening Intervention
  ○ Universal Baseline Screening
  ▪ Point-of-care/rapid testing approaches
• Outcomes
  ○ Cost-effectiveness (e.g. cost-utility, or cost–benefit analyses cost per diagnosis of syphilis in pregnant individuals; cost per averted adverse birth outcomes; cost per quality-adjusted life
	Antenatal screening is the most cost-effective, feasible, and practical solution to congenital syphilis, with significant potential to reduce disease prevalence and adverse pregnancy outcomes (9)
	• The advent of newer rapid tests, including immunochromatographic syphilis strip (ICS), dual-point of care (dual-POC), and the decentralized syphilis control programs incorporated into the universal screening program, has the potential to eliminate congenital syphilis
	• In Zambia and other resource-limited settings, a same-day test and treatment with penicillin should be prioritized to achieve the goal of eliminating congenital syphilis
	• Universal screening of pregnant individuals in clinics can reduce the annual number of stillbirths, neonatal deaths, and incidence of congenital syphilis and can avert up to 2.6 million disability-adjusted life years (DALYs) at an estimated annual direct medical cost of US$20.8 million
		High	No	3/10	Not reported	No	• Place of residence

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
years (QALY); and the total cost of screening pregnant individuals for syphilis approaches)							

• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
  ○ Enhanced screening (more frequent intervals based on risk factors)
	Service quality improvements, bidirectional text messaging systems, and opt-out screening policy interventions were associated with an increase in antenatal syphilis screening rates; however, more syphilis focused intervention efforts are required (10)
	• The review assessed the impact outcomes of different antenatal screening interventions designed to increase screening rates for syphilis (and HIV, Hepatitis B) in LMICs
	• Syphilis screening interventions included:
	  ○ service quality improvement including a plan-do-study act that increased screening rates from 93.8% to 99.9%
	  ○ health technology interventions including bidirectional text messaging systems that increased syphilis rates
	  ○ policy interventions such as opt-out screening as opposed to opt-in screening showed an increase in HIV screening rates
	  ○ the review noted that HIV was the primary focus of interventions, resulting in a disparity in syphilis screening intervention efforts and suggesting syphilis screening should integrate into broader antenatal care efforts
		High	No	6/10	2023	Yes	• None reported

• Screening Intervention
  ○ Universal Baseline Screening
  ▪ Point-of-care/rapid testing approaches
• Outcomes
  ○ Harms of screening (e.g., false-positive and false-negative results, stigma, psychosocial harms)
	Rapid ICS strip tests show high sensitivity and specificity, comparable to traditional non-treponemal screening tests; however, the frequency of false negatives needs further investigation (11)
	• Examined the test characteristics of new cost-effective rapid ICS tests and the sensitivity/specificity in two clinical settings (antenatal clinics and STI clinics)
	• 15 studies were included
	• ICS syphilis tests showed high sensitivity (median 0.86, IQR 0.75–0.94) and high specificity (median 0.99, IQR 0.98–0.99) and showed comparable accuracy to traditional non-treponemal screening tests
	• ICS tests are valuable in low-income countries where traditional screening tests are less accessible
	• False negatives need to be further investigated due to frequency of positive ICS test results in previously treated individuals
		Medium	No	5/11	2010	No	• None reported

Appendix 4: Detailed data extractions from single studies about effect of prenatal screening strategies for prevention, diagnosis and treatment of syphilis during pregnancy

