Improving the Diagnosis and Linkage to Care of Chlamydia and Gonorrhea Infection in Prenatal Females in Edmonton, Alberta

by

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Abstract

Chlamydia and gonorrhea (CTNG) are sexually transmitted infections (STIs) that can lead to complications in males and females. If a pregnant individual is infected with CTNG, they risk passing the infection to their newborn through vertical transmission during delivery, which can lead to newborn pneumonia or ophthalmia neonatorum, potentially resulting in blindness. To prevent vertical transmission to the infant, in 2018, the Alberta government updated prenatal screening guidelines to include universal CTNG screening during the first trimester of pregnancy and an additional third-trimester screen for those at high risk for infection. This screening process depends on physicians' awareness of CTNG prenatal guidelines and knowledge of patients' lifestyles, which may not capture all females at risk for infection.

Additionally, antimicrobial susceptibility testing (AST) is routinely conducted on positive NG isolates throughout Alberta to determine strains with antimicrobial resistance (AMR). Up-to-date AST results are essential to ensure that the most effective treatment is available for strains present in the province.

This thesis investigates provincial AST results from 2016 to 2022, CTNG prenatal screening proportions from 2019 to 2022, and results from the establishment of a pilot “at delivery” universal screening program.

To develop an antibiogram of Alberta’s NG isolates, AST results were collected for six antimicrobials: penicillin, tetracycline, ciprofloxacin, azithromycin, cefixime, and ceftriaxone, between the years 2016 and 2022, along with individual demographic data. The lowest susceptibilities were observed in penicillin, followed by ciprofloxacin and tetracycline. As of 2022, susceptibility rates were 100% for ceftriaxone and cefixime, followed by azithromycin (99%), tetracycline (34%), ciprofloxacin (27%), and penicillin (7%). Higher frequencies of

strains non-susceptible to penicillin, ciprofloxacin, tetracycline, or azithromycin were found in individuals from higher income quintiles. The frequency of strains with azithromycin non-susceptibility was also higher in individuals from Edmonton health zones (51.90%, p=0.001).

To determine guideline adherence for first-trimester screening, a retrospective analysis of laboratory data from January 1, 2019, to December 31, 2022, was conducted. 85.7% of distinct pregnancies received a CTNG screen. Of those tested, 68.6% underwent screening in the first trimester, and 8.3% of those screened in the first trimester were additionally screened in the third trimester following high-risk screening protocols. When adjusting for confounders, females testing positive at least once during their pregnancy were more likely to be screened according to first-trimester protocols if they were from income quintiles Q3 (p=0.047), Q4 (p=0.27), or Q5 (p=0.003) compared to individuals from Q1, the lowest income quintile. Individuals from southern Alberta health zones were less likely to be screened in the first trimester (p=0.026) compared to those from northern Alberta health zones.

An “at delivery” CTNG screening program was established at the Royal Alexandra Hospital (RAH) in Edmonton, Alberta. Females delivering at the RAH were approached to participate in CTNG screening at delivery (17.7%), and 11.5% of females approached opted out of screening, with the majority citing the decision not to provide a sample as their primary reason for opting out (71.1%). In total, 15.7% of the target population provided a sample for testing, with 2.20% of results positive for a CT, NG, or CTNG infection. Results from this study were similar to proportions observed in the previous year from province-wide high-risk screening (14.2% screened following high-risk protocol and 2.40% positive).

In conclusion, this thesis develops a complete antibiogram for provincial NG isolates, describes factors associated with the likelihood of being screened following first-trimester

CTNG screening guidelines, and identifies barriers and perspectives on universally screening individuals at a later perinatal time point.

Preface

This thesis is an original work by Taylor Walsh. No part of this thesis has been previously published.

Dedication

To my beloved grandmother, who passed away on April 17th of this year.

Grandma, your unwavering support and enthusiasm for knowledge and healthcare have been a guiding light throughout my academic journey. As a nurse, you dedicated your life to caring for others and sharing your wisdom with us, your grandchildren. Your passion for learning and your endless encouragement inspired me to pursue my studies in the sciences and strive for excellence in all that I do.

Your comforting presence, prayers, and words of motivation have been my anchor during the most challenging times. Though you are not here with me now, I feel your spirit beside me, smiling down with pride and joy. This thesis is a testament to your influence and love, and I know you would have been the first to read it and celebrate this achievement with me.

Thank you, Grandma, for being my biggest supporter. This work is dedicated to you, with all my love and gratitude.

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Table of Contents

List of Tables

List of figures

List of Abbreviations

ABC	African Caribbean Black
AH	Alberta Health
AHS	Alberta Health Services
AMR	Antimicrobial resistance
AST	Antimicrobial susceptibility testing
CDC	Centers for Disease Control and Prevention
CDOM	Communicable Disease & Outbreak Management Database
CEACAM	Carcinoembryonic antigen-related cell adhesion molecules
China-GRSP	China Gonococcal Resistance Surveillance Program
CLSI	Clinical Laboratory and Standards Institute
CPS	Canadian Pediatric Society
CT	*Chlamydia trachomatis*
CTNG	*Chlamydia trachomatis* and *Neisseria gonorrhea*
DAD	Discharge abstract database
DGI	Disseminated gonococcal infection
EB	Elementary body: the infectious, non-dividing form of *Chlamydia trachomatis*
ESC	Extended spectrum cephalosporins
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
GASP	Gonococcal Antimicrobial Susceptibility Program
gbMSM	Gay or bisexual men who have sex with men

GLASS	Global antimicrobial surveillance system
HA	Hydrophobic agents/hydrophobic antimicrobials
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
LIS	Laboratory Information Systems
MIC	Minimum inhibitory concentration
NAAT	Nucleic acid amplification test
NG	*Neisseria gonorrhea*
NG-MAST	*Neisseria gonorrhea* multi-antigen sequence typing
NML	National Microbiology Laboratory
OOP	Out of province
Opa	Opacity proteins present on NG
PBP2	Penicillin binding protein 2
Perilink	AHS Perinatal metadata source
PHAC	Public Health Agency of Canada
PHN	Personal Health Number
PID	Pelvic inflammatory disease
POC	Point of care
PorB	Bacterial membrane protein porin B
ProvLab	Alberta Provincial Laboratory
QALY	Quality adjusted life-years
RAH	Royal Alexandra Hospital

RB	Reticulate body: the non-infectious, dividing form of *Chlamydia trachomatis*
ST	Sequence typing
STBBI	Sexually transmitted and blood borne infections
STI	Sexually transmitted infection
STICS	Sexually Transmitted Infection Centralized Services
T3SS	Type 3 secretion system
TFI	Tubal factor infertility
TOC	Test of cure
US	United States
WHO	World Health Organization

Chapter 1 Introduction

1.1 *Chlamydia trachomatis* overview

1.1.1 Epidemiology

Chlamydia trachomatis (CT) is an obligate intracellular cocci bacterium affecting eukaryotic cells causing the sexually transmitted infection (STI) chlamydia (1). The World Health Organization (WHO) estimated 129 million new chlamydia infections were diagnosed globally in 2020 (2). In 2021, 104,426 cases of chlamydia were reported across Canada, with 59% of infections occurring in females (3). The prairie provinces (Alberta, Saskatchewan, and Manitoba) and northern provinces/territories (Nunavut, Yukon, Northwest Territories) all reported CT cases above the national rate of 273.2 cases per 100,000 population in 2021 (3). In Alberta, 16,809 cases of chlamydia were identified in 2022, representing a 19% increase in total infections over the previous year (4). However, true infection rates tend to be underrepresented due to asymptomatic CT infections. Reports estimate up to 75% of CT infections in females and 50% of infections in males are asymptomatic (5,6).

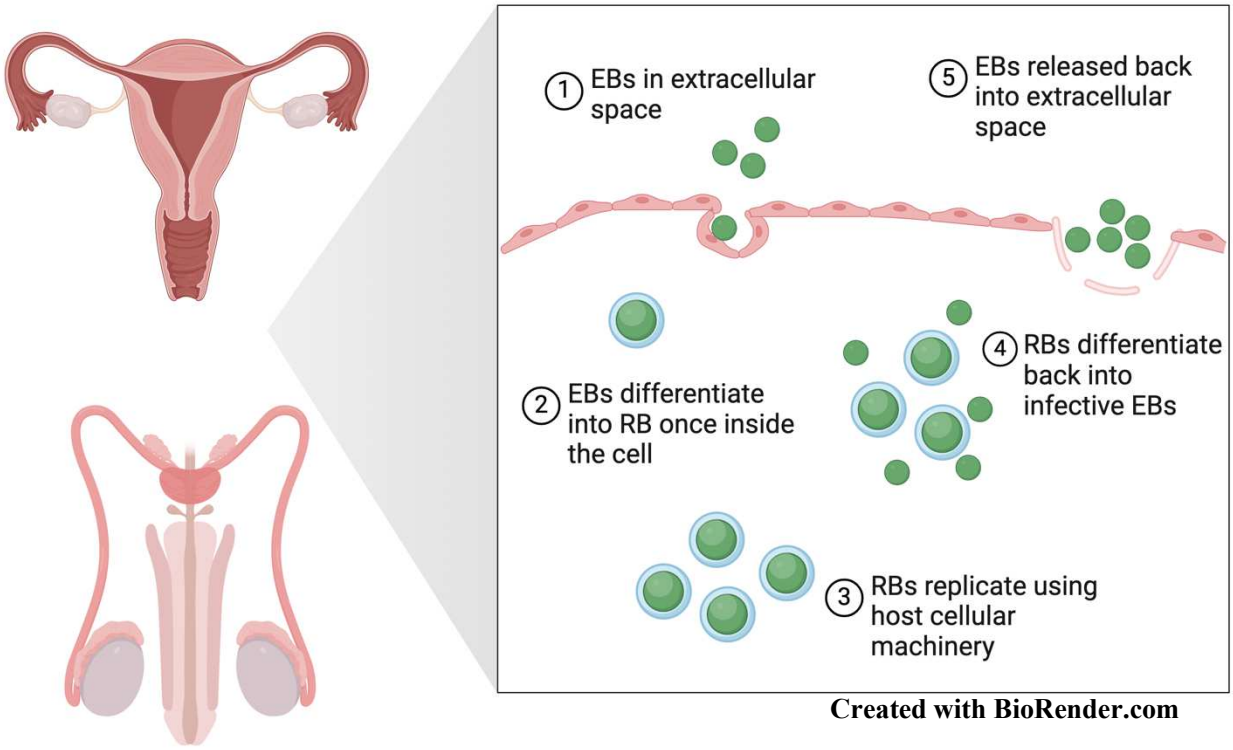
Risk factors associated with CT infection include: (1) less than 25 years of age, (2) multiple sexual partners, and (3) casual sexual contacts (5–10). Females are more at risk for infection with significantly higher prevalence rates compared to males from the same general population (11,12). Racial disparities are also strongly associated with CT infection. Individuals self-identifying as African Caribbean Black (ACB) ethnicity were twice as likely to screen positive for CT compared to other ethnic groups in a study conducted in England (13). In the US, individuals identifying as non-Hispanic blacks were seven times more likely to be diagnosed

with CT infection compared to those identifying as non-Hispanic white (14). In conclusion, the disparities of chlamydia infection can be observed globally.

1.1.2 Pathogenesis

There are at least 18 distinct CT serotypes identified, where specifically serovars B and D-K contribute to urinogenital infections in humans (9,15). The unique life cycle of CT shifts between two distinct forms once inside the host; the elementary body (EB) and the reticulate body (RB) (5). EBs are metabolically inactive but infectious, while RBs are metabolically active but non-infectious once inside host epithelial cells (5). EBs infect the extracellular space and contain proteins responsible for energy metabolism, transcription and translation (16). EBs manufacture and produce proteins responsible for the bacterial membrane type 3 secretion system (T3SS). T3SS are transmembrane proteins that translocate virulence effector proteins into the host cell by direct contact with cellular membranes (17). These proteins aid in bacterial entry into the host cell and ensure survival and successful replication. The specific localization of T3SS on the cell membrane may enhance the speed and efficiency of CT infection by concentrating the delivery of effector proteins through the T3SS channel (17). OmcA and OmcB are other membrane proteins that interact with the host extracellular matrix to ensure adhesion and endocytosis of the bacterium into the host cell (16). Once the EB is endocytosed into the host, it differentiates into a RB and commandeers host cellular machinery to ensure pathogen replication (5) (**Figure 1.1**).

Figure 1.1 *Chlamydia trachomatis* lifecycle in female and male epithelial cells



1.1.3 Clinical Manifestations

1.1.3.1 CT infection in males

CT infection is one of the leading causes for non-gonococcal urethritis in males, with symptoms of dysuria and whitish-grey urethral discharge after 7-21 days of bacterial incubation (5,8,9,18). Complications of infection can occur when the bacterium ascends to the upper urogenital tract. Epididymo-orchitis, marked by testicular pain and swelling, or Reiter's syndrome, marked by reactive arthritis commonly involving inflammation of lower extremities, can result, with epididymitis contributing to male infertility (5,8,9,18).

1.1.3.2 CT infection in females

CT infection of the cervix leads to cervicitis (5,6,8,9), which can cause vaginal discharge, dysuria, abdominal pain, and bleeding (5,8). Acute salpingitis, or inflammation of the fallopian tubes, is another consequence of infection in females (1,9). Complications, such as pelvic inflammatory disease (PID), can occur when cervical infection ascend into the upper genital tract (5,9,19). PID can result from chronic infection, reinfection, or untreated infection, with initial symptoms including chronic pelvic pain, fever, nausea, and chills (6). Studies in the UK found the progression of CT into PID to be estimated at 17.1% (20). Further, PID can lead to ectopic pregnancies and tubal factor infertility (TFI) (5,6,8). TFI incidence following a mild case of PID is 0.6%, which increases to 21.4% in severe PID cases (21). Each repeat episode of PID doubles the proportion of TFI development (21).

Additionally, when CT enters the upper genetical tract, the natural immune system recruits inflammatory leukocytes and cytokines to induce an inflammatory response (19). However, the natural inflammatory response contributes to tissue damage and eventual scarring, which leads to the hallmark of chlamydia-induced oviduct disease. Damaged ciliated cells in the fallopian tubes

are unable to transport a fertilized ovum to the uterus leading to ectopic pregnancies (15). Overall, up to two-thirds of reported TFI cases and one-third of ectopic pregnancies may be attributed to CT infection (8,22,23).

1.1.3.3 Transmission of CT between males and females

Females appear to be more susceptible to STIs than males as observed in the literature. Studies show between 3 to 8 times more STIs occur when transmission is from male-to-female compared to female-to-male (24,25). This is additionally true for CT, where transmission is more efficient from male to female than female to male (26).

1.1.3.4 CT infection in neonates

CT infection can be transmitted from a female to her neonate via vertical transmission during the birthing process (1,5). Conjunctivitis is the most prevalent outcome from neonatal CT infection followed by pneumonia (27,28). Conjunctivitis can develop 7 to 21 days after birth (5,9,26) causing erythema and edema of the eyelid and palpebral conjunctivae with conjunctival discharge (26). Inhalation of infected secretions can result in infant pneumonia (1,5), which is characterized by repetitive staccato cough, dyspnea, and low-grade fever (26).

CT infection during pregnancy is associated with premature rupture of membranes, preterm birth, low birth weight, and postpartum endometritis (15,29). One study found 42.2% of newborns with a CT infection were premature with an increased incidence of preterm births overall compared to CT negative babies (30). For CT positive females, 31-76% of neonates developed ophthalmia neonatorum (31)(32), and the risk of vertical transmission was positively correlated with the duration of labour (33). The majority of cases of vertical transmission occurs via vaginal delivery, however, transmission via cesarian section has also been reported (34).

