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HEALTH TECHNOLOGY ASSESSMENT REPORT

Screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* During Pregnancy: A Health Technology Assessment

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Clinical review authors: Dr. Ismat Kanga,[1] Dr. Dinsie Williams[1], Dr. Todd Hatchette,[2] Stacey Burns[3]

Economic analysis authors: Hyosung Jung,[1] Dr. Bernice Tsoi,[1]

Patients' perspectives and experiences review authors: Dr. Francesca Brundisini,[4] Dr. Deirdre DeJean[5]

Information Specialists: Caitlyn Ford, [1] David Kaunelis[1]

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[1] CADTH, Ottawa, Ontario
[2] Nova Scotia Health Authority, Halifax, Nova Scotia
[3] PEI Department of Health and Wellness, Charlottetown, Prince Edward Island
[4] McMaster Univeristy, Hamilton, Ontario
[5] University of Ottawa, Ottawa, Ontario

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
CCI	Canadian Classification of Health Interventions
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CPS	Canadian Paediatric Society
CT	*Chlamydia trachomatis*
DNA	deoxyribonucleic acid
EPDS	Edinburgh Postnatal Depression Scale
GC	*Neisseria gonorrhoeae*
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
HUI3	Health Utilities Index 3
ICD10CA	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
M/L	moderate-to-late
NAATs	nucleic acid amplification tests
NR	not reported
OCCI	Ontario Case Costing Initiative
ON	opthalmia neonatorum
OR	odds ratio
PCR	polymerase chain reaction
PHAC	Public Heatlh Agency of Canada
PRISMA	Preferred Reporting Items for Systematic Reviews
QALY	Quality-adjusted life year
RoBANS	Risk of Bias Assessment Tool for Non-randomized studies
SD	standard deviation
SDA	strand displacement amplification
SR	systematic review
SROC	Summary receiver operating characteristic
STIs	sexually transmitted infections
TMA	transcription mediated amplification
TOC	test-of-cure
USPSTF	United States Preventive Services Task Force

Protocol Amendments

Section	Amendment	Page
Clinical Review	The protocol indicated that studies using more than one test type would be excluded if results using NAATs and culture are not reported independently. As only eight citations met the inclusion/exclusion criteria, two additional studies were also included – one that reported findings separately for NAATs and culture and one that did not report the screening test.	p. 9
Clinical Review	Data abstraction was not piloted on a random sample of three publications. Due to the small number of eligible studies, piloting was deemed unnecessary. The data abstraction was completed by one reviewer and verified by a second reviewer.	p. 13
Clinical Review	GRADE evidence profile tables were not created using the GRADEpro software package. Tables were created using Microsoft Word.	p. 15
Economic Analysis	The research question was revised to better align the economic analysis to the narrower scope of the HTA	p.7, 16 and 20
Economic Analysis	The time horizon was shifted to capture the period from the time of first trimester screening (12 weeks gestation) to 19 weeks postpartum.[1]	p. 16

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Context Rationale and Policy Issues

Background / Setting in Canada

In Canada, chlamydia (CT) and gonorrhea (GC) are the most commonly reported sexually transmitted infections (STIs). [2] The bacterium Chlamydia trachomatis causes chlamydia infections, while the bacterium Neisseria.gonorrhoeae causes gonorrhea infections. [2] These infections are a significant public health concern, as their rates continue to increase despite numerous prevention and treatment strategies.[2] In 2015, 116,499 cases of CT and 19,845 cases of GC were reported in Canada, corresponding to rates of 325.0 and 55.4 per 100,000 individuals, respectively. [3] The overall rate of CT infections are disproportionately higher in females than in males (398.7 versus 249.1 per 100,000). [4] The overall GC rates are higher in males than in females (70.2 versus. 40.6 per 100,000). [3 4] High-risk groups for contracting CT and GC infections include sexually active youth under 25 years of age, sex workers, homeless persons, persons with a previous history of STI, persons afflicted with substance abuse disorder, and men who sleep with other men (including bisexual men).[5 6]

CT and GC infections are commonly found at genitourinary, rectal, and pharyngeal sites.[7] Though often asymptomatic in females, early detection and treatment of CT and GC infections are necessary to prevent potential complications, sexual transmission, and transmission to neonates in the perinatal period. [8] When signs and symptoms do develop, in females they are often nonspecific and include dysuria, vaginal discharge, vaginal bleeding, and abdominal or pelvic pain.[9] In males, CT infections are more commonly asymptomatic than GC infections.[9] Symptomatic infections in males may present as dysuria; urethral discharge or pruritus; or testicular, epididymal, or scrotal pain.[9]

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 CT or GC infections can lead to pelvic inflammatory disease and its deleterious sequelae, including infertility, ectopic pregnancy, and chronic pain.[9] During pregnancy, these infections and their complications can result in spontaneous abortion, stillbirth, preterm delivery,[10] low birth weight, and perinatal mortality. [11] CT and GC during pregnancy can be transmitted to the neonate resulting in substantial morbidity.[11,12] GC infection can be transmitted to the fetus in utero if there is prolonged rupture of the membranes.[12] Neonatal conjunctivitis or ophthalmia neonatorum (ON) develops in 15% to 44% of neonates born to a birthing parent infected with CT,[11] and 30% to 42% of neonates born to a birthing parent infected with GC.[12] Of all the cases of ON in Canada, CT and GC are responsible for 40% and 1%, respectively.[7] In neonates born to a birthing parent infected with CT during pregnancy, 50% are at risk for the infection, and 10% to 20% are at risk of developing pneumonia.[13]

Early detection of CT or GC can prevent significant adverse gynecological and non-gynecological health outcomes, neonatal morbidity, and perinatal mortality. Historically

to prevent ON, the clinical management has focused on universal neonatal ocular prophylaxis.[14] The Canadian Paediatric Society (CPS) no longer recommends neonatal ocular prophylaxis for the prevention of ON.[13] 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.[13]

Several guidelines exist at the provincial or national level for the screening of CT and GC during pregnancy. The CPS recommends universal screening for CT and GC at the first prenatal visit.[13] Furthermore, the CPS recommends repeat screening after treatment for persons who test positive, and for persons who initially test negative and/or are at high risk of acquiring the infections later in their pregnancy (e.g., persons who are not in a monogamous relationship).[13] 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 Canadian guidelines on Sexually Transmitted Diseases recommends that all pregnant women be screened for CT and GC during their first prenatal visit.[15] Women with risk factors should be rescreened during the second and third trimesters.[15] If either CT or GC is detected, treatment is recommended for both the pregnant woman and sexual partner(s).[15]

The 2015 Society of Obstetricians and Gynaecologists of Canada's *Adolescent Pregnancy Guidelines* recommends screening for CT and GC when an adolescent (i.e., a pregnant person less than 20 years of age) first presents for prenatal care, in the third trimester, at any other time during the pregnancy if risks arise, and postpartum.[16]

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 to infection, or if the pregnant person and/or partner exhibit risky behaviour or have certain risk factors. The guidelines do not explicitly describe risky behaviour, but they describe risk factors for contracting STIs.[17] These risk factors include, but are not limited to, having a new sexual partner, having multiple concurrent sexual partners, having sexual encounters with anonymous partners, being 25 years or younger, coming from areas where STIs are endemic, living in Cree-James Bay Terrestrial Region or Nunavik (Quebec), having a history of incarceration, and drug and alcohol use.[17] 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.[17]

The only national government screening guidelines for all pregnant persons were published in 1996 by the Canadian Task Force on Preventive Health Care.[18] The guidelines were based on a SR of the published literature that included five studies published between 1983 and 1995, and recommend screening pregnant persons for CT infections in their first trimester.[18] 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.[18]

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.[8,9] For this reason, 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 specimens vary across Canada. A number of nucleic acid amplification tests (NAATs) (e.g., polymerase chain reaction, transcription-mediated amplification) are used to detect CT and GC on urine, vaginal, or cervical samples.[15] According to the Canadian Guidelines on Sexually Transmitted Infections, NAATs are considered the most sensitive and specific tests for CT infection and the most sensitive tests for GC infection.[15] False positive results may arise due to possible cross-reaction with other Neisseria species.[15]Based on a systematic review, the Agency for Healthcare Research and Quality reports that, across all specimens, the sensitivity of NAAT-tests cleared by the Food and Drug Administration ranges from 86% to 100% for CT, and the specificity is greater than 97%.[8] Across all specimens and tests, the sensitivity for GC ranges from 90% to 100%, and the specificity is greater than 97%.[8] GC can also be detected using cultures from endocervical or urethral specimens.

All confirmed cases of CT and GC require treatment with antibiotics.[6,19] A test-of-cure visit for CT using a NAAT is recommended for pregnant women three to four weeks post-treatment.[19] 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.[6]

Given the potential for the variation in tests (e.g., type of NAATs, culture), specimen (e.g., urine, vaginal, cervical), timing (e.g., first trimester, test-of-cure, third trimester, at delivery), approach (i.e., unversal or targeted), and frequency (i.e., once or multiple times) for CT and GC screening during pregnancy, 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.

In this report, gender-neutral language has been used where possible in order to be inclusive of all gender identities. When reporting results from published manuscripts, gender-neutral language was not used in order to be consistent with the terms used in the source material.

Policy Question

How should Canadian health care providers screen pregnant persons for *Chlamydia trachomatis (CT)* and/or *Neisseria gonorrhoeae (GC)* — at what time(s) during

pregnancy, using what specimen, with what frequency, and using a universal or a targeted approach?

Objective(s)

The purpose of this health technology assessment (HTA) is to address the policy question through an assessment of the clinical effectiveness and safety, cost-effectiveness, and pregnant persons', partners', and health care providers' perspectives and experiences regarding the screening of pregnant persons for CT and GC.

Research Questions

The HTA addresses 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 Analysis

2. What is the most cost-effective screening strategy during pregnancy for Chlamydia trachomatis and/or Neisseria gonorrhoeae in pregnant persons and their infants up to the postpartum period?

Patients' Perspectives and Experiences Review

3. What are the experiences and perspectives of pregnant persons and their partners with respect to undergoing screening for sexually transmitted infections (STIs)? And, what are their health care providers' perspectives on screening for STIs during pregnancy?

Analytical Framework

The analytic framework informing this HTA is presented in Appendix 1.

Clinical Review

The clinical review addresses 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?

Systematic Review

A de novo SR of primary comparative clinical studies was conducted to address question 1. This clinical review was prepared in consideration of relevant reporting guidelines for SRs (i.e., Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA][20] and PRISMA harms).[21] A protocol was developed a priori and registered on the PROSPERO database (CRD42018087016). All deviations have been identified in the Protocol Amendments table.

Methods

Literature Search Methods

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

Information was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates, Embase (1974–), and 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 was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were chlamydia, gonorrhea, pregnancy, and screening.

Retrieval was limited to English- or French-language documents added to the databases since January 1, 2003. Where possible, retrieval was limited to the human population. No methodological filters were applied to limit retrieval by study type. Conference abstracts were excluded from the search results.

The search was completed January 25, 2018. Regular alerts were established to update the searches until the publication of the final report. Regular search updates were performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review haven been incorporated into the analysis if they were identified prior to the completion of the stakeholder feedback period of the final report. Any studies that were identified after the stakeholder feedback period are 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) was identified by searching the Grey Matters checklist (https://www.cadth.ca/grey-matters), which

includes the websites of HTA agencies, clinical guideline repositories, systematic review repositories, economics-related resources, public perspective groups, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. The complete search strategy is presented in Appendix 2.

Inclusion criteria

Full-text publications were included if they were published between January 1, 2003 to the present in English and met 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.[15] The current laboratory diagnosis recommendations published by the Public Health Agency of Canada do not include these tests, and accordingly studies using these tests were excluded.[15] Studies were eligible for inclusion if NAATs were used to diagnose CT and/or GC or culture was used for the diagnosis of infection with GC. The population of interest included all pregnant adults and pregnant adolescents aged 12 years and older. If the population was mixed (e.g., included both pregnant and non-pregnant persons), the study was included if the results for pregnant persons were reported separately. Studies reporting on a mixed population were also included if more than 80% of the total population comprised of the population of interest, even if results were not reported separately.

Primary clinical studies with a comparison group conducted in countries with a health care context comparable to Canada's were eligible for inclusion. Therefore, inclusion was restricted to studies conducted in Australia, Canada, New Zealand, the US, the UK, or members of the European Economic Area. Countries were considered to have comparable health care contexts based on the clinical opinion of the expert co-authors consulted on this review. (T.H: expert opinion, Dec 19, 2017 Jun; S.B: expert opinion, Dec 19, 2017).

Exclusion criteria

Publications describing case reports, case series, literature reviews letters, editorials, conference abstracts, and presentations were not eligible for inclusion. Duplicate publications and multiple publications of the same study were also excluded unless they provided unique findings of interest.

Eligibility criteria for clinical studies are outlined in Table 1.

Table 1: Eligibility Criteria for the Clinical Review (Research Question 1)

Population(s)	Pregnant adult and adolescent females (≥ 12 years of age, up to and including delivery)
Intervention(s)	A screening strategy involving: • NAAT for CT and NAAT 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 screening test is performed) • any frequency (i.e., number of times the screening test is conducted during pregnancy) • any or no subsequent management of pregnant persons with confirmed infection.
Comparator(s)	• An alternative screening strategy conducted with an alternative test, specimen, approach, at an alternative point, with a different frequency, or with any or no subsequent management strategy for pregnant persons with confirmed infection • No screening strategy

Outcome(s)	**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 obstetric 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.
	
	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 Design(s)	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, case series, reviews, letters, editorials, conference abstracts, and presentations were excluded

Selection method

Two reviewers independently screened titles and abstracts of all citations retrieved from the literature search using the pre-determined eligibility criteria outlined in Table 1. The citations were screened in DistillerSR using standardized screening forms.[22] Titles and abstracts deemed to be potentially eligible by either reviewer were retrieved for full-text review. The same two reviewers independently reviewed the full-text reports using the eligibility criteria and compared the list of included and excluded citations. Any disagreements were resolved through discussion until a consensus was reached.

Data Extraction

Data extraction for the included studies was conducted using standardized data extraction forms, which were 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
- participant characteristics including, number of pregnant persons, age, comorbidities, and risk factors for infection (where reported)
- description of intervention, including screening test, specimen, timing of screening, frequency of screening, setting of screening, and subsequent management of people (pregnant persons and neonates) identified as positive
- description of comparator(s), including screening test, specimen, timing of screening, frequency of screening, setting of screening, and subsequent management of people (pregnant persons and neonates) identified as positive
- description of outcomes reported, follow-up duration, and study loss to follow-up
- description of subgroups of interest and outcomes reported by subgroups, where available

- results for each outcome (i.e., detection yield, clinical utility, and harms)

Outcomes

Detection yield was the primary outcome of interest for this review. Detection yield was defined as the number and per cent of positive tests for CT and/or GC identified by differing screening strategies or the number and per cent of false-positive and false-negative tests for CT and/or GC. Secondary outcomes included clinical utility and harms. Further details on the outcomes are presented in Table 1.

Quality Assessment of Individual Studies

The Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) was used to guide the quality assessment of the included non-randomized studies.[23] 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).[23]

The two reviewers piloted the RoBANS tool independently and in duplicate on a random sample of three publications and discussed discrepancies until they reached consistency in their assessments. After piloting, both reviewers independently conducted the quality assessment on the remaining included studies and compared findings. Discrepancies between the two reviewers were discussed until consensus was reached. The findings of the methodological assessments for each included study are reported, including an assessment of the strengths, and limitations across studies using a table and a narrative description.

Additional criteria to assess external validity, sources of funding, and competing interests were also included in the quality assessment of the included primary studies. The results from the quality assessment were not used to further include or exclude studies, but rather to assess the certainty of the evidence.

Quality Assessment of the Body of Evidence

The overall quality of the body evidence was assessed using the GRADE framework to provide an assessment of the overall confidence in the estimated effect for each outcome of interest.[24] To determine the outcomes of interest, the list of primary and secondary outcomes from Table 1 were sent to decision makers and stakeholders. They were asked to rate the relative importance of each outcome on a scale of 0 to 9. A rating of 0 to 3 indicated the outcome was not important, 3 to 6 indicated that the outcome was important, and a rating of 6 to 9 indicated that the outcome was of critical importance for making a decision. An outcome rated six and higher by any of the decision makers and stakeholders was considered an outcome of interest and included in the Results section (Assessment of the Overall Body of Evidence) and in the GRADE evidence profile tables in Appendix 8.

The GRADE approach categorizes the quality of evidence, by outcome, from high to very low.[24] According to GRADE, randomized controlled trials begin with a high-quality rating but can be rated down for numerous reasons, including risk of bias, inconsistency of results, indirectness of evidence, imprecision, and publication bias.[24]

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 presence of plausible biases that would decrease an apparent effect. The assessments were performed independently by two reviewers.[24] Any discrepancies between the reviewers was discussed until consensus was reached. The final GRADE quality was classified as high, moderate, low, or very low. All assessments were presented in GRADE evidence profile tables.

Data Analysis Methods

A descriptive summary of study and participant characteristics was prepared that included the study design, year and country of publication, sample size, population, intervention, comparator, and outcomes of each study, where applicable.

Results were not meta-analyzed due to the presence of substantial clinical and methodological heterogeneity. Rather, a narrative synthesis of the results of the included primary studies was conducted. The findings, where possible, were grouped by infection outcome. Direct comparisons and indirect comparisons between interventions were reported as presented in the studies. No formal testing was conducted to indirectly compare interventions not directly compared against each other in the studies. Tables were organized to emphasize screening strategy characteristics, including screening test, test specimen, timing, frequency, and infection management strategy, and accompany the narrative summaries to ensure the consistency of the presented information across all studies and to facilitate study comparisons.

Subgroup analyses by age were reported in five of the included studies and are presented as reported in each included study along with the results from the full study population. There was insufficient information to perform subgroup analysis across multiple studies.

Assessment of publication bias graphically or objectively using Egger's regression test and Begg's rank correlation test[25] was not feasible as at least ten citations of a given study design and a particular outcome were not identified.

Results

Quantity of Research Available

The literature search identified a total of 1,696 citations. After review of titles and abstracts, 69 citations were deemed potentially relevant and retrieved for full-text review. Two potentially-relevant reports were retrieved from other sources (i.e., grey

literature, hand searching, and search alerts). Of these 71 potentially-relevant reports, ten[26-35] reports were found to be eligible and were included in this review.

The study selection process is outlined in Appendix 3 using a PRISMA flow diagram. Lists of included and excluded citations are provided in Appendix 4 and Appendix 5, respectively.

Study Characteristics

The characteristics of the ten [26-35] included primary studies, with respect to the country, study design, funding, analytical methods, patient characteristics, clinical setting, interventions, comparators, outcomes, and subgroup analyses conducted are summarized in Appendix 7.

Nine[27-35] of the ten included studies were applicable to detection yield outcomes and six[26-28,33-35] were applicable to clinical utility outcomes. The literature search did not identify any studies reporting the harms of screening during pregnancy.

Study Dates, Locations, Funding, and Design

The ten included primary studies were published between 2003 and 2014.[26-35] One study was published in 2014,[26] one in 2012,[27] two in 2011,[28,29] two in 2010,[30,31] one in 2009,[32] two in 2005,[33,34] and one in 2003.[35]

Seven studies were conducted in the United States,[26-29,31,34,35] one was conducted in Canada,[30] one in Germany,[32] and one in the United Kingdom.[33]

Three studies reported their sources of funding,[28,31,34] three reported there were no conflicts of interest,[29,30,32] and one reported sources of funding and declared competing interests.[27] Three primary studies did not report their sources of funding nor did they declare competing interests.[26,33,35]

Five studies were retrospective chart reviews.[27,30,31,34,35] Two studies were retrospective cohort studies,[26,32] two were cross-sectional studies,[29,33] and one was a secondary analysis of a prospective cohort study.[28]

Population

Pregnant adult and adolescent (less than 20 years of age) females were the population of interest in eight studies [26,27,29,31-35] and pregnant adolescents were the population of interest in two studies.[28,30] The total number of pregnant persons screened in each study varied from 125[28] to 760,864.[27]

Three studies reported the age ranges for included participants: [27,28,30] the youngest was 12 years of age, and eldest was 40 years of age.[27] The mean ages were reported in three studies as 16.1 years,[30] 26.9 years,[29] and 29.3 years.[33] Two studies reported median ages of 17 years[28] and 28 years,[32] and one reported an age range of 16 to 40 years.[27] While some studies reported age using more than one measure (mean,

median, range or standard deviation), four studies did not report on ages of included females.[26,31,34,35]

Comparisons, Outcomes, and Subgroups

Four major groups of comparisons between the screening strategies were identified:

- Detection yield for initial screening for CT and/or GC in comparison to repeated screening at another point during pregnancy (including test-of-cure) for CT and/or GC.[27,28,30,34,35] The data from these studies was used to calculate combined detection yield (i.e., at initial screening plus repeat screening)
- Detection yield for routine screening for CT compared to targeted screening using the United States Preventive Services Task Force (USPSTF) criteria.[31] The USPSTF criteria recommends that pregnant persons should be tested for CT if they are 24 years of age or younger, are single, and are black or Hispanic).[36]
- Detection yield and preferences for urine, vaginal or endocervical specimens.[29,32,33]
- Clinical utility of early versus late detection and treatment of CT.[26,34,35]

Detection yield outcomes were reported in nine studies.[27-35] The number and per cent of CT and/or GC infections were addressed in all nine studies.[27-35] Clinical utility outcomes that were addressed included the number and/or per cent of females screened in accordance with guidelines,[27] the number of females treated for CT and/or GC infections,[28,34,35] the number of individuals declining screening,[33] preference for screening strategies,[33] number and/or per cent of females with obstetric and gynaecological outcomes,[26] and number and/or per cent of adverse neonatal outcomes.[26,34,35]

Outcomes based on age groups were reported in five studies.[26,27,32,34,35] In Blatt et al. (2012),[27] the number and per cent of CT and/or GC infections were evaluated based on age in accordance with the USPSTF and CDC guidelines. The CDC guidelines suggest that all pregnant women should be screened for CT during their first prenatal visit.[37] High-risk women (i.e., those ≤ 25 years and/or have a new or multiple sexual partners) should be rescreened during the third trimester.[37] Miller et al. (2003)[35] and Miller et al.(2005)[34] reported the number and/or per cent of CT or GC infections and neonatal outcomes by age group. Folger (2014)[26] stratified the effect of early detection and treatment of CT infections by age group on moderate-to-late preterm and spontaneous moderate-to-late preterm birth. Lastly, Böhm et al. (2009)[32] compared the prevalence of CT infections in the cohort of females sampled with cervical swabs versus urine samples, by age group.

Quality Assessment of Individual Studies

The RoBANS tool[23] was used to guide the quality assessment conducted on the ten included studies[26-35] as summarized in Appendix 6. The RoBANS rating was low risk for the blinding of outcome assessment and selective outcome reporting criteria in all of the included studies.[26-35] The quality assessment rating was mixed for the

remaining four criteria – selection of participants, confounding variable, intervention measurement, and incomplete outcome data. For selection of participants, nine[26-31,33-35] of the ten studies had retrospective study designs, including one[28] that involved a secondary analysis of a prospective cohort study. The studies were rated as having a high risk of bias because they relied on medical records that were not configured to provide data on the primary and secondary outcomes of interest. Some studies also failed to provide sufficient information on inclusion/exclusion criteria, and demographic and clinical characteristics; leaving uncertainty regarding selection of patients. The lack of demographic and clinical information makes it challenging to assess whether the results can be generalized. There was a risk that the researchers were biased toward selecting participants because they had specific characterisitcs. For example, one study enrolled pregnant persons who sought medical care and chose to be tested,[27] while another used data from employees of a private laboratory.[27] The patient populations in three studies[28,34,35] were from areas with a high prevalence of STIs, and one study was conducted in a miscarriage population,[29] meaning these results may not be generalized to a broader population of pregnant persons. These reasons suggest that the nine studies were at a high risk of bias regarding patient selection.

In addition, data inaccuracy, incompleteness, and errors in abstraction are potential concerns. External validity, funding sources and competing interests were also taken into consideration. Three studies[28,31,34] declared their sources of funding, three studies[29,30,32] declared no competing interests and three studies[26,33,35] failed to declare sources of funding. One study[26] was rated as having a high risk of bias with respect to confounding, eight were rated as having a low risk of bias,[27-32,34,35] and one was rated as having an unclear risk of bias.[33] For intervention measurement, six studies were rated as having a low risk of bias,[26,27,29,33-35] and four studies were rated as unclear.[28,30-32] For the incomplete outcome data criterion, nine studies were rated as having a low risk of bias,[27-35] and one study was rated as having a high risk of bias.[26]

Data Analysis and Synthesis

Findings are presented by outcomes of detection yield and clinical utility, first summarizing study findings in which pregnant persons were screened for both CT and GC infections, and then CT or GC infections only.

Detection Yield

Nine[27-35] of the ten included primary studies contributed detection yield outcome data.

Initial vs. Initial + Repeat Screening

CT and GC Infections

Three studies[27,28,30] provided outcome data on the detection yield of screening once for both CT and GC at entry into prenatal care in comparison to screening at entry into prenatal care and again (i.e., repeat screening) at another point in pregnancy.

Across the three studies, the prevalence of CT at initial screening ranged from 2.7% to 19.2%.[27,28,30] The prevalence of CT at repeated screening ranged from 0.97% to 13.7%.[27,28,30]

The prevalence of GC at initial screening ranged from 0.46% to 10.4%.[27,28,30] The prevalence of GC at repeated screening ranged from 0.95% to 7.4%.[27,28,30]

In each of the three studies, repeat screening at another time point in pregnancy resulted in the identification of new and repeat infections. In the Blatt et al.(2012)[27] study, 2,187 (1.9%) new CT infections and 2,885 (2.54%) re-infections would have been missed if repeat screening had not been conducted at another timepoint in pregnancy. In addition, 817 (0.78%) new GC infections and 276 (0.26%) re-infections would have been missed. In the Berggren and Patchen (2011)[28] study, four (4.2%) new CT infections and nine (9.47%) re-infections would have been missed. For GC, four (4.2%) new infections and three (3.15%) re-infections would have missed. In the study by Aggarwal et al. (2010),[30] five new infections with CT (2.89%) and five new cases (2.89%) with GC would have been left undiagnosed.[30] Of the five new GC infections, one was a new co-infection in an adolescent previously diagnosed with CT.[30]

The Blatt et al.(2012)[27] study was conducted on a large nationally representative sample of pregnant females aged 16 to 40 years of age, that may be generalizable to the Canadian population, although there is uncertainty, due to the lack of reported clinical data (e.g., risk factors, antenatal information). The prevalence of CT and GC infections in the Blatt et al.(2012)[27] study was lower than the Aggarwal et al.(2010)[30] and the Berggren and Patchen (2011)[28] studies likely due to differences in the populations studied. Adolescents aged 13 to 18 years of age were the population of interest in the Aggarwal et al.(2010)[30] study and adolescents aged 15 to 19 years were the population of interest in the Berggren and Patchen (2011)[28] study. In addition, the Berggren and Patchen (2011)[28] study was conducted in an urban area with a high prevalence of STIs. The Berggren and Patchen (2011)[28] and Aggarwal et al.(2010)[30] studies were conducted in high risk populations (i.e., females less than 20 years of age) and their findings may not be generalizable to populations with a lower risk and/or low prevalence of STIs.

CT Infections Only

One study[34] provided outcome data on the detection yield of screening for CT once at entry into prenatal care in comparison to screening at entry to prenatal care and repeat screening at 34 weeks of gestation. The population comprised 752 pregnant females in an area with a high prevalence and risk factors for CT infections.[34] The prevalence of CT at initial screening was 14.0%, and at repeat screening was 5.72%. The lack of repeat screening at 34 weeks of gestation would have left 29 new infections (3.86%) and 14 repeat infections (1.86%) undetected.[34]

Subgroup analysis performed by maternal age demonstrated that females aged 19 years and younger had a significantly higher prevalence of CT infections at both initial and repeat testing compared to females aged 20 years and older ($P < 0.001$).[34] Limiting the repeat testing to females 19 years of age and younger would have missed

eight (1.06%) CT infections. Whereas, limiting the repear testing to persons 20 years of age and older would have missed 21 CT infections.

The findings from this study may overestimate the prevalence of CT infection as it was conducted in an area with a high prevalence of infection and had the risk factors for infection. The findings, therefore, may not be generalizable to populations with a lower CT prevalence or with lower risk factors for infection.

GC Infections Only

One study[35] provided outcome data on the detection yield of screening once at entry into prenatal care in comparison to screening at entry into prenatal care and repeat screening at 34 weeks of gestation. The population comprised 751 females in an underserved area with a high prevalence of GC infections.[35] The prevalence of GC at initial screening was 5.1% and at repeat screening was 2.7%.[34] The absence of screening at 34 weeks of gestation would have missed 19 (2.53%) new infections and one (0.13%) re-infection.

Subgroup analysis performed by maternal age demonstrated that females aged 19 years and younger had a higher prevalence of GC infections at initial and repeated testing than females aged 20 years and older.[34] Limiting the repeat testing to females less than 20 years of age would have missed eight (1.06%) GC infections. However, no analyses were reported to determine statistical significance of the difference in prevalence.

As the population of interest for this study was derived from an area with both a high prevalence of infection and risk factors for infection, the prevalence of GC infection is likely overestimated. The findings may not be generalizable to populations with a lower GC prevalence.

The prevalence of CT and GC infections, the number of new and repeat infections, and the proportion of total infections detected at repeat screening can be found in Table 2.

Table 2: Detection Yield: Initial vs. Initial + Repeat Screening

Author, Publication Year, Country, Study Design,	Patient Characteristics	Intervention, Comparator(s), Specimen, Screening test	Results
CT and GC Infections			
Blatt et al., 2012[27] United States Retrospective chart review	760,864 and 743,810 pregnant females aged 16 to 40 years of age tested for CT and GC infections Median age: NR (range 16 to 40 years)	Intervention: Initial screening for CT and GC n = 760,864 and 743,810 Comparator[a]: Initial + Repeat screening for CT and GC at another point during pregnancy (including TOC for CT within 6 weeks of initial screen) n = 113,275 and 104, 828 Specimen: NR Diagnostic tests: (i) 70% - SDS (ii) 20% - DNA hybridization (iii) 10% - target capture, TMA dual-kinetic assay	**CT** Prevalence of CT at initial screening : 2.7% (20,489/760,864) Prevalence of CT at repeat screening:* 0.97% (5,027/113,275) New infections identified:* 1.93% (2,187/113,275) Repeat infections identified:* 2.54% (2,885/113,275) Total number of CT infections identified:* 25,561 (20,489 + 5,027) Proportion of total CT infections identified at repeat screening:[b]* 19.67% (5,027/25,561) **GC** Prevalence of GC at initial screening: 0.46% (3,435/743,810) Prevalence of GC at repeat screening:* 1.04% (1,093/104,828) New infections identified:* 0,78% (817/104,828) Repeat infections identified:* 0.26% (276/104,828) Total number of GC infections identified:* 4,428 (3,435+993) Proportion of total GC infections identified at repeat screening:[a]* 22.43% (993/4428)
Berggren et al.2011[28] United States Prospective cohort study	125 pregnant adolescents; aged 12 to 18 years Median age at delivery: 17 years	Intervention: Screening for CT and GC at entry to prenatal care n = 125 Comparator[a]: Screening for CT and GC at entry and during the third trimester (~36 weeks of gestation)[c] n = 95[d] Specimen: Endocervical culture or urine samples Diagnostic test: urine NAAT	**CT** Prevalence of CT at initial screening: 19.2% (24/125) Prevalence of CT at repeat screening:* 13.7% (13/95) New infections identified:* 4.2 % (4/95) Repeat infections identified:* 9.47% (9/95) Total number of infections identified:* 37 (24 + 13) Proportion of total infections identified during the third trimester:[b]* 35.14% (13/37) **GC** Prevalence of GC at initial screening: 10.4% (13/125); 5 were co-infected with CT Prevalence of GC at repeat screening:* 7.4% (7/95) New infections identified:* 4.2 % (4/95) Repeat infections identified:* 3.15% (3/95) Total number of infections identified:* 20 (13 + 7) Proportion of total infections identified during the third trimester:[b]* 35% (7/20)
Aggarwal et al.2010[30] Canada Retrospective chart review	211 pregnant adolescents (including 10 repeat pregnancies) Mean age: 16.1 years	Intervention: Screening at first prenatal (i.e., baseline) visit for CT and GC N = 211(14 patients had their baseline screening during their third trimester)	**CT** Prevalence of CT at initial screening:* 14.21% (30/211) Prevalence of CT at repeat screening:* 3.46 % (6/173) New infections identified:* 2.89% (5/173) Repeat infections identified:* 0.58% (1/173)

	(range, 13 to 18 years)	Comparator[a]: Screening at first prenatal visit and during the third trimester n = 173 (excludes 14 who had their baseline screen during the third trimester)[d] Specimen: Cervical swab Diagnostic tests: CT: NAAT (SDA assay) GC: Cervical culture with confirmation by immunofluorescence	Total number of infections identified with initial and repeat screening:* 36 (30 +6) Proportion of total infections identified at repeat screening:[b*] 16.67% (6/36) **GC** Prevalence of GC at initial screening:* 0.94% (2/211) Prevalence of infections at repeat screening:* 2.89% (5/173) New infections identified:* 2.89% (5/173) (one new co-infection with CT and GC) Total number of infections identified with initial and repeat screening:* 7(2+5) Proportion of total infections identified at repeat screening:[a*] 71.43% (5/7)
CT Infections Only			
Miller, Maupin, and Nsuami, 2005 [34] United States Retrospective chart review	752 pregnant females Mean age: NR	Intervention: Screening for CT at entry into a prenatal program n = 752 Comparator[a]: Screening at entry and repeat screening at 34 weeks n = 752 Specimen: NR Diagnostic test: Direct DNA assay (Gen-Probe, San Diego, CA	Prevalence of CT at initial screening: 14.0% (105/752) Prevalence of CT at repeat screening: 5.72% (43/752) New infections identified:* 3.86% (29/752) Repeat infections identified:* 1.86% (14/752) Total number of infections identified with Initial and Repeat screening:* 148 (105 + 43) Proportion of total infections identified with Initial + Repeat screening: [b*] 29.1% (43/148) <u>Subgroup Analysis[e]:</u> Screened at entry into prenatal program (maternal age ≤ 19 years vs. ≥ 20 years): 19.4% (62/319) vs. 9.9% (43/433) were diagnosed with CT, *P* < 0.001; OR = 2.29 (95% CI, 1.44 to 3.23) Repeat screening at 34 weeks of gestation following a negative test at entry into prenatal program (maternal age ≤ 19 years vs. ≥ 20 years): 8.2% (21/257) vs. 2.1% (8/390) were diagnosed with CT, *P* < 0.001; OR = 4.24 (95% CI, 1.85 to 9.74)
GC Infections Only			
Miller et al., 2003,[35] United States Retrospective chart review	751 pregnant females Mean age : NR	Intervention: Screening for GC at entry into a prenatal program n= 751 Comparator[a]: Screening at entry and repeat screening at 34 weeks n= 751 Specimen: NR Diagnostic test: Direct DNA assay (Gen-Probe, San Diego, CA	Prevalence of GC at initial screening: 5.1% (38/751); 19 of the 38 were co-infected with CT Prevalence of GC at repeat screening:* 2.7% (20/751); 8 of the 19 newly infected were co-infected with CT Total number of infections identified with Initial and Repeat screening*: 58 (38 + 20) Proportion of total infections identified with Initial + Repeat screening: [b*] 34.48% (20/58) <u>Subgroup Analyses[e]:</u> Screened at entry into prenatal program (maternal age ≤ 19 years vs. ≥ 20 years): • 7.2% (23/318) vs. 3.5% (15/433) were diagnosed with GC, *P* = NR Repeat screening at 34 weeks of gestation following a negative test at entry into prenatal program (maternal age ≤ 19 years vs. ≥ 20 years): • 3.5% (11/318) vs. 1.8% (8/433) were diagnosed with GC, *P* = NR

CI = confidence interval; CT = *C. trachomatis*; DNA= deoxyribonucleic acid; GC = *N. gonorrhoeae*; NAAT = nucleic acid amplification test; NR = not reported; OR = odds ratio; SDA = Strand Displacement Amplification; STI = sexually-transmitted infection; TMA = transcription mediated amplification; TOC = test-of-cure

[a]The comparator groups is comprised of the same population of females as in the intervention group

[b]The proportion of total infections identified with initial + repeat screening was calculated by dividing the number of infections identified during repeat testing by the total number of infections identified at initial and repeat testing.
[c]A test-of-cure was also performed 4 weeks after positive initial test and treatment but the study reported no data for this outcome
[d]The number of females differed in the intervention and comparator group due to loss to follow-up
[e]Subgroup analyses were also conducted on variables including sociodemographic characteristics, other STIs, and gynecological/obstetric factors but are not included in this report.
*The number and percent of CT and GC infections was calculated from data presented in the individual studies.

Universal vs. Targeted Risk Factor Based Screening

CT Infections

One study[31] reported outcome data on the prevalence of CT infections diagnosed during routine screening in comparison to targeted risk factor based screening using the USPSTF recommendations.[31] The medical records of 2,127 pregnant females with singleton live births and full antenatal records were analyzed.[31] A total of 2104 were screened for CT during pregnancy. The majority (72.6%) were screened once at or before 20 weeks of gestation.[31] Of these 2104 females screened, 98 cases of CT were identified, suggesting a prevalence of 4.7%.[31] Based on medical records, applying the USPSTF criteria would have resulted in a prevalence rate of 1.33% or diagnosis of 28 cases of CT.[31] Risk factor based targeted screening would have have potentially missed 70 (3.32%) CT infections .[31]

The primary limitation of this study is that the criteria used to define which individuals were routinely screened was not reported, limiting reproducilbility and generalizability. Furthermore, the study did not report the occurrence of repeat screening. The findings are summarized below in Table 3.

Table 3: Detection Yield: Universal vs. Targeted Risk Factor Based Screening

Author, Publication Year, Country, Study Design, Quality	Patient Characteristics	Intervention, Comparator(s), Specimen, Screening test	Results
CT Infections Only			
Silveira et al. 2010 [31] United States Retrospective chart review	2127 pregnant adults and adolescents with antenatal records who gave birth to a singleton at ≥ 20 weeks of gestation Mean age: NR	Intervention: Routine screening for CT at any time point during pregnancy; inclusive population n=2104 Comparator[a]: Screening for CT at any time point in pregnancy using USPSTF criteria (≤ 24 years old, single, and black of Hispanic) n= 2104 Specimen: NR Diagnostic test: NAAT	Females routinely screened for CT[b] during pregnancy (criteria for screening NR) • The prevalence of CT infections was 4.7% (95% CI, 3.8% to 5.6%; n = 98/2104) Applying the USPSTF criteria (≤ 24 years old, single, and black or Hispanic) to the screening for CT: • The prevalence* of CT infections would have been 1.33% (28/2014) • 29.0% (95% CI, 21.0% to 38.0%;) of the CT cases that were detected through routine screening would have been identified • Population with potential missed infections: 3.32%(70/2104)

CI = confidence interval; CT = *C. trachomatis*; GC = *N. gonorrhoeae*; NAAT = nucleic acid amplification test; NR = not reported; USPSTF = United States Preventive Services Task Force
[a]The comparator group is comprised of the same population of females as in the intervention group
[b]GC infections were also documented; 24 females had GC infections; 13 were co-infected with GC and CT; however the study does not report on GC outcomes
*The number and per cent of CT infections was calculated from data presented in the individual study.

Specimen Detection Yield

CT Infections Only

Three studies[29,32,33] reported outcome data on the detection yield of CT infections in females by specimen type. Two of the studies compared detection yield using cervical swabs versus urine samples,[29,32] while one study (Logan et al.)[33] additionally compared vulval samples. Roberts et al. (2011)[29] found no difference in the prevalence rates of CT infection detected by NAATs between endocervical and urine samples. Bohm et al. (2009)[32] found a significant difference in the detection yield of CT when comparing cervical swabs to pooled urine samples in the 21 to 25 years, 26 to 30 years, and 31 to 35 years age groups. In these subgroups, the detection yield was significantly higher with cervical swabs than with pooled urine samples, as cervical swabs were reported to identify 1.12%, 1.07% and 0.82% more infections than urine samples in each age group, respecitvely.[32] For females between ages 36 and 40 years, the detection yield was higher with cervical swabs than with pooled urine samples, but the difference was not statistically signficant.[32] For females ≤ 20 years old, the prevalence was lower with cervical swabs than with pooled urine samples, but the difference was not statistically significant.[32] Logan et al. (2005)[33] reported the detection yield of CT was 2.2%, 3.9%, and 1.5% in cervical, vulval, and urine samples, respectively.[33] Though no statistical analyses were performed, the study authors report that urine samples may have decreased test performance in comparison to cervical and vulval samples.[33]

The results from these three studies on the detection rate of endocervical, vulval, and urine samples are summarized in Table 4.

Table 4: Detection Yield: Specimen Detection Yield

Author, Publication Year, Country, Study Design,	Patient Characteristics	Intervention, Comparator(s), Specimen, Screening test	Results
CT Infections Only			

Roberts et al. 2011[29] United States Cross-sectional study	2018 pregnant adults and adolescents Mean age (± SD): 26.9 ± 6.1 years	Intervention: Screening of urine samples for CT at 35 to 37 weeks of gestation n = 2018 Comparator[a]: Screening of endocervical[b] tissue samples for CT at 35 to 37 weeks of gestation n= 2018 Specimen: Urine samples and endocervical[a] tissue samples Diagnostic test: NAAT (Aptima Combo 2 Assay, Tigris DTS system)	• 83 samples were positive for CT by endocervical swab and urine sample; 3 samples were positive by endocervical swab but negative by urine • CT prevalence was 4.3% (95% CI, 3.4% to 5.2%) for endocervical samples (86/2,018) and 4.1% (95% CI, 3.3% to 5.1%) for urine samples (83/2,018) • There was no statistically significant difference in detection rate between the two samples by McNemar's test: 0.15% (95% CI, -0.02% to 0.32%), *P* = 0.083 • Agreement between endocervical and urine samples: κ statistic 0.982 (95% CI, 0.961 to 1.00)
Böhm et al.2009[32] Germany Retrospective cohort study	50,025 females aged 13 to 50 years Median age: 28 years (range, 13 to 50 years)	Intervention: Screening for CT using cervical swabs n=31,856 Comparator[a]: Screening for CT using pooled urine samples n=18,169 Specimen: Cervical swabs and urine samples Diagnostic test: Semi-automated real-time PCR [*artus* C.Trachomatis Plus RG PCR Kit (Qiagen, Hilden, Germany)]	Prevalence of CT in cervical swabs 3.26%* (1,039/31,856) vs. pooled urine samples was 2.93%* (533/18,169) <u>Sub-group Analysis[c]:</u> • CT prevalence stratified by age (cervical swab vs. urine samples): ○ ≤ 20 years: 10.18% (95% CI, 9.34% to 11.11%) vs. 10.91% (95% CI, 9.77% to 12.20%), q = NR ○ 21 to 25 years: 5.66% (95% CI, 5.22% to 6.14%) vs. 4.54% (95% CI, 4.05% to 5.11%), q < 0.05 ○ 26 to 30 years: 2.63% (95% CI, 2.13% to 2.61%) vs. 1.56% (95% CI, 1.32% to 1.85%), q < 0.01 ○ 31 to 35 years: 1.76% (95% CI, 1.53% to 2.03%) vs. 0.94% (95% CI, 0.72% to 1.22%), q < 0.01 ○ 36 to 40 years: 1.27% (95% CI, 1.00% to 1.64%) vs. 0.73% (95% CI, 0.51% to 1.20%), q = NR
Logan et al. 2005[33] United Kingdom Cross-sectional study	207 adults and adolescents admitted for early pregnancy assessment with a positive pregnancy test, history of vaginal bleeding and < 24 weeks of gestation Mean age (SD) (n = 207): 29.3 (5.9) years	Intervention: Screening followed by semi-structured questionnaire Comparator: Screening by an alternate specimen Specimen: Endocervical (n = 139)[b], self-collected vulval (n= 205), or first-void urine (n= 205) samples Diagnostic test: BD ProbeTec ET System	A total of 207 females provided ≥ 1 sample. 2 samples that could not be assayed were excluded from the analysis. • The per cent and number of positive CT tests by specimen type: Endocervical vs. vulval vs. urine samples: 2.2% (3/139) vs 3.9% (8/205) vs 1.5% (3/205); all positive cases were from patients < 30 years old

CI = confidence interval; CT = *C. trachomatis*; GC = *N. gonorrhoeae*; NAAT = nucleic acid amplification test; NR = not reported; PCR = polymerase chain reaction; SD = standard deviation

[a] The comparator group is comprised of the same population of females as in the intervention group

[b] The endocervix is the inner part of the cervix[38]

[c] *"Multiple application of Fisher's exact test was allowed for in the line-wise comparison of the observed infection prevalence in cervical swabs and urine samples by controlling the false discovery rate q, using a SIMES procedure."* (p.S29)[32]

*The number and per cent of CT infections was calculated from data presented in the invididual study

Adherence to Guideline-based Screening

CT and GC Infections

One study[27] reported on the number of females screened according to the Centers for Disease Control and Prevention (CDC), The American College of Obstetricians and Gynecologists (ACOG), and USPSTF recommendations. Blatt et al. (2012)[27] reviewed data of 1,293,423 pregnant females from a private clinical laboratory data warehouse in the United States. Of these 37% were screened at their first prenatal visit for CT in accordance with the 2010 CDC[37] and 2007 ACOG[39] guidelines, and 39% were screened in accordance with the 2007 USPSTF[36] guidelines. For GC infections, 37% were screened in accordance with the 2010 CDC[37] and 2007 USPSTF[36] guidelines.[27]

Adherence with repeat testing recommendations was also evaluated.[27] Females with a positive result at initial screening were not included so as to isolate the influence of age on retesting.[27] 19.1% and 22.1% of high-risk females who had a negative initial test were retested for CT and GC, respectively in accordance with the 2010 CDC guidelines.[27] Of the females considered high-risk who were rescreened, 3.4% and 1.1% had at least 1 subsequent positive test for CT and GC, respectively. Also, 1.9% and 0.6% were positive for CT and GC, respectively, at their last test.[27] Some females were rescreened more than once.