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
  ▪ Traditional algorithm (nontreponemal with reflex to treponemal)
  ○ Screening Frequency Patterns
  ▪ Dual screen (first visit + third trimester)
• Comparator
  ○ No comparator
• Outcomes
  ○ Vertical transmission of syphilis (incidence of congenital syphilis)
  ○ Stillbirth
  ○ Maternal or infant morbidity and mortality
  ○ Cases of infectious syphilis in pregnancy that were effectively treated
	More comprehensive screening and treatment for maternal syphilis at early stages of pregnancy is associated with decreased risks of adverse pregnancy outcomes (12)
	• All pregnant individuals in Zhejiang province receive an integrated HIV, syphilis, and hepatitis B screening program at their first antenatal care (ANC) visit (<13 gestational weeks) and at time of delivery
	  ○ Syphilis screening tests used include rapid plasma regain, or toluidine red unheated serum test, and *Treponema pallidum* Hemagglutination Assay test or *Treponema pallidum* particle agglutination
	• Syphilis screening coverage increased from 96.31% in 2015 to 99.4% in 2020
	  ○ Average syphilis incidence was 0.38%
	  ○ In the same period treatment coverage increased significantly
	• From 2015–2020 there was no significant decrease in overall incidence of adverse pregnancy outcomes (APOs)
	  ○ Incidence of perinatal death, congenital syphilis (CS), and other neonatal complications decreased significantly
	  ○ In 2020, incidences of perinatal death, CS, and other APOs were 6.14%, 2.36%, and 0.57% respectively
	• Females who had their first ANC appointment – and the accompanying syphilis screening – in the first and second trimester had significantly less risk of APOs than females who had their first ANC visit in the third trimester
	  ○ Adequate syphilis treatment was also associated with decreased APOs
		High	Publication date: 2023
			
			Jurisdiction studied: Zhejiang province, China
			
			Methods used: Retrospective study using data from the Zhejiang provincial eliminating mother-to-child transmission of syphilis
				• Gender/sex

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
  ▪ Traditional algorithm (nontreponemal with reflex to treponemal)
  ▪ Reverse sequence algorithm (treponemal with reflex to nontreponemal)
	Maternal prenatal syphilis screening is effective as a cost-avoidance measure, and would produce more savings if the program was universally successful in screening maternal syphilis cases (13)
	• Cost-avoidance analysis of expanded prenatal syphilis testing in Manitoba's outbreak situation at the time of publication
	• The total cost of expanded syphilis screening (three-time prenatal screening at first trimester, 28–32 weeks, and delivery) was CA$139,608.00 per year
		High	Publication date: 2023
			
			Jurisdiction studied: Manitoba, Canada
			
			Methods used: Conservative cost-
				• Gender/sex

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
○ Risk-Based Additional Screening ▪ Additional screening at 28–32 weeks in outbreak areas ▪ Screening at delivery for those with ongoing risk ○ Screening Frequency Patterns ▪ Triple screen (first visit + third trimester + delivery) • Comparator ○ No screening • Outcomes ○ Cost-effectiveness (e.g. cost-utility, or cost–benefit analyses cost per diagnosis of syphilis in pregnant individuals; cost per averted adverse birth outcomes; cost per quality-adjusted life years (QALY); and the total cost of screening pregnant individuals for syphilis approaches)	• For the 125 low-risk syphilis-exposed infants in Manitoba in 2021, successful identification of these cases with prenatal screening was associated with a cost-avoidance ratio of 16.25 • There were 206 syphilis-exposed infants in Manitoba in 2021, if all of these infants had been successfully identified with screening, the associated cost-avoidance ratio would be 26.78		avoidance analysis	
• Population ○ Asymptomatic pregnant individuals • Screening Intervention ○ Universal Baseline Screening ▪ Traditional algorithm (nontreponemal with reflex to treponemal) ▪ Point-of-care/rapid testing approaches • Comparator ○ No screening • Outcomes ○ Vertical transmission of syphilis (incidence of congenital syphilis) ○ Stillbirth ○ Maternal or infant morbidity and mortality ○ Cases of infectious syphilis in pregnancy that were effectively treated	Maternal patients in antenatal care testing positive for syphilis with concordant point-of-care tests and Treponemal pallidum hemagglutination assays (TPHA) is significantly associated with low birth weight (LBW) in infants; however greater prevalence of LBW being more than five times greater among these individuals despite receiving standard penicillin treatment during pregnancy.(14) • Population included pregnant individuals receiving ANC who were screened for syphilis with a point-of-care (POC) test at their first appointment • Data was included from 51 case patients (patients who tested positive for syphilis on their ANC POC test) and 100 control patients ○ All case patients received treatment for syphilis • There was no statistically significant difference between cases and controls on the duration of pregnancy, prevalence of preterm births, or mean birthweights • Prevalence of LBW and adverse pregnancy outcomes were higher in case patients, though not statistically significant • A sub-analysis was conducted with 109 females who had concordant POC tests and TPHA ○ In the sub-analysis LBW was significantly associated with preterm birth and positive result on syphilis POC and TPHA testing ○ Compared to females testing negative for syphilis in this subset, females who tested positive at enrolment had a greater-than-five-times higher prevalence of LBW	High	Publication date: 2022 Jurisdiction studied: Western Kenya Methods used: Matched case-control cohort study	• Gender/sex