1.1.4 Diagnosis of CT

1.1.4.1 Traditional centralized laboratory testing

Rapid detection of CT is essential for effective patient care. With technological advances in detection of CT infection, the gold standard for diagnosis has improved over time. Microscopy was the standard diagnostic technique used in the early 1900's; which was replaced with culture methods (15,35). Antibody detection followed by nucleic acid amplification tests (NAAT) were introduced in the early 1990's (35,36), and NAAT is currently the most sensitive test for CT detection, which is used routinely across Canada (9,37). Commonly deployed NAATs use urine or swabs to collect bodily fluid from the cervix, vagina, urethra, rectum, throat, or eyes (9,38) and the Public Health Agency of Canada (PHAC) does not recommend one source over another for diagnosis (37). CT NAAT diagnostic sensitivity was equivalent for urine and cervical or urethral swabs (39), however, vaginal swabs have improved sensitivity compared to urine (40,41). In Alberta, NAATs are resulted within 1-7 days from time of collection with a reported turnaround time of 72 hours to 7 days depending on laboratory site (38). For diagnosis of neonatal CT infection, NAAT is additionally performed from nasopharyngeal swabs (26,37).

CT is considered a reportable infection where positive results are shared with public health teams both provincially and federally (42). This can include the provincial STI services program, or the provincial/Zonal Communicable Disease team. This is done for surveillance purposes and partner notification groups to ensure proper treatment administration.

1.1.4.2 Point of care testing

Point of care testing (POC) is a highly valuable tool to provide timely results in non-laboratory settings and allows same day treatment. Currently in Canada, there are no approved POC tests for CT diagnosis, however, several are available with FDA approval. The binx health

io molecular POC test was compared to three commercially available NAATs (43). A diagnostic sensitivity and specificity of 96.1% and 99.1% for females and 92.5% and 99.3% for males was observed respectively. The molecular POC "GeneXpert" test used in a remote community had an overall CT concordance of 99.4% with centralized laboratory NAATs (44). Authors concluded this molecular single cartridge POC test could be effectively used in remote settings where traditional batched laboratory NAATs are not feasible. Finally, the molecular Visby Medical Sexual Health Test can deliver results in less than 30 minutes and does not require a desktop PCR device to run, unlike the other CT POC tests (45). This device had a diagnostic sensitivity of 97.6% and diagnostic specificity of 98.3% for CT, similar to other POC devices available; however, it had a superior time to result and ease of use (45). Mathematical models established POC testing is sufficient to overcome hurdles such as loss-to-follow up and lag time between care-seeking and treatment initiation (43). Overall, POC testing may be the future of CT diagnosis.

1.1.5 Treatment

Treatment guidelines as outlined by the WHO include the use of azithromycin or doxycycline for the treatment of uncomplicated CT infections with alternative therapies including tetracycline, erythromycin, or ofloxacin (46). In Alberta, preferred treatment for cervical, urethral, pharyngeal and conjunctival infection is azithromycin or alternatively, doxycycline; while infections in pregnant individuals front-line treatment is azithromycin or amoxicillin (47). Doxycycline is not recommended in pregnancy due to the risk it poses to infant bone and teeth development (48). Preferred treatment for rectal infection is doxycycline (47). Any infants born to individuals with untreated CT infection are to be closely monitored for symptoms; while conjunctival and nasopharyngeal secretions from symptomatic neonates are

tested before treatment is administered (49). Following therapy completion, rescreening of adolescents or adults is recommended after 6 months (47). A test of cure (TOC) is recommended 3-4 weeks after treatment completion when an individual is pregnant or pre-pubertal, when compliance is uncertain, or when a non-genital site is infected (47).

Literature has shown suboptimal rescreening proportions for those testing positive for CT. Screening for reinfection after treatment completion was determined in a college population to uncover compliance with retesting recommendations (50). In multivariate analysis, males with multiple sex partners were the least compliant in TOC testing following a positive CT result (50). Successful treatment is essential for CT elimination and prevention of transmission.

1.2 *Neisseria gonorrhea* overview

1.2.1 Epidemiology

Neisseria gonorrhoeae (NG) is a diplococcal, gram-negative bacterium targeting epithelial cells in human tissues and is the etiological factor of the second most commonly reported STI, gonorrhea (51). In 2020, there was an estimated 82 million cases of NG infection globally (2). Canada reported 32,192 cases of NG in 2021, reflecting a 4% increase from 2020 reports (3). In 2022, 4,984 cases of NG were reported in Alberta, representing a slight decrease from 2021 numbers (4). NG can cause asymptomatic infections, thus the true level of infection is likely underestimated (52). Most rectal and pharyngeal infections are asymptomatic and are commonly diagnosed in gay and bisexual males who have sex with males (gbMSM) (51). Asymptomatic rates were reported as high as 82% for rectal infections and 92% for pharyngeal infections from individuals identifying as gbMSM (53). High levels of asymptomatic infection is additionally

observed in females, with studies showing 47.9% of infections being asymptomatic compared to only 7% of urethral infections in heterosexual males (51,54,55).

gbMSM disproportionately account for the majority of NG cases (7), while reports reveal rates of NG infection 2 to 5 times higher in males than females (3,7). In Canada, diagnosed cases in males were highest amongst those 25-29 followed by those 30-39 years old, while cases in females were highest amongst those 20-24 followed by those 25-29 years old (3). Like CT, racial disparities are prevalent with NG infections. Those of African or Aboriginal ethnicity are disproportionately affected with high infection levels in studies conducted across North America (51,56,57).

1.2.2 NG Pathogenesis

NG primarily infects mucosal epithelial cells of the urogenital tract, rectum, pharynx, and conjunctiva (51,58). Several proteins are essential for the optimal colonization of NG. The type IV pilus is a membrane protein responsible for the initial adhesion to the host cell (59). The pilus attaches quickly to receptor sites of epithelial cells with saturation occurring within 20-60 minutes (59). Additionally, this protein provides NG with the ability to crawl along host cells and tissues and create biofilms via its twitching motility (60). Another group of membrane proteins essential for adherence are the opacity (Opa) protein family. After initial type IV pili contact, Opa proteins regulate bacterial adherence to the host cell (51,58). Opa proteins specifically target carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) which allow tight association between the bacteria and host cell membranes (61,62). These proteins are responsible for cellular invasion through actin filament reorganization of host cells (63,64). Once inside the host cell, the bacterial membrane porin (PorB), secretes outer membrane vesicles targeting host mitochondria, signaling a time-dependant cellular apoptosis event for the eventual

release of newly produced NG (65). Interestingly, both type IV pili and Opa proteins share the capability of phase and antigenic variation. Specifically, the genes which control the production of these proteins contain conserved and variable regions which allow changeability between each protein product or lack of product providing NG with an effective form of immune evasion, and rendering NG an effective pathogenic agent (66–68).

1.2.3 Clinical Manifestations

1.2.3.1 NG infection in males

Urethritis is the most common symptom of infection in males which is characterized by urethral discharge, dysuria, and urethral itch (51,52,69). Additionally, NG can infect the rectal or pharyngeal epithelial cells, while these infections are typically asymptomatic (53), symptoms can include rectal pain and discharge with proctitis (69). Untreated infection can progress from the urethra into the upper genital tract leading to epididymitis or epididymo-orchitis with infertility resulting in rare cases (52,69).

1.2.3.2 NG infection in females

In females, cervicitis is the most common sequelae of bacterial infection and can result in vaginal discharge, lower abdominal pain, dysuria, cervical discharge, bartholinitis, and deep dyspareunia, although many infections are asymptomatic (52,69). Rectal and pharyngeal infections are less commonly reported. Untreated or undiagnosed infections can progress from primary sites and result in more complicated sequelae such as PID leading to perihepatitis, ectopic pregnancies, or TFI. PID caused by NG is linked to more severe outcomes and hospitalizations compared PID caused by CT (70,71).

1.2.3.3 Disseminated gonococcal infection

When NG spreads from primary mucosal sites into the blood stream it can cause a disseminated gonococcal infection (DGI) (52,69). DGI results is a spectrum of conditions including arthritis, tenosynovitis, or more rarely, meningitis. It is believed DGI can occur in up to 3% of untreated individuals with mucosal NG infections (52). Children over 30 days are more likely to present with DGI than adults (69). In comparison, CT infection has the ability to extend from the genital tract through the lymph node into the gastrointestinal tract (72,73).

1.2.3.4 NG in neonates

NG can be vertically transmitted to neonates via vaginal delivery, most commonly resulting in ophthalmia neonatorum, however scalp abscesses can also occur (52,69). Signs of neonatal conjunctivitis can occur in neonates delivered via cesarian section (30). CT and NG both contribute to ophthalmia neonatorum, however gonococcal conjunctivitis is likely to be established sooner and result in more severe clinical outcomes (31,74).

1.2.4 Transmission rates

NG transmission occurs at different rates between infected males and females. Holmes *et al*., estimated the risk of uninfected males acquiring NG from infected females to be approximately 22% (75), while Lin *et al*., found a 73% transmission rate of NG from positive-male to uninfected female (76). Lipooligosaccharide found on the membrane of NG readily binds to receptors present on sperm cells, which may account for the higher rate of male-to-female transmission (77). Vertical transmission of NG causing conjunctivitis in neonates was reported in 33-42% of cases (31,32).

1.2.5 Coinfection of NG and CT

Unsurprisingly, NG and CT co-infection has been reported; however there is a greater likelihood of coinfection when an individual has symptomatic gonorrhea compared with an individual who has chlamydia (78,79). In a high-risk population in China, 65% of female sex workers with gonorrhea also had a CT infection, while only 42% of those with chlamydia had gonorrhea (80).

1.2.6 Diagnosis of NG

1.2.6.1 Traditional centralized laboratory testing

NG can be detected by Gram stain and microscopy, where is it identified as a Gram negative diplococci and can be useful for initial evaluation of infection (52,81). However, diagnosis through Gram staining does not have consistent sensitivity and/or specificity depending upon specimen source, which does not make it suitable as a first-line diagnostic tool. Culture is another method used in the detection of NG (51). It is lower cost compared to current NAATs (51), and allows for antimicrobial susceptibility testing (AST) to detect resistance (51,81). Nevertheless, NAATs are the most commonly used diagnostic tests due to their superior diagnostic sensitivity over other detection methods (51,52,81,82). Furthermore, NAATs can detect CT and NG simultaneously and do not require viable organisms for detection, allowing for less stringent preparation procedures (51,52,81). PHAC strongly recommends combined culture and NAAT testing when an infection is believed to be acquired in a country with high antimicrobial resistance (AMR), for test of cure, or suspected treatment failure (81) to allow for susceptibility testing. Combined testing is also recommended for symptomatic individuals, those with PID, or those who are pregnant.

When using NAAT for NG detection, specificity and sensitivity remains consistent between urine and cervical or urethral swabs, while vaginal swabs have higher sensitivity than urine specimens (39–41). PHAC recommends NAAT using first catch urine over urethral swabs for males and vaginal swabs over other sources for females for NG detection, though all specimen types can be used (81).

Being considered a reportable infection in Alberta, results of individuals testing positive are shared with the provincial STI services program or communicable disease team to ensure them and their partners are treated successfully (42).

1.2.6.2 Point of care testing

POC testing has superior turnaround time compared to traditional laboratory techniques by allowing for same-day diagnosis. Currently, no POC tests are approved by Health Canada, while FDA approval has been granted to the binx health *io* CTNG assay, the GeneXpert CT/ NG assay, and the Visby Medical Sexual Health Test (83). Studies have found the sensitivity and specificity of the binx health *io* platform in females to be 100% and 99.9%, respectively; and 97.3% and 100%, for males (43), while the GeneXpert CTNG assay shows 100% sensitivity and 99.9% specificity to NG infections (44), and the Visby Medical Sexual Health test showed a 97.4% sensitivity and 99.4% specificity for NG in self-collected vaginal specimens (45). Overall, these tests have been associated with substantial reduction in the number of infections and PID and can overcome hurdles of loss-to-follow-up and treatment lag time (43).

1.2.6.3 Antimicrobial Susceptibility Testing

There is currently no rapid molecular method for AST and culture remains the most effective tool (84). Due to the availability of rapid high-throughput automated diagnostic NAAT, laboratories are performing less culture testing, leading to the reduction of phenotypic AST data.

Future diagnostic tests produced should strive to include AST to maintain diligence against gonococcal antibiotic resistance (84).

1.2.4 Treatment

Current treatment for uncomplicated NG infection in cervical, urethral, and anorectal sites for males and females include a dual therapy regimen of oral cefixime or intramuscular ceftriaxone paired with oral azithromycin (47,52,85,86). This regimen should be administered the same day to ensure effective treatment (52). Local geographic and population antibiograms can additionally be used to assess best front-line treatment (85,86). Dual therapy is also recommended for pharyngeal infections, however, bacterial clearance is more difficult at this site (52,85,86), and for pregnant individuals (47,86). For neonate gonococcal conjunctivitis, monotherapy with ceftriaxone is recommended (47,87).

NAAT TOC is recommended 3-4 weeks after initial treatment for all positive sites and, where available, the use of culture is recommended 3-7 days after treatment (47,86). Additionally, a screen for reinfection is recommended at 6 months post-treatment due to high reinfection rates which has been found to be as high as 14.36% in one study (88).

Previous studies have shown that only 43% of individuals with a NG positive result were retested with an average time of rescreening at 2.7 months (89). Individuals who were male or part of indigenous ethnic groups were less likely received TOC compared to females and those with European ancestry (90). Furthermore, males with CTNG coinfection, individuals aged 15-19 years, or those from indigenous ethnic groups were more likely to screen positive for CT or NG upon retest. Concerningly, retesting disparities are identified in individuals who are at higher risk for reinfection.

1.3 Antimicrobial Resistance in NG

1.3.1 Mechanisms of Resistance

Decades of consistent use of antibiotics against NG infection has resulted in a rise of resistance where certain strains are no longer susceptible to treatment regimens (91). Numerous mechanisms of resistance have decreased the effectiveness of many antibiotic treatments. For example, efflux pumps, such as the Mtr system, are present within the NG membrane and have been shown to be essential for AMR (92–96). Hagman *et al*., showed inactivation of the *mtrC* gene resulted in gonococci which were hyper susceptible to hydrophobic agents (HAs), including hydrophobic antibiotics (92). Conversely, mutations in the *mtrR* gene resulting in overexpression of MtrC led to increased resistance to HAs, concluding the MtrR protein is a regulator for other Mtr components. This was confirmed with clinical isolates showing HA resistance with mutations in the *mtrR* gene. Golparian and others, determined the loss of the Mtr system, specifically, had the greatest impact on strains with AMR towards extended-spectrum cephalosporins (ESCs) and azithromycin, even rendering some back to a susceptible state (96). Overall, authors were able to reiterate the importance of efflux pump overexpression for successful AMR as seen in NG.

Other mechanisms responsible for AMR seen in NG strains include the *penB* gene responsible for encoding altered forms of porin B protein (97). Particularly, *penB* mutations in conjunction with overexpression of Mtr efflux proteins, result in a decreased permeability of NG contributing to AMR.

Penicillin binding protein 2 (PBP2) is a primary target for β-lactam antibiotics (98). *PenA* is responsible for coding PBP2 and studies have found there are 5 major mutations resulting in changes to the PBP2 protein, rendering phenotypic AMR as seen in NG strains resistant to

penicillin (99). Specifically, mutations in codon insertion and C-terminal substitutions led to penicillin resistance (100,101). The conformational state of PBP2 does not drastically change with the above mutations present, but the kinetics and thermal stability of the enzyme significantly changes resulting in the inhibition of β-lactam antibiotics (99).

ESCs, such as cefixime and ceftriaxone, are currently recommended to treat NG infections (85), however mutations can render a strain resistant to these antibiotics. Lindberg and others found NG strains isolated with resistance or decreased susceptibility to ESCs contained previously described mutations in the *penA* gene, *mtrR* gene, and/or *penB* genes (93). Similar results were found from a new mutation in the *penA* gene resulting in a strain with a high level of ceftriaxone resistance (95).

