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CADTH HEALTH TECHNOLOGY ASSESSMENT REPORT

Screening for *Chlamydia Trachomatis* and *Neisseria Gonorrhoeae* During Pregnancy — Project Protocol

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Background and Rationale

In Canada, chlamydia (CT) and gonorrhea (GC) are the most commonly reported sexually transmitted infections (STIs).[1] The bacterium Chlamydia trachomatis causes chlamydia infections, while the bacterium Neisseria gonorrhoeae causes gonorrhea infections.[1] These infections are a significant public health concern, as their rates continue to increase despite numerous prevention and treatment strategies.[1] In 2014, 109,263 cases of CT and 16,285 cases of GC were reported, corresponding to rates of 307.4 and 45.8 per 100,000 individuals, respectively.[2] CT infections are disproportionately higher in females than in males across all age groups (382.5 versus 230.5 per 100,000).[2] The overall GC rates are higher in males than in females (58.8 versus. 32.9 per 100,000).[2] However, amongst 15- to 19-year-olds, females have higher rates of GC.[2] High-risk groups for contracting infections include sexually active youth under 25 years of age, sex workers, homeless persons, persons with a previous history of STI, and persons afflicted with substance abuse.[3]

CT and GC are associated with genitourinary, rectal, and pharyngeal infections.[4] In females, CT and GC infections are often asymptomatic.[5] Though asymptomatic, early detection and treatment of these infections is necessary to prevent potential complications, sexual transmission, and transmission to neonates in the perinatal period.[5,6] When symptoms develop, genitourinary signs and symptoms of infection in females are nonspecific and include dysuria, vaginal discharge, vaginal bleeding, and abdominal or pelvic pain.[5] Asymptomatic CT infections are more common in males than GC infections.[5] Symptomatic infections in males may present as dysuria; urethral discharge or pruritus; or testicular, epididymal, or scrotal pain.[5]

As infection rates for both CT and GC are highest in individuals of child-bearing age, the potential to cause substantial downstream sequelae make them a particular concern. Untreated infections with CT or GC can lead to pelvic inflammatory disease and its deleterious sequelae, including infertility, ectopic pregnancy, and chronic pain.[5] During pregnancy, these infections and their complications can result in spontaneous abortion, stillbirth, preterm delivery,[7] low birth weight, and perinatal mortality.[8] CT and GC during pregnancy can be transmitted to the neonate resulting in substantial morbidity.[8,9] GC infection can be transmitted to the fetus in utero if there is prolonged rupture of the membranes or it may manifest as other pathologies such as gonococcal arthritis.[9] Neonatal conjunctivitis or ophthalmia neonatorum (ON) develops in 15% to 44% of neonates born to birthing parents infected with CT,[8] and 30% to 42% of neonates born to birthing parents infected with GC.[9] Of all the cases of ON in Canada, CT and GC are responsible for 40% and 1%, respectively.[4] In neonates born to birthing parents infected with CT during pregnancy, 50% are at risk for the infection, and 10% to 20% are at risk of developing pneumonia.[10]

Early detection can prevent significant adverse gynecological and non-gynecological health outcomes, neonatal morbidity, and perinatal mortality. For infants, the most common cause of morbidity of being born to a birthing parent who is actively infected with CT and/or GC is ON, and, historically, the clinical management has focused on universal neonatal ocular prophylaxis.[11] The Canadian Paediatric Society (CPS) no longer recommends neonatal ocular prophylaxis for the prevention of ON.[10] The CPS decision to shift the focus away from universal neonatal ocular prophylaxis to prenatal screening was based on the low prevalence rates of ON in Canada, the availability of prenatal screening and treatment, and the questionable effectiveness of erythromycin as prophylaxis for ON.[10,12]

Several screening guidelines exist for the screening of CT and GC during pregnancy. However, they all differ with respect to their target population, recommendations, and their scope at the provincial or national level. The CPS recommends that all pregnant persons must be screened for CT and GC at their first prenatal visit.[10] Furthermore, the CPS recommends repeat screening after treatment for persons who test positive, and for persons who initially test negative and are at high risk of acquiring the infections later in their pregnancy (e.g., persons who are not in a monogamous relationship).[10] The CPS recommendations were not formulated based on a systematic review (SR) of the evidence, and therefore the quality of evidence upon which the recommendations are based or the strength of the recommendations remain unclear.

The 2015 Society of Obstetricians and Gynaecologists of Canada's *Adolescent Pregnancy Guidelines* recommends routine screening for CT and GC when an adolescent first presents for prenatal care, in the third trimester, postpartum, and at any other time during the pregnancy if risks arise.[13] The Province of Quebec's evidence-based screening guidelines for STIs and blood-borne infections recommends universal screening for CT and GC as part of basic prenatal care, and repeat screening if the pregnant person is exposed, or if the pregnant person and/or partner exhibit risky behaviour. If repeat screening is necessary, the guidelines recommend screening be performed around the 28th week of pregnancy and at the time of delivery. Furthermore, screening is also recommended for persons presenting for termination of pregnancy.[14]

The only national screening guidelines for all pregnant persons were published in 1996 by the Canadian Task Force on Preventive Health Care.[15] The guidelines were based on a SR of the literature that included five studies published between 1983 and 1995, and recommend screening pregnant persons for CT infections in their first trimester.[15] The guidelines were exclusive to CT infections and did not include a recommendation for GC infections. Additionally, there was no recommendation included on the optimal timing and frequency of repeat screening during pregnancy and the types of tests and specimens that should be utilized.[15] Patients with GC infections are commonly co-infected with CT, and both infections can be identified using similar tests on the same specimen, making screening of both these infections at the same time ideal.[5,6] The Canadian Task Force on Preventive Health Care is currently in the process of developing guidelines for screening CT and GC in the general population, but screening in the pregnant population will not be included within the scope of those guidelines.

In addition to the variation in screening guidelines, the use of diagnostic tests and speciments vary across Canada. A number of nucleic acid amplification tests (e.g., polymerase chain reaction, transcription-mediated amplification) are used to detect CT and GC.[16] According to the Canadian Guidelines on Sexually Transmitted Infections, nucleic acid amplification tests (NAATs) are considered the most sensitive and specific tests for CT infection and the most sensitive tests for GC infection.[16] GC can also be detected using cultures from endocervical or urethral specimens. CT and GC may be detected using urine, vaginal, or cervical samples.[16] Across all specimens and tests, the sensitivity for CT ranges from 86% to 100%, and the specificity is greater than 97%.[6] The sensitivity for GC ranged from 90% to 100%, and the specificity is greater than 97%.[6]

All confirmed cases of CT and GC require treatment with antibiotics.[17,18] For CT and GC, repeat screening is recommended six months after treatment initiation.[17,18] A test-of-cure visit has been recommended during pregnancy to ensure treatment has not failed. The test-of-cure visit for CT using a NAAT has been recommened three to four weeks post-

treatment.[17] The test-of-cure visit for GC has been recommended three to seven days post-treatment if using culture and two to three weeks after treatment if using NAATs.[18]

Given the potential for the variation in tests (e.g., type of NAATs, culture), specimen, timing, and frequency for CT and GC screening during pregnancy, and the variation in national and provincial guidelines, there is a pan-Canadian need for updated guidance. A comprehensive and multidisciplinary review of the literature is required to inform the formulation of new national guidelines and to guide policy-makers on important considerations for a screening strategy, including the optimal timing and frequency of screening during pregnancy, the test itself, type of specimen, and approach (i.e., universal or targeted). CADTH will conduct a health technology assessment (HTA) that will assess the clinical effectiveness and cost-effectiveness of screening for CT and GC during pregnancy, as well as the perspectives of pregnant persons, their partners, and their health care providers regarding these screening strategies to ensure the feasibility and acceptability of resulting guidelines.

Policy Question

How should Canadian health care providers screen pregnant persons for *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* — at what time(s) during pregnancy, using what specimen, with what frequency, and using a universal or a targeted approach?

Objectives

The purpose of this HTA is to address the policy question through an assessment of the clinical effectiveness and safety, and cost-effectiveness, and patients', partners', and health care providers' perspectives and experiences regarding the screening of pregnant persons for CT and GC. An analytic framework for the HTA can be found in Appendix 1.

Research Questions

The proposed HTA will address the following research questions:

Clinical Review:

1. What is the comparative detection yield, clinical utility, and harms of differing screening strategies for the detection of *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* during pregnancy?

Economic Review:

2. What is the most cost-effective screening strategy for *Chlamydia trachomatis* and/*or Neisseria gonorrhoeae* in pregnant persons?

Perspectives and Experiences of Pregnant Persons, their Partners and Health Care Providers :

3. What are the experiences and perspectives of pregnant persons and their partners with respect to undergoing screening for *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae*? And, what are their health care providers' perspectives on screening for *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* during pregnancy?

Methods

To inform the preparation of the clinical, economic, and patient and provider experiences and perspectives, sections of the protocol, a preliminary scoping review of existing HTAs, systematic reviews (SRs), and primary studies were completed. The protocol was developed a priori and will be followed throughout the HTA process. The protocol has also been prospectively registered in the PROSPERO database[19] and any deviations will be disclosed in the final report. Similarly, any updates will accordingly be made to the PROSPERO submission.

Specific study designs and methods have been developed to address each research question of this HTA, which are elaborated according to the particular research question.

Clinical Review

The protocol for the clinical review has been developed and reported in consideration of the Preferred Reporting Items for SRs and Meta-Analyses Protocols (PRISMA-P) checklist[20] for guidance on clarity and completeness.

The clinical review will address the following research question:

Research question 1: What is the comparative detection yield, clinical utility, and harms of differing screening strategies for the detection of *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* during pregnancy?