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
  ▪ Reverse sequence algorithm (treponemal with reflex to nontreponemal)
  ○ Screening Frequency Patterns
  ▪ Single screen (first visit only)
• Comparator
  ○ No comparator
• Outcomes
  ○ Vertical transmission of syphilis (incidence of congenital syphilis)
  ○ Prevalence of congenital syphilis after implementation of a screening program
  ○ Cases of infectious syphilis in pregnancy that were effectively treated
	Prevalence of congenital syphilis among infants whose mothers were screened and tested positive for syphilis was 7.7% (15)
	• Prevalence of maternal and congenital syphilis in a private specialist healthcare setting was determined
	• Maternal patients were screened on their first prenatal visit using the reverse sequence algorithm process
	  ○ Maternal patients who tested positive were treated with penicillin; infants whose mothers did not complete the treatment course were also treated
	• The prevalence of congenital syphilis among infants whose mothers tested positive for syphilis during pregnancy was 7.7%
	• 38.5% of infants whose mothers tested positive for syphilis during pregnancy tested positive on the Architect Syphilis TP test
		Medium	Publication date: 2022
			
			Jurisdiction studied: Durban, South Africa
			
			Methods used: Retrospective cohort study
				• Gender/sex

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
  ▪ Traditional algorithm (nontreponemal with reflex to treponemal)
  ▪ Reverse sequence algorithm (treponemal with reflex to nontreponemal)
  ○ Risk-Based Additional Screening
  ▪ Screening at delivery for those with ongoing risk
  ○ Screening Frequency Patterns
  ▪ Single screen (first visit only)
  ▪ Dual screen (first visit + third trimester)
  ▪ Triple screen (first visit + third trimester + delivery)
• Comparator
  ○ No screening
• Outcomes
	Of maternal patients screened for syphilis less than half of newly identified patients with active syphilis infections during pregnancy gave birth to infants classified as possible congenital syphilis risk (16)
	• Maternal patients received routine syphilis screening at their first prenatal visit, and once again in the third trimester and at delivery for high-risk patients
	  ○ In 2019 new recommendations were introduced that all patients should receive early third trimester screening
	• 221 patients tested positive on initial screening for syphilis; 183 were false positives (FP) and 38 were true positives (TP)
	• Infants whose mothers received TP syphilis screens had a lower mean birth weight
	• Of the FP maternal patients, two received unnecessary evaluation and treatment, and one infant received unnecessary evaluation and treatment
	  ○ Four FP maternal patients had previously received unnecessary syphilis treatment
	• Of the FP maternal patients, 27 received a rapid plasma reagin (RPR) test at delivery
	  ○ One infant had a serum RPR and a cerebrospinal fluid Venereal Disease Research Laboratory at birth
		High	Publication date: 2022
			