Molecular characterization was determined for 149 isolates collected at the Ontario Public Health Laboratory over one month to better understand the mechanisms underlying resistance phenotypes (94). Tetracycline resistance, penicillin nonsusceptibility, ESC reduced susceptibility, and erythromycin nonsusceptibility were all related to mutations in the *mtrR* gene. All ESC isolates with reduced susceptibility had PBP2 mosaic structures contributing to their phenotype. Mutations present in *gyrA* and *parC* contributed to isolates with ciprofloxacin resistance.

In conclusion, there are numerous molecular mechanisms behind AMR. NG has an overwhelming ability to adapt, and continues to do so, as antimicrobial use is currently the only line of defence (91).

1.3.2 Gonococcal Antimicrobial Surveillance Programme

In 1992, the WHO established the Gonococcal Antimicrobial Surveillance Programme (GASP) where, as of 2018, 68 countries, including Canada, monitor and collate data on patterns

of AST (102). Objectives of the program include sentinel surveillance of AMR to inform treatment guidelines, effective clinical management of infected patients and their partners, and to establish a strategy for the rapid detection of infections following treatment failure to cefixime or ceftriaxone. Unemo and others compared the 2017-2018 WHO GASP and Global antimicrobial surveillance system (GLASS) data and the 2015-2016 data (103). 73 countries provided AST data for one or more antibiotic in 2017-2018 compared to 67 from 2015-2016. Resistance or decreased susceptibility to ceftriaxone (68 reporting countries) and cefixime (51 reporting countries), increased over previous years from 24% to 31% and 45% to 47%, respectively. Azithromycin resistance, likewise, increased to 84% (51 of 61 reporting countries) from 81% in 2015-2016. Of countries reporting findings for ciprofloxacin (70 reporting countries), 100% reported resistance. Overall, these findings are disconcerting as NG strains with decreased susceptibility and increasing resistance to first-line treatments are becoming more prevalent.

NG antimicrobial susceptibility trends in Canada were analyzed in 2021 from 3,439 isolates (104). Results from this population may skew national susceptibility trends a due to the inability for NAATs to perform susceptibility testing and that specimens receiving AST are from individuals more at risk for resistant strains. However, it is beneficial to be aware of resistant strains present in the country to be vigilant against AMR. 72.7% of isolates had resistance to at least one antibiotic, not including cases detected by NAAT where no AST takes place. 2,006 cultures were sent to the National Microbiology Laboratory (NML) in Manitoba for AST and an additional 903 provincial AST outcomes were submitted to NML. Most isolates came from males. Findings reflected increased susceptibility for cefixime compared to 2020, but a significant decrease compared to 2017 outcomes (1.5% vs. 2.8% and 1.5% vs. 0.6%, respectively). The Clinical Laboratory and Standards Institute (CLSI) is used in Canada for

minimum inhibitory concentration (MIC) breakpoint definitions and laboratory standards for performing AST. When using the CLSI definition for azithromycin resistance, at an MIC of 2μg/mL, a significant decrease of resistant strains was observed in 2017. However, when the MIC breakpoint was analyzed at 1μg/mL, which is the breakpoint in other countries and the epidemiological cut-off value from the European Committee on Antimicrobial Susceptibility Testing (EUCAST), there was a significant increase in resistant strains. Overall, these findings are concerning as current first-line treatments are showing decreased susceptibilities and increased resistance.

1.3.3 Rapid Diagnostics for NG AMR

Samples that are culture positive for NG are reflexed to AST regardless of specimen source (105). Quantitative MIC-based methods are the gold standard for AST, which follow specific validation and implementation of standardized methods outlined in the EUCAST or the CLSI (103). However, as NAATs continue to replace culture as the main diagnostic tool, high throughput and fast AST diagnostics need to become readily available to keep up with testing rates. A real time PCR-assay allowing for direct detection of ciprofloxacin susceptibility from residual NAAT samples was tested and found to have 95.8% sensitivity and 100% specificity compared to traditional AST detection (106). Another high-resolution PCR melting assay had 95% sensitivity and 96% specificity for diagnosis of NG with additional AST for cefixime (42.52% and 96.29%), ceftriaxone (79.10% and 99.3%), and azithromycin (31.34% and 99.52%) (107). Overall, these molecular AST diagnostic tools show promise for the detection of resistant strains using non-culture methods which allows for faster and higher throughput results. Though none are currently available for commercial use, the development of a rapid tool for AMR detection remains essential in the race against NG resistance.

1.3.4 Novel Treatment for Resistant NG Strains

In 2018, a patient with a positive NG infection had a recorded treatment failure using recommended combination therapy ceftriaxone and azithromycin (85,108). Due to the rise of AMR seen in many NG strains, it is imperative to identify novel treatments to cure infections against resistant strains. Pre-clinical trials have been conducted on some alternative treatment options. One such prospect includes solithromycin, a treatment with considerably lower MIC levels than azithromycin and high activity against strains with ESC resistance (109). Another option could be spiropyrimidinetrione AZD0914, a DNA gyrase inhibitor with lower MIC levels compared to other antimicrobials currently in use and effective against ciprofloxacin resistant strains (110). Further studies would have to be conducted for these novel treatments, including pharmacokinetics and pharmacodynamics, before potential clinical trials can occur.

1.4 Prenatal Screening of CTNG

1.4.1 Screening Recommendations

To prevent ophthalmia neonatorum from CT or NG infection, the Canadian Paediatric Society recommends prenatal screening as a more effective preventative measure than ocular prophylaxis (87). Following this line of thinking, PHAC recommendations state all pregnant females should be screened in their first antenatal visit, ideally in the first trimester (111). In March 2023, an additional screen for all individuals in their third trimester was added to the recommendations. Since 2018, prenatal screening guidelines in Alberta recommend a universal first trimester screen for CTNG (49), with a third trimester screen for high-risk individuals. This includes those who (1) are under 25 years of age, (2) have a history of a sexually transmitted and blood borne infection (STBBI), (3) have a new sexual partner or more than 2 sexual partners in

the last year, and (4) belong to a vulnerable population (persons who inject drugs or other substances, sex workers and their clients, unstably housed) (18,47,69).

1.4.2 Screening in Practice

Despite recommended screening guidelines, not all high-risk groups may be tested for CTNG. For example, since 2012 the Centers for Disease Control and Prevention (CDC) recommends all females are screened for CT at their first prenatal visit, however only 37% of individuals were screened during the recommended time period (112). Unfortunately, this finding is not uncommon. In two separate studies analyzing CTNG screening adherence in Toronto and Montréal, respectively, authors found 15.3% and 16.5% of females did not receive a screen during their pregnancy (113,114). Overall engagement in the communicable disease screening program in Alberta (which uses a blood sample to screen for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis and immunity to rubella and varicella) is estimated to be over 95% of all pregnancies (115), however, as a separate sample is required for CTNG testing (urine or swab) and the testing is not done through a centralized provincial program (as is the infectious disease blood testing), the number of females participating in CTNG testing in Alberta is currently unknown (115). Although not every country has CTNG screening recommendations in place (116), when individuals were asked to participate in CTNG screening, uptake rates ranged between 85-99% for females in 6 different low-to-middle income countries (117). This implies most females are willing to be screened for these infections, even when a universal protocol is not in place.

1.4.2.1 Factors Influencing Screening Adherence

Whether an individual is screened as per guidelines can be influenced by numerous factors. A study investigating screening compliance for syphilis in Alberta identified individuals who

were least likely to be screened at recommended timepoints as those who were unmarried, had midwifery care, lived in non-metropolitan areas, and were from lower income quintiles (118). In a Toronto study, CTNG testing rates were found to be highest among females who used midwives, followed by those who used family practitioners (113). Two separate studies conducted in the United States (US) found CTNG and STI screening was more likely to occur in individuals younger than 25 years old or identifying as African American (112,119). This is directly opposed to recent findings in Alberta, where CTNG screening was less likely to occur in those younger than 25 years, followed by those older than 35 (120). Finally, multivariate analysis showed low parity was significantly associated with higher screening rates in a Montréal birthing and tertiary care center (114). Altogether, screening trends are distinct and programs in place should be developed to reflect local high-risk individuals.

1.4.2.2 Factors Influencing Positive CTNG Screening in Pregnancy

There are significant factors associated with the likelihood of testing positive for CT or NG during pregnancy. Individuals younger than 25 have an increased likelihood of screening positive (112,114,119,120). Current or previous infection with an STI was found to be associated with increased likelihood of positive CTNG infection (121–123). And the later the initiation of prenatal care significantly increased the likelihood of a positive CT or NG infection in pregnancy in a large scale US study (123).

1.4.3 Rationale for Universal Third Trimester Screening

In 2023, PHAC updated prenatal CTNG screening recommendations to include an additional universal screen in the third trimester (111). A hospital site in Toronto adopted third trimester universal screening for females 36 gestational weeks or later (124). Despite universal screening policy, only 69.7% of females were screened for CTNG. 7 results were positive; 3 were from

individuals presenting late to prenatal care (over 28 gestational weeks) and 3 were from individuals who previously screened negative (124). In a hospital in Montréal, 11.4% of individuals younger than 25 initially testing negative were positive when screened later on in pregnancy (114). Overall, these studies emphasize a singular universal screen in the first trimester may not be sufficient to capture all cases of those who initially test negative, or for those who participate in prenatal care at a later timepoint in their pregnancy.

1.4.4 Cost Effectiveness of Screening

To determine if targeted prenatal screening approaches would be effective compared to universal approaches, Ong *et al*., determined if the CT prevalence was greater than 5% in a population, the quality of life gained from universal screening would outweigh use of targeted screening (125). Similarly, while Ditkowsky and others found increased cost with a universal screening system, there was a significant reduction in morbidity to mother-infant pairs (126). These studies emphasize universal screening measures are most effective in reducing morbidity and improving quality of life while remaining cost-effective in cases where population infection rates continue to increase.

1.5 Rationale and Goals of the Study

1.5.1 Background

Chlamydia and gonorrhea are sexually transmitted infections; in Alberta in 2022, there were 16,809 reported cases of chlamydia and 4,984 cases of gonorrhea (4). However, these values are likely an underrepresentation of true infection rates due to their predominantly asymptomatic presentation (9,52). Concerningly, NG has developed resistance to first-line antibiotic treatments,

yet there are no updated antibiograms for the province of Alberta (91). In 2018, the Alberta government updated the prenatal guidelines to include universal CTNG screening for the first trimester of pregnancy and risk-based screening in the third trimester (4). However, risk-based screening relies on physician knowledge of patient lifestyle and may not capture all females at risk for CTNG infection.

1.5.2 Project Aims

This research seeks to:

(1) Update the AST antibiogram for *Neisseria gonorrhoeae* in the province of Alberta between 2016 and 2022 (**Chapter 2)**

(2) Understand the proportion of universal first trimester CTNG screening performed in the province of Alberta **(Chapter 3)**

(3) Perform a pilot universal "at delivery" CTNG screening program at a single hospital site in Edmonton **(Chapter 4)**

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Chapter 2 *Neisseria gonorrhoeae* antimicrobial resistance in Alberta from 2016-2022

2.1 Introduction

NG causes infections by targeting the mucus membranes in the genitals, rectum, throat, and eyes in both males and females (1). Factors that contribute to whether an individual is high risk for NG infection, include a higher number of lifetime sexual partners, higher instances of casual sex, and decreased educational levels (2). Additionally, unprotected sex, being younger than 25, history of previous STBBIs, and exchanging sex for money or drugs all contribute to increased risk of acquiring gonorrhea (3).

In 1943, penicillin was employed as the first-line treatment for NG infection and maintained decades long treatment success. However, by 1967, the proportion of strains showing decreased susceptibility or resistance to penicillin was increasing (4). Similarly, tetracycline was used to treat NG infection starting in the 1940's in those allergic to penicillin, with high proportions of resistance seen by 1985 (5). These high proportions of resistance to both penicillin and tetracycline spurred the Centers for Disease Control and Prevention (CDC) to remove both as routine treatment options by 1989 (6,7). Ciprofloxacin was introduced as a treatment option in the mid-1980s, but by the 1990's, strains with reduced susceptibility and resistance were detected, and continued to rise (5,8). By 2007, ciprofloxacin was no longer recommended as an empiric treatment option for gonorrhea (6).

The current treatment recommendation for NG in Canada (established in 2013), is combination therapy using cefixime and azithromycin or ceftriaxone and azithromycin (9–11). Unfortunately, treatment failures with both ceftriaxone and cefixime have been reported (12). Japan reported the first treatment failure with cefixime in 1999 (13), and the United Kingdom

(12) reported the first dual therapy treatment failure with ceftriaxone and azithromycin in a pharyngeal infection in 2016. In 2018, Alberta reported a treatment failure in NG urethritis treated with ceftriaxone and azithromycin (14). Researchers determined this NG strain contained the same genetic alterations as a strain first identified in Japan in 2015 (15). The current AMR trends are concerning, and decreased susceptibility may outpace available treatment regimens.

The WHO established the GASP to "monitor AMR trends, identify emerging AMR, and inform refinements of global, international and national clinical management guidelines and public health policies" in collaboration with participating countries (16). 67 countries are actively reporting to the GASP, including Canada.

Gonococcal surveillance provides demographics, genotyping, and AMR findings of NG isolates cultured throughout the provinces and territories of Canada. A total of 3,439 cultures were tested for AMR in laboratories across the country in 2021 (17). A significant increase in NG resistance to cefixime (1.5%) compared to 2017 findings (0.6%) was reported, while no significant changes were observed in the resistance of ceftriaxone with only one isolate resistant. Azithromycin resistance decreased (7.6%) compared to 2017 findings (11.7%); although, there was a significant increase in the number of isolates with higher minimum inhibitory concentrations (MIC) than previous years.

AMR surveillance was established in Alberta in 2001 (18). Results from 2012-2016 reflect the most completed findings for the province. 2,888 NG culture positive isolates underwent AST during this period. All isolates were susceptible to ceftriaxone; in 2014, 4 isolates had decreased susceptibility to cefixime with all isolates susceptible in subsequent years. Resistance to azithromycin ranged between 0.4% to 1.8% with no distinct trends over time observed.

The aim of chapter 2 is to determine the NG AST results for the province of Alberta from 2016 to 2022. Additionally, demographics will be examined to better understand NG AMR trends in Alberta's population. This will be accomplished by analyzing provincial datasets and interpreting findings.

2.2 Methods

2.2.1 NG Testing in Alberta

Alberta Health Services (AHS) and Alberta Health (AH) recommend gonorrhea testing for symptomatic, high-risk, and pregnant individuals, and recommend retesting after treatment completion (19). Testing every 3 to 6 months is recommended for those with a new sex partner, more than one partner, or anonymous sex partner(s). Individuals can receive testing at any STI clinic across the province or be referred for testing by a medical professional. Primary diagnostic testing is completed using NAAT on urine or swabbed specimens from the vagina, cervix, urethra, rectum, pharynx, or eyes (20). AH recommends culture and AST in addition to NAATs, when treatment failure occurs, or when a sexual contact was from an area with high AMR prevalence. E-tests are used for susceptibility testing for azithromycin, cefixime, ceftriaxone, ciprofloxacin, penicillin, and tetracycline.

2.2.2 Creation of the Susceptibility Dataset

AST results on culture positive isolates from ProvLab during 2016-2022 were extracted from Millennium and Beaker databases. Results were retrospectively analyzed by year based on date of sample collection. MICs were defined as susceptible, intermediate, or resistant based on the CLSI M100 guideline (21). The following interpretive criteria were used: penicillin: susceptible at ≤ 0.064 μg/mL, intermediate between 0.094-1 μg/mL, and resistant at ≥ 1.5

μg/mL; ceftriaxone and cefixime: susceptible at ≤ 0.25 μg/mL; tetracycline: susceptible at ≤ 0.25 μg/mL, intermediate at 0.38-1 μg/mL, and resistant at ≥ 1.5 μg/mL; ciprofloxacin: susceptible at ≤ 0.064 μg/mL, intermediate at 0.094-0.5 μg/mL, and resistant at ≥ 0.75 μg/mL; and azithromycin: susceptible at ≤ 1.5 μg/mL.

