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EVIDENCE BRIEF

Universal Prenatal Syphilis Screening and Congenital Syphilis

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Key Findings

- Evidence on the effectiveness of universal enhanced screening during pregnancy in preventing congenital syphilis is limited. However, a lack of repeat screening in the third trimester contributes to missed opportunities for preventing congenital syphilis.
- Adherence to third-trimester syphilis screening varies widely. However, most studies identified risk factors associated with lower access to additional screening, which may lead to undetected and untreated syphilis infections in pregnant people.
- The cost-effectiveness of rescreening pregnant people in the third trimester is typically higher in areas with relatively higher syphilis rates. There is limited evidence that implementing universal screening at the first trimester, third trimester and at delivery is cost-avoidant in the context of an outbreak.

Issue and Research Question

Maternal and congenital syphilis are significant public health problems due to the risk of adverse pregnancy outcomes, such as pre-term labour and stillbirth, and severe infant outcomes, including nerve damage, hearing loss and infant death.[1] There is a high likelihood of syphilis transmission to the fetus, particularly for pregnant people with untreated primary or secondary infections, with the vast majority of congenital syphilis cases occurring in-utero versus through exposure to infectious lesions during delivery. Prevention of congenital syphilis requires access to adequate and timely maternal syphilis screening, diagnosis, and treatment. Early treatment of maternal infection is effective at treating fetal infection and preventing congenital syphilis.[2,3]

Approximately 77% of untreated maternal infectious syphilis cases result in adverse fetal outcomes, including serious outcomes such as spontaneous abortion, stillbirth or hydrops fetalis. [4,5] Clinical manifestations of syphilis infection in infants range in severity and include anemia, thrombocytopenia, lymphadenopathy, hepatosplenomegaly, neurosyphilis and osteochondritis. The onset of symptoms is often delayed, meaning many live infants with the infection are asymptomatic at birth.[6] This delay can make it more difficult to identify and/or diagnose congenital syphilis at the time of birth, particularly in circumstances where maternal infection status at time of delivery is unknown.

Rates of syphilis have been increasing in Canada over the past 10 years across all genders, but particularly among females of childbearing age. In Canada, the rate in females increased by 773% from 1.7 cases per 100,000 in 2016 to 14.9 cases per 100,000 in 2020. The majority (87%) of these cases are between 15–39 years of age. [7] A corresponding increase in congenital syphilis cases has also been observed in Canada since 2017, with seven reported cases in 2017 compared to 96 reported cases in 2021.[8] The United States (US) is also observing an increased in the incidence of infectious maternal syphilis and congenital syphilis, particularly since 2012. In 2020, 2,148 cases of congenital syphilis cases were reported in the US.[9]

The Canadian Guidelines for Sexually Transmitted Infections (CGSTI) recommend syphilis screening for all pregnant people in their first trimester or at first prenatal visit.[10] Using a risk-based approach, the CGSTI recommend syphilis rescreening in the third trimester (at 28–32 weeks gestation) and at delivery for pregnant people living in areas with syphilis outbreaks and/or for individuals at ongoing risk of infection. Health care providers may also consider more frequent screening during pregnancy for those at higher risk of infection. Individual risk factors for syphilis include history of anonymous sex, unstable housing, substance use, sexual contact with a known case of syphilis, recent history of a sexually-transmitted or blood-borne infection (STBBI) and/or member of a vulnerable population.[11]

Some jurisdictions have responded to the changing epidemiology of infectious syphilis among women and subsequent increases in congenital syphilis by recommending additional universal prenatal screening in the third trimester and/or at delivery (e.g., Manitoba and British Columbia in Canada). Repeated screening for syphilis during pregnancy can detect persons that have seroconverted after first trimester screening, such as when syphilis is acquired after the initial prenatal screening test or when an early syphilis infection was not detected during the initial prenatal screening (i.e., tested after exposure, but prior to seroconversion). Rescreening in the third trimester aims to identify maternal infection and initiate early treatment in order to reduce the risk of congenital syphilis. This is in contrast to screening at delivery, which aims to detect congenital syphilis cases and provide appropriate and timely treatment.[6]

The objective of this evidence brief is to summarize the available evidence regarding universal prenatal syphilis screening during third trimester and/or delivery as a strategy to prevent congenital syphilis.