Study Design

The scoping review identified four SRs[6,21-23] and 14 potentially relevant primary clinical studies on CT and GC screening.[24-37] The 14 primary clinical studies[24-37] were not included in the body of evidence in the identified SRs. Three of the four SRs[6,21,22] were conducted to inform the U.S. Preventive Services Task Force (USPSTF) recommendations and their subsequent updates, but the target population included men and women, pregnant adults, and adolescents. The latest USPSTF recommendations were based on an SR by Nelson et al.(2014)[6]. A comprehensive evaluation of the accuracy of tests for CT and GC was included in the review. The test sensitivity for CT ranges from 86% to 100%, and the specificity is greater than 97%.[6] The test sensitivity for GC ranged from 90% to 100%, and the specificity is greater than 97%.[6] The methodological quality of this review was considered acceptable, and the details of the methods section are reported comprehensively and transparently to verify the credibility of the results. Therefore, in order to reduce redundancy and not duplicate effort, the diagnostic test accuracy of tests for CT and GC will not be explored in this report. Rather, results from the review will be leveraged to aid in the interepretation of the evidence with regards to the screening for CT and/or GC during pregnancy.A *de novo* SR of primary clinical studies will be conducted for question 1 to address the policy question to ensure Canadian contextual relevance.

Literature Search Methods

The literature search will be performed by an information specialist, using a peer-reviewed search strategy.

Information will be identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates, Embase (1974–), the Cochrane Central Register of Controlled Trials via Ovid; Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO; and PubMed. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be chlamydia, gonorrhea, pregnancy, and screening.

To address research question 1, no methodological filters will be applied to limit retrieval by study type. Retrieval will be limited to documents added to the databases since January 1, 2003. Case reports, cases series, reviews, meta-analyses, letters, editorials, conference abstracts, and presentations will be excluded from the search results. The search will be limited to English- or French-language publications.

The initial searches will be completed in January 2018. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review will be incorporated into the analysis if they are identified prior to the completion of the stakeholder feedback period of the final report. Any studies that are identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies to the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) will be identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, economics-related resources, patient perspective groups, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Study Eligibility

Inclusion and Exclusion Criteria

Full-text publications will be included if they are published between January 1, 2003 to the present in English and meet the eligibility criteria outlined in Table 1. The 2003 date was chosen as prior to this date, now obsolete tests such as antigen detection, direct fluorescent antibody tests, and nucleic acid hybridization tests were routinely used to detect CT and GC.[16] The current laboratory diagnosis recommendations published by the Public Health Agency of Canada do not include these tests, and accordingly studies using these tests will be excluded from this review.[16] Studies using more than one test type will be excluded if results using NAATs and culture are not reported independently. Publications describing case reports, cases series, and literature reviews will be excluded, as will letters, editorials, conference abstracts, and presentations. Duplicate publications and multiple publications of the same study will be excluded unless they provide unique findings of interest. The population of interest is all pregnant adults and pregnant adolescents aged 12 years and

older. If the population is mixed (e.g., includes non-pregnant persons), the primary clinical study will be included if the results of the population of interest are reported separately. Studies reporting on a mixed population will also be included if more than 80% of the total population comprises the population of interest.

Primary clinical studies conducted in countries with a health care context comparable to Canada's will be eligible for inclusion. Therefore, inclusion will be restricted to studies conducted in Australia, Canada, New Zealand, the US, the UK, or a member of the European Economic Area.

Primary clinical studies will be included that report on the detection yield, clinical utility, and harms of one or more screening strategies involving NAAT or culture tests conducted on samples taken from pregnant persons. The primary outcome of interest is the assessment of detection yield (i.e., the number or per cent of positive tests, the number or per cent of false-positives for CT and GC, and the number or per cent of false-negatives for CT and GC). Secondary outcomes of interest include clinical utility and harms. Outcomes of interest in the assessment of clinical utility will include but will not be limited to the number or per cent of pregnant persons eligible for screening who obtain screening in accordance with recommendations, the number or per cent of people eligible who decline screening, the number or per cent of persons referred for treatment, the number or per cent of persons obtaining treatment, the number or per cent of pregnant persons obtaining resolution or cure of infection, the optimal timing of the test-of-cure visit, the number of repeat infections identified, patient satisfaction with screening strategy, adverse gynecological and non-gynecological health outcomes related to CT or GC infection (i.e., infertility, ectopic pregnancy, spontaneous abortion, preterm labour, pelvic inflammatory disease, chronic abdominal pain), and adverse infant health outcomes related to CT or GC infection (i.e., pneumonia, ON and its sequelae, prematurity, low birth weight, infection with CT or GC, mortality). Any measure of harms related to the screening strategy (i.e., anxiety, fear of stigmatization, adverse pregnancy outcomes, and negative impacts of false-positives and false-negatives) will be considered as outcomes of interest.

Eligibility criteria for clinical studies are outlined in Table 1.

Table 1: Inclusion Criteria for the Clinical Review (Question 1)

Components	Description
Population	Pregnant adult and adolescent females (≥ 12 years of age, up to and including delivery)
Intervention	A screening strategy involving: • NAAT for CT and GC or culture for GC • urine, vaginal, or cervical samples for NAATs; urethral or endocervical samples for cultures • using a universal or targeted approach • any timing (i.e., the point during pregnancy at which the initial diagnostic test is performed) • any frequency (i.e., number of times the diagnostic test is conducted during pregnancy) • any subsequent management of pregnant persons with confirmed disease.
Comparator	• An alternate screening strategy conducted with an alternate NAAT or culture test, test specimen (urine, vaginal, or cervical samples), or approach (universal or targeted), at an alternate point or frequency during pregnancy, or with any subsequent management strategy for pregnant persons with confirmed disease. • No screening strategy

Outcomes	**1. Primary outcomes:**
	Detection yield:
	Any measure of detection yield including but not limited to:
	• number/per cent of positive tests for CT and/or GC
	• number/per cent of false-positive tests for CT and/or GC
	• number/per cent of false-negative tests for CT and/or GC.
	
	2. Secondary outcomes:
	Clinical Utility:
	Any measure of clinical utility including but not limited to:
	• number/per cent of pregnant persons eligible for screening who obtain screening in accordance with recommendations
	• number/per cent of pregnant persons eligible for screening who decline screening
	• number/per cent of pregnant persons referred for treatment
	• number/per cent of pregnant persons referred for treatment who obtain treatment
	• number/per cent of pregnant persons obtaining resolution or cure of infection
	• optimal timing of the test-of-cure visit
	• number/per cent of repeat infections identified, number/per cent of repeat infections missed
	• patient satisfaction with screening strategy (as assessed by a standardized questionnaire)
	• any measure of adverse gynecological and non-gynecological health outcomes associated with CT and/or GC infection including but not limited to:
	  ○ infertility
	  ○ ectopic pregnancy
	  ○ spontaneous abortion
	  ○ preterm labour
	  ○ pelvic inflammatory disease
	  ○ chronic abdominal pain
	• any measure of adverse neonatal health outcomes associated with CT and/or GC infection including but not limited to:
	  ○ neonatal pneumonia
	  ○ neonatal ocular infection
	  ○ ocular infection sequelae (e.g., blindness, corneal infection)
	  ○ stillbirth
	  ○ prematurity
	  ○ low birth weight
	  ○ infection with CT and/or GC
	  ○ perinatal mortality.

Components	Description

	Harms:
	• Any measure of harm from undergoing screening by any method or strategy including but not limited to:
	  ○ anxiety (as measured by a standardized scale)
	  ○ fear of stigmatization (as measured by a standardized scale)
	  ○ number and type of adverse pregnancy outcomes (e.g., miscarriage)
	  ○ negative impacts of false-positives and false-negatives.

Time Frame	2003 to present
Study Designs	Primary clinical studies that include eligible active intervention and eligible comparison group (including randomized controlled trials and non-randomized controlled studies of any design) [a]
Countries	Australia, Canada, European Economic Area, New Zealand, the UK, and the US

CT = *Chlamydia trachomatis;* GC = *Neisseria gonorrhoeae;* NAATs = nucleic acid amplification tests
[a] Case reports, cases series, reviews, letters, editorials, conference abstracts, and presentations will be excluded

Study Selection

Study selection will be conducted in DistillerSR[38] using standardized screening forms. Two reviewers will independently screen titles and abstracts of all citations retrieved from the literature search relevant to research question 1 and those deemed potentially relevant by either reviewer will be retrieved in full. The same strategy will be used for literature identified through electronic databases and the grey literature. The two same reviewers will then independently review all full-text articles applying the eligibility criteria outlined in Table 1 and compare selections. Discrepancies between reviewers will be resolved through discussion or by consulting a third reviewer, as necessary. The study selection process will be presented in a PRISMA flow chart.

The draft list of included studies will be posted online for stakeholder review for ten business days, during which stakeholders may submit feedback or additional publications for potential inclusion. Any additional publications identified will be screened using the same two-stage process as described previously. The final list of included and excluded studies, along with a rationale for exclusion, will be included in the final report.

Data Extraction

Data extraction for the included studies will be conducted using standardized data extraction forms in a Microsoft Excel spreadsheet, which has been designed to extract relevant information from the studies, including but not limited to:

- first author's name, publication year, country, funding sources, and reported conflicts of interest
- study design
- eligibility criteria
- participant characteristics including, number of pregnant persons, age, comorbidities, and risk factors for infection (where reported)
- description of intervention, including diagnostic test, specimen, timing of screening, frequency of screening, setting of screening, and subsequent management of people identified as positive, including pregnant persons pre-and post-natal and neonates

- description of comparator(s), including diagnostic test, specimen, timing of screening, frequency of screening, setting of screening, and subsequent management of people identified as positive including pregnant persons pre- and post-natal and neonates
- description of outcomes reported, follow-up duration, and study loss to follow-up
- description of subgroups of interest and outcomes reported by subgroups
- results for each outcome (i.e., detection yield, clinical utility, and harms)
  - If available, outcomes will be extracted by subgroups of interest.

Two reviewers will pilot the use of the data extraction form, independently in duplicate, on a small representative sample of included studies (up to three) until consistency is reached; i.e., the reviewers are in agreement as to the consistent extraction of data relevant to this review. After calibration, one reviewer will extract the data and the second reviewer will verify the extraction for accuracy. Disagreements will be resolved through discussion, involving a third reviewer, as necessary. Data from figures will be extracted if relevant numerical data are not provided. Authors of included clinical studies will be contacted for missing information, clarification of issues, and verification of extraction.