Age at time of collection was used to group individuals into age categories at 10-year increments as follows: 10-20, 21-30, 31-40, 41-50, 51-60, 61-70, and >70 years. Health zones based on patient region, were divided into Calgary, Central, Edmonton, North, and South zones. 2021 Alberta census estimates provided income quintile and geographic region (rural, urban, or metropolitan) variables using postal codes matched to the AST dataset.

2.2.3 Evaluating Susceptibilities

Six antibiotics were assessed for AMR. Duplicates were removed for individuals with more than one isolate submitted on the same day, under the assumption NG strains were the same regardless of sample source. Susceptibility was determined by dividing the number of susceptible isolates over the total number of isolates tested. Susceptibility was calculated by year for penicillin, tetracycline, ciprofloxacin, azithromycin, cefixime, and ceftriaxone.

Females of childbearing age as defined by the Alberta government are those 15 to 49 years old (22). To assess susceptibility results for this cohort, males were removed from the dataset along with females below 15 years or over 49 years. Duplicates were removed for individuals with more than one isolate submitted on the same day. Susceptibilities were calculated as above.

2.2.4 Data Analysis

Data was compiled and analyzed using STATA v.17 (StataCorp, College Station, Texas); tables were produced using Microsoft PowerPoint (Microsoft Corporation, Redmond, Washington), and figures were produced using Microsoft Excel (Microsoft Corporation, Redmond, Washington). Demographics for patients with NG antibiotic susceptibility were analyzed. Geographic region (rural, urban, or metropolitan) and income quintiles were determined using postal code data from the 2021 Alberta census estimates. If an individual had more than one culture positive isolate per year, only the most recent result was used. *p-values* were calculated using Chi^2 or Fisher's Exact tests for small cell counts (< 5) with significant values reflected as $\alpha \leq 0.05$.

2.2.5 Ethical Statement

Ethics was approved by the University of Alberta Research Ethics Board Pro00130642.

2.3 Results

2.3.1 Alberta susceptibility results

After removal of duplicates submitted on the same day, a total of 4,056 NG isolates collected in Alberta underwent AST between 2016 and 2022. Penicillin susceptibility was the lowest of all antibiotics for all years analyzed, followed by tetracycline, then ciprofloxacin, until 2021 when ciprofloxacin susceptibility dropped lower than tetracycline (**Fig. 2.3.1**). All isolates were susceptible to ceftriaxone and cefixime, except for one isolate in 2018 which showed resistance to both (840/841). Azithromycin susceptibility remained relatively stable with the lowest susceptibility observed in 2018 at 88% (745/842). Since 2022, 100% of all isolates (391)

were susceptible to ceftriaxone and cefixime, 99% (386) to azithromycin, 34% (131) to tetracycline, 27% (106) to ciprofloxacin, and 7% (27) to penicillin.

3,617 unique individuals had culture positive NG isolates during the study period. Higher frequencies of non-susceptible NG strains were observed in males for all antimicrobials except tetracycline, where females had higher frequencies of non-susceptible tetracycline strains (18.77% vs. 17.50%). (**Table 2.3.1A/B**). Patient sex had a significant association with penicillin and azithromycin susceptibility ($p=0.006$ & $p=0.001$, respectively). Across all antimicrobials, higher frequencies of non-susceptibility were seen in those from higher income quintiles; Q3, Q4, or Q5. Penicillin and azithromycin susceptibility were significantly associated with health zone, where higher frequencies of non-susceptible penicillin and azithromycin strains were seen in Calgary and Edmonton ($p<0.001$ & $p=0.001$ respectively). The one isolate showing resistance to cefixime and ceftriaxone came from a 36 year-old male residing in the Calgary region with travel history to a country with higher rates of cefixime and ceftriaxone AMR (data not shown) (14).

Figure 2.3.1 NG susceptibility by year in culture positive isolates from Alberta between 2016 and 2022.

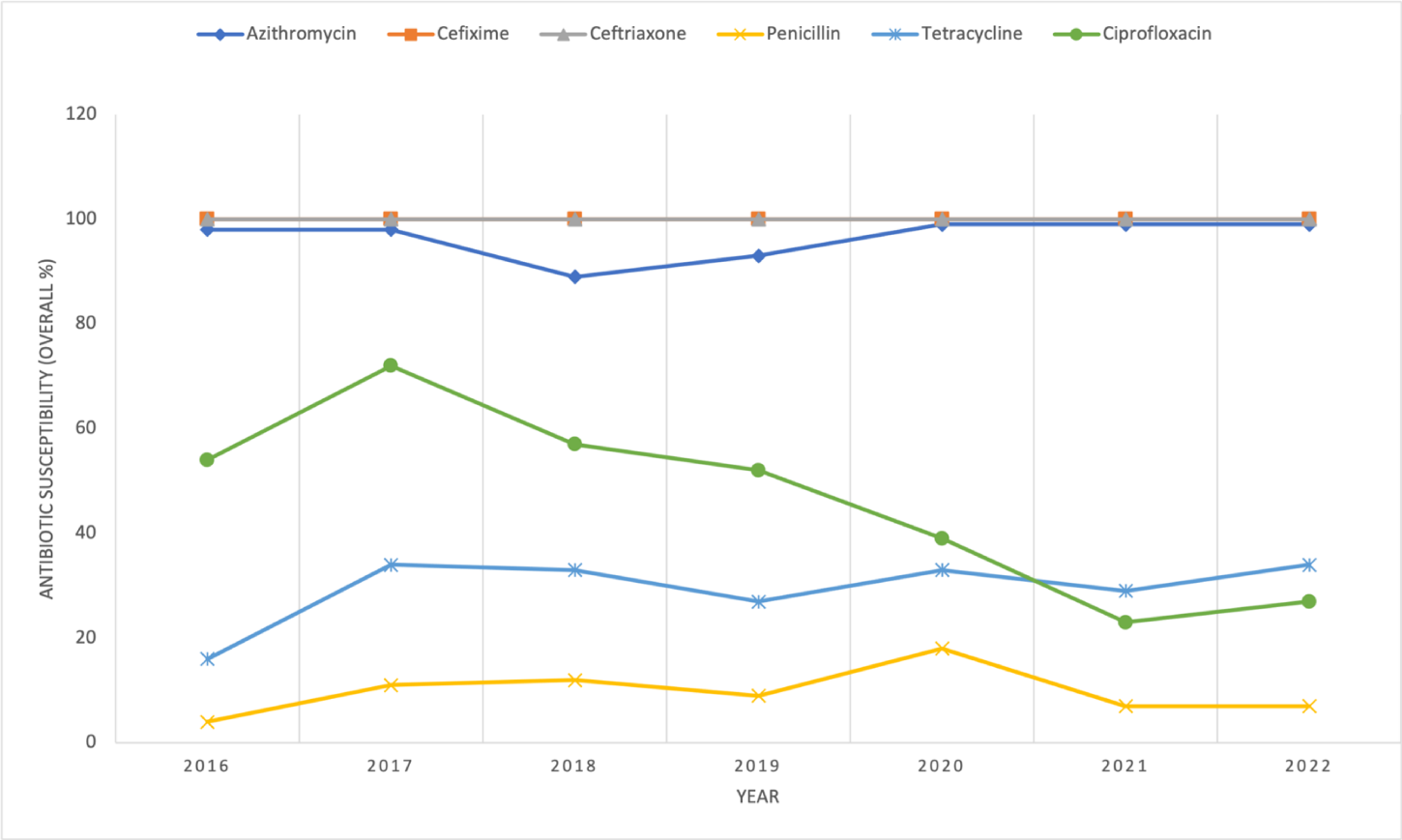

Figure 2.3.1 Legend. Susceptibilities calculated for antibiotics each year by dividing the number of susceptible isolates by the total number of isolates tested.

Table 2.3.1 A: Patient demographics of gonorrhea cases and corresponding AST with penicillin and tetracycline in Alberta from 2016-2022.

	Penicillin (n= 3,594)				*Tetracycline (n=3,592)*		
	Susceptible n (%)	**Non-Susceptible n (%)**	**p-value***		**Susceptible n (%)**	**Non-Susceptible n (%)**	**p-value***
Patient Age (years) (n=3,592)			0.202	**Patient Age (years) (n=3,590)**			0.221
[a]10-20 (n=252)	36 (10.68)	216 (6.64)		*[a]10-20 (n=251)*	76 (7.15)	175 (6.93)	
21-30 (n=1,520)	139 (41.25)	1,381 (42.43)		*21-30 (n=1,521)*	421 (39.60)	1,100 (43.53)	
31-40 (n=1,184)	112 (33.23)	1,072 (32.93)		*31-40 (n=1,183)*	368 (34.62)	815 (32.25)	
41-50 (n=399)	33 (9.79)	366 (11.24)		*41-50 (n=399)*	124 (11.67)	275 (10.88)	
51-60 (n=191)	15 (4.45)	176 (5.41)		*51-60 (n=191)*	65 (6.11)	126 (4.99)	
61-70 (n=40)	2 (0.59)	38 (1.17)		*61-70 (n=40)*	8 (0.75)	32 (1.27)	
[b]>70 (n=6)	0 (0)	6 (0.18)		*[c]>70 (n=5)*	1 (0.09)	4 (0.16)	
Patient Gender (n=3,590)			0.006*	**Patient Gender (n=3,588)**			0.368
Male (n=2,928)	257 (76.04)	2,671 (82.13)		*Male (n=2,928)*	877 (82.50)	2,051 (81.23)	
Female (n=662)	81 (23.96)	581 (17.87)		*Female (n=660)*	186 (17.50)	474 (18.77)	

Health Zone (n=3,562)			<0.001*	***Health Zone (n=3,561)***			0.092
Calgary (n=2,039)	146 (43.58)	1,893 (58.66)		*Calgary (n=2,037)*	575 (54.55)	1,462 (58.32)	
Central (n=59)	8 (2.39)	51 (1.58)		*Central (n=59)*	12 (1.14)	47 (1.87)	
Edmonton (n=1,330)	159 (47.46)	1,171 (36.29)		*Edmonton (n=1,331)*	423 (40.13)	908 (36.22)	
North (n=113)	20 (5.97)	93 (2.88)		*North (n=113)*	37 (3.51)	76 (3.03)	
South (n=21)	2 (0.60)	19 (0.59)		*South (n=21)*	7 (0.66)	14 (0.56)	
Geographic Region (n=1,653)			0.085	***Geographic Region (n=1,653)***			0.796
Metro (n=1,478)	144 (85.21)	1,334 (89.89)		*Metro (n=1,478)*	466 (90.14)	1,012 (89.08)	
Urban (n=50)	5 (2.96)	45 (3.03)		*Urban (n=50)*	14 (2.71)	36 (3.17)	
Rural (n=125)	20 (11.83)	105 (7.08)		*Rural (n=125)*	37 (7.16)	88 (7.75)	
Income Quintile (n=1,653)			0.303	***Income Quintile (n=1,653)***			0.953
Q1 (lowest) (n=438)	48 (28.40)	390 (26.28)		*Q1 (lowest) (n=438)*	137 (26.50)	301 (26.50)	
Q2 (n=300)	38 (22.49)	262 (17.65)		*Q2 (n=300)*	98 (18.96)	202 (17.78)	
Q3 (n=300)	25 (14.79)	275 (18.53)		*Q3 (n=300)*	95 (18.38)	205 (18.05)	
Q4 (n=288)	31 (18.34)	257 (17.32)		*Q4 (n=288)*	90 (17.41)	198 (17.43)	
Q5 (highest) (n=327)	27 (15.98)	300 (29.22)		*Q5 (highest) (n=327)*	97 (18.76)	230 (20.25)	

n: sample size, %: column frequencies
*: p<0.05 is significant. Chi2 or Fisher's exact tests used on small cell counts
a: 5 individuals < 15 years old
b: 6 individuals > 70 years old
c: 5 individuals > 70 years old

Table 2.3.1 B: Patient demographics of gonorrhea cases and corresponding AST with ciprofloxacin and azithromycin in Alberta from 2016-2022.

	Ciprofloxacin (n= 3,593)				*Azithromycin (n=3,591)*		
	Susceptible n (%)	**Non-Susceptible n (%)**	**p-value***		**Susceptible n (%)**	**Non-Susceptible n (%)**	**p-value***
Patient Age (years) (n=3,591)			<0.001*	**Patient Age (years) (n=3,589)**			0.374
[a]10-20 (n=252)	156 (8.35)	96 (5.57)		*[a]10-20 (n=251)*	239 (6.97)	12 (7.59)	
21-30 (n=1,521)	833 (44.59)	688 (39.93)		*21-30 (n=1,520)*	1,463 (42.64)	57 (36.08)	
31-40 (n=1,183)	588 (31.48)	595 (34.53)		*31-40 (n=1,183)*	1,126 (32.82)	57 (36.08)	
41-50 (n=399)	186 (9.96)	213 (12.36)		*41-50 (n=399)*	382 (11.13)	17 (10.76)	
51-60 (n=191)	91 (4.87)	100 (5.80)		*51-60 (n=191)*	177 (5.16)	14 (8.86)	
61-70 (n=40)	14 (0.75)	26 (1.51)		*61-70 (n=40)*	39 (1.14)	1 (0.63)	
[b]>70 (n=5)	0 (0)	5 (0.29)		*[b]>70 (n=5)*	5 (0.15)	0 (0)	
Patient Gender (n=3,589)			<0.001*	**Patient Gender (n=3,587)**			0.001*
Male (n=2,928)	1,426 (76.38)	1,502 (87.22)		*Male (n=2,928)*	2,783 (81.16)	145 (91.77)	
Female (n=661)	441 (23.62)	220 (12.78)		*Female (n=659)*	646 (18.84)	13 (8.23)	

Health Zone (n=3,562)			<0.001*	***Health Zone (n=3,560)***			0.001*
Calgary (n=2,037)	885 (47.73)	1,152 (67.45)		*Calgary (n=2,037)*	1,968 (57.85)	69 (43.67)	
Central (n=59)	33 (1.78)	26 (1.52)		*Central (n=59)*	54 (1.59)	5 (3.16)	
Edmonton (n=1,332)	845 (45.58)	487 (28.51)		*Edmonton (n=1,331)*	1,249 (36.71)	82 (51.90)	
North (n=113)	81 (4.37)	32 (1.87)		*North (n=112)*	110 (3.23)	2 (1.27)	
South (n=21)	10 (0.54)	11 (0.64)		*South (n=21)*	21 (0.62)	0 (0)	
Geographic Region (n=1,654)			<0.001*	***Geographic Region (n=1,652)***			0.652
Metro (n=1,479)	705 (86.50)	774 (92.25)		*Metro (n=1,478)*	1,413 (89.32)	65 (92.86)	
Urban (n=50)	36 (4.42)	14 (1.67)		*Urban (n=49)*	47 (2.97)	2 (2.86)	
Rural (n=125)	74 (9.08)	51 (6.08)		*Rural (n=125)*	122 (7.71)	3 (4.29)	
Income Quintile (n=1,654)			0.002*	***Income Quintile (n=1,652)***			0.133
Q1 (lowest) (n=439)	249 (30.55)	190 (22.65)		*Q1 (lowest) (n=438)*	421 (26.61)	17 (24.29)	
Q2 (n=300)	155 (19.02)	145 (17.28)		*Q2 (n=300)*	290 (18.33)	10 (14.29)	
Q3 (n=300)	135 (16.56)	165 (19.67)		*Q3 (n=300)*	287 (18.14)	13 (18.57)	
Q4 (n=288)	127 (15.58)	161 (19.19)		*Q4 (n=288)*	268 (16.94)	20 (28.57)	
Q5 (highest) (n=327)	149 (18.28)	178 (21.22)		*Q5 (highest) (n=326)*	316 (19.97)	10 (14.29)	

n: sample size, %: column frequencies
*: p<0.05 is significant. Chi2 or Fisher's exact tests used on small cell counts
a: 5 individuals < 15 years old
b: 5 individuals > 70 years old

2.3.2 Alberta susceptibility results for females of childbearing age

682 NG isolates were collected in Alberta from females aged 15-49 years between 2016 and 2022. Similar susceptibility trends to the general population are observed in this cohort. Susceptibility to penicillin was the lowest each year, followed by tetracycline and ciprofloxacin (**Figure 2.3.2**). In 2021, ciprofloxacin susceptibility dropped below tetracycline (33% vs. 38%) and rebounded in 2022 (43% vs. 41%). All tested isolates were susceptible to ceftriaxone and cefixime. Azithromycin susceptibilities were always over 95%, with the lowest susceptibility observed in 2019 (96%). In 2022, isolates were 100% susceptible to ceftriaxone and cefixime (46/46), 98% susceptible to azithromycin (45/46), 41% susceptible to tetracycline (19/46), 43% susceptible to ciprofloxacin (20/46), and 13% susceptible to penicillin (6/46).