The study demonstrated that at least 60% of females were not being screened in adherence with guidelines, potentially resulting in a number of undiagnosed CT and GC infections. At least 75% of high-risk females (younger than age 25 years) who initially tested negative for either CT or GC did not receive repeat screening. The findings are summarized in Table 5.

Table 5: Clinical Utility: Adherence to Guidelines-based Screening

Author, Publication Year, Country, Study Design	Patient Characteristics	Intervention, Comparator(s), Specimen, Screening test	Results
CT and GC Infections			
Blatt et al., 2012[27] United States Retrospective chart review	760,864 and 743,810 pregnant females tested for CT and GC infections Median age: NR (range 16 to 40 years)	Intervention: Initial screening for CT and GC n = 760, 864 and 743,810 Comparator[a]: Initial + Repeat screening for CT and GC at another point during pregnancy (including TOC for CT within 6 weeks of initial screen) n=113, 275 and 104, 828 Specimen: NR Diagnostic tests: (i) 70% - SDA	**CT** Number and per cent of females screened at their first prenatal visit in accordance with current guidelines: • 37% (483,845/1,293,243[b]) were screened for CT in accordance with 2010 CDC[37] and 2007 ACOG[39] guidelines • 39% (143,019/368,550) aged 16 to 24 years were screened for CT in accordance with the 2007 USPSTF[36] guidelines Repeat testing of females 16 to 25 years of age, considered to be at highest risk for CT infection in accordance with the 2010 CDC[37] guidelines: • 19.1% (50,959/266,472) of females testing negative were retested[c] • 3.4% (1746/50,959) retested had ≥ 1 positive subsequent test result • 1.9% (978/50,959) retested were still positive on their last test **GC**

		(ii) 20% - DNA with chemiluminescent detection (iii) 10% - Target capture, TMA, dual-kinetic assay	Number and per cent of females screened at their first prenatal visit in accordance with current guidelines: • 37% (137,612/368,550) aged 16 to 24 years were screened for GC in accordance with the 2010 CDC[37] and 2007 USPSTF[36] guidelines Repeat testing of females 16 to 24 years of age, considered to be at highest risk for GC infection according to 2010 CDC[37] guidelines: • 22.1% (51,077/231,014) of females testing negative were retested[c] • 1.1% (564/51,077) retested had ≥ 1 positive subsequent test result • 0.6% (288/51,077) retested were still positive on their last test

ACOG = American College of Obstetricians and Gynecologists; CDC = Centers for Disease Control and Prevention; CT = *C. trachomatis*; GC = *N. gonorrhoeae*; SDA = Strand Displacement Amplification; STI = sexually-transmitted infection; TMA = transcription mediated amplification; TOC = test-of-cure; USPSTF = United States Preventive Services Task Force

[a] The comparator group is comprised of the same population of females as in the intervention group, however a smaller percentage of females were re-screened

[b] The laboratory database contained data for 1,293,243 pregnant females, of which 760,864 and 743,810 received testing for CT and GC, respectively.

[c] Positive results excluded to remove the impact of age on retesting

Gynaecological and Obstetric Outcomes

CT Infections Only

One study[26] reported on the effect of early detection (i.e., at or before 20 weeks of gestation) and treatment for CT in comparison to late detection (i.e., after 20 weeks of gestation) and treatment of CT on birth outcomes (preterm birth, spontaneous preterm birth, moderate-to-late preterm birth, spontaneous moderate-to-late preterm birth, very preterm birth, and spontaneous very preterm birth). The population of interest comprised 3,354 pregnant adults and adolescents (i.e., 19 years of age and younger) in an urban county in the United States who were retrospectively found to have had live births and CT infections.[26] The early detection and treatment group had significantly lower moderate-to-late and spontaneous moderate-to-late preterm births than the late detection and treatment group.[26] The early detection group reported 12.2% moderate-to-late preterm births as compared to 14.4% in the late detection group ($P = 0.05$), and 8.2% spontaneous moderate-to-late preterm births, as compared to 10.8% in the late detection group ($P = 0.01$). The differences in the other birth outcomes were not statistically significant.[26]

A subgroup analysis stratified by maternal age (i.e.,< 20 years, 20 to 29 years and > 29 years).[26] The findings demonstrated that early detection of CT reduced the risk of moderate-to-late preterm (adjusted relative risk [aRR] 0.64; 95% CI, 0.47 to 0.86) and moderate-to-late (aRR; 0.54; 95% CI, 0.37 to 0.80) spontaneous preterm birth in females less than 20 years of age but not in females 20 to 29 years of age and 29 years of age and older.[26] Females in the less than 20 years of age group were more frequently diagnosed with chorioamnionitis, suggesting that they had a greater incidence of more invasive and severe upper genital tract infections.[26] As a result, the early diagnosis and treatment of infection reduced the risk of moderate-to-late and spontaneous moderate-to-late preterm birth.[26]

The findings are summarized in **Table 6**.

Table 6: Clinical Utility: Obstetric and Gynaecological Outcomes

Author, Publication Year, Country, Study Design	Patient Characteristics	Intervention, Comparator(s), Specimen, Screening test	Results
CT Infections Only			
Folger 2014[26] United States Retrospective cohort study	3,354 pregnant adults and adolescents with live births and documented CT infections (identified retrospectively) Mean age: NR	Intervention: Early detection i.e., screening and treatment for CT at or before 20 weeks of gestation without subsequent detection n = 2,009 Comparator[a]: Late detection i.e., screening and treatment for CT at or after 20 weeks of gestation or recurrent/persistent infection[b] n = 1,345 Specimen: NR Diagnostic test: NR	Prevalence of preterm birth in early detection vs. recurrent/persistent or late detection groups: • Preterm: 15.5% (312/2009) vs. 16.6% (223/1345), *P* = 0.42 • Spontaneous preterm: 10.5% (211/2009) vs. 12.0% (162/1345), *P* = 0.16 • M/L preterm: 12.2% (244/2009) vs. 14.4% (194/1345), *P* = 0.05 • Spontaneous M/L preterm: 8.2% (165/2009) vs. 10.8% (145/1345), *P* = 0.01 • Very preterm [c]: 3.4% (68/2009) vs. 3.2% (29/1345), *P* = 0.74 • Spontaneous very preterm: 2.3% (46/2009) vs.1.9% (17/1345), *P* = 0.44 Risk of preterm birth in the early detection group[d] (aRR): [no late detection values to compare] • Preterm: 0.96 (95% CI, 0.81 to 1.13) • Spontaneous preterm: 0.92 (95% CI, 0.75 to 1.13) • M/L preterm: 0.85 (95% CI, 0.71 to 1.02) • Spontaneous M/L preterm: 0.80 (95% CI, 0.63 to 1.00) • Very preterm: 1.06 (95% CI, 0.62 to 1.80) • Spontaneous very preterm: 1.17 (95% CI, 0.61 to 2.23) <u>Sub-group Analyses:</u> Age-specific risk of preterm birth in the early detection group[e] (aRR): • M/L preterm: ○ < 20 years : 0.64* (95% CI, 0.47 to 0.86) ○ 20 to 29 years:1.02 (95% CI, 0.80 to 1.30) ○ > 29 years: 0.94 (95% CI, 0.44 to 2.02) • Spontaneous M/L preterm: ○ < 20 years: 0.54* (95% CI, 0.37 to 0.80) ○ 20 to 29 years: 0.98 (95% CI, 0.73 to 1.32) ○ > 29 years: 1.15 (95% CI, 0.42 to 3.10)

aRR = adjusted relative risk; CI = confidence interval; CT = *C. trachomatis*; M/L = moderate to late; NR = not reported
* Statistically significant
[a] The intervention group and comparator group are two distinct populations
[b] Recurrent/persistent infection was defined as infections detected at or before 20 weeks of gestation and after 20 weeks of gestation, but at least 7 days apart.
[c] Reference group restricted to 920 mothers with CT infections detected at 21-31 weeks of gestation
[d] Adjusted for combination of variables including age, race, preconception infection (CT/GC), co-infection (CT/GC), plurality, maternal education, marital status, previous preterm birth, smoking, payer source, pre-pregnancy/gestational diabetes, pre-pregnancy/gestational hypertension, pre-pregnancy weight, and primiparousity
[e] Adjusted for variables including race, preconception infection, plurality, maternal education, previous preterm birth, smoking, and Medicaid payer source.

Neonatal Outcomes

CT Infections Only

Two studies reported on the effect of CT infections on various neonatal outcomes. The first study by Folger (2014)[26] evaluated the effect of early detection and treatment of CT (i.e. at or before 20 weeks of gestation) in comparison to late detection and treatment for CT (i.e. after 20 weeks of gestation) on neonatal birth outcomes (rate of low birth weight, infant mortality, mean gestational age, and mean birth weight) in 3,354 females in an urban county in the United States. Infant mortality was significantly higher (2.2% vs. 0.9%, *P* = 0.003) and mean gestational age was significantly lower (37.9 weeks vs. 38.1 weeks, *P* = 0.048) in the early detection group compared with the late detection group. There were no

statistically significant differences in the proportion of neonates born with low birth weight and in their mean birth weight. In the second study, Miller et al. (2005)[34] evaluated the gestational age and birth weight of babies born to mothers in a cohort of 752 pregnant females from a population with a high prevalence of CT (i.e., 19.7%, 148/752). There were no statistically significant differences in gestational age and birth weight of neonates born to females with infections identified at initial screening versus repeat screening.[34]

The findings from the two studies on the effect of CT infection on neonatal outcomes was mixed. Miller et al.(2005) reported no difference in outcomes in neonates born to females who had their infections identified at initial screening versus repeated screening. Folger et al.(2014) found significant differences between groups with respect to infant mortality and mean gestational age. The authors speculate that the increase in infant mortality may be due to increased severity of the infection in the early detection group.[26] The difference in mean gestational age between the early antenatal detection group and the recurrent or late detection group was 0.2 weeks.[26] Though this finding is statistically significant, the difference is not clinically significant..

GC Infections Only

One study reported on birth weight and gestational age of neonates born to females who underwent initial testing for GC at entry into a prenatal program and again at 34 weeks of gestation.[35] The population of interest was comprised of 751 pregnant females from a population with high prevalence of GC (i.e., 7.8%).[35] No significant differences were found in birth weight and gestational age between females with infections identified at intial screening versus repeat screening.[35]

The findings are summarized in Table 7.

Table 7: Clinical Utility: Neonatal Outcomes

Author, Publication Year, Country, Study Design	Patient Characteristics	Intervention, Comparator(s), Specimen, Screening test	Results
CT Infections Only			
Folger 2014[26] United States Retrospective cohort study	3,354 pregnant females with documented CT infections Mean age: NR	Intervention: Early detection i.e., screening and treatment for CT at or before 20 weeks of gestation without subsequent detection n = 2,009 Comparator[a]: Late detection i.e., screening and treatment for CT at or after 20 weeks of gestation or recurrent/persistent infection[b] n = 1,345 Specimen: NR Diagnostic test: NR	Neonatal outcomes in early detection vs. recurrent/persistent or late detection groups: • Proportion with low birth weight: 13.8% (277/2009) vs. 14.6% (196/1345), *P* = 0.52 • Infant mortality[c]: 2.2% (45/2009) vs. 0.9% (12/1345), *P* = 0.003 • Mean gestational age at birth: 37.9 weeks vs. 38.1 weeks, *P* = 0.048 • Mean birth weight: 3,060.2 grams vs. 3,039.7 grams, *P* = 0.40
Miller, Maupin, and Nsuami, 2005[34] United States Retrospective chart review	752 pregnant females	Intervention: Screening for CT at entry into a prenatal program n= 752 Comparator[d]: Screening at entry and repeat screening at 34 weeks of gestation n = 752 Specimen: NR Diagnostic test: Direct DNA assay (Gen-Probe, San Diego, CA)	Neonatal outcomes (Negative initial and repeat screen vs. initial test positive vs. repeat test positive): • Mean gestational age (SD) at delivery: 276.9 (10.9) days vs. 275.9 (±13.4) days vs. 276.0 (± 13.4) days, *P* = NS • Mean birth weight (SD): 3237 (479) grams vs. 3257 (489) grams vs. 3153 (547) grams, *P* = NS
GC Infections Only			
Miller et al., 2003[35]	751 pregnant females	Intervention: Screening for GC at entry into a prenatal program	Neonatal outcomes (Negative initial and repeat screen vs. initial test positive vs. repeat test positive):

United States Retrospective chart review		n = 751 Comparator[d]: Screening at entry and repeat screening at 34 weeks of gestation n = 751 Specimen: NR Diagnostic test: Direct DNA assay (Gen-Probe, San Diego, CA)	• Mean gestational age (SD) at delivery [days]: 276.7 (11.4) vs. 276.5 (11.7) vs. 279.7 (8.0), *P* = NS • Mean birth weight (SD) [grams]: 3242 (490) vs. 3172 (424) vs. 3160 (312), *P* = NS

CT = *C. trachomatis*; GC = *N. gonorrhoeae* NR = not reported; NS = not significant; SD = standard deviation
[a] The intervention group and comparator group are two distinct populations
[b]Recurrent/persistent infection was defined as infections detected at or before 20 weeks of gestation and after 20 weeks of gestation, but at least 7 days apart.
[c]Data available for years 2007 to 2011
[d] The comparator group is comprised of the same population of females as in the intervention group

Preference for Specimen Sampling

CT Infections Only

Logan et al. (2005)[33] reported on patient preferences with respect to the type of specimen sampled in a cohort of females with suspected miscarriages.[33] Two hundred and seven females who agreed to participate in the study were asked to provide three samples – urine, endocervical, and self-collected vulval samples. 32.8% (68/207) of study participants agreed to provide urine and vulval samples and declined to provide the more invasive endocervical samples. An acceptability questionnaire completed after screening, revealed that urine sampling was significantly preferred over vulval and endocervical sampling ($P < 0.001$);[33] whereas vulval sampling was significantly preferred over endocervical sampling ($P < 0.001$).[33]

A smaller number of females (n = 139) agreed to provide the more invasive endocervical samples in comparison to the self-collected vulval (n = 207) and urine sampling (n = 207).[33] The study demonstrated that non-invasive sampling by urine is preferred over vulval and endocervical sampling. The findings are summarized in Table 8.

Table 8: Clinical Utility: Preference for Specimen Sampling

Author, Publication Year, Country, Study Design	Patient Characteristics	Intervention, Comparator(s), Specimen, Screening test	Results
CT Infections Only			
Logan et al. 2005[33] United Kingdom Cross-sectional study	207[a] admitted to early pregnancy assessment with a positive pregnancy test, history of vaginal bleeding and less than 24 weeks of gestation	Intervention: Screening for CT with endocervical[b], self-collected vulval, or urine sample followed by semi-structured questionnaire Comparator: Screening for CT by an alternate specimen Specimen: Endocervical (n = 139)[a], self-collected vulval (n = 205), or first-void urine (n = 205) samples Diagnostic test: BD ProbeTec ET System	32.8% (68/207) agreed to non-invasive sampling with urine samples or self-collected vulval samples and declined providing endocervical samples Preferred method of sampling[b]: • Urine sampling was significantly preferred compared to vulval sampling ($P < 0.0001$) and endocervical sampling ($P < 0.0001$) • Vulval sampling significantly preferred when compared to endocervical sampling ($P < 0.0001$) .

CT = *C. trachomatis*; NR = not reported
[a] Two samples were excluded as they leaked, leaving 205 samples for analysis
[b]The endocervix is part of the cervix[38]
[c] The number of females who provided samples differed from the number who stated their preference for method of sampling. Females provided more than . Data are presented here as reported in the study.

Number of Females Declining Screening

CT Infections Only

Logan et al. (2005)[33] also reported on the number of females who declined screening. Of the three hundred and ten females with suspected miscarriages invited to participate in the screening, 21 were excluded due to antibiotic use in the past four weeks. Of the 289 females who were eligble to be screened, 26.6% or 77 of the females declined the invitation to participate. Reasons for declining included, *"I have enough to deal with already"* (p.104)[33], " *I do not think I have C.trachomatis"* (p.104)[33] and *"I have been tested before*" (p.104). The distress of undergoing a miscarriage may have contributed to a number of females declining screening.[33] The findings are summarized in Table 9.

Table 9: Clinical Utility: Number of Females Declining Screening

Author, Publication Year, Country, Study Design	Patient Characteristics	Intervention, Comparator(s), Specimen, Screening test	Results
CT Infections Only			
Logan et al. 2005[33] United Kingdom Cross-sectional study	207[a] females admitted to early pregnancy assessment with a positive pregnancy test, history of vaginal bleeding and less than 24 weeks of gestation Median age: 28 years	Intervention: Screening followed by semi-structured questionnaire Comparator: Screening by an alternate specimen Specimen: Endocervical (n = 139)[b], self-collected vulval (n = 205), or first-void urine (n = 205) samples Diagnostic test: BD ProbeTec ET System	Females declining invitation to participate in screening: Of the 289 of the females eligible to participate: • 77 (26.6%) of 289 declined to participate; 212 were eligible for inclusion in the study; 5 samples were then excluded[a] leaving 207 females

CT = *C. trachomatis*; NR = not reported
[a] Two samples were excluded as they leaked, leaving 205 samples for analysis.
[b]Three endocervical samples were not taken by staff and two samples leaked and were excluded from the study

Number of Females Treated for CT and/or GC Infections

CT and GC Infections

Of the studies reviewed, one study[28] provided outcome data on the number of CT and GC infections identified through screening and subsequently treated. In the study by Berggren and Patchen (2011),[28] all (100%) positive CT and GC infections were treated with 1 g oral azithromycin and 125 mg intramuscular ceftriaxone, respectively. At entry into prenatal care, 24 (100%) women were treated for CT, eight (100%) were treated for GC, and five (100%) were treated for co-infection with CT and GC.[28] At repeat screening, 13 (100%) were treated for CT infections and seven (100%) were treated for GC.[28]

Without repeat screening the diagnosis and treatment of 13 CT infections and seven GC infections would have potentially been missed.

CT Infections Only

Of the studies reviewed, one study[34] reported on the number of CT infections identified through screening and how they were subsequently treated. In the study by Miller et al. (2005)[34] all (100%) infections were treated with 1 g oral azithromycin. At entry into the prenatal program, 105 infections with CT were diagnosed and treated.[34] Repeat screening at 34 weeks of gestation resulted in the detection and treatment of 43 (100%) infections of CT.[34]

Without repeat screening at 34 weeks of gestation the diagnosis and treatment of 43 cases of CT would have potentially been missed.[34] Of these 43 cases, 29 were new infections and 14 were repeat

infections. However, additional details regarding whether the infection was from the same sexual partner or new partner were not provided.

GC Infections Only

One study[35] reported on the number of GC infections identified through screening and subsequently treated. In the study by Miller et al. (2003)[35] all (100%) positive infections were treated with a 400 mg dose of oral cefixime. At entry into the prenatal program, 38 (100%) infections with GC were diagnosed and treated.[35] Of these 38 females, 19 were also treated for co-infection with CT.[35] Repeat screening at 34 weeks of gestation resulted in the detection and treatment of 20 (100%) infections of GC.[35] Eight of these females were also treated for co-infection with CT.[35]

The lack of repeat screening at 34 weeks of gestation would have potentially missed the diagnosis and treatment of 20 cases of GC and 8 co-infections with CT.[35] Of these 20 cases, 19 (95%) were new infections and one (5%) was a repeat infection.[35]

The findings are summarized in Table 10.

Table 10: Clinical Utility: Number of Females Treated for CT and GC Infections

Author, Publication Year, Country, Study Design	Patient Characteristics	Intervention, Comparator(s), Specimen, Screening test	Results
CT and GC Infections			
Berggren and Patchen, 2011[28] United States Prospective cohort study	125 pregnant adolescents Median age at delivery: 17 years (range, 12 to 18 years)	Intervention: Screening for CT and GC at entry to prenatal care n= 125 Comparator[a]: Initial and repeat screening for CT and GC during the third trimester[b] n = 95 Specimen: Endocervical culture or urine samples Diagnostic test: NAAT	All females testing positive were treated with 1 g oral azithromycin for CT and 125 mg intramuscular ceftriaxone for GC Screened at entry into prenatal care: • The prevalence of CT was 19.2% (24/125) • The prevalence of GC was 10.4% (13/125); 5 were co-infected with CT as well 24 (100%) were treated for CT infections; 8 (100%) were treated for GC; and 5 (100%) were treated for co-infection Repeat screening during third trimester or at 4 weeks TOC for CT: • The prevalence* of CT was 13.7% (13/95); 9.5% (9/95) were diagnosed with CT re-infections and 4.2% (4/95) with new CT infections • The prevalence* of GC was 7.4% (7/95); 3.2% (3/95) were diagnosed with GC re-infections and 4.2% (4/95) with new GC infections 13 (100%) were treated for CT infections and 7 (100%) were treated for GC infections
CT Infections Only			
Miller, Maupin, and Nsuami, 2005[34] United States Retrospective chart review	752 pregnant females Mean age: NR	Intervention: Initial screening for CT at entry into a prenatal program n= 752 Comparator[c]: Initial screening at entry and repeat screening at 34 weeks of gestation n = 752 Specimen: NR Diagnostic test: Direct DNA assay (Gen-Probe, San Diego, CA	All females testing positive were treated with 1g oral azithromycin for CT Screened at entry into prenatal program: • The prevalence of CT was 14.0% (105/752) 105 (100%) were treated for CT infections Repeat screening at 34 weeks of gestation: • The prevalence* of CT was 5.7% (43/752); of these, 3.85% (29/752) were new cases and 1.86% (14/752) were diagnosed with CT at entry had a positive repeat test indicating re-infection or treatment failure 43 (100%) were treated for CT infections
GC Infections Only			
Miller et al., 2003,[35] United States Retrospective chart review	751 pregnant females Mean age : NR	Intervention: Initial screening for GC at entry into a prenatal program n = 751 Comparator[c]: Initial screening at entry and repeat screening at 34 weeks of gestation n =751 Specimen: NR Diagnostic test: Direct DNA assay	All females testing positive were treated with 400 mg dose of oral cefixime for GC Screened at entry into prenatal program (n = 751): • The prevalence of GC was 5.1% (38/751); 19 were co-infected with CT 38 (100%) were treated for GC infections; 19 were also treated for CT infections Repeat screening at 34 weeks of gestation (n = 751): • The prevalence of GC was 2.7% (20/751); 2.5% (19/751) were new cases; 0.13% (1/151) were diagnosed with GC at entry had a positive repeat test indicating re-infection or treatment failure • 1.1% (8/751) were co-infected with CT 20 (100%) were treated for GC infections; 8 were also treated for CT infection

		(Gen-Probe, San Diego, CA	

CT = *C. trachomatis*; DNA = deoxyribonucleic acid; GC = *N. gonorrhoeae*; NAAT = nucleic acid amplification test; NR = not reported; TOC = test-of-cure

[a] The comparator group is comprised of the same population of females as in the intervention group, however the difference in sample size between the intervention and comparator groups is due to loss to follow-up

[b] A test-of-cure visit was administered 4 weeks after the initial positive test and treatment, but the study does not include the results

[c] The comparator group is comprised of the same population of females as in the intervention group

*The number and per cent of CT and GC infections was calculated from data presented in the study.

Assessment of the Overall Body of Evidence

The outcomes for detection yield, clinical utility, and harms were rated as important or critical by the decision makers and stakeholders who were consulted for this review, therefore, they were all included in the evidence profile tables.

The initial level of confidence of the evidence included in the report for detection yield and clinical utility started out as low based on study design, as all ten included citations were non-randomized studies.

Based on the quality assessment of the included citations, there was a high risk of bias related to patient selection in nine of the ten included studies. Patient selection was considered to be a serious limitation and the level of confidence for all outcomes was further downgraded by one, from low to very low.

Serious inconsistency was identified for three outcomes – detection yield: endocervical vs. urine vs. vulval samples, clinical utility: mean gestational age, and clinical utility: mean birth weight. For the detection yield outcome (Table 15), the level of confidence was downgraded as the wide range of values reported could not be explained by a specific source of heterogeneity. For the clinical utility outcomes (Table 19), inconsistency was considered serious due to the heterogeneity in the intervention and comparators across studies.

Indirectness was a serious concern for detection yield: initial versus initial plus repeat screening (Table 13) as all the included studies reported outcomes for screening once at entry into prenatal care compared with screening once at another timepoint. There was no direct comparison between screening once versus screening multiple times.Values for detection yield at initial plus repeat screening were extracted from the studies.

Imprecision could not be assessed as most results were not reported as point estimates with 95% confidence intervals.

A formal assessment of publication bias was not feasible as at least ten citations of a given study design and a particular outcome were not identified.

The final GRADE evidence quality level for all detection yield and clinical utility outcomes was very low. There was no evidence identified with respect to the harms of differing screening strategies during pregnancy.

The GRADE evidence profile tables for detection yield, clinical utility, and harms of screening for CT and/or GC during pregnancy can be found in Appendix 8.

Summary of Clinical Results

Detection Yield

The evidence on prevalence rates for CT and/or GC infections for pregnant persons may warrant repeat testing regardless of the outcome of the initial test. The evidence suggests that irrespective of having been tested at entry into prenatal care, as much as 13.7% of pregnant persons may have an infection for CT detected in their third trimester. In one study, universal screening at least once during pregnancy detected a greater proportion of CT infections compared with using risk factor based screening. There is conflicting evidence on whether the detection rate of CT infections vary by cervical, vulval, or urine samples. One study found no statistically significant difference in the prevalence of CT infections using endocervical and urine samples. Findings from two other studies suggest that urine samples may have decreased test performance.

Clinical Utility

Findings from a large study suggest that just over 60% of females were not being screened in accordance with guidelines, potentially resulting in a number of undiagnosed CT and GC infections. The early detection and treatment of CT infections in females less than 20 years of age reduced the risk of moderate-to-late preterm and moderate-to-late spontaneous preterm birth by 64% and 54%, respectively. The evidence was mixed with regards to the effect of detection and treatment of CT infections at entry into prenatal care versus another time point in pregnancy on neonatal outcomes. One study reported that the detection and treatment of CT infections earlier in the pregnancy was associated with lower mean gestational age, higher infant mortality, but had no statistically significant impact on birth weight.[26] Another study confirmed that there was no impact on brth weight, however, there was also no association with mean gestational weight.[34] The findings from another study reported that GC infections early in pregnancy in comparison to late in pregancy had no effect on mean gestational age and birth weight.[35]

Approximately a third of females in one study agreed to non-invasive sampling by self-collected vulval swabs or urine samples. Although the same number of women provided urine and vulval samples, urine samples were preferred over vulval and cervical samples. A quarter of the participants invited to screen declined to participate in the study.

Repeat screening at another time point in pregnancy resulted in the detection and treatment of a substantial number of new infections and re-infections with CT and GC which would have been potentially been left undiagnosed.

Harms

No evidence was found regarding the harms of differing screening strategies during pregnancy.

Economic Analysis

The economic analysis addresses the following research question:

Research Quesiton 2: What is the most cost-effective screening strategy during pregnancy for *Chlamydia trachomatis* and/*or Neisseria gonorrhoeae* in pregnant persons and their infants up to the postpartum period?

Review of Economic Studies

A review of the published literature was conducted to identify relevant economic evaluations that assessed the cost-effectiveness of strategies for screening of CT and GC infections during pregnancy. Three unique economic evaluations were identifiedthat evaluated the cost-effectiveness of at least one CT screening strategy in comparison to another CT screening strategy in adult and adolescent pregnant persons.[40-42] These economic evaluations, none of which were conducted in a Canadian setting, generally considered the time from gestation to the postpartum period at minimum, and included outcomes for the mother (e.g., pelvic inflammatory disease), pregnancy (e.g., preterm birth), and the infant (e.g., conjunctivitis and pneumonia). Appendix 9 provides further details on each economic evaluation. An economic evaluation that addressed the economic impact of GC screening in pregnant persons was not identified in the published literature.

All three economic evaluations on CT screening were decision tree models, of which two were based on a one year time horizon and focused specifically on a high-risk populations of adolescent and young pregnant women under a third-party payer perspective.[40,41] The third study assessed the effectiveness of screening strategies in a general pregnant population under a societal perspective and adopted an undefined time horizon that appeared to be longer than one year as it accounted for subsequent pregnancies and long term consequences such as infertility and chronic pelvic pain.[42] All three studies were also unclear regarding the strategy for CT infection screening as it did not describe the timing or type of screening interventions assessed.[40]

In the cost-utility analysis by Ong et al., with a one year time horizon, antenatal screening of pregnant women aged 16 to 25 years old was found to be cost-effective at the willingness-to-pay threshold of $50,000 (in 2014 Australian dollars) per quality-adjusted life year (QALY) compared to no antenatal screening or to selective screening of 16 to 19 year olds or those who have

had multiple sexual partners within a year.[40] Antenatal screening was also found to be dominant (i.e., less costly and more effective) compared to no antenatal screening if the prevalence of CT was higher than 11%.[40] In another cost-utility analysis by Rours et al., that adopted a longer time horizon, universal antenatal screening was found to bedominant compared to no antental screening.[42] In the cost-benefit analysis by Ditkowsky et al., prenatal screening for CT in 15 to 24 year old high-risk pregnant women was found to be more costly but also resulted in reduced morbidity to mother and infant pairs compared to no prenatal screening.[41] The analysis also found that such prenatal screening could be cost-saving if CT prevalence was higher than 16.9%.[41]

Given that none of the studies fully addressed our stated decision problem, a de novo economic model was deemed necessary.

Methods

The objective of the economic analysis was to evaluate the associated costs, health outcomes, and cost-effectiveness of different screening strategies for CT and GC infection in pregnant persons for the duration of the pregnancy and its subsequent impact on both the birthing parent and the infant up to 19 weeks of age.

A protocol developed *a priori* for the economic analysis was adhered to.[43] As noted in the Protocol Amendments table, the only deviations to the protocol were the changes in the research question and the associated time horizon for the analysis. Greater clarity was provided in the revised research question to highlight the fact that the economic analysis aligned with the more focused scope defined by this HTA by addressing immediate impacts of screening during pregnancy and did not consider any potential further long-term impacts of CT and GC infection beyond the postpartum period. The start of the time horizon was shifted from the beginning of the pregnancy to the time at first trimester screening (i.e., gestational age of 12 weeks) to limit the model to only account for the periods that would be affected by the screening decisions. The end of the time horizon was changed from three months postpartum to 19 weeks postpartum to account for the full incubation period for CT pneumonia in infants.[1]

Type of Analysis

To facilitate comparisons of the wide-ranging health benefits associated with screening of CT and GC infection in pregnancy to both the pregnant person and the infant, QALYs were estimated in the base case, reflecting a cost-utility analysis. In addition, cost-effectiveness analyses in which clinical outcomes were defined as the number of prevented adverse pediatric and obstetric outcomes were also evaluated.

Target Population and Settings

The target population of this economic analysis was pregnant adults and adolescents of age 12 years and older in Canada and their offspring from the pregnancy. The age distribution in the model represented the Canadian pregnant population, based on the number of live births and fetal loss, between the ages of 15 to 44 years of age (excluding induced abortions) as reported by Statistics Canada for the years of 2001 to 2005.[44] This distribution was deemed appropriate as pregnancies in individuals aged under 15 years and over 44 years of age are relatively rare.[44]

High-risk individuals were defined in this model based on age as those younger than the age of 25 years. This definition of high-risk reflects one of the risk criteria within the Public Health Agency of Canada's (PHAC) Canadian Guidelines on Sexually Transmitted Infections.[45] Although other high risk factors exist, such as sexual history and injection drug use[45] that may also be of interest, this study limited the exploration of additional subgroups to age specifically due to the availability of data. To explore screening strategies that target screening or repeat screening in high-risk individuals, age subgroups were defined (i.e., < 25 years of age and ≥25 years or older) and modelled separately with model parameters specific to these age groups incorporated where possible.

Table 1: Modelled Age Distribution

Age Group	Value (Probabilistic)	Reference
<25 Years	21.37% (Range: 20.35% to 22.45%)	Statistics Canada, 2010[44]
≥25 Years	78.63% (Range: 77.55% to 79.65%)	

The obstetric outcome and infection status of the birthing parents were also linked to the infants. The level of prematurity was assumed to affect the infant's health utility. Infants born to individuals with CT or GC infections were at risk of vertical transmission and, amongst those newborns infected, they are associated with a higher risk of the infection manifesting as conjunctivitis or pneumonia.

The setting for the analysis reflected the Canadian health care system. The care of the mother-infant pair can span multiple clinical settings including prenatal visits, labour and delivery ward, neonatal intensive care unit, and pediatric outpatient clinic. The initial contact with the health care system and all subsequent prenatal care was assumed to occur as an outpatient visit. All modelled obstetrical events (i.e. term birth, preterm birth, extremely preterm birth, and second and third trimester stillbirths) were assumed to be cared for in an inpatient setting. Prophylactic care of the neonate with suspected exposure to CT or GC during delivery was assumed to occur during the postpartum care period. Symptomatic pediatric CT and GC infections were assumed to be managed in a follow-up outpatient setting except for GC conjunctivitis which was assumed to be treated in an inpatient setting due to higher risk of blindness.(Table 4) Conjunctivitises in extremely premature

infants were also assumed to be treated in an inpatient setting as their length of stay in inpatient postpartum care tends to be longer and encompass the expected onset of symptoms for these infections.

Time Horizon

As per the economic research question, the analysis reflected the period between a prenatal visit in the first trimester of pregnancy (i.e., start of the time horizon) and anchored to 19 weeks after birth or stillbirth (i.e., end of the time horizon) to capture the immediate impacts of screening. The timing of the first trimester screen (i.e., gestational age of 12 weeks) was informed by a clinician feedback.The period of up to 19 weeks after birth was selected as one of the manifestation of CT infection, pneumonia, can arise between 2 to 19 weeks after birth.[1]

Therefore, while all liveborn infants have an identical time horizon of nineteen weeks, the time horizon for the pregnant persons can differ given that the 19-week postpartum period was anchored to births and stillbirths, both of which can occur at different time points within one's pregnancy. For example, those who delivered preterm had a shorter time horizon than those who delivered at term. To determine the expected gestational age for each obstetrical event, 2012 to 2016 Statistics Canada data on live births by weeks of gestational age[46] was consulted.

Defining the time of occurrence of events in the model was necessary to calculate the risk of new infections or re-infections over the duration of the pregnancy and, thus, the potential cost and clinical impacts of screening. The expected gestational ages of each obstetrical event within the model and the timing of prenatal visits n which CT and GC test would be performed within each trimester of pregnancy are further described in Table 2.

By setting a time horizon that was approximately one year in duration, maternal consequences of CT and GC infection that would require longer time to develop (e.g., pelvic inflammatory disease, ectopic pregnancy, and infertility) were not captured as part of this analysis. Consequences of pediatric infection that occur over longer term such as blindness were also not captured as part of the analysis. It is important to note that these consequences have lifelong impacts and may alter the cost-effectiveness of CT and GC screening strategies if the decision problem was considered over a longer time horizon.

Given that the time horizon was approximately one year, discounting was not applied.

Table 2: Timing of Key Events in the Economic Model

Event	Gestational Age	Source

First Trimester Prenatal Visit	12 Weeks	(Dr. Isabelle Boucoiran, University of Montreal, Montreal, QC: personal communication, 2018 Jun 27)
Second Trimester Prenatal Visit	20 Weeks	Statisics Canada's obstetric outcome timing data.[46] The prenatal visit was assumed to occur before any of the second trimester obstetric outcomes that the screening at the visit could have influenced.
Extremely Preterm Birth	24.1 Weeks	Weighted average of gestational ages at extremely preterm birth reported by Statistics Canada.[46]
Second Trimester Stillbirth	24.1 Weeks	Assumption
Third Trimester Prenatal Visit	28 Weeks	Statisics Canada's obstetric outcome timing data.[46] The prenatal visit was assumed to occur before any of the third trimester obstetric outcomes that the screening at the visit could have influenced.
Preterm Birth	34.2 Weeks	Weighted average of gestational ages at preterm birth reported by Statistics Canada.[46]
Third Trimester Stillbirth	38.7 Weeks	Assumption
Term Birth	39 Weeks	Weighted average of gestational ages at term birth reported by Statistics Canada.[46]

Screening Strategies

As per clinical experts consulted as part of this review, the prevalent CT and GC screening technology in Canada is a combination NAAT that screens for both CT and GC at the same time and this screening technology was assumed for this analysis.

Screening strategies varied according to the population, timing and frequency of screening. The current recommended screening strategy involves universal CT and GC screening for all mothers during the first trimester prenatal visit, with consideration for rescreening in every trimester for mothers deemed to be at high risk,(e.g., age< 25 years of age) and follow-up screening in the third trimester for those who were tested positive for CT or GC in an earlier trimester in their pregnancy.[45] In those with no history of screening over the course of their pregnancy, variations exist in whether pregnant persons are screened at labor and delivery. Eleven other screening strategies were further incorporated into the model in consultation with clinical experts and are described in Table 3. Screening strategies were compared against the strategy of no prenatal visit screening (NNNM) to examine the added health benefits and costs of introducing programmatic screening before labour and delivery.

Detailed clinical management associated with screening for CT and GC infections in pregnant persons and infants are described in the Decision Analytic Model section below.

Table 3: Modelled Screening Strategies in Pregnant Persons

Strategy Name[a]	First Trimester	Second Trimester	Third Trimester	At labour and delivery
UTTM (Current Practice)	Universal	Targeted	Targeted	Screen, if no prior history of CT or GC screening[b]
TTUM	Targeted	Targeted	Universal	Screen, if no prior history of CT or GC screening[b]
TTTM	Targeted	Targeted	Targeted	Screen, if no prior history of CT or GC screening[b]
UNUM	Universal	None	Universal	Screen, if no prior history of CT or GC screening[b]
UNTM	Universal	None	Targeted	Screen, if no prior history of CT or GC screening[b]
TNUM	Targeted	None	Universal	Screen, if no prior history of CT or GC screening[b]
TNTM	Targeted	None	Targeted	Screen, if no prior history of CT or GC screening[b]
UNNM	Universal	None	None	Screen, if no prior history of CT or GC screening[b]
NNUM	None	None	Universal	Screen, if no prior history of CT or GC screening[b]
TNNM	Targeted	None	None	Screen, if no prior history of CT or GC screening[b]
NNTM	None	None	Targeted	Screen, if no prior history of CT or GC screening[b]
NNNM	None	None	None	Screen, if no prior history of CT or GC screening[b]

[a] Strategies are named after the type of screening scheduled at the prenatal visit in each trimester. Each type of screening schedule is coded as: N = No screening at trimester ; T = Targeted screening (age <25 years) at trimester; U = Universal screening at trimester; M= mixed. Strategy NTUM for example, indicates no screening at first trimester, targeted screening at second trimester, and universal screening at third trimester and screen at labour and delivery if individual presenting for term birth has no prior history of screening.

[b]Assumed in the model to occur only in individuals presenting for term births. Due to the uncertainty regarding the actual rate of screening at labour and delivery, it was assumed that only 50% of individuals with no history of screening would be screened at labour and delivery. CT and GC screening at labour and delivery was assumed to not occur in extremely pre-term and pre-term births.

Perspective

The perspective of a publicly funded Canadian health care payer was adopted, consistent with CADTH guidelines for the conduct of economic evaluations.[43] As such, direct medical costs were captured including the costs of diagnostic tests, physician services, management of CT and GC infections (including prophylactic treatment) and hospital-related costs.

Decision Analytic Model

A decision tree was developed to capture the impact of CT and GC screening on treatment, the risk of reinfection between prenatal visits, and the potential vertical transmission to infants during delivery in infected pregnant persons. In a decision tree, consequences of a decision are arranged in a logical order to highlight the relationships between competing courses of action (in terms of the possible sets of decisions that could be made) and the resulting set of chance events. To facilitate an efficient model that would explicitly address key outcomes related to CT and GC screening over the entire modelled time horizon, a series of subtrees were built reflecting the decision to screen the pregnant person at each trimester, the screening practice for the pregnant person during labour and delivery, and the screening practice for the infant after birth. The outcomes from a prior subtree were then linked to the next subtree in a chronological fashion. An overview of how the modelled pregnant population and their infant flows through the resulting decision tree is summarized in Figure 1. In summary, infection statuses of the modeled pregnant population were subject to change pending participation in screening at each trimester, additional screening at labour and delivery, and the risk of new infections or re-infection between the trimesters of pregnancy. Furthemore, at labour and delivery, infected parents are at risk of vertically transmitting the infection to the infant. Current clinical management of CT and GC infections were assumed in the model (see Modelled Screening Strategies section).. Expected health benefit and costs were accrued within the model based on the maternal and infant's infection status, the obstetrical outcomes and the pediatric outcomes.

