McMaster University | Health Forum

Rapid evidence synthesis

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

27 February 2025

[MHF product code: RES 126]

Context

Syphilis infection during pregnancy continues to be a significant global public health concern, with congenital syphilis rates reaching their highest levels in over two decades. In 2016, an estimated 98,800 maternal syphilis infections occurred worldwide, causing substantial adverse pregnancy outcomes.(1)

In Canada, the situation is particularly concerning. Since 2017, multiple provinces and territories have declared outbreaks of both infectious and congenital syphilis.(2) The rate of congenital syphilis increased dramatically by 599% between 2018 and 2022, reaching 31.7 cases per 100,000 live births.(3) During this same period, infectious syphilis rates rose by 109%, with females now representing 35% of all cases compared to 21% in 2018.(4)

Screening during pregnancy is crucial because syphilis, caused by *Treponema pallidum*, can be transmitted vertically from mother to fetus at any stage of gestation and also during delivery. Untreated maternal syphilis carries significant risks: approximately 25% result in late spontaneous abortion or stillbirth, 13% in premature birth or low birthweight, 11% in neonatal death, and 20% in infants born with clinical signs of congenital syphilis.(5) These adverse outcomes can largely be prevented through early detection and appropriate treatment with penicillin.(6)

Box 1: Evidence and other types of information

+ Global evidence drawn upon

Evidence syntheses selected based on relevance, quality, and recency of search

- No forms of domestic evidence used

- No other types of information used

*** Additional notable features**

Prepared in 30 business days using an 'all hands on deck' approach

Two main screening approaches are currently used: 1) the traditional algorithm (nontreponemal testing with reflex to treponemal testing); and 2) the reverse sequence algorithm (treponemal testing with reflex to nontreponemal testing). Additionally, rapid diagnostic tests (RDTs) or point-of-care (POC) tests represent an important third strategy, providing results within minutes without requiring specialized laboratory infrastructure. These tests typically detect treponemal antibodies and can be performed using a finger-prick blood sample, making them particularly valuable in resource-limited settings and for immediate clinical decision-making.(7) While the cost-effectiveness of syphilis screening during pregnancy has been demonstrated in various settings, questions remain about the optimal screening sequence to detect infection, ensure timely treatment, and prevent congenital syphilis transmission.(8) The World Health Organization (WHO) considers prenatal syphilis screening and treatment a key strategy for eliminating congenital syphilis.

However, prenatal screening may also result in unintended harms, especially from false-positive and false-negative results, that should be accounted for when weighing the potential value of different syphilis screening approaches. In general, false-positive and false-negative screening results might result in psychological and/or health-related harms, as well as late or unnecessary treatment.(8; 9)

The objective of this evidence synthesis is to synthesize the available evidence on the effectiveness of different syphilis screening approaches during pregnancy. We aim to examine various prenatal screening strategies, including the timing, frequency, and methods of testing, to determine the most effective approach for preventing congenital syphilis and other adverse pregnancy outcomes. Our findings will inform the development of evidence-based screening recommendations by the National Advisory Committee on Sexually Transmitted and Blood-Borne Infections and support the Public Health Agency of Canada in program activities related to prenatal syphilis screening.

Note on terminology: Throughout this report, we primarily use the term 'females' when discussing pregnancy, reflecting both the terminology used in the original research studies cited and current best practices in inclusive scientific writing.(10) We acknowledge that pregnancy can be experienced by individuals across the gender spectrum. The research referenced in this report primarily focused on cisgender females, which is reflected in our terminology. We recognize the ongoing evolution of inclusive language in this field and have aimed to balance accuracy in reporting research findings with respect for diverse gender identities.

Questions

1) What are the effects of different prenatal screening strategies (including screening frequency, timing, and testing algorithms) to diagnose syphilis at any time during pregnancy on access to timely treatment and prevention (e.g., reducing the incidence of congenital syphilis in newborns)?
2) What are the harms of screening for syphilis in pregnant individuals?
3) What is the most cost-effective strategy for syphilis screening during pregnancy?

Note that for question 3, our goal was to identify cost-effectiveness studies retrieved through the literature search, but to focus our analysis on any Canadian cost-effectiveness analyses. Given this, non-Canadian cost-effectiveness studies have been excluded from the scope of question 3.

Box 2: Approach and supporting materials

We identified evidence addressing the question by searching Medline and Embase via OVID, Health Systems Evidence, and HealthEvidence.org to identify evidence syntheses, protocols for evidence syntheses, and primary studies. We limited the search date between 1 January 2010 and 20 January 2025. The search strategies used are included in Appendix 1.