Figure 2.3.2 Annual NG susceptibility from culture positive isolates in females of childbearing age in Alberta between 2016 and 2022.

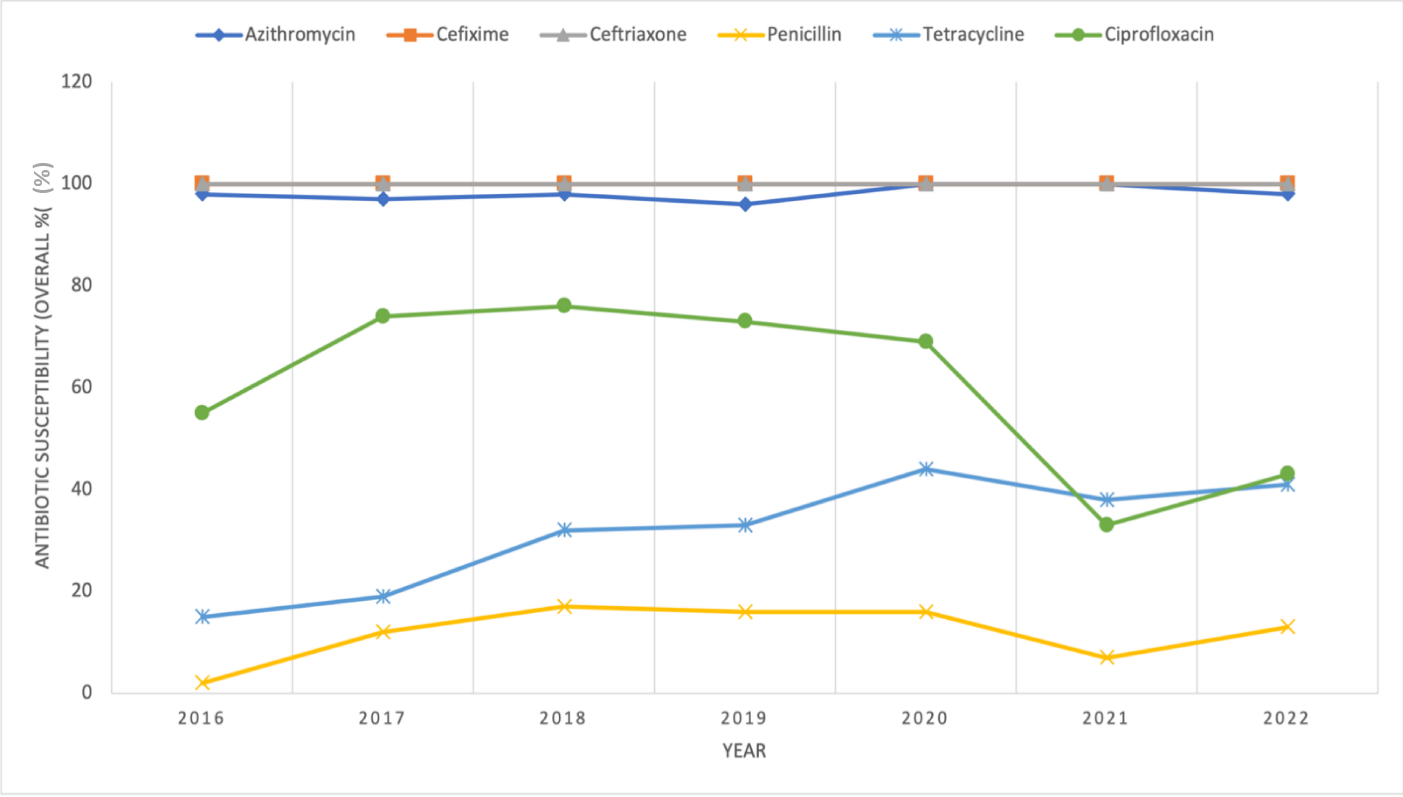

Figure 2.3.2 Legend. Susceptibilities calculated for antibiotics each year by dividing susceptible isolates by total isolates tested.

2.4 Discussion

Reports from 2021 show Canadian NG rates are higher among males than females (23). Similarly, over 80% of culture positive NG cases from Alberta 2016 to 2022 came from males, suggesting more males experience situations requiring a culture. Preferred NG treatment in Alberta is cefixime and oral azithromycin as a single dose or alternatively, an intramuscular injection of ceftriaxone and oral azithromycin (11). Concerningly, males exhibited higher frequencies of azithromycin non-susceptible strains compared to females (91.77% vs. 8.23%) and gbMSM populations are reported to be a high risk group for acquiring NG infection (3).

Resulting AMR trends reflect the history of antibiotic use against NG. As penicillin and tetracycline have been deployed as treatment for NG the longest (5), it is unsurprising that these antimicrobials had the lowest susceptibility each year. This was closely followed by ciprofloxacin, which was deployed as treatment shortly after tetracycline removal. NG strains are now developing resistance to azithromycin, and though ceftriaxone and cefixime remained 100% susceptible in Alberta, emerging strains are developing resistance to these antimicrobials in other countries (24,25).

The China Gonococcal Resistance Surveillance Program (China-GRSP) recently reported their NG AMR findings from 2022 (24). A substantial increase of ceftriaxone resistance was reported in 2022 compared to 2017 (8.1% vs. 2.9% respectively), with some provinces reporting resistance levels greater than 10%. Cefixime and azithromycin resistance levels were reported at 16% and 16.9%, respectively. Taken together, it could be possible for strains to develop resistance to all 3 antimicrobials. In 2023, a novel strain in the US exhibited reduced

susceptibility to five classes of antibiotics, including ceftriaxone (25). Treatment guidelines in Europe and the UK now recommend an increased dose of ceftriaxone to combat rising reduced susceptibility to this antimicrobial (26–28). The rise of NG strains showing resistance to ceftriaxone and azithromycin and other previous first-line treatments is evident in countries throughout the world. The need for more effective treatment options is imperative to combat AMR.

One such option is zoliflodacin, a DNA biosynthesis inhibitor. In a phase 2 clinical trial, zoliflodacin was as effective as ceftriaxone at curing urogenital infections and rectal infections in randomly assigned individuals, but was not as effective as ceftriaxone when treating pharyngeal infections (29). Overall, this antimicrobial shows promise as another treatment option for uncomplicated urinogenital and rectal NG infections. Another option, gepotidacin, inhibits bacterial DNA replication and recently underwent a phase 3 clinical trial for uncomplicated urogenital NG infections(30,31). Gepotidacin was as effective as dual-therapy ceftriaxone and azithromycin in treating infection. Overall, maintaining up-to-date AMR surveillance can aid in the global fight against antimicrobial resistant NG and lead to the development of fast and effective treatment options.

This study was limited by the availability and completeness of the AST data and provincial census data. Any individuals not matched back to census data through recorded postal codes were not included in income quintile and geographic region demographic analysis (n=1,956). Additionally, any individuals missing data for antimicrobial testing were not included in the denominator for susceptibility results.

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Chapter 3 Retrospective analysis of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* prenatal screening positivity in the province of Alberta between 2019 and 2022

3.1 Introduction

CTNG are bacteria that can cause STIs through the direct contact with infected mucosal membranes and secretions (1,2). Presenting symptoms for males include urethral discharge, testicular pain, dysuria, and urethral itch for either infection (1,2). Females have higher proportions of asymptomatic infections compared to males and urethritis, cervicitis, endocervicitis, endometritis, or salpingitis can result (3,4). Among females, the progression of either infection can lead to pelvic inflammatory disease contributing to risk of ectopic pregnancy and infertility (3,4). If a woman is pregnant, and has a chlamydial and/or gonorrheal infection, she risks passing infection to her infant via vertical transmission (1–4). Additionally, CTNG can be transmitted during cesarian deliveries (5,6). Consequential infection in the newborn or infant can range from chlamydial pneumonia, scalp abscess or, more often, ophthalmia neonatorum which can lead to blindness in severe cases (1,2,4,7). Studies have shown transmission rates of CT from an individual to their newborn can range from 28% to 31% while NG transmission can range from 30% to 42% (8–10).

A study conducted in Ontario analyzed the cost and quality adjusted life-years (QALY) associated with universal antimicrobial prophylaxis compared to prenatal screening in prevention of ophthalmia neonatorum (11). Authors determined that eye prophylaxis leads to very high costs on a population level and for this prevention to continue as cost-effective, CTNG prevalence in pregnancy must be higher. These data suggest that prenatal screening may be an effective replacement for universal prophylaxis. The CDC in the US first recommended screening for CT during pregnancy in 1993 (12). Kohlhoff and others analyzed the effectiveness of screening for

CT during pregnancy at preventing ophthalmia neonatorum based on the CDC recommendations (13). They found screening implementation significantly decreased perinatal CT positivity proportions from 15.6% before recommendations to 1.8% after recommendations, suggesting gestational screening may have prevented neonates from acquiring infection. As of 2015 (reaffirmed January 2024) the Canadian Pediatric Society (CPS) recommends replacing universal prophylaxis with prenatal screening for the prevention of ophthalmia neonatorum (14).

In response to CPS recommendations, Alberta implemented universal first trimester screening for CTNG in 2018 (15). An additional third trimester screen is recommended for high-risk individuals and those having no prior screening. High risk individuals are defined as those who are sexually active under 25 years of age, those with new, anonymous, or multiple sexual partner(s) in the last year, or those belonging to a marginalized community. Chlamydia and gonorrhea are reportable infections under the Alberta Public Health Act (16), requiring healthcare staff to notify the STI Medical Director via Sexually Transmitted Infection Centralized Services (STICS) and the Chief Medical Officer of Health of confirmed cases within 48 hours (17,18). Infected individuals are required to complete a Notification of STI form which is sent to the Medical Director to ensure partner notification for any sexual contacts who may be at risk (16).

The aims for Chapter 3 are to: (1) understand levels of universal first-trimester screening in the province of Alberta from 2019 to 2022; (2) examine individual demographics of those screened compared to those not screened; (3) estimate prenatal CTNG positivity; and (4) describe factors contributing to CT or NG infection in Alberta's prenatal population.

3.2 Methods

3.2.1 Testing and Samples

The retrospective analysis of CTNG screening during pregnancy was conducted for provincial deliveries from January 1, 2019 to December 31, 2022. CTNG screening was conducted using NAAT (APTIMA Combo 2 Assay, Panther, Hologic) or culture methodologies. Urine, or cervical, vaginal, throat, and rectal swabs were used as specimen sources.

3.2.2 Data Collation

Provincial birth records with deliveries of at least 15 weeks' gestation from January 1, 2019 to December 31, 2022 were extracted from AHS Perinatal metadata source (Perilink), providing maternal identifiers, and the discharge abstract database (DAD), providing admittance and discharge dates for hospital deliveries. CTNG screening results from January 1, 2018 through December 31, 2022 were extracted from the Alberta Provincial Laboratory (ProvLab) and DynaLife Medical Labs Laboratory Information Systems (LIS). Annual communicable disease prenatal screening panels results from 2018 to 2022 were extracted from ProvLab LIS databases and appended to the CTNG dataset to create a complete prenatal communicable disease panel dataset from January 1, 2018 to December 31, 2022. CTNG screening data and communicable panel data were merged using *rangejoin* to the provincial deliveries list by maternal Personal Health Number (PHN) using STATA v. 17.0 (StataCorp, College Station, Texas, USA), creating a master dataset. Variables such as maternal PHN and specimen collection date were formatted across each dataset to ensure consistency when using *rangejoin*. Postal code data from 2021 Alberta census estimates provided income quintile and geographic region (rural, urban, or metropolitan) information which was merged to the master dataset using maternal postal codes.

Females delivering with no recorded PHN, an out of province (OOP) PHN and/or an OOP postal code were removed from the dataset (n=1,220), where Alberta physician postal codes were used as a proxy variable for individuals with an OOP postal code. The resulting dataset contained all information needed for further analysis.

3.2.3 Variable Creation

Estimated conception date in days was calculated by subtracting gestational age in weeks (Perilink) (multiplied by 7) from delivery date. Admission date from the DAD was used as a proxy when delivery date was not provided (n=14,575) and mean gestational age of 38 weeks was used if gestational age was not provided (n=257). The trimester when screening was performed was calculated by subtracting the CTNG sample collection date from estimated conception date. First trimester screening was defined as testing in the first 0-91 days from estimated conception date, second trimester as 92-182 days, third trimester as 183-273 days. Screening performed on date of delivery and up to two days later, was defined as "At Delivery". A screening variable was created to define an individual as "screened" (at least one valid CTNG screening result between estimated conception date and 2 days after delivery) or "not screened" (results outside this range, or lack of testing results). Pregnancies were examined separately for individuals delivering multiple times throughout the study period. By combining maternal PHN's with the delivery date and combining maternal PHN's with the specimen collection date, distinct pregnancies and distinct screening events could be analyzed. Positive screening results are defined by detectable bacterial ribosomal RNA in a collected specimen. These results were divided into CT positive, NG positive, or CTNG co-infection.

An age variable using 10-year increments (10-20, 21-30, 31-40, 41-50, and 51-60) was created to categorize individuals based on maternal age at delivery. Health zones, based on

patient region, were divided into North, South, Central, Calgary, and Edmonton zones. Geographic region was divided into Metropolitan, Urban, and Rural, where moderate metro influence (areas immediately surrounding Edmonton and Calgary) was categorized as Metropolitan, moderate urban influence (areas surrounding the 5 urban centers: Grand Prairie, Fort McMurray, Red Deer, Lethbridge, Medicine Hat) was categorized as Urban, and rural center area (populations less than 100,000 and up to 200 km away from a metro or urban center) and rural remote (greater than 200 km away from a metro or urban center) was categorized as Rural. Income quintiles were provided through the merging of 2021 Alberta census data to the birth dataset. Income quintiles are defined as Q1 ($1 - $35,808), Q2 ($35,809 - $59,521), Q3 ($59,522 - $88,658), Q4 ($88,659 - $133,468), and Q5 (greater than $133,569) (19). History of sexually transmitted and blood borne infections (STBBI) was based on results from the prenatal communicable disease panel from January 1, 2018 to December 31, 2022, where previous positives or new active cases were defined for HIV, syphilis, HBV, and HCV. If testing results were reactive for HIV, syphilis, HBV, or HCV, or cases were previously confirmed, an individual was defined as having a history of an STBBI. Social behavioural factors including ethnicity, substance use/addiction, unstable housing, high-risk sexual behaviours, and sex work was provided using the Communicable Disease & Outbreak Management Database (CDOM).