Methods

A grey literature search on prenatal syphilis screening programs was performed on November 17, 2022 using keyword searches in the Google search engine and government websites. Prenatal syphilis screening guidelines were reviewed for all Canadian provinces and the following OECD jurisdictions: the US, Australia (national), United Kingdom (UK) and New Zealand.

The PHO Library Services team conducted literature searches on prenatal syphilis screening in MEDLINE on November 4, 2022 (n=162 articles) and in Embase, Biosis Previews and CINAHL Complete databases on November 8, 2022 (n=341 articles). The searches included English language studies conducted in Organisation for Economic Co-operation and Development (OECD) member countries and published from January 1, 2012 up to the search dates. A final search in PubMED and medRxiv (preprints) to identify articles that were missed or published since the initial searches was conducted on November 22, 2022. Two reviewers from PHO screened articles reporting on prenatal syphilis screening programs, prioritizing those with third-trimester screening and/or at delivery screening; articles focused on point-of-care tests in prenatal screening were excluded. 41 articles were selected for full text review and ultimately 19 articles were included. The search strategies for this evidence brief are available upon request.

Main Findings

Prenatal Syphilis Screening Policies

> In Canada, Manitoba, Nunavut and the Northwest Territories have universal screening policies for syphilis in pregnant people at the first trimester, third trimester and at delivery. Nova Scotia has universal screening in the first and third trimester. Alberta, British Columbia and the Yukon recommend universal screening in the first trimester and at delivery. The remaining provinces have a policy of universal screening at the first trimester and risk-based screening for the third trimester and at delivery.

Appendix A outlines the current syphilis screening policies for the jurisdictions examined. In Canada, all 13 provinces and territories (PTs) recommend universal first trimester screening in pregnant people; 1/13 recommend universal screening in the first and third trimester (or other mid-gestational timeframe); 3/13 recommend universal screening in the first trimester and at/or near delivery; 3/13 have universal screening at first trimester, third trimester and at delivery. 6/13 PTs recommend risk-based decision making for syphilis rescreening in the third trimester and/or at delivery.

The United States (US) national guidelines from the CDC recommend universal screening in the first trimester, with risk-based screening in the third trimester and at delivery, and repeat screening in areas with high syphilis morbidity. However, US prenatal syphilis screening is mandated at the state level with significant heterogeneity across the country. Warren et al. (2018) reported that as of 2016, 45 out of 51 states require prenatal syphilis screening. Of the 45 states with screening requirements, 38 require first trimester screening or at first prenatal visit, 12 require universal third trimester screening, and five require third trimester screening only if the patient is at high risk of infection. An additional three states require screening at delivery, and five only require screening at delivery if the patient is at higher risk.[12]

All international jurisdictions examined (US, Australia, Western Australia, UK and New Zealand) recommend universal screening in the first trimester, with three out of five utilizing risk-based screening in the third trimester and at delivery (e.g. Australian national guidance). However, the Australian state of Western Australia recommends universal screening in both first and third trimesters.

Missed Opportunities for Congenital Syphilis Prevention

> The included literature agreed that a lack of repeated third trimester screening contributed to missed opportunities to prevent congenital syphilis cases.