			Jurisdiction studied: Northeast Ohio, United States
			
			Methods used: Retrospective review of clinical data
				• Gender/sex

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
○ Harms of screening (e.g., false-positive and false-negative results, stigma, psychosocial harms)	• Among the 38 TP patients, 21 had past syphilis diagnoses and 17 were newly identified, with 15 being identified by screening during pregnancy • Two high-risk patients were not rescreened at delivery and were diagnosed with syphilis after discharge; each of their infants was diagnosed with congenital syphilis • 93% (n = 14) of the 15 newly identified TP patients were identified in or prior to the early third trimester ○ Seven of their infants were classified as less likely to have congenital syphilis ○ Seven infants received a higher congenital syphilis classification status due to maternal treatment less than four weeks before delivery, inappropriate maternal treatment, concern for maternal reinfection/relapse, or inadequate follow-up care			
• Population ○ Asymptomatic pregnant individuals • Screening Intervention ○ Universal Baseline Screening ▪ First trimester screening or at first prenatal visit (universal) ○ Screening Frequency Patterns ▪ Single screen (first visit only) ▪ Dual screen (first visit + third trimester)	Rapid diagnostic testing for HIV and syphilis in antenatal care demonstrated strong acceptability and feasibility (17) • The purpose of this study was to assess the feasibility and acceptability of the WHO prequalified HIV/syphilis rapid diagnostic tests in antenatal care clinics • Participants included in this study were unaware of HIV/syphilis status (asymptomatic) • Participants were provided with dual HIV/syphilis rapid diagnostic testing kits, using a finger stick sample • Participants were screened at the first and second trimester • Screening comparators included: ELISA, CLIA, and PA • The uptake in screening from the first to second trimester was 90% using rapid testing • Approximately 95% of participants were willing to have rapid testing	High	Publication date: 8 August 2018 Jurisdiction studied: China Methods used: Implementation study	• Gender/sex
• Population ○ Asymptomatic pregnant individuals • Outcomes ○ Vertical transmission of syphilis (incidence of congenital syphilis) ○ Stillbirth	Approximately 1/4022 of females obstetrical facilitates in Japan were infected with syphilis (18) • The purpose of this study was to evaluate the prevalence of syphilis among pregnant individuals in Japan • A total of 1,919 participants from 2,458 obstetric facilitates participated in this study ○ Participants delivered at 22 weeks gestation • Approximately 78% of participants infected with syphilis were diagnosed in their first trimester • Adverse outcomes related to syphilis experienced by participants were 8% premature delivery, 4% stillbirth, and 14% deformities	Medium	Publication date: 14 December 2016 Jurisdiction studied: Japan Methods used: Descriptive	• Gender/sex
• Population ○ Asymptomatic pregnant individuals	There is variability in the uptake of screening across antenatal clinics in Botswana from 2005 to 2007 (19)	High	Publication date: 4 April 2017	• Gender/sex

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations

	• The purpose of this study was to evaluate trends in syphilis screening of pregnant individuals in Botswana
	• A total of 26,875 females were screened for syphilis and 4,346 were not screened
	  ○ This number of screened increased in 2005 (5,775)
	  ○ The number decreased in 2006 (4,490)
	  ○ The number screened increased in 2007 (4,093)
	  ○ No explanations for the variations in trends were provided
			Jurisdiction studied: United States
			
			Methods used: Descriptive analysis	

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
  ○ Screening Frequency Patterns
  ▪ Single screen (first visit only)
• Outcomes
  ○ Vertical transmission of syphilis (incidence of congenital syphilis)
  ○ Stillbirth
	Approximately 85% of females included in this study had syphilis testing; most testing was constrained to the first month and to females in southern regions of the states (20)
	• The purpose of this study was describe commercially insured pregnant persons use of MarketSan to determine syphilis screening
	• A total of 338,854 participants were included in this analysis; of that, 85% of females had a syphilis test at least once during their pregnancy
	• Persons in the south were more likely to receive a test, compared to females in other regions
	• A total of six cases of syphilis was identified
	• Testing was most common in the first trimester (80%)
	• Stillbirth prevalence was higher in females without prenatal syphilis testing at least first month before delivery (0.66%) than female with prenatal syphilis testing at lease 1 month before delivery (0.45%)
		Medium	Publication date: 2 October 2023
			
			Jurisdiction studied: Botswana
			
			Methods used: Cross-sectional
				• Gender/sex
				• Geographical location

• Screening Intervention
  ○ Universal Baseline Screening
  ▪ Point-of-care/rapid testing approaches
• Outcomes
  ○ Harms of screening (e.g., false-positive and false-negative results, stigma, psychosocial harms)
	The comparison of Dual Path Platform (DPP) with traditional screening methods in pregnant individuals showed no decrease in unnecessary syphilis treatments and an underestimation of those requiring treatment (21)
	• Estimated the potential reduction in overtreatment when comparing treponemal-rapid diagnostic test (T-RDT) and a newer rapid test (DPP Screen Confirm Assay, Chembio) detecting both treponemal and non-treponemal antibodies
	• Of the 242 pregnant individuals included in the study, 37.6% had presumptive active syphilis and 19.0% had passive plasma reagin titres ≥8
	• DPP testing did not reduce the number of pregnant individuals who would have been over treated compared with T-RDT and had a higher proportion of under diagnosis
		High	Publication date: December 2018
			