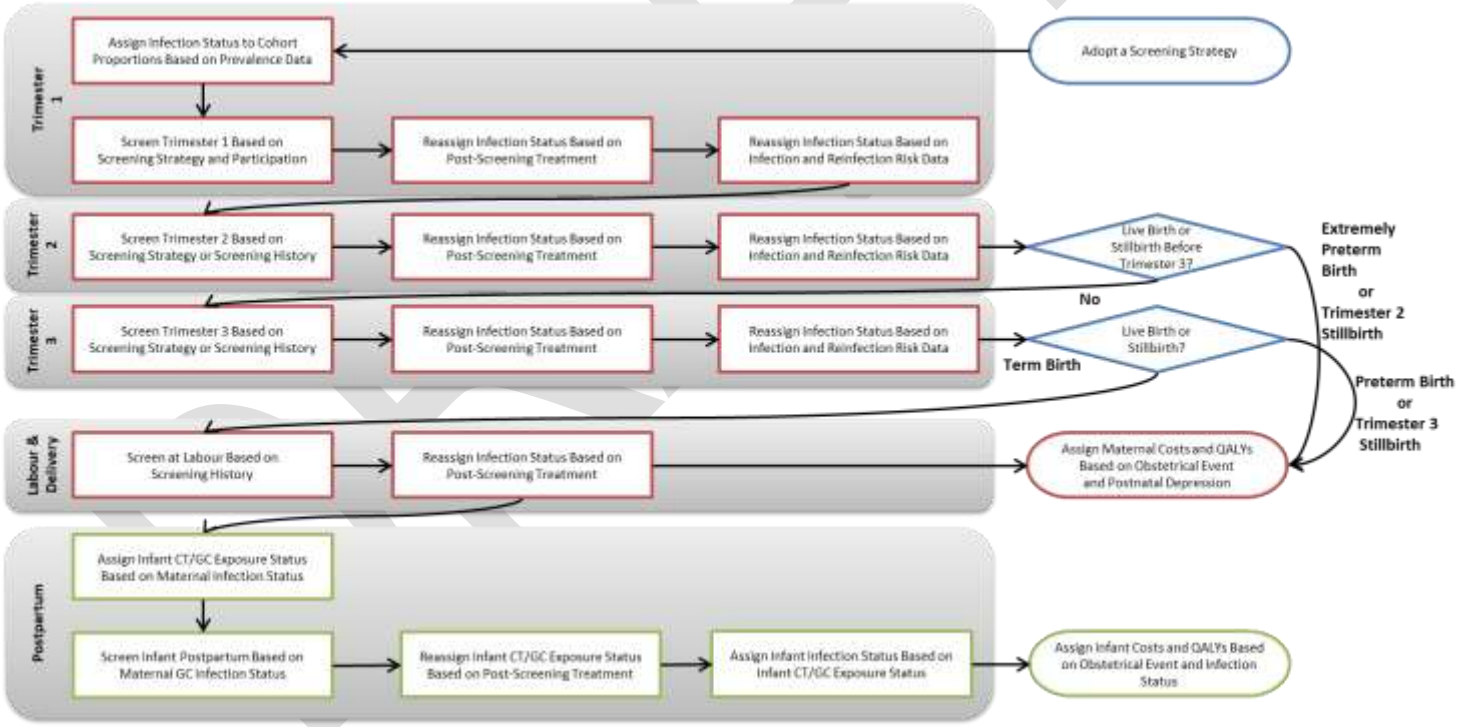
As noted, the population represented the general Canadian pregnancy population containing a mixed cohort with varying infection statuses (i.e., uninfected, CT infected, GC infected, CT and GC co-infected). Although an infection may be detected and treated with each screening, the cohort is subjected to continued risk of infection (if previously uninfected) or reinfection (if previously infected) from continued sexual activity over the course of their pregnancy.

Relationships between CT and GC infections and a number of pediatric outcomes were captured within the modelled time horizon . Manifestations of infections included in the analysis captured the most common infections

observed in clinical practice. CT conjunctivitis, CT pneumonia, and GC conjunctivitis were ultimately considered the most prevalent consequences of CT and GC neonatal infection (Dr. Joan Robinson: personal communication, 2018 Jun**)** and were included in the economic model. Infantile hypertrophic pyloric stenosis, an adverse event from CT infections requiring antibiotic treatment, was considered rare (Dr. Joan Robinson: personal communication, 2018 Jun**)** and thus excluded from the analysis.

As existing evidence suggests an unclear relationship between CT and GC infection and adverse obstetric outcomes (i.e., exteremely preterm birth, preterm birth, term birth, second trimester stillbirth, and third trimester stillbirth),[47] the base-case model assumed CT and GC infections had no impact on these obstetrical outcomes. An exploratory analysis was conducted in which a potential association between obstetrical events and CT or GC infection were assessed.

Figure 1: Overview of Decision Tree



CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; QALY = Quality-adjusted life years.
Red boxes refer to processes relevant for the mother. Green boxes refer to processes relevant for the infant.

Modelling Screening Strategies

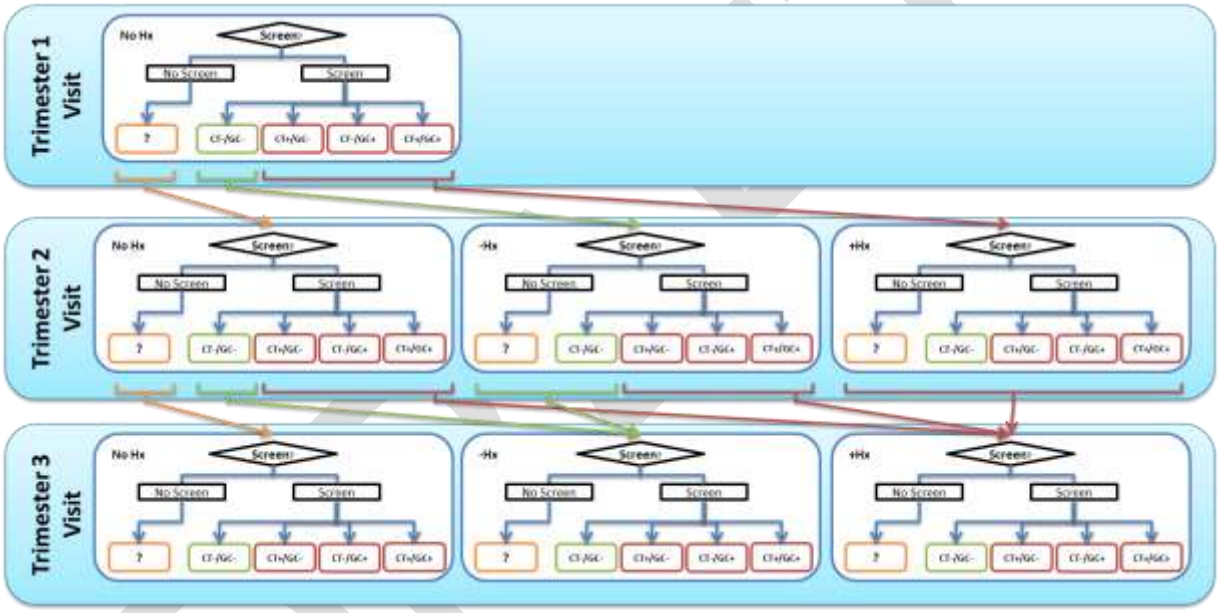
The modelled screening practice reflected an understanding of the pregnant person's medical history in terms of their past screening results and their obstetrical outcomes (Table 4) given that this impacts the individual and their infant's subsequent clinical management.

Table 4: Assumptions Applied to All CT and GC Screening Strategies

Screening Practice Assumptions
• 22.1% of mothers are not screened for CT or GC during a prenatal visit, independent of selected screening strategy, reflecting general screening participation rate.[48] • If a screening strategy involved first or second trimester screening (i.e., all strategies except for strategy NNNM, NNTM, and NNUM), 35% of mothers with positive CT or GC test results pregnancy will be rescreened at their third trimester prenatal visit. This reflects current adhererence rate for rescreening based on recommended screening guideline in which mothers with a known history of infections during pregnancy are encouraged to be rescreened in their third trimester.[48] • Mothers who present for extremely preterm birth or preterm birth were not assumed to be screened at labour and delivery for CT and GC in the base case model, regardless of the maternal infection status. As CT and GC screenings may be performed for spontaneous extremely preterm birth and spontaneous preterm births in some Canadian hospitals, (Dr. Isabelle Boucoiran, University of Montreal, Montreal, QC: personal communication, 2018 Jun 27) a sensitivity analysis was conducted to explore the impact of CT and GC screening in such circumstances. • Mothers presenting for term labour who do not have a history of CT and GC screening were assumed to be screened for both organisms. (Dr. Isabelle Boucoiran: personal communication, 2018 Jun) Due to the uncertainty regarding the rate of such screenings, the rate was assumed to be approximately 50%. Note that this means that, in the case of no scheduled prenatal visit screening (e.g., strategy NNNM), nearly half of pregnant persons would be screened at the time of labour and delivery. Mothers presenting for term labour who have a history of CT or GC were assumed to be rescreened for both organisms. (Dr. Isabelle Boucoiran: personal communication, 2018 Jun) • It was assumed that mothers who tested positive for GC at presentation for labour received an antibiotic treatment. However, due to the uncertainty regarding whether timely treatment can be offered to effectively prevent GC exposure to the infants, these infants were assumed to be screened for potential vertical transmission and prophylactically treated with an antibiotic if found to be infected with GC. (Dr. Joan Robinson: personal communication, 2018 Jun) • Infants born to mothers who tested positive for CT at presentation for labour were assumed to not be screened for potential vertical transmission. The infants were observed for any development of symptoms that would be consistent with CT infection. (Dr. Joan Robinson: personal communication, 2018 Jun)

Three groups were tracked in the pregnant population according to their screening history until presentation at birth or stillbirth as described in Figure 2: i) Pregnant population without any screening history (No Hx), ii) Pregnant population with exclusively infection-negative history (-Hx), and iii) Pregnant population with at least one infection-positive screening result during their pregnancy (+Hx). These groupings were used to guide further maternal screening decisions at presentation for birth.

Figure 2: Diagram representing the mechanics behind the decision tree to track Screening History Group Assignments Based on Previous Trimester's Screening Decisions and Results



CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; Hx = Screening history; N/A = Screening result not available; - = Infection-negative screening result; + = Infection-positive screening result.

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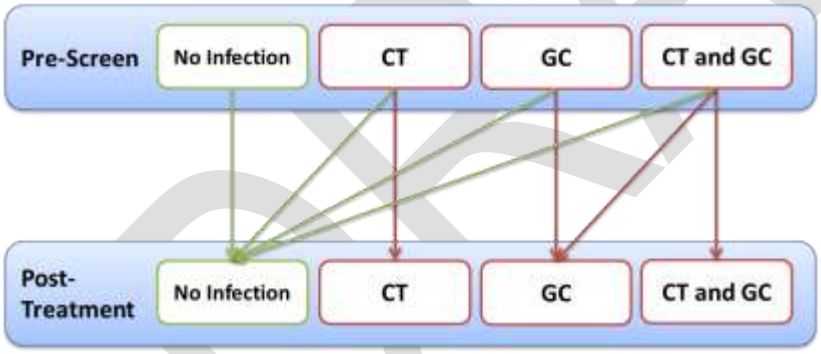
At presentation for birth, if a pregnant person's CT and GC screening history indicated a prior infection during their pregnancy, the individual received further screening for CT and GC. If the screening history instead indicated at least one infection-negative test result and no infection-positive test result, the individual did not undergo additional screening. As such, if their prior screening results were false negatives, this would mean that their infants would be at risk from vertical transmission of CT and GC given that the pregnant person remained infected.

Modelling Infections

The points of screening in the model served to detect and manage CT and GC infections to reduce the prevalence of infections in mothers and the likelihood of vertical transmission and symptomatic infections in infants. In the model, infection status changed following screening, as illustrated in Figure 3 for pregnant person, and Figure 4 for infants borned to individuals with known active GC infection.

Therefore, in the economic analysis, infection and exposure status changes were informed by the screening decision, the diagnostic performance of NAATs at the time of screening, and the subsequent treatment regimen administered based on the screening results. For instance, in individuals with both CT and GC co-infection, choosing to not screen at a particular point in the model time horizon or a false negative screening result for both CT and GC infections when participating in programmatic screening, would allow the existing infections to continue. Similarly, screening tests in an individual with both CT and GC co-infection that produced a CT-positive and GC-negative screening result would lead to inadequate treatment as only the CT portion of the co-infection would be treated. Of note, those co-infected who screen positive for GC but negative for CT would be treated for both infections as the treatment regimen for GC for mothers includes azithromycin which is also used for to resolve CT infections.[45]

Figure 3: Potential Change in Infection Statuses For Pregnant Persons At Screening

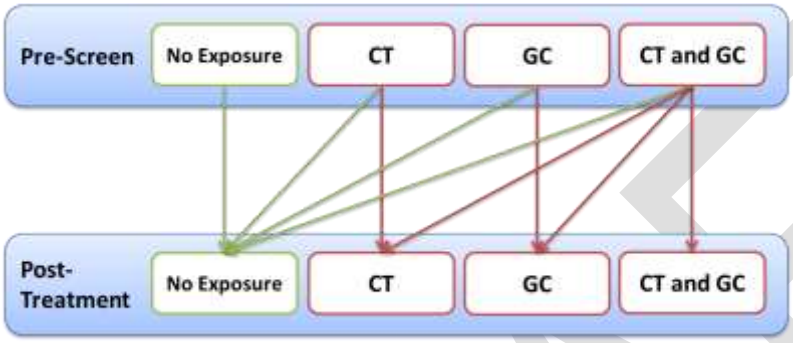


CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae.
Green arrow = Curative treatment; Red arrow = Inadequate treatment based on a false negative or positive screening result.

The analysis modelled vertical transmissions based on the mother's infection status and screening history. For infants born to infected mothers who were not screened at presentation for labour and delivery, they were assumed to be exposed to the same microbes the mother was infected with. For those infants born to mothers who were screened and treated during labour and delivery, there is uncertainty regarding the timeliness of screening and administration of antibiotic treatments to effectively prevent vertical transmission to the infant. It was therefore assumed that the risk of vertical transmission in this situation was approximately 50%. .

As described previously in Table 4, infants born to mothers with GC-positive screening results during labour and delivery were further screened for exposure to GC after birth, reflecting current clinical practice. Figure 4 illustrates how the various pre-screen exposure statuses of these infants could change pending treatment based on the infants' screening results.

Figure 4: Potential Change in CT and GC Exposure Statuses For Infants With Mothers Who Were GC-Positive At Presentation for Labour



CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae.
Green arrow = Curative treatment that clears any previous exposure to CT and/or GC; Red arrow = Inadequate treatment based on a false negative or positive screening result.

For those infants who were exposed to CT or GC from vertical transmission, a range of infection manifestations were modelled. An exposure to CT or GC can either develop to a symptomatic manifestation, or resolve without infection. As noted, exposure of CT in infants can led to the development of CT conjunctivitis or CT pneumonia as infections, while an infant exposed to GC could only potentially develop GC conjunctivitis as an infection.

Clinical Inputs

Natural History

Obstetric outcomes

The probabilities for the obstetric outcomes in the model were informed by the number of fetal deaths and live births that have been reported across a range of gestational ages by Statistics Canada between 2012 and 2016.[46,49] Live births that occurred between 20 to 27 weeks of gestational age were labelled as extremely preterm births, those that occurred between 28 to 36 weeks were labelled as preterm births, and those that occurred between 37 to 41 weeks were labelled as term births. Post term births, defined as those occurring after 41 weeks of gestational age, were not accounted for in the model as these were rare events that occurred in only 0.4% of births.[46] Stillbirths were labelled as occurring in the second trimester if the fetal death occurred between 20 to

27 weeks of gestation age and occurring in the third trimester if occurring at a later time point.

Odds of obstetric outcomes were calculated, based on the number of live births and fetal deaths reported by Statistics Canada. [46,49] These odds were in turn, converted to probabilities at second and third trimester using the formula:

$$\text{Probability} = \frac{\text{Odds}}{1 + \text{Odds}}$$

The resulting conditional probabilities of obstetric outcomes by trimester are reported in Table 5.

Table 5: Calculated Mean Obstetric Outcome Probabilities by Trimester

Obstetric outcome for a Pregnant Person at the Beginning of:	Mean Probability
Second Trimester	
Extremely Preterm Birth	0.5 %
Second Trimester Stillbirth	0.5 %
Continue Gestation to Third Trimester	99.0 %
Third Trimester	
Term Birth	92.4 %
Preterm Birth	7.4 %
Third Trimester Stillbirth	0.3 %

Infections

The underlying prevalence of CT and GC infections at the beginning of the model was informed by a retrospective study of at least 19 weeks pregnant women in a Quebec hospital (n=2,221).[50] CT was found in 1.9% of the pregnant women, GC in 0.2%, and CT and GC co-infections in 0.1%.[50]

Amongst those without a prior history of CT and GC infection during the course of their pregnancy, the model incorporated a probability of acquiring a new infection at both the second and third trimester. This was based upon the annual incidence of CT and GC infections from PHAC's 2015 national surveillance data. [4 3] The annual incidence rates in the pregnant population were assumed to be equal to those in the general female population, and were converted to annual probabilities. Data for multiple age groups were incorporated into the modelled age group of under 25 years old (15 to 19 years and 20 to 24 years) and 25 years old and older (25 to 29 years, 30 to 39 years, and 40 to 59 years) (Table 6).

CT and GC infections were assumed independent and the probability of new co-infections over the course of the pregnancy was based on multiplying the probability of CT incidence and GC incidence. Although this assumption likely leads to an underestimation (i.e., as the association between CT and GC is unlikely to be independent due to shared risk factors), a joint correlation

between CT and GC infection was not available in this patient population to calculate the probability of co-infection.

Re-infection in pregnant persons who had been previously infected during the model time horizon was based on reinfection rates informed by a retrospective study of GC infection based on 1997 to 2003 Alberta surveillance data.[51] The annual probability of GC reinfection was calculated to be 2.31% (95% CI, 2.07% to 2.56%), with those under the age of 25 years showing a trend of increased risk of re-infections compared to those aged 25 years or older (mean relative risk 1.12; 95% CI, 0.95 to 1.43). The probability of CT reinfection was assumed to be equal to the calculated probability of GC reinfection given the paucity of literature on this topic. As noted in the Time Horizon section, the above annual probabilities of infection and re-infection were converted to appropriate time-dependent infection and re-infection probabilities for each trimester and for labour and delivery.

Table 6: Infection Probabilities Input Parameters

Parameter	Value (Probabilistic)	Reference
CT Prevalence	1.9%	Boulay et al., 2018[50]
GC Prevalence	0.2%	
CT and GC Coinfection Prevalence	0.1%	
Probability of CT Infection Age <25 Years Age ≥25 Years	 2.15% (Range: 1.78% to 2.25%) 0.63% (Range: 0.06% to 1.06%)	Choudhri et al., 2018[4]
Probability of GC Infection Age <25 Years Age ≥25 Years	 0.16% (Range: 0.11% to 0.18%) 0.14% (Range: 0.03% to 0.21%)	Choudhri et al., 2018[3]
Annual GC Reinfection Rate (All ages)	0.0234 (95% CI: 0.0209 to 0.0259)	De et al., 2007[51]
GC Reinfection Relative Risk (Age <25 years vs. ≥25 Years)	1.12 (95% CI: 0.95 to 1.43)	
Annual CT Reinfection Rate (All ages)	0.0234 (95% CI: 0.0209 to 0.0259)	Assumed same as GC
CT Reinfection Relative Risk (Age <25 years vs. ≥25 Years)	1.12 (95% CI: 0.95 to 1.43)	

CI = Confidence interval; CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae.

Vertical Transmission and Pediatric Infections

The model parameters for CT pediatric infections were informed by a 2003 CT oral prophylaxis modelling study that had conducted a literature search for incidence of CT conjunctivitis and pneumonia in infants who were exposed to CT at birth and derived a pooled incidence for both manifestations of CT infection.[52] For GC, a range of GC opthalmia rates cited by the Canadian Pediatric Society (CPS)[13] were used to inform incidence of GC conjunctivitis in infants exposed to GC at birth. The probabilities of pediatric infections in CT or GC exposed infants are listed in Table 7.

Table 7: Probability of Symptomatic CT and GC Infections in Exposed Infants

Probability	Value (Probabilistic)	Reference
GC Conjunctivitis	40% (Range: 30% to 50%)	Moore and Macdonald, 2015 [13]
CT Conjunctivitis	15% (Beta: α=156; β=899)	Rosenman et al., 2003[52]
CT Pneumonia	7% (Beta: α=42; β=555)	

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae.

Diagnostic Test Performance

To inform the accuracy of NAAT in the model, a meta-analysis was conducted on the reported NAAT diagnostic test accuracy for the female population, extracted from the US Preventative Services Task Force (USPSTF) recommendation for CT and GC screening.[53] Methodology for the meta-analysis are further detailed in Appendix 10.

The calculated pooled sensitivity and specificity for CT NAAT were 0.93 (95% CI, 0.91 to 0.946) and 0.996 (95% CI, 0.994 to 0.998) respectively, while for GC NAAT were 0.917 (95% CI, 0.87 to 0.948) and 0.998 (95% CI, 0.996 to 0.999) respectively. Due to the limited available information for NAAT performance in infants, the same diagnostic test accuracy as the mother was assumed.

The parameters for the summary receiver operating characteristic (SROC) curve generated for the above meta-analysis were incorporated into the model to permit probabilistic analysis while preserving the correlation between diagnostic measures. Specifically, the bivariate model described by Harbord et al., 2007 [54] was used to derive stochastically generated sets of sensitivity and (1-specificity) parameters.

Health Utilities

Pregnant Persons

Baseline health utilities were informed by the Health Utilities Index 3 (HUI3) measurements taken from the 2013-2014 Canadian Community Health Survey.[55] Specifically, utilities values from a female population were weighted by the expected Canadian pregnancy age distribution to derive utilities for women under 25 years of age and for those who were 25 years and older. These utility values were applied to the duration of life years accumulated by pregnant persons between the first trimester screening and 19 weeks after delivery.

Infants

Health utilities based on gestational maturity (Table 8) were applied to infants from birth to the end of the modelled time horizon. HUI3 utility values for various levels of gestational outcomes were informed by a 2017 meta-

regression of pediatric health utilities.[56] Specifically, the baseline coefficient of the meta-regression was used to inform the utility weight associated with term birth. Utility decrements were calculated for preterm birth and, for extremely preterm births. Specifically, the study separated utilities for extremely pre-term birth by the presence of major co-morbidity. In the economic model, it was assumed that 67.6% of extremely preterm births were associated with a major comorbidity.[57]

As CT and GC conjunctivitises tend to resolve quickly within a few days after treatment (Dr. Joan Robinson: personal communication, 2018 Jun), utility decrement associated with these infections were assumed to have a negligible impact to the model outcomes and thus were not incorporated into the analysis. For CT pneumonia, the associated utility decrement was proxied by the utility decrement of influenza and pneumonia in the aforementioned meta-regression, and was applied to a period of one week to reflect the average time to recovery after treatment (Dr. Joan Robinson: personal communication, 2018 Jun).

Table 8: Postpartum Infant Utility Values

Parameter	Value (Probabilistic)	Reference
Baseline Infant Utility (Term Birth)	0.876 (SE: 0.045)	Kwon et al., 2017[56]
Utility Decrement of Preterm Birth[a]	0.021 (SE: 0.014)	
Utility Decrement of Extremely Preterm Birth With Major Comorbidity Without Major Comorbidity	 0.268 (SE: 0.065) 0.081 (SE: 0.037)	
Proportion of Major Comorbidity in Extremely Preterm Birth	67.6%	Anderson et al., 2016[57]
Utiltiy Decrement of CT Pneumonia[b]	0.256 (SE: 0.071)	Kwon et al., 2017[56]

CI = Confidence interval.
[a]Utility decrement of preterm birth was proxied by the utility decrement of very preterm birth.
[b]Utility decrement of CT pneumonia was proxied by the utility decrement of influenza and pneumonia.

Costs and Resources

All costs and resource use data informing the economic analysis were derived from Canadian data. If 2018 costs were not available, costs from another year were inflated to estimate March 2018 price based on the Canadian consumer price index (CPI).[58,59] Where costs may also be attributed to other payers (e.g., private, individual payers), such as outpatient care drug costs, they were assumed to be covered by a publicly funded insurance plan to capture the analytic perspective of the publicly funded Canadian health care payer to the fullest extent.

Costs associated with obstetric outcomes

Although obstetric outcomes did not differ between pregnant persons with different infection statuses in the base case model (i.e., no differences in rates of obstetric adverse events by different screening strategy), costs associated with these outcomes were estimated for the purposes of informing the

exploratory analysis that assumed an association of CT and GC infection with adverse obstetric outcomes.

All births and stillbirths in the analysis were assumed to have involved a single fetus and to have occurred in an inpatient setting. Procedure costs were informed by 2016 Ontario Case Costing Initiative (OCCI)[60] that accounted for both direct medical costs such as nursing, laboratory, and pharmacy costs, and administration costs. Given the complexity of physician billing codes for extremely preterm and preterm births, more accurate estimates of obstetric outcome costs were not pursued. Given the high costs associated with extremelt premature births, the unaccounted physicial billings would be expected to have a marginal impact.

Cases were defined by relevant International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD10CA) diagnostic codes and Canadian Classification of Health Interventions (CCI) procedure codes were consulted when the appropriate case costs could not be identified by ICD10CA (Table 9).

Table 9: Obstetric Outcome Costs

Obstetric outcome	Value (Probabilistic)	Reference
Pregnant Person		
Term Birth	$3,493 (SE: $3,271)	OCCI[60]
Preterm Birth	$4,620 (SE: $4,802)	
Extremely Preterm Birth[a]	$4,620 (SE: $4,802)	
Stillbirth	$5,817 (SE: $5,144)	
Infant		
Term Birth	$1,120 (SE: $710)	OCCI[60]
Preterm Birth	$7,830 (SE: $14,204)	
Extremely Preterm Birth	$70,385 (SE: $80,615)	

OCCI = Ontario case costing initiative; SE = Standard error.
[a] Assumed same as preterm birth cost.
Costs reported in 2018 Canadian Dollars

Screenings costs

As each screening and test of cure was assumed to be conducted with the same CT and GC combination NAAT technology, the cost of these test were informed by 2018 British Columbia Ministry of Health's Schedule of Fees for Laboratory Services. The specimen sample costed was urine NAATs for maternal tests ($29.94), and swab-based NAATs ($28.85) for infants, when screening was performed.[61] Of note, these costs do not include confirmatory testing for GC that are done in some Canadian jurisdictions and represent a conservative cost estimate. Physician fees associated with prenatal visits were not incorporated into the analysis as these would have been billed as part of regular prenatal visit costs.

Cost to manage infections in the pregnant person

Oral pharmacotherapy associated with CT and GC infections in pregnant persons were informed by PHAC's guidelines on sexually transmitted

infections[45] and Ontario Drug Benefit list prices.[62] Description of the treatment for each infection and its cost, including the test of cure, is listed in Table 10.

Table 10: Maternal Infection Treatment Costs

Infection	Treatment Regimen	Cost
CT	Azithromycin 1 g p.o. single dose	$14.01
	Test of Cure	$29.94
	Total	**$43.95**
GC	Cefixime 800 mg p.o. single dose	$5.43
	Azithromycin 1g p.o. single dose	$14.01
	Test of Cure	$29.94
	Total	**$49.38**
CT and GC	**Total[a]**	**$49.38**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; p.o.; orally.
[a]Includes test of cure cost. Assumed same as GC as Azithromycin is already present in GC therapy.
Costs reported in 2018 Canadian Dollars

Pediatric Infections

As antibiotic treatment in infants are often prescribed by weight, Fenton growth charts for preterm infants[63] were consulted to inform expected infant weight at birth and at the time of symptomatic CT and GC infection. Expected incubation periods for the pediatric infections were informed by PHAC guideline on sexually transmitted infections, and from consulting clinical experts involved in this review. Sex-specific infant weights from Fenton growth charts were weighted by average proportion of male (51.3%) and female (48.7%) Canadian live births reported by Statistics Canada for 2012 to 2016[46].

CT conjunctivitis and pneumonia were assumed to be managed in the outpatient setting, while GC conjunctivitis was assumed to be managed as an inpatient care lasting 2 to 4 days (Dr. Joan Robinson: personal communication, 2018 Jun). A bottom-up costing approach was used to estimate cost for GC conjunctivitis care. Costs for hospitalization based on a per-diem charge for uninsured Canadian residents ($825 per day)[64], diagnostic test and test of cure, pediatrician ($167.00) and infectious disease specialist ($165.50) consultation from the Ontario schedule of benefits for physician services[65], and a single intramuscular injection of ceftriaxone (average of 25 to 50 mg/kg assumed [37.5 mg], maximum 125 mg;[45] cost variable by weight: $4.29 to $5.90[62]) based on Ontario Drug Benefit list price were included.

For those infants who were screened shortly after birth due to suspected GC vertical transmission and had a positive test outcome for GC, the costs of an infectious disease specialist consultation, intramuscular injection drug and service, and test of cure were included. Pediatrician cost and hospitalization costs were assumed to have been already included as part of newborn clinical care.

For CT conjunctivitis, 2016 OCCI ambulatory care case cost corresponding to neonatal CT conjunctivitis and dacryocistitis (ICD10CA code P39.1, mean

2018 cost $558.47)[60], pediatrician and infectious disease specialist consultation costs, and the treatment cost consisting of 14 days of oral erythromycin therapy (erythromycin base 20 to 40 mg/kg/day variable by age and weight;[45] total costs: $0.31 to $2.88,[62]) were included.

As the 2016 OCCI ambulatory care case cost corresponding specifically to CT pneumonia in neonates was unavailable, this cost was proxied with 2015 OCCI ambulatory care case cost for congenital peneumonia of unspecified organism (ICD10CA code P23.9, mean 2018 cost $538.47)[60]. Pediatrician and infectious disease specialist consultations costs, and cost for a day of oral azithromycin therapy (average of 12 to 15 mg/kg assumed [13.5 mg/kg];[45] $0.46 to $1.06[62]) were also included in the event of managing CT pneumonia.

For the above CT costs, screening and test of cure costs were not included as these have been assumed to be included in the case cost. Mean calculated pediatric infection costs are listed in Table 11.

Table 11: Mean Calculated Pediatric Infection Treatment Costs

Treatment	Term Infant	Preterm Infant	Extremely Preterm Infant
GC Intramuscular Prophylaxis	$200.20	$199.56	$198.61
GC Conjunctivitis	$2,871.10	$2,870.48	$2,869.49
CT Conjunctivitis	$574.47	$573.66	$332.81
CT Pneumonia	$865.56	$865.37	$864.96

Statistical Analysis and Management of Uncertainty

Sensitivity Analyses

The base case analysis was conducted probabilistically to account for parameter uncertainty. Conventional parameter distributions were applied: beta distributions defined parameters bound between zero and one such as probabilities; gamma distributions were used to vary those parameters bound to a single lower bound such as costs; and normal distribution was used to vary random variables that were normally defined such as the SROC curve parameters. Sensitivity analyses were performed to account for additional parameter and structural uncertainties.

In terms of parameter uncertainty on the epidemiology of infections , the prevalence for CT and GC infections have been reportedhigher among some Canadian adolescent pregnant persons(i.e., 14.69% CT-only infection; 0.47% GC-only infection; 0.47% coinfections).[30]Therefore, a scenario analysis that would reflect a higher risk pregnant population was performed that incorporated this higher prevalence rate and set the probability of infection and reinfection to be at the upper limit of the 95% confidence interval of the base-case values (CT infection: 2.25% annually age <25 years, 1.06% age ≥25; GC infection: 0.18% annually age <25 years, 0.21% age ≥25; CT and GC reinfections: 2.79% annually age <25 years, 2.49% age ≥25 years)..

Given the paucity of literature on CT reinfection rates, a scenario analysis was also conducted that equated the CT reinfection rate to the initial CT incidence rate (approximately 2.15% annually age <25 years; 0.63% age ≥25 years) instead of the GC reinfection rate (approximately 2.53% annually age <25 years; 2.25% age ≥25 years) as was done for the base case analysis.

Amongst infants born of mothers who have an infection, a lower probability of symptomatic presentation amongst infants was set as the base case literature sources for these rates[13,52] were synthesized from settings that may not reflect that of Canadian perinatal care (e.g. China,[66] Kenya,[67] and Cameroon[68]) nor the pharmacological agent presently used for ocular prophylaxis in Canada (i.e., erythromycin). Given the prevalence of legal enforcement of neonatal ocular prophylaxis using erythromycin in Canada despite calls to reconsider this practice,[13 69] and the finding that erythromycin ocular prophylaxis is more efficacious than other prophylactic agents previously used for CT conjunctivitis,[70] it is possible that these infection rates could be an overestimate. Indeed, this has been a limitation criticized in other studies of CT modelling.[71] In this regard, a scenario analysis was conducted with lower pediatric infection probabilities that were observed in an American ocular prophylaxis study that included erythromycin as part of the study (Table 12).[72]

Table 12: Alternate Probability of Symptomatic CT and GC Infections in Exposed Infants

Infection	Probability	Source
GC Conjunctivitis	0.1%	Hammerschlag et al., 1989[72]
CT Conjunctivitis	14%	
CT Pneumonia	0%	

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae.

Furthermore, ggiven the lack of literature to inform some input parameters, sensitivity analyses were conducted to assess the robustness of the cost-effectiveness results. This included:

- 100% screening of extremely preterm or preterm births at presentation for labour
- 100% screening rates at presentation for labour for pregnant persons without prior history of screening
- 0% screening rates at presentation for labour for pregnant persons without prior history of screening
- no screening of infants born to mothers with GC-positive test results
- 100% rate of vertical transmission prevention in pregnant persons who have received antibiotic treatment during labour and delivery which would mean that treatment was not effective in preventing vertical transmission
- 0% rate of vertical transmission prevention in pregnant persons who have received antibiotic treatment during

labour and delivery which would mean that treatment was 100% effective in preventing vertical transmission.

Subgroup analyses of pregnant persons who were under the age of 25 years and who were aged 25 years or older were also performed to examine whether differences in cost-effectiveness of screening exist for different risk subgroups.

Lastly, an exploratory analysis was conducted that assumed an association between CT and GC infection and adverse obstetric outcomes. Odds ratios for preterm birth and stillbirths associated with CT and GC infection compared to uninfected pregnant persons were extracted from a 2013 Australian study of singleton birth records. [47 30] These odds ratios were then applied to the existing odds of preterm birth and stillbirth reported for the general Canadian population.[46 49] and converted into CT and/or GC-specific probabilities that were incorporated into the exploratory analysis (Table 13).

Table 13: Calculated Probability of Adverse Obstetric Outcome, by Infection Status (For Exploratory Analysis)

Obstetric outcome for a Pregnant Person at:	CT Infection	GC Infection	No Infection
Second Trimester Prenatal Visit			
Extremely Preterm Birth	0.5 %	1.1 %	0.5 %
Second Trimester Stillbirth	0.4 %	0.7 %	0.3 %
Continue Gestation to Third Trimester	99.1 %	98.3 %	99.2%
Third Trimester Prenatal Visit			
Term Birth	91.1 %	92.4 %	92.4 %
Preterm Birth	8.5 %	7.4 %	7.3 %
Third Trimester Stillbirth	0.4 %	0.7 %	0.3 %

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae.

In this exploratory analysis, differences in the pregnant persons' utilities due to adverse obstetric outcome were also accounted for. As no literature was identified reporting the utility weights of pregnant persons following adverse obstetric outcomes, utilities were estimated based on the relationship between adverse obstetric outcomes and postnatal depression. Specifically, the Edinburgh Postnatal Depression Scale (EPDS) scores from an Austrian longitudinal study of pregnant women[73] were used to determine whether pregnant persons with specific obstetric outcomes in the model would experience postnatal depression. The EPDS score for term birth was proxied as the reported EPDS scores for "pregnancies without complications" while the EPDS scores for extremely preterm births and stilbirths were conservatively assumed to be equal to that of the preterm births.

Table 14: EPDS Scores by Obstetric outcome

Obstetric outcome	Value (Probabilistic)	Reference
Term Birth	5.085 (SE: 4.655)	Mautner et al., 2009[73]
Preterm Birth	8.220 (SE: 5.675)	
Extremely Preterm Birth[a]	8.220 (SE: 5.675)	
StillBirth[a]	8.220 (SE: 5.675)	

EPDS = Edinburgh postnatal depression scale; SE = Standard error.[a]EPDS score of stillbirth and extremely preterm birth were assumed to be at least that of extremely preterm or preterm birth.

Pregnant person was considered to have postnatal depression if their EPDS score was at least equal to the threshold score of 14/30, a score clinically interpreted as a probable depression.[74]For pregnant persons with postnatal depression, a health utility decrement (0.17) associated with depression was applied to the postpartum period b ased on the difference of HUI3 utilities between non-depressed and depressed populations reported in a Canadian study (Table 15).[75] The utility values in the Canadian study were similar to those reported for postnatal depression in the UK.[76]

Table 15: Postnatal Depression Utility Decrement[a] Parameters

Parameter	Value (Probabilistic)	Reference
Utility in Individuals Without Depression	0.85 (95% CI: 0.84 to 0.86)	Patten et al., 2014[75]
Utility in Individuals With Depression	0.68 (95% CI: 0.64 to 0.71)	

CI = Confidence interval.
[a]Utility decrement of postnatal depression nwas calculated from the difference of the two health utility values in the table (Mean 0.17).

Validation

Face validity was achieved through numerous consultation with Canadian clinical experts who practice in obstetrics and gynecology, pediatrics, infectious diseases, medical microbiology, and communicable diseases. These consultations were used to ensure that the model was consistent with Canadian practice and that no significant evidence was omitted from consideration. Internal validity was ensured via tests of extreme parameter values and the model underwent an independent technical review.

Summary of Key Assumptions

The base case analysis was conducted under the following key assumptions listed onTable 16.

Table 16: Summary of Key Assumptions and Sensitivity Analyses

Assumption	Sensitivity Analysis
A representative Canadian pregnancy population (range	High risk population (Prevalence: 14.69% CT-

of ages between 15 to 44)was modelledand the overall prevalence of CT and GC infection was 1.9% and 0.2% respectively.	only infection, 0.47% GC-only infection, 0.47%, coinfections [30]; CT infection: 2.25% annually age <25 years, 1.06% age ≥25; GC infection: 0.18% annually age <25 years, 0.21% age ≥25; CT and GC reinfections: 2.79% annually age <25 years, 2.49% age ≥25)
Modelled time horizon was between first prenatal visit (12 weeks) and 19-weeks postpartum. Long-term implications of infection and screening was not captured given the defined time horizon within the model.	
Each pregnancy produced a single birth.	
All obstetric outcomes were assumed to be treated in-hospital	
No impact of CT or GC infections on the development of adverse obstetric outcomes (i.e., exteremely preterm birth, preterm birth, stillbirths).	Exploratory analysis – ORs of CT and GC-associated adverse obstetric outcomes from an Australian birth record study[47] wereapplied.
Pregnant persons were assumed to be at continued risk of CT and GC infections from sexual activities until live birth or stillbirth event.	
CT reinfection probability equaled GC reinfection probability	CT reinfection probability equivalent to that of the initial CT incidence.
CT and GC infections were assumed to be independent of each other.	
Current screening practices and clinical management of infections were modelled (detailed in **Table 4)** for both the pregnant person and the infant.	• 100% of pregnant persons who experience extremely pretern birth or preterm births were screened for CT and GC at presentation for labour. • 100% of the pregnant persons without history of screening at term were screened. • 0% of the pregnant persons without history of screening at term were screened. • 0% of infants whose parents tested positive for GC at presentation for labour were screened after birth
All screenings for the mother involved urine sample NAAT that tested both for CT and GC. The diagnostic test accuracy of NAAT was assumed to be similar to the reported diagnostic test accuracy of NAATs in the general female population.	
All screenings for the infant involved swab-based NAAT that tests both for CT and GC. It was assumed that the tests would have the same diagnostic test accuracy as the maternal urine sample NAAT.	
Mothers or infants who test positive for CT or GC at any point received corresponding antibiotic treatment. All CT and GC treatments were assumed to be curative and treatment-related complications were not captured.	
Approximately 50% of treatments administered to mothers who test positive for CT or GC at presentation did not prevent vertical transmission to infant.	• 100% of treatments administered to mothers at presentation prevented vertical transmission. • 0% treatments administered to mothers at presentation prevented vertical transmission

CT and GC pediatric infections were mutually exclusive – although infants could be exposed to both, they could only develop either a CT or GC symptomatic infection.	

Results

Base Case Results

Cost-Utility Analysis

The sequential results of the base case are presented in tables below, ordered by lowest to highest total cost. Table 17 highlights those strategies that have not been dominated (i.e., more costly and less effective against another strategy) or extendedly dominated (i.e., more costly and less effective than a combination of screening strategies) when defining effectiveness based on QALYs. The highlighted strategies represent the efficiency frontier, a series of strategies that produces the highest health benefits at different costs. The current Canadian screening strategy (UTTM) was dominated by strategy TNUM, indicating that offering targeted screening in the first trimester for individuals under the age of 25 years and universal screening to all pregnant women in the third trimester would be less costly but also generate more health benefits compared to current practice. Complete cost-utility and cost-effectiveness results are presented in Appendix 12.

Table 17: Expected Costs and QALYs Associated With Different Screening Strategies Per 100,000 Pregnant Persons – Sequential Incremental Cost-Utility Ratio (Probabilistic Base Case)

Strategy[a]	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM[b]	113,489.73	561,663,327	0.00	0	Reference
NNTM	113,489.83	561,898,833	0.10	235,506	2,328,518
NNUM	113,490.15	562,780,614	0.32	881,780	2,775,685
TNUM	113,490.15	563,302,024	0.01	521,410	63,780,330
UNUM	113,490.18	565,220,320	0.03	1,918,296	65,160,515
Current Strategy					
UTTM[c] (vs. TNUM)	113,490.12	563,823,445	-0.03	521,421	Dominated

ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.
[a]Other strategies that were either dominated or extendedly dominated are omitted from this table.
[b]Current strategy UTTM is not part of the efficiency frontier, included here for information.

Not offering a prenatal visit screening program for CT and GC in pregnant women (i.e., strategy NNNM) was the least costly but also the least effective option. If one's willingness-to-pay (λ) was under $2.3 million per QALY, this screening strategy was also most likely to be considered cost-effective.

Other screening strategies generated more QALYs from preventing more pediatric infections. In terms of the frequency of screening, offering screening once during the pregnancy was associated with lower costs but also fewer

clinical benefits. This was due to the fact that less frequent screening resulted in fewer averted pediatric infections compared to strategies that screened at multiple time points during a pregnancy. Similarly, as the base case analysis assumed no impact of CT and GC infections on obstetric outcomes, the analysis found that screening in the third trimester would be less costly and more effective than a corresponding strategy involving screening in an earlier trimester (e.g., NNTM versus TNNM). Therefore, between a λ of $2.3 million to $63.8 million per QALY, offering a prenatal visit screening during the third trimester would be considered cost-effective; otherwise, offering screening at both the first and third trimester of the pregnancy would be considered cost-effective at a higher λ threshold.

Within the general trends noted above, another emerged with respect to the screening approach. The analysis found that targeted screening compared to universal screening was associated with lower costs and QALYs as fewer individuals would undergo screening and, similarly, fewer benefit from averted pediatric infections. Targeted approaches were associated with more true positive detection whereas, universal approaches were associated with more true negative detection.

Of the screening strategies on the efficiency frontier, implementing those with increasingly larger coverage and frequency were found to decrease the prevalence of CT and GC infections in the pregnant population but correspondingly increased the rate of false positive findings and reduced the rate of false negative findings. Adopting targeted screening in the third trimester (NNTM), for example, was found to increase the proportion of false positives from 4.01% to 4.04% compared to the no prenatal visit screening strategy (NNNM) and reduce the proportion of false negatives from 0.18% to 0.16%. As a reminder, it was possible for the no prenatal visit screening strategy to generate false positive and negative findings in this analysis as approximately 50% of individuals presenting at labour and delivery without a history of CT and GC screening during the pregnancy would have CT and GC screening performed. Per 100,000 pregnant persons screened, this would mean an additional increase in 30 false positive cases and a reduction of five false negative cases. Expanding the strategy to universal screening in the third trimester (NNUM) was found to produce 59 more false positive cases and 14 fewer false negative cases per 100,000 pregnant persons screened compared to a targeted screening in the third trimester (NNTM).