In contrast to our rapid evidence profiles, which provide an overview and insights from relevant documents, this rapid evidence synthesis provides an in-depth understanding of the evidence.

We appraised the methodological quality of evidence syntheses that were deemed to be highly relevant using the first version of the AMSTAR tool. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial, or governance arrangements within health systems or implementation strategies.

A separate appendix document includes:
1) methodological details (Appendix 1)
2) a summary of highly relevant single studies organized by outcomes (Appendix 2)
3) a summary table of evidence synthesis (Appendix 3)
4) a summary table of single studies (Appendix 4)
5) studies excluded at the last stages of reviewing (Appendix 5)
6) PRISMA flow diagram (Appendix 6).

Critical appraisal: The risk of bias (ROB) of individual studies was assessed using validated ROBINS-I. Judgements were decided by one reviewer and the overall ROBINS-I assessments are provided in Appendix 2. A PRISMA flow diagram is provided in Appendix 6.

High-level summary of key findings

- Implementation of universal prenatal syphilis screening consistently improved screening coverage and treatment coverage across diverse geographical setting.
- Various intervention types of syphilis screening demonstrated different levels of effectiveness in increasing screening coverage:
  - quality improvement initiatives (e.g., audit-feedback mechanisms, provider training, supportive supervision) demonstrated substantial increases in screening rates
  - other interventions (e.g., policy changes for POC testing without addressing broader system factors) demonstrated no significant improvement
  - screening rates varied considerably between clinics (3.1% to 33.6% non-screening rates in Botswana), suggesting inconsistencies in program implementation.
- Rapid testing approaches and POC proved particularly effective at improving screening uptake, especially in resource-limited settings.
  - Rapid testing implementation significantly increased screening rates regardless of geographic setting, rural/urban location, or baseline screening levels.
  - In Uganda, screening rates increased dramatically from 1.7% to 96.4% following rapid test introduction.
  - Dual HIV/syphilis RDTs increased the proportion of women tested in their first and second trimester from 76.0% to 90.1% in China, with 98.3% receiving same-day results.
- Setting innovations expanded screening access.
  - Implementation of opt-out rapid testing in emergency departments significantly improved screening rates among pregnant patients (from 2% to 56.4% in a Texas study).
  - Reaching pregnant individuals in non-traditional care settings helped engage those who might otherwise miss routine prenatal screening.
- Evidence showed mixed results of syphilis screening impact on treatment completion.
  - Some studies showed improved adequate treatment rates, reduced treatment delays, and enhanced partner treatment.
  - Other studies revealed concerning decreases in treatment coverage despite increased screening.
- Strong evidence demonstrates early screening and treatment significantly reduced adverse outcomes.
- Timing of screening and treatment proved critical in determining outcomes, and evidence supports different screening frequency patterns.
  - Single screening at first antenatal visit has shown effectiveness but with limitations for late presenters.
  - Females screened and treated in first or second trimester had significantly better outcomes (e.g., reduction in perinatal death and stillbirth), and females screened in third trimester were more than twice as likely to experience adverse outcomes (e.g., prematurity and congenital syphilis).
  - Dual screening (first visit and third trimester) was mandated in some settings (e.g., Botswana) and showed higher coverage with POC testing.
- Limited evidence addressed potential harms and cost-effectiveness of prenatal syphilis screening.
  - Some studies reported false results, but one reported the harms associated with these results.
  - Specific test types showed varying performance: rapid POC tests in Kenya had a sensitivity of 75.0% and specificity of 83.0%.
  - Multiple screening tests throughout pregnancy may mitigate impacts of false results.
- We identified limited Canadian cost-effectiveness evidence for prenatal syphilis screening.
  - One Canadian study found expanded three-time prenatal screening (first trimester, 28–32 weeks, delivery) to be cost-effective.
  - The cost-avoidance ratio ranged from 16.25 to 26.78, depending on the proportion of syphilis-exposed infants identified.