Risk of Bias Assessment

The Cochrane Risk of Bias tool[39] will be used to assess the risk of bias in randomized controlled trials (RCTs) and the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) will be used to assess the included non-randomized studies. The Cochrane Risk of Bias tool[39] contains seven items across six domains. A judgment “Low Risk of Bias,” “High Risk of Bias,” or “Unclear Risk of Bias” is assigned to each item to indicate an overall judgment of “Low Risk of Bias,” “High Risk of Bias,” or “Unclear Risk of Bias” to each included RCT.[39] The RoBANS tool contains six domains, and a judgment of “high,” “low,” or “unclear” can be assigned to each domain in alignment with the Cochrane Risk of Bias Tool and Grading of Recommendations Assessment, Development and Evaluation (GRADE).[40]

Two researchers will pilot the quality assessment tools on a random sample of three publications and discuss discrepancies until they are in agreement that they have reached consistency in their assessments. Subsequent to piloting, both reviewers will independently conduct the methodological assessment on the remaining included studies and compare findings. Discrepancies between the two reviewers will be discussed until consensus is reached or by consulting a third reviewer, as necessary. The findings of the methodological assessments for each included study will be reported, including an assessment of the strengths, and limitations across studies will be summarized using tables and a narrative description. The results from the methodological assessments will not be used to further include or exclude studies.

Data Analysis

A descriptive summary of study and participant characteristics will be prepared to describe the quantity of studies by study design, year and country of publication, sample size, population, intervention, comparator, settings, and outcomes, where applicable. Tables will be organized to emphasize screening strategy characteristics, including diagnostic test, test specimen, timing, frequency, and infection management strategy, and will accompany the narrative summary to ensure the consistency of the presented information across all studies and facilitate study comparisons by the reader.

In addition, tables will be created to summarize outcomes of interest as identified in Table 1, with a separate table being prepared for each reported outcome. Each table will include data elements that are expected to impact on the heterogeneity of results between studies, including screening program characteristics (e.g., test used, specimen used) and population characteristics (e.g., risk factors). Using these tables as a foundation, a narrative synthesis of the results of included primary clinical studies will be conducted. The tables will also be used to inform an assessment of methodological and clinical heterogeneity, and therefore a decision will be taken as to whether to proceed with synthesizing outcomes data using a meta-analysis or narrative approach. Clinical experts will be consulted to inform the assessment of clinical heterogeneity, and also to identify patient and intervention factors that are expected to influence clinical outcomes. Results will not be meta-analyzed in the presence of substantial heterogeneity.

If the included studies are deemed homogeneous concerning clinical and methodological characteristics, meta-analysis using a random-effects model will be pursued to derive pooled estimates of effect for each outcome of interest reported by two or more studies. Input from clinical experts will be obtained to determine which studies describing which interventions are reasonable to consider for pooling. In the event that studies of different designs assess the same outcome of interest, studies using different designs will be considered separately for pooling.

When deemed appropriate, dichotomous outcomes (e.g., perinatal mortality) will be summarized using relative risks and 95% confidence intervals (CIs). Continuous outcomes (e.g., per cent of positive tests) will be pooled using mean differences and corresponding 95% CIs. Forest plots will be created for individual summary estimates. Meta-analyses will be carried out using Cochrane Review Manager software (version 5.3, or the most up-to-date version available).

Statistical heterogeneity will be assessed visually using graphical presentations (e.g., forest plots) and statistically through calculations of the I^2 and Cochran's chi-square test and statistics. Statistical heterogeneity will be interpreted based on the Cochrane handbook, where ≥ 75% will be interpreted as considerable heterogeneity.[41] If the *P* value for Cochran's chi-square test is < 0.10, heterogeneity will be considered statistically significant and will be further explored.[41]

If the data permits, the reasons for heterogeneity will be explored using subgroup or meta-regression analyses. Potential subgroups of interest to be examined in the exploratory analysis include age, persons presenting for termination of pregnancy, persons with ectopic pregnancy, and persons at high risk for contracting infections during pregnancy. Individual contrasts will be explored amongst subgroups of interest, and consistency assessed. Meta-analysis will not proceed in the event of unexplained heterogeneity. If meta-analysis does proceed, summary measures and CIs will be calculated and reported. Sensitivity analyses may be considered to evaluate the robustness of findings because of variation in study characteristics, including but not limited to study size, study design, and methodological quality.

If pooling is not appropriate because of significant heterogeneity that cannot be addressed analytically, the findings will be synthesized narratively. The synthesis will describe the direction and size of any observed effects across primary clinical studies and it will include an assessment of the likelihood of clinical benefit (i.e., diagnostic detection yield, clinical utility) or harms (i.e., anxiety, fear of stigmatization). Direct comparisons between interventions will be reported as presented in the studies. There will be no formal testing

conducted to indirectly compare interventions not directly compared against each other. The findings will be grouped by infection and outcome, and the type of diagnostic test, test sample site or specimen, and screening strategy employed will be highlighted.

Depending on the amount of data available, the researchers will additionally aim to present findings based on the following subgroups: age, persons presenting for termination of pregnancy, persons with ectopic pregnancy, and persons at high risk for contracting infections during pregnancy. High-risk groups for contracting infections include sexually active youth under 25 years of age, sex workers, homeless persons, persons with a previous history of STI, and persons afflicted with substance abuse.[3]

If 10 or more studies of a given study design and a particular outcome are identified, publication bias will be assessed graphically using funnel plots and objectively using Egger's regression test and Begg's rank correlation test.[41]

Overall Body of Evidence

The overall quality of the body evidence will be assessed using the GRADE framework to provide an assessment of the overall confidence in the effect for each outcome of interest.[42] The GRADE approach categorizes the quality of evidence, by outcome, from high to very low.[42] According to GRADE, RCTs begin with a high-quality rating but can be rated down for a number of reasons, including study limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias.[42] Non-randomized studies start with a low-quality rating but can be rated up if there is a very large magnitude of effect, dose-response gradient, or the presence of plausible biases that would decrease an apparent effect. The assessments will be performed independently by two reviewers.[42] Any discrepancies between the reviewers will be discussed until consensus is reached or by consulting a third reviewer, if necessary. All assessments will be conducted using the GRADEpro software package and presented in GRADE evidence profile tables.

Reporting of Findings

The final report will be prepared in consideration of relevant reporting guidelines for SRs; i.e., PRISMA[43] and PRISMA harms.[44] The strengths and limitations of the review, applicability of the review findings, and the policy implications will be addressed in the final report.

Economic Review

Research question 2: What is the most cost-effective screening strategy for CT and/or GC in pregnant persons?

To address research question 2, a primary economic analysis will be conducted to evaluate the cost-effectiveness of screening strategies in pregnant persons for CT and/or GC infections.

Primary Economic Analysis

A decision-analytic model will be developed to assess the costs and health outcomes associated with different screening strategies for CT and GC in pregnant persons. The economic analysis will determine whether screening is cost-effective and, if yes, what screening strategy would most likely be considered cost-effective. In defining screening strategies, aspects under consideration will include the test (e.g., NAAT for CT and GC, or culture for GC), test specimen (e.g., cervical, vaginal, urine samples), the screening approach (e.g., universal or targeted), timing (e.g., first trimester, second trimester, third trimester), and the frequency (e.g., single, twice).The final set of screening strategies to be evaluated in the economic analysis will be defined through consultation with clinical experts and other relevant stakeholders and will reflect the available evidence from the clinical review.

As CT and/or GC infection can lead to higher risk of complications for the pregnant person (e.g., pelvic inflammatory disease), the fetus (e.g., preterm birth, spontaneous abortion), and the infant (e.g., vertical transmission of infection, ON, lower-tract respiratory infection), the model will capture the sequela of infection until the first three months of infancy for both the pregnant person and the infant.

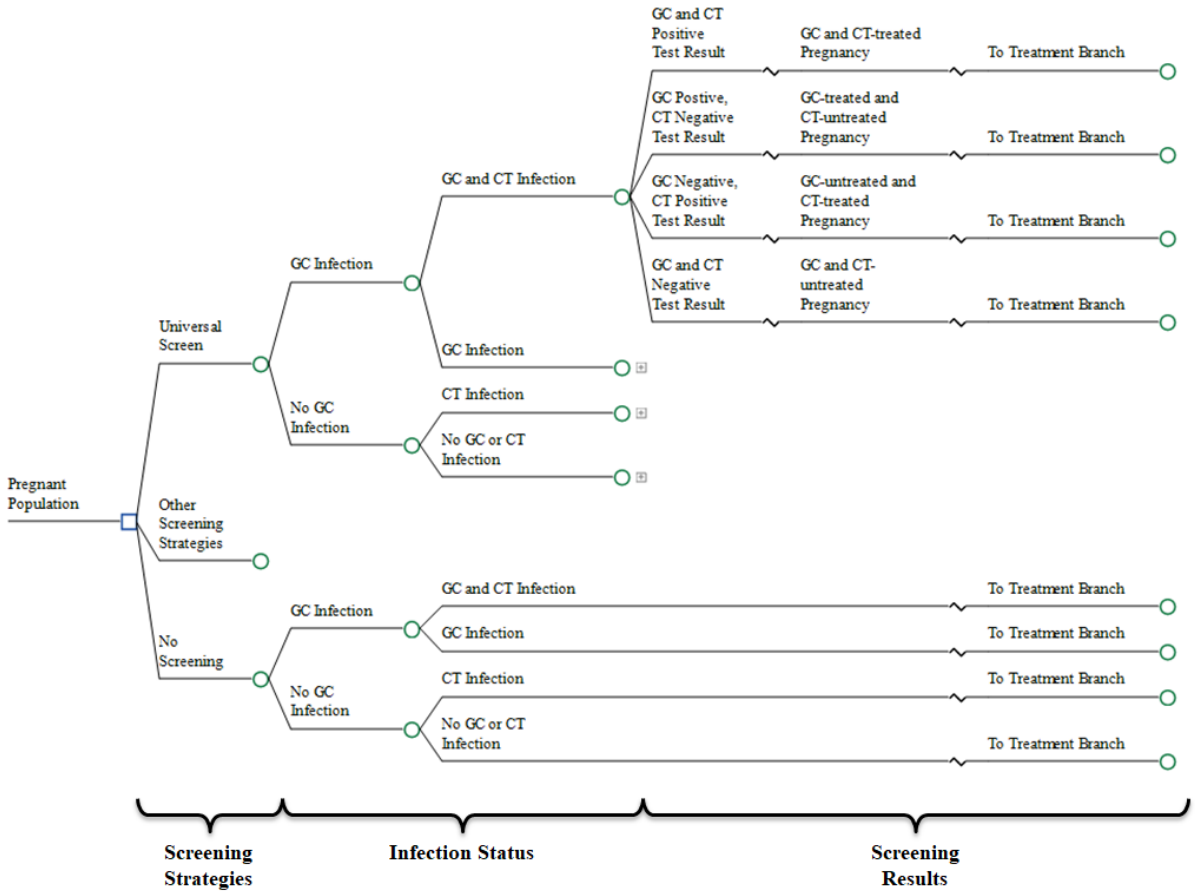
Model Design

The decision-analytic model will be in the form of a decision tree and capture the period from pregnancy up to three months postpartum. Although this may not capture the long-term implications of screening — notably the prevention of long-term complications for the infant (e.g., blindness) — this was considered appropriate given that these serious complications are rare.[12,45] As the prevention of long-term complications will not be attributed to the screening and management of CT or GC infections in the economic model, the cost-effectiveness of screening strategies will likely represent a conservative estimate.