Table 18: Overall Diagnostic Outcomes across Entire Pregnancy (Probabilistic Base Case)

Strategy[a]	True Positive (%)	False Positive (%)	True Negative (%)	False Negative (%)
NNNM	2.40	4.01	93.41	0.18
NNTM	2.33	4.04	93.45	0.18
NNUM	2.15	4.10	93.59	0.16
TNUM	1.84	4.11	93.91	0.14
UNUM	1.22	4.14	94.54	0.09
Current Strategy				

UTTM[b]	1.50	4.13	94.25	0.12

[a]Other strategies that were either dominated or extendedly dominated are omitted from this table.
[b]Current strategy UTTM is not part of the efficiency frontier, included here for information.

The reported ICURs for introducing CT and GC screening during pregnancy in the third trimester before labour and delivery were in the millions due to the small incremental QALY gain (i.e., 0.10 QALYs per 100,000 pregnant persons). To aid interpretation of such results in more concrete epidemiological context, cost-effectiveness analysis results are provided below in which the clinical outcomes compared are in terms of pediatric infections averted.

Cost-Effectiveness Analysis

Table 19 shows that compared to the current screening strategy (UTTM), strategies with universal screening in third trimester visits (i.e., NNUM, TNUM, and UNUM) reduced more cases of pediatric infections. These results also align with the trends reported in the cost-utility analysis: increasing coverage and frequency of screening decreased pediatric infections in the population, albeit at an incremental cost. For example, adopting targeted third trimester screening (NNTM) compared to no prenatal visit screening (NNNM) would reduce approximately 74 pediatric infections per 100,000 pregnant persons and would cost $11,595 per prevented pediatric infection.

Table 19: Expected Pediatric Outcomes of Screening Strategies on the Efficiency Frontier Per 100,000 Live Births – Sequential Cost-Effectiveness Ratio (Probabilistic Base Case)

Strategy[a]	Total					Incremental				
	GC Conjunctivitis	CT Conjunctivitis	CT Pneumonia	Pediatric Infections[a]	Cost ($)	GC Conjunctivitis	CT Conjunctivitis	CT Pneumonia	Pediatric Infection Prevented[a]	Cost ($)
NNNM	80.4	276.7	132.0	489.1	561,663,327	0.0	0.0	0.0	0.0	0
NNTM	69.1	234.1	111.7	414.8	561,898,833	-11.4	-42.6	-20.3	74.3	235,506
NNUM	27.7	100.4	47.9	176.0	562,780,614	-41.3	-133.7	-63.8	238.9	881,780
TNUM	27.3	96.9	46.2	170.5	563,302,024	-0.4	-3.4	-1.6	5.5	521,410
UNUM	25.8	84.5	40.3	150.7	565,220,320	-1.5	-12.4	-5.9	19.8	1,918,296
Current Strategy										
UTTM (vs. TNUM)	36.8	110.8	52.8	200.4	563,823,445	9.5	13.8	6.6	-29.9	521,421

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICER = Incremental cost-effectiveness ratio; QALY = Quality-adjusted life years.
[a]Other strategies that were either dominated or extendedly dominated are omitted from this table.
[b]Accounts for GC conjunctivitis, CT conjunctivitis, and CT pneumonia in aggregate.
[c]Current strategy UTTM is not part of the efficiency frontier, included here for information.

Sensitivity Analyses

Scenario Analysis

All scenarios analyses reflected the trends observed in the base case analysis (See results in Appendix 12) with the exception of two scenarios related to different risk profiles. In the scenario reflective of ahigher risk pregnant population Prevalence: 14.69% [CT-only infection], 0.47% [GC-only infection], 0.47% [coinfections]; Probability of infection and re-infection at 95% confidence interval upper limit; Table 20), introducing screening in an earlier trimester (UNNM) was found to be less costly and more effective than the corresponding strategy that screened at a later trimester (NNUM). When the λ was between $67,183 and $458,282 per QALY screening in the first trimester was found to be the most likely cost-effective strategy. Targeted screening strategies were also found not to be cost-effective at any λ threshold.

Table 20: Expected Costs and QALYs per 100,000 Pregnant Persons – Sequential Incremental Cost-Utility Ratio (High Risk Population Scenario)

Strategy[a]	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM[b]	113,486.17	563,874,495	0.00	0	Reference
UNNM	**113,489.00**	**564,064,703**	**2.83**	**190,208**	**67,183**
NNUM	**113,489.08**	**564,098,759**	**0.07**	**34,056**	**458,282**
UNUM	113,489.36	566,205,416	0.28	2,106,657	7,452,270

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.
[a] Other strategies that were either dominated or extendedly dominated are omitted from this table.

In the scenario with lower incidence of pediatric infections (i.e., pediatric infection probabilities: 0.1% GC conjunctivitis, 14% CT Conjunctivitis, 0% CT pneumonia; Table 28), no prenatal visit screening strategy (NNNM) was found to always be the most cost-effective strategy across all λ values and dominated all other stratetgies. Of note, this result reflected a scenario where CT pneumonia would not occur and, as this outcome was the only one that contributed to lowered utilities, there were no differences in expected utilities across all strategies.

Subgroup Analysis

Subroup analyses of pregnant persons aged under 25 years, and 25 years and older were conducted to explore potential differences in cost-effectiveness between age subgroups due to patient heterogeneity. Of note, targeted screening strategies were not evaluated in this subgroup analysis as targeted screening for high-risk patients was defined by age. The findings in terms of frequency and timing reflected the trends observed in the base case analysis (Table 21). No prenatal visit screening strategy (strategy NNNM) was found to be cost-effective if λ was below $2.3 million per QALY in the under 25 years of

age subgroup, and $2.8 million per QALY in the subgroup aged 25 years and older. Screening in the third trimester was cost-effective at higher λ thresholds up to $64.0 million per QALY in the under 25 years of age subgroup, and $65.1 million per QALY in the subgroup aged 25 years and older. Screening in both first and third trimesters were cost-effective at λ thresholds beyond these levels and, for the under 25 years of age subgroup, screening at each trimester (strategy UUUM) was found to be cost-effective if λ threshold was beyond $214.7 million per QALY.

Of note, the ICURs of screening strategies were found to be lower in the under the age of 25 subgroup compared to those over the age of 25 subgroup. This result highlights the potential value of offering targeted screening to younger patients who are considered at higher-risk of infection and re-infection.

Table 21: Expected Costs and QALYs Associated With Different Screening Strategies Per 100,000 Pregnant Persons – Sequential Incremental Cost-Utility Ratio (Subgroup Analyses)

Strategy[a]	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
Age < 25					
NNNM[b]	112,340.51	561,746,315	0.00	0	Reference
NNUM	112,340.99	562,848,514	0.47	1,102,199	2,327,685
UNUM	112,341.02	565,288,586	0.04	2,440,071	63,952,184
UUUM	112,341.04	567,637,448	0.01	2,348,862	214,675,621
Age ≥ 25					
NNNM[b]	113,802.11	561,640,776	0	0	Reference
NNUM	113,802.52	562,762,156	0.40	1,121,380	2,775,918
UNUM	113,802.56	565,201,763	0.04	2,439,607	65,111,848

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.
[a] Other strategies that were either dominated or extendedly dominated are omitted from this table.

Exploratory Analysis

An exploratory analysis was conducted that incorporated the potential impact of CT or GC-infections on adverse obstetric outcomes. The base case analysis omitted this consideration due to clinical studies that have reported on an unclear association between these infections and adverse pregnancy outcomes. Under this exploratory analysis, the efficiency frontier differed from the base case analysis.

The exploratory analysis observed larger utility differences between strategies as adverse obstetric outcome had utility impacts on both the neonate and birthing parent. compared to the base case results. As such, the reported ICURs for introducing programmatic CT and GC screening before labour and delivery were correspondingly lower.

Table 22: Expected Costs and QALYs Associated With Different Screening Strategies Per 100,000 Pregnant Persons – Sequential Incremental Cost-Utility Ratio (Exploratory Analysis: CT and GC Infection Impact Adverse Obstetric Outcomes)

Strategy[a]	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM[b]	113,486.92	561,858,682	0.00	0	Reference
UNNM	113,495.35	562,500,298	8.43	641,616	76,145
UNTM	113,495.66	562,991,234	0.32	490,935	1,554,224
UNUM	113,496.30	564,850,808	0.64	1,859,574	2,905,194

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

[a] Other strategies that were either dominated or extendedly dominated are omitted from this table.

Summary of Results

The results indicate that the currently recommended screening strategy (UTTM)[45]is not cost-effective as there are strategies such as TNUM that generate more health benefit at a lower cost.

In particular, the economic evaluation found that expanding the population screened from targeted to universal screening and increasing the frequency of screening at both first and third trimesters (UNUM) generated the most health benefit but was associated with the highest costs. In the base-case analysis, the ICUR for programmatic screening based on UNUM strategy was found to be greater than $65.2 million per QALY gained or $96,816 per pediatric infection prevented. The screening strategy with the lowest costs but lowest clinical benefits involved no prenatal screening with a proportion of patients offered CT and GC screening at labour and delivery. The model was robust as these results remained consistent despite varying the proportion of patents who would be offered screening at labour and delivery from 0% to 100%.

To tradeoff between costs and health outcomes (i.e., QALYs gained or prevention of a pediatric infection), the economic model highlighted that reducing the frequency of screening and targeting high risk populations may be optimal. If CT and GC infection has no impact on obstetric outcomes, strategies involving targeted screening in the third trimester was associated with a lower ICUR and would be the most likely cost-effective strategy if the the willingness-to-pay was between $2.3M to $2.8M per QALY or $3,171 to $3,692 per pediatric infection prevented. Increasing screening frequency and coverage was found to increase false positive rates while reducing false negative rates. The results were mostly robust across all the sensitivity analyses as the order of ranked strategies on the efficiency frontier based on QALYs and on prevented pediatric infections were generally aligned. The results were most sensitive to scenarios that reflected a higher risk pregnant

population (higher infection and re-infection rates) or that indicated lower risks of acquiring pediatric infections. The findings highlight how sensitive the economic model is to the clinical tradeoff of risks and benefits. In a higher-risk situations in which the risk of infection and re-infection is higher amongst the pregnant population, strategies on the efficiency frontier entailed those that expanded the population screened (i.e., universal), Furthermore, if screening could only be offered once during pregnancy, the model found that introducing screening earlier in the first trimester (UNNM) was found to be less costly and less effective than third trimester universal screening (NNUM). In situations where the benefit of screening is reduced (i.e., lower risks of infants born by infected person in developing pediatric infections), a screening strategy that entailed no prenatal visit with screening performed at labour and delivery (NNNM) was found to be cost effective across all λ threshold, This finding was mainly driven by the fact that the risk of CT pneumonia was reduced to zero and therefore, there were no differences in expected utilities across all screening strategies.

In an exploratory analysis in which CT and GC infections were assumed to impact obstetric outcomes, then it would differ as universal screening in the first trimester emerged as being the most likely cost-effective strategy if the willingness-to-pay was between $76,145 to $1,554,224 per QALY.

Of note, the model's time horizon was limited to approximately one year in duration and therefore, only captured the immediate impact of screening in terms of reducing pediatric infection (in the main analyses) and preventing obstetric complications (in the exploratory analysis). However, there may be longer-term benefits to offering screening during pregnancy that could not captured under the current scope of this HTA and the economic evaluation. As described, a longer-term model was published that captured the impact of CT and GC infection on both obstetric/gynecological complications to the pregnant person (e.g., subsequent pelvic inflammatory disease, ectopic pregnancy, and infertility) and pediatric complications and pediatric complications to the child (e.g., blindness). These consequences have lifelong impacts that are likely to lower the ICURs of strategies that screen pregnant persons during prenatal visits.

Patients' Preferences and Experiences Review

The patients' perspectives and experiences review addresses the following research question:

Research Question 3: What are the experiences and perspectives of pregnant persons and their partners with respect to undergoing screening for sexually transmitted infections (STIs)? And, what are their health care providers' perspectives on screening for STIs during pregnancy?

To ensure the relevance of the analysis to the objectives of the broader HTA, a secondary set of research questions were explored during data extraction and analysis:

- What do pregnant persons and their partners value or expect with regards to screening for STIs?
- How do pregnant persons and their partners experience and perceive screening options (vaginal and cervical swabs, and urine specimen) for STIs?
- What are the ways in which screening for STIs and its frequency and timing affect pregnant person's lives and the lives of their partners?
- What are health care providers' experiences and perceptions on when and how to screen for STIs during pregnancy?
- What are health care provides' perspectives regarding targeted or universal screening?
- Are there differences in perceptions and experiences relating to screening for STIs between pregnant persons and their partners, or between pregnant persons and their partners and health care providers?

Systematic Review and Qualitative Meta-synthesis

A systematic review and qualitative meta-synthesis of empirical studies describing pregnant persons' experiences and perceptions of screening for STIs during pregnancy was conducted. Studies that include the perspectives of their partners and health care providers on screening for STIs were also included. Following an iterative approach consistent with the inductive principles of qualitative research, the a priori planned methods (cite protocol) were actively refined and amended at a few stages. Of note, while a research question was established a priori, given the scarcity of qualitative evidence on screening specifically for GC and CT during pregnancy, in order to ensure a sufficient evidence base to inform the policy question this research question was refined and the scope of this review expanded to include screening for other sexually transmitted infections during pregnancy.

Methods

Literature Search Methods

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

Information related to patient preferences was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO; PubMed; and Scopus. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. In both iterations of this search, methodological filters were applied to limit retrieval to qualitative studies, including surveys or questionnaires.

The initial formal search was completed on January 15, 2018 and included the concepts of chlamydia, gonorrhea, pregnancy, and screening. Retrieval was limited to human, English or French-only publications from January 1, 2003 onward. The second search was performed on February 23, 2018 and was broadened to include the concept of all STIs, in addition to the previously specified chlamydia and gonorrhea. Retrieval was limited to English-only publications and did not have a date limit. This final search was set as a regular alert to update the searches until the publication of the final report. Regular search updates were performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review have been incorporated into the analysis if they were identified prior to the completion of the stakeholder feedback period of the final report. Any studies that were identified after the stakeholder feedback period are 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) was identified by searching the Grey Matters checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, systematic review repositories, economics-related resources, public perspective groups, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. The complete search strategy is presented in Appendix 2.

Selection criteria

English language reports describing studies using any descriptive or interpretive qualitative methodology that explored the experiences or perspectives of pregnant persons and their partners or health care providers with respect to screening for STIs during pregnancy were eligible. Eligibility criteria are presented in Table 11.

Papers that were not peer-reviewed (e.g., reports, theses), case reports commentaries or editorials, not in English, reported animal or in vitro data, reported non-empirical studies, used non-qualitative methods, or were off-topic (that is, not addressing the topic of experiences of screening for STIs) were excluded. Due to the limited information available in abstracts, studies or results presented in abstract form only were excluded.

Table 11: Selection Criteria for Patients' Perspectives and Experiences Review

Topical parameters	Screening for STIs 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 of the screening (at any point and frequency during pregnancy)); pregnant persons' experiences, expectations and perceptions of screening for STIs; partners of pregnant persons' experiences and perceptions of screening for STIs during pregnancy; health care providers' perceptions of screening for STIs during pregnancy.
Population parameters	Pregnant persons, partners of pregnant persons, health care providers screening for STIs (family doctors, midwives, obstetrician-gynecologists, etc.)
Temporal parameters	No limits on timeframe
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 artefact 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

Screening and Selecting Studies for Inclusion

Two reviewers screened all citations retrieved from the literature searches based on the eligibility criteria. Titles and abstracts were reviewed to identify papers addressing pregnant persons' experiences and perceptions of screening for STIs during pregnancy, as well as the perspectives of their partners or of their health care providers. The full-text of all potentially relevant reports was retrieved for detailed review and screened in duplicate according to the eligibility criteria. The screening and sorting of eligible papers was managed using Endnote X7 for Mac,[77] which is a reference management software package.

Data collection and extraction

Two types of data were extracted from each primary study: descriptive study characteristics and the study results relevant to the research topic. One reviewer extracted descriptive data into an a priori developed standardized electronic form, which was checked for accuracy by a second reviewer.

Descriptive data included such items as first author, year of publication, article title, study objectives, participant characteristics, and study design.

Both reviewers used NVivo 11[78] (QSR International Pty Ltd Version 11, 2017) to extract and manage the second type of qualitative data from included reports, that is, the qualitative result statements of each included study relevant to the research question. Result statements are typically presented within the "results" section of a report, and are characterized as data-driven and integrated findings based on participant experiences.[79] Before being coded, each result statement was assessed to ensure it was differentiated from raw data, methods, external data, and researchers' conclusions and implications. Only qualitative data were extracted; the quantitative component of mixed methods studies was not included in our analysis. Given that discrepancies have been noted between results presented within abstracts and main reports, only results presented within the main report were extracted.[80] Extraction was subsequently compared and verified among the two reviewers.

Quality assessment

Two reviewers with experience in qualitative research design and synthesis independently assessed the quality of included papers. Assessments on the major strengths and limitations of studies in terms of their credibility, transferability, dependability, and confirmability were guided by the Critical Appraisal Skills Programme (CASP) quality appraisal checklist for qualitative research,[81] the Critical Appraisal of a Survey tool,[82] and the CASP Systematic Review Checklist for systematic reviews.[83] Papers were not excluded from the review on the basis of indicators of quality. This approach recognizes that procedural details are typically under-reported and that theoretically sophisticated findings are not necessary to contribute valuable information to a synthesis of multiple studies, or to inform health policy questions. Disagreements in assessments were resolved through discussion.

Data analysis

Included qualitative studies were analyzed using techniques of integrative qualitative meta-synthesis,[79,84-86] and also defined as qualitative research integration. Qualitative meta-synthesis summarizes and integrates findings across a set of qualitative studies with the aim of combining results across multiple articles. The objective of qualitative meta-synthesis is twofold: first, the aggregated sum of results reflects the range of findings across studies while retaining the original meaning; second, by comparing and contrasting findings across studies, a new integrative interpretation is produced.

The analysis followed a staged coding process similar to grounded theory and passed through three stages: open or line-by-line coding, descriptive coding, and development of analytic themes.[87] The constant comparison method was adapted to include comparing codes across reviewers, comparing codes across codes and across studies.[87]

In analyzing the data, secondary research questions were used as sensitizing concepts to assist the researchers in interpreting findings and concepts in the

data. They provided general guidelines for approaching the data, to open up and refine inquiry, without imposing or prescribing a specific analytical lens.[87,88] Secondary questions provided a beginning point for constructing the analysis during the line-by-line and descriptive coding process. During this stage, reviewers sought for empirical instances of pregnant persons, their partners', and health care providers' perspectives on pregnant persons' experiences of undergoing STIs screening, STIs screening options (vaginal and cervical swabs, and urine specimen), its frequency and timing. Sensitizing concepts derived from secondary questions further informed the analysis helping to refine the initial descriptive codes into abstract categories and themes.

Line-by-line and Descriptive analysis

Two reviewers independently conducted line-by-line coding of an initial set of four papers. Line-by-line coding encourages 'staying close to the data,' a process that encourages the inductive development of codes that identify and describe the data's meaning and content. Upon completing this initial set, the reviewers met to discuss and reflect on the coding process, and identify patterns appearing in the codes used. At this time, it was determined that line-by-line coding was sufficient (i.e., patterns emerged in the codes used and there was stability in their application), and subsequently each reviewer independently descriptively coded the first set of coded studies and four more papers. During this stage, larger passages of text were used to group and cluster codes in categories using descriptive concepts that still remained close to the data. Descriptive codes were compared and contrasted between each other and across the papers. Upon completion of the descriptive coding, the reviewers met and discussed the coding process and reflected on emergent concepts to refine the coding set, noting that through discussion and comparison of codes new interpretative insights emerged leading to a more abstract level of analysis. As the descriptive codes became hierarchical and the relationship between codes became the subject of the analysis, at this point, we were confident that the coding of individual analysts was sufficiently aligned, so coding for the rest of the dataset proceeded with both researchers descriptively coding the rest of the studies and with a move from descriptive coding to analytic synthesis.

A note on the iterative nature of the coding process for the analysis of qualitative data. Sometimes coding moves in a linear fashion from descriptive codes close to the data to higher-level conceptual categories and ultimately to abstract themes; but sometimes the process of identifying categories and themes happens simultaneously, especially in the second and final stages of coding.[87] For example, descriptive coding provides accounts of what is happening in the data but does not integrate the ideas into a set of interrelated concepts from which the researcher develops explanations. However, during this stage, some focused and theoretical coding work is also accomplished as the initial codes are condensed and grouped into preliminary abstract conceptual categories.[87] At the same time, sometimes the analysis directs the analyst to rethink a high-level category or theme, pushing the analyst to go back to the data, the line-by-line coding or descriptive coding to identify or organize the data in a different way.[87]

Thematic analysis

Analytic synthesis is the development of themes or abstracted constructs that are interpretations of the data. The two reviewers independently began to develop analytic themes using sensitizing concepts and memos to assemble and sort the previously established descriptive codes, going back to the data to further develop the relationship between themes and codes. Once a first stage of analytical coding was completed, the two reviewers met and discussed whether the preliminary categories and themes were theoretically relevant to the research question and policy concern facing decision-makers and theoretically rich to support further inquiry across the body of literature.[86] At times where we did not agree on both points, we refined the list of categories, themes and their relationships and then re-applied the schema to the data independently before meeting to re-assess sufficiency and alignment. Once we were confident with our analytic scheme, we were able to work more independently, coding larger sets of data before meeting to discuss. Throughout all stages of analysis, we met regularly to discuss emerging results, and preliminary analytic ideas. To facilitate these discussions, we kept explicit notes using the memo and annotation features in NVivo to record decisions made regarding coding and theme development, as a means to help ensure rigour in the analysis. In all stages of coding, analysts pay attention to the transferability of results across different contexts as a way to determine whether some results might only apply to certain sub-groups. Analytical synthesis ended once themes and their relationships had been richly described and were stable, with no additional descriptive or interpretive insights arising from further analysis.

Reflexivity is an epistemological principle and methodological approach in qualitative research that recognizes the role of the researcher as instrument.[87] 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 review employed the reflexive practices of memoing and frequent dialogue among reviewers to probe and position reviewers in relation to the analysis. Within the context of the current study, the two reviewers considered the ways in which their perspectives were influenced by their own professional and personal background, experiences and prior assumptions. An important question they addressed in drawing conclusions from the data concerned whether or not their personal background could have influenced their approach to the analysis. As a result of this reflexive practice, both reviewers (FB and DD) acknowledged their similar perspective and approach to data analysis as both are qualitative researchers from non-clinical backgrounds, women, and without children.

Results

The bibliographic database searches yielded 4068 papers (with duplicates removed). Two reviewers screened all titles and abstracts, and subsequently the full-texts, to confine the database to qualitative research articles eligible according to the criteria listed in Table 11. In total, 36 papers were deemed

eligible and are included in the analysis. Appendix 13 presents the PRISMA flow diagram for the patients' perspectives and experiences review.

Descriptive analysis

Of the 36 included papers, four[89-92] addressed chlamydia and one study[93] addressed both chlamydia and gonorrhea. Twenty-eight reported experiences and perspectives pertaining to HIV screening.[69,94-120] An additional two papers reported perspectives about syphilis screening,[121,122] while one paper sought perspectives relevant to general STI screening.[123] As presented in Table X, twenty-eight studies reported the experiences and perspectives of pregnant persons.[69,89-91,94-98,100,102-113,115-120] Five studies reported the perspectives of health care providers,[92,93,99,101,114] and three studies reported the experiences and perspectives of both pregnant persons and health care providers (e.g., physicians, nurses, midwives).[121-123] 14 of the 36 included studies also included perspectives of non-pregnant women, although studies reporting experiences of pregnant persons were in the majority.[69,91,94,96,102,103,107,109,111,113,115,116,122,124] None of the included studies reported experiences or perceptions of partners of pregnant persons.

Twenty-one included papers reported on primary qualitative research studies.[69,94,96-98,100,101,105-113,116,119-122,124] One paper reported on a systematic review of qualitative studies.[101] Ten papers reported the qualitative component of a mixed methods study,[89-91,95,102,103,115,117,118,123] while four papers described survey designs.[93,99,104,114] Many (n=17) of the research studies reported a general "qualitative study" or interview study, without further mention of the theoretical or analytical approach. Twenty-five of the included primary research studies collected data using interviews and four studies used focus groups. Five studies collected data using open-ended questionnaires. One paper reported collecting secondary data from case interviews.

Fifteen studies reported experiences of participants from the United States,[93,96,102,105,106,108,121] with an additional 13 studies from the United Kingdom.[90-92,95,97,100,101,104,107,110,113,118,119] Two studies were conducted in Australia,[89,123] two in New Zealand,[99,112] two in Canada,[98,103] one in Spain[94] and one in Ukraine.[120]

Quality assessment

A narrative assessment of the major strengths and weaknesses of included papers, based on the CASP checklist for qualitative studies, the Critical Appraisal of a Survey for survey studies and CASP Systematic Review Checklist for systematic reviews, is presented in Appendix 15.[81,82] The methodological quality of the included papers was mixed, but generally strong. Notably, only four studies considered the role of the researcher in the study,[94,110,111,123] thus the extent to which the findings may have been influenced by the researchers' own backgrounds or beliefs is unclear. Three of the papers failed to report whether the study had received ethics

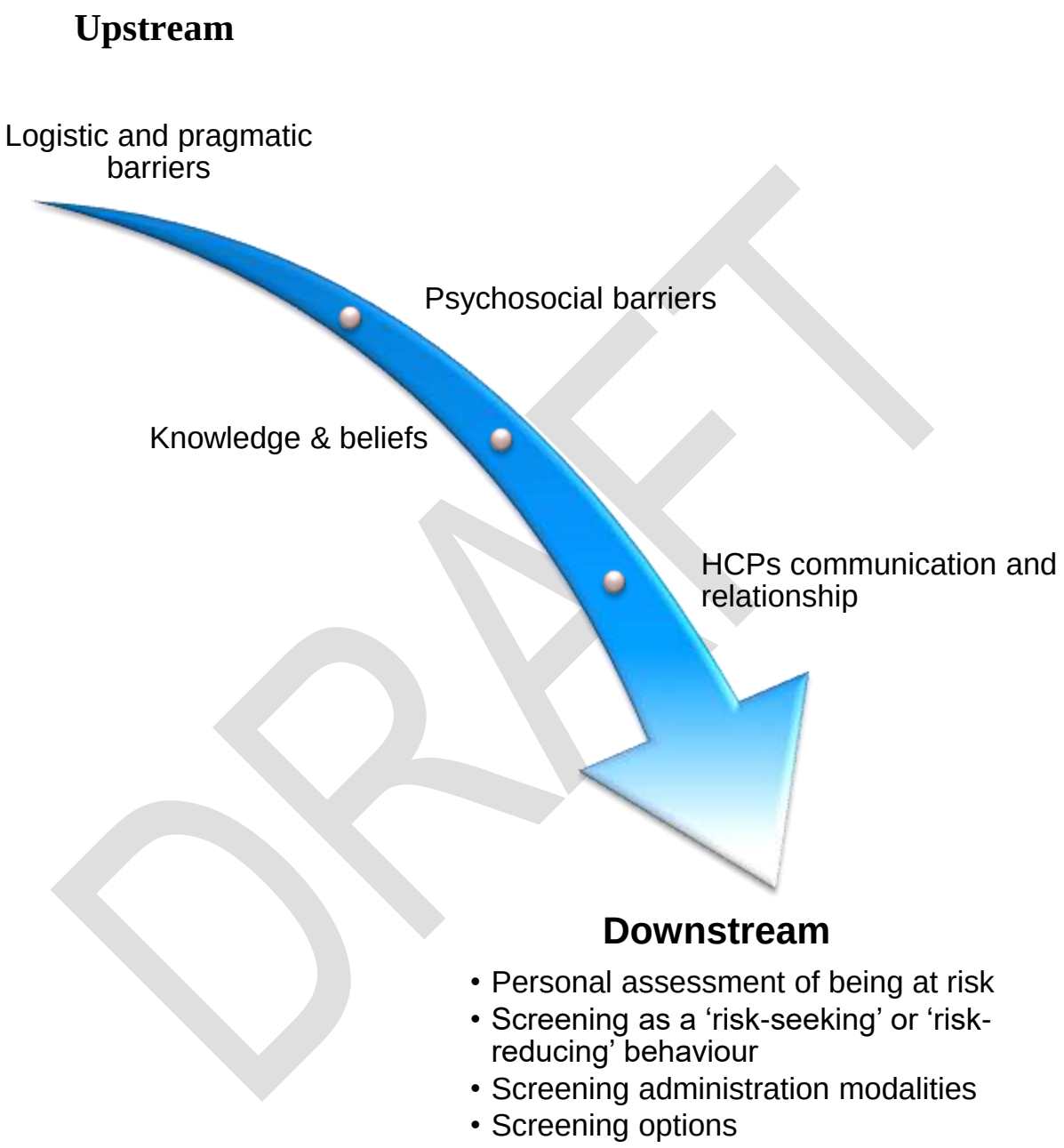
approval.[69,97,102] The survey studies generally lacked a rigorous analysis process for the collected qualitative data; one study noted coding the responses for emerging themes, but subsequently quantified the results.[114] However, most papers were clear about the research aims of the study, and the research reported was a valuable contribution to the current policy concern.

Thematic Analysis

The following sections explore the results of the thematic analysis. In accordance with our analytic plan, the analytic themes represent the meaning of those experiences and perspectives of pregnant persons with respect to undergoing screening for STIs (GC/CT, syphilis, herpes, HPV, and HIV), as well as their health care providers' perspectives on screening for STIs during pregnancy. As noted above, the studies included in this review primarily focused on pregnant persons' perspectives. Partners' perspectives were not represented in the included studies, whereas healthcare providers' perspectives were represented to a small extent. The thematic analysis reflects this discrepancy of perspectives available in the literature.

A multilevel analytic structure (See Figure 2) emerged during the analysis that describes a number of factors that act as opportunities or barriers to pregnant persons' decision-making about participation in STI screening. Two analytical themes emerged within the analysis: upstream and downstream factors that inform pregnant persons' decisions to engage with STI screening. Upstream factors situate pregnant persons' approach to screening within a wider framework of overarching conditions that directly and indirectly frame downstream factors, which in turn address pregnant persons' direct incentives and disincentives to screening. Upstream factors include logistic and pragmatic barriers to antenatal care, knowledge and beliefs, psychosocial barriers, and healthcare provider relationship and communication. Downstream factors include personal assessment of health and risk, screening as a 'risk-seeking' or 'risk-reducing' behaviour, screening administration modalities, and screening options. We will discuss each factor in turn, detailing how for each level – upstream and downstream – it could act as incentive or disincentive for screening. For example, a pregnant person's understanding of their own risk was reported to be closely related to their sense of motherhood and moral responsibility to protect their baby's health, as well as to their understanding of STIs and medical treatment. Some categories were more closely connected than others. These findings have implications for implementation of STI screening at the levels of policy, and for provider and patient education.

Figure 5: Multilevel Analytic Structure



Analytical theme 1: Upstream factors

The first analytical theme encompasses a set of factors that pregnant persons perceive to broadly encourage or discourage their decision to screen for STIs. These factors include logistic and pragmatic barriers to antenatal care,

knowledge and beliefs, psychosocial barriers, and healthcare provider relationship and communication.

Logistic and pragmatic barriers to antenatal care

Logistic challenges acted as a strong disincentive to screening. A general lack of time was commonly reported by both health care providers[123] and by pregnant persons, which required the latter to strike a balance between multiple priorities, such as family and work commitments, and STI screening.[102,119,121,122]

Pregnant persons in American-based studies often mentioned health insurance and the cost of screening as a logistical barrier, although this topic was not prevalent in countries that cover costs of STIs screening through a universal health care system.[119,121,122] For these pregnant persons, the cost of STI screening was a strong reason to abstain from screening. Structural barriers, such as discontinuity in healthcare and insurance services, lack of prenatal clinics, and long wait times also limited pregnant persons' antenatal STI screening.[114,119,121,122]

Finally, in some studies pregnant persons and their prenatal care providers noted healthcare providers' lack of training in managing STIs. [122] Both pregnant persons and healthcare providers perceived the role of prenatal care providers and general practitioners as "diagnosing, but not managing" STI-positive pregnant persons, which they considered to be the work of specialists.[120,122,123] These providers would subsequently refer pregnant persons to clinics, where staff in turn complained about being overburdened, and long wait times ensued.[122]. Overall, discontinuity in the delivery of care inhibited pregnant persons' and health care providers' STI screening behaviours.

Knowledge and beliefs

Pregnant persons reported not having accurate or complete knowledge about STIs and reported that the lack of access to adequate and credible information about STIs and STI testing was a disincentive to screening. In the included studies, pregnant persons identified a lack of information on such issues as their source, transmission, treatment, health and social consequences, risk factors, practicalities of screening options (e.g., the time it takes to obtain and interpret test results, and the next steps after diagnosis), reliability of testing, the purpose of screening tests, and the risks for the fetus related to the treatment. In particular, they rarely acknowledged the link between screening and preventative care.[98,100,105,109,116,122,124] Social taboos surrounding discussions of sex and STIs and fear of stigma limited access to information;[113,122] whereas, too much information provided only in written form hindered pregnant persons' ability to retain information.[97] These pregnant people reported a need for education on the purpose for STI screening and information related to the procedure.[89,96,98,116] Participants identified educational interventions or campaigns as important sources of information and motivation to participate in screening.[89,100,105,109] Even though they had access to informal sources of information, such as family, school sexual

education, and peers,[89,100,105,109] they also identified educational campaigns as significant motivators to screening; in particular, it enabled them to understand the different aspects of STIs and STI screening and to be more informed and confident in making health care decisions.[89,100,105,109]

Psychosocial barriers

Some participants viewed their choice to undergo STI screening as driven by social and psychological factors. Stigma perceived to be associated with promiscuity and social isolation[110,111,124] was a major concern for the participants due to the nature of the transmission of the infection.[89,95,103] Negative moral connotation associated with STI screening and positive STI test results either in the healthcare setting, their community, or from broader society was a commonly reported concern that discouraged screening behaviour, regardless of the screening modality.[89,94,95,100,102,103,107,109-111,113,115,116,119,122-124] Psychosocial barriers also included pregnant persons' fear of disruption of their relationship with their partners, including fear of rejection, partner desertion, or partner abuse.[89,100,103,107,110,111,117,121] This stigma and relationship disruption were a significant barrier to accepting screening for STIs, [89,95,100,103,107,109-111,113,115-117,121-124] but was less of a concern for pregnant persons who were informed, more prepared, and who consciously prioritized protecting the health of their babies.[115]

Pregnant persons with high-risk lifestyles, such as commercial sex workers and drug users, reported fears and distress about social stigmatization and discrimination, both in healthcare settings and in the community, which ultimately influenced their decision to avoid screening.[102,110,122] Even though in some instances pregnant persons with high-risk life styles perceived motherhood as a motivating factor to reduce risky behaviours and reported the belief that all pregnant persons should be tested, they also reported feeling not willing to pursue preventative care measures – such as STI screening – due to external factors beyond their control, such as the perceived stigma and discrimination associated with their life-style and their previous negative experiences within the healthcare and community setting.[102]

Similarly, teen pregnancy stigma represented a barrier for young pregnant persons to accessing STI screening during pregnancy. Seeking and undergoing STI screening would have disclosed their pregnancy status to the family and community, exposing them to stigma and social isolation.[102,123]

Relationship and communication with healthcare providers

Healthcare providers' communication and interpersonal relationship style had a substantial effect on their relationship with pregnant persons, which in turn affected participants' preferences about when and how to engage with the health care system, including participation in STIs screening during pregnancy.

When pregnant persons felt supported in making decisions about their health and the health of their child, they positively perceived recommendations for STI screening from their prenatal care provider.[95,97,109,111,113,116] Healthcare

provider support contributed to the trust relationship between pregnant persons and provider, and when not present led to barriers in pregnancy care. Pregnant persons provided examples of experiences with healthcare providers related to STI screening that undermined trust: when they did not feel they were allowed to ask questions concerning their health,[112,113,116] not receiving timely test results in person,[97,112] experienced paternalistic attitudes when recommending or offering the test,[97,98,100,105,107,111,112,115,122] perceived their providers to hold negative beliefs about pregnant persons living with STIs,[89,111,116] experienced breaches of confidentiality,[111] and experienced physicians' abandonment of pregnant persons with high-risk lifestyles (such as, sex workers and drug users).[106,116] A lack of trust with the healthcare providers also influenced pregnant persons' feelings of concern for their privacy and confidentiality, as some participants felt offended when offered the STI screening as they perceived the offer as a judgment of promiscuity.[95,99] Overall, pregnant persons were less likely to participate in STI screening when they were not in a trusting relationship with their care provider,[111,116,117] or felt stigmatized or disrespected,[89,97,100,105,111,115,116] or when their autonomy in making informed decisions was eroded.[98,102,107] In one study, a small number (4) of healthcare providers reported similar concerns. In this study, health care providers believed that the lack of clear and open communication with pregnant persons hindered pregnant persons' acceptance of undergoing screening.[123] However, in the same study, most of the care providers also believed that providers' efforts and sense of "moral responsibility" in ensuring pregnant persons' engagement with STI screening was not sufficient to improve pregnant persons' participation in screening. [123] Ultimately, pregnant persons' reported previous negative experiences with the health care system and care providers as acting as a barrier to engaging with the health care system in general as well, not just the particular health care provider. [97,106,117]

However, when pregnant persons had a trusting relationship with their health care providers they were more likely to decide to undergo STI screening.[95,97,109,111-113,116] When pregnant persons were satisfied with the information received in a confidential way, they felt reassured and empowered,[95,97,109,111-113,116] and comfortable to share personal sexual history information with the provider.[89] An important feature of this positive experience was having the healthcare professional explain the screening procedure, which enabled pregnant persons to make informed decisions about participation and reduce anxiety and fear of the screening process and the results.[97,109,111,112,116]

Analytical Theme 2: Downstream factors

The second analytical theme captures factors that directly incentivize and dis-incentivize pregnant persons' decisions of undergoing STIs at the individual level. Downstream factors include personal assessment of health and risk, screening as a 'risk-seeking' or 'risk-reducing' behaviour, screening administration modalities, and screening options.

Personal assessment of health and risk status

The way in which pregnant persons identify their own personal risk for STIs, including beliefs and perceptions of vulnerability, as well as their related concepts of health and health care, influences their decisions and behaviours concerning screening practices.[89,96,98,100,102,103,107,109,115,116,122,124] Although these factors are interwoven with their knowledge of personal risk (i.e., general understanding of STIs and its risk factors, screening procedures, and the link with pregnancy), and how they see themselves in relation to these factors, there are specific elements that are enacted in the moment that pregnant persons make screening decisions.

Most pregnant persons were not always clear on why they should have undergone STI screening. Confusion mostly resulted from the lack of symptoms of STI diseases and from participants' perceptions of health and their awareness of attending prenatal care.[69,89-93] Pregnant persons generally perceived themselves as being at low risk of STIs.[95,103,108,115,122,123] As illustrated above, barriers to access to information about infection and transmission, and about medical treatments and preventative measures against transmission of infection to the fetus contributed to low levels of awareness of risk influencing pregnant persons' thoughts on whether screening should occur or not.[97,107,108,122,123] In one study, pregnant persons believed chlamydia to be a minor infection, "like herpes," and did not completely understand the consequences of the infection for them and for the fetus.[89] This low perception of risk led pregnant persons to conceptualize health care as crisis management rather than preventative care, which for some, led to a refusal of screening.[108,115,122,123]

Opinions about why they should have undergone STI screening then reflected pregnant persons personal understandings of risk rather than physician-based recommendations. The appraisal of one's personal risk draws on pregnant persons' perceptions of their health status in relation to lifestyle behaviours, relationship status, and non-promiscuous sexual behaviours.[95,108,115,122,123] Pregnant persons reported a belief that long-term and monogamous relationships did not pose a risk of being infected by STIs.[103,108,109] Participants believed that having a long-term committed relationship with one partner signaled a risk prevention behaviour that did not warrant the need for STI screening.[97,103,108,111] However, pregnant persons in both long-term and short-term relationships were more likely to accept screening when there was a lack of trust in the relationship with their partner, showing that trust in particular influenced pregnant persons' thoughts on whether screening should occur or not.[108,109]

Screening as a "risk-seeking" or "risk-reducing" behaviour

Pregnant persons also assessed screening based on the way they framed the risks of undergoing STI testing. On one hand, pregnant persons defined screening as a 'risk-seeking' behaviour when they framed STI testing as the traumatic experience of receiving positive test results. On the other hand, they framed STI screening as a 'risk-reducing' behaviour when they felt empowered to take control over the uncertainty of the disease and its adverse health outcomes for themselves and mostly for the wellbeing of their baby.

In the first instance, pregnant persons reported to frame screening based on the adverse outcomes of a positive test result, rather than emphasizing the benefits of screening. They perceived screening as a "risk seeking" behaviour.[100] Stigma, feelings of guilt, and inability to cope with a positive result were perceived as factors adding stress to the pregnancy and the fetus, which discouraged pregnant persons from undergoing screening.[69,95,99,100,102,109,111,119] Most pregnant persons felt emotionally unprepared when receiving the diagnosis, reporting feelings of confusion, "shock," and "disbelief." [89,95-97,107,110-113,115,117,119,120] These participants described the disruptive effect and trauma that resulted from an antenatal diagnosis of STIs. In these instances, pregnant persons believed that knowing their positive results and status was disempowering.[95,100,102,109,111,119] For these participants, framing knowledge as disempowering meant focusing more on the adverse outcomes of receiving a positive test result.[100] Most participants ascribed these reactions to being emotionally and mentally unprepared to receive such diagnosis, and some reacted with denial.[96,97,100,110,117]

Other pregnant persons reacted more positively, seeking information from their healthcare providers as well as from other sources.[94,100,107,109] Partner support played an important role in mitigating the traumatic effects of the diagnosis.[95,110,117] Most of these participants expressed the desire to have been better informed before undergoing the test. When informed, pregnant persons defined knowledge as "empowering."[89,97,100,107,109,111,113,116] Knowledge helped to "mitigate" the confusion, fears, and adverse outcomes of positive test results of screening.[97,100,116] Knowing about screening benefits meant understanding the advantages of prevention and medical treatment both for the mother and the fetus.[89,97,100,107,109,111,113,116] With knowledge participants gained awareness and a "special sense of responsibility" to safeguard the baby's health.[95,97,100,102,105,107-109,115-117] Maternal responsibility framed pregnant persons' views of health and rationale for screening.[89,95,97,100,102,105,107-109,115-117] Protecting the health of the baby was the most important benefit and the "main motivating factor in the acceptability of screening."[89,95,97,100,102,105,107-109,115-117] The sense of maternal responsibility gained with knowledge about STIs empowered some pregnant persons to take action in accepting STI screening, and to gain control over the risk of transmitting the infection to the child with appropriate prenatal care.[89,107,108,111,115,117] For those who based the risk assessment of screening on maternal responsibility as a pregnant person, they framed STIs screening as "risk reducing." [89,95,97,100,102,105,107-109,115-117] If they understood screening and treatment to be safe during pregnancy,[105,108] participants reported feelings of reassurance which transcended any potential harm and concern about screening.[100,105,107-109] Unlike many other types of prenatal testing (where, for example, there might be risk of harm to the baby), some pregnant persons were concerned about the risk of *not* doing the screening and of missing an opportunity to minimize risks of infection for the baby, as opposed to the risk of the screening procedure.