Framework to organize what we looked for

- 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)
    - Point-of-care/rapid testing approaches
  - Risk-based additional screening
    - Geographic risk
    - Additional screening at 28–32 weeks in outbreak areas
    - Screening at delivery in outbreak areas
    - Individual risk factors
    - Additional screening at 28–32 weeks for those with ongoing risk
    - More frequent screening intervals for high-risk populations
    - Screening at delivery for those with ongoing risk
    - Pregnancy outcome-based screening
    - Screening for cases of stillbirth after 20 weeks gestation
  - Screening frequency patterns
    - Single screen (first visit only)
    - Dual screen (first visit + third trimester)
    - Triple screen (first visit + third trimester + delivery)
  - Enhanced screening (more frequent intervals based on risk factors)
  - Other screening method
- Comparator
  - No screening
  - No comparator
- Outcomes
  - Vertical transmission of syphilis (incidence of congenital syphilis)
  - Prevalence of congenital syphilis after implementation of a screening program
  - Stillbirth
  - Maternal or infant morbidity and mortality
  - Cases of infectious syphilis in pregnancy that were effectively treated
  - Harms of screening (e.g., false-positive and false-negative results, stigma, psychosocial harms)
  - 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)

What we found

We identified 29 evidence documents relevant to the question, of which we deemed 23 to be highly relevant and seven of medium relevance. Only the high-relevance studies were included in the report, and the medium- and low-relevance studies can be found in the appendices. The highly relevant evidence documents include:

- 10 evidence synthesis
- 13 single studies
  - six studies were assessed as serious risk (ROBINS-I)
  - seven assessed were as moderate risk (ROBINS-I).

We outline in narrative form below our key findings related to the question from highly relevant evidence documents (see Box 2 for more details).

A summary of the evidence organized by outcomes is provided in Appendix 2. Detailed data extractions from each of the included evidence documents is provided in Appendix 3 and 4, and hyperlinks for documents excluded at the final stage of reviewing in Appendix 5.

Key findings from highly relevant evidence sources

Q1: What are the effects of different prenatal screening strategies to diagnose syphilis at any time during pregnancy on access to timely treatment and prevention?

Overall, the evidence synthesis demonstrates that implementing universal syphilis screening programs consistently improves screening coverage across diverse geographical settings, with particularly strong results from China. Point-of-care and rapid testing approaches significantly enhanced screening uptake and timeliness of results, with increases observed across multiple low- and middle-income countries (LMICs), while dual HIV/syphilis testing further improved coverage. Early screening and treatment significantly reduced adverse pregnancy outcomes, with penicillin treatment associated with substantial reductions in stillbirth, preterm delivery, and neonatal deaths. The timing of screening was found to be critical, with females screened and treated in the first or second trimester experiencing significantly better outcomes than those treated later. Many screening programs demonstrated dramatic declines in congenital syphilis rates, though geographic variations in implementation highlight persistent challenges in achieving optimal coverage, particularly in resource-limited settings where most studies were conducted.

First trimester screening or at first antenatal care visit (universal)

Most studies screened pregnant individuals during routine antenatal care visit, typically at the first visit. Multiple studies from China showed substantial increases in coverage over time. A medium-quality evidence synthesis by Lin (2018) examining the effectiveness and harms of screening for syphilis in pregnancy found one key observational study from China that demonstrated significant effectiveness of syphilis screening during pregnancy.(8) This included study, which evaluated over 2.4 million pregnant individuals between 2002–2012, showed that implementing widespread universal screening led to dramatic improvements in screening coverage, which increased from 89.8% to 97.2% over the 10-year period. The timing of screening pregnant females was not reported in this study; however, the mean gestational week in which treatment occurred was 26.5 weeks (SD 11.2 weeks; range 3–43 weeks). The screening for syphilis was conducted using a nontreponemal test, with additional treponemal testing performed if initial results were positive. Those with positive serology received follow-up care including treatment, health education, partner notification, and the option to end their pregnancy. As screening coverage increased, the incidence of congenital syphilis decreased dramatically from 109.3 to 9.4 cases per 100,000 live births – an approximately 11-fold reduction. Moreover, the proportion of females with syphilis who chose to continue their pregnancies rather than terminate it increased from 44.5% to 83.5% during this period, possibly reflecting greater confidence in treatment outcomes. Concurrently, the prevalence of adverse outcomes declined substantially from 42.7% to 19.2% for all adverse outcomes, from 11.7% to 3.2% for congenital syphilis, from 15.8% to 2.6% for miscarriage, and from 19.0% to 3.3% for stillbirth or fetal loss.(11)

A systematic review and meta-analysis by Blencowe (2011) examined the effectiveness of detecting and treating active syphilis during pregnancy to reduce adverse outcomes. The study suggested that early screening before 24–28 weeks of pregnancy offers the best chance to prevent devastating outcomes, as the fetal inflammatory response to syphilis infection intensifies during the second trimester. The study found that timely detection and treatment of syphilis with at least 2.4 million units of penicillin reduced the incidence of clinical congenital syphilis by 97% (95% CI 93–98%) and treatment with penicillin is associated with an 82% reduction in stillbirth (95% CI 67–90%), a 64% reduction in preterm delivery (95% CI 53–73%), and an 80% reduction in neonatal deaths (95% CI 68–87%). It was noted that while these effect estimates were large and consistent across studies, few studies adjusted for potential confounding factors, resulting in an overall low quality of evidence.(12) Similarly, Ishaque (2011) examined the effectiveness of syphilis

screening and treatment in reducing stillbirths and cited compelling evidence from the meta-analysis above by Blencowe.(12) Ishaque noted that this finding was consistent with other observations from different regions including Sub-Saharan Africa, Russia, Asia, and South America, where syphilis is a significant cause of perinatal death.(13)