The decision tree will model the infections, screening, and treatment (Figure 1) and incorporate various health events related to the natural history and clinical outcomes of these infections. Identical patient cohorts reflecting the characteristics of pregnant persons in Canada will proceed through the screening strategies of interest (e.g., no screening, different screening strategies). Incidence of CT, GC, and co-infections will inform the proportion of patients in the cohort with an existing STI. The proportion of patients who test positive or negative will be based on the performance of the test (e.g., sensitivity and specificity) and the underlying prevalence of these infections within the pregnant population. The impact of screening (treatment of these STIs or treatment withheld) will be modelled. In cases of true-positive screening results, for instance, treatment would be offered to the pregnant person, thereby reducing the probabilities of adverse disease outcomes for both the pregnant person (Figure 2) and the infant (Figure 3). In cases of false-negative

screening results, on the other hand, treatment would be withheld and expose both the pregnant person and the infant to a higher risk of encountering the consequences of persistent infection.

Figure 1: Proposed Model Structure Describing the Health Outcomes Following CT and GC Screening in Pregnant Persons

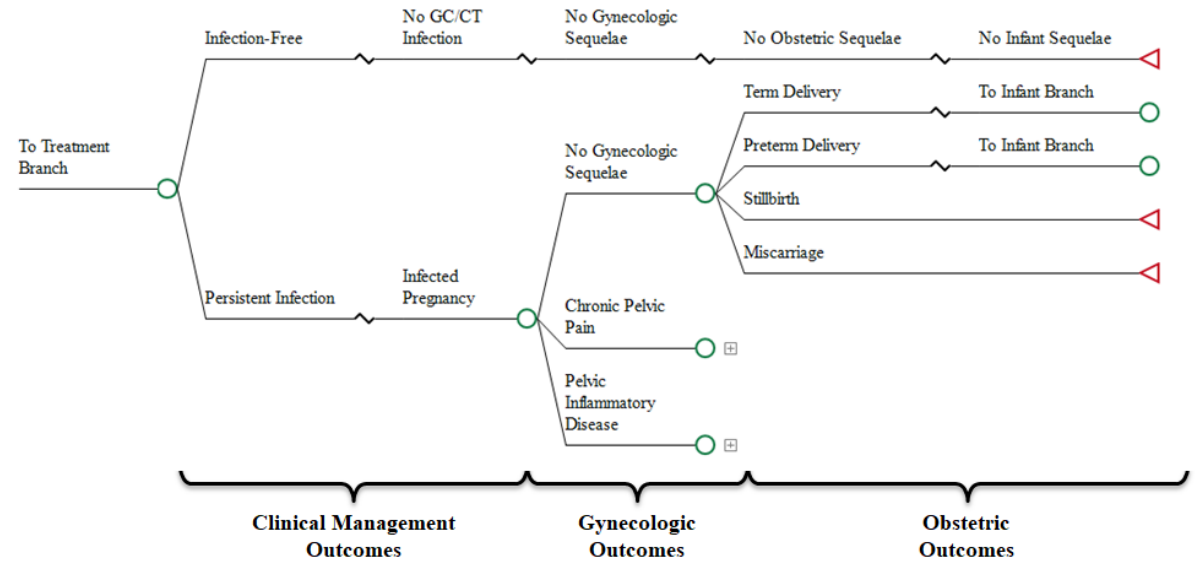


CT = *Chlamydia trachomatis;* GC = *Neisseria gonorrhoeae.*

□ = decision node; ○ = chance node; ⊞ = further branch structures to the right identical to the branches above.

Note: Although not explicitly shown, the sequence for the other screening strategies resembles the "universal screen" strategy.

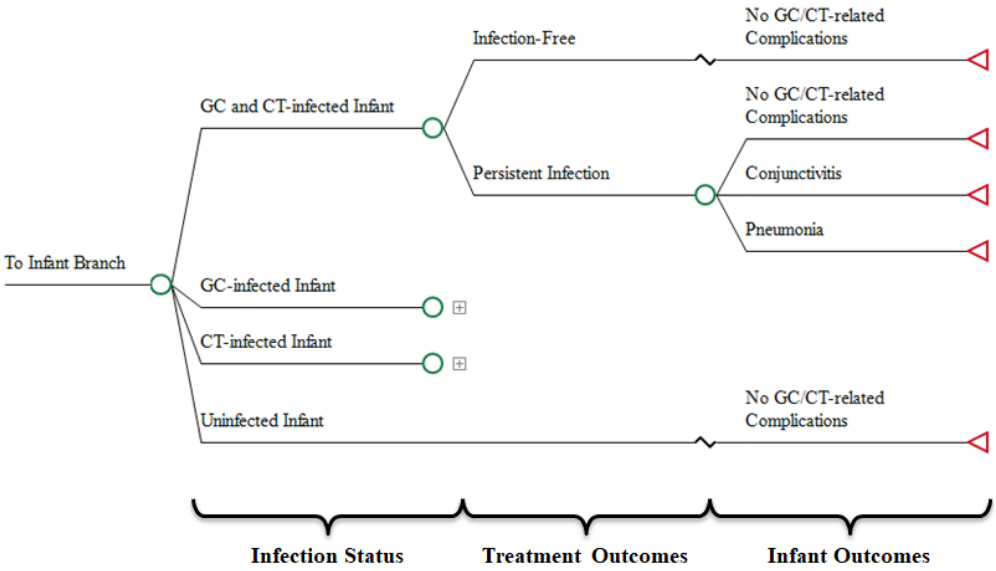
Figure 2: Proposed Model Structure on Gynecologic and Obstetric Outcomes



CT = *Chlamydia trachomatis;* GC = *Neisseria gonorrhoeae.*

○ = chance node; ◁ = terminal node; ⊞ = further branch structures to the right identical to the branches above.

Figure 3: Proposed Model Structure on Infant Outcomes



CT = *Chlamydia trachomatis;* GC = *Neisseria gonorrhoeae.*

○ = chance node; ◁ = terminal node; ⊞ = further branch structures to the right identical to the branches above.

Based on feedback from the broader CADTH project team, the clinical experts, and other stakeholders, the decision tree will be developed to ensure face validity. This would mean that the model structure will be reflective of existing clinical literature and Canadian clinical practice. Checks on the internal and external validity of the model will be performed to assess for any logical discrepancies. The decision-analytic model will be constructed in Microsoft Excel 2010.

Perspective

The decision-analytic model will reflect the perspective of a publicly funded health care system (i.e., provincial Ministry of Health).

Resource Use and Cost Data

The costs captured will reflect the perspective of the analysis by capturing the costs to the health care system associated with chlamydia and gonorrhea screening, and infection during pregnancy, and up to three months postpartum. These costs will include the cost of tests, treatments arising from correct or incorrect diagnoses, and any medical costs related to disease-related morbidity.

Canadian-specific costs will be used when available. If unavailable, costs will be estimated from the medical literature and, ideally, from comparable health systems. If necessary, costs will be adjusted to 2017 Canadian dollars using the consumer price index.[46]

Utilities

Given that numerous complications can be reduced with screening, utilities were considered the most appropriate measure to reflect patient preferences in avoiding these complications for themselves and their infant. Utilities associated with each health state will be obtained from the literature and from Canadian sources, when possible. [47] The intent will be to conduct a cost-utility analysis, although a secondary analysis evaluating cost-effectiveness will also be considered.

Clinical Parameters

Natural history: The disease epidemiology of CT and GC infection in pregnancy and the infected infant will be informed from peer-reviewed medical literature and medical registries. If estimates from Canada are not possible, sources from comparable health systems will be used.

Diagnostic accuracy: The diagnostic accuracy of each screening test (e.g., sensitivity and specificity) will be obtained from systematic literature reviews. Where multiple potential data sources exist, input data will be selected based on the criteria of fitness for purpose, credibility, and consistency. [47] These inputs, with the data on disease prevalence, will allow determination of post-test probability of various possible screening outcomes (e.g., true-positive, false -positive, true-negative, and false-negative).

Outcomes

The model will estimate the expected costs and quality-adjusted life-years (QALYs) associated with each screening strategy over the model's time horizon.[47] QALY will be the primary clinical outcome measurement, as this single measure provides a common metric to capture the multiple potential morbidity implications to both the pregnant person and the

infant. The primary results of this model will be the incremental cost-effectiveness ratios, measured in terms of the incremental costs per QALY gained, of the screening strategies on the efficiency frontier. In addition, the model will report the number of correct and missed cases.

Time Horizon and Discounting

As previously justified above, the scope of this model will capture the start of pregnancy, up to three months into infancy. The model duration will be approximately one year and discounting, therefore will not be performed.[47]

Sensitivity Analysis

The base-case analysis will ideally present the probabilistic findings, capturing the impact of parameter uncertainty, with results presented on the cost-effectiveness acceptability curve (CEAC). The CEAC will highlight screening strategies that are most likely to be cost-effective across different willingness-to-pay thresholds. Uncertainty in the model will be further evaluated in a number of ways. Scenario and subgroup analysis will be performed to evaluate key model assumptions, while retaining the probabilistic element of the model. Potential scenarios and subgroups of interest may include:

- prevalence of CT and/or GC infection
- high-risk patients, as defined in the clinical review section.

Other analyses to address parameter uncertainty may include varying sets of related inputs (e.g., sensitivity and specificity of tests) or extreme scenarios (e.g., best- and worst-case analysis, threshold scenarios). This may help identify key inputs driving the results of the cost-effectiveness analysis.