Administration modality of screening

Pregnant persons reported voluntary screening within a framework of autonomous informed decision-making process as an incentive to STI

screening. Many pregnant persons believed in the need for routine universal prenatal STI screening, while allowing pregnant persons the final control over this decision.[89,91,95,97,100,102,103,105,107,109,111,112,115-117,119] *Routine* screening refers to the established and regularly followed care process that does not require healthcare providers' assessment of risk for STI infection to offer a test to the patient. Many pregnant persons reported routine as easing access to STIs screening,[103] because it removed the fear of stigmatization and discrimination and normalized the testing practice.[89] As one study participant highlights: "Well you [get] tested for everything else, all these other things that can harm the baby, don't you? I mean there's a test for Hep B, HIV, all these other things that can harm the baby. I mean if chlamydia is an infection that can harm the baby, go for it. Why would you want to put your baby through any [potential harm]?"[89] Additionally, screening can be *universal*, that is, offered to all pregnant persons, or *targeted*, that is targeted to a specific subpopulation of patients identified as at high risk of contracting the STI, typically defined on the basis of behavior, clinical, or demographic characteristics. Normalized universal routine practice removed stigma surrounding STI screening and provided an opportunity for pregnant persons who engaged in high-risk lifestyle behaviours to undergo testing that they otherwise would have missed because of stigma.[102,103,109,115,117] Participants also supported routinized universal STI screening because of the asymptomatic nature of STIs.[91] Pimenta and colleagues note that: "in the absence of symptoms, many respondents reported that they would not have been sufficiently motivated to seek out screening themselves".[91] Finally, universal routine screening complied with pregnant persons sense of maternal responsibility in protecting the fetus health.[89] Regardless of their relationship status, whether they had been tested previously for STIs, and had past distressful experiences with false positive results, many pregnant persons supported routine STIs screening during pregnancy.[89,91,95,97,100,102,103,105,107,109,111,112,115-117,119] Health care providers in one study addressed this aspect, and reported instead that targeting young pregnant persons was the appropriate, however suggesting to extend the age range beyond the age of 25 to the age of 30.[92]

Studies presented contradictory findings about the mandatory or voluntary method of administrating routine testing. *Mandatory* screening requires care providers to offer and perform screening to all patients that seek care without the patient's explicit consent. This screening administration modality does not consider patients declining testing. *Voluntary* testing instead allows patients to refuse screening in two ways. First, in the *opt-out* screening modality, care providers perform STI screening after informing the patient that the test will be performed and that the patient may decide to decline or defer testing. Assent is inferred unless the patient declines testing. Second, in *opt-in* screening modality, care providers perform STI screening only after informing the patient that the test is recommended and after the patient's explicit and written consent to perform the screening.

Sense of maternal responsibility as opposed to value for individual autonomy and choice influenced pregnant persons' preferences for administering STI screening. Some pregnant persons were convinced of the need for healthcare providers to recommend testing, and for pregnant persons to participate in

mandatory preventative screening programs to minimize risks for the fetus and for reasons of public health.[95,102,111,117] Other pregnant persons experienced mandatory screening as a loss of autonomy and right to choose, pointing out that tests should be a pregnant persons' choice "but mandatory for the baby,"[102,117] thus offered and not demanded by healthcare providers. Based on the belief that autonomous individuals are placed in a better position to evaluate their best interests, these participants valued pregnant persons' autonomy and right to choose independently from public health policies and health care providers' recommendations.[95,100,102,105,111,115-117,120] As such, these pregnant persons indicated voluntary opt-in testing as the preferred method to administer STIs testing.[95,100,102,105,111,115-117,120]

While some pregnant persons supported voluntary routine STI screening policy to encourage high uptake and to minimize fetal risks, some questioned routine screening's compatibility with informed consent.[97,98,100,102,105,107,111,116] Several participants described routine screening as a "voluntary-compulsory sequence," reducing pregnant persons' awareness and understanding of the need for testing.[98,102,107] They perceived routine testing as eroding their autonomy in making informed decisions as it "was often equated with lack of choice."[98,102,107] Pre-test communication between pregnant persons and healthcare providers focused on medical information, often omitting to inform them about opt-out options if policies were in place, and assuming that the healthcare provider would make treatment decisions in the patient's best interest.[97,98,100,102,105,107,111,115,116,120] Feeling pressured and confused, participants often reacted by accepting that their concerns would go unanswered and by consenting without thoughtful deliberation.[97,98,100,102,105,107,111,115,116,120]

Screening options

Pregnant persons who engaged in screening did not mention physical discomfort, but indicated that urine screening procedures were preferable to cervical or vaginal swabs taken by care providers because less invasive and less embarrassing.[89-91] Some pregnant persons expressed preferences regarding the location of the testing because of stigma and confidentiality concerns. These participants preferred attending STI screening in hospitals or in clinics in towns rather than family practices to avoid privacy breeches and stigmatization within the community.[103,120]

Summary of Patients' Perspectives and Experiences Results

This review aimed to describe pregnant persons' experiences with GC/CT screening and their resultant perspectives on barriers, facilitators and preferences for the same. Given the relatively small qualitative literature on GC/CT screening during pregnancy, we broaded the review to include other STI screening that is transferable or relevant to evidence-informed decisions regarding the optimal screening policy for CT and/or GC during pregnancy.

Informed by the iterative and emergent nature of qualitative inquiry, broadening the review to include other STI screening, while focusing on those aspects of screening that are transferrable across STIs, allowed us to draw on a more comprehensive, yet relevant, evidence base than focusing on the limited qualitative literature on CT and/or GC alone.

Our review outlines a number of factors related to STI screening that may impact pregnant persons' experiences and participation. We identified a multilayered thematic framework that situates incentives and disincentives to STIs screening within two connected levels of factors that inform pregnant persons' decisions to engage with STI screening: one upstream and another downstream. Upstream factors are broader social and systemic conditions that offer opportunities for or barriers to STI screening for pregnant persons, which in turn have a cascade effect on downstream factors. Upstream factors include logistic and pragmatic barriers to antenatal care, knowledge and beliefs, psychosocial barriers, healthcare provider relationship and communication. Downstream factors encompass individual behavioural incentives or disincentives to screening, which include: personal assessment of health and risk, screening administration modalities, screening as a risk-seeking and risk-reducing behaviour, and screening options.

Along the upstream-downstream continuum, many of these factors closely interact with and influence each other. Both upstream and downstream factors work synergistically at the individual level, incentivizing or deterring pregnant persons' acceptance and experience of STI screening. In this review, logistic upstream conditions create barriers to prenatal care. Pragmatic barriers, such as family and work commitments, lack of accessible clinical sites or, as reported in American-based studies, elaborated insurance policies, limit pregnant persons' ability to access and participate in STI screenings. Psychosocial factors, such as social stigma and discrimination associated to STIs, also exacerbate pregnant persons' willingness to seek STI screening. In most studies, participants perceived STIs has having a negative moral connotation and as being a self-inflicted problem unsuitable for empathetic understanding. Embarrassment, shame, and vulnerability were found to be strong deterrents of screening acceptance. These perceptions in turn can have a downstream cascade effect on pregnant persons' personal assessment of risk, which can shape participants' decision-making process for undergoing screening. This personal risk assessment then was seen to rest on the beliefs of many pregnant persons' in relation to their lifestyle behaviours, relationships status, and sexual activities. Whereas commercial sex workers and drug users often reported to perceive themselves as high-risk due to their lifestyle and sexual behaviours, other pregnant persons in long-term monogamous relationships tended to perceive themselves at low-risk of STIs. Both self-perceived high-risk and low-risk status can lead pregnant persons to abstain from screening, fearing social isolation and discrimination.

While pregnant persons assessed their personal risk of STIs in relation to their lifestyle behaviours, relationships status, and sexual activities, perceptions about the purposes and need for STIs screening heightened pregnant persons' maternal responsibility to minimize the risks of infections for their

neonate and not miss an opportunity for screening. These pregnant persons reported relief and reassurance for the health of the infant as their prime motivators for screening. Pregnant persons' perceptions of the value of screening were also related to reassurance of the neonate's health after a negative screening result was received and for the hope of preventing risks of transmission in case of positive results. As knowledge and awareness empowered pregnant persons to take action and gain control over the risk of infection and mother-to-child transmission, education that focuses on the risk factors of STIs and mother-to-child transmission may improve acceptance to undergo STIs screening.

Potential of community stigma and isolation related to screening participation and sexual activity, and perceptions of healthcare provider's judgement and discrimination at the clinical encounter were reported to impede STI screening during pregnancy. Many pregnant persons described that sensitive, clear communication from the health care provider that emphasizes the importance of STIs screening during pregnancy could improve participation. Effective patient–provider relationships also emerged as a potential strategy that pregnant persons felt could contribute to women's decisions to accept prenatal STIs testing. Trust built on clear and confidential disclosure of information from the healthcare professional was reported to contribute to nurturing an effective relationship that mitigated feelings of embarrassment and of fear of stigmatization.

Healthcare providers' clear communication and respect of pregnant persons' autonomy in making informed decisions was also a determining factor for screening acceptability. Generally, participants perceived routine universal prenatal STI screening as normalizing STI screening practice and believed it to be the best method of screening administration. Opinions on the mandatory or voluntary nature of this routine screening diverged among pregnant persons, some preferring mandatory screening to voluntary prenatal STI screening policies. However, most pregnant persons believed in voluntary routine STI screening policies. Based on the belief that autonomous individuals are best placed to assess their best interests, our review found that participants believed that autonomous, well-informed, and deliberate decisions are factors that improve acceptability of STIs screening.

Discussion

Integration of Findings

This HTA report provides evidence to support decisions to improve existing CT and GC screening strategies across Canada. The report examines evidence across multiple disciplines: clinical, economic, and the perspectives and experiences of pregnant persons, partners and health care providers. In this discussion, several themes of interest are integrated across the various disciplines.

Screening Approach, Timing and Frequency

The clinical review findings suggest that a universal screening strategy at entry into prenatal care and at another time point in pregnancy may result in better detection yields when compared to targeted screening at entry into prenatal care only; but the effect on health outcomes may be mixed. Given that adolescents (< 20 years of age) are more likely to have a positive test for CT and/or GC at any time point,[35 34] targeting this population for screening may potentially result in higher detection yield than universal screening. However, the results from one study suggest that targeted screening using the USPSTF criteria (24 years old or younger, being single, and being black or Hispanic) could potentially miss a substantial number of CT and GC infections in persons older than 24 years.[31] This form of targeted screening would leave patients older than 24 years at a higher risk for infection. Similarly, while early detection of CT infection (at or before 20 weeks of gestation) was associated with a lower risk of M/L preterm and M/L spontaneous preterm births in adolescents, the effect was not significant in pregnant persons 20 years of age and older.[26] The same study reported that across all age groups, the detection (and treatment) of CT infections earlier in pregnancy was associated with lower mean gestational age at birth and higher infant mortality.[26] The findings from yet another study reported that GC infections detected early in pregnancy in comparison to late in pregancy had no effect on mean gestational age at birth and birth weight.[35]

Similar trends were observed in the overall economic evaluation. Of note, the findings of the economic analysis indicate that not offering a prenatal visit screening program for CT and GC in pregnant women (i.e., NNNM) would be the least costly but also the least effective option. In assuming that there are no impacts of CT and GC infections on obstetric outcomes, NNNM would most likely be cost-effective if one's willingness-to-pay was under $2.3 million per QALY. In an exploratory analysis in which CT and GC were assumed to impact obstetric outcomes, NNNM would be considered cost-effective should a decision maker's willingness-to-pay was less than $76,145 per QALY, and NNTM would be considered cost-effective if the willingness-to-pay was between $76,145 to $1.6 million per QALY. The economic evaluation shed

further light that aligned with the clinical findings. Offering screening once during the pregnancy was associated with lower costs but also fewer clinical benefits compared to screening at multiple time point as, by increasing the frequency of screening, the false negative rates reduced and therefore resulted in more cases of pediatric infections adverted. Targeted screening of high risk groups may prevent adverse health outcomes associated with pediatric infections conditional on one's willingness-to-pay threshold. In the base-case analysis, age-targeted (i.e. younger than 25 years of age) screening at third trimester was found to be cost-effective if the willingness-to-pay was between $2.3 million to $2.8 million per QALY or $3,171 to $3,692 per pediatric infection prevented. If the willingness-to-pay increased beyond this level up to $63.8 million per QALY, a single universal screening in the third trimester would become cost-effective instead. This highlights the fact that, with a targeted approach to screening, fewer individuals would undergo screening and, overall, there would be cases of maternal infection missed that would have implications to pediatric infections. All else equal, targeted approaches were associated with higher true positive and false negative detection rates whereas, universal approaches were associated with higher true negative and false positive detection rates. In the base case analysis, the analysis found that screening in the third trimester would be less costly and more effective than a corresponding strategy involving screening in an earlier trimester (e.g., NNTM versus TNNM) as the main benefit to screening would be in preventing vertical transmission to the infant and the subsequent development of pediatric clinical manifestation of CT and GC infections. These trends however differ in population at higher risks in which earlier and broader approach to screeening (i.e., universal) may be more cost-effective.

The review of the perspectives and experiences of pregnant persons, their partners and health care providers included a broader scope compared to the clinical review, in that literature of all STIs rather than just GC/CT was reviewed. The findings suggest that pregnant persons believed in the need for universal prenatal STI screening. Conversely, the perspectives and experiences among health professionals was addressed in just one study on the acceptability of CT screening, reporting that targeting young pregnant persons was the appropriate approach to STI screening, however suggesting to extend the age limit from the age of 25 to the age of 30.[92] No evidence on the perspectives and experiences of the partners of pregnant persons was found. Even though most pregnant persons reported the belief that all pregnant persons should be tested, they perceived stigma and discrimination as a barrier to screening. In particular, teens and high-risk pregnant persons are at risk of missing screening opportunities, as embarrassment, vulnerability, and fear of social isolation due to stigma ultimately influence their decision to avoid screening, regardless of the screening modality.

Specimen selection

Regarding the type of specimen to use during screening, the clinical review findings indicated that pregnant persons appear to prefer urine or self-collected vulval sampling over the more invasive cervical sampling.[33] The preference for urine sampling is at odds however, with evidence that urine samples may have decreased detection yield.[33] As the clinical review noted

limited difference between different types of specimen and prior systematic reviews have combined all specimens types in the determination of the pooled sensitivity and specificity of screening, the economic evaluation did not distinguish or assess the cost-effectiveness of different types of specimen collection. In the review of the perspectives and experiences of pregnant persons, their partners and health care providers, findings suggested that pregnant persons who engaged in screening do not mention physical discomfort, but indicated that urine screening procedures are preferable to cervical or vaginal swabs taken by care providers because they are less invasive and less embarrassing.

Screening behaviours

One included study in the clinical review demonstrated that at least 60% of women were not being screened in accordance with established guidelines, potentially resulting in a number of undiagnosed infections. [27] At least 75% of females less than 25 years of age, who were considered to be at high risk for infections, did not receive repeat screening at another time point in pregnancy. The study did not disclose whether the screening rate was driven by women declining screening or whether they were not offered screening.

The economic model incorporated screening behavior based on real-world screening participation rate[48] . Furthermore, as noted in **Error! Reference source not found.**Table 4, the economic analysis reflected current obstetric and pediatric screening practices. Extensive sensitivity analysis that evaluated different patient and clinician screening behaviour found that results were robust to changes in screening behaviour.

In the review of the perspectives and experiences of pregnant persons, their partners and health care providers, pregnant persons described pragmatic barriers, such as family and work commitments, lack of accessible clinical sites or complicated insurance policies, limiting their ability to access and participate in STI screening. Both pregnant persons and health care providers identified discontinuity in the delivery of care as a barrier to STI screening participation. Psychosocial factors, such as social stigma and discrimination associated with STIs, also exacerbate pregnant persons' willingness to seek both STI screening and information regarding screening. The lack of access to accurate, complete and useful information about STI screening became a disincentive to screening. Pregnant persons reported educational campaigns as a motivator factor for screening, providing the opportunity to make informed and deliberate decisions when engaging with STI screening.

Both self-perceived high-risk and low-risk status, based on the beliefs in relation to lifestyle, relationships status, and sexual activities, can lead pregnant persons to abstain from screening, fearing social isolation and discrimination. Similarly, when pregnant persons framed screening based on the adverse outcomes of a positive test result they perceived screening as "risk seeking" behaviour, describing testing as adding stress to the pregnancy. However, for those who framed screening based on the sense of maternal

responsibility, they framed STI screening as “risk reducing.” When these pregnant persons understood screening and treatment to be safe during pregnancy, they reported feelings of reassurance which transcended any potential harm and concern about screening.

Many pregnant persons believed in the need for routine, universal prenatal STI screening, while allowing pregnant persons the final control over the decision. However, other pregnant persons were convinced of the need for healthcare providers to recommend testing, and for pregnant persons to participate in mandatory preventative screening programs to minimize risks for the fetus. Normalized universal routine practice was seen to remove stigma surrounding STI screening and ease access to STI screening, providing an opportunity for pregnant persons who engaged in high-risk lifestyle behaviours to undergo testing that they otherwise would have missed because of stigma. Routine universal STI screening was also viewed as beneficial because of the asymptomatic nature of STIs. However, most pregnant persons believed in routine, universal, voluntary opt-in STI screening policies. Our review found that participants believed that autonomous, well-informed, and deliberate decisions are factors that improve acceptability of STI screening.

Health care provider and pregnant person relationship

In the review of the perspectives and experiences of pregnant persons, their partners and health care providers, both pregnant persons and healthcare providers believed that clear communication and respect of pregnant persons’ autonomy in making informed decisions was a determining factor for screening acceptability. Many pregnant persons described that sensitive, clear communication from the health care provider that emphasizes the importance of STIs screening during pregnancy could improve participation. Trust built on clear and confidential disclosure of information from the healthcare professional was reported to contribute to nurturing an effective relationship that mitigated feelings of embarrassment and of fear of stigmatization.

Limitations

Evidence Gaps

While five studies in the clinical review provided outcome data on pregnant persons who received initial screening as well as repeat screening at another time point during their pregnancy,[27 28 30 35 34] no literature reported on the detection yield of other screening strategies. Other options for comparing detection yield may have included screening one group of pregnant persons in the first trimester only while screening a different group in the third trimester only. There was no evidence identified on the harms of differing screening strategies during pregnancy. Five of the included studies performed subgroup analyses based on age, which is a known risk factor for CT and GC infections.[27 26 32 35 34] The studies failed to mention whether the pregnants

persons belonged to other high-risk groups including sex workers, homeless persons, persons with a previous history of STIs, and persons with a history of drug misuse and abuse. In addition, as all the studies relied on medical records not designed to provide data on the primary and secondary outcomes of interest, they failed to provide sufficient information on inclusion/exclusion criteria and other clinical characteristics.[27 26 32 35 34 28 30 31 29 33] The lack of clinical information also made it impossible to ascertain whether the infections identified at repeat screening were due to treatment failure or re-infection, and also whether it was a repeat infection with a the same sexual partner or new partner. The secondary outcome of interest in this review was the effect of differing screening strategies on the detection and treatment of adverse obstetric, gynaecological or neonatal outcomes. Given our focus on screening and treatment, the authors of this report are unable to comment on the link between CT or GC infection and adverse health outcomes.

There were several gaps in the clinical literature on the natural history and epidemiology of CT and GC infection that could only be explored through exploratory and scenario analysis and, in several instances, the economic model was found to be most sensitive to these explorations. For instance, in the current economic analysis, high risk was solely defined based on an age criteria, but, as per the PHAC guidelines, risk factors do extend beyond age and may includes factors such as sexual history and injection drug-use. Given the limited data describing how rates of infection and re-infection may differ in high-risk individuals beyond age, a scenario analysis was conducted on a population with a higher prevalence of CT and GC and higher re-infection rates/ Under such a scenario, universal screening at the first trimester was found to be cost effective at willingness-to-pay thresholds between $67,183 to $458,282 per QALY. Similarly, current literature is unclear in whether a CT and GC infection can result in adverse obstetric outcomes. In the base-case analysis, the benefits of screening is solely attributed to reducing the risk of vertical transmission to infant by clearing pregnant persons of CT and GC infections in order to prevent subsequent pediatric manifestation of an infection. Based on discussions with the clinical experts involved in this review, it was noted that a potential benefit to screening could be in preventing adverse obstetric outcomes. Given that the clinical literature is limited on the causal relationship between infections and adverse obstetric outcomes, an exploratory analysis was conducted that assumed screening can prevent these events,. Under these circumstances, due to the high costs and low quality of life associated with some of the adverse obstetric outcomes such as an extremely preterm birth, introducing a universal prenatal screening in the first trimester was found to be cost-effective at willingness-to-pay threshold between $76,145 to $1.6 million per QALY. It remains unclear though whether one of the clinical and economic benefits to prenatal screening is in preventing adverse obstetric outcomes but the economic evaluation does highlight the sensitivity of the cost-effectiveness results if such clinical benefits are incorporated.

A limitation of the review of the perspectives and experiences of pregnant persons, their partners and health care providers is the lack of partners' perspectives and limited representation of health care providers' perspectives in the included studies. While some data was available to assess the importance of these perspectives through pregnant persons' experiences (e.g., for partners specifically changing relationships, desertion, abuse), it was not possible to explore these perspectives in depth.

Inconsistency of Results

Within the clinical review, inconsistency of results was noted with respect to specimen detection yield. Three non-randomized studies were included that compared the detection yield of urine samples, vaginal, and/or cervical specimens. All of the studies reported lower detection rates in urine samples compared with endocervical samples. Yet, the first found a statistically significant decrease in persons between the ages of 20 and 35 years but did not report the significance for persons 20 years or younger or persons between ages 36 and 40 years;[32] the second study reported that the difference across their population was not statistically significant, [29] and the third study did not report on statistical significance.[33]

Also, while one study reported that early detection and treatment of CT infection reduced the risk of M/L preterm and M/L spontaneous preterm birth in adolescents a similar effect was not observed in those older than 20 years of age, this study did not adequately account for confounding variables (e.g., antenatal care, socioeconomic status, other determinants of health) that would also impact the birth outcomes.[26]

Study design and quality

The body of evidence was comprised of non-randomized studies.[27 26 32 35 34 28 30 31 29 33] The literature search identified no randomized controlled trials on differing screening strategies during pregnancy. Screening once at entry into prenatal care was compared to screening once at entry into prenatal care and another timepoint in pregnancy in five studies.[27 28 30 35 34] For the primary outcome of interest (i.e., detection yield), there were no studies identified that compared screening strategies at entry into prenatal care only versus another timepoint in pregnancy only (i.e, screening in the first trimester only versus screening in the second or third trimester only). The researchers writing this report had to extract detection yield values for the second screening by subtracting the number of infections found during baseline screening (i.e., at entry into prenatal care) from the total number of infections found during each study. Also, no studies were identified that compared universal versus targeted screening at multiple timepoints in pregnancy.

Overall, the body of evidence in the clinical review was rated as having a high risk of bias, primarily due to concerns with regards to patient selection in nine of the ten included studies.[27 26 35 34 28 30 31 29 33] The retrospective review of medical records provided data for the primary and secondary outcomes of interest, which are subject to convenience sampling, data inaccuracy and

abstraction errors. In addition, they lacked sufficient clinical and demographic information, which limits the generalizability. See Appendix 6 for the quality assessment of individual studies for further details on the studies included in the clinical review.

This review of the perspectives and experiences of pregnant persons, their partners and health care providers empirically describes pregnant persons' experiences and perceptions of screening for STIs during pregnancy. The methodological quality of the included papers was mixed, but generally strong. Notably, only four studies considered the role of the researcher in the study,[94 110 111 123] thus the extent to which the findings may have been influenced by the researchers' own backgrounds or beliefs are unclear. Three of the papers failed to report whether the study had received ethics approval.[97 102 69] The survey studies generally lacked a rigorous analysis process for the collected qualitative data; one study noted coding the responses for emerging themes, but subsequently quantified the results.[114] However, most papers were clear about the research aims of the study, and the research reported was a valuable contribution to practice or policy.

Assumptions

In the clinical review, one included study did not report the screening test utilized and it was assumed that the diagnostic test utilized was a NAAT.[26] One included study, did not independently report the results of culture and NAATs for CT and GC infection.[28] It was assumed that the majority of samples were tested by NAAT. The type of specimen utilized was also not reported in five of the ten included studies.[27 35 34 31 26] It was assumed that these were either cervical, urine and/or vaginal samples.

Where possible, the economic evaluation conducted a range of sensitivity analyses to test model assumptions. However, one key assumption made to the economic evaluation was in restricting the model's time horizon by approximately one year to reflect the narrower scope of the overall HTA. As such, only immediate impact of screening in terms of reducing pediatric infection (in the main analyses) and preventing obstetric complications (in the exploratory analysis) could be captured. Longer term implications of CT and GC screening such as pelvic inflammatory disease and infertility for the pregnant person, and blindness and other long-term complications associated with CT or GC infection (i.e., arthritis, meningitis and endocarditis) for the exposed offspring were not incorporated into this analysis given this defined model time horizon. These unincorporated outcomes may have potential to significantly impact a person's quality of life up to their lifetime and acrue costs that may render the present model's results as more conservative by not considering a longer time horizon. If the time horizon was expanded beyond the immediate one-year.the ICURs of screening strategies during prenatal visits may in fact be lower

Strengths

The protocol for this HTA was prepared *a priori*, with explicit methodology and is registered with PROSPERO. The protocol was also reviewed by clinical context experts, peer reviewers and stakeholders external to CADTH. The literature searches conducted by the information specialist were based on peer-reviewed search strategies. For both the clinical review and the review of perspectives and experiences, the selection of eligible citations, quality assessment of the included studies, and data extraction were independently conducted by two reviewers. Additionally, quality assessment was guided by tools broadly acknowledged within the evidence synthesis community. Finally, the results of the HTA are generalizable to the Canadian context as only primary studies conducted in countries with a health care context comparable to Canada were eligible for inclusion.

The economic model reflects the most comprehensive economic analysis to date by assessing different screening strategies that varied by timing, frequency, and approach to maternal CT and GC screening and considered the impact of screening on both the pregnant person and the infant, up to 19 weeks after birth. Where there was variability in clinical practice or uncertainty in the structure of the model, appropriate sensitivity analyses were conducted.

Our review did not provide the opportunity to collect primary data, or query participants about issues that may be important to their preferences and perspectives specifically about GC/CT, but that were not covered in the literature. To address this concern and remain able to inform the policy question, our findings report perspectives and experiences of undergoing screening for a broader range of STIs, specifically GC/CT, herpes, syphilis, HPV, and HIV during pregnancy. Informed by the iterative and emergent nature of qualitative inquiry, broadening the review to include other STI screening, while focusing on those aspects of screening that are transferrable across STIs, allowed us to draw on a more comprehensive, yet relevant, evidence base than focusing on the limited qualitative literature on CT and/or GC alone. This a priori planned refinement was aimed at situating the search for literature in a thread of analysis relevant to this review's research objective. To do so, after screening an initial set of available literature focused on CT/GC alone and perfoming preliminary empirical data analysis on that data set, we identified inclusion criteria that were tranferable across different STI screenings, for example whether there might have been missed (or not) opportunities for screening. At the same time we identified exclusion criteria that could filter out analytical and conceptual threads not relevant for our research aim, such as tests that are harmful for the mother and the baby. Unlike many other types of prenatal testing (where, for example, there might be risk of harm to the baby in undergoing testing), CT/GC screening in our initial sample of literature appeared to be mostly about the risk of not participating in screening. As a result, although this study does not focus exclusively on CT/GC screening, the inclusion of a related set of STIs has enabled this review to advance the conceptual understanding of the experience of undergoing CT/GC screening during pregnancy and to enhance the depth and relevance of the analysis. In particular, the comparison and

integration of screening experiences between STIs strengthened the experiences described in the studies that specifically addressed CT/GC. The only major difference observed among the different types of STI screening was pregnant persons' perceptions of CT adverse health outcomes of a positive test result compared to HIV negative outcomes. While only in one study pregnant persons reported the risk of long-term infertility as major adverse health outcome,[91] pregnant persons undergoing HIV screening associated a positive test result as a "death sentence," situating their experience of undergoing HIV screening within deeper negative narratives of death.[116 97 109 95] Of notice, maternal responsibility instead represented a dominating motivating factor for engaging in STI screening regardless of the type of STI and regardless the different kinds of adverse outcomes. All other aspects of screening experiences and perspectives – including logistical barriers, stigma, personal assessment of risk, knowledge and beliefs, relationship and communication with healthcare providers, administration of screening modality, and screening options – are all transferrable across the STIs included in this review.

Generalizability of Findings

The clinical review of the evidence found that universal screening at two time points may be warranted for all pregnant persons, starting at entry into prenatal care. This finding was based on data from five included studies.[27 30 28 35 34] Four were conducted in high risk populations[30 28 35 34] and out of these four, one was conducted in Canada.[30] As the majority of studies were conducted in high risk populations, caution is warranted when extrapolating the findings to populations with low prevalences. Further studies are required that explore the effectiveness of differing screening strategies in low prevalence populations, particularly with respect to false positives and their impact on sexual partners.

Where possible, Canadian data sources were selected and this model is expected to be broadly generalizeable to a Canadian setting. The economic findings in this report may imply that the screening at presentation for labour and delivery and shortly after birth seem to be the most cost-effective approach at conventionally reported willingness-to-pay thresholds ($50,000 to $100,000 per QALY). Although fewer cases of pediatric infections would arise with more frequent screening and in broadening the population screened from a targeted to universal approach, the additional costs associated with these screening strategies were considerably high. However, these findings assume that the benefits to screening is in reducing the risk of vertical transmission to an infant in the immediate short-term. Some caution may be warranted in interpreting the base-case findings of the economic model as the exploratory analysis demonstrated that, if the benefit of screening extends to prevention of adverse obstetric outcomes, universal screening in the first trimester may in fact be considered cost-effective at conventionally reported willingness-to-pay thresholds (i.e., $50,000 to $100,000 per QALY). Furthermore, the economic analysis highlighted similar findings in a higher-risk populations. Extending

universal screening to both the first and third trimesters did appear on the efficiency frontier although it would only be cost-effective if willingness-to-pay was greater than $7.5 million per QALY given that the additional costs of screening was considerable compared to the QALY gained.

Qualitative research in review of the perspectives and experiences of pregnant persons, their partners and health care providers provides theoretical and contextual insights into the experiences of limited numbers of people in specific settings. Qualitative research findings are not intended to generalize directly to populations, although meta-synthesis across a number of qualitative studies builds an increasingly robust understanding that is more likely to be transferable between settings. Qualitative insights often enlighten the understanding of experiences and are important for planning services across different settings. The findings of the studies reviewed here – and of this synthesis – do generalize to the Canadian (or any specific) population. However, the findings are limited to the conditions included in the body of literature synthesized (i.e., STI screening).

Directions for future research

Future research should be directed towards identifying the detection yield and other outcomes of varying screening strategies, particularly in the Canadian setting. Further studies are also required exploring the harms of varying screening strategies during pregnancy. Lastly, understanding baseline screening rates for STIs during pregnancy across the provinces would allow assessment of the effectiveness of future changes to policies involving screening interventions.

. Given the findings of the economic evaluation, future research of greatest value would relate to conducting studies that explore the relationship between prevalence, incidence, and reinfection rates of CT and GC across different high risk groups. Furthermore, as the literature on rates of vertical transmission and the impact of CT and GC on adverse obstetric outcomes is derived from older literature, more recent studies that capture current clinical management would be of value. Furthermore, given the potential long term consequences of CT and GC infection, extending the time horizon in the current economic evaluation would better adhere to existing guidelines for the conduct of economic evaluations that state the time horizon of a model should be long enough to capture all relevant differences in costs and outcomes associated with an intervention. By capturing the longer-term impacts of screening, different conclusions may be reached on the possible cost-effectiveness of introducing CT and GC screening during prenatal visit.

Finally, the absence of qualitative literature on GC/CT screening during pregnancy should not be interpreted as a lack of importance of GC/CT for pregnant persons, or that it is not relevant to their experiences or perspectives.

Rather, the topic should be considered unexplored. A lack of primary research on pregnant persons' and their partners' perspectives on GC/CT screening can be ascribed mainly to the lack of awareness about the available screening benefits on pregnant persons' part. Unlike other types of prenatal testing that may involve risks of harming the fetus, this screening seems to be mostly about the risk of *not* doing the screening, and seems to rest on healthcare providers' duty to not miss opportunities for screening. Therefore, pregnant persons' and their partners' perspectives on GC/CT screening represent an important area to explore in future research. Additonally, health care providers' attitudes toward the value of this screening and investigating best practices for communicating with clients regarding screening is also an area of research that would be benefincial to explore further .

Conclusions and Implications for Decision or Policy Making

The clinical review of the evidence found that screening that targets high-risk (i.e., 24 years old or younger, single, and black or Hispanic), pregnant persons at entry into prenatal care, may potentially result in a number of infections going undiagnosed in pregnant persons of any ethnicity who are older than 25 and in persons who develop infections or re-infections at later points in their pregnancies. The findings suggest that universal screening at entry into prenatal care and at another time point during pregnancy using endocervical specimens will result in the highest detection yield although the health outcomes may be mixed. Pregnant persons' who prefer to use urine specimen may be accommodated through supplemental screening tests if one is found, as urine samples were shown to have decreased detection yield relative to endocervical samples. Given that the screening costs associated with universal screening is intuitively more costly than targeted screening, determining the optimal screening strategy requires a consideration of the economic evidence.

While the economic analysis found that a universal screen in the first and third trimester produced the most health, the expected total cost was also the highest over the modelled time horizon. The incremental gain in health based on the additional resources required resulted in an ICUR greater than $65.2 million per QALY. The evaluation found that current screening strategy of universal screening in the first trimester with a follow up screening for high risk populations (strategy UTTM) was also not cost-effective. The screening strategy that excluded prenatal visit screenings, apart from some patients being screening at labour and delivery,(strategy NNNM) was cost-effective if the willingness-to-pay threshold was below $2.3 million per QALY or $3,171 per pediatric infection adverted.Targeting prenatal screening to a high risk population in the third trimester could potentially be cost-effective if the willingness-to-pay threshold is between $2.3 million to $2.8 million per QALY or between $3,171 to $3,692 per pediatric infection adverted. These findings however, were sensitive to some uncertainties related to population risk profile and the potential impact of CT and GC on obstetrical outcomes. While the screening strategy that excluded prenatal visit screening was dominant (i.e, less costly, equally effective) if CT pneumonia in infants do not occur, universal screening in the first trimester was found to be cost-effective at a willingness-to-pay of $67,183 per QALY in a higher-risk population. If CT and GC infections do cause adverse obstetrical outcomes, the economic analysis also found that a universal screening at first trimester could also be cost-effective at a willingness-too-pay of $76,145 per QALY.

The review of the perspectives and experiences of pregnant persons, their partners and health care providers outlines a number of factors related to STI screening that may impact pregnant persons' experiences and participation. Pregnant persons identified both upstream and downstream opportunities for or against pregnant persons' engagement with STI screening. In the upstream level, both pragmatic and psychosocial barriers influenced their decision to avoid screening, addressing stigma as a major deterrent to STI screening. At the individual level, a key aspect of pregnant persons participation in STI screening is pregnant persons' sense of maternal responsibility. Ensuring the health of the baby was the most important benefit and one of the main driving factors for engaging in screening. A trusting and supportive relationship with the health care provider based on accessible and clear communication could also improve participation in screening. However, pregnant persons also framed screening within a framework of autonomous informed decision-making processes, considering routine and universal voluntary opt-in screening policies as acting as an incentive for a pregnant person's participation in screening.

In summary, the clinical review contributed some key findings that may help to answer the policy question on how Canadian health care providers should screen pregnant persons for CT and/or GC. . Evidence was extracted from a small number of studies and the body of evidence had an overall GRADE of very low. The economic analysis found that excluding all prenatal visit screenings (strategy NNNM) was the least costly strategy but also was associated with the highest number of pediatric infections. It was considered the most likely cost-effective screening strategy for CT and GC in pregnant persons in Canada

if one's willingness to pay threshold is under $2.3 million per QALY. The current strategy of universal screening in the first trimester followed by targeted screening for high risk individuals (strategy UTTM) was dominated by other more efficient screening strategies.The findings of the review of perspectives and experiences of pregnant persons, their partners and health care providers report pregnant persons' experiences of undergoing screening for GC/CT, herpes, syphilis, HPV, and HIV, as well as their health care providers' perspectives on screening for STIs during pregnancy. The experiences and perspectives described for the set of STI screenings included in this review are transferable or relevant to evidence-informed decisions regarding the optimal screening policy for CT and/or GC during pregnancy.

REFERENCES

1. American Academy of Pediatrics. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Itasca (IL): American Academy of Pediatrics; 2015.
2. Centre for Communicable Diseases and Infection Control. Report on sexually transmitted infections in Canada : 2012. Ottawa (ON): Infectious Disease Prevention and Control Branch, Public Health Agency of Canada; 2015: https://www.canada.ca/en/public-health/services/infectious-diseases/surveillance-epidemiology-sexually-transmitted-infections-hep-b-c/report-2012.html. Accessed 2017 Nov 22.
3. Choudhri Y, Miller J, Sandhu J, Leon A, Aho J. Gonorrhea in Canada, 2010-2015. *Can Commun Dis Report.* 2018;44(2):37-42. https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2018-44/issue-2-february-1-2018/article-1-gonorrhea-2010-2015.html.
4. Choudhri Y, Miller J, Sandhu J, Leon A, Aho J. Chlamydia in Canada, 2010-2015. *Can Commun Dis Report.* 2018;44(2):49-54. https://www.canada.ca/content/dam/phac-aspc/documents/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2018-44/issue-2-february-1-2018/ccdrv44i02a03-eng.pdf. Accessed 2018 May 18.
5. Public Health Agency of Canada. Section 2: Canadian guidelines on sexually transmitted infections – Primary care and sexually transmitted infections Ottawa (ON): Government of Canada; 2013: https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections/canadian-guidelines-sexually-transmitted-infections-17.html#a2. Accessed 2017 Dec 2.
6. Public Health Agency of Canada. Canadian guidelines on sexually transmitted infections - Management and treatment of specific infections - Gonococcal infections. Ottawa (ON): Goverment of Canada; 2017: https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections/canadian-guidelines-sexually-transmitted-infections-34.html. Accessed 2017 Nov 22.
7. Matejcek A, Goldman RD. Treatment and prevention of ophthalmia neonatorum. *Can Fam Phys.* 2013;59(11):1187-1190.
8. Nelson HD, Zakher B, Cantor A, Deagas M, Pappas M. Screening for gonorrhea and chlamydia: Systematic review to update the U.S. Preventive Services Task Force recommendations. Rockville (MD): Agency for Healthcare Research and Quality; 2014: https://www.ncbi.nlm.nih.gov/books/NBK248299/. Accessed 2017 Nov 28.
9. Workowski K. In the clinic. Chlamydia and gonorrhea. *Ann Intern Med.* 2013;158(3):ITC2-1.
10. Ammerdorffer A, Stojanov M, Greub G, Baud D. Chlamydia trachomatis and chlamydia-like bacteria: new enemies of human pregnancies. *Curr Opin Infect Dis.* 2017;30(3):289-296.
11. Genc MR. Treatment of genital Chlamydia trachomatis infection in pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2002;16(6):913-922.
12. Brocklehurst P. Antibiotics for gonorrhoea in pregnancy. *Cochrane Database Syst Rev.* 2002(2):Cd000098.
13. Moore DL, MacDonald NE, Canadian Paediatric Society Infection Diseases and Immunization Committee. Preventing ophthalmia neonatorum. *Paediatr Child Health.* 2015;20(2):93-96.
14. Canadian Paediatric Society. Recommendations for the prevention of neonatal ophthalmia. *Paediatr Child Health.* 2002;7(7):4.
15. Public Health Agency of Canada. Canadian guidelines on sexually transmitted infections : Laboratory diagnosis of sexually transmitted infections. Ottawa (ON): Government of Canada; 2017: https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections/canadian-guidelines-sexually-transmitted-infections-18.html. Accessed 2017 Nov 22.
16. Flemming N, O'Driscoll, T., Becker, G., & Spitzer, R.F. . Adolescent pregnancy guideline. *Journal of Obstetrics and Gynaecology Can.* 2015;37(8):740–756.
17. Ministère de la Santé et des Services sociaux. La mise à jour 2017: Guide québécois de dépistage des infections transmissibles sexuellement et par le sang a été effectuée par le ministère de la Santé et des Services sociaux. Montreal (QC): Gouvernement du Québec; 2017: http://publications.msss.gouv.qc.ca/msss/fichiers/2017/17-308-06W.pdf. Accessed 2017 Oct 28.
18. Davies HD, Wang EE. Periodic health examination, 1996 update: 2. Screening for chlamydial infections. Canadian Task Force on the Periodic Health Examination. *CMAJ.* 1996;154(11):1631-1644.
19. Public Health Agency of Canada. Canadian guidelines on sexually transmitted infections - Management and treatment of specific infections - Chlamydial Infections Ottawa (ON): Government of Canada; 2016: https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-

infections/canadian-guidelines/sexually-transmitted-infections/canadian-guidelines-sexually-transmitted-infections-30.html. Accessed 2017 Oct 18.
20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *Ann Intern Med.* 2009;151:30.
21. Zorzela L, Loke YK, Ioannidis JPA, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ.* 2016;352.
22. *DistillerSR [computer program].* Ottawa (ON): Evidence Partners; 2017.
23. Kim SY, Park J, Lee Y, et al. Testing a tool for assessing the risk of bias in nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol.* 2013;66(4):8.
24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;33:3.
25. Deeks JJ, Higgins JP, Altman DG, Editors. Analysing data and undertaking meta-analyses. *Cochrane handbook for systematic reviews of interventions* Vol Version 5.1.0. Oxford (GB): The Cochrane Collaboration 2011.
26. Folger AT. Maternal Chlamydia trachomatis infections and preterm birth:the impact of early detection and eradication during pregnancy. *Maternal and child health journal.* 2014;18(8):1795-1802.
27. Blatt AJ, Lieberman JM, Hoover DR, Kaufman HW. Chlamydial and gonococcal testing during pregnancy in the United States. *Am J Obstet Gynecol.* 2012;207(1):55.e51-58.
28. Berggren EK, Patchen L. Prevalence of Chlamydia trachomatis and Neisseria gonorrhoeae and repeat infection among pregnant urban adolescents. *Sex Transm Dis.* 2011;38(3):172-174.
29. Roberts SW, Sheffield JS, McIntire DD, Alexander JM. Urine screening for Chlamydia trachomatis during pregnancy. *Obstet Gynecol.* 2011;117(4):883-885.
30. Aggarwal A, Spitzer RF, Caccia N, Stephens D, Johnstone J, Allen L. Repeat screening for sexually transmitted infection in adolescent obstetric patients. *JOGC.* 2010;32(10):956-961.
31. Silveira MF, Erbelding EJ, Ghanem KG, Johnson HL, Burke AE, Zenilman JM. Risk of Chlamydia trachomatis infection during pregnancy: effectiveness of guidelines-based screening in identifying cases. *Int J STD AIDS.* 2010;21(5):367-370.
32. Bohm I, Groning A, Sommer B, Muller HW, Krawczak M, Glaubitz R. A German Chlamydia trachomatis screening program employing semi-automated real-time PCR: results and perspectives. *J Clin Virol.* 2009;46 Suppl 3:S27-32.
33. Logan S, Browne J, McKenzie H, Templeton A, Bhattacharya S. Evaluation of endocervical, first-void urine and self-administered vulval swabs for the detection of Chlamydia trachomatis in a miscarriage population. *BJOG.* 2005;112(1):103-106.
34. Miller JM, Maupin RT, Nsuami M. Initial and repeat testing for chlamydia during pregnancy. *J Matern Fetal Neonatal Med.* 2005;18(4):231-235.
35. Miller JM, Jr., Maupin RT, Mestad RE, Nsuami M. Initial and repeated screening for gonorrhea during pregnancy. *Sex Transm Dis.* 2003;30(9):728-730.
36. Meyers D, Wolff T, Gregory K, et al. USPSTF recommendations for STI screening. *Am Fam Physician.* 2008;77:6.
37. Sexually transmitted diseases treatment guidelines 2010. *MMWR Morb Mortal Wkly Rep.* 2010;59:110. https://www.cdc.gov/std/treatment/2010/default.htm. Accessed May 10, 2018.
38. National Cancer Institute. Endocervix. *NCI Dictionary of Cancer Terms*. Bethesda (MD): National Institutes of Health; 2018: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/endocervix. Accessed 2018 Apr 6.
39. *Guidelines for perinatal care.* 6th ed. Washington, DC: American Academy of Pediatrics, American College of Obstetricians and Gynecologists; 2008.
40. Ong JJ, Chen M, Hocking J, et al. Chlamydia screening for pregnant women aged 16-25 years attending an antenatal service: a cost-effectiveness study. *BJOG.* 2016;123(7):1194-1202.
41. Ditkowsky J, Shah KH, Hammerschlag MR, Kohlhoff S, Smith-Norowitz TA. Cost-benefit analysis of Chlamydia trachomatis screening in pregnant women in a high burden setting in the United States. *BMC Infect Dis.* 2017;17(1):155.
42. Rours GI, Smith-Norowitz TA, Ditkowsky J, et al. Cost-effectiveness analysis of Chlamydia trachomatis screening in Dutch pregnant women. *Pathog Glob Health.* 2016;110(7-8):292-302.
43. CADTH. Screening for chlamydia trachomatis and neisseria gonorrhoeae during pregnancy - Project protocol. 2018; https://cadth.ca/sites/default/files/ht0023_screening_during_pregnancy_final.pdf. Accessed 2018 Jun 8.
44. Statistics Canada. Pregnancy outcomes, by age group, Canada, provinces and territories, annual (CANSIM 106-9002). *Statistics Canada*. Ottawa (ON): Government of Canada; 2010: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310016701. Accessed 2018 Jun 5.
45. Public Health Agency of Canada. Canadian guidelines on sexually transmitted infections. 2018; https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections.html. Accessed 2018 May 25.