			Jurisdiction studied: Déou, Burkina Faso
			
			Methods used: Cross-sectional
				• None reported

• Screening Intervention
  ○ Universal Baseline Screening
  ▪ Point-of-care/rapid testing approaches
	Incorporating dual test kits into routine antenatal clinics could potentially increase uptake of testing and treatment for HIV and syphilis among pregnant individuals and reduce the risk of mother-to-child transmission (22)
	• Included 3,212 pregnant individuals and assessed the field performance, acceptability, and feasibility of two dual HIV/syphilis rapid diagnostic
		Medium	Publication date: November 2018
			
			Jurisdiction studied: Zambia
				• None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
	tests: the Chembio DPP HIV-syphilis Assay and the SD Bioline HIV/syphilis Duo in antenatal clinics • Both rapid diagnostic tests were evaluated as highly acceptable and feasible • In field settings, the performances of both rapid diagnostic tests aligned with findings from other published evaluations, demonstrating reliability and suitability for use		Methods used: Cross-sectional	

• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
  ○ Risk-Based Additional Screening
  ▪ Geographic Risk
  ▪ More frequent screening intervals for high-risk populations
	Inadequate antenatal care utilization at prevention of mother-to-child transmission (PMTCT) sites remains a significant barrier to eliminating congenital syphilis in Nigeria; the current levels of maternal syphilis screening and treatment are insufficient to meet elimination goals, emphasizing the urgent need for a rapid scale-up of antenatal screening and treatment to prevent a potential epidemic (23)
	• The purpose of this study was to determine the prevalence of and treatment coverage trend for syphilis among pregnant individuals in the national PMTCT programme in Nigeria
	• Performed an analysis of validated national health sector performance data examined pregnant individuals attending antenatal care at prevention of mother-to-child transmission clinics in Nigeria from 2013 to 2016
	• The findings showed a significant increase in the proportion of new antenatal care attendees receiving annual serological testing for syphilis, rising from 12.2% in 2013 to 16.3% in 2016
	• During the same period, maternal syphilis prevalence declined from 3.2% to 1.4%
	• Syphilis treatment coverage during pregnancy decreased from 71.3% in 2013 to 54.9% in 2016, highlighting a concerning gap in treatment despite increased screening efforts
		High	Publication date: December 2018
			
			Jurisdiction studied: Nigeria
			
			Methods used: Retrospective analysis
				• None reported

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Universal Baseline Screening
  ▪ Point-of-care/rapid testing approaches
• Outcomes
  ○ Prevalence of congenital syphilis after implementation of a screening program
	Post implementation of a screening program, syphilis prevalence decreased in pregnant individuals and children (24)
	• The purpose of this study was to describe the effectiveness of antenatal screening for syphilis and HIV testing in the Netherlands
	• Syphilis was diagnosed in less than five newborns/year
	• Active infections were seen in 17% of pregnant individuals
	• The risk of transmission from mother to child was 20% to 30%
		Medium	Publication date: 30 June 2011
			
			Jurisdiction studied: Netherlands
			
			Methods used: Descriptive
				• Gender/sex

• Population ○ Asymptomatic pregnant individuals • Screening Intervention	A pre- and post-implementation study showed the introduction of an opt-out and rapid syphilis testing program for pregnant individuals visiting the emergency department (ED) increased screening rates from 2% to 56.4%	High	Publication date: December 2024	• None