Assumptions

During the course of the development of the model, assumptions and limitations will be identified and acknowledged in the report. Where possible, assumptions will be tested through the conduct of appropriate sensitivity analyses.

Patients', Partners', and Health Care Providers' Perspectives and Experiences

Research Question 3: What are the experiences and perspectives of pregnant persons and their partners with respect to undergoing screening for CT and/or GC? And, what are their health care providers' perspectives on screening for CT and/or GC during pregnancy?

Study Design

A SR and qualitative meta-synthesis of primary empirical studies describing pregnant person's experiences and perceptions of screening for CT and/or GC during pregnancy will be conducted. Studies that include the perspectives of pregnant persons' partners and health care providers screening for CT and/ or GC will also be included. The results of these primary qualitative studies will be synthesized using thematic synthesis,[48] resulting in descriptive and interpretive findings that address the policy question of this HTA and that will be useful for decision-makers.

This protocol offers a general outline of the methods to be used at each stage of the study. Following an iterative approach consistent with the inductive principles of qualitative research, the protocol will be actively refined at several stages. The research questions have been established a priori in consultation with the broader research team. However, given the scarcity of qualitative evidence on the use of specific technologies for particular populations, it is possible that little relevant qualitative research exists for these particular questions. To accommodate this possible outcome, ongoing decisions will be made about the available qualitative studies and the final study selection. As the relevant literature is identified and reviewed, the research question and method might be refined within the scope of this HTA to ensure it can meaningfully inform decision-making. Any refinements will be documented along with their rationale. The qualitative meta-synthesis will be conducted by two researchers who have experience and training in undertaking both primary qualitative research and SRs of qualitative research.

Secondary Research Questions

Given that the policy question of this HTA aims to examine the screening strategy, timing, and frequency of screening during pregnancy, this review will include findings relevant to pregnant persons, their partners, and health care providers' perspectives on these specific issues. To ensure the relevance of the analysis to the objectives of the broader HTA, a secondary set of research questions will be explored during data extraction and analysis:

A. What do pregnant persons and their partners value or expect with regards to screening for CT and/ or GC?
B. How do pregnant persons and their partners experience and perceive screening options (vaginal and cervical swabs, and urine specimen) for CT and/or GC?
C. What are the ways in which screening for CT and/or GC and its frequency and timing affect pregnant person's lives and the lives of their partners?
D. What are health care providers' experiences and perceptions on when and how to screen for CT and/ or GC during pregnancy?
E. What are health care providers' perspectives regarding targeted or universal screening?

F. Are there differences in perceptions and experiences relating to screening for CT and/or GC between pregnant persons and their partners, or between pregnant persons and their partners and health care providers?

The predefined topic (screening for CT and/or GC during pregnancy) and primary research question will orient the data collection, data extraction, and analysis. The secondary research questions will be used as sensitizing concepts to assist the researchers in interpreting findings and concepts to explore the broader policy implications. During data collection and analysis, primary and secondary questions will be further refined, with the possible addition of questions to address new and unexpected ways of thinking about the data.

Literature Search Methods

The literature search will be performed by an information specialist using a peer-reviewed search strategy.

Information related to patients', partners', and health care providers' perspectives and experiences will be identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates, CINAHL (1981–) via EBSCO; PubMed; and Scopus. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be chlamydia, gonorrhea, pregnancy, and screening.

Methodological filters will be applied to limit retrieval to qualitative studies, including surveys or questionnaires that answer open-ended "why" questions. Retrieval will be limited to documents added to the databases since January 1, 2003, to correspond to changes in the delivery of screening strategies. The search will be limited to English- or French-language publications.

The initial searches will be completed in January 2018. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review will be incorporated into the analysis if they are identified prior to the completion of the stakeholder feedback period of the final report. Any studies that are identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies to the results of the analysis conducted for this report.

Grey literature will be identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Iterative Search Process

Qualitative research can be difficult to find because of inconsistency in index terms and the challenges in retrieving qualitative studies using search filters.[49] Hence, the literature search may be modified and re-run depending on the set of studies that meet the inclusion criteria. The search strategy will be developed and refined as follows: initially, all qualitative research

relevant to screening for CT and/or GC during pregnancy will be retrieved and then screened for eligibility. During the completion of the full-text review of eligible studies, the initial search may return a small number of included studies (< 30 studies) or may identify a new term or concept found in the literature that is relevant for inclusion. While it is possible to describe the results from a small set of studies, it is difficult to reorder and reimagine the perceptions, experiences, and themes reported to produce a new integrative interpretation. In this case, the search may be refined to either broaden it (e.g., to include studies with persons who experienced screening for other STIs during pregnancy) or to capture additional experiences or constructs of interest (e.g., living with infertility caused by CT and/or GC infection during pregnancy).

After judging the sufficiency of the research data, an iterative approach will be adopted to refine the question, together with an appraisal of available evidence. [50] This iterative refinement is common to many qualitative approaches and requires familiarity with the data set. [50,51] This process starts with the initial research question previously stated. The titles and abstracts of included articles will be reviewed to pull aside potentially relevant articles for full-text review. As articles are reviewed, memos on the topics, emphases, and populations of the articles will be kept to develop an understanding of what type of information is present in the topic-specific library. At this point, an assessment will be made about whether the initial research question is answerable with this data set. This consideration includes whether this question overlooks any particular areas of strength in the literature. The refinement of the research question remains an open question as analysis continues. As data are extracted from relevant studies and analyzed, the breadth and depth of these data will be discussed to consider whether they answer the proposed question, and whether the question could be refined to optimize the strengths of the available data. As the data set will be appraised for relevance to refine the research question and search strategy, the HTA context and decision-makers' priorities will be considered. The evolution of the question and search strategy will be documented to maximize the authenticity of the final account. [52]

Literature Selection Criteria

Inclusion Criteria

Eligible studies will be primary English-language qualitative studies and mixed-methods studies, with separate reporting of the qualitative component. For the purpose of this review, qualitative studies are studies that use qualitative data collection methods (e.g., document analysis, interviews, or participant observation) and qualitative data analysis methods (e.g., constant comparative method, content analysis). Only the qualitative component of mixed-method studies will be included. Studies that have multiple publications using the same data set will be included if they report on distinct research questions; duplicate publications using the same data with the same findings will be excluded. Only studies conducted in countries with comparable health care systems are included. These are defined as Canada, the US, New Zealand, Australia, and European Economic Area countries. Studies that report pregnant persons' partners or providers' perspectives will also be included. To be eligible, studies must explore or assess participants' own perspectives directly, not indirectly (i.e., through another person). Excluding "indirect" perspectives is not the exclusion of other participants' perspectives but, rather, it is the exclusion of what one participant might think another participant is experiencing. For example, findings reporting what a partner thinks the pregnant person experiences when undergoing CT and/or GC screening will be excluded. However, both the pregnant person and the partner's direct experience in participating in the

screening process and what screening for CT and/or GC means for the pregnant person and the partner will be included. Similarly, health care providers' perspectives on how pregnant people experience screening will be excluded, whereas health care providers' perspectives about providing screening to pregnant people will be included. Table 2 describes the eligibility criteria to be used.

Table 2: Eligibility Criteria for Patient Perspectives and Experiences Review

Topical Parameters	Screening for CT and/or GC during pregnancy; context in which technology is used (e.g., setting [home, primary care settings, sexual health centres, or general community settings], resource allocation considerations, health and human resources issues); how technology fits in the process of patient care; screening method (i.e., testing options, including urine tests, self-administered swabs, pelvic exams and clinician-collected swabs, home-testing options, self-testing options, mobile health vans); screening strategy (e.g., targeted or universal), timing and frequency of the screening; pregnant persons' experiences, expectations, and perceptions of screening for CT and/or GC; partners of pregnant persons' experiences and perceptions of screening for CT and/or GC during pregnancy; health care providers' perceptions of screening for CT and/or GC during pregnancy
Population Parameters	Pregnant persons, partners of pregnant persons, health care providers screening for CT and/or GC (family doctors, midwives, obstetrician-gynecologists, etc.)
Temporal Parameters	2003 to present
Methodological Parameters	Primary qualitative empirical research (using any descriptive or interpretive qualitative methodology) and the qualitative component of mixed-methods studies in which authors use methods for both qualitative data collection and analysis that include the following: • in-depth or open-ended interviews or focus groups, lengthy participant or field observations, or document or artifact review • techniques for analysis and interpretation of data that move beyond the data generated • descriptive qualitative surveys to answer open-ended "why" questions • qualitative syntheses that provide novel interpretations of existing data
Countries	Australia, Canada, European Economic Area, New Zealand, UK, and US

There is no standard approach to including both primary studies and syntheses in a qualitative synthesis. Typically, in a quantitative synthesis, only primary studies are included to avoid the issue of "double counting" or giving undue weight to one set of study findings. Following these principles, qualitative syntheses which, based on a full-text review of study methods and findings, provide novel interpretations of existing data will be included, and studies with findings that are aggregative and descriptive will be excluded. However, to produce a *de novo* interpretive analysis, data from syntheses will be analyzed once the analysis is nearly completed and after theoretical saturation is confirmed, using syntheses to triangulate the findings with those additionally in the literature.

Exclusion Criteria

Exclusion criteria includes:

- animal and in vitro studies
- studies addressing topics other than CT and/or GC screening
- commentaries, case reports, or editorials
- non–full-text publications (i.e., abstracts)

- work that has not been peer-reviewed or is not published (e.g., theses, editorials, letters to the editor)
- book chapters
- studies labelled “qualitative” but do not use a qualitative descriptive or interpretive methodology (e.g., case studies, experiments, surveys, or observational analyses using qualitative categorical variables)
- quantitative component of mixed-methods studies
- studies not involving the perspectives of pregnant persons, their partners, and health care providers with respect to screening for CT and/or GC.

Literature Screening and Selection

Two reviewers will independently assess titles and abstracts of potentially eligible studies in DistillerSR.[38] Disagreements about eligibility at the title and abstract level will be resolved through discussion, involving a third reviewer if required. Full-text screening and assessment of studies for inclusion will be conducted independently by two reviewers. Again, differing judgments about study inclusion will be resolved through discussion. Study selection will be documented and reported using a PRISMA flow diagram in a final report.[53]

After the completion of full-text screening, two researchers will review the set of included studies and discuss whether the final set of included studies is judged to include sufficient data for analysis or if there is need to modify the literature search and selection criteria. Reflection on the potential need to refine primary and secondary research questions will occur should modifications to literature search and selection criteria be necessary.