Building on these findings, Wang (2023) evaluated 3.6 million pregnant women in Zhejiang province, China between 2015–2020. The study found that implementing universal syphilis screening combined with treatment interventions led to significant improvements in maternal and infant outcomes. Screening coverage during pregnancy increased from 96.31% to 99.24%, and first trimester antenatal care coverage rose from 55.27% to 77.82%. The screening protocol used both non-treponemal tests (rapid plasma reagin (RPR) or Toluidine Red Unheated Serum Test (TRUST)) and treponemal tests (Treponema pallidum hemagglutination assay (TPHA) or Treponema pallidum particle agglutination (TPPA)), with additional confirmatory testing available when necessary. The treatment coverage increased significantly from 88.30% to 98.25%, and adequate treatment rates rose from 66.92% to 83.37%. These interventions resulted in substantial reductions in adverse outcomes: perinatal deaths decreased by 19.30% annually; congenital syphilis declined by 26.55% annually; and other neonatal complications dropped by 14.67% annually. By 2020, congenital syphilis rates had fallen to 2.36 cases per 1,000 births, demonstrating the effectiveness of the comprehensive eliminate mother-to-child transmission (EMTCT) program.(14)

Different prenatal syphilis screening approaches

Various intervention types of syphilis screening demonstrated varied effectiveness in increasing screening coverage. Two medium-quality evidence syntheses found the effectiveness of interventions to improve antenatal syphilis screening varied considerably. First, an older evidence synthesis by Hawkes (2011), evaluated interventions to improve antenatal syphilis screening across 10 studies conducted between 1986–2008. The interventions primarily consisted of universal screening approaches targeting all pregnant individuals attending antenatal care. Nine studies implemented decentralized testing and treatment, with eight using RPR testing at POC settings to enable same-day results and treatment. The screening protocols varied but generally involved either RPR testing alone or combined with treponemal testing. Most studies (9/10) also incorporated health-system strengthening components such as healthcare provider training, laboratory support, supply chain management, or monitoring. Only two studies specifically focused on encouraging women to seek earlier antenatal care. The interventions demonstrated significant reductions in adverse pregnancy outcomes: perinatal death decreased by 54% (pooled from three studies); stillbirth reduced by 58% (pooled from three studies); and congenital syphilis was reduced in all four studies measuring this outcome, though with heterogeneous results. Partner notification was reported in only three studies, with higher rates in intervention groups. The authors concluded that interventions to improve antenatal syphilis screening could reduce syphilis-attributable stillbirths and perinatal deaths by approximately 50%, representing a worthwhile investment for improving maternal and neonatal health outcomes even in diverse healthcare settings.(15)

A systematic review by Harrison (2024) revealed a concerning pattern in antenatal screening efforts across LMICs, finding that while HIV receives considerable attention, syphilis screening has been comparatively neglected.(16) Among the 27 interventional studies examined, only six (22%) focused on syphilis screening, highlighting a significant gap in addressing this preventable cause of adverse pregnancy outcomes. The evidence for syphilis-specific interventions showed several promising approaches. Quality improvement initiatives demonstrated particularly strong results, with one study by Althabe and colleagues showing a remarkable improvement in syphilis screening rates from 93.8% to 99.9% using a plan-do-study-act approach. This intervention involved opinion leaders, reminders, audit and feedback, and supportive supervision activities, underscoring the importance of comprehensive quality improvement strategies. Community-based interventions also showed potential for increasing syphilis screening access, though these were less commonly implemented for syphilis compared to HIV. Policy changes, such as transitioning to POC testing for syphilis, showed mixed results. Dassah and colleagues found no significant improvement following a policy change to POC testing in Ghana, suggesting that technology introduction alone may be insufficient without addressing broader health system barriers. Health technology interventions, including a bidirectional text messaging system studied by Oliveira-Ciabati and colleagues, effectively improved syphilis screening but faced implementation challenges. Infrastructure improvements through the introduction of rapid testing showed promise but were most effective when combined with

health-systems strengthening activities. The review identified several critical gaps in syphilis screening research. Unlike HIV, which benefited from congregation-based approaches and community health worker programs, syphilis lacked tailored community-based interventions. Additionally, few studies examined the integration of syphilis screening with other health services or the use of financial incentives to boost uptake. The authors emphasize the importance of addressing syphilis within a holistic triple elimination approach that includes HIV and hepatitis B. They suggest that the manufacturing of three-in-one testing cassettes could advance this goal, as duo-test kits already exist for HIV and syphilis. Ultimately, strengthening health systems appears fundamental to ensuring reliable and sustainable improvements in antenatal syphilis screening across LMICs.