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
○ Universal Baseline Screening ▪ Point-of-care/rapid testing approaches	and enhanced syphilis detection in a high-prevalence region of Southeastern Texas (25) • The program identified a syphilis prevalence of 3.5% among those tested, with all four positive cases receiving immediate treatment in the ED • The study also showed high acceptability of testing, with approximately 80% of pregnant patients finding syphilis testing acceptable and 100% of these willing to accept the rapid Syphilis Health Check point-of-care test • 57% of tested patients were scheduled for prenatal care follow-up by research navigators, regardless of test results		Jurisdiction studied: Houston, Texas, United States Methods used: Pre-and post-implementation study	
• Population ○ Asymptomatic pregnant individuals • Screening Intervention ○ Universal Baseline Screening ▪ First trimester screening or at first prenatal visit (universal) • Outcomes ○ Vertical transmission of syphilis (incidence of congenital syphilis) ○ Prevalence of congenital syphilis after implementation of a screening program	The decade-long (2002–2012) syphilis screening program for pregnant individuals in Shenzhen, China successfully increased screening coverage, and decreased the incidence of all adverse outcomes, congenital syphilis, stillbirth, and fetal loss (26) • Screening coverage reached 97.2% in 2012 (from 89.8% in 2002) • Congenital syphilis rates in Shenzhen significantly decreased from 109.3 cases in 2002 to 9.9 cases in 2012 per 100,000 live births (compared to China's increasing trend from 5.9 to 97.4 cases per 100,000 live births during the same period) • The prevalence rate declined from 42.7% to 19.2% for all adverse pregnancy outcomes • Rates declined from 19.0% to 3.3% for stillbirth or fetal loss • Rates decreased from 15.8% to 2.6% for miscarriage • The proportion of positive syphilis results detected before 28 weeks of pregnancy increased from 55.4% in 2003 to 67.1% in 2012 • The proportion of continuing pregnancies in syphilitic females increased from 44.5% to 83.5%	High	Publication date: June 2014 Jurisdiction studied: Shenzhen, China Methods used: Prospective cohort study	• Education level, occupation, residency status
• Population ○ Asymptomatic pregnant individuals • Screening Intervention ○ Universal Baseline Screening ▪ First trimester screening or at first prenatal visit (universal) ▪ Initial screening test algorithms: ▪ Traditional algorithm (nontreponemal with reflex to treponemal) ▪ Reverse sequence algorithm (treponemal with reflex to nontreponemal) • Comparator ○ No comparator	When conducting initial syphilis screening on pregnant individuals using a reverse sequence algorithm with a chemiluminescent microparticle immunoassay as the initial test, 60.3% of positive tests were false positives (27) • This study examines the performance of a chemiluminescent microparticle immunoassay (CMIA) treponemal test as an initial syphilis-screening method among pregnant individuals at their first antenatal care visit ○ Females with reactive results were retested using an RPR and a Treponema pallidum particle agglutination (TPPA) test to confirm the results • 65 (0.56%) of 11,640 females screened with CMIA had reactive results ○ 7 (10.8%) of 65 had RPR and TPPA reactive results	High	Publication date: 2016 Jurisdiction studied: Bangkok, Thailand Methods used: Retrospective, descriptive study	• Gender/sex

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations

• Outcomes
  ○ Harms of screening (e.g., false-positive and false-negative results, stigma, psychosocial harms)
	○ 58 (89.2%) of 65 had RPR non-reactive results
	  ▪ Of the 58, 35 (60.3%) were TPPA non-reactive, suggesting that the CMIA results were a false positive
	  ▪ Of the 23 out of 58 who had RPR non-reactive and TPPA non-reactive results, seven had been previously treated for syphilis and 16 had untreated, late, latent syphilis
	  ▪ The 16 untreated cases would have been missed with a traditional screening algorithm			

• Population
  ○ Asymptomatic pregnant individuals
• Screening Intervention
  ○ Universal Baseline Screening
  ▪ First trimester screening or at first prenatal visit (universal)
  ▪ Initial screening test algorithms:
  ▪ Reverse sequence algorithm (treponemal with reflex to nontreponemal)
  ○ Screening Frequency Patterns
  ▪ Dual screen (first visit + third trimester)
• Comparator
  ○ No comparator
• Outcomes
  ○ Harms of screening (e.g., false-positive and false-negative results, stigma, psychosocial harms)
	Out of 106,100 births there were 156 false positive syphilis screening results with a positive chemiluminescence immunoassay (CIA) test followed by a negative RPR test (28)
	• Pregnancy and birth/neonatal outcomes among females who received a positive CIA test followed by a negative RPR test in their antenatal syphilis screening were examined
	• 156 (80%) out of 194 females with discordant results were confirmed syphilis negative with a TPPA assay, meaning their initial positive results with CIA test were a false positive
	• 18 (9%) of the 194 females were treated for syphilis
	  ○ These were early latent (n = 3), late latent (n = 14), and unspecified latent (n = 1) syphilis
	  ○ The majority of these females had received a positive TPPA test
	  ○ No adverse birth outcomes were linked to TPPA or syphilis status
		High	Publication date: 2015
			