Data Extraction

One reviewer will extract data describing study and sample characteristics for each study using standardized electronic data extraction forms with a second reviewer checking data extraction. Relevant characteristics include: study objectives, design, setting, sample size, data collection methods, participants’ age, screening method, screening strategy, and timing of screening. Data extraction will begin by testing these forms with both reviewers extracting information from a small sample of studies (approximately six) to ensure that they facilitate the consistent extraction of study and sample details that are informative for this review. Modifications to the data extraction forms will be made based on the reviewers discussing the extraction process and identifying possible differences in interpreting fields and information contained in studies not captured by the existing form.

Quality Assessment

Two reviewers will independently critically appraise all included studies concurrently with data extraction and checking. The ten items of the Critical Appraisal Skills Programme Qualitative Checklist will be used as prompts to guide the critical appraisal. Reviewers will independently document their assessments on the major strengths and limitations of studies in terms of their credibility, transferability, dependability, and confirmability using a table of quality appraisal. Disagreements in assessments will be resolved through discussion, involving a third reviewer if required. Quality appraisal in qualitative evidence synthesis supports the evaluation of the credibility of the conclusions and aims at ensuring that findings represent the relevant literature; however, studies will not be excluded from the review on the basis of the quality appraisal.

Data Analysis

NVivo 11[54] will be used to extract and manage qualitative data from included studies. Sections of the publications reporting findings will be coded (i.e., not background and discussion sections) to ensure the capture of qualitative data and findings (and not findings or interpretations of background literature or authors' conclusions).

The analysis will follow a staged coding process similar to grounded theory and pass through three stages: open or line-by-line coding, descriptive coding, and developing analytic themes. [55] The constant comparison method will be adapted to include comparing codes across reviewers, and comparing codes across codes and across studies.

Two reviewers will independently conduct line-by-line coding of an initial set of four to six studies. Line-by-line coding encourages "staying close to the data" — a process that encourages the inductive development of codes. Upon completing this initial set, the reviewers will meet to discuss and reflect on the coding process and a decision will be made to either continue line-by-line coding or move toward developing descriptive codes. Further line-by-line coding will be warranted if there are no patterns appearing in the open codes used and if each passage being coded continues to gives rise to a new set of codes (i.e., there is no stability in the codes being used). In this case, the two reviewers will return to the data, repeating the process of line-by-line coding of a subset of studies (approximately four), and again meet to review their experiences of the coding process.

Once reviewers decide that line-by-line coding is sufficient (i.e., patterns have emerged in the codes used), they will begin descriptive coding. Two reviewers will use the secondary research questions as guides and begin to develop and refine a set of descriptive codes by coding a subset of studies (approximately five or less). During this period of descriptive coding, reviewers will use larger passages of text to group and cluster codes using descriptive concepts that remain close to the data. Upon completing this subset, the reviewers will meet and discuss the coding process and reflect on the breadth of descriptive codes and their related concepts, as part of refining the coding set. Once the reviewers have come to consensus about a set of codes that describe the dimensions of the data relevant to the primary and secondary research questions, the reviewers will code the remaining studies using the set of descriptive codes.

The reviewers will continue to verify descriptive codes through a review of codes and their structure, and through coding data. The reviewers will compare and contrast their descriptive codes between each other and across the studies. Frequent meetings of the qualitative review team will be held to discuss coding structure, data interpretation, and to encourage reflection on the relationship between descriptive codes and the secondary research questions. Coding is an iterative process and as new codes emerge inductively, the reviewers will divide the studies amongst themselves and recode already coded studies to identify all instances of the concept. As the descriptive codes become hierarchical (i.e., the reviewers are able to identify higher-order constructs or categories for which descriptive codes are dimensions or facets) and the relationship between codes becomes the subject of the analysis, the review team moves from descriptive coding to analytic synthesis.

Analytic synthesis is the development of themes or abstracted constructs that are interpretations of the data. To develop analytic themes, memoing and diagramming will be used to assemble and sort the previously established descriptive codes, going back to the data to further develop the relationship between themes and codes. In keeping with the iterative nature of qualitative analysis, the reviewers may revert to descriptive coding to

additionally describe dimensions or facets of particular codes or themes in order to develop themes that are conceptually rich (meaning described in rich detail and clearly supported by data). This analytical approach ensures that the review is more than a summary of findings of qualitative studies; that it is, rather, a new synthesis or interpretation of the existing published data in relation to the policy question.

Preliminary findings will be presented to stakeholders (i.e., clinical experts engaged in the project), where possible. Broader stakeholder feedback will be sought through posting a draft report on the CADTH website. This will be done in order to explore whether the findings of the analysis are supported by the data and if there are known themes in the literature or delivery landscape not adequately accounted for in the analysis. Taking these perspectives into account, the reviewers will return to the data and refine the analysis accordingly. At this point, any included qualitative synthesis will be analyzed and its findings will be compared and contrasted to the preliminary analysis. Triangulating this analysis with other syntheses and exploring reasons for differences and similarities will strengthen this analysis by accounting for divergent cases. Analytical synthesis will stop once themes (findings) and their relationships have been richly described and are stable, with no additional descriptive or interpretive insights arising from further analysis.

Data that are relevant to the questions of this review but do not feature prominently in the data set will be coded and analyzed even if there is an absence of theoretical saturation around those codes and they remain descriptive versus analytic. Similarly, in an effort to ensure the findings are relevant to the concrete policy questions under consideration, the analysis will be conducted for overall participant experience and by technology and subpopulations, where applicable. Exploring concepts and themes that may uniquely or particularly apply to particular types of screening (e.g., self-administered swabs, clinician-collected swabs) or subpopulations (e.g., young pregnant persons younger than 25 years of age) will help inform decision-making.

Reflexivity is an epistemological principle and methodological approach in qualitative research that recognizes the role of the researcher as instrument. Reflexive practices and techniques are those that allow for and facilitate making researcher's observations and interpretations transparent and explicit versus implicit and unacknowledged. They aim to provide cognitive and emotional space of the researcher from the act of analysis to reflect on this act of observation and interpretation itself. This study will employ the reflexive practices of memoing and frequent dialogue amongst team members to probe and position reviewers in relation to the analysis. Further, the review team will proactively search for possible alternative interpretations of the analytic findings and triangulate them with additional empirical sources to identify possible observations and alternative interpretations not yet considered.

Protocol Amendments

If amendments to the protocol are required at any time during the study, reasons for changes will be recorded and reported in the final report.

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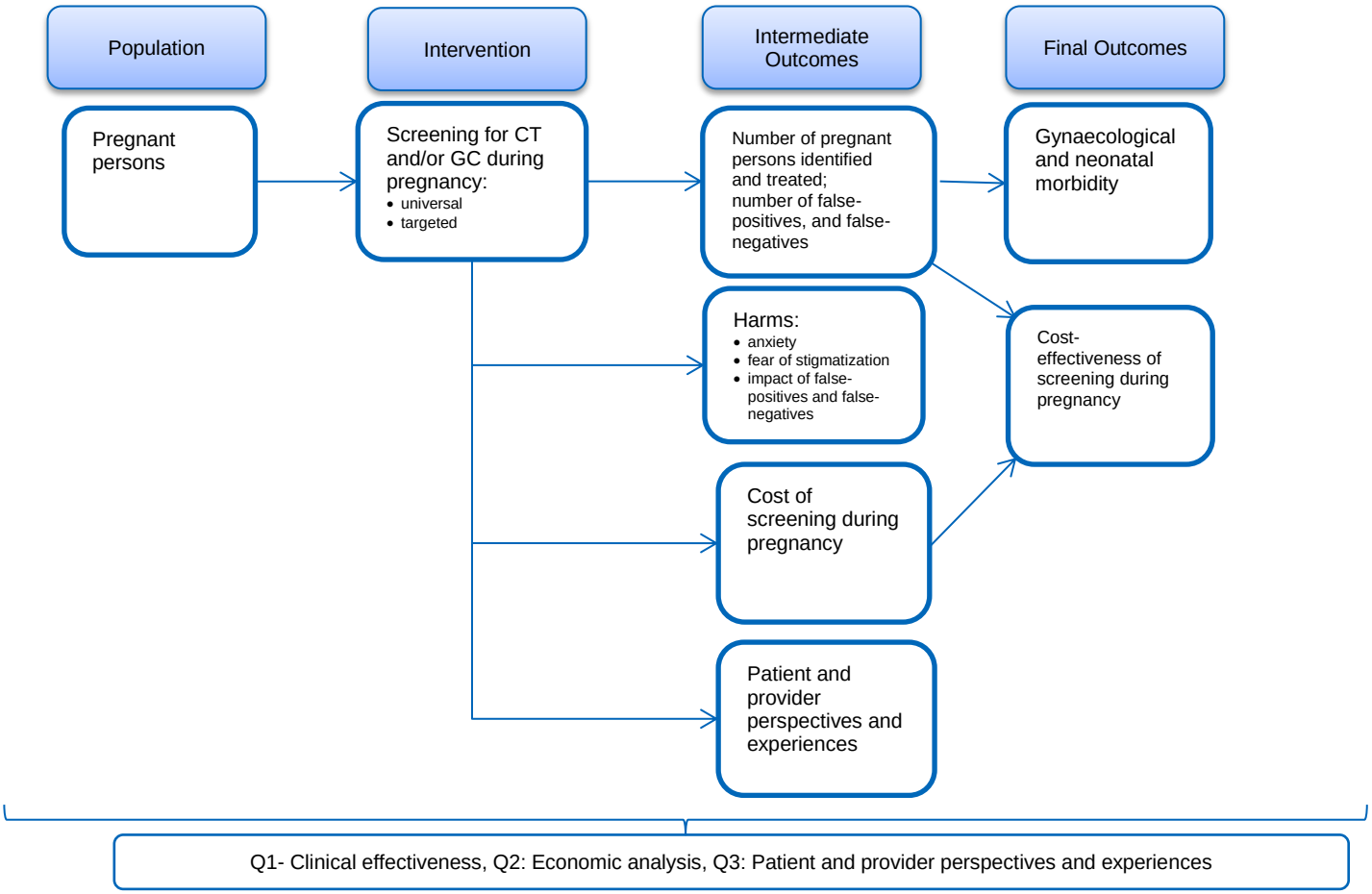
Appendix 1: Analytic Framework

Policy Question: How should Canadian health care providers screen pregnant persons for *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* — at what time(s) during pregnancy, using what specimen, with what frequency, and using a universal or a targeted approach?