Ganiyu (2017) conducted a comprehensive evaluation of Botswana's syphilis screening program across 15 public healthcare facilities in Gaborone between 2004–2008. Data collected from antenatal registers in September 2009 revealed that out of 31,221 pregnant women registered for antenatal care over the five-year period, 26,875 (86.1%; 95% CI 85.7–86.5) were screened for syphilis, while 4,346 (13.9%; 95% CI 13.5–14.3) were not screened. The screening coverage followed a fluctuating pattern: initially increasing from 87.2% (95% CI 86.4–88.0) in 2004 to 89.7% (95% CI 89.0–90.4) in 2005, then declining to 79.0% (95% CI 77.9–80.1) in 2006, before increasing again to 82.0% (95% CI 81.0–83.0) in 2007 and reaching 91.2% (95% CI 90.5–91.9) in 2008.(17) The study uncovered significant variations in screening implementation between facilities, with proportions of women not screened ranging from as low as 3.1% to as high as 33.6% across different clinics and years. Only two clinics (BH 1 and Phase 2) demonstrated consistent improvement in screening coverage throughout the study period. According to Botswana's national guidelines, screening for syphilis with non-treponemal tests (venereal disease research laboratory (VDRL) or RPR) was mandatory in both the first and third trimesters of pregnancy. While the overall trend showed improved screening coverage during 2004–2008 with 75% of clinics showing rising trends in screening proportions, the significant facility-level variations highlighted implementation inconsistencies. The authors recommended further investigation into factors causing these variations in screening coverage between facilities.

Rapid testing approaches/point-of-care in antenatal care settings

Rapid testing approaches were found to be particularly effective at improving screening uptake. A medium-quality evidence synthesis by Swartzendruber (2015) examined the impact of introducing rapid syphilis testing (RST) in antenatal care settings and found substantial increases in antenatal syphilis testing following the introduction of RST in all included studies (n = 6) across eight low- and middle-income countries in Africa, Asia, and Latin America.(18) The improvements occurred regardless of geographic setting, rural/urban location, existing HIV testing infrastructure, or baseline screening levels. Even in settings where syphilis testing was previously almost non-existent (1–2% of pregnant female), high screening coverage was quickly achieved. For example, in Uganda, syphilis screening among first-time antenatal care attendees increased dramatically from 1.7% to 96.4% following RST introduction. RST introduction did not negatively impact existing HIV screening in facilities already offering rapid HIV testing and, in some cases, increased HIV screening rates. The simultaneous introduction of RST and rapid HIV testing was found to be particularly effective, with one study reporting an increase from 9% to 98% screening for both infections.

A high-quality systematic review on strategies of testing for syphilis during pregnancy by Shahrook (2014) included two cluster-randomized controlled trials.(7) One of included clinical studies was conducted in Mongolia and implemented a treponemal POC test (SD Bioline Syphilis 3.0) in a cluster-randomized trial of pregnant individuals attending their first antenatal visit (antenatal care clinics) and at the third trimester. The study reported significantly higher screening rates for women receiving the POC test at first antenatal visit (99.0%) and third trimester (99.7%) compared to those receiving conventional laboratory RPR+TPHA testing at first antenatal visit (79.6%) and third trimester (62.1%). Treatment rates were also significantly higher in the POC test group (98.9% versus 89.6%). Most importantly, this study demonstrated a substantial 93% reduction in congenital syphilis cases in the treponemal POC test group compared to laboratory testing (0.13 versus 1.95 cases per 1,000 pregnancies), highlighting a clear positive association between treponemal POC tests and improved pregnancy outcomes.