			Jurisdiction studied: United States
			
			Methods used: Retrospective analysis
				• Gender/sex

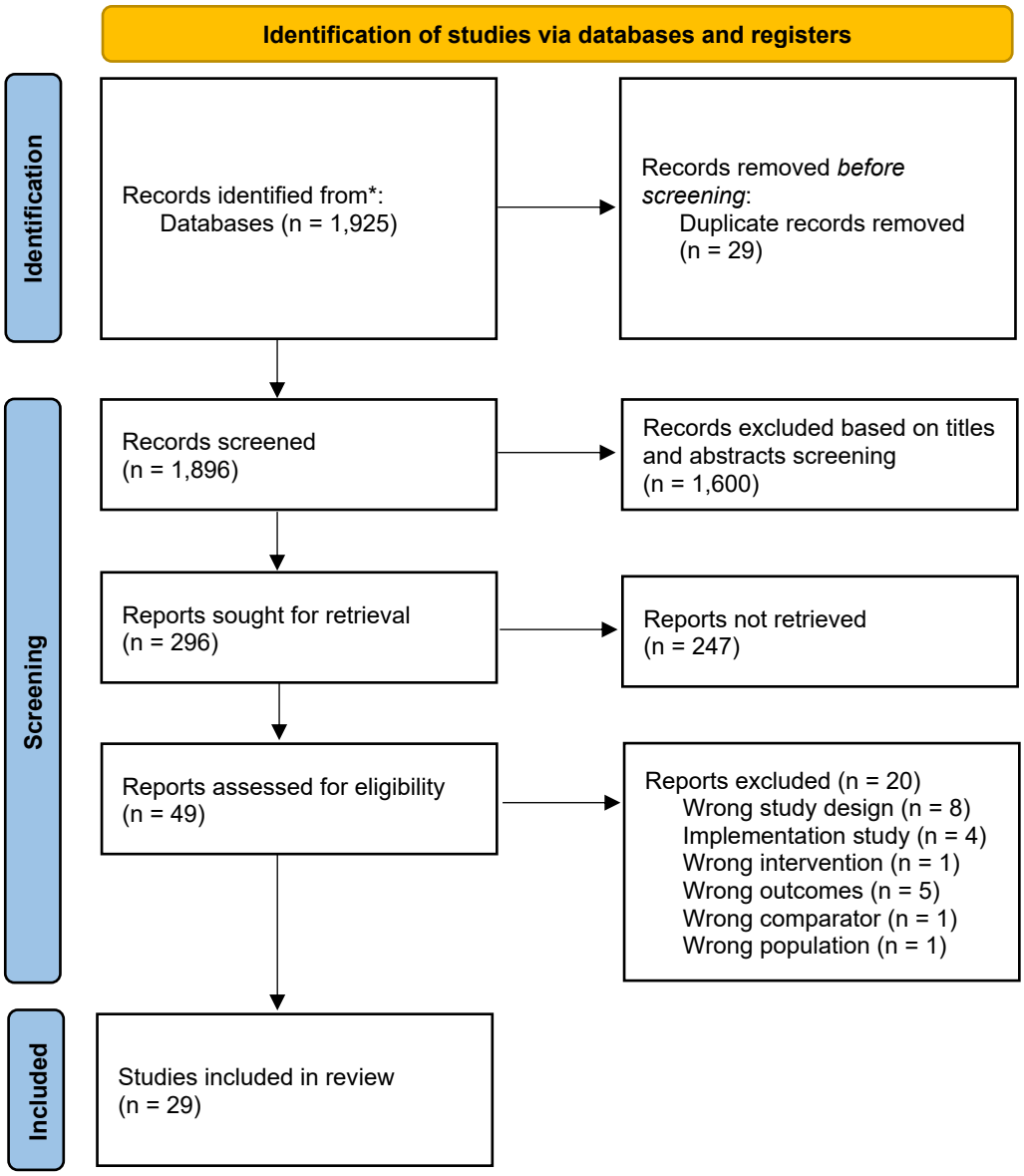
• Screening Intervention
  ○ Risk-Based Additional Screening
  ▪ Geographic Risk
  ▪ Additional screening at 28–32 weeks in outbreak areas
  ▪ Additional screening at 28–32 weeks for those with ongoing risk
• Outcomes
  ○ Cost-effectiveness (e.g. cost-utility, or cost–benefit analyses cost per diagnosis of syphilis in pregnant individuals; cost per averted adverse birth outcomes; cost per quality-adjusted life years (QALY); and the total cost of screening pregnant individuals for syphilis approaches)
	Additional routine syphilis screening in the early third trimester does not appear to be clinically beneficial; while syphilis screening during pregnancy is essential, it is recommended to reserve the additional venereal disease research laboratory (VDRL) test at 28–32 weeks for patients with new or ongoing acute risk factors for infection (29)
	• This study examined the clinical utility and cost of repeating syphilis testing in the third trimester of pregnancy in a high-risk urban population
	• A retrospective cohort analysis was performed for patients delivering from January 1993 through December 2009
	• In this 17-year cohort of 58,569 deliveries, 113 new syphilis cases were identified
	• Among 17 detected seroconversions, 10 patients who weren't rescreened in the third trimester tested positive at delivery, suggesting they could have benefited from routine VDRL testing at 28–32 weeks
	• The cost of evaluating and treating a neonate for syphilis was US$11,079
		High	Publication date: March 2014
			