Eight studies were reviewed including one from Manitoba, Canada and seven from the US that examined lack of additional prenatal screening as a missed opportunity for congenital syphilis prevention or that identified a lack of repeated prenatal screening later in pregnancy as a risk factor for congenital syphilis.[13-20] Benoit et al. (2022) reviewed 60 cases of congenital syphilis in Winnipeg, Manitoba from 2018 to 2020, where it was observed that 40.0% (24/60) of cases did not receive any prenatal care and 23.3% (14/60) received some prenatal care but were likely at high-risk of infection in their third trimester.[13]

Seven studies from the US reported on additional screening as congenital syphilis prevention opportunity, specifically additional screening in the first and third trimesters.[14-20] Two studies specifically reported that late identification of seroconversion in pregnancy was a missed opportunity for congenital syphilis. Late seroconversion in pregnancy was defined in the studies as cases that had a negative test early in pregnancy, but tested positive <30 days before delivery, on the day of delivery, or ≤90 days after delivery. In a US study of 1,306 congenital syphilis cases from 2013–18, Kimball et al. (2020) reported that 146/1,306 (11.2%) of the cases were due to a late identification of seroconversion in pregnancy. Kimball et al. also found that there was wide geographical disparity, with the proportion of cases attributed to late seroconversion, ranging from 6.5% in the west to 39.6% in the northeast US.[14] In another study of congenital syphilis cases in New York City (2013–20), late identification of seroconversion was a significant missed prevention opportunity in 31/51 (60.8%) of reported cases. 23/31 (80.7%) of these maternal cases were not screened in the third trimester.[15]

Five studies across different jurisdictions in the US reported on the role of third trimester screening in congenital syphilis prevention. In a congenital syphilis review board study of 79 cases of congenital syphilis in Louisiana, Rahman et al. (2019) reported that 15 (19%) cases could have been prevented if their mothers had received state mandated third trimester screening.[16]. In an Arizona outbreak of 57 cases of congenital syphilis (2017–18), Sykes et al. (2020) reported that repeated third trimester screening could have prevented 14 (24.6%) cases of congenital syphilis.[17] In a report of 18 infectious syphilis cases among pregnant people in Minnesota (MN Department of Health 2019) (2016–17), five cases would have been missed if only first trimester screening had been performed. [18] In New York City from 2010 to 2016, Slutsker et al. (2018) reported that among the 68 associated maternal cases, 22 acquired syphilis during pregnancy of which 15 did not receive additional third trimester screening. 12/15 (80%) of those who did not receive additional third trimester screening had a known risk factor for syphilis.[19] In a two time-period observational study conducted in 2013–14 and repeated in 2018–19 in Florida, Matthias et al. (2022) reported on 1,213 pregnant females with syphilis that resulted in 341 cases of congenital syphilis. During the earlier period, 21/83 (25.3%) of mothers were not rescreened in the third trimester while 36/258 (13.9%) were not rescreened in the latter period.[20]

Adherence to Prenatal Syphilis Screening Recommendations

> Adherence to prenatal syphilis screening in third trimester and/or at delivery (both universal and risk-based) varied widely. Factors associated with to lower access to additional screening included maternal age (≤20 years), lower socioeconomic status, non-English primary language and being Black, Hispanic or First Nation.

Among reviewed studies, five examined adherence to prenatal screening syphilis recommendations, including three studies conducted in the US and two in Canada (i.e., Alberta and Manitoba). Prior to 2012, Alberta recommended that all pregnant people receive syphilis screening in the first trimester (1–12 weeks gestation), at mid-gestation (24–28 weeks gestation) and at delivery (±3 days of delivery). In a cohort study of 99,609 pregnancies in Alberta from 2010 to 2011, Plitt et al. (2016) determined the proportion of pregnant females that received the three recommended prenatal syphilis tests. This study showed 20.7% of pregnant females received all three recommended screenings and 13.9% received first trimester and mid-gestation screenings. Risk factors for not receiving all three screening tests included First Nations status (adjusted odds ratio [aOR]: 1.8; 95% confidence interval [95% CI]: 1.62–1.96), rural remote residence (aOR: 3.6; 95% CI: 3.10–4.20) and sole use of a midwife for prenatal care (aOR: 13.7; 95% CI: 9.20–20.39). Additional risk factors included not being married, smoking during pregnancy, having lower income and being younger than 20 years old.[21] In a descriptive study of syphilis screening in 77,000 pregnant females in Manitoba (2015–19), Shaw et al. (2022) reported that the proportion of females screened at all intervals (first trimester, third trimester, delivery) increased annually from 0.2% in 2015 to 13.6% in 2019. In addition, combined first and third trimester screening increased during the study from 1.5% to 19.4%. [22] Manitoba introduced universal prenatal syphilis screening at third trimester and at delivery in 2019.