46. Statistics Canada. Live births, by weeks of gestation and sex, Canada, provinces and territories, annual (CANSIM 102-4512). *Statistics Canada*. Ottawa: Government of Canada; 2018: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310042501. Accessed 2018 Jun 5.
47. Liu B, Roberts CL, Clarke M, Jorm L, Hunt J, Ward J. Chlamydia and gonorrhoea infections and the risk of adverse obstetric outcomes: a retrospective cohort study. *Sex Transm Infect.* 2013;89(8):672-678.
48. Poliquin V, Wylie J, Cole R, Yudin MH, Van Caesseele P. Preparedness for Implementing Change in Neonatal Ocular Prophylaxis Policies. *Journal of Obstetrics and Gynaecology Canada.* 2016;38(1):7-8.
49. Statistics Canada. Fetal deaths (20 weeks or more of gestation) and late fetal deaths (28 weeks or more of gestation) Canada, provinces and territories, annual (CANSIM 102-4514). *Statistics Canada*. Ottawa: Government of Canada; 2018: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310042701. Accessed 2018 Jun 5.
50. Boulay A, Labbe A, Benoit J, Aouinati S, Mandel R, Lavallee C. Prenatal screening of Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) among women who deliver at HMR ["Dépistage prénatal des infections à Chlamydia trachomatis (CT) et Neisseria gonorrhoeae (NG)"]. Public Health 2018 | Sante Publique 2018; May 23-31 2018; Montreal, QC.
51. De P, Singh AE, Wong T, Kaida A. Predictors of gonorrhea reinfection in a cohort of sexually transmitted disease patients in Alberta, Canada, 1991-2003. *Sex Transm Dis.* 2007;34(1):30-36.
52. Rosenman MB, Mahon BE, Downs SM, Kleiman MB. Oral erythromycin prophylaxis vs watchful waiting in caring for newborns exposed to Chlamydia trachomatis. *Arch Pediatr Adolesc Med.* 2003;157(6):565-571.
53. Nelson HD, Zakher B, Cantor A, Deagas M, Pappas M. *Screening for Gonorrhea and Chlamydia: Systematic Review to Update the U.S. Preventive Services Task Force Recommendations.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2014.
54. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JAC. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics.* 2007;8(2):239-251.
55. Guertin JR, Feeny D, Tarride J-E. Age- and sex-specific Canadian utility norms, based on the 2013–2014 Canadian Community Health Survey. *CMAJ : Canadian Medical Association Journal.* 2018;190(6):E155-E161.
56. Kwon J, Kim SW, Ungar WJ, Tsiplova K, Madan J, Petrou S. A Systematic Review and Meta-analysis of Childhood Health Utilities. *Med Decis Making.* 2017;38(3):277-305.
57. Anderson JG, Baer RJ, Partridge JC, et al. Survival and Major Morbidity of Extremely Preterm Infants: A Population-Based Study. *Pediatrics.* 2016;138(1).
58. Statistics Canada. Consumer Price Index (CPI), annual (CANSIM 326-0021). *Statistics Canada*. Ottawa (ON): Government of Canada; 2018: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000501. Accessed 2018 Jun 5.
59. Bank of Canada. Consumer Price Index, 2000 to Present. Ottawa (ON): Bank of Canada; 2018: https://www.bankofcanada.ca/rates/price-indexes/cpi/. Accessed 2018 May 3.
60. Ontario Ministry of Health and Long-Term Care OCCI costing analysis tool. *Health Data Branch Web Portal*. Toronto (ON): Queen's Printer for Ontario; 2016: https://hsim.health.gov.on.ca/hdbportal/. Accessed 2018 May 6. Registration required.
61. Schedule of fees: For the laboratory services outpatient payment schedule. Victoria: British Columbia Ministry of Health; 2018: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/laboratory-services-diagnostic-services/laboratory-services/information-for-laboratory-operators/laboratory-services-outpatient-payment-schedule. Accessed 2018 May 6.
62. e-Formulary: Ontario drug benefit formulary/comparative drug index. Toronto (ON): Ontario Ministry of Health and Long-Term Care; 2018: https://www.formulary.health.gov.on.ca/formulary/.
63. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr.* 2013;13(1):59.
64. Hospital fees for childbirth centre patients without Canadian provincial or federal health insurance. Ottawa (ON): Queensway Carelton Hospital; 2018: https://www.qch.on.ca/uploads/Finance/Hospital%20fees%20Website%20version%20for%20Uninsured%20Res%20Non-Resident%20Childbirth%20April%201%202018.pdf. Accessed 2018 Jun 5.
65. Schedule of benefits: Physician services under the Health Insurance Act. *Ontario Health Insurance Plan: OHIP schedule of benefits and fees*. Toronto (ON): Ontario Ministry of Health and Long-Term Care; 2016: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/. Accessed 2018 May 6.
66. Wu S, Shen L, Liu G. Study on vertical transmission of Chlamydia trachomatis using PCR and DNA sequencing. *Chin Med J.* 1999;112(5):396-399.
67. Laga M, Plummer FA, Piot P, et al. Prophylaxis of gonococcal and chlamydial ophthalmia neonatorum. A comparison of silver nitrate and tetracycline. *N Engl J Med.* 1988;318(11):653-657.
68. Galega FP, Heymann DL, Nasah BT. Gonococcal ophthalmia neonatorum: the case for prophylaxis in tropical Africa. *Bull World Health Organ.* 1984;62(1):95-98.

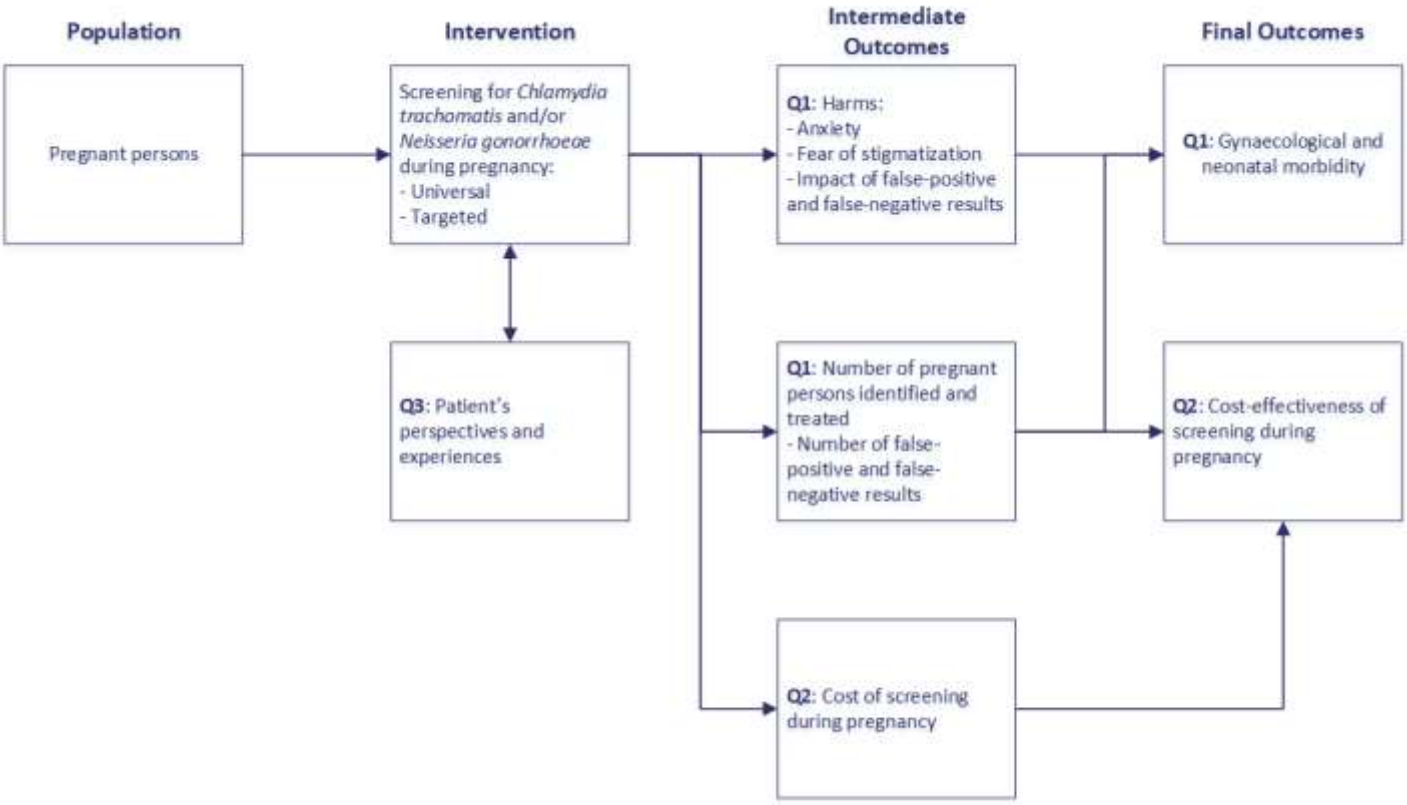
69. Williams AB. Reproductive concerns of women at risk for HIV infection. *J Nurse Midwifery.* 1990;35(5):292-298.
70. Darling EK, McDonald H. A Meta-analysis of the Efficacy of Ocular Prophylactic Agents Used for the Prevention of Gonococcal and Chlamydial Ophthalmia Neonatorum. *Journal of Midwifery & Women's Health.* 2010;55(4):319-327.
71. van Valkengoed IG, Morre SA, van den Brule AJ, Meijer CJ, Bouter LM, Boeke AJ. Overestimation of complication rates in evaluations of Chlamydia trachomatis screening programmes--implications for cost-effectiveness analyses. *Int J Epidemiol.* 2004;33(2):416-425.
72. Hammerschlag MR, Cummings C, Roblin PM, Williams TH, Delke I. Efficacy of neonatal ocular prophylaxis for the prevention of chlamydial and gonococcal conjunctivitis. *N Engl J Med.* 1989;320(12):769-772.
73. Mautner E, Greimel E, Trutnovsky G, Daghofer F, Egger JW, Lang U. Quality of life outcomes in pregnancy and postpartum complicated by hypertensive disorders, gestational diabetes, and preterm birth. *J Psychosom Obstet Gynaecol.* 2009;30(4):231-237.
74. BC Reproductive Mental Health Program, Perinatal Services BC. Best practice guidelines for mental health disorders in the perinatal period. Vancouver (BC): BC Reproductive Mental Health Program; 2014: http://www.perinatalservicesbc.ca/Documents/Guidelines-Standards/Maternal/MentalHealthDisordersGuideline.pdf. Accessed 2018 Jun 5.
75. Patten SB, Williams JVA, Lavorato DH, Bulloch AGM, Currie G, Emery H. Depression and painful conditions: patterns of association with health status and health utility ratings in the general population. *Qual Life Res.* 2014;23(1):363-371.
76. Littlewood E, Ali S, Dyson L, et al. Health Services and Delivery Research. *Identifying perinatal depression with case-finding instruments: a mixed-methods study (BaBY PaNDA - Born and Bred in Yorkshire PeriNatal Depression Diagnostic Accuracy)*. Southampton (UK): NIHR Journals Library; 2018.
77. *Endnote* [computer program]. Version X7. Philadelphia (PA)2016.
78. *Nvivo 11* [computer program]. Version 11.42017.
79. Sandelowski M, Barroso J. Toward a metasynthesis of qualitative findings on motherhood in HIV-positive women. *Res Nurs Health.* 2003;26(2):153-170.
80. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Med Res Methodol.* 2008;8:45-45.
81. CASP Qualitative research checklist. Oxford (GB): Critical Appraisal Skills Programme; 2017: http://www.casp-uk.net/casp-tools-checklists. Accessed 2018 Mar 17.
82. Critical appraisal of a qualitative study. Leiden (NLD): Center for Evidence-Based Management (CEBMa); 2014: https://www.cebma.org/wp-content/uploads/Critical-Appraisal-Questions-for-a-Qualitative-Study-july-2014.pdf. Accessed 2018 Jul 9.
83. CASP Systematic Review Checklist. Oxford (GB): Critical Appraisal Skills Programme; 2017: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Systematic-Review-Checklist-Download.pdf. Accessed 2018 Mar 22.
84. Sandelowski M, Barroso J. *Handbook for synthesizing qualitative research.* New York (NY): Springer Publishing Company; 2006.
85. Sandelowski M, Barroso J. Creating metasummaries of qualitative findings. *Nurs Res.* 2003;52(4):226-233.
86. Finfgeld DL. Metasynthesis: the state of the art--so far. *Qual Health Res.* 2003;13(7):893-904.
87. Charmaz K. *Constructing grounded theory.* 2nd ed. Thousand Oaks (CA): Sage; 2014.
88. Bowen GA. Grounded Theory and Sensitizing Concepts. *International Journal of Qualitative Methods.* 2006;5(3):12-23.
89. Bilardi JE, De Guingand DL, Temple-Smith MJ, et al. Young pregnant women's views on the acceptability of screening for chlamydia as part of routine antenatal care. *BMC Public Health.* 2010;10:505.
90. Logan S, Browne J, McKenzie H, Templeton A, Bhattacharya S. Evaluation of endocervical, first-void urine and self-administered vulval swabs for the detection of Chlamydia trachomatis in a miscarriage population.[Erratum appears in BJOG. 2005 Apr;112(4):528]. *BJOG.* 2005;112(1):103-106.
91. Pimenta JM, Catchpole M, Rogers PA, et al. Opportunistic screening for genital chlamydial infection. I: acceptability of urine testing in primary and secondary healthcare settings. *Sex Trans Inf.* 2003;79(1):16-21.
92. Perkins E, Carlisle C, Jackson N. Opportunistic screening for Chlamydia in general practice: the experience of health professionals. *Health Soc Care Community.* 2003;11(4):314-320.
93. Hack JBH, C. Emergency physicians' patterns of treatment for presumed gonorrhea and chlamydia in women: one center's practice. *J Emerg Med.* 2009;37(3):257-263.
94. Alvarez-Del Arco D, Rodriguez S, Perez-Elias MJ, et al. Role of HIV in the desire of procreation and motherhood in women living with HIV in Spain: a qualitative approach. *BMC Womens Health.* 2018;18(1):24.
95. Baxter JB, R. What do pregnant women think about antenatal HIV testing? *RCM Midwives Journal.* 2000;3(10):308-311.
96. Blake BJ, Jones Taylor GA, Reid P, Kosowski M. Experiences of women in obtaining human immunodeficiency virus testing and healthcare services. *J Am Acad Nurse Pract.* 2008;20(1):40-46.

97. Boyd FM, Simpson WM, Hart GJ, Johnstone FD, Goldberg DJ. What do pregnant women think about the HIV test? A qualitative study. *AIDS Care.* 1999;11(1):21-29.
98. Bulman D, Mathews M, Parsons K, O'Byrne N. HIV testing in pregnancy: using women's voices to inform policy. *Women Birth.* 2013;26(1):e37-40.
99. Chambers ST, Heckert KA, Bagshaw S, Ussher J, Birch M, Wilson MA. Maternity care providers' attitudes and practices concerning HIV testing during pregnancy; results of a survey of the Canterbury and upper South Island region. *NZ Med J.* 2001;114(1144):513-516.
100. de Zulueta P, Boulton M. Routine antenatal HIV testing: the responses and perceptions of pregnant women and the viability of informed consent. A qualitative study. *J Med Ethics.* 2007;33(6):329-336.
101. Evans C, Nalubega S, McLuskey J, Darlington N, Croston M, Bath-Hextall F. The views and experiences of nurses and midwives in the provision and management of provider-initiated HIV testing and counseling: a systematic review of qualitative evidence. *JBI Database System Rev Implement Rep.* 2016;13(12):130-286.
102. Fielder O, Altice FL. Attitudes toward and beliefs about prenatal HIV testing policies and mandatory HIV testing of newborns among drug users. *AIDS Public Policy J.* 2005;20(3-4):74-91.
103. Gahagan JC, Fuller JL, Proctor-Simms EM, Hatchette TF, Baxter LN. Barriers to gender-equitable HIV testing: going beyond routine screening for pregnant women in Nova Scotia, Canada. *International journal for equity in health.* 2011;10:18.
104. Jones D. Understanding why women decline HIV testing. *RCM Midwives.* 2004;7(8):344-347.
105. Katz A. HIV screening in pregnancy: what women think. *JOGNN: Journal of Obstetric, Gynecologic & Neonatal Nursing.* 2001;30(2):184-191.
106. Kelly PJ, Doran T, Duggan SN. HIV testing experiences of pregnant women in south Texas. *Texas Journal of Rural Health.* 2001;19(3):43-51.
107. Kelly C, Alderdice F, Lohan M, Spence D. Creating continuity out of the disruption of a diagnosis of HIV during pregnancy. *J Clin Nursing.* 2012;21(11-12):1554-1562.
108. Kelly K, Hampson SC, Huff J. Prenatal HIV testing: the compartmentalization of women's sexual risk exposure and the return of the maternal fetal conflict. *Women Health.* 2012;52(7):700-715.
109. Lee King PAP, D. J. Perinatal HIV testing among African American, Caucasian, Hmong and Latina women: exploring the role of health-care services, information sources and perceptions of HIV/AIDS. *Health Educ Res.* 2014;29(1):109-121.
110. Lingen-Stallard A, Furber C, Lavender T. Testing HIV positive in pregnancy: A phenomenological study of women's experiences. *Midwifery.* 2016;35:31-38.
111. Mawn B. Integrating women's perspectives on prenatal human immunodeficiency virus screening: toward a socially just policy. *Res Nurs Health.* 1998;21(6):499-509.
112. McAllister S, Lovell S, Dickson N. The impact of repeat testing in the New Zealand antenatal HIV screening programme: a qualitative study. *J Med Screen.* 2013;20(1):1-6.
113. McLeish JR, M. 'We have beaten HIV a bit': a qualitative study of experiences of peer support during pregnancy with an HIV Mentor Mother project in England. *BMJ Open.* 2016;6(6):e011499.
114. Meyerson BE, Navale SM, Gillespie A, Ohmit A. Routine HIV Testing in Indiana Community Health Centers. *Am J Public Health.* 2014;105(1):91-95.
115. Njie-Carr V, Sharps P, Campbell D, Callwood G. Experiences of HIV-positive African-American and African Caribbean childbearing women: a qualitative study. *J Natl Black Nurses Assoc.* 2012;23(1):21-28.
116. Rothpletz-Puglia P, Storm D, Burr C, Samuels D. Routine prenatal HIV testing: women's concerns and their strategies for addressing concerns. *Maternal & Child Health Journal.* 2012;16(2):464-469.
117. Simpson BJ, Forsyth BW. State-mandated HIV testing in Connecticut: personal perspectives of women found to be infected during pregnancy. *J Assoc Nurses AIDS Care.* 2007;18(5):34-46.
118. Stevens A, Victor C, Sherr L, Beard R. HIV testing in antenatal clinics: the impact on women. *AIDS Care.* 1989;1(2):165-171.
119. Treisman K, Jones FW, Shaw E. The experiences and coping strategies of United Kingdom-based African women following an HIV diagnosis during pregnancy. *J Assoc Nurses AIDS Care.* 2014;25(2):145-157.
120. Tripathi V, King EJ, Finnerty E, Koshovska-Kostenko N, Skipalska H. Routine HIV counseling and testing during antenatal care in Ukraine: a qualitative study of the experiences and perspectives of pregnant women and antenatal care providers. *AIDS Care.* 2013;25(6):680-685.
121. DiOrio D, Kroeger K, Ross A. Social Vulnerability in Congenital Syphilis Case Mothers: Qualitative Assessment of Cases in Indiana, 2014-2016. *Sex Transm Dis.* 2018.
122. Kroeger K, Sangaramoorthy T, Loosier PS, Schmidt R, Gruber D. Pathways to congenital syphilis prevention: A rapid qualitative assessment of barriers, and the public health response, in Caddo Parish, Louisiana. *Sex Transm Dis.* 2018.

123. Bar-Zeev S, Barclay L, Kruske S, Kildea S. Factors affecting the quality of antenatal care provided to remote dwelling Aboriginal women in northern Australia. *Midwifery.* 2014;30(3):289-296.
124. Wong VS, Kawamoto CT. Understanding cervical cancer prevention and screening in Chuukese women in Hawaii. *Hawaii Med J.* 2010;69(6 Suppl 3):13-16.
125. Norman JE, Wu O, Twaddle S, et al. An evaluation of economics and acceptability of screening for Chlamydia trachomatis infection, in women attending antenatal, abortion, colposcopy and family planning clinics in Scotland, UK. *BJOG.* 2004;111(11):1261-1268.
126. van Valkengoed IG, Postma MJ, Morre SA, et al. Cost effectiveness analysis of a population based screening programme for asymptomatic Chlamydia trachomatis infections in women by means of home obtained urine specimens. *Sex Trans Inf.* 2001;77(4):276-282.
127. Bernstein KT, Mehta SD, Rompalo AM, Erbelding EJ. Cost-effectiveness of screening strategies for Gonorrhea among females in private sector care. *Obstet Gynecol.* 2006;107(4):813-821.
128. Postma MJ, Welte R, van den Hoek JA, van Doornum GJ, Jager HC, Coutinho RA. Cost-effectiveness of partner pharmacotherapy in screening women for asymptomatic infection with Chlamydia Trachomatis. *Value Health.* 2001;4(3):266-275.
129. Postma MJ, Welte R, Morre SA. Cost-effectiveness of widespread screening for Chlamydia trachomatis. *Expert Opin Pharmacother.* 2002;3(10):1443-1450.
130. Gillespie P, O'Neill C, Adams E, et al. The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. *Sex Trans Inf.* 2012;88(3):222-228.
131. Nyari T, Nyari C, Woodward M, et al. Screening for Chlamydia trachomatis in asymptomatic women in Hungary. An epidemiological and cost-effectiveness analysis. *Acta Obstet Gynecol Scand.* 2001;80(4):300-306.
132. Gaydos CA, Van Der Pol B, Jett-Goheen M, et al. Performance of the Cepheid CT/NG Xpert Rapid PCR Test for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae. *J Clin Microbiol.* 2013;51(6):1666-1672.
133. Schoeman SA, Stewart CM, Booth RA, Smith SD, Wilcox MH, Wilson JD. Assessment of best single sample for finding chlamydia in women with and without symptoms: a diagnostic test study. *BMJ.* 2012;345:e8013.
134. Taylor SN, Van Der Pol B, Lillis R, et al. Clinical evaluation of the BD ProbeTec Chlamydia trachomatis Qx amplified DNA assay on the BD Viper system with XTR technology. *Sex Transm Dis.* 2011;38(7):603-609.
135. Van Der Pol B, Liesenfeld O, Williams JA, et al. Performance of the cobas CT/NG test compared to the Aptima AC2 and Viper CTQ/GCQ assays for detection of Chlamydia trachomatis and Neisseria gonorrhoeae. *J Clin Microbiol.* 2012;50(7):2244-2249.
136. Van Der Pol B, Taylor SN, Lebar W, et al. Clinical evaluation of the BD ProbeTec Neisseria gonorrhoeae Qx amplified DNA assay on the BD Viper system with XTR technology. *Sex Transm Dis.* 2012;39(2):147-153.
137. *R: A language and environment for statistical computing* [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2017.
138. *RStudio: Integrated Development for R* [computer program]. Boston, MA: RStudio, Inc.; 2015.
139. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* 2005;58(10):982-990.
140. Doebler P, Holling H. Meta-analysis of Diagnostic Accuracy and ROC Curves with Covariate Adjusted Semiparametric Mixtures. *Psychometrika.* 2015;80(4):1084-1104.

Appendix 1: Analytical 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?



Appendix 2: Literature Search Strategy

Clinical Literature Search Strategy

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:	January 25, 2018
Alerts:	Monthly search updates until project completion.
Study Types:	No filters used
Limits:	Publication years 2003 forward English or French language Humans

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
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

Multi-database Strategy	
#	**Clinical 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/
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 anlyses 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 amplication or RAPD or random amplified polmorphic)).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 PoobeTecET 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	limit 57 to yr="2003 -Current"
59	limit 58 to english language
60	58 and french.lg.
61	59 or 60

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	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions.

Via Ovid	
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform.

Grey Literature

Dates for Search:	January 2-8, 2018
Keywords:	Included terms for chlamydia, gonorrhea, screening and pregnancy
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

Patients Perspectives Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	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.
Date of search:	January 15, 2018 February 23, 2018
Alerts:	Monthly search updates until project completion
Study Types:	Qualitative studies, including surveys or questionnaires
Limits:	Please refer to each search strategy for limits 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
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

Multi-database Strategy

Patient Preferences Search Strategy – Medline – Strategy #1 – January 15, 2017

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/
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 anlyses 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 amplication or RAPD or random amplified polmorphic)).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 PoobeTecET 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	"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.
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

Patient Preferences Search Strategy – Medline – Strategy #2 – February 23, 2018

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	exp Sexually Transmitted Diseases/
9	(STI or STIs or STD or STDs).ti,ab,kf.
10	Sexually transmitted*.ti,ab,kf.
11	(venereal adj3 (infection* or disease*)).ti,ab,kf.
12	exp Papillomavirus Infections/ or exp PAPILLOMAVIRIDAE/
13	(HPV* or hrHPV* or Papillomavirus* or Papilloma Virus*).ti,ab,kf.
14	exp HIV/
15	(Human Immunodeficiency Virus* or Human Immuno deficiency Virus* or AIDS or Acquired Immunodeficiency Syndrome* or Acquired Immuno deficiency Syndrome* or HIV or HTLV?III or LAVHTLV?III).ti,ab,kf.
16	exp Herpes Simplex/
17	(Herpes* or herpessymplex* or herpetic* or HSV?2 or HSV or HSVI).ti,ab,kf.

18	exp SYPHILIS/
19	(syphilis or chancre or neurosyphilis or syphilitic*).ti,ab,kf.
20	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp Mass Screening/ or exp diagnosis/ or exp Monitoring, Physiologic/
22	(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.
23	((detect* or screening) adj3 program*).ti,ab,kf.
24	21 or 22 or 23
25	3 and 20 and 24
26	exp Empirical Research/ or Interview/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or exp Narration/ or Nursing Methodology Research/ or Narrative Medicine/
27	Interview/
28	interview*.ti,ab,kf.
29	qualitative.ti,ab,kf,jw.
30	(theme* or thematic).ti,ab,kf.
31	ethnological research.ti,ab,kf.
32	ethnograph*.ti,ab,kf.
33	ethnomedicine.ti,ab,kf.
34	ethnonursing.ti,ab,kf.
35	phenomenol*.ti,ab,kf.
36	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.
37	(life stor* or women* stor*).ti,ab,kf.
38	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.
39	(data adj1 saturat$).ti,ab,kf.
40	participant observ*.ti,ab,kf.
41	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf.
42	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.
43	(humanistic or existential or experiential or paradigm*).ti,ab,kf.

44	(field adj (study or studies or research or work)).ti,ab,kf.
45	(human science or social science).ti,ab,kf.
46	biographical method.ti,ab,kf.
47	theoretical sampl*.ti,ab,kf.
48	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.
49	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.
50	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.
51	((lived or life) adj experience*).ti,ab,kf.
52	cluster sampl*.ti,ab,kf.
53	observational method*.ti,ab,kf.
54	content analysis.ti,ab,kf.
55	(constant adj (comparative or comparison)).ti,ab,kf.
56	((discourse* or discurs*) adj3 analys?s).ti,ab,kf.
57	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
58	(van adj manen*).ti,ab,kf.
59	(van adj kaam*).ti,ab,kf.
60	(corbin* adj2 strauss*).ti,ab,kf.
61	or/26-60
62	"Surveys and Questionnaires"/
63	Health Care Surveys/
64	self report/
65	questionnaire*.ti,ab,kf.
66	survey*.ti,ab,kf.
67	or/62-66
68	61 or 67
69	25 and 68
70	limit 69 to english language

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, excluding study types and Human restrictions.
Scopus	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Scopus database.
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform.

Grey Literature

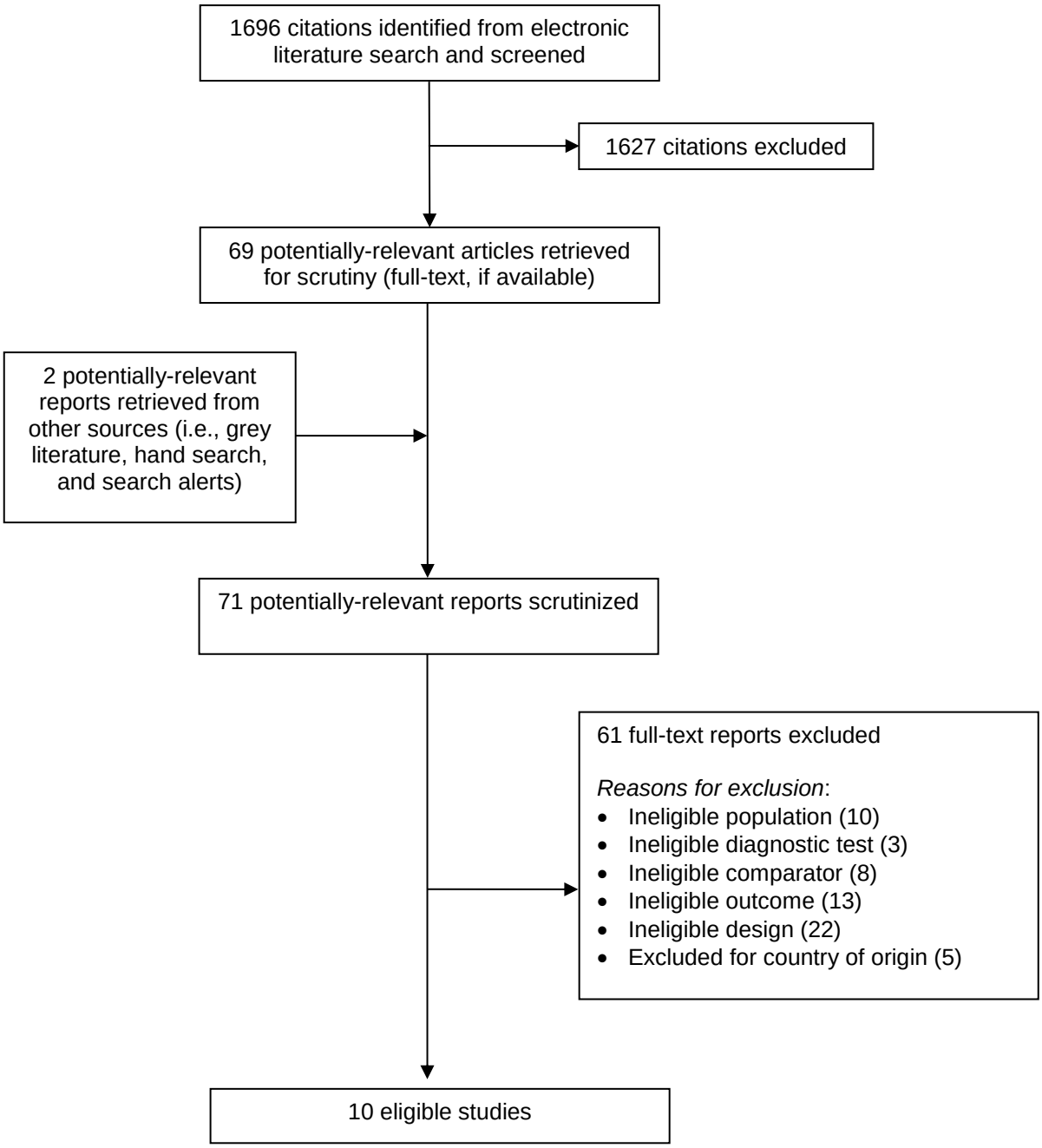
Dates for Search:	January 2-8, 2018
Keywords:	Included terms for chlamydia, gonorrhea, screening and pregnancy
Limits:	Publication years 2003 to present; English or French language

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

Appendix 3: Study Selection Flow Diagrams — Clinical Review

PRISMA Flowchart of Selected Reports



Appendix 4: List of Included Studies — Clinical Review

1. Folger AT. Maternal Chlamydia trachomatis infections and preterm birth: The impact of early detection and eradication during pregnancy. *Matern Child Health J.* 2014;18(8):1795-1802.

2. Blatt AJ, Lieberman JM, Hoover DR, Kaufman HW. Chlamydial and gonococcal testing during pregnancy in the United States. *Am J Obstet Gynecol.* 2012;207(1):55.e51-58.

3. Berggren EK, Patchen L. Prevalence of chlamydia trachomatis and neisseria gonorrhoeae and repeat infection among pregnant urban adolescents. *Sex Transm Dis.* 2011;38(3):172-174.

4. Roberts SW, Sheffield JS, McIntire DD, Alexander JM. Urine screening for chlamydia trachomatis during pregnancy. *Obstetrics and gynecology.* 2011;117(4):883-885.

5. Aggarwal A, Spitzer RF, Caccia N, Stephens D, Johnstone J, Allen L. Repeat screening for sexually transmitted infection in adolescent obstetric patients. *JOGC.* 2010;32(10):956-961.

6. Silveira MF, Erbelding EJ, Ghanem KG, Johnson HL, Burke AE, Zenilman JM. Risk of chlamydia trachomatis infection during pregnancy: Effectiveness of guidelines-based screening in identifying cases. *Int J STD AIDS.* 2010;21(5):367-370.

7. Böhm I, Gröning A, Sommer B, Müller H-W, Krawczak M, Glaubitz R. A German chlamydia trachomatis employing semi-automated real-time PCR: Results and perspectives. *Journal of Clinical Virology.* 2009;46(S3):S27-S32.

8. Logan S, Browne J, McKenzie H, Templeton A, Bhattacharya S. Evaluation of endocervical, first-void urine and self-administered vulval swabs for the detection of chlamydia trachomatis in a miscarriage population. *BJOG.* 2005;112(1):103-106.

9. Miller JM, Maupin RT, Nsuami M. Initial and repeat testing for chlamydia during pregnancy. *J Matern Fetal Neonatal Med.* 2005;18(4):231-235.

10. Miller JM, Jr., Maupin RT, Mestad RE, Nsuami M. Initial and repeated screening for gonorrhea during pregnancy. *Sex Transmitted Dis.* 2003;30(9):728-730.

Appendix 5: List of Excluded Studies and Reasons for Exclusion — Clinical Review

Irrelevant population (i.e., not pregnant persons)

O'Higgins AC, Jackson V, Lawless M, et al. Screening for asymptomatic urogenital Chlamydia trachomatis infection at a large Dublin maternity hospital: results of a pilot study. *Ir J Med Sci.* 2017;186(2):393-397.

Hoover KW, Tao G, Nye MB, Body BA. Suboptimal adherence to repeat testing recommendations for men and women with positive Chlamydia tests in the United States, 2008-2010. *Clin Infect Dis.* 2013;56(1):51-57.

Anschuetz GL, Asbel L, Spain CV, et al. Association between enhanced screening for Chlamydia trachomatis and Neisseria gonorrhoeae and reductions in sequelae among women. *J Adolesc Health.* 2012;51(1):80-85.

Andersen B, van Valkengoed I, Sokolowski I, Moller JK, Ostergaard L, Olesen F. Impact of intensified testing for urogenital Chlamydia trachomatis infections: a randomised study with 9-year follow-up. *Sex Trans Inf.* 2011;87(2):156-161.

Stevens MP, Tan SE, Horvath L, Fairley CK, Garland SM, Tabrizi SN. Absence of a Chlamydia trachomatis variant, harbouring a deletion in the cryptic plasmid, in clients of a sexually transmissible infection clinic and antenatal patients in Melbourne. *Commun Dis Intell Q Rep.* 2008;32(1):77-81.

Manhart LE, Marrazzo JM, Fine DN, Kerani RP, Golden MR. Selective testing criteria for gonorrhea among young women screened for Chlamydial infection: contribution of race and geographic prevalence. *J Infect Dis.* 2007;196(5):731-737.

Low N, Egger M, Sterne JA, et al. Incidence of severe reproductive tract complications associated with diagnosed genital chlamydial infection: the Uppsala Women's Cohort Study. *Sex Trans Inf.* 2006;82(3):212-218.

Church DL, Zentner A, Semeniuk H, Henderson E, Read R. Reasons for testing women for genital Chlamydia trachomatis infection in the Calgary region. *Can J Infect Dis.* 2003;14(1):35-40.

Macmillan S, McKenzie H, Templeton A. Parallel observation of four methods for screening women under 25 years of age for genital infection with Chlamydia trachomatis. *Eur J Obstet Gynecol Reprod Biol.* 2003;107(1):68-73.

Pimenta JM, Catchpole M, Rogers PA, et al. Opportunistic screening for genital chlamydial infection. I: acceptability of urine testing in primary and secondary healthcare settings. *Sex Trans Inf.* 2003;79(1):16-21.

Irrelevant diagnostic test (i.e., not NAAT for GC or CT and culture for CT

Angelova M, Kovachev E, Tsankova V, Koleva I, Mangarova S. Role and Importance of Chlamydia Trachomatis in Pregnant Patients. *Open Access Macedonian Journal of Medical Sciences.* 2016;4(3):410-412.

Hood EE, Nerhood RC. The utility of screening for chlamydia at 34-36 weeks of gestation. *W V Med J.* 2010;106(6):10-11.

Ayuk PT, Dudley S, McShane H, Rees M, Mackenzie IZ. Efficacy of follow-up and contact tracing of women who test positive for genital tract chlamydia trachomatis prior to pregnancy termination. *J Obstet Gynaecol.* 2004;24(6):687-689.

No relevant comparator (i.e., not comparative clinical study)

Reekie J, Roberts C, Preen D, et al. Chlamydia trachomatis and the risk of spontaneous preterm birth, babies who are born small for gestational age, and stillbirth: a population-based cohort study. *Lancet Infect Dis.* 2018.

Lazenby GB, Korte JE, Tillman S, Brown FK, Soper DE. A recommendation for timing of repeat Chlamydia trachomatis test following infection and treatment in pregnant and nonpregnant women. *Int J STD AIDS.* 2017;28(9):902-909.

Hill MG, Menon S, Smith S, Zhang H, Tong X, Browne PC. Screening for Chlamydia and Gonorrhea Cervicitis and Implications for Pregnancy Outcome. Are We Testing and Treating at the Right Time? *J Reprod Med.* 2015;60(7-8):301-308.

Tao G, Hoover KW, Nye MB, Body BA. Age-specific chlamydial infection among pregnant women in the United States: evidence for updated recommendations. *Sex Transmitted Dis.* 2014;41(9):556-559.

Mathur M, Robertson C, Caird L, Ho-Yen DO. Chlamydia infection among pregnant women and those seeking termination. *J Obstet Gynaecol.* 2007;27(4):409-412.

Barney OJ, Nathan M. A study of the prevalence of sexually transmitted infections and related conditions in pregnant women attending a sexual health service. *Int J STD AIDS.* 2005;16(5):353-356.

Grio R, Bello L, Smirne C, et al. Chlamydia trachomatis prevalence in North-West Italy. *Minerva Ginecol.* 2004;56(5):401-406.

Bachmann LH, Pigott D, Desmond R, et al. Prevalence and factors associated with gonorrhea and chlamydial infection in at-risk females presenting to an urban emergency department. *Sex Transmitted Dis.* 2003;30(4):335-339.

Irrelevant outcome (i.e., not detection yield, clinical utility or harms)

Dahlberg J, Hadad R, Elfving K, et al. Ten years transmission of the new variant of Chlamydia trachomatis in Sweden: prevalence of infections and associated complications. *Sex Trans Inf.* 2018;94(2):100-104.

Ong JJ, Chen M, Hocking J, et al. Chlamydia screening for pregnant women aged 16-25 years attending an antenatal service: a cost-effectiveness study. *BJOG.* 2016;123(7):1194-1202.

Rours GI, Smith-Norowitz TA, Ditkowsky J, et al. Cost-effectiveness analysis of Chlamydia trachomatis screening in Dutch pregnant women. *Pathogens and Global Health.* 2016;110(7-8):292-302.

Lavoue V, Morcel K, Voltzenlogel MC, et al. Scoring system avoids Chlamydia trachomatis overscreening in women seeking surgical abortions. *Sex Transmitted Dis.* 2014;41(8):470-474

Krivochenitser R, Jones JS, Whalen D, Gardiner C. Underrecognition of cervical Neisseria gonorrhoeae and Chlamydia trachomatis infections in pregnant patients in the ED. *Am J Emerg Med.* 2013;31(4):661-663.

Gillespie P, O'Neill C, Adams E, et al. The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. *Sex Trans Inf.* 2012;88(3):222-228.

Fjerstad M, Trussell J, Lichtenberg ES, Sivin I, Cullins V. Severity of infection following the introduction of new infection control measures for medical abortion. *Contraception.* 2011;83(4):330-335.

Chen MY, Fairley CK, De Guingand D, et al. Screening pregnant women for chlamydia: what are the predictors of infection? *Sex Trans Inf.* 2009;85(1):31-35.

Bernstein KT, Mehta SD, Rompalo AM, Erbelding EJ. Cost-effectiveness of screening strategies for Gonorrhea among females in private sector care. *Obstet Gynecol.* 2006;107(4):813-821.

French JI, McGregor JA, Parker R. Readily treatable reproductive tract infections and preterm birth among black women. *Am J Obstet Gynecol.* 2006;194(6):1717-1726; discussion 1726-1717.

Rours GI, Verkooyen RP, Willemse HF, et al. Use of pooled urine samples and automated DNA isolation to achieve improved sensitivity and cost-effectiveness of large-scale testing for Chlamydia trachomatis in pregnant women. *J Clin Microbiol.* 2005;43(9):4684-4690.

Chong S, Jang D, Song X, et al. Specimen processing and concentration of Chlamydia trachomatis added can influence false-negative rates in the LCx assay but not in the APTIMA Combo 2 assay when testing for inhibitors. *J Clin Microbiol.* 2003;41(2):778-782.