3.2.4 Analyzing Datasets

To uncover retrospective CTNG prenatal screening results for 2019-2022, the number of individuals having a valid CTNG test result during pregnancy was divided by the total number of distinct deliveries in the province. The number of distinct pregnancies receiving a screen in the first trimester was divided by the total number of distinct screening events, representing the proportion of screening where first trimester universal guideline recommendations were

followed. Merging screening events taking place in the first trimester with those occurring in the third trimester by maternal PHN combined with delivery date, resulted in matched individuals who were screened in the first and third trimester, following high-risk guidelines. This value was divided by the total number of individuals receiving a first trimester screen to determine the proportion of high-risk screening taking place throughout the province. Values were additionally calculated using overall distinct deliveries as the denominator for each screening analysis. This analysis was stratified by year. Two prenatal cohorts were assessed for screening demographics: 1) individuals delivering a baby (live birth or stillborn) between 2019 to 2022 based on most recent delivery (if they had multiple deliveries during the study period); and 2) individuals screened at least once for CTNG during their most recent pregnancy. Demographic variables in cohort one was stratified by "screened" vs. "not screened" and cohort two was stratified by whether first-trimester universal screening guidelines were "met" or "not met". Pearson Chi-squared tests were used to determine statistical significance set at $p \leq 0.05$ between the categorical data.

CTNG positivity was calculated by dividing the number of prenatal patients testing positive for CTNG by the total number of distinct pregnancies receiving at least one valid screening result. CTNG positivity was determined each year to assess any differences in positivity on a year-by-year basis. CT and NG positivity were also assessed separately using the same approaches outlined above.

Individuals testing positive for CTNG in the prenatal period were assessed for demographic analysis stratified by first-trimester universal screening guidelines being "met" or "not met". Pearson Chi-squared tests were used to determine differences between categories using a statistical significance set at $p \leq 0.05$.

3.2.5 Statistical Analysis

The data was assembled and analyzed using STATA v. 17.0 (StataCorp, College Station, Texas, USA) and tables were produced using Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, Washington). Pearson Chi-squared tests were used to determine variables significantly associated with the results analyzed, and likelihood ratio tests were used to determine the fitness of variables to the logistic regression model. Statistically significant p-value cut-offs are set at $p \leq 0.05$. Logistic regression analysis was performed using purposeful model building by backwards elimination. The outcome variable was coded as 0 for first trimester screening guidelines not met, and 1 for first trimester screening guidelines being met. Univariate analyses using Pearson's Chi-squared tests to screen variables for significance at $p<0.20$ and variables were checked for collinearity before being included in multivariable models. Clinically and statistically significant variables were analyzed for interaction while confounders were assessed using the formula $|\beta(\text{with confounder})- \beta(\text{without confounder})/\beta(\text{with confounder})|*100\%$; variables that altered beta values by more than 15% were considered confounders. All statistically significant, clinically significant, and confounding variables were retained in final models.

3.2.6 Ethical Statement

Ethics was approved by the University of Alberta Research Ethics Board Pro00139334.

3.3 Results

3.3.1 Provincial Screening Results

In Alberta, 194,386 distinct deliveries occurred between January 1, 2019 and December 31, 2022. 85.7% of these deliveries received at least one CTNG test at any point during the prenatal period. Of those tested, 68.6% were screened in the first trimester (universal guidelines) and 8.28% received a second CTNG screen in the third trimester (high-risk guidelines). Overall, 58.8% of provincial deliveries were screened for CTNG in the first trimester, 24.0% of provincial deliveries had a second trimester screen, 14.0% had a third trimester screen, and 0.21% had an "At Delivery" screen. 4.87% were screened in the first and third trimester, following high-risk screening protocol (**Figure 3.3.1**). Per year, the highest level of screening occurred in 2022, where 86.8% of pregnancies were screened for CTNG at least once during the prenatal period (**Figure 3.3.2 D**). However, 2021 had the highest level of first trimester screening where 69.7% of screened pregnancies were performed in the first trimester (**Figure 3.3.2 C**). 2019 showed the greatest level of high-risk screening, where 11.5% of pregnancies receiving a first trimester screen were also screened in the third trimester (**Figure 3.3.2 A**).

164,894 distinct individuals delivered at least once in the province from January 1, 2019 to December 31, 2022. Because of the high sample size, all demographic variables were shown to have a significant association with CTNG screening ($p \leq 0.001$). Urban and rural geographic regions had higher proportions of individuals not screened compared to those screened at least once from the same region (16.05% vs. 11.59% & 24.67% vs. 18.00%, respectively). Individuals in the lowest income quintiles, Q1 and Q2, also showed higher proportions of no CTNG screening during pregnancy compared to those screened at least once from the same income quintile (22.76% vs. 18.62% & 20.09% vs. 18.58%, respectively). Finally, those residing in non-

metropolitan Alberta health zones (northern, southern, central) had higher proportions of individuals not screened compared to individuals residing in the same health zones (18.21% vs. 11.56%, 12.07% vs. 6.31%, & 11.31% vs. 9.92%, respectively). Individuals with a history of STBBI had a higher frequency of receiving a CTNG screen, with a statistically significant increase in those with a history of syphilis (90.55%, $p < 0.001$) (**Table 3.3.1**).

144,151 individuals were screened at least once for CTNG during their most recent pregnancy. High sample sizes contributed to all demographic variables being significantly associated to the result. Only those aged 31-40 and 51-60 years had a higher, or equal, frequency of individuals screened in the first trimester compared to those screened outside the first trimester (54.89% vs. 51.18% & 0.01% vs. 0.01%, $p < 0.001$ for both, respectively). All other age categories had a higher frequency of individuals screened outside the first trimester. Higher frequencies of those residing in rural geographic regions were screened outside the first trimester (19.63% vs. 17.65%, $p < 0.001$). Higher frequencies of individuals in Q1 and Q2, or those residing in the southern Alberta health zone, were screened outside the first trimester (23.45% vs. 16.88% & 20.39% vs. 18.04% & 7.85% vs. 5.78%, $p < 0.001$ respectively). A significant association was observed between those screened in first trimester compared to those screened outside first trimester with history of syphilis, HBV, or HCV infection ($p < 0.001$) (**Table 3.3.2**).

Figure 3.3.1 CTNG prenatal screening results in Alberta from January 1, 2019, to December 31 2022.

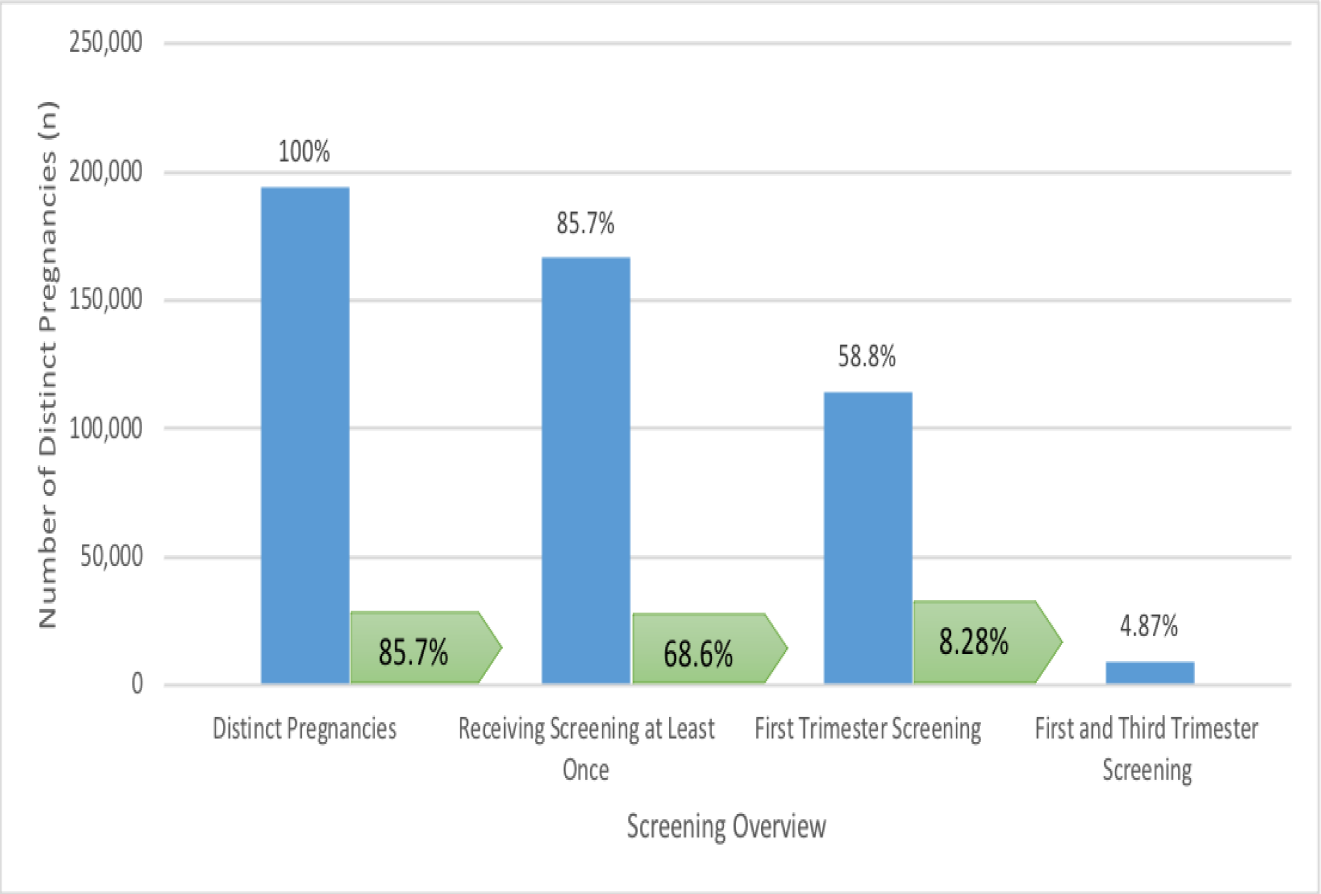
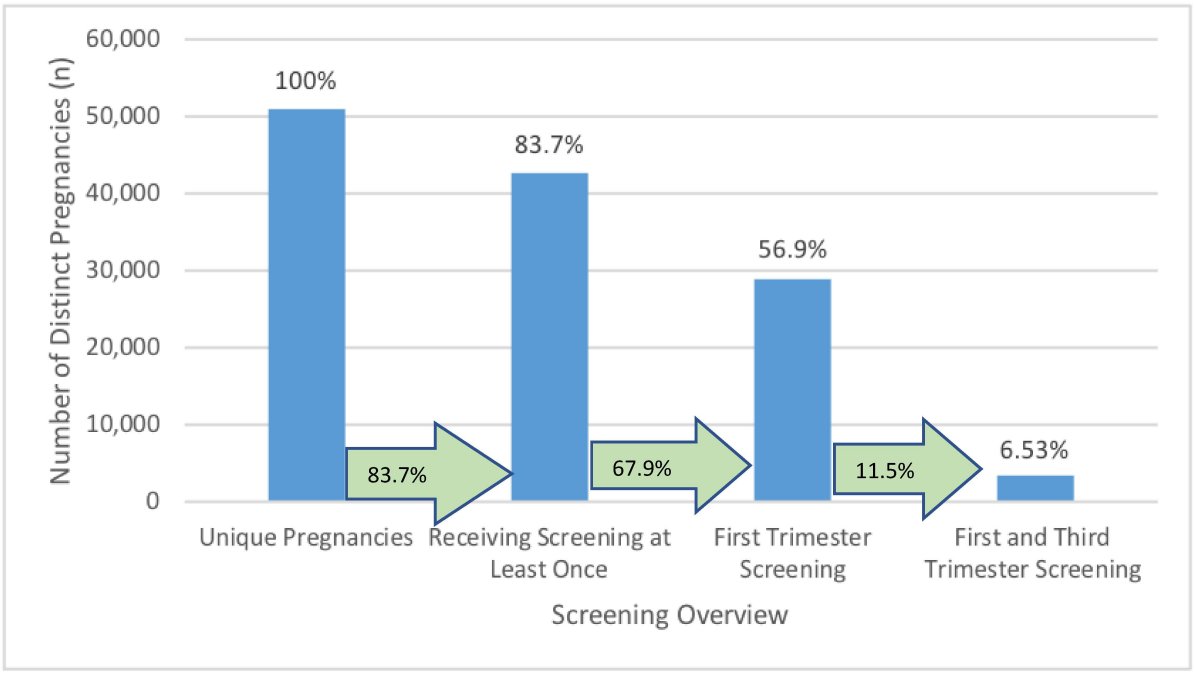


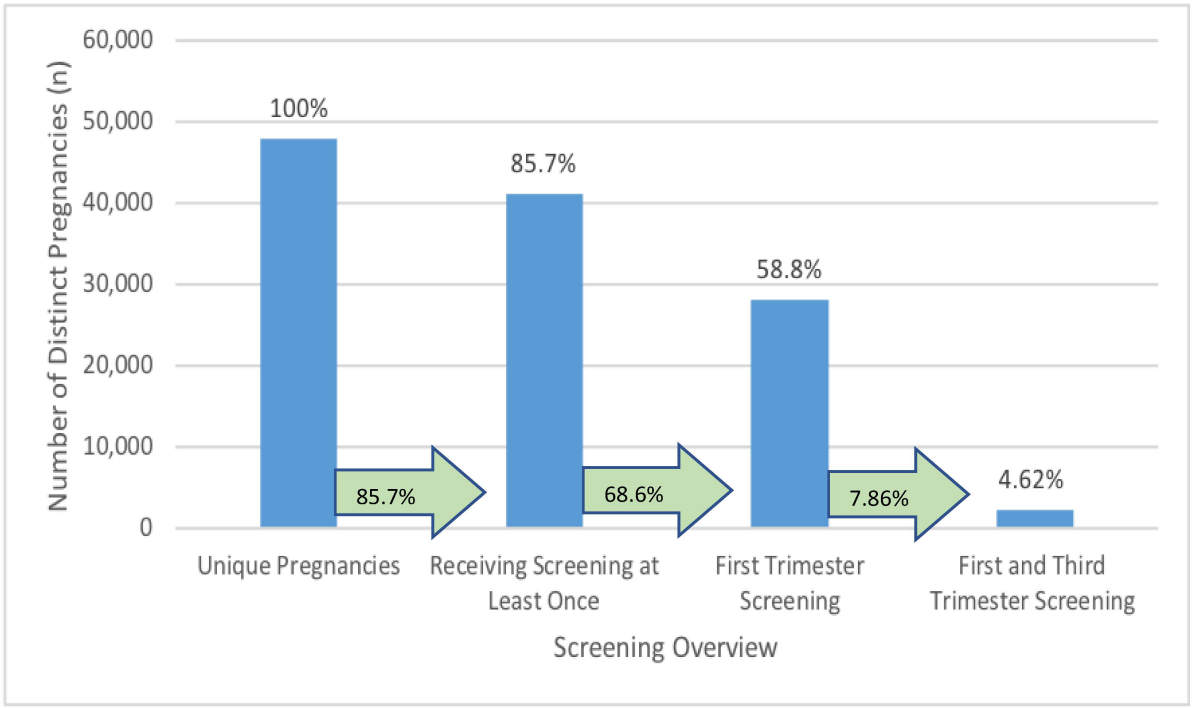
Figure 3.3.1 Legend. Green arrows represent proportions calculated by using the numerator denominator calculation. Proportions above blue bars are calculated using distinct pregnancy events as denominator.