In the US, adherence to first and third trimester syphilis screening was typically low at less than 50%.[23-25] In a retrospective cohort study of 9,048 pregnant females in Illinois (2015–18), Clement et al. (2022) reported that while 96.9% of patients had syphilis screening at their first prenatal visit, just 24.4% of pregnant females received screening during their third trimester, despite it being mandated at the state level since 1999. In Illinois, risk factors for not receiving third-trimester screening included being ≤19 years old (aOR: 2.2; 95% CI: 1.26–3.73), being Black (aOR: 1.3; 95% CI: 1.12–1.59), Hispanic (aOR: 1.3; 95% CI: 1.10–1.54), non-English primary language (aOR: 1.6; 95% CI: 1.18–2.25) and having public insurance (aOR: 2.6; 95% CI: 2.18–2.99). [23] In a study of 504,943 pregnant females on Medicaid in six US states (i.e., Georgia, Kentucky, Louisiana, North Carolina, South Carolina, and Tennessee) from 2017 to 2019, Lanier et al. (2022) reported that the mean rate of first trimester screening was 39% (range among states: 15%–62%) and the mean rate of third trimester screening was 30% (range: 9%–55%). Third trimester screening was universal in Georgia, Louisiana, North Carolina; however, it was risk-based in Tennessee and not required in Kentucky and South Carolina. Third trimester screening rates were lower in states where it was not mandated [24]

In a cross-sectional cohort study of 21,260 pregnancies among 19,574 women in Indianapolis, Indiana (2014–16), Ojo et al. (2021) reported that 81.7% of pregnancies had syphilis testing in any trimester plus at the time of delivery. Because Indiana uses risk-based screening recommendations, Ojo et al. also examined prenatal syphilis screening among high-risk women. Individuals were classified as “high-risk” based on their residence in a zip code with a high prevalence of syphilis. 89.1% of high-risk pregnancies had prenatal syphilis testing anytime during pregnancy plus at the time of delivery. In both groups, the proportion receiving screening at any time during pregnancy plus delivery increased over time. [25]

Cost-effectiveness of Universal Rescreening in Pregnancy

> The cost-effectiveness of rescreening pregnant people in the US in the third trimester was typically higher when local or regional syphilis rates were relatively higher. Limited Canadian data demonstrated a cost avoidance of implementing universal screening at the first trimester, third trimester, and at delivery in the context of a provincial syphilis outbreak.