Another included clinical study that was conducted in South Africa, took a different approach by implementing a non-treponemal onsite RPR test performed bedside using battery-powered equipment. While this study showed a notable reduction in adverse outcomes (58% reduction in miscarriages and 55% reduction in perinatal deaths) compared to laboratory-based RPR testing, these differences did not reach statistical significance. Unlike the Mongolia study, there was no significant difference in treatment rates between groups (64.1% versus 68.6%), despite a considerable reduction in treatment delay (an average of 16 days) for POC test patients. The study attributed these results partially to unexpectedly lower adverse outcomes in the control group and technical challenges in performing the more complex onsite RPR test in field conditions.(19) A medium-quality evidence synthesis by Brandenburger and Ambrosino (2021) (18) examined the impact of antenatal syphilis POC test on pregnancy outcomes in LMICs and included seven modelling studies and the same two clinical studies as evidence synthesis by Shahrook (2014).(7)

Similarly, a low-quality evidence synthesis Akhtar (2018) including one study reported that the implementation of rapid syphilis tests (RSTs) in antenatal care led to an increase in screening rates from 10.6% at baseline to 67.5% at midline, though it later declined to 56.3% in Kalomo District, Zambia.(20) Wang (2018) assessed the feasibility and acceptability of using WHO-prequalified dual HIV/syphilis RDTs for same-day results in antenatal care (ANC) clinics (21 rural and urban township hospitals in Guangdong and Anhui provinces) in China from 2014 to 2015 and found that the proportion of females tested in their first and second trimester increased from 76.0% with standard blood tests to 90.1% with the dual RDT. Additionally, 98.3% of those tested received their results on the same day, enabling timely diagnosis and intervention.(21)

A single study by Adeyinka (2018) conducted a retrospective analysis of maternal syphilis screening and treatment data from Nigerian prevention of mother-to-child transmission (PMTCT) initiative from 2013 to 2016. The study examined data from 9,713,724 women who attended antenatal care during this period. Despite an estimated 6,633,183 pregnant women annually in Nigeria, only 36.6% (2,428,431) accessed antenatal care services at PMTCT sites each year. This study found that while the proportion of pregnant individuals receiving syphilis testing increased from 12.2% in 2013 to 16.3% (still far below the 95% target set by the WHO for elimination) in 2016, treatment coverage for those who tested positive actually decreased from 71.3% to 54.9%. Overall, only 64.9% of syphilis-positive pregnant individuals received treatment.(22) The study highlighted inadequate antenatal care utilization (36.6%) as a major barrier to elimination efforts.

Rapid testing approaches in emergency department

Beyond traditional antenatal settings, Stafford (2024) demonstrated that implementing an opt-out and rapid POC syphilis testing program in an emergency department significantly improved syphilis screening among pregnant patients in Southeastern Texas, increasing the screening rate from 2% in the pre-implementation phase to 56.4% post-implementation, representing a 28-fold increase. The program detected a syphilis prevalence of 3.5% among tested pregnant individuals, with all positive cases receiving immediate treatment before discharge.(23)

Risk-based additional screening

Limited evidence specifically addressed geographic risk-based screening. Harrison's (2024) systematic review noted that syphilis screening approaches varied significantly across different geographical contexts, suggesting that location-specific factors influence implementation strategies.(16) The review emphasized the need for tailored approaches based on local epidemiology and health-system capabilities. Hawkes's (2011) systematic review included studies from various geographic settings and noted that interventions were effective across diverse healthcare contexts, suggesting that geographic targeting of interventions may be valuable.(15) Wang (2023) noted increasing syphilis rates among specific demographic groups, including females under 20 or over 35 years old, multiparous females, and those with pregnancy complications, suggesting the need for targeted interventions for these populations.(14) Stafford (2024) highlighted the importance of implementing opt-out testing in emergency departments to reach pregnant females who may otherwise miss routine prenatal screening, particularly among underserved populations who may rely more heavily on emergency departments for healthcare.(23)

Screening frequency patterns

Many of the studies reviewed focused on screening at first antenatal visit, with Lin (2018) and Wang (2023) both examining the effectiveness of universal screening at first visit in China.(8; 14)

The timing of screening and treatment was found to be critical in determining congenital syphilis outcomes. A systematic review and meta-analysis by Hawkes (2013) demonstrated that the timing of antenatal care screening interventions (during first antenatal care visit) makes a significant difference in preventing adverse outcomes due to syphilis.(24) This systematic review and meta-analysis included five studies with nearly 3,000 pregnancies and found that females who were screened and treated for syphilis in the first or second trimester had significantly lower odds of adverse pregnancy outcomes compared to those screened in the third trimester (OR = 2.24, 95% CI 1.28–3.93), indicating that females screened and treated later were more than twice as likely to experience adverse outcomes. Among specific outcomes, the odds of congenital syphilis in infants were higher when screening and treatment occurred later in pregnancy (OR = 2.92, 95% CI 0.66–12.87). There was also a notable increased risk of prematurity (OR = 2.09, 95% CI 1.09–4.00) in mothers presenting late to antenatal care.(24) The authors concluded that encouraging all pregnant women to seek care in the first two trimesters should be a priority for health programs worldwide.