Figure 3.3.2 Annual CTNG prenatal screening results in Alberta from January 1 to December 31

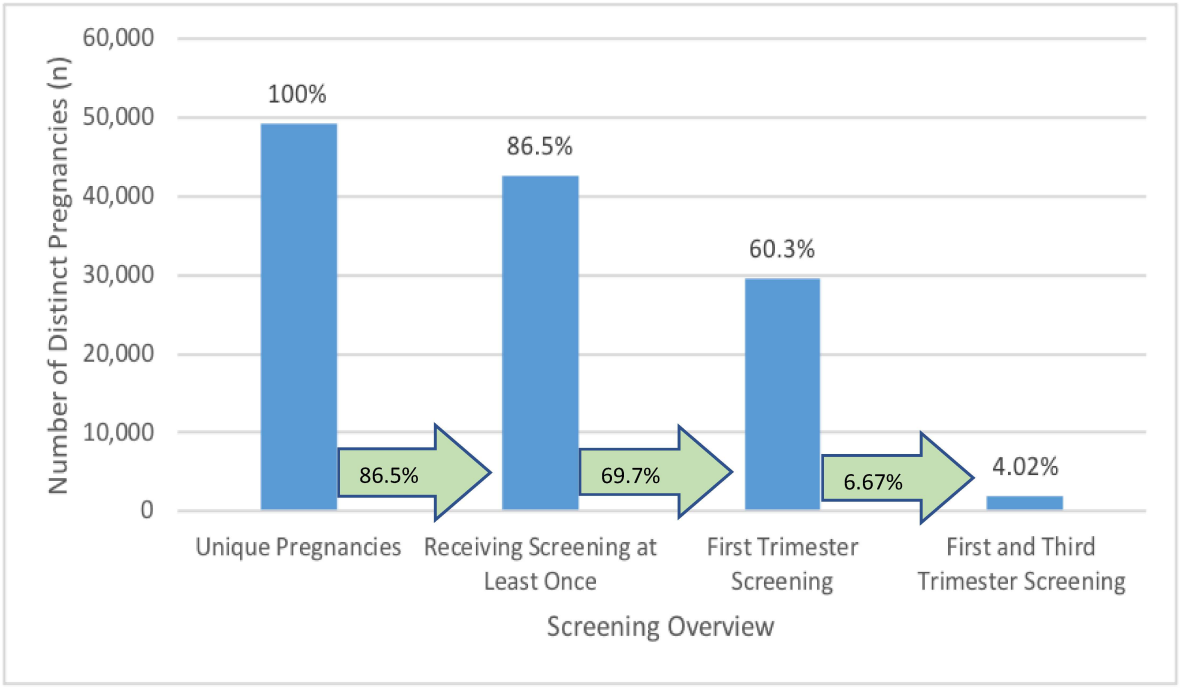
A



B



C


60,000
50,000
40,000
30,000
20,000
10,000
0
Number of Distinct Pregnancies (n)
100%
86.5%
60.3%
4.02%
86.5%
69.7%
6.67%
Unique Pregnancies
Receiving Screening at Least Once
First Trimester Screening
First and Third Trimester Screening
Screening Overview

D

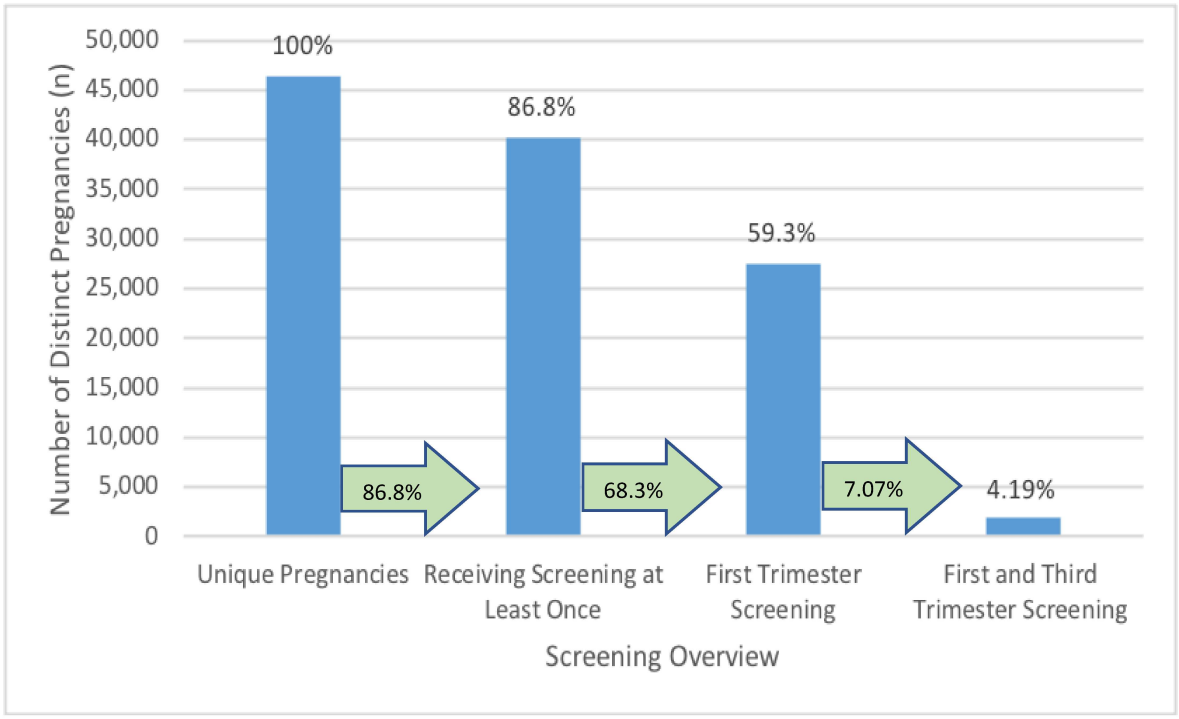

50,000
45,000
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
Number of Distinct Pregnancies (n)
100%
86.8%
59.3%
4.19%
86.8%
68.3%
7.07%
Unique Pregnancies
Receiving Screening at Least Once
First Trimester Screening
First and Third Trimester Screening
Screening Overview

Figure 3.3.2 Legend. Green arrows represent proportions calculated by using the numerator denominator calculation. Proportions above blue bars are calculated using distinct pregnancy events as the denominator. A) Screening results from January 1, 2019, to December 31, 2019. B) Screening results from January 1, 2020, to December 31, 2020. C) Screening results from January 1, 2021, to December 31, 2021. D) Screening results from January 1, 2022, to December 31, 2022.

Table 3.3.1 Descriptive statistics for prenatal patients delivering in Alberta between January 1, 2019, and December 31, 2022

	Screened n(%) 141,420 (85.76)	Not Screened n(%) 23,474 (14.24)	p-value
Patient Age (years) (n=164,894)			<0.001*
[a] 10-20 (n=3,971)	3,394 (2.40)	577 (2.46)	
21-30 (n=66,380)	56,788 (40.16)	9,592 (40.89)	
31-40 (n=89,620)	77,164 (54.56)	12,456 (53.06)	
41-50 (n=4,911)	4,065 (2.87)	846 (3.60)	
[b] 51-60 (n=12)	9 (0.01)	3 (0.01)	
Geographic Region (n=163,778)			<0.001*
Metro (n=112,720)	98,949 (70.40)	13,771 (59.28)	
Urban (n=20,021)	16,292 (11.59)	3,729 (16.05)	
Rural (n=31,037)	25,305 (18.00)	5,732 (24.67)	
Income Quintile (n=153,789)			<0.001*
Q1 lowest (n=29,552)	24,545 (18.62)	5,007 (22.76)	
Q2 (n=28,907)	24,488 (18.58)	4,419 (20.08)	
Q3 (n=27,347)	23,609 (17.91)	3,738 (16.99)	
Q4 (n=33,235)	29,050 (22.04)	4,185 (19.02)	
Q5 highest (n=34,748)	30,094 (22.84)	4,654 (21.15)	

Health Zone (n=144,223)			<0.001*
North (n=17,812)	14,710 (11.57)	3,102 (18.22)	
Edmonton (n=50,070)	44,456 (34.95)	5,614 (32.97)	
Central (n=14,539)	12,614 (9.92)	1,925 (11.30)	
Calgary (n=51,719)	47,387 (37.26)	4,332 (25.44)	
South (n=10,083)	8,027 (6.31)	2,056 (12.07)	
Trimester (n=141,420)			†
First (n= 90,088)	90,088 (63.70)	-	
Second (n=34,088)	34,088 (24.10)	-	
Third (n=17,016)	17,016 (12.03)	-	
At Birth (n=228)	228 (0.16)	-	
[c‡] ***History of STBBI (n=2,058)***			
Syphilis (n=1,164)	1,054 (90.55)	110 (9.45)	<0.001*
HIV (n=80)	70 (87.50)	10 (12.50)	0.657
HBV (n=620)	548 (88.39)	72 (11.61)	0.061
HCV (n=194)	162 (83.51)	32 (16.49)	0.368

n: sample size, %: proportion using **column** totals

*: p-value showing significance by comparing variables between guidelines being followed or not.

†: cannot do p-value across zero counts

a: 18 individuals under the age of 15.

b: 12 individuals over the age of 50.

c: Syphilis positivity defined as any reactive eia result. HIV, HBV, and HCV positivity defined as reactive results including previous positives and cases

‡: proportion using **row** totals

Table 3.3.2 Descriptive statistics for prenatal patients screened for CTNG in Alberta between January 1, 2019, and December 31, 2022

	First Trimester Screen n(%) 102,774 (71.30)	Screening Outside First Trimester n(%) 41,377 (28.70)	p-value
Patient Age (years) (n=144,151)			<0.001*
[a] 10-20 (n=3,635)	2,137 (2.08)	1,498 (3.62)	
21-30 (n=58,897)	41,508 (40.39)	17,389 (42.03)	
31-40 (n=77,587)	56,411 (54.89)	21,176 (51.18)	
41-50 (n=4,023)	2,712 (2.64)	1,311 (3.17)	
[b] 51-60 (n=9)	6 (0.01)	3 (0.01)	
† **Screening Result (n= 144,151)**			<0.001*
Negative (n= 142,420)	101,709 (71.41)	40,711 (28.59)	
Positive (n= 1,731)	1,065 (61.53)	666 (38.47)	
Geographic Region (n=143,251)			<0.001*
Metro (n=100,461)	71,817 (70.31)	28,644 (69.68)	
Urban (n=16,689)	12,296 (12.04)	4,393 (10.69)	
Rural (n=26,101)	18,032 (17.65)	8,069 (19.63)	
Income Quintile (n=134,683)			<0.001*
Q1 lowest (n=25,278)	16,198 (16.88)	9,080 (23.45)	
Q2 (n=25,209)	17,314 (18.04)	7,895 (20.39)	
Q3 (n=24,134)	17,230 (17.95)	6,904 (17.83)	
Q4 (n=29,493)	21,812 (22.73)	7,681 (19.84)	
Q5 highest (n=30,569)	23,409 (24.39)	7,160 (18.49)	

Health Zone (n=129,569)			<0.001*
North (n=15,221)	11,078 (11.82)	4,143 (11.57)	
Edmonton (n=45,232)	32,999 (35.20)	12,233 (34.16)	
Central (n=12,901)	9,447 (10.08)	3,454 (9.64)	
Calgary (n=47,990)	34,814 (37.13)	13,176 (36.79)	
South (n=8,225)	5,415 (5.78)	2,810 (7.85)	
[c]† ***History of STBBI (n=1,846)***			
Syphilis (n=1,064)	604 (56.77)	460 (43.23)	<0.001*
HIV (n=73)	45 (61.64)	28 (38.36)	0.068
HBV (n=549)	349 (63.57)	200 (36.43)	<0.001*
HCV (n=160)	85 (53.13)	75 (46.88)	<0.001*

n: sample size, %: proportion using **column** totals

*: p-value showing significance by comparing variables between being screened or not.

†: proportion using **row** totals

a: 17 individuals under the age of 15.

b: 9 individuals over the age of 50

c: Syphilis positivity defined as any reactive eia result. HIV, HBV, and HCV positivity defined as reactive results including previous positives and cases

3.3.2 Provincial Positivity Results

Overall, 2,555 (1.53%) positive results were observed from initial screening of distinct pregnancies where an individual could be positive for CT, or NG, or CT and NG. Of the 114,273 pregnancies tested for CTNG in the first trimester, 1,465 (1.28%) positives were identified. 37,990 pregnancies were first screened for CTNG during the second trimester with 689 (1.81%) positives identified, while 14,055 were first screened in the third trimester with 393 (2.8%) positives identified. Finally, 188 pregnancies were first screened for CTNG "At Delivery" with 8 (4.26%) positives observed (**Figure 3.3.3**). Similar trends were observed in positivity for CT-only and NG-only infections based on timing of first CTNG screen, with higher positivity seen for screening performed closest to delivery date (Supplementary **Figure A.1 and A.2**).

A total of 9,462 pregnancies were screened in the first and third trimester (high-risk guidelines). 515 (5.44%) were positive in the first trimester and negative in the third, 49 (0.52%) were negative in the first trimester and positive in the third, and 30 pregnancies (0.32%) were positive in the first and third trimester.

2,780 (1.67%) positive results were observed for Alberta's prenatal population screened for CTNG between January 1, 2019 and December 31, 2022. Overall CT positivity was 1.53% (2,555), while NG positivity was 0.24% (402).

In 2019, 50,891 pregnancies were screened at least once for CTNG with a positivity of 1.47% (747), 48,015 pregnancies were screened in 2020 with a positivity of 1.51% (725), 49,149 pregnancies were screened in 2021 with a positivity of 1.33% (652), and finally, 46,334 pregnancies were screened in 2022 with a positivity of 1.42% (656). (**Figure 3.3.4**). CT positivity was lowest in 2021(1.21%), while NG positivity was lowest in 2019 (0.18%) (Supplementary **Figure A.3 and A.4**).

2,721 distinct individuals tested positive for CT, NG, or CT and NG at least once during the study period. A higher proportion of those aged 10-20 years and those residing in rural geographic regions were screened outside the first trimester (22.15% vs. 18.47%, p=0.129, & 34.38% vs. 32.80%, p=0.694). Additionally, a higher proportion of individuals participating in sex work (CDOM) were screened outside the first trimester (52.63% vs. 47.37%). A significant difference in screening outcome across income quintiles at p=0.04 and health zone at p=0.001 was observed (**Table 3.3.3**).

Univariate analysis identified 27% increased odds of individuals aged 21-30 being screened in the first trimester compared to individuals aged 10-20 (p=0.019). Individuals in income quintile Q4 and Q5 had 31% and 60% increased odds, respectively, of screening in the first trimester compared to those in Q1; and those residing in central and southern health zones were at 33% and 44% decreased odds of being screened in the first trimester compared to those in the northern health zone (**Table 3.3.4**). After adjusting for confounders, individuals in Q3, Q4, and Q5 had a 31%, 35%, and 57% increased odds of being screened in the first trimester compared to Q1; and compared to the northern health zone, those residing in southern health zones had a 35% (p=0.026) decreased odds of being screened in the first trimester (**Table 3.3.4**).

Figure 3.3.3 Positivity (CT, NG, or CTNG) by first performed CTNG test for distinct pregnancies in Alberta from January 1, 2019, to December 31, 2022.