Six studies examined the cost-effectiveness of repeated screening for the prevention of congenital syphilis.[22, 26-30] Five of the six studies modelled cost-effectiveness in the US, while one was modelled for Manitoba. Application of the findings from these studies should use caution, as all but one study modelled US data that are based on healthcare payee models that vary from Canada. Four of the six studies reported that third trimester screening was cost effective in preventing cases of congenital syphilis.[17, 26, 29-30] For example, in a 2020 study out of Arizona, it was estimated that based on 14,716 pregnant females insured in Arizona in 2017, the cost of additional third trimester screening (and subsequent treatment of identified cases) would cost $113,413. However, the combined hospitalization savings from preventing nine cases of congenital syphilis among infants who are publicly insured would be $113,940 with a net savings of $527 per year.17 Modelling a theoretical cohort of 3.9 million females in the US, Hersh et al. (2018) reported that the addition of third trimester screening resulted in better outcomes for mothers and newborns and higher quality-adjusted life-years (QALYs) compared to screening only in the first trimester. The authors reported that third trimester screening resulted in 41 fewer cases of congenital syphilis, 73 fewer cases of intrauterine fetal demise and 27 fewer neonatal and infant deaths, leading to cost savings of $52 million and 4,000 additional QALYs. [26] In a short-term cost-avoidance analysis out of Manitoba (using 2021 syphilis case and pregnancy data, Boodman et al. (2022) modelled cost avoidance of congenital syphilis by expanding screening from no prenatal screening or first trimester screening only to universal screening in the first trimester, third trimester and at delivery. The cost-avoidance ratio was calculated from the direct short-term cost of uncomplicated congenital syphilis treatment in 2021 divided by the cost of universal expanded syphilis screening. With the assumption of 16,800 annual pregnancies, 81 cases of congenital syphilis, and the prevention of 125 congenital syphilis cases due to timely identification of maternal syphilis infection with prenatal screening, the screening program would result in a cost avoidance ratio of 16.3 compared to first trimester screening only, and 26.8 if no screening program existed.[30]

Two of the five studies found that third trimester screening resulted in increased costs; however, both studies demonstrated cost effectiveness under specific local syphilis infection rates, highlighting possible thresholds for when third trimester screening can be cost effective.[27-28] Modelling cost effectiveness using a theoretical cohort per 4 million pregnant females in the US that screened negative in the first trimester, Albright et al. (2015) reported that at a seroconversion rate of 0.012%, third trimester rescreening would prevent 60 cases of congenital syphilis and seven neonatal or newborn deaths. Preventing one case of congenital syphilis would require third trimester screening of 65,790 pregnant females. Universal third trimester screening would only be cost effective if the seroconversion rate was 0.017%; the model was sensitive to incidence of syphilis seroconversion in a region with increased cost effectiveness with increased seroconversion rates. The authors concluded that for third trimester rescreening to be cost-effective (at least at local or regional scales), the rate of primary and secondary syphilis in females would need to be 19 times higher than the national average of 0.0009%.[27] Similarly, in a retrospective cohort study of 58,569 deliveries (over 17 years in a high-risk community in the US), Shiber et al. (2014) reported that for rescreening in the third trimester to be cost-effective, the rate of congenital syphilis in newborns would have to be 3.5% (3,500 cases/100,000 deliveries).[28]

Discussion and Conclusions

Ontario is experiencing a significant surge in cases of infectious syphilis among females of childbearing age and as a result is seeing historic congenital syphilis case counts. Precipitating factors for these increases are not well understood.

Evidence on the effectiveness of universal enhanced syphilis screening during pregnancy is limited, though additional screening in pregnancy is associated with congenital syphilis prevention. Several jurisdictions have opted to increase syphilis screening among pregnant people as an approach to prevent congenital syphilis cases. The impact and cost-effectiveness of additional screening can be influenced by adherence to screening recommendations by patients and providers, the local burden of congenital syphilis, and the incidence of late seroconversion of syphilis in pregnancy. In 2018, the United States Preventative Task Force (USPSTF) reported no new evidence on the effectiveness of repeated screening during pregnancy, while the CDC and joint guidelines from the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) endorse repeat screening in the third trimester and at delivery in females at high risk of syphilis[31-33] High-risk pregnant people include those living in areas with a relatively higher prevalence of syphilis, incarcerated, living with HIV and those involved in sex work.[12,34]

Limitations of Risk-Based Screening

Some jurisdictions that have moved to universal enhanced prenatal syphilis screening have remarked on the limitations of risk-based screening for identifying people that would benefit from additional syphilis screening in pregnancy.[35,36] The stigmatization of identified risk factors, including substance use, housing instability or multiple sex partners, may lead to a lack of disclosure by the individual. Additionally, health care providers may not sufficiently screen individuals for risk factors due to stigma, discomfort or a lack of capacity among other factors.[35-37]