CT = *Chlamydia trachomatis*; GC= *Neisseria gonorrhoeae*.

Appendix 2: Literature Search Strategies

OVERVIEW	
Interface:	Ovid
Databases:	Ovid Embase Ovid MEDLINE 1946 to Present Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	TBD
Alerts:	Monthly search updates until project completion.
Study Types:	No filters used
Limits:	Publication years 2003 forward English or French language Human-only

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.dv	Device trade name (Embase)
.dq	Candidate term word (Embase)
medall	Ovid database code; Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy – MEDLINE, Embase**
1	exp Prenatal Care/ or exp Pregnancy/ or exp Pregnant Women/ or exp Pregnancy Complications/
2	(pregnancy or pregnancies or pregnant or gestation or gestational or parous or gravid or gravidity or gravida or multigravid* or multiparous or nulliparous or primagravid* or prenatal or perinatal or maternity or maternal).ti,ab,kf.
3	1 or 2
4	exp chlamydiaceae/ or exp chlamydia/ or exp Chlamydiaceae Infections/ or exp chlamydia infections/
5	(Chlamydi* or C trachomatis or Chlamydiaceae* or Chlamydophila* or Trachoma*).ti,ab,kf.
6	exp Gonorrhea/ or exp Neisseria gonorrhoeae/

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy – MEDLINE, Embase**
7	(Gonorrhea* or gonorrhoea* or gonorrhoeae* or Gonococc* or Neisseria*).ti,ab,kf.
8	4 or 5 or 6 or 7
9	exp Mass Screening/ or exp diagnosis/ or exp Monitoring, Physiologic/
10	(diagnosis or diagnostic or diagnose or diagnoses or diagnosing or diagnosed or monitoring or monitor or detect or detection or detecting or detected or test or tests or testing or assess or assessing or assessment or screen or screening or screened).ti,ab,kf.
11	((detection or screening) adj3 (strategy or strategies or strategic or program*)).ti,ab,kf.
12	exp Nucleic Acid Amplification Techniques/
13	(nucleic adj3 acid* adj3 (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
14	((NAT or NAAT or NABT or TMA or NASBA or NAP) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
15	(((DNA or RNA) adj3 amplifi*) and (techni* or test or tests or testing or analysis or analyses or probe or probes or assay or assays)).ti,ab,kf.
16	(transcription* adj3 mediat* adj3 amplifi* adj3 (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
17	(Ligase adj2 Chain* adj2 React*).ti,ab,kf.
18	(polymerase adj2 chain* adj2 react*).ti,ab,kf.
19	(Self-Sustain* adj2 Sequenc* adj2 Replicat*).ti,ab,kf.
20	(Nucleic Acid adj3 Sequenc* adj3 Amplifi*).ti,ab,kf.
21	Amplified Fragment Length Polymorphism Analysis.ti,ab,kf.
22	((LCR or PCR or RTPCR or RFLP or AFLP or RAPD or LCX or SDA or CTNRA) adj3 (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
23	((PCR or polymerase chain*) adj5 (multiplex or triplex or quantiplex or probe amplification or RAPD or random amplified polymorphic)).ti,ab,kf.
24	((DNA or RNA) adj5 (hybrid* or multiplex or triplex or quantiplex or probe amplification)).ti,ab,kf.
25	((DNA or RNA) adj3 amplifi*).ti,ab,kf.
26	(strand adj2 displacement* adj2 amplifi*).ti,ab,kf.
27	exp Culture Techniques/ or exp DNA, Bacterial/ or exp Cell Culture Techniques/ or exp Antibodies, Bacterial/an
28	(bacterial adj5 (culture or plate or cultures or plates or Thayer martin)).ti,ab,kf.
29	((vaginal or cervical or urine or genital) adj5 culture*).ti,ab,kf.
30	(McCoy adj3 culture*).ti,ab,kf.
31	(pathfinder adj3 chalymidia adj3 confirmat*).ti,ab,kf.
32	((amptima or hologic or genprobe or gen-probe or pelvo check or pelvocheck) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
33	((cobas or amplicor or cobas4800 or cobasamplicor) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
34	(hologic adj5 (combo2 or aptima)).ti,ab,kf.
35	((realtime CT NG or realtime CT or realtimeNG or realtimeCTNG or realtimeCT) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
36	((probetech or viper XTR or viperXTR or ProbeTecETQx or ProbeTech ET Qx or ProbeTecET Qx or ProbeTec ET or ProbetechCT* or Probetech CT or PACE or PACE2 or Light Cycler or Lightcycler) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy – MEDLINE, Embase**
37	((genprobe or gen probe or APTIMA or APTIMAcombo or APTIMAGC or gonospot or gonostat) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
38	((genprobe or gen probe or APTIMA or APTIMAcombo or APTIMAGC) and (CT or NG or CTNG)).ti,ab,kf.
39	((probetech or viper XTR or viperXTR or ProbeTecETQx or ProbeTecET or ProbetechCT* or GenoQuick or AMPT or Accuprobe or hybrid capture) adj5 (CT or NG or CTNG)).ti,ab,kf.
40	(BD adj3 MAX adj3 (CT or GC or TV or CTGCTV or MCGT)).ti,ab,kf.
41	(BD adj2 (MAX or probetec or probe tec)).ti,ab,kf.
42	((Cepheid or intermedico) adj5 (xpert or genexpert or CT or NG or CTNG)).ti,ab,kf.
43	(xpert adj3 (CT or NG or CTNG)).ti,ab,kf.
44	Rapid Diagnostic System for Chlamydia*.ti,ab,kf.
45	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46	3 and 8 and 45
47	exp animals/
48	exp animal experimentation/ or exp animal experiment/
49	exp models animal/
50	nonhuman/
51	exp vertebrate/ or exp vertebrates/
52	or/47-51
53	exp humans/
54	exp human experimentation/ or exp human experiment/
55	or/53-54
56	52 not 55
57	46 not 56
58	57 use medall
59	exp prenatal care/ or exp pregnancy/ or exp pregnant woman/ or exp pregnancy complication/
60	(pregnancy or pregnancies or pregnant or gestation or gestational or parous or gravid or gravidity or gravida or multigravid* or multiparous or nulliparous or primagravid* or prenatal or perinatal or maternity or maternal).ti,ab,kw,dq.
61	59 or 60
62	exp chlamydiaceae/ or exp chlamydia/ or exp Chlamydiaceae Infection/ or exp chlamydia infections/
63	(Chlamydi* or C trachomatis or Chlamydiaceae* or Chlamydophila* or Trachoma*).ti,ab,kw,dq.
64	exp Gonorrhea/ or exp Neisseria gonorrhoeae/
65	(Gonorrhea* or gonorrhoea* or gonorrhoeae* or Gonococc* or Neisseria*).ti,ab,kw,dq.
66	62 or 63 or 64 or 65
67	exp screening/ or exp diagnosis/ or exp physiologic monitoring/
68	(diagnosis or diagnostic or diagnose or diagnoses or diagnosing or diagnosed or monitoring or monitor or detect or detection or detecting or detected or test or tests or testing or assess or assessing or assessment or screen or screening or screened).ti,ab,kw,dq.
69	((detection or screening) adj3 (strategy or strategies or strategic or program*)).ti,ab,kw,dq.
70	exp nucleic acid amplification/ or exp Chlamydia rapid test/ or exp chlamydia multiplex PCR assay/
71	(nucleic adj3 acid* adj3 (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kw,dq.

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy – MEDLINE, Embase**
72	((NAT or NAAT or NABT or TMA or NASBA or NAP) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kw,dq.
73	(((DNA or RNA) adj3 amplifi*) and (techni* or test or tests or testing or analysis or analyses or probe or probes or assay or assays)).ti,ab,kw,dq.
74	(transcription* adj3 mediat* adj3 amplifi* adj3 (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kw,dq.
75	(Ligase adj2 Chain* adj2 React*).ti,ab,kw,dq.
76	(polymerase adj2 chain* adj2 react*).ti,ab,kw,dq.
77	(Self-Sustain* adj2 Sequenc* adj2 Replicat*).ti,ab,kw,dq.
78	(Nucleic Acid adj3 Sequenc* adj3 Amplifi*).ti,ab,kw,dq.
79	Amplified Fragment Length Polymorphism Analysis.ti,ab,kw,dq.
80	((LCR or PCR or RTPCR or RFLP or AFLP or RAPD or LCX or SDA or CTNRA) adj3 (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kw,dq.
81	((PCR or polymerase chain*) adj5 (multiplex or triplex or quantiplex or probe amplification or RAPD or random amplified polymorphic)).ti,ab,kw,dq.
82	((DNA or RNA) adj5 (hybrid* or multiplex or triplex or quantiplex or probe amplification)).ti,ab,kw,dq.
83	((DNA or RNA) adj3 amplifi*).ti,ab,kw,dq.
84	(strand adj2 displacement* adj2 amplifi*).ti,ab,kw,dq.
85	exp bacterium culture/ or exp bacterial DNA/ or exp Cell Culture/
86	(bacterial adj5 (culture or plate or cultures or plates or Thayer martin)).ti,ab,kw,dq.
87	((vaginal or cervical or urine or genital) adj5 culture*).ti,ab,kw,dq.
88	(McCoy adj3 culture*).ti,ab,kw,dq,dv.
89	(pathfinder adj3 chlymidia adj3 confirmat*).ti,ab,kw,dq,dv.
90	((amptima or hologic or genprobe or gen-probe or pelvo check or pelvocheck) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kw,dq,dv.
91	((cobas or amplicor or cobas4800 or cobasamplicor) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kw,dq,dv.
92	(hologic adj5 (combo2 or aptima)).ti,ab,kw,dq,dv.
93	((realtime CT NG or realtime CT or realtimeNG or realtimeCTNG or realtimeCT) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kw,dq,dv.
94	((probetech or viper XTR or viperXTR or ProbeTecETQx or ProbeTech ET Qx or ProbeTecET Qx or ProbeTec ET or ProbetechCT* or Probetech CT or PACE or PACE2 or Light Cycler or Lightcycler) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kw,dq,dv.
95	((genprobe or gen probe or APTIMA or APTIMAcombo or APTIMAGC or gonospot or gonostat) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kw,dq,dv.
96	((genprobe or gen probe or APTIMA or APTIMAcombo or APTIMAGC) and (CT or NG or CTNG)).ti,ab,kw,dq,dv.
97	((probetech or viper XTR or viperXTR or ProbeTecETQx or ProbeTecET or ProbetechCT* or GenoQuick or AMPT or Accuprobe or hybrid capture) adj5 (CT or NG or CTNG)).ti,ab,kw,dq,dv.
98	(BD adj3 MAX adj3 (CT or GC or TV or CTGCTV or MCGT)).ti,ab,kw,dq,dv.
99	(BD adj2 (MAX or probetec or probe tec)).ti,ab,kw,dq,dv.
100	((Cepheid or intermedico) adj5 (xpert or genexpert or CT or NG or CTNG)).ti,ab,kw,dv,dq.
101	(xpert adj3 (CT or NG or CTNG)).ti,ab,kw,dq,dv.