			Jurisdiction studied: Ohio, United States
			
			Methods used: Retrospective cohort analysis
				• None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
	• Implementing an additional VDRL screen at 28–32 weeks would cost US$1,991,346 • A 3.5% syphilis prevalence would be required for the cost of universal third-trimester screening to match the potential healthcare savings			

Appendix 5: Documents excluded at the final stage of reviewing

Hyperlinked title	Exclusion reasons
An opt-out emergency department screening intervention leads to major increases in diagnosis of syphilis	Wrong study design
Cost-effectiveness of interventions for HIV/AIDS, malaria, syphilis, and tuberculosis in 128 countries: A meta-regression analysis	Wrong study design
Analysis of maternal and congenital syphilis rates at a New Jersey University Hospital	Wrong study design
Repeat screening for syphilis in pregnancy as an alternative screening strategy in the UK: A cost-effectiveness analysis	Wrong study design
Evaluating coverage of maternal syphilis screening and treatment within antenatal care to guide service improvements for prevention of congenital syphilis in Countdown 2030 Countries	Wrong study design
Barriers and facilitators to HIV and syphilis rapid diagnostic testing in antenatal care settings in low-income and middle-income countries: A systematic review	Implementation study
Antenatal care visit attendance frequency and birth outcomes in rural Uganda: A prospective cohort study	Wrong intervention
Using surveillance data to respond to an outbreak of congenital syphilis in Arizona through third-trimester screening policies, 2017-2018	Wrong population
Screening for syphilis infection in pregnant individuals: Updated evidence report and systematic review for the US preventive services task force	Duplicate study
Effectiveness of prenatal screening and treatment to prevent congenital syphilis, Louisiana and Florida, 2013–2014	Wrong study design
Rapid syphilis testing is cost-effective even in low-prevalence settings: The CISNE-Peru experience	Wrong study design
Bottlenecks in the implementation of essential screening tests in antenatal care: Syphilis, HIV, and anemia testing in rural Tanzania and Uganda	Implementation study
Scaling down to scale up: A health economic analysis of integrating point-of-care syphilis testing into antenatal care in Zambia during pilot and national rollout implementation	Implementation study
Integration of antenatal syphilis screening in an urban HIV clinic: A feasibility study	Wrong outcomes
Sero-conversion rate of Syphilis and HIV among pregnant individuals attending antenatal clinic in Tanzania: A need for re-screening at delivery	Wrong outcomes
Discordant syphilis immunoassays in pregnancy: Perinatal outcomes and implications for clinical management	Wrong outcomes
An eight-year retrospective analysis of antenatal screening results for syphilis: Is it still cost effective?	Wrong outcomes
Cost-effectiveness of integrated routine offering of prenatal HIV and syphilis screening in China	Wrong study design
Finding a needle in the haystack: The costs and cost-effectiveness of syphilis diagnosis and treatment during pregnancy to prevent congenital syphilis in Kalomo District of Zambia	Wrong outcomes
Cost and clinical utility of repeated syphilis screening in the third trimester in a high-risk population	Wrong study design
Simultaneous triple point-of-care testing for HIV, syphilis and hepatitis B virus to prevent mother-to-child transmission in India	Wrong comparator
Point-of-care tests to strengthen health systems and save newborn lives: The case of syphilis	Implementation study
The cost-effectiveness of syphilis screening in pregnant individuals: A systematic literature review	Wrong study design

Appendix 6: PRISMA flow diagram



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