A matched cohort study conducted at a single site in western Kenya by Laktabai (2022) found that despite appropriate treatment with benzathine penicillin, pregnant individuals with latent syphilis at antenatal care enrolment had significantly higher risk of delivering low birthweight babies compared to females without syphilis. Females with positive syphilis POC and TPHA test results had a more than five-fold increased risk of low birthweight babies (adjusted prevalence ratio: 5.84; 95% CI 1.08–31.5) compared to test-negative females, even after receiving treatment.(25) It was suggested that current implementation of syphilis screening and treatment at routine antenatal enrolment (which occurred at an average of 22 weeks gestation) is insufficient to mitigate the risks of syphilis to offspring and earlier screening and treatment during pregnancy may be necessary to improve pregnancy outcomes.

Dual screen (first visit + third trimester)

Ganiyu (2017) noted that according to Botswana's national guidelines, screening for syphilis with non-treponemal tests (VDRL or RPR) was mandatory in both the first and third trimesters of pregnancy and found overall screening coverage increased from 87.2% in 2004 to 91.2% in 2008, despite a temporary decline to 79.0% in 2006.(17) The Mongolia study in Shahrook's (2014) systematic review implemented a treponemal POC test at both first antenatal visit and third trimester, reporting significantly higher screening rates compared to conventional laboratory testing at both time points (99.0% versus 79.6% at first visit; 99.7% versus 62.1% at third trimester).(7) In their systematic review, Hawkes (2011) reported that third-trimester screening was substantially higher in intervention groups compared to controls (no screening). Munkhuu and colleagues reported 95.3% versus 61.2% in controls, while Hira and colleagues found 15.1% versus 1.6% in controls.(15)

Q2: What are the harms of screening for syphilis in pregnant persons?

Overall, the potential harms of prenatal screening for syphilis are poorly studied. Some studies we identified reported on false results, but did not examine the harms associated with these false results explicitly. We identified one medium-quality evidence synthesis and six single studies (all high-relevance) that reported the number of false-positive or false-negative results, which may result in unintended harms attributable to prenatal screening. A medium-quality evidence synthesis examining the impacts and specificity of various laboratory syphilis screening measures employing both reverse (n = 6) and traditional (n = 1) sequence algorithms found that false positives/false negatives for syphilis in immunoassays ranged from 46.5% to 88.2% of the total positives/negatives identified in studies that reporting a sufficient number of positive/negative results.(8)

A retrospective cohort study conducted in the United States found that a VDRL test at initial prenatal visit and delivery (traditional algorithm) led to 24 false-positive/false-negative results (10.2%) out of a total of 236 positive and negative results that were confirmed through fluorescent treponemal antibody absorption test (FTA).(26) The total number of false-positives and false-negatives reported in relation to the total tests conducted (122,408) was 0.19%. A second U.S. study using a retrospective cohort design and employing standard laboratory tests with a reverse sequence algorithm identified 183 false positives (82.8%) out of 221 positive screens, but the false discovery rate across all tests was 0.83% (95% CI 0.77–88).(27) Notably, false discovery rates were similar for traditional (used prior to 2014 before this study was conducted) and reverse algorithms, as well as for syphilis Immunoglobin and total assays. Finally, a retrospective evaluation of the laboratory test LIASON Treponema Assay, which is used to qualitatively determine total antibodies directed against *Treponema pallidum* in human serum, identified 194 tests identified as positive or negative, of which 156 were identified as false-positive or false-negative results, representing 88.2% of the total number of positive/negative results conducted in a U.S. sample.(28)

Two other studies outside of the United States reporting false-positive/negative results were identified. A retrospective evaluation of the ARCHITECT Syphilis TP Assay, a chemiluminescent microparticle immunoassay for qualitative detection of antibodies (IgG and IgM) against *Treponema pallidum* in human serum and plasma, identified 35 false-positive and false-negative results out of a total 11,640 tests conducted in Thailand.(29) Among the 11,640 syphilis tests conducted, 65 were classified as reactive, of which 35 were identified as likely false-positive, representing 53.8% of the total number of reactive results. Finally, we identified two studies that did not use standard laboratory testing. A prospective cohort study conducted in Burnika Faso using two different RDTs (SD Bioline T-RDT and DPP Screen and Confirm Assay), found that DPP testing did not reduce the number of overtreated pregnant individuals compared to T-RDT, and also had a higher proportion of under diagnosis (48.4% versus 2.2%; p>0.001).(30) A matched cohort study conducted in western Kenya found that syphilis POC testing (a syphilis-only test or an HIV-syphilis dual test) at antenatal care enrollment led to 29 false results (19.3%) out of 150 positive and negative results that were confirmed through TPHA. Specifically, there were 18 false-positive results (17.0% of TPHA-negative cases) and 11 false-negative results (25.0% of TPHA-positive cases), indicating a sensitivity of 75.0% and specificity of 83.0% when using TPHA as the reference standard.(25)