Pimenta JM, Catchpole M, Rogers PA, et al. Opportunistic screening for genital chlamydial infection. II: prevalence among healthcare attenders, outcome, and evaluation of positive cases.[Erratum appears in Sex Transm Infect. 2004 Apr;80(2):156]. *Sex Trans Inf.* 2003;79(1):22-27.

Irrelevant Study Design (i.e., not primary clinical study)

Shannon CL, Klausner JD. Keep Screening! Maternal Gonococcal Infection and Adverse Birth Outcomes. *Sex Transmitted Dis.* 2017;44(5):272-273.

Balendra A, Oakeshott P, Hayes K, Planche T, Hay PE. Chlamydia screening in an early pregnancy unit. *Sex Trans Inf.* 2016;92(3):231.

Gilbert L. Infections of concern during pregnancy: Prevention and interventions. *Med Today.* 2016;17(8):14-24.

Low N, Redmond S, Uuskula A, et al. Screening for genital chlamydia infection. *Cochrane Database Syst Rev.* 2016;9:Cd010866.

Anonymous. Chlamydia screening can prevent harm to newborns. *Australian Nursing & Midwifery Journal.* 2015;23(4):26.

Vermund SH. Screening for Sexually Transmitted Infections in Antenatal Care Is Especially Important Among HIV-Infected Women. *Sex Transmitted Dis.* 2015;42(10):566-568.

Hurt W, Peeling RW. What impact will new screening techniques have on the epidemiology of STIs worldwide? *Clinical Practice.* 2014;11(1):1-4.

Raychaudhuri M. False positive chlamydia results in pregnancy: should we retest them? *Sex Trans Inf.* 2013;89(8):665.

Curran G. Universal antenatal chlamydia screening by rural midwives. *Aust Nurs J.* 2012;19(7):30-32.

Kalwij SA. Opportunistic chlamydia screening in a general practice consultation. *BMJ.* 2011;343:d5108.

Gottlieb SL, Berman SM, Low N. Screening and treatment to prevent sequelae in women with Chlamydia trachomatis genital infection: how much do we know? *J Infect Dis.* 2010;201 Suppl 2:S156-167.

Kalwij S, Macintosh M, Baraitser P. Screening and treatment of Chlamydia trachomatis infections. *BMJ.* 2010;340:c1915.

Low N, Bender N, Nartey L, Shang A, Stephenson JM. Effectiveness of chlamydia screening: systematic review. *Int J Epidemiol.* 2009;38(2):435-448.

Moreno MA, Furtner F, Rivara FP. Advice for patients. Chlamydia screening: a routine test. *Arch Pediatr Adolesc Med.* 2009;163(6):592.

Lin KW, Ramsey L. Screening for chlamydial infection. *Am Fam Physician.* 2008;78(12):1349-1350.

Cheney K, Chen MY, Donovan B. Chlamydia trachomatis infection among antenatal women in Sydney. *Aust N Z J Public Health.* 2006;30(1):85-87.

Hope A. Chlamydia trachomatis among antenatal women in Sydney [3]. *Aust N Z J Public Health.* 2006;30(3).

Low N, Harbord RM, Egger M, et al. Screening for chlamydia [2] (multiple letters). *Lancet.* 2005;365(9470):1539-1540.

Quinlan JD. Sexually transmitted diseases in pregnancy. *Clinics in Family Practice.* 2005;7(1 SPEC. ISS):127-137.

Goold PC, Carlin EM. Chlamydia testing before termination of pregnancy. *Sex Trans Inf.* 2003;79(4):352.

Gray J, Huengsberg M, Mann M, et al. A multidisciplinary approach to chlamydia screening in women undergoing termination of pregnancy: how well are we doing? *Int J STD AIDS.* 2003;14(4):287-288.

Oakeshott P, Hay P. 10-Minute consultation: Cervical Chlamydia trachomatis infection. *Br Med J.* 2003;327(7420).

Country of Origin (i.e., not comparable to Canadian context)

Sethi S, Roy A, Garg S, Sree Venkatesan L, Bagga R. Detection of Chlamydia trachomatis infections by polymerase chain reaction in asymptomatic pregnant women with special reference to the utility of the pooling of urine specimens. *Indian Journal of Medical Research, Supplement.* 2017;146(Supplement):59-63.

Adachi K, Klausner JD, Xu J, et al. Chlamydia trachomatis and Neisseria gonorrhoeae in HIV-infected Pregnant Women and Adverse Infant Outcomes. *Pediatr Infect Dis J.* 2016;35(8):894-900.

Savitha S, Madhavan S, Vinoth Raja R. Incidence of chlamydial infection in women. *Journal of Pharmaceutical Sciences and Research.* 2009;1(1):26-33.

Kajaia D, Merabishvili N, Burkadze G. Pap testing and direct immunofluorescence for Chlamydia trachomatis infection in pregnant women. *Georgian Med News.* 2006(131):27-30.

Rastogi S, Das B, Salhan S, Mittal A. Effect of treatment for Chlamydia trachomatis during pregnancy. *Int J Gynaecol Obstet.* 2003;80(2):129-137.

APPENDIX 6 :QUALITY ASSESSMENT - CLINICAL REVIEW

Author, Publication Year	Risk of Bias Domains						Justification
	Selection of Participants	Confounding Variable	Intervention (exposure) Measurement	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	
Folger, 2014[26]	High	High	Low	Low	Unclear	Low	- Study conducted in an urban county. May not be representative of the general population -Data missing for inadequate antenatal care in both groups - Due to incomplete data BMI, birth spacing and adequacy of antenatal care not appropriately adjusted for -1,834 females not included as they were not linked to the dataset (47% of eligible patients); rate of spontaneous PTB higher in this population, underestimating the effect estimate -Potential selection bias due to convenience sampling from retrospective review of medical records - Deterministic linking strategy used to join two separate databases; potential for bias due to misclassification of linked records -Potential conflicts of interest not declared -Assumed that patients were screened and treated in accordance with

Author, Publication Year	Risk of Bias Domains						Justification
	Selection of Participants	Confounding Variable	Intervention (exposure) Measurement	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	
							CDC guidelines, which could underestimate the number of females diagnosed with infections
Blatt et al., 2012[27]	High	Low	Low	Low	Low	Low	-Possible selection bias towards those who sought medical care and agreed to be tested, underestimating the prevalence of infection -The laboratory data based lacked sufficient clinical data and therefore authors unable to determine if follow-up positive result due to treatment failure or reinfection - Conflict of interest as study funded by Quest Diagnostics and most study authors employees of Quest Diagnostics - Patient characteristics and risk factors not reported; Only a small percentage of those with a negative test received repeat testing; unable to ascertain the reasoning for testing or not testing, underestimating the prevalence of infection
Berggren and Patchen, 2011[28]	High	Low	Unclear	Low	Low	Low	- No baseline demographic information provided to determine if sample is representative of the general

Author, Publication Year	Risk of Bias Domains						Justification
	Selection of Participants	Confounding Variable	Intervention (exposure) Measurement	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	
							population - Secondary analysis of a prospective cohort study; adequate inclusion/exclusion criteria not specified and therefore there is potential selection bias -Potential conflicts of interest not declared -Unclear what percentage of sample tested using culture versus NAATs for CT and GC; CT for culture may underestimate the prevalence of infection
Roberts et al., 2011[29]	High	Low	Low	Low	Low	Low	-Limited baseline demographic information provided to determine if sample is representative of the general population
Aggarwal et al., 2010[30]	High	Low	Unclear	Low	High	Low	-Potential selection bias due to retrospective review of medical records; inclusion criteria not reported, possible convenience sampling -Screening test utilized not reported -May not be generalizable to the adult pregnant population as adolescents are considered a high-risk group
Silveira et al., 2010 [31]	High	Low	Unclear	Low	Low	Low	-Potential selection bias due

Author, Publication Year	Risk of Bias Domains						Justification
	Selection of Participants	Confounding Variable	Intervention (exposure) Measurement	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	
							to retrospective review of medical records -Black and Hispanic individuals were underrepresented in the study population -Screening test utilized not reported -Potential conflicts of interest not reported
Böhm et al., 2009[32]	Low	Low	Unclear	Low	Low	Low	Although justification is not provided for the selected study date range, pregnant persons were enrolled in sequence, minimizing the possibility of selection bias -Authors report that pooling multiple urine samples have nearly the same sensitivity and specificity as individuals, specific details NR - Urine sample group was much smaller than cervical swab group; as prevalence rate was higher in the cervical swab group, the lack of demographic information raises concern of potential selection bias
Logan et al., 2005[33]	High	Unclear	Low	Low	Low	Low	-No baseline demographic information provided to determine if sample is representative of the general population -Fewer

Author, Publication Year	Risk of Bias Domains						Justification
	Selection of Participants	Confounding Variable	Intervention (exposure) Measurement	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	
							participants agreed to invasive endocervical swabs; due to lack of baseline demographic information there is a potential for selection bias -Source of funding or potential conflicts of interest not reported -Population limited to those potentially suffering a miscarriage, therefore not be generalizable to all pregnant persons
Miller, Maupin and Nsuami, 2005[34]	High	Low	Low	Low	Low	Low	-Population from an underserved area, may have different CT rates in comparison to general population and may not be generalizable -Potential selection bias due to retrospective review of medical records , inclusion/exclusion criteria not reported; possible convenience sampling.
Miller et al., 2003[35]	High	Low	Low	Low	Low	Low	-Population from an underserved area, may have different GC rates in comparison to the general population and may not be generalizable -Potential selection bias due to retrospective review of medical records as inclusion/exclusion criteria not provided; possible convenience sampling -Source of funding

Author, Publication Year	Risk of Bias Domains						Justification
	Selection of Participants	Confounding Variable	Intervention (exposure) Measurement	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	
							not reported

CDC = Centers for Disease Control and Prevention; CT = *C.trachomatis*; GC = *N.gonorrhoeae*; NAAT= nucleic acid amplification test; NR = not reported; PTB = preterm birth

APPENDIX 7: STUDY CHARACTERISTICS – CLINICAL REVIEW

Table 38: Study Characteristics

Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Patient Characteristics, Clinical Setting, Risk Factors Identified	Intervention Comparator(s)	Specimen, Screening Test	Study Period, Follow-up, Loss to Follow-up	Outcomes Measures	Subgroup Analyses
CT and/ or GC Infections							
Blatt et al. 2012[27] United States Funded by Quest Diagnostics Potential conflicts of interest disclosed (authors employed and/or have equity interest in Quest Diagnostics)	Retrospective chart review Descriptive analysis, Multivariate logistic regression analysis	760,864 and 743,810 pregnant adults and adolescents aged 16 to 40 years tested for CT and GC separately Clinical setting: Laboratory data from Quest Diagnostics Informatics Data Warehouse Risk factors[a]: Younger age (16 to 24 years) and race (African American)	Intervention: Initial screening for CT and GC n = 760, 864 and 743,810 Comparator: Initial + Repeat screening for CT and GC at another point during pregnancy (including TOC for CT within 6 weeks of initial screen) n=113, 275 and 104, 828	Specimen: NR Screening tests: (i) 70% - Strand displacement amplification (Beckman Dickinson and Co) (ii) 20% - Deoxyribonucleic acid hybridization with chemiluminescent detection (Gen-Probe Inc) (iii) 10% - Target capture, transcription-mediated amplification, dual-kinetic assay (Gen-Probe Inc)	Study period: June 1, 2005 to May 30, 2008 Follow-up: N/A Loss to follow-up: N/A Not included in the analysis: Data unavailable for 647,589 and 638,982 females for CT and GC, respectively	Detection yield: (i) Number/per cent of positive CT and GC tests identified at initial and repeat testing Clinical Utility: (i) Number/per cent of individuals eligible for screening who obtained screening in accordance with recommendations	Guidelines-based screening by age: (i) CT – 16 to 25 years of age (ii) GC – 16 to 24 years of age
Berggren et al. 2011[28] United States Funded by APHPA002026-04-00 United States DHHS; the Summit Fund of Washington; the Alexander and Margaret Stewart Trust; and NICHD grant number 1 T32 HD-30672-01	Prospective cohort study (secondary analysis) Descriptive Analysis	125 pregnant adolescents Age (range): 12 to 18 years Median age at delivery: 17 years Clinical setting : Urban academic medical center Risk factors: NR	Intervention: Screening for CT and GC at entry to prenatal care n=125 Comparator: Screening for CT and GC at entry and during the third trimester (~36 weeks of gestation) n=95	Specimen: Endocervical[d] swab or urine samples Detection test: endocervical culture or urine NAAT	Study period: February 2003 to April 2005 Follow-up: 4 weeks for test-of-cure Loss to follow-up: N/A Not included in the analysis: 30	Detection yield: (i) Number/per cent of positive CT and GC tests at initial and repeat testing Clinical Utility: (i) Number of CT and GC infections treated	None

Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Patient Characteristics, Clinical Setting, Risk Factors Identified	Intervention Comparator(s)	Specimen, Screening Test	Study Period, Follow-up, Loss to Follow-up	Outcomes Measures	Subgroup Analyses
Aggarwal et al. 2010[30] Canada No potential conflicts of interest	Retrospective chart review Descriptive analysis	211 adolescent pregnancies (including 10 adolescents with repeat pregnancies) Mean age: 16.1 years (range 13 to 18 years) Clinical Setting: Hospital-based Risk factors: NR	Intervention: Screening at first prenatal (i.e., baseline) visit for CT and GC[b] n=211. Fourteen patients had their baseline screening during their third trimester Comparator: Screening at first prenatal visit and during the third trimester n=173 (excludes 14 who had their baseline screen during the third trimester)	CT: NAAT (strand displacement amplification assay) using cervical swab GC: Cervical culture with confirmation by immunofluorescence	Study period: January 2003 to December 2007 Follow-up: N/A Loss to follow-up: N/A Not included in the analysis: Data were unavailavle for 11	Detection yield: (i) Number/per cent of positive CT and/or GC tests at initial and repeat testing	None
CT Infections Only							
Folger 2014[26] United States No disclosure of financial or competing interests	Retrospective cohort study using linked public health databases Chi square and Student's *t* tests. Multivariate logistic regression using generalized estimating equations to calculate relative risk	3,354 pregnant adults and adolescents with live births and documented CT infections[b] during pregnancy Mean age: NR Clinical setting: Population-based; data retrieved from Hamilton County Public Health communicable disease records Risk factors: NR	Intervention: Early detection i.e., screening and treatment for CT at or before 20 weeks of gestation without subsequent detection n= 2,009 Comparator: Late detection i.e., screening and treatment for CT at or after 20 weeks of gestation or recurrent/persistent infection[c] n= 1,345	Specimen: NR Type of screening test: NR	Study period: 2006 to 2011 Follow-up : NR Loss to follow-up : NR	Clinical Utility: (i) Number/per cent of adverse maternal outcomes: a. Preterm birth b. Spontaneous preterm birth c. M/L preterm birth d. Spontaneous M/L preterm birth e. Very preterm birth f. Spontaneous very preterm birth (ii) Risk of preterm birth (iii) Number/ per cent of adverse neonatal outcomes: a. Low birth weight b. Infant deaths c. Mean gestational age (weeks) d. Mean birth weight (grams)	Age: (i) < 20 years (ii) 20 to 29 years (iii) > 29 years
Roberts et al. 2011[29] United States No potential conflicts of interest	Cross-sectional study McNemar's test and agreements	2018 pregnant adults and adolescents Mean age (±SD): 26.9 ± 6.1 years Clinical Setting:	Intervention: Screening of urine samples for CT at 35–37 weeks of gestation n= 2018 Comparator:	Specimen: Urine samples and endocervical[d] tissue samples Detection test: NAAT (Aptima	Study period: May 4 to September 2, 2009 Follow-up: N/A Loss to follow-up: None	Detection yield: (i) Number/per cent of positive CT tests	None

Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Patient Characteristics, Clinical Setting, Risk Factors Identified	Intervention Comparator(s)	Specimen, Screening Test	Study Period, Follow-up, Loss to Follow-up	Outcomes Measures	Subgroup Analyses
	reported by the κ statistic	Family planning and hospital obstetric clinic Risk factors: NR	Screening of endocervical tissue samples for CT at 35–37 weeks of gestation n=2018	Combo 2 Assay, Tigris DTS system)			
Silveira et al. 2010 [31] United States Author's postdoctoral scholarship funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)	Retrospective chart review Descriptive analysis	2,127 pregnant adults and adolescents with antenatal records who gave birth to a singleton at ≥ 20 weeks of gestation Mean age: NR Clinical Setting: Medical center Risk factors[a]: Age (<20 years), race (black), marital status (single), smoking , bacterial vaginosis, GC infection	Intervention: Routine screening for CT at any time point during pregnancy; inclusive population n=2104 Comparator: Screening for CT at any time point in pregnancy using USPSTF criteria (≤ 24 years old, single, and black or Hispanic) n= 2104	Specimen: NR Diagnostic test: NAAT	Study period: July 2005 to February 2008 Follow-up: N/A Loss to follow-up: N/A Missing data: n = 23	Detection yield: (i) Number/ per cent of positive CT cases	None
Böhm et al.2009[32] Germany No potential conflicts of interest	Retrospective cohort study Fisher's exact test	50,025 asymptomatic pregnant adults and adolescents Median age: 28 years Clinical setting: Specimens collected by gynaecologists, clinical setting unclear Risk factors: NR	Intervention: Screening for CT using cervical swabs n=31,856 Comparator: Screening for CT using pooled urine samples n=18,169	Specimen: NR Screening test: Semi-automated real-time PCR [*artus* C.Trachomatis Plus RG PCR Kit (Qiagen, Hilden, Germany)]	Study period: April to December 2008 Follow-up: N/A Loss to follow-up: N/A	Detection yield : (i) Number/per cent of positive CT cases	Age: (i) ≤ 20 years (ii) 21 to 25 years (iii) 26 to 30 years (iv) 31 to 35 years (v) 36 to 40 years (vi) > 40 years (vii)
Logan et al. 2005[33] United Kingdom No disclosure of financial or competing interests	Cross-sectional study Student's *t* test and Chi square test	207 adults and adolescents admitted for early pregnancy assessment with a positive pregnancy test, history of vaginal bleeding and less than 24 weeks of gestation Mean age (SD) : 29.3 (5.9) years	Intervention: Screening for CT followed by semi-structured questionnaire n = 205 Comparator: Screening for CT by an alternate specimen n= 205	Specimen: Endocervical (n = 139)[d], self-collected vulval (n= 205), or first-void urine (n= 205) samples Screening test: BD ProbeTec ET System	Study period: September to December 2001 Follow-up: N/A Loss to follow-up: N/A Missing data: Samples from two women leaked and were excluded	Detection yield: (i) Number/per cent of positive CT tests Clinical utility: (i) Number/per cent of participants who declined screening (ii) Patient preference with screening strategy	None

Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Patient Characteristics, Clinical Setting, Risk Factors Identified	Intervention Comparator(s)	Specimen, Screening Test	Study Period, Follow-up, Loss to Follow-up	Outcomes Measures	Subgroup Analyses
		Clinical setting: hospital-based Risk factors: NR					
Miller, Maupin, and Nsuami, 2005[34] United States Funded in part by Louisiana Board of Regents Health Excellence Fund Grant (HEF (2001-06) 04)	Retrospective chart review Chi square test and *t*-test	752 pregnant adults and adolescents Mean age : NR Clinical setting: Community-based prenatal setting Risk factors[a]: Marital status (single), younger age, less gravid, less parous, fewer prenatal visits, GC infection	Intervention: Screening for CT at entry into a prenatal program n= 752 Comparator: Screening at entry and repeat screening at 34 weeks n= 752	Specimen: NR Screening test: Direct DNA assay (Gen-Probe, San Diego, CA)	Study Period: January 1998 to May 2000 Follow-up: N/A Loss to follow-up: N/A	Detection yield: (i) Number/per cent of positive CT tests Clinical utility: (i) Number of CT infections treated (ii) Number/ per cent of adverse neonatal outcomes: a. Gestational age at delivery (days) b. Birth weight (grams)	Age[e]: (i) ≤ 19 years (ii) ≥ 20 years
GC Infections							
Miller et al., 2003,[35] United States No disclosure of financial or competing interests	Retrospective chart review Chi square test and analysis of variance	751 pregnant persons Mean age : NR Clinical setting: Community-based prenatal setting Risk factors[a]: Younger age, CT infection	Intervention: Screening for GC at entry into a prenatal program n= 751 Comparator: Screening for GC at entry and repeat screening at 34 weeks n= 751	Specimen: NR Screening test: Direct DNA assay (Gen-Probe, San Diego, CA)	Study Period: January 1998 to May 2000 Follow-up: N/A Loss to follow-up: N/A	Detection yield: (i) Number/per cent of positive GC tests Clinical utility: (i) Number of GC infections treated (ii) Number/ per cent of adverse neonatal outcomes: a. Gestational age at delivery (days) b. Birth weight (grams)	Age[e]: (i) ≤ 19 years (ii) ≥ 20 years

CT = *C. trachomatis*; DHHS = Department of Health and Human Services; GC = *N. gonorrhoeae*; M/L = moderate to late; NAAT = nucleic acid amplification test; NICHD = Eunice Kennedy Shriver National Institute of Child Health; NR = not reported; NS = non-significant; PCR = polymerase chain reaction; SD = standard deviation; STI = sexually-transmitted infection; USPSTF = United States Preventive Services Task Force

[a] The risk factors reported in the tables represent variables that were statistically significant

[b] Patients with other STIs not included in the report

[c] Recurrent/persistent infection was defined as infections detected at or before 20 weeks of gestation and after 20 weeks of gestation, but at least 7 days apart.

[d] The endocervix is the inner part of the cervix[38]

[e] Sub-group analyses were also conducted on risk factors including sociodemographic characteristics, other STIs, and gynecological/obstetric factors but are not within the scope of this report.

Appendix 8 : GRADE Assessment

Table 39: GRADE Assessment of the Evidence for Detection Yield: Initial vs. Initial + Repeat Screening

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Outcome: Number and Per cent of Positive Infections									
5	Retrospective chart review[27,30,34,35] (4) Prospective cohort study [secondary analysis][28] (1)	Serious limitations[a]	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision[d]	Undetected	Repeat screening resulted in higher detection yield in high-risk populations than one-time screening at entry into prenatal care.	⨁◯◯◯ Very Low	Critical

[a]Due to high risk of bias related to patient selection in all included studies
[b]The wide range of prevalences can be attributed to heterogeneity in patient population
[c]All included studies reported outcomes for screening once (i.e., at entry into prenatal care) versus screening multiple times (i.e, at entry and after treatment or at another time)
[d]Imprecision could not be assessed, as results were not reported as point estimates with a 95% confidence intervals.

Table 40: GRADE Assessment of the Evidence for Detection Yield: Universal vs. Targeted Risk Factor Based Screening

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Outcome: Number and Per cent of Positive Infections									
1	Retrospective chart review[31] (1)	Serious limitations[a]	No serious inconsistency[b]	No serious indirectness	No serious imprecision	Undetected	Universal screening at least once in pregnancy is recommended for all pregnant persons.	⨁◯◯◯ Very Low	Critical

[a]Due to high risk of bias related to patient selection in the one included study
[b]A single study provided data for the outcome, therefore inconsistency was not identified.

Table 41: GRADE Assessment of the Evidence for Detection Yield: Endocervical vs. Urine vs. Vulval Sample Screening

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Outcome: Detection Yield: Number and Per cent of Positive Infections									
3	Cross-sectional study (2)[29,33] Retrospective cohort study (1)[32]	Serious limitations[a]	Serious inconsistency[b]	No serious indirectness	No serious imprecision[c]	Undetected	Urine samples may have decreased test performance in comparison to cervical and vaginal samples.	⨁◯◯◯ Very Low	Critical

[a]Due to high risk of bias related to patient selection in the two of the three included studies
[b]Due to a wide range of reported values that cannot be explained by a specific source of heterogeneity
[c]Imprecision could not be assessed, as results were not reported as point estimates with a 95% confidence intervals in two of the three studies

Table 42: GRADE Assessment of the Evidence for Clinical Utility: Initial vs. Initial + Repeat Screening

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Outcome: Clinical Utility : Adherence to Guidelines-based Screening									
1	Retrospective chart review (1)[27]	Serious limitations[a]	No serious inconsistency[b]	No serious indirectness	No serious imprecision[c]	Undetected	A large percentage of females are not being screened in accordance with guidelines.	⨁◯◯◯ Very Low	Critical

[a]Due to high risk of bias related to patient selection in the one included study
[b]A single study provided data for the outcome, therefore inconsistency was not identified.
[c]Imprecision could not be assessed, as results were not reported as point estimates with a 95% confidence intervals

Table 43: GRADE Assessment of the Evidence for Clinical Utility: Early Detection vs. Late Detection

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Outcome: Clinical Utility: Number and Per cent of Preterm Births									
1	Retrospective cohort study (1)[26]	Serious limitations[a]	No serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	There was no statistically significant difference in the rates of preterm births in the early detection versus late detection group.	⨁◯◯◯ Very Low	Critical

Outcome: Clinical Utility: Number and Per cent of Spontaneous Preterm Births									
1	Retrospective cohort study (1)[26]	Serious limitations[a]	No serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	There was no statistically significant difference in the rates of spontaneous preterm births in the early detection versus late detection group.	⨁◯◯◯ Very Low	Critical
Outcome: Clinical Utility: Number and Per cent of Moderate-to-late Preterm Births									
1	Retrospective cohort study (1)[26]	Serious limitations[a]	No serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	There was no statistically significant difference in the rates of moderate-to-late preterm births in the early detection versus late detection group.	⨁◯◯◯ Very Low	Critical
Outcome: Clinical Utility: Number and Per cent of Moderate-to-late Spontaneous Preterm Births									
1	Retrospective cohort study (1)[26]	Serious limitations[a]	No serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	There was no statistically significant difference in the rates of moderate-to-late spontaneous preterm births in the early detection versus late detection group.	⨁◯◯◯ Very Low	Critical
Outcome: Clinical Utility: Number and Per cent of Very Preterm Births									
1	Retrospective cohort study (1)[26]	Serious limitations[a]	No serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	There was no statistically significant difference in the rates of very preterm births in the early detection versus late detection group.	⨁◯◯◯ Very Low	Critical
Outcome: Clinical Utility: Number and Per cent of Spontaneous Very Preterm Births									
1	Retrospective	Serious	No serious	No Serious	No serious	Undetected	There was no	⨁◯◯◯	Critical

	cohort study (1)[26]	limitations[a]	inconsistency[b]	indirectness	imprecision[c]		statistically significant difference in the rates of spontaneous very preterm births in the early detection versus late detection group.	Very Low	

[a]Due to high risk of bias related to patient selection in the included study
[b]A single study provided data for the outcome, therefore inconsistency was not identified.
[c]Imprecision could not be assessed, as results were not reported as point estimates with a 95% confidence intervals

Table 44: GRADE Assessment of the Evidence for Clinical Utility: Early Detection vs. Late Detection

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Outcome: Proportion with Low Birth Weight									
1	Retrospective cohort study[26] (1)	Serious limitations[a]	No serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	There was no statistically significant difference in the proportion of neonates born with low birth weight in the early detection versus late detection group.	⨁◯◯◯ Very Low	Critical
Outcome: Infant Mortality									
1	Retrospective cohort study[26] (1)	Serious limitations[a]	No serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	There was a statistically significant, but clinically insignificant difference in mortality of neonates born to mothers in the early detection versus late detection group.	⨁◯◯◯ Very Low	Critical

[a]Due to high risk of bias related to patient selection in the included study
[b]A single study provided data for the outcome, therefore inconsistency was not identified.
[c]Imprecision could not be assessed, as results were not reported as point estimates with a 95% confidence intervals

Table 45: GRADE Assessment of the Evidence for Clinical Utility: Detection and Treatment at Initial vs. Repeat Screening

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Outcome: Mean Gestational Age									
3	Retrospective cohort study[26] (1) Retrospective chart review[34,35] (2)	Serious limitations[a]	Serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	The findings suggest that infection with CT or GC has no impact on mean gestational age.	⨁◯◯◯ Very Low	Important
Outcome: Mean Birth Weight									
3	Retrospective cohort study[26] (1) Retrospective chart review[34,35] (2)	Serious limitations[a]	Serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	The findings suggest that infection with CT or GC has no impact on mean birth weight.	⨁◯◯◯ Very Low	Important

[a]Due to high risk of bias related to patient selection all the included studies
[b]Due to heterogeneity in the intervention and comparators
[c]Imprecision could not be assessed, as results were not reported as point estimates with a 95% confidence intervals for one included study

Table 46: GRADE Assessment of the Evidence for Clinical Utility: Endocervical vs. Urine vs. Vulval Sampling

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Outcome: Preference for Specimen Sampling									
1	Cross-sectional study[33] (1)	Serious limitations[a]	No Serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	Non-invasive sampling with either urine or self-collected vulval swabs is preferred to cervical sampling.	⨁◯◯◯ Very Low	Important

[a]Due to high risk of bias related to patient selection in the included study.

[b]A single study provided data for the outcome, therefore inconsistency was not identified.
[c]Imprecision could not be assessed, as results were not reported as point estimates with a 95% confidence intervals

Table 47: GRADE Assessment of the Evidence for Clinical Utility: Endocervical vs. Urine vs. Vulval Sampling

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
	Outcome: Number of Females Declining Screening								
1	Cross-sectional study[33] (1)	Serious limitations[a]	No Serious inconsistency[b]	No Serious indirectness	No serious imprecision[c]	Undetected	Approximately a quarter of women declined screening for CT infection during pregnancy.	⨁◯◯◯ Very Low	Critical

[a]Due to high risk of bias related to patient selection in the included study.
[b]A single study provided data for the outcome, therefore inconsistency was not identified.
[c]Imprecision cannot be assessed, as results were not reported as a point estimate with a 95% confidence interval

Table 48: GRADE Assessment of the Evidence for Clinical Utility: Initial vs. Initial + Repeat Screening

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Outcome: Number of Females Treated for Infection									
3	Retrospective chart review[34,35] (2) Prospective cohort study [secondary analysis][28] (1)	Serious limitations[a]	No Serious inconsistency	No Serious indirectness	No serious imprecision[b]	Undetected	100% of CT and GC infections detected at entry and repeat screening were treated.	⨁◯◯◯ Very Low	Critical

[a]Due to high risk of bias related to patient selection all the included studies.
[b]Imprecision could not be assessed, as results were not reported as point estimates with a 95% confidence intervals

Table 49: GRADE Assessment of the Evidence for Harms

Quality assessment							Summary of findings		
Number of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Impact**	**Certainty**	**Importance**
Anxiety: No evidence identified									
Fear of Sigmatization: No evidence identified									

Adverse Pregnancy Outcomes (e.g., miscarriage): No evidence identified
Negative impacts of false-positives and false-negatives : No evidence identified

Appendix 9: Characteristics of Economic Evaluation Literature Included in the Review of Economic Studies

Characteristic	Rours, 2016	Ditkowsky, 2017	Ong, 2016
Country	Netherlands	United States	Australia
Study Population	All pregnant women in the Netherlands	Pregnant women aged 15 to 24 in a higher burden setting	Pregnant women aged 16 to 25 in antenatal clinics
Perspective	Societal	Third-party payer	Third-party payer
Time Horizon	Unclear, beyond one year	1 Year	1 Year
Study Type	Cost-utility analysis	Cost-benefit analysis	Cost-utility analysis
Decision Problem	To analyze the cost-effectiveness of antenatal CT screening.	To determine the cost-benefit of screening all pregnant women aged 15–24 for CT infection compared with no screening.	To determine the cost-effectiveness of screening all pregnant women aged 16–25 years for chlamydia compared with selective screening or no screening.
Interventions Assessed	Screening until 1,000 CT cases identified versus not (26,605 women if prevalence is 3.9%), unclear screening implementation ; "assumed screening to be incorporated in existing routine antenatal care of testing for HIV, syphilis, and other infections. We included the use of NAATs to test urine specimens for CT"	Screening all pregnant women versus not, unclear at which time point this would occur	Screening all pregnant women versus selective screening (subsets of teenagers aged 16 to 19 years, or people with more than one sexual partner) versus not at all
Modelling Approach	Decision-tree	Decision-tree	Decision-tree
Health Outcomes	Maternal: Pelvic inflammatory disease, chronic pelvic pain, tubal infertility Obstetric: Preterm delivery, ectopic pregnancy Pediatric: Conjunctivitis, pneumonia	Maternal: Pelvic inflammatory disease Obstetric: Preterm delivery, pregnancy aborted Pediatric: Conjunctivitis, pneumonia	Maternal: Pelvic inflammatory disease, postpartum endometritis Pediatric: Conjunctivitis, pneumonia, low birth weight

Findings	Antenatal screening for CT is dominant compared to no antenatal screening.	Prenatal screening for CT resulted in increased expenditures, but reduced morbidity to women-infant pairs.	Screening all pregnant women was likely to be cost-effective compared with no screening and selective screening.
Uncertainty Analyses	Varied test costs; prevalence; screening in whole population versus pregnant women only	Altered screening rates	Altered CT prevalence

CT = Chlamydia trachomitis; HIV = Human immunodeficiency virus; NAAT = Nucleic acid amplification test.

Note: A number of other economic evaluations were identified assessing screening strategies for CT and GC that had a broader focus on the general population rather than pregnant persons specifically in which incorporated neonatal infections from vertical transmission.[125-131] Of note, the most commonly included neonatal infections within these models were neonatal conjunctivitis and pneumonia.

Appendix 10: Diagnostic Test Accuracy Meta-Analysis Methodology

The pooled diagnostic test accuracy, sensitivity, and specificity, were based on the statistics in the contingency tables of diagnostic test accuracy (DTA) studies included in 2014 U.S. preventive services task force (USPSTF) recommendation for GC and CT screening. [53] Only statitistics for the female population in NAAT vs. NAAT studies[132-136] were extracted for the purposes of this health technology assessment. The data were imported to R environment (v3.4.2)[137] and RStidio (1.0.143).[138] A bivariate random-effects model available within the mada package was used for the meta-analysis.[139,140]The pooled sensitivities and specificities were reported with 95% CIs along with the characteristics of SROC curves, including theta, lambda, and beta parameters.

Meta-Analysis of CT NAATs

There were 17 arms from 4 studies for meta-analysis: Gaydos et al. 2013,[132] Schoeman et al. 2012,[133] Taylor et al. 2011,[134] and Van Der Pol et al. 2012.[135] The arms are summarized by sample collection method and reference tests in Table 50 and Table 51. Based on the numbers of combinations, it was possible to pool the DTA data based on endocervical samples and reference tests that included Aptima Combo 2 (AC2) test.

Table 50: Summary of CT NAAT Devices and Sample Collection Method

	Clinician-Collected Vaginal	Endocervical	FCU	Self-Collected Vaginal
AC2	0	3	2	1
ACT	1	1	1	1
Amplicor	1	1	1	1
c4800	0	1	1	0
CT/GC Qx	0	1	1	0
CTQ	0	1	1	0
PTCT	0	1	1	0
Xpert	0	1	1	1

AC2 = Aptima Combo 2; ACT = Aptima *Chlamydia trachomatis* test; Amplicor = Roche cobas Amplicor test; c4800= Roche cobas 4800 CT and NG test; CTQ = Becton Dickinson ProbeTec CT Qx amplified DNA assay on the Viper system; CT/GC Qx = Becton Dickinson ProbeTec CT and NG Qx amplified DNA assay; FCU = first-catch urine; PTCT = Becton Dickinson ProbeTech ET CT amplified DNA assay.

Table 51: Summary of CT NAAT Devices and Reference Tests

Index Test	AC2, CT/GC Qx	AC2, PTCT	AC2, PTGC	Aptima CT	Vulture
AC2	2	2	0	2	0
ACT	0	0	0	0	4
Amplicor	0	0	0	0	4
c4800	2	0	0	0	0
CT/GC Qx	2	0	0	0	0
CTQ	0	2	0	0	0
PTCT	0	2	0	0	0
Xpert	0	0	3	0	0

AC2 = Aptima Combo 2; ACT = Aptima *Chlamydia trachomatis* test; Amplicor = Roche cobas Amplicor test; c4800= Roche cobas 4800 CT and NG test; CTQ = Becton Dickinson ProbeTec CT Qx amplified DNA assay on the Viper system; CT/GC Qx = Becton Dickinson ProbeTec CT and NG Qx amplified DNA assay PTCT = Becton Dickinson

ProbeTech ET CT amplified DNA assay; PTGC = Becton Dickinson ProbeTech ET amplified DNA assay for CT and NG.

All arms were merged to derive pooled DTA using a bivariate random-effects model. The pooled sensitivity was 0.93 (95% CI = 0.91 to 0.946). The pooled specificity was 0.996 (95% CI = 0.994 to 0.998). The SROC curve and its parameters are presented in Figure 8 and Table 52.

Figure 8: CT NAAT SROC Curve

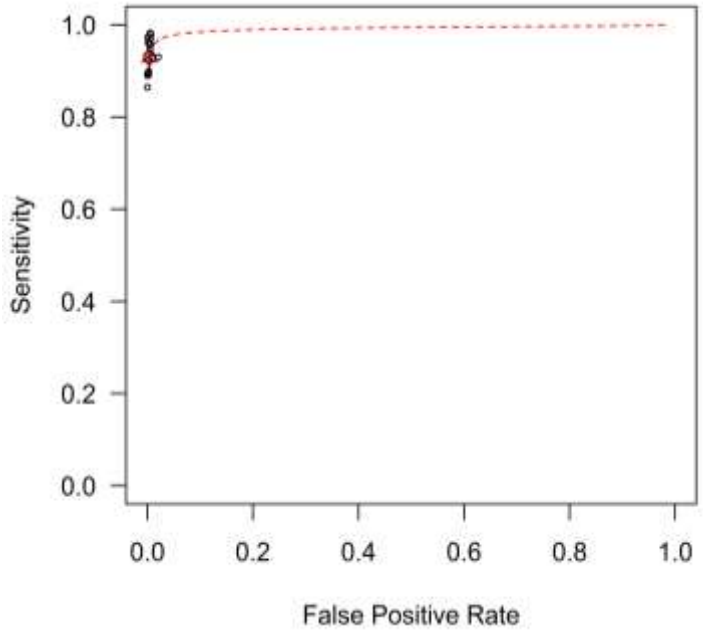


Table 52: CT NAAT SROC Curve Parameters

Parameter	Mean	Variance
Theta	-0.024	0.2007
Lambda	7.5826	0.2548
Beta	0.755	

Meta-Analysis of GC NAATs

There were 15 arms from 3 studies for meta-analysis: Gaydos, et al., 2013, [132] Van Der Pol et al. 2012,[135] and Van Der Pol et al. 2012.[136]. The arms are summarized by sample collection method and reference tests in Table 53 and Table 54. Based on the numbers of combinations, it was possible to pool the DTA data based on endocervical samples and reference tests that included the AC2 test.

Table 53: Summary of GC NAAT Devices and Sample Collection Method

	Endocervical	FCU	Self-Collected Vaginal
AC2	2	2	0
c4800	1	1	0
CT/GC	1	1	0

Qx			
GCQ	1	1	0
PTNG	1	1	0
Xpert	1	1	1

AC2 = Aptima Combo 2; AGC = Aptima NG test; c4800= cobas 4800 CT and NG test; CT/GC Q^{x} = Becton Dickinson ProbeTech CT and NG Q^{x} amplified DNA assay; FCU = first-catch urine; GCQ = Becton Dickinson ProbeTec NG Q^{x} amplified DNA assay on Viper system; PTNG = Becton Dickinson ProbeTech ET NG amplified DNA assay.

Table 54: Summary of GC NAAT Devices and Reference Tests

	AC2 , CT/GC Qx	AC2 , PTGC	AC2, PTNG
AC2	2	0	2
c4800	2	0	0
CT/GC Qx	2	0	0
GCQ	0	0	2
PTNG	0	0	2
Xpert	0	3	0

AC2 = Aptima Combo 2; AGC = Aptima NG test; c4800= cobas 4800 CT and NG test; CT/GC Q^{x} = Becton Dickinson ProbeTech CT and NG Q^{x} amplified DNA assay; GCQ = Becton Dickinson ProbeTec NG Q^{x} amplified DNA assay on Viper system; PTGC = Becton Dickinson ProbeTech ET for CT and NG; PTNG = Becton Dickinson ProbeTech ET NG amplified DNA assay.

All arms were merged to derive pooled DTA using a bivariate random-effects model. The pooled sensitivity was 0.917 (95% CI = 0.87 to 0.948). The pooled specificity was 0.998 (95% CI = 0.996 to 0.999). The SROC curve and its parameters are presented in Figure 9 Figure 8and Table 55.

Figure 9: GC NAAT SROC Curve

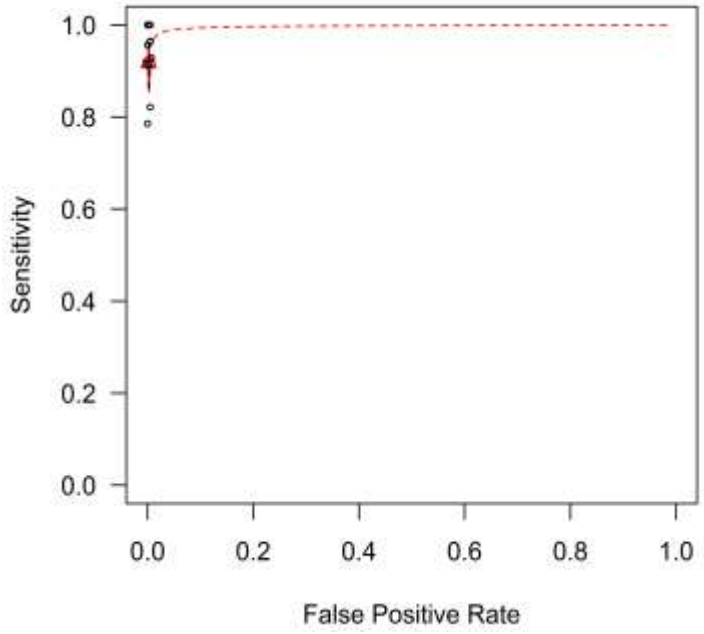


Table 55: GC NAAT SROC Curve Parameters

Parameter	Mean	Variance
Theta	-1.073411	0.0797126
Lambda	7.961082	1.173086
Beta	0.3803803	

Appendix 11: Obstetric Outcome Case Definitions

Table 50: Obstetric Outcome Costs

Obstetric outcome	ICD10CA Case or CCI Procedure Code(s)
Term Birth	CCI labour and delivery intervention codes that focus on delivery in description - 5MD50AA, 5MD50GH, 5MD51ZZ, 5MD52KV, 5MD53JD, 5MD53JE, 5MD53KH, 5MD53KJ, 5MD53KK, 5MD53KL, 5MD53KM, 5MD53KN, 5MD53KP, 5MD53KS, 5MD54KH, 5MD54KJ, 5MD54KK, 5MD54KL, 5MD54KM, 5MD54KN, 5MD54NE, 5MD54NF, 5MD55KH, 5MD55KJ, 5MD55KK, 5MD55KL, 5MD55KM, 5MD55KN, 5MD55KQ, 5MD55KR, 5MD56AA, 5MD56GH, 5MD56NL, 5MD56NM, 5MD56NN, 5MD56NP, 5MD56NQ, 5MD56NR, 5MD56NU, 5MD56NV, 5MD56NW, 5MD56PA, 5MD56PB, 5MD56PC, 5MD56PD, 5MD56PE, 5MD56PF, 5MD56PG, 5MD56PH, 5MD56PJ, 5MD60AA, 5MD60CB, 5MD60CC, 5MD60CD, 5MD60CE, 5MD60CF, 5MD60CG, 5MD60JW, 5MD60JX, 5MD60JY, 5MD60JZ, 5MD60KA, 5MD60KB, 5MD60KC, 5MD60KD, 5MD60KG, 5MD60KT, 5MD60RA, 5MD60RB, 5MD60RG, 5MD60RH
Preterm Birth	ICD10CA Code O60.101 - Preterm spontaneous labour with preterm delivery, with or without mention of antepartum condition; O60.301 - Preterm delivery without spontaneous labour, with or without mention of antepartum condition.
Extremely Preterm Birth	Assumed same as preterm birth.
Stillbirth	ICD10CA Codes O36.421, O36.423, O36.431, O36.433, O36.491, O36.493: Maternal care for intrauterine death.
Term Birth	ICD10CA Codes Z37.000, Z37.001 - Single live birth; Z38.000, Z38.001, Z38.010, Z38.011 - Singleton, born in hospital.
Preterm Birth	ICD10CA Code P07.3 - Other preterm infants.
Extremely Preterm Birth	ICD10CA Code P07.2 - Extremely immaturity.