MULTI-DATABASE STRATEGY	
#	**Clinical Search Strategy – MEDLINE, Embase**
102	Rapid Diagnostic System for Chlamydia trachomatis.ti,ab,kw,dq,dv.
103	or/67-102
104	61 and 66 and 103
105	exp animals/
106	exp animal experimentation/ or exp animal experiment/
107	exp models animal/
108	nonhuman/
109	exp vertebrate/ or exp vertebrates/
110	or/105-109
111	exp humans/
112	exp human experimentation/ or exp human experiment/
113	or/111-112
114	110 not 113
115	104 not 114
116	115 use oemezd
117	58 or 116
118	limit 117 to yr="2003 -Current"
119	limit 118 to english language
120	118 and french.lg.
121	119 or 120
122	121 not conference abstract.pt.
123	remove duplicates from 122

MULTI-DATABASE STRATEGY	
#	**Patient Preferences Search Strategy – MEDLINE**
1	exp Prenatal Care/ or exp Pregnancy/ or exp Pregnant Women/ or exp Pregnancy Complications/
2	(pregnancy or pregnancies or pregnant or gestation or gestational or parous or gravid or gravidity or gravida or multigravid* or multiparous or nulliparous or primagravid* or prenatal or perinatal or maternity or maternal).ti,ab,kf.
3	1 or 2
4	exp chlamydiaceae/ or exp chlamydia/ or exp Chlamydiaceae Infections/ or exp chlamydia infections/
5	(Chlamydi* or C trachomatis or Chlamydiaceae* or Chlamydophila* or Trachoma*).ti,ab,kf.
6	exp Gonorrhea/ or exp Neisseria gonorrhoeae/
7	(Gonorrhea* or gonorrhoea* or gonorrhoeae* or Gonococc* or Neisseria*).ti,ab,kf.
8	4 or 5 or 6 or 7
9	exp Mass Screening/ or exp diagnosis/ or exp Monitoring, Physiologic/
10	(diagnosis or diagnostic or diagnose or diagnoses or diagnosing or diagnosed or monitoring or monitor or detect or detection or detecting or detected or test or tests or testing or assess or assessing or assessment or screen or screening or screened).ti,ab,kf.
11	((detection or screening) adj3 program*).ti,ab,kf.
12	exp Nucleic Acid Amplification Techniques/

MULTI-DATABASE STRATEGY	
#	**Patient Preferences Search Strategy – MEDLINE**
13	(nucleic adj3 acid* adj3 (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
14	((NAT or NAAT or NABT or TMA or NASBA or NAP) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
15	(((DNA or RNA) adj3 amplifi*) and (techni* or test or tests or testing or analysis or analyses or probe or probes or assay or assays)).ti,ab,kf.
16	(transcription* adj3 mediat* adj3 amplifi* adj3 (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
17	(Ligase adj2 Chain* adj2 React*).ti,ab,kf.
18	(polymerase adj2 chain* adj2 react*).ti,ab,kf.
19	(Self-Sustain* adj2 Sequenc* adj2 Replicat*).ti,ab,kf.
20	(Nucleic Acid adj3 Sequenc* adj3 Amplifi*).ti,ab,kf.
21	Amplified Fragment Length Polymorphism Analysis.ti,ab,kf.
22	((LCR or PCR or RTPCR or RFLP or AFLP or RAPD or LCX or SDA or CTNRA) adj3 (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
23	((PCR or polymerase chain*) adj5 (multiplex or triplex or quantiplex or probe amplification or RAPD or random amplified polymorphic)).ti,ab,kf.
24	((DNA or RNA) adj5 (hybrid* or multiplex or triplex or quantiplex or probe amplification)).ti,ab,kf.
25	((DNA or RNA) adj3 amplifi*).ti,ab,kf.
26	(strand adj2 displacement* adj2 amplifi*).ti,ab,kf.
27	exp Culture Techniques/ or exp DNA, Bacterial/ or exp Cell Culture Techniques/ or exp Antibodies, Bacterial/an
28	(bacterial adj5 (culture or plate or cultures or plates or Thayer martin)).ti,ab,kf.
29	((vaginal or cervical or urine or genital) adj5 culture*).ti,ab,kf.
30	(McCoy adj3 culture*).ti,ab,kf.
31	(pathfinder adj3 chalymidia adj3 confirmat*).ti,ab,kf.
32	((amptima or hologic or genprobe or gen-probe or pelvo check or pelvocheck) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
33	((cobas or amplicor or cobas4800 or cobasamplicor) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
34	(hologic adj5 (combo2 or aptima)).ti,ab,kf.
35	((realtime CT NG or realtime CT or realtimeNG or realtimeCTNG or realtimeCT) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
36	((probetech or viper XTR or viperXTR or ProbeTecETQx or ProbeTech ET Qx or ProbeTecET Qx or ProbeTec ET or ProbetechCT* or Probetech CT or PACE or PACE2 or Light Cycler or Lightcycler) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
37	((genprobe or gen probe or APTIMA or APTIMAcombo or APTIMAGC or gonospot or gonostat) and (techni* or test or tests or testing or analysis or analyses or assay or assays)).ti,ab,kf.
38	((genprobe or gen probe or APTIMA or APTIMAcombo or APTIMAGC) and (CT or NG or CTNG)).ti,ab,kf.
39	((probetech or viper XTR or viperXTR or ProbeTecETQx or ProbeTecET or ProbetechCT* or GenoQuick or AMPT or Accuprobe or hybrid capture) adj5 (CT or NG or CTNG)).ti,ab,kf.
40	(BD adj3 MAX adj3 (CT or GC or TV or CTGCTV or MCGT)).ti,ab,kf.
41	(BD adj2 (MAX or probetec or probe tec)).ti,ab,kf.
42	((Cepheid or intermedico) adj5 (xpert or genexpert or CT or NG or CTNG)).ti,ab,kf.

MULTI-DATABASE STRATEGY	
#	**Patient Preferences Search Strategy – MEDLINE**
43	(xpert adj3 (CT or NG or CTNG)).ti,ab,kf.
44	Rapid Diagnostic System for Chlamydia*.ti,ab,kf.
45	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46	3 and 8 and 45
47	"Surveys and Questionnaires"/
48	Health Care Surveys/
49	self report/
50	questionnaire*.ti,ab,kf.
51	survey*.ti,ab,kf.
52	or/47-51
53	exp Empirical Research/ or Interview/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or Narration/ or Nursing Methodology Research/
54	Interview/
55	interview*.ti,ab,kf.
56	qualitative.ti,ab,kf,jw.
57	(theme* or thematic).ti,ab,kf.
58	ethnological research.ti,ab,kf.
59	ethnograph*.ti,ab,kf.
60	ethnomedicine.ti,ab,kf.
61	ethnonursing.ti,ab,kf.
62	phenomenol*.ti,ab,kf.
63	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.
64	(life stor* or women* stor*).ti,ab,kf.
65	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.
66	(data adj1 saturat$).ti,ab,kf.
67	participant observ*.ti,ab,kf.
68	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf.
69	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.
70	(humanistic or existential or experiential or paradigm*).ti,ab,kf.
71	(field adj (study or studies or research or work)).ti,ab,kf.
72	(human science or social science).ti,ab,kf.
73	biographical method.ti,ab,kf.
74	theoretical sampl*.ti,ab,kf.
75	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.
76	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.
77	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.
78	((lived or life) adj experience*).ti,ab,kf.
79	cluster sampl*.ti,ab,kf.

MULTI-DATABASE STRATEGY

#	Patient Preferences Search Strategy – MEDLINE
80	observational method*.ti,ab,kf.
81	content analysis.ti,ab,kf.
82	(constant adj (comparative or comparison)).ti,ab,kf.
83	((discourse* or discurs*) adj3 analys?s).ti,ab,kf.
84	narrative analys?s.ti,ab,kf.
85	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
86	(van adj manen*).ti,ab,kf.
87	(van adj kaam*).ti,ab,kf.
88	(corbin* adj2 strauss*).ti,ab,kf.
89	or/53-88
90	46 and 52
91	46 and 89
92	90 or 91
93	limit 92 to yr="2003 -Current"
94	limit 93 to english language
95	93 and french.lg.
96	94 or 95
97	exp animals/
98	exp animal experimentation/ or exp animal experiment/
99	exp models animal/
100	nonhuman/
101	exp vertebrate/ or exp vertebrates/
102	or/97-101
103	exp humans/
104	exp human experimentation/ or exp human experiment/
105	or/103-104
106	102 not 105
107	96 not 106

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane DARE via Wiley	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.	
Cochrane Database of Systematic Reviews via Wiley	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.	
Cochrane Central Via Ovid	Same MeSH, keywords, and date limits used as per Medline search, with Human restrictions.	
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform. For Patient Preferences Search only.	

Grey Literature

Dates for Search:	TBD
Keywords:	Included terms for screening, various test names, diseases and specific population
Limits:	Publication years 2003 to present; English or French language

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search