Overall, false positives and false negatives in syphilis screening approaches are relatively low compared to the overall number of tests administered in studies for which this was reported, but relatively high compared to the overall number of positive and negative results identified through those tests. This finding suggests that conducting multiple antenatal screening tests for syphilis at different time points throughout pregnancy may be a prudent approach to mitigate the potential impacts of false-positive and false-negative results.

Q3: What is the most cost-effective strategy for syphilis screening during pregnancy? (Canadian evidence)

Only one study conducted in Canada addressing the potential costs avoided by expanding three-time prenatal syphilis screening through standard serological testing using the reverse algorithm (first trimester, 28–32 weeks, and delivery) was identified.(31) Prior standard practice consisted of a single standard serological test at first prenatal encounter (usually first trimester) using the reverse algorithm, followed by a secondary non-treponemal test (RPR or VDRL) to confirm a positive result. The direct short-term cost of treating one uncomplicated case of congenital syphilis was CA$18,151.40. The total cost of expanded syphilis screening was CA$139,608 per year which, for the 125 low-risk syphilis-exposed infants in Manitoba identified in 2021, was associated with a cost-avoidance ratio of 16.25. If all 206 syphilis-exposed infants in Manitoba were identified in 2021, the associated cost avoidance ratio would be 26.78. This study highlights the potential cost-effectiveness of more frequent prenatal screening using standard serological testing at different stages of pregnancy in Canada.

Next steps based on the identified evidence

The following recommended actions, synthesized from a comprehensive review of the evidence on prenatal syphilis screening, address critical knowledge gaps and implementation challenges. They provide a structured framework to enhance screening strategies, treatment protocols, and health system responses across diverse settings. These

recommendations aim to strengthen our understanding of screening effectiveness while improving maternal and infant outcomes.

- Research Priorities
  - Conduct comparative effectiveness studies that directly compare different screening approaches (universal vs. risk-based, single vs. multiple screenings, different testing algorithms).
  - Investigate optimal timing of screening to determine the earliest gestational age that maximizes prevention of adverse outcomes, given evidence that even screening at 22 weeks may be insufficient.
  - Evaluate the clinical implications of false-positive and false-negative results from different testing approaches, which remain poorly studied despite their potential impact.
- Screening and Treatment Strategies
  - Develop integrated testing approaches that combine syphilis screening with other antenatal tests (HIV, hepatitis B) to increase efficiency and coverage.
  - Implement POC rapid testing more widely, particularly in settings with limited laboratory infrastructure or where women present late for antenatal care.
  - Create standardized protocols for partner notification and treatment to reduce reinfection rates, which were inconsistently addressed in existing research.
  - Enhance early antenatal care engagement strategies to facilitate first-trimester screening, when intervention is most effective.
  - Explore multiple screening timepoints for all pregnant women, given evidence that single screening may miss infections acquired later in pregnancy.
  - Develop approaches for screening in non-traditional settings (emergency departments, community settings) to reach women who may not access routine antenatal care.
- System Strengthening and Policy Implications
  - Strengthen health systems to support sustainable screening programs, particularly in low-resource settings where implementation challenges are greatest.
  - Develop context-specific implementation models that account for geographic variations in health system capacity and syphilis prevalence.
  - Create policies supporting triple screening approaches (first trimester, 28–32 weeks, delivery) in high-prevalence settings, based on cost-effectiveness evidence.
  - Establish surveillance systems to monitor screening coverage, treatment completion, and congenital syphilis rates to evaluate program effectiveness.
  - Develop strategies to maintain adequate treatment completion rates in settings where screening has improved but treatment rates remain suboptimal.

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This rapid evidence synthesis was funded by the Public Health Agency of Canada. The McMaster Health Forum receives both financial and in-kind support from McMaster University. The views expressed in the rapid evidence synthesis are the views of the authors and should not be taken to represent the views of the Public Health Agency of Canada or McMaster University.

ISSN 2819-5639 (online)