Studies examining the characteristics of pregnant people with syphilis identified a significant number do not disclose a risk factor that would prompt additional screening as per existing guidelines. Studies in the US and the UK reported 49% and 42%, respectively, of pregnant females with infectious syphilis did not disclose risk factors typically associated with being ‘high risk’ for infectious syphilis (e.g., history of drug use, history of incarceration, male partner who reports sex with men).[38-39]

Potential Harms of Syphilis Screening

The primary harm of the screening can be a false-positive result, which require increased clinical evaluation, increased anxiety for the mother, improper use of antibiotics and potential for penicillin-induced anaphylaxis in mothers.[31] Phlebotomy is routinely performed during routine prenatal care at 28 weeks and at delivery, so it is not thought that there would be an additional risk compared to standard care.[30]

Implications for Practice

Implementing universal prenatal syphilis screening at third trimester and/or delivery will depend on a number of factors, including but not limited to feasibility, public and provider acceptability, cost, laboratory capacity, sustainability of the program and syphilis epidemiological trends. Modifications to screening recommendations should be accompanied by provider outreach and education to support adherence to recommendations.

Inadequate access to prenatal care is associated with congenital syphilis across many jurisdictions. Access to prenatal care often intersects with risk factors that prompt repeated syphilis screening, such as unstable housing, belonging to a vulnerable subpopulation and substance use. Equitable access to additional prenatal screening opportunities is an important consideration to ensure this intervention reaches those who may benefit most. [13,14, 17, 40-42] Modifications to screening recommendations should go hand-in-hand with efforts to understand and improve access to culturally safe prenatal care among those who disproportionately receive inadequate care. This includes the important step of recognizing and working to mitigate the impact of colonization and structural racism on social determinants of health, vulnerability to STBBI and trust in health care.

Appendix A: Syphilis Prenatal Screening Recommendations by Jurisdiction

Table 1: Syphilis Prenatal Screening Recommendations: Canadian Jurisdictions

Jurisdiction	First Trimester Screen	Third Trimester/ Mid-Gestation Screen	Screen at Delivery	Additional details
Yukon[43]	Universal	Risk-based	Universal	N/A
Northwest Territories[44]	Universal	Universal	Universal	N/A
Nunavut[45]	Universal	Universal	Universal	N/A
British Columbia[46]	Universal	Risk-based	Universal	N/A
Alberta[47]	Universal	Risk-based	Universal	Alberta previously recommended universal rescreening in second trimester but this was discontinued in 2012[48]
Saskatchewan[49]	Universal	Risk-based	Risk-based	N/A
Manitoba[50]	Universal	Universal	Universal	Monthly syphilis testing during pregnancy and again at delivery if: newly diagnosed with syphilis or reinfection during the pregnancy; or had a previous syphilis infection, but received or is receiving treatment during current pregnancy
Ontario[51]	Universal	Risk-based	Risk-based	N/A
Quebec[52]	Universal	Risk-based	Risk-based	N/A
New Brunswick[53]	Universal	Risk-based	Risk-based	N/A
Nova Scotia[54]	Universal	Universal	Risk-based	N/A
PEI[55]	Universal	Risk-based	Risk-based	N/A
Newfoundland & Labrador[56]	Universal	Risk-based	Risk-based	N/A

N/A: Not applicable

Table 2: Syphilis Prenatal Screening Recommendations: International Jurisdictions

Jurisdiction	First Trimester Screen	Third Trimester/ Mid-Gestation Screen	Screen at Delivery	Additional details
US (CDC)[32]	Universal	Risk-based	Risk-based	Variability across states
Australia[57]	Universal	Risk-based	Risk-based	N/A
Western Australia[58]	Universal	Universal	N/A	Universal rescreening at 36 weeks
UK[59]	Universal	N/A	N/A	Additional screening is based on risk assessment, no specific timeframe
New Zealand[60]	Universal	Universal	N/A	Universal rescreening offered with second antenatal screening tests

N/A: Not applicable

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