ICD10CA = International statistical classification of diseases and related health problems, tenth revision, Canada; CCI = Canadian classification of health interventions.

Appendix 12: Complete Economic Analysis Results

Table 51: Cost-Utility Analysis Results per 100,000 Pregnant Persons (Probabilistic Base Case)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,489.73**	**561,663,327**	**0.00**	**0**	**Reference**
NNTM	**113,489.83**	**561,898,833**	**0.10**	**235,506**	**2,328,518**
TNNM	113,489.79	561,910,887	-0.03	12,054	Dominated
TNTM	113,489.84	562,420,243	0.01	521,410	Extendedly Dominated
NNUM	**113,490.15**	**562,780,614**	**0.32**	**881,780**	**2,775,685**
UNNM	113,490.08	562,812,155	-0.07	31,541	Dominated
TTTM	113,489.84	562,922,177	-0.31	141,564	Dominated
TNUM	**113,490.15**	**563,302,024**	**0.01**	**521,410**	**63,780,330**
UNTM	113,490.12	563,321,511	-0.04	19,487	Dominated
TTUM	113,490.16	563,803,958	0.00	501,934	Extendedly Dominated
UTTM (Current Strategy)	113,490.12	563,823,445	-0.03	521,421	Dominated
UNUM	**113,490.18**	**565,220,320**	**0.03**	**1,918,296**	**65,160,515**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 23: Pediatric Cost-Effectiveness Analysis Results per 100,000 Pregnant Persons (Probabilistic Base Case)

Strategy	Total					Incremental					ICER ($ Per Pediatric Infection Prevented[a])
	GC Conjunctivitis	CT Conjunctivitis	CT Pneumonia	Pediatric Infections[a]	Cost ($)	GC Conjunctivitis	CT Conjunctivitis	CT Pneumonia	Pediatric Infection Prevented[a]	Cost ($)	
NNNM	**80.4**	**276.7**	**132.0**	**489.1**	**561,663,327**	**0.0**	**0.0**	**0.0**	**0.0**	**0**	**Reference Strategy**
NNTM	**69.1**	**234.1**	**111.7**	**414.8**	**561,898,833**	**-11.4**	**-42.6**	**-20.3**	**74.3**	**235,506**	**3,171**
TNNM	72.2	248.5	118.5	439.1	561,910,887	3.1	14.3	6.8	-24.3	12,054	Dominated
TNTM	68.6	230.7	110.0	409.3	562,420,243	-0.4	-3.4	-1.6	5.5	521,410	Extendedly Dominated
NNUM	**27.7**	**100.4**	**47.9**	**176.0**	**562,780,614**	**-41.3**	**-133.7**	**-63.8**	**238.9**	**881,780**	**3,692**
UNNM	40.5	129.5	61.8	231.8	562,812,155	12.7	29.2	13.9	-55.8	31,541	Dominated
TTTM	68.5	229.7	109.5	407.8	562,922,177	40.8	129.3	61.7	-231.8	141,564	Dominated
TNUM	**27.3**	**96.9**	**46.2**	**170.5**	**563,302,024**	**-0.4**	**-3.4**	**-1.6**	**5.5**	**521,410**	**94,688**
UNTM	36.9	111.7	53.3	202.0	563,321,511	9.6	14.8	7.1	-31.5	19,487	Dominated
TTUM	27.2	95.9	45.8	168.9	563,803,958	-0.1	-1.0	-0.5	1.6	501,934	Extendedly Dominated
UTTM (Current Strategy)	36.8	110.8	52.8	200.4	563,823,445	9.5	13.8	6.6	-29.9	521,421	Dominated
UNUM	**25.8**	**84.5**	**40.3**	**150.7**	**565,220,320**	**-1.5**	**-12.4**	**-5.9**	**19.8**	**1,918,296**	**96,816**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICER = Incremental cost-effectiveness ratio.
[a]Accounts for GC conjunctivitis, CT conjunctivitis, and CT pneumonia in aggregate.

Table 24: Cost-Utility Analysis Results per 100,000 Pregnant Persons (Aged Under 25 Years Subgroup)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**112,340.51**	**561,746,315**	**0.00**	**0**	**Reference**
NNUM	**112,340.99**	**562,848,514**	**0.47**	**1,102,199**	**2,327,685**
UNNM	112,340.83	562,904,948	-0.16	56,434	Dominated
UNUM	**112,341.02**	**565,288,586**	**0.04**	**2,440,071**	**63,952,184**
UUUM	**112,341.04**	**567,637,448**	**0.01**	**2,348,862**	**214,675,621**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 25: Cost-Utility Analysis Results per 100,000 Pregnant Persons (Aged 25 Years and Older Subgroup)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,802.11**	**561,640,776**	**0**	**0**	**Reference**
NNUM	**113,802.52**	**562,762,156**	**0.40**	**1,121,380**	**2,775,918**
UNNM	113,802.47	562,786,937	-0.04	24,781	Dominated
UUUM	113,802.47	562,786,937	-0.04	24,781	Dominated
UNUM	**113,802.56**	**565,201,763**	**0.04**	**2,439,607**	**65,111,848**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 26: Cost-Utility Analysis Results per 100,000 Pregnant Persons (High Risk Population Scenario)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,486.17**	**563,874,495**	**0.00**	**0**	**Reference**
TNNM	113,486.77	563,916,728	0.60	42,233	Extendedly Dominated
NNTM	113,486.80	563,921,470	0.63	46,975	Extendedly Dominated
UNNM	**113,489.00**	**564,064,703**	**2.83**	**190,208**	**67,183**
NNUM	**113,489.08**	**564,098,759**	**0.07**	**34,056**	**458,282**
TNTM	113,486.86	564,372,189	-2.22	273,430	Dominated
UNTM	113,489.09	564,520,164	0.02	421,405	Extendedly Dominated
TNUM	113,489.14	564,549,479	0.06	450,720	Extendedly Dominated
TTTM	113,486.87	564,812,054	-2.21	713,295	Dominated
UTTM (Current Strategy)	113,489.10	564,960,029	0.02	861,270	Extendedly Dominated
TTUM	113,489.15	564,989,344	0.07	890,585	Extendedly Dominated
UNUM	**113,489.36**	**566,205,416**	**0.28**	**2,106,657**	**7,452,270**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 27: Cost-Utility Analysis Results per 100,000 Pregnant Persons (Alternate CT Reinfection Rate Scenario)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,489.73**	**561,663,327**	**0.00**	**0**	**Reference**
NNTM	**113,489.83**	**561,898,794**	**0.10**	**235,467**	**2,326,666**
TNNM	113,489.79	561,910,866	-0.03	12,073	Dominated
TNTM	113,489.84	562,420,218	0.01	521,424	Extendedly Dominated
NNUM	**113,490.15**	**562,780,058**	**0.32**	**881,264**	**2,766,816**
UNNM	113,490.08	562,811,808	-0.07	31,750	Dominated
TTTM	113,489.84	562,922,156	-0.31	142,097	Dominated
TNUM	**113,490.16**	**563,301,482**	**0.01**	**521,424**	**64,109,577**
UNTM	113,490.12	563,321,160	-0.04	19,678	Dominated
TTUM	113,490.16	563,803,420	0.00	501,938	Extendedly Dominated
UTTM (Current Strategy)	113,490.12	563,823,098	-0.03	521,615	Dominated
UNUM	**113,490.18**	**565,219,999**	**0.03**	**1,918,517**	**66,670,859**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 28: Cost-Utility Analysis Results per 100,000 Pregnant Persons (Low Pediatric Infection Rates Scenario)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,490.38**	**561,307,195**	**0.00**	**0**	**Reference**
TNNM	113,490.38	561,591,222	0.00	284,027	Dominated
NNTM	113,490.38	561,594,633	0.00	287,438	Dominated
TNTM	113,490.38	562,118,795	0.00	811,600	Dominated
TTTM	113,490.38	562,621,506	0.00	1,314,311	Dominated
UNNM	113,490.38	562,637,443	0.00	1,330,247	Dominated
NNUM	113,490.38	562,655,617	0.00	1,348,422	Dominated
UNTM	113,490.38	563,165,016	0.00	1,857,820	Dominated
TNUM	113,490.38	563,179,779	0.00	1,872,584	Dominated
UTTM (Current Strategy)	113,490.38	563,667,727	0.00	2,360,531	Dominated
TTUM	113,490.38	563,682,491	0.00	2,375,295	Dominated
UNUM	113,490.38	565,107,950	0.00	3,800,754	Dominated

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 29: Cost-Utility Analysis Results per 100,000 Pregnant Persons (100% Preterm and Extremely Preterm Screening Scenario)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,489.76**	**561,889,688**	**0.00**	**0**	**Reference**
NNTM	**113,489.86**	**562,130,105**	**0.10**	**240,417**	**2,506,849**
TNNM	113,489.82	562,141,652	-0.03	11,547	Dominated
TNTM	113,489.86	562,651,866	0.01	521,762	Extendedly Dominated
NNUM	**113,490.16**	**563,029,087**	**0.30**	**898,983**	**2,980,497**
UNNM	113,490.09	563,059,114	-0.07	30,027	Dominated
TTTM	113,489.87	563,153,845	-0.29	124,758	Dominated
TNUM	**113,490.17**	**563,550,849**	**0.01**	**521,762**	**68,028,430**
UNTM	113,490.13	563,569,329	-0.03	18,480	Dominated
TTUM	113,490.17	564,052,828	0.00	501,979	Extendedly Dominated
UTTM (Current Strategy)	113,490.13	564,071,308	-0.03	520,459	Dominated
UNUM	**113,490.19**	**565,470,440**	**0.03**	**1,919,591**	**69,706,362**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 30: Cost-Utility Analysis Results per 100,000 Pregnant Persons (0% Screening of Pregnant Persons Without Screening History at Presentation for Term Labour Scenario)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNN	**113,407.01**	**561,029,756**	**0.00**	**0**	**Reference**
NNTN	**113,407.16**	**561,486,347**	**0.14**	**456,591**	**3,211,120**
TNNN	113,407.12	561,488,293	-0.03	1,946	Dominated
TNTN	113,407.16	562,007,754	0.01	521,407	Extendedly Dominated
TTTN	113,407.17	562,509,780	0.01	1,023,433	Extendedly Dominated
UNNN	113,407.52	563,174,139	0.36	1,687,792	Extendedly Dominated
NNUN	**113,407.59**	**563,190,091**	**0.43**	**1,703,744**	**3,947,489**
UNTN	113,407.56	563,693,599	-0.03	503,508	Dominated
TNUN	**113,407.60**	**563,711,498**	**0.01**	**521,407**	**64,081,729**
UTTN (Current Strategy)	113,407.56	564,195,626	-0.03	484,128	Dominated
TTUN	113,407.60	564,213,524	0.00	502,027	Extendedly Dominated
UNUN	**113,407.63**	**565,628,657**	**0.03**	**1,917,160**	**65,517,600**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 31: Cost-Utility Analysis Results per 100,000 Pregnant Persons (100% Screening of Pregnant Persons Without Screening History at Presentation for Term Labour Scenario)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,407.41**	**563,694,035**	**0.00**	**0**	**Reference**
NNTM	**113,407.47**	**563,711,869**	**0.06**	**17,835**	**299,167**
TNNM	113,407.44	563,733,909	-0.03	22,040	Dominated
NNUM	**113,407.67**	**563,782,264**	**0.20**	**70,395**	**349,055**
UNNM	113,407.61	563,861,131	-0.07	78,867	Dominated
TNTM	113,407.48	564,233,276	-0.19	451,012	Dominated
TNUM	**113,407.68**	**564,303,671**	**0.01**	**521,407**	**64,081,737**
UNTM	113,407.65	564,360,498	-0.03	56,827	Dominated
TTTM	113,407.48	564,735,303	-0.20	431,632	Dominated
TTUM	113,407.68	564,805,697	0.00	502,027	Extendedly Dominated
UTTM (Current Strategy)	113,407.65	564,862,524	-0.03	558,853	Dominated
UNUM	**113,407.71**	**566,220,830**	**0.03**	**1,917,160**	**65,517,600**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 32: Cost-Utility Analysis Results per 100,000 Pregnant Persons (0% Screening of Infants with Mothers Who Are GC-Positive at Presentation for Labour Scenario)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,489.71**	**561,668,891**	**0.00**	**0**	**Reference**
NNTM	**113,489.82**	**561,901,069**	**0.10**	**232,178**	**2,238,298**
TNNM	113,489.78	561,913,821	-0.03	12,752	Dominated
TNTM	113,489.83	562,420,863	0.01	519,794	Extendedly Dominated
NNUM	**113,490.14**	**562,772,340**	**0.33**	**871,271**	**2,673,384**
UNNM	113,490.07	562,806,882	-0.07	34,542	Dominated
TTTM	113,489.83	562,921,532	-0.32	149,192	Dominated
TNUM	**113,490.15**	**563,292,134**	**0.01**	**519,794**	**63,781,894**
UNTM	113,490.12	563,313,924	-0.04	21,790	Dominated
TTUM	113,490.15	563,792,803	0.00	500,669	Extendedly Dominated
UTTM (Current Strategy)	113,490.12	563,814,593	-0.03	522,459	Dominated
UNUM	**113,490.18**	**565,204,447**	**0.03**	**1,912,313**	**64,977,361**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 33: Cost-Utility Analysis Results per 100,000 Pregnant Persons (100% Effective Vertical Transmission Prevention Treatment Scenario)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,407.61**	**562,293,004**	**0.00**	**0**	**Reference**
NNTM	**113,407.67**	**562,547,128**	**0.07**	**254,124**	**3,872,647**
TNNM	113,407.64	562,559,138	-0.03	12,010	Dominated
TNTM	113,407.68	563,068,373	0.01	521,245	Extendedly Dominated
NNUM	**113,407.89**	**563,482,687**	**0.22**	**935,559**	**4,258,452**
UNNM	113,407.83	563,514,402	-0.07	31,715	Dominated
TTTM	113,407.69	563,570,129	-0.21	87,442	Dominated
TNUM	**113,407.90**	**564,003,932**	**0.01**	**521,245**	**60,491,799**
UNTM	113,407.87	564,023,638	-0.04	19,706	Dominated
TTUM	113,407.91	564,505,688	0.00	501,756	Extendedly Dominated
UTTM (Current Strategy)	113,407.87	564,525,393	-0.03	521,461	Dominated
UNUM	**113,407.93**	**565,922,361**	**0.03**	**1,918,429**	**65,192,633**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 34: Cost-Utility Analysis Results per 100,000 Pregnant Persons (0% Effective Vertical Transmission Prevention Treatment Scenario)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,407.27**	**562,477,188**	**0.00**	**0**	**Reference**
NNTM	**113,407.40**	**562,694,616**	**0.14**	**217,428**	**1,598,394**
TNNM	113,407.37	562,706,565	-0.03	11,949	Dominated
TNTM	113,407.41	563,216,216	0.01	521,601	Extendedly Dominated
NNUM	**113,407.82**	**563,524,390**	**0.41**	**829,775**	**2,006,843**
UNNM	113,407.75	563,555,486	-0.07	31,096	Dominated
TTTM	113,407.41	563,718,333	-0.40	193,943	Dominated
TNUM	**113,407.83**	**564,045,991**	**0.01**	**521,601**	**67,618,924**
UNTM	113,407.79	564,065,137	-0.03	540,747	Dominated
TTUM	113,407.83	564,548,107	0.01	1,023,717	Extendedly Dominated
UTTM (Current Strategy)	113,407.79	564,567,254	-0.02	1,042,864	Dominated
UNUM	**113,407.86**	**565,964,258**	**0.04**	**2,439,868**	**65,775,959**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 35: Cost-Utility Analysis Results per 100,000 Pregnant Persons (Exploratory Analysis: CT and GC Infection Impact Adverse Obstetric Outcomes)

Strategy	Total		Incremental		ICUR ($ Per QALY Gained)
	QALYs	Costs ($)	QALYs	Costs ($)	
NNNM	**113,486.92**	**561,858,682**	**0.00**	**0**	**Reference**
TNNM	113,488.70	561,997,796	1.78	139,114	Extendedly Dominated
NNTM	113,488.21	562,010,159	1.29	151,477	Extendedly Dominated
TNTM	113,489.02	562,488,731	2.09	630,049	Extendedly Dominated
UNNM	**113,495.35**	**562,500,298**	**8.43**	**641,616**	**76,145**
NNUM	113,492.51	562,611,664	-2.83	111,365	Dominated
TTTM	113,489.16	562,983,633	-6.18	483,335	Dominated
UNTM	**113,495.66**	**562,991,234**	**0.32**	**490,935**	**1,554,224**
TNUM	113,493.32	563,090,236	-2.35	99,002	Dominated
UTTM (Current Strategy)	113,495.81	563,486,135	0.15	494,902	Extendedly Dominated
TTUM	113,493.47	563,585,137	-2.20	593,904	Dominated
UNUM	**113,496.30**	**564,850,808**	**0.64**	**1,859,574**	**2,905,194**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICUR = Incremental cost-utility ratio; QALY = Quality-adjusted life years.

Table 36: Pediatric Cost-Effectiveness Analysis Results per 100,000 Pregnant Persons (Exploratory Analysis: CT and GC Infection Impact Adverse Obstetric Outcomes)

Strategy	Total					Incremental					ICER ($ Per Pediatric Infection Prevented[a])
	GC Conjunctivitis	CT Conjunctivitis	CT Pneumonia	Pediatric Infections[a]	Cost ($)	GC Conjunctivitis	CT Conjunctivitis	CT Pneumonia	Pediatric Infection Prevented[a]	Cost ($)	
NNNM	**86.0**	**277.4**	**132.3**	**495.8**	**561,858,682**	**0.0**	**0.0**	**0.0**	**0.0**	**0**	**Reference**
TNNM	76.8	249.0	118.8	444.6	561,997,796	-9.2	-28.4	-13.6	51.2	139,114	Extendedly Dominated
NNTM	**73.9**	**234.8**	**112.0**	**420.6**	**562,010,159**	**-12.2**	**-42.7**	**-20.4**	**75.2**	**151,477**	**2,014**
TNTM	73.3	231.3	110.3	414.9	562,488,731	-0.6	-3.5	-1.7	5.7	478,572	Extendedly Dominated
UNNM	41.6	129.6	61.8	233.0	562,500,298	-32.2	-105.2	-50.2	187.5	490,139	Extendedly Dominated
NNUM	**29.7**	**100.7**	**48.0**	**178.4**	**562,611,664**	**-44.2**	**-134.0**	**-63.9**	**242.2**	**601,504**	**2,484**
TTTM	73.2	230.3	109.8	413.3	562,983,633	43.5	129.6	61.8	-234.9	371,969	Dominated
UNTM	38.1	111.8	53.3	203.3	562,991,234	8.5	11.1	5.3	-24.9	379,570	Dominated
TNUM	**29.1**	**97.2**	**46.4**	**172.7**	**563,090,236**	**-0.6**	**-3.5**	**-1.7**	**5.7**	**478,572**	**84,013**
UTTM (Current Strategy)	38.0	110.9	52.9	201.7	563,486,135	8.9	13.6	6.5	-29.0	395,900	Dominated
TTUM	29.0	96.2	45.9	171.1	563,585,137	-0.1	-1.0	-0.5	1.6	494,902	Extendedly Dominated
UNUM	**27.1**	**84.7**	**40.4**	**152.2**	**564,850,808**	**-2.0**	**-12.5**	**-6.0**	**20.5**	**1,760,572**	**85,826**

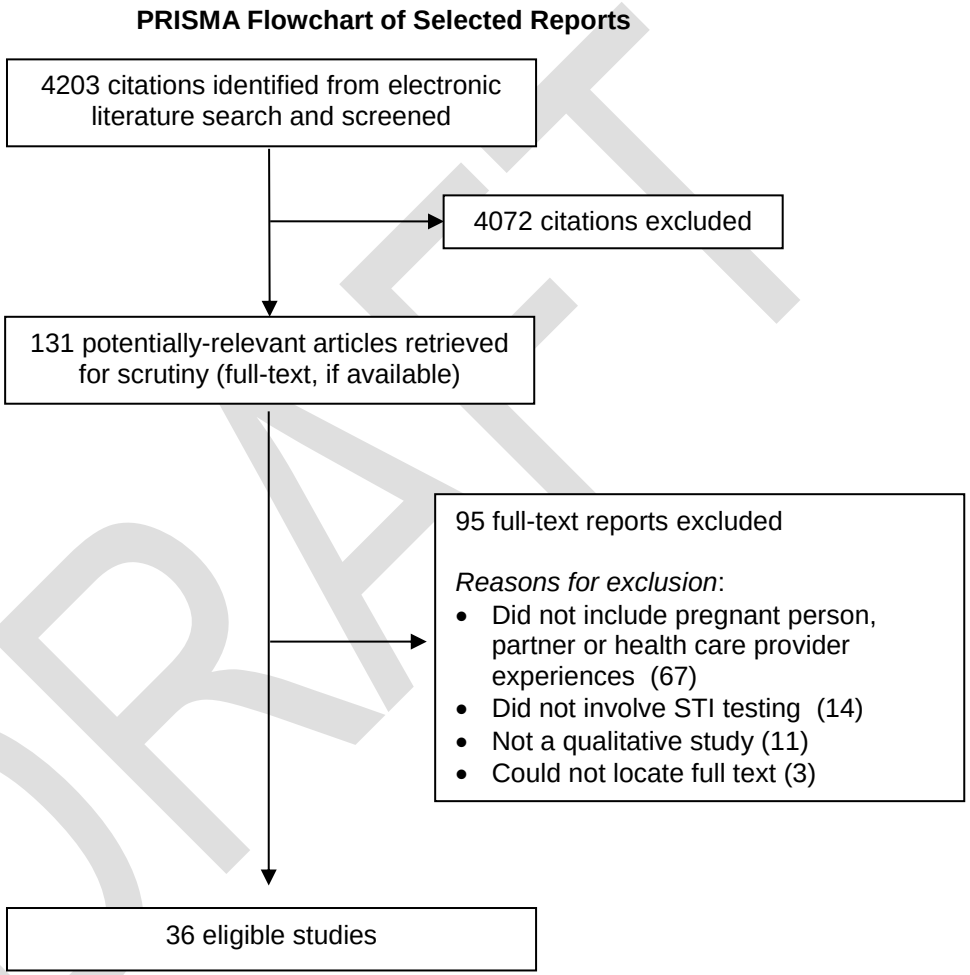
CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICER = Incremental cost-effectiveness ratio.
[a]Accounts for GC conjunctivitis, CT conjunctivitis, and CT pneumonia in aggregate.

Table 37: Obstetric Outcomes Cost-Effectiveness Analysis Results per 100,000 Pregnant persons (Exploratory Analysis: CT and GC Infection Impact Adverse Obstetric Outcomes)

Strategy	Total					Incremental					ICER ($ Per Adverse Obstetric Outcome Prevented[a])
	Preterm Birth	Extremely Preterm Birth	Stillbirth	Adverse Obstetric Outcomes[a]	Cost ($)	Preterm Birth	Extremely Preterm Birth	Stillbirth	Adverse Obstetric Outcomes Prevented[a]	Cost ($)	
NNNM	**7301.0**	**459.5**	**806.4**	**8566.8**	**561,858,682**	**0.0**	**0.0**	**0.0**	**0.0**	**0**	**Reference**
TNNM	7293.4	458.9	804.8	8557.1	561,997,796	-7.6	-0.6	-1.5	9.7	139,114	Extendedly Dominated
NNTM	7291.4	459.5	805.7	8556.5	562,010,159	-9.6	0.0	-0.7	10.3	12,363	Extendedly Dominated
TNTM	7291.2	458.9	804.7	8554.8	562,488,731	-9.8	-0.6	-1.7	12.0	478,572	Extendedly Dominated
UNNM	**7265.3**	**456.9**	**799.3**	**8521.4**	**562,500,298**	**-35.7**	**-2.6**	**-7.1**	**45.4**	**490,139**	**14,139**
NNUM	7259.4	459.5	803.4	8522.3	562,611,664	-5.9	2.6	4.2	-0.9	111,365	Dominated
TTTM	7291.1	458.8	804.5	8554.4	562,983,633	25.8	1.9	5.2	-33.0	371,969	Dominated
UNTM	**7263.1**	**456.9**	**799.1**	**8519.1**	**562,991,234**	**-2.2**	**0.0**	**-0.2**	**2.3**	**7,601**	**209,783**
TNUM	7259.2	458.9	802.4	8520.6	563,090,236	-3.9	2.0	3.4	-1.5	99,002	Dominated
UTTM (Current Strategy)	7263.1	456.8	798.9	8518.8	563,486,135	0.0	-0.1	-0.2	0.3	395,900	Extendedly Dominated
TTUM	7259.2	458.8	802.3	8520.2	563,585,137	-4.0	1.9	3.2	-1.2	99,002	Dominated
UNUM	**7258.5**	**456.9**	**798.8**	**8514.1**	**564,850,808**	**-4.6**	**0.0**	**-0.3**	**4.9**	**1,265,670**	**375,869**

CT = Chlamydia trachomitis; GC = Neisseria gonorrhoeae; ICER = Incremental cost-effectiveness ratio.
[a]Accounts for preterm birth, extremely preterm birth, and stillbirth in aggregate.

Appendix 13: Study Selection Flow Diagrams — Patients' preferences and Experiences Review



Appendix 14: Study Characteristics – Patients' preferences and Experiences Review

First Author, Publication Year, Setting	Research Objective	Reported Study Design or Analytic Approach	Participant Characteristics
HIV			
Alvarez-Del Arco, 2018, Spain[94]	To analyze elements shaping the desire for procreation among women living with HIV, and to specifically investigate the impact of HIV.	Qualitative Study	20 HIV-positive women, of which 11 had children
Baxter, 2000, United Kingdom[95]	To examine the attitudes of a group of pregnant women to the routine offer of the HIV test in pregnancy	Qualitative Study	12 pregnant women, 6 of whom accepted the test & 6 who did not
Blake, 2008, United States[96]	To describe personal experiences of women in obtaining HIV testing and healthcare services in east Texas.	Secondary qualitative data analysis	64 women, 23 of whom were HIV-positive and 41 who were high-risk HIV negative,
Boyd, 1999, United Kingdom[97]	To investigate the opinions of a sample drawn from a general population of pregnant women within the context of an HIV test offer.	Qualitative Study, with reference to Grounded Theory analysis	29 pregnant women
Bulman, 2013, Canada[98]	To (1) obtain an increased understanding of the information women receive about HIV/AIDS during the opt-out screening process and (2) to advance the policy related dialogue around best practices in HIV screening within the province of Newfoundland and Labrador.	Qualitative Descriptive Study	12 pregnant women
Chambers, 2001, New Zealand[99]	To assess current attitudes and practice toward antenatal HIV risk assessment, HIV testing and barriers towards implementation of these among midwives, general practitioners and obsetricians	Survey	100 midwives 293 general practitioners 14 obstetricians
De Zulueta, 2007, United Kingdom[100]	To explore pregnant women's responses to routine HIV testing, examine their reasons for declining or accepting the test, and assess how far their responses fulfill standard criteria for informed consent	Qualitative cross-sectional survey	32 pregnant women
Evans, 2016, United Kingdom (included studies from USA,	To explore nurses' and midwives' views and experiences of the provision and management of provider-initiated HIV testing and counseling.	Systematic Review of Qualitative	21 publications from 18 research studies Nurses and midwives; Studies whose sample included different cadres of

Canada & UK)[101]		Evidence, data were pooled using a pragmatic meta-aggregative approach	healthcare providers were included if more than 50% were nurses or midwives.
Fielder, 2005, USA[102]	To examine the attitudes and health beliefs among drug users about mandatory HIV testing of newborns and about voluntary versus mandatory testing of pregnant women; to examine to what extent negative experiences and stigmatization affected attitudes toward HIV testing	Mixed Methods, "Qualitative Focus Group Study"	For Qualitative Component: 25 HIV-infected and uninfected, drug-using men and women Does not report pregnancy status, but participants refer to having had children in findings
Gahagan, 2011, Canada[103]	To explore the various individual and structural barriers and facilitators to HIV counselling and testing experienced among a sample of adult women and men living in Nova Scotia, Canada.	Mixed Methods	For Qualitative Component: 30 women 19 men 1 trans-gendered person Does not report pregnancy status, but "several participants interviewed had been tested for HIV while they were pregnant."
Jones, 2004, United Kingdom[104]	To explore the reasons women gave when they declined HIV testing	Survey/Audit	2138 pregnant women
Katz, 2001, USA[105]	To describe the experience of screening for human immunodeficiency virus (HIV) in pregnancy from the perspective of pregnant women.	Descriptive Study, analyzed using a combination of grounded theory and content analysis	32 pregnant women
Kelly, 2001, USA[106]	To examine the experience of testing and receipt of positive HIV test results by pregnant women in Texas who were tested after the mandatory perinatal testing law went into effect	Interview Study	29 HIV-positive pregnant women
Kelly, 2012, United Kingdom[107]	To understand the uniqueness of the experience of testing HIV positive from the perspective of pregnant women.	Qualitative Study	4 pregnant women
Kelly, 2012, USA[107]	To investigate how women who were being tested for HIV during their pregnancies were evaluating, conceptualizing, and negotiating their risk of infection	Qualitative Component of Mixed Methods, analyzed in accordance to grounded theory method	30 pregnant women

Lee King, 2014, USA[109]	To explore women's perspectives on these factors together to inform comprehensive perinatal HIV testing communication	Qualitative descriptive research design, analyzed using Content Analysis	37 pregnant women, 32 of whom were HIV-negative and 5 HIV-positive (separate focus groups)
Lingen-Stallard, 2016, United Kingdom[110]	To explore women's experiences of receiving a positive HIV test result following antenatal screening	Phenomenology	13 women who had received a positive HIV diagnosis in an antenatal HIV testing programme
Mawn, 1998, USA[111]	To include the voices of laywomen at risk for or living with human immunodeficiency virus (HIV) in the ongoing debate on prenatal and newborn HIV screening	Phenomenology	33 women, 16 of whom were HIV-positive
McAllister, 2013, New Zealand[112]	To investigate the impact on women, and their healthcare providers, of initial-reactive HIV test results which required re-testing in the New Zealand antenatal HIV screening programme.	Qualitative Study, analyzed using thematic analysis	19 general practitioners 11 midwives 7 pregnant women
McLeish, 2016, USA[113]	To explore the experiences of women living with HIV in England who received or gave Mentor Mother (trained mother-to-mother) volunteer peer support during pregnancy and early motherhood.	Qualitative Descriptive Study, theoretically informed by phenomenology	12 HIV-positive pregnant women
Meyerson, 2014, USA[114]	To identify the extent to which community health centres in Indiana implement routine HIV testing	Community participatory research	28 community health centres reporting
Njie-Carr, 2012, USA[115]	To describe and explore African-American and African Caribbean women's knowledge, attitudes, beliefs, feelings, interpersonal experiences related to participating in voluntary counseling and testing (VCT), disclosing their HIV status, and their decisions related to pregnancy care and parenting practices.	Qualitative Study	23 women, of which 20 were pregnant and 3 were parenting with an infant that was less than 12 months of age
Rothpletz-Puglia, 2012, USA[116]	To solicit women's opinions about the process of routine prenatal HIV testing to identify strategies for routine testing that will address women's concerns, increase their level of comfort with testing, and support universal prenatal HIV testing	Exploratory Study	25 women, of which 24 were non-pregnant and one had given birth within the last year
Simpson, 2007, USA[117]	To elicit the personal perspectives of a unique group of women who first learned of their HIV diagnosis during pregnancy and to report their views of the benefits and the negative consequences of laws that mandate HIV testing for pregnant women.	Survey	22 pregnant women, of which 11 were HIV-positive and 11 were HIV-negative
Stevens, 1989, United Kingdom[118]	To examine women's attitudes to HIV testing in two antenatal clinics in central London	Survey	155 pregnant women
Treisman, 2014, USA[119]	To explore the following research question: How do United Kingdom-based African women perceive, make sense of, and manage a diagnosis of HIV during pregnancy, and after delivery?	Qualitaive investigation, analyzed using	12 pregnant women

		interpretive phenomenological analysis	
Tripathi, 2013, Ukraine[120]	To explore women's and providers' experiences of HIV testing during antenatal care, with a focus on consent, counseling, and confidentiality.	Qualitative Study	25 health providers who conduct HIV testing of pregnant women 60 pregnant women, of whom 15 were HIV-positive
Williams, 1990, USA[69]	To investigate knowledge about perinatal transmission of HIV and perceptions of the childbearing role among women at risk of AIDS	Content Analysis	21 women
Syphillis			
DiOrio, 2018, USA[121]	To understand the etiology of congenital syphilis through qualitative examination of case mother characteristics and behavior	Qualitative methods	23 pregnant women
Kroeger, 2018, USA[122]	To elicit perspectives of providers and community members in Caddo Parish, Louisiana, on the persistence of congenital syphillis in the community	Qualitative Interviews	69 participants: 58 females and 11 males
Chlamydia			
Bilardi, 2010, Australia[89]	To determine the acceptability of screening pregnant women aged 16-25 years for chlamydia as part of routine antenatal care.	Qualitative Component of Mixed Methods	100 pregnant women, 69 who had tested negative for chlamydia and 31 positive for chlamydia.
Logan, 2005, United Kingdom[90]	To compare, in parallel, different approaches of opportunistically screening women with bleeding in early pregnancy for Chlamydia trachomatis	Cross-sectional study	207 pregnant women
Perkins, 2003, United Kingdom[92]	To assess the feasibility and acceptability of opportunistic screening both to the target population and to the healthcare professionals participating in the programme	Qualitative evaluation component of Mixed Methods	13 GPs, 14 practice nurses, 15 practice receptionists and 11 practice managers
Pimenta, 2003, United Kingdom[91]	To determine the acceptability of opportunistic screening for Chlamydia trachomatis in young people in a range of healthcare settings.	Qualitative evaluation component of programme evaluation	For qualitative component: 24 women and one man
Chlamydia & Gonorrhea			
Hack, 2009, USA[93]	To discern whether there were any specific patterns of treatment or triggers during the examination that emergency physicians use when selecting to treat or not treat patients	Survey	145 emergency physicians
General STIs			
Bar-Zeev, 2014, Australia[123]	To assess adherence to antenatal guidelines by clinicians and identify factors affecting the quality of antenatal care delivery to remote dwelling Aboriginal women.	Retrospective cohort study, interview component	27 health providers

Appendix 15: Quality assessment of included studies- Patients' Perspectives and Experiences Review

First Author	Strengths	Weaknesses
Alvarez-del Arco, 2018[94]	Specifically describes characteristics of the research team, e.g.: experience and training & gender composition Ethics approval sought Theoretical framework underlying analysis In-depth description of the analysis process Includes implications for health providers and policy makers	Data saturation was discussed among researchers although resource limitations did not allow us for increasing the number of interviews
Bar-Zeev, 2014[123]	Recruitment continued until data saturation had been reached in the analysis. Qualitative and quantitative data sources were used to corroborate findings around the issue of the quality of care Ethics approval	Qualitative part of a mixed-methods study: no explanation of how the qualitative component adds to the quantitative part. Appears to be a single author analysis, under supervision of another author; no description of initial independent coding
Baxter, 2000[95]	Qualitative and questionnaire data obtained, to gain a wider perspective Ethics approval sought	Relatively small sample size (n=12), no mention that saturation was obtained Only one researcher analyzed most interviews (independent person checked and confirmed coding of one transcript) Researcher has not clearly justified the selection of research methodology based on her research objective.
Bilardi, 2010[89]	Two authors reviewed the transcripts separately before meeting to discuss codes and emergent and recurrent themes, with a third author reviewing 10% of the transcripts independently to confirm coding and themes Ethics approval sought High participation rate (100 women of 101 invited)	Interviews were relatively short (approximately 10 – 15 minutes) and lacked the depth of conventional qualitative interviews, as women were limited for time Relationship between researcher and participants has not been adequately discussed.
Blake, 2008[96]	Independent analysis by multiple researchers	Structured qualitative focus groups (collected as part of quality improvement project) Use of focus groups versus interviews for sensitive topic Not clear how many researchers participated in the analysis process.
Boyd, 1999[97]	Included comparison between	No mention of ethics approval or consent

	interviewees and refusers The transcripts were analyzed independently by two researchers to enhance the dependability of the analysis	
Bulman, 2013[99]	The researcher has clearly justified the research design Ethics approval sought Includes recommendations for practice and future research	Low response rate and relatively small sample, no mention that saturation was obtained (all those who were interested and eligible participated) (n=12)
Chambers, 2001[99]	Steps were taken to ensure rigour and trustworthiness, e.g., the questionnaire was reviewed by a nurse scholar	Descriptive questionnaire study, no qualitative analysis of open-ended questions Although a trustworthy survey, the research question would likely have been better addressed by a qualitative study
de Zulueta, 2007[100]	Compares demographic variables of refusers versus interviewees Theoretical framework underlying analysis	Use of interpreter for non-English speaking women, for sensitive and nuanced subject matter
DiOrio, 2018[121]	No particular strengths to note; study was deemed poor quality	Unclear interview data collection procedure Poor description of analytical procedure
Evans, 2016[101]	Systematic review Includes recommendations for practice and for research	Half of included studies were from developing countries excluded from the current synthesis
Fielder, 2005[102]	Focus group data used to clarify responses from longitudinal cohort study Inclusion of males with the rationale that a male partner may be involved in a woman's decision to access prenatal care and/or obtain an HIV test	Female focus groups conducted by single researcher Use of focus groups versus interviews for sensitive topic No mention of ethics approval or consent
Gahagan, 2011[103]	Ethics approval sought Representation from various populations and communities was sought (Aboriginal, African Nova Scotian, Caucasian and Immigrant populations, urban and rural participants) Combination of quantitative and qualitative data sources Clear description of the role of the qualitative component	Unclear how many individuals analyzed the data, and whether independently
Hack, 2009[93]	Questionnaire is likely to be valid and reliable	Questionnaire study, no qualitative analysis of open-ended questions
Jones, 2004[104]	No strengths to report	This was an audit; no qualitative analysis
Katz, 2001[105]	Ethics approval sought Mechanisms to ensure credibility (3 participants validated themes) and fittingness (discussing findings with health care professionals) Included comparison between interviewees and refusers	Unclear if analysis was independent
Kelly, 2001[106]	Ethics approval	Unclear if analysis was independent and/or done by multiple researchers
Kelly, 2012[108]	Theoretical framework underlying	Relatively small sample (4 case studies),

	analysis Rich case study analysis, e.g., repeat interview model used Ethics approval All members of the research team independently read and coded a selection of the original transcripts Clear explanation of the study's relevance to clinical practice	with no mention of data saturation or justification for a small sample size
Kelly, 2012b[107]	Three authors independently read and coded all interview transcripts Ethics approval sought	Non-testers not included Use of focus groups for sensitive topic (focus groups were constructed to oversample Hispanic and African American women due to the difficulty in recruiting, arranging for, and completing individual interviews with prenatal patients from these populations)
Kroeger, 2018[122]	Study includes both women and providers Ethics approval sought Entire team coded interviews Description of the relevance of the study findings in the context of the subsequent policy actions taken by the state to mitigate barriers in the pathways to CS prevention.	No weaknesses to note
Lee King, 2014[109]	Ethics approval sought Use of data-derived codes from one focus group applied systematically across focus group data Two interpreters reviewed the original interpretation for accuracy and completeness	Use of focus groups versus interviews for sensitive topic Use of interpreters Unclear if analysis was independent
Lingen-Stallard, 2016[110]	Ethics approval sought Nondirective and flexible approach to in-depth interviews allowing discussions to be participant-led, providing more relevance and depth. At the end of each interview, women were given contact details relevant to their interview (e.g. health professionals, counsellor support workers). Field notes were made during and following the interviews, and they included women's reactions such as laughter, crying, eye contact, facial expression and signs of discomfort. The researchers, all midwives, were integral to the analysis process, acknowledging their influence on the interpretation.	Relatively small sample (n=13), with no mention of data saturation or justification for a small sample size
Logan, 2005[90]	Ethics approval sought	Limited qualitative analysis (lack of description of data analysis)
Mawn, 1998[111]	Ethics approval sought Study included acknowledgment of the investigator's own experiences and assumptions about the phenomenon of study	No weakenesses to note

	Clear description of domain and theme development	
McAllister, 2013[112]	Three researchers conducted analysis, using cross-checking of coding strategies and seeking agreement of a coding scheme Ethics approval sought Inclusion of both pregnant persons and healthcare providers Thematic saturation among the small sample of women participants reached due to the relative homogeneity in feelings expressed	Relatively small sample of pregnant persons (n=7) compared to the number of included healthcare providers (n=30), however with justification as data saturation was obtained Interviews were relatively short (approximately 10 minutes) and lacked the depth of conventional qualitative interviews, to fit the schedules of women and providers
McLeish, 2016[113]	Paper includes researcher demographics (white, UK-born, women with children) and notes that they worked reflexively, sensitive to role as 'outsider' researcher Ethics approval Each researcher independently analyzed the transcript to ensure validity of the analysis Relatively small number of participants (n=12)(even though authors described reaching data saturation).	Unable to compare refusers and participants due to recruitment process
Meyerson, 2014[114]	NB: deemed exempt from ethics review	Qualitative data from questionnaire were "coded textually for emerging themes" but subsequently quantified, leading to an analysis with limited depth
Njie-Carr, 2012[115]	Theoretical framework underlying analysis Ethics approval sought Both qualitative and quantitative data sources were used Recruitment continued until data saturation (n=23) Interview guide was reviewed by a nurse scholar whose area of expertise is women, maternal and child health Four investigators independently conducted analysis Clear description of implication for midwifery practice	No weaknesses to report
Perkins, 2003[92]	Relatively long, in-depth interviews (approximately 1 – 1.5 hours) - in two waves of interviews, at the beginning and the end of the screening pilot Ethics approval sought Two researchers conducted initial coding independently Diverse sets of participants (13 general practitioners, 14 practice nurses, 15 practice receptionists and 11 practice managers) Includes implications for policy and practice	No weaknesses to report

Pimenta, 2003[91]	Qualitative and quantitative data sources were used Ethics approval sought	Very superficial description of the analysis ("The open coding method of content analysis was used to identify themes that related to the main study aims.")
Rothpletz-Puglia, 2012[116]	Ethics approval sought	Use of focus groups versus interviews for sensitive topic Analysis was conducted by only one investigator
Simpson, 2007,[117]	Ethics approval sought Includes implications for policy and practice Contrasts perspectives of those who tested positive and those who tested negative	Analysis was largely conducted by one investigator (second investigator reviewed categorization of themes)
Stevens, 1989[118]	Availability of "on-call AIDS psychologist" for participants demonstrating anxiety	Closed questionnaire, no qualitative analysis
Treisman, 2014[119]	Ethics approval sought	Relatively small sample (n=12), although authors note that it was a "purposive, carefully situated" sample Analysis was conducted largely by one investigator (with other 2 researchers conducting an independent audit process on transcripts)
Tripathi, 2013[120]	Ethics approval sought Transcript coding and initial analysis were done in the original language. Study includes both women and providers	No weaknesses to report
Williams, 1990[69]	Purposive sampling Field testing of interview guide and review by experts	Analysis conducted by a single investigator No mention of ethics approval or consent