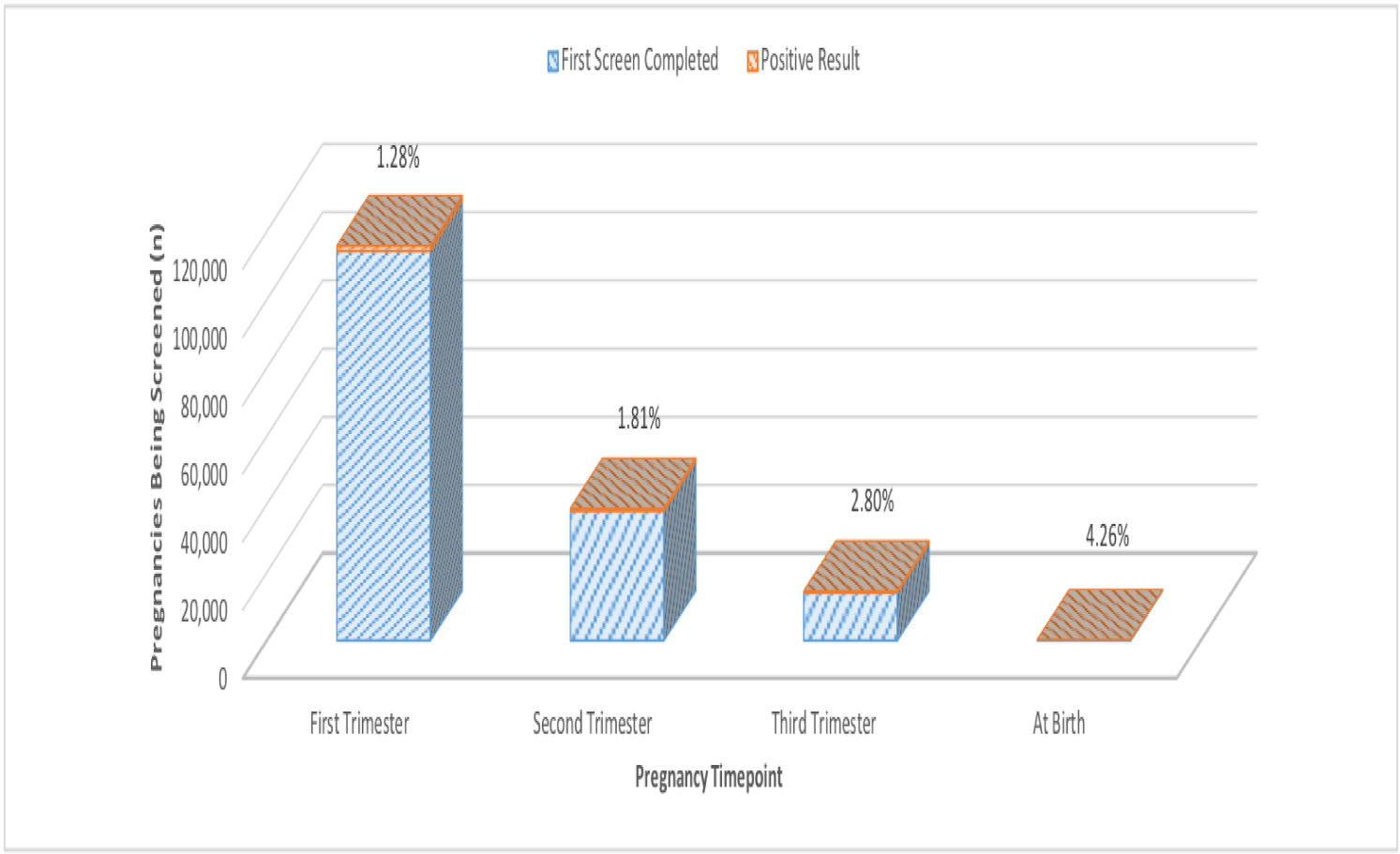


Figure 3.3.3 Legend. Proportions above the bar represent calculation using pregnancies screened at distinct timepoint as denominator. Blue bar represents total pregnancies screened at that timepoint. Orange bar represents positive screening results.

Figure 3.3.4 Annual positivity (CT, NG, or CTNG) stratified by distinct pregnancies screened for CTNG in Alberta from January 1, 2019, to December 31, 2022

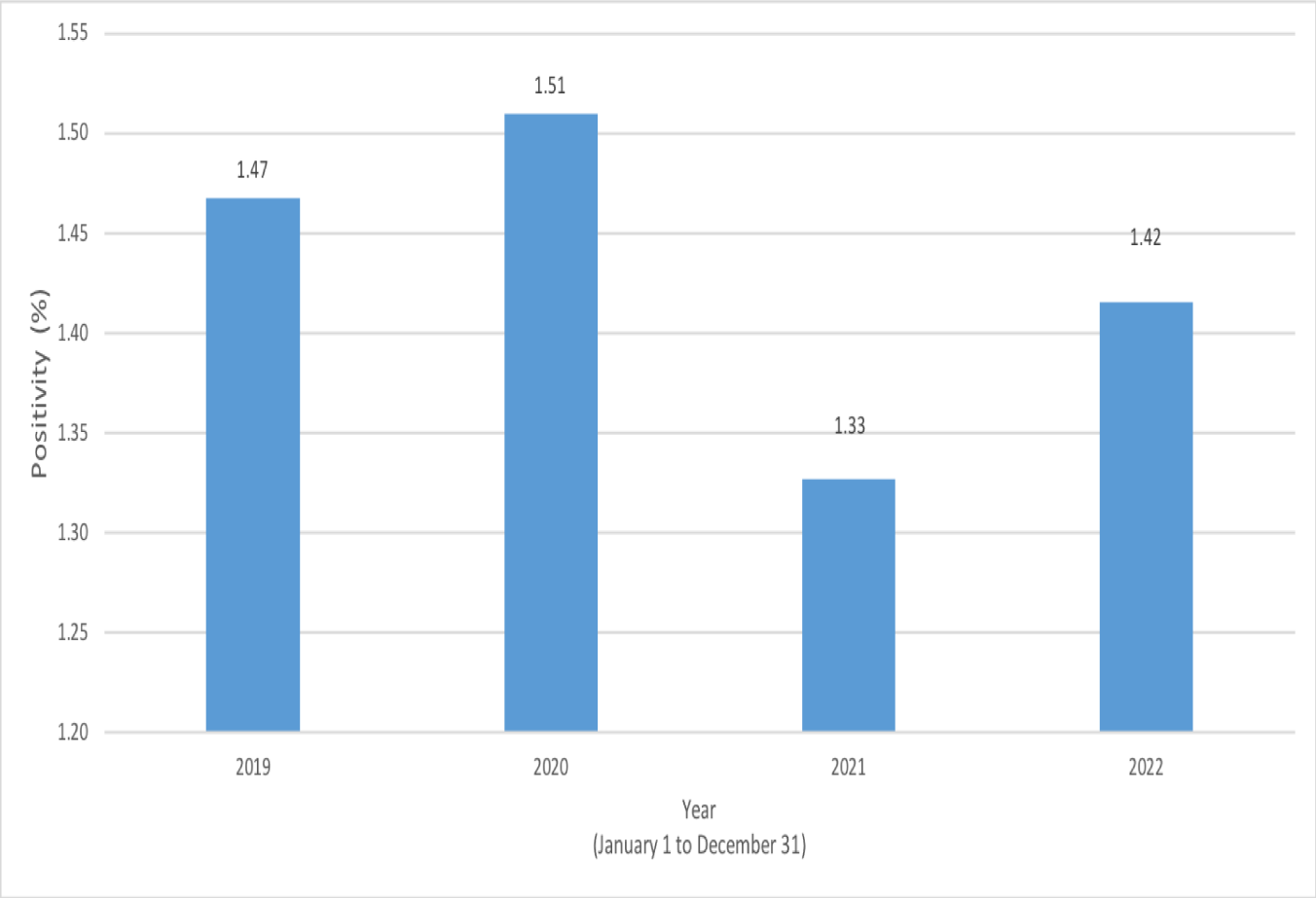


Figure 3.3.4 Legend. Numbers above the bar represent population positivity per year using distinct pregnancies testing positive at any time as numerator and total distinct deliveries per year as denominator.

Table 3.3.3 Descriptive statistics for prenatal patient screened positive for CTNG in Alberta between January 1, 2019, and December 31, 2022

	First Trimester Screen n (%) 1,624 (59.68)	Screening Outside First Trimester n (%) 1,097 (40.32)	p-value
[a] **Patient Age (years) (n=2,721)**			0.129
10-20 (n=543)	303 (18.47)	243 (22.15)	
21-30 (n=1,572)	959 (59.05)	613 (55.88)	
31-40 (n=580)	349 (21.49)	231 (21.06)	
41-50 (n=26)	16 (0.99)	10 (0.91)	
Geographic Region (n=2,698)			0.694
Metro (n=1,476)	891 (55.24)	585 (53.92)	
Urban (n=320)	193 (11.97)	127 (11.71)	
Rural (n=902)	529 (32.80)	373 (34.38)	
Income Quintile (n=2,569)			0.004*
Q1 lowest (n=962)	538 (34.94)	424 (41.21)	
Q2 (n=524)	311 (20.19)	213 (20.70)	
Q3 (n=390)	244 (15.84)	146 (14.19)	
Q4 (n=381)	238 (15.45)	143 (13.90)	
Q5 highest (n=312)	209 (13.57)	103 (10.01)	

Health Zone (n=2,326)			0.001*
North (n=542)	350 (24.58)	192 (21.29)	
Edmonton (n=808)	498 (34.97)	310 (34.37)	
Central (n=315)	173 (12.15)	142 (15.74)	
Calgary (n=502)	323 (22.68)	179 (19.84)	
South (n=159)	80 (5.62)	79 (8.76)	
[b]† ***History of STBBI (n=252)***			
Syphilis (n=213)	120 (56.34)	93 (43.66)	0.300
HIV (n=5)	3 (60.00)	2 (40.00)	1.000
HBV (n=4)	3 (75.00)	1 (25.00)	0.652
HCV (n=30)	14 (46.67)	16 (53.33)	0.144
[c]† ***Unstably Housed (n=2,721)***			0.168
No (n=2,684)	1,606 (59.84)	1,078 (40.16)	
Yes (n=37)	18 (48.65)	19 (51.35)	

† **Intravenous Drug User (n=196)**			0.973
No (n=145)	80 (55.17)	65 (44.83)	
Yes (n=51)	28 (54.90)	23 (45.10)	
† ***Sex Worker (n=229)***			0.434
No (n=210)	119 (56.67)	91 (43.33)	
Yes (n=19)	9 (47.37)	10 (52.63)	
† **Sex with Intravenous Drug User (n=198)**			0.949
No (n=165)	89 (53.94)	76 (46.06)	
Yes (n=33)	18 (54.55)	15 (45.45)	
† **Anonymous Partner (n=322)**			0.331
No (n=231)	131 (56.71)	100 (43.29)	
Yes (n=91)	57 (62.64)	34 (37.36)	

n: sample size, %: proportion of cases using column totals

*: p-value showing significance using Chi2 or Fisher's Exact for small cell counts.

a: 2 individuals under the age of 15.

b: Syphilis positivity defined as any reactive eia result. HIV, HBV, and HCV positivity defined as reactive results including previous positives and cases

c: Assume if individual did not check off "Homeless" then they are stably housed

†: Row totals provide proportion (%)

Table 3.3.4. Crude and adjusted odds ratios of receiving a first trimester CTNG screen during pregnancy in Alberta, 2019-2022

	COR (CI)	p-value	AOR (CI)	p-value
Patient Age (years) (n=2,721)				
10-20 (n=543)	Ref (1.0)			
21-30 (n=1,572)	1.27 (1.04 - 1.54)	0.019		
31-40 (n=580)	1.22 (0.96 - 1.55)	0.095		
41-50 (n=26)	1.30 (0.58 - 2.91)	0.529		
Geographic Region (n=2,698)				
Metro (n=1,476)	1.07 (0.91 - 1.27)	0.407		
Urban (n=320)	1.07 (0.83 - 1.39)	0.603		
Rural (n=902)	Ref (1.0)			
Income Quintile (n=2,569)				
Q1 lowest (n=962)	Ref (1.0)		Ref (1.0)	
Q2 (n=524)	1.15 (0.93 - 1.43)	0.202	1.13 (0.89 - 1.43)	0.320
Q3 (n=390)	1.32 (1.03 - 1.68)	0.025	1.31 (1.00 - 1.72)	0.047*
Q4 (n=381)	1.31 (1.03 - 1.67)	0.029*	1.35 (1.03 - 1.75)	0.027*
Q5 highest (n=312)	1.60 (1.22 - 2.09)	0.001*	1.57 (1.16 - 2.11)	0.003*

Health Zone (n=2,326)				
North (n=542)	Ref (1.0)		Ref (1.0)	
Edmonton (n=808)	0.88 (0.70 - 1.10)	0.273	.91 (0.72 - 1.15)	0.444
Calgary (n=502)	0.99 (0.77 - 1.28)	0.937	1.04 (0.80 - 1.35)	0.784
Central (n=315)	0.67 (0.50 - 0.89)	0.005*	0.75 (0.56 - 1.00)	0.052
South (n=159)	0.56 (0.39 - 0.79)	0.001*	0.65 (0.45 - 0.95)	0.026*
History of STBBI (n=252)				
Syphilis (n=213)	0.86 (0.65 - 1.14)	0.300		
HIV (n=5)	1.01 (0.17 – 6.07)	0.989		
HBV (n=4)	2.03 (0.21 - 19.52)	0.540		
HCV (n=30)	0.59 (0.29 - 1.21)	0.148		
Unstably Housed (n=2,721)				
No (n=2,684)	Ref (1.0)			
Yes (n=37)	0.64 (0.33 - 1.22)	0.172		

Intravenous Drug User (n=196)		
No (n=145)	Ref (1.0)	
Yes (n=51)	0.99 (0.52 - 1.88)	0.973
Sex Worker (n=229)		
No (n=210)	Ref (1.0)	
Yes (n=19)	0.69 (0.27 - 1.76)	0.436
Sex with Intravenous Drug User (n=198)		
No (n=165)	Ref (1.0)	
Yes (n=33)	1.02 (0.48 - 2.17)	0.949
Anonymous Partner (n=322)		
No (n=231)	Ref (1.0)	
Yes (n=91)	1.28 (0.78 - 2.11)	0.332

COR: Crude odds ratio, CI: 95% Confidence interval, AOR: Adjusted odds ratio

*: p-value significant at ≤ 0.05

3.4 Discussion

Since the implementation of a universal CTNG first trimester screen by the Alberta government in 2018 (15), program assessment has been reported in one other study (20). This current retrospective review determined the provincial CTNG prenatal screening prevalence between 2019 and 2022. The overall CTNG screening proportion was 85.7% for distinct pregnancies where testing occurred at least once. Lower screening levels observed for CTNG testing compared to the prenatal infectious disease panel (current benchmark) could be due to the need for an additional specimen collection for CTNG testing (swab or urine), which is processed at multiple laboratory sites across the province, whereas the benchmark universal testing program uses a single blood specimen (which can test for multiple communicable diseases) and is tested centrally through a long-standing provincial program (established in 2002) that reaches over 95% of pregnant females in the province (21,22). Additionally, over 31% of individuals screened were not receiving CTNG testing during the recommended first trimester. Both results emphasize the gaps present in Alberta's prenatal CTNG screening program. In Calgary health zones, 91% of females were screened for CTNG at least once during their pregnancy, with lowest screening levels observed in southern health zones where only 79% of females were screened at least once during their pregnancy, identifying jurisdictions in the province where screening may be falling short. Similar findings were observed in a study conducted in Alberta from a 2018-2022 retrospective evaluation of the same CTNG screening program (20). Authors found overall screening was 85.1% (vs. 85.7% from current chapter findings) for the prenatal population, despite universal recommendations, and highest screening levels were from Calgary health zones. Findings from this chapter add to the literature by identifying demographic factors significantly associated with screening following first trimester guidelines, which has not been

previously evaluated. Univariate and multivariate analyses conducted here identified income quintile and health zone as significant factors in increased and decreased likelihood of an individual screened following first trimester protocol. Another study in Toronto assessed prenatal CTNG screening in a tertiary care hospital (23). 15% of individuals were not screened despite routine recommendations. In Manitoba, suboptimal CTNG prenatal screening was noted in the province (24), with >30% not screened during pregnancy. The current study and above-mentioned literature conclude suboptimal prenatal CTNG screening levels are observed despite provincial universal recommendations. Higher screening levels are needed to fill the current gap.

Overall prenatal CT and NG positivity results were similar to what was observed in other literature for the province of Alberta from 2018-2022 analysis (20). The current study found NG positivity at 0.24% and CT positivity at 1.53%, while McCullough *et al*., found NG positivity at 0.24% and CT positivity at 1.58% (20). The marginal differences in CT positivity likely represent the additional year (2018) that was included in the McCullough study. This thesis additionally identifies increasing positivity for pregnancies first screened at a later prenatal timepoint. As of 2022, CT positivity in Alberta's prenatal population was observed at 1.29% while Alberta's general population had a reported CT prevalence of 0.37%; and prenatal NG positivity was 0.21% and reported NG positivity in the general population was 0.11% (25). Due to the asymptomatic nature of CT and NG infections, positivity in the general population is likely higher than reported values. One study conducted in Ontario used modelling to determine if testing levels across the sexes had a role in CT prevalence and transmission (26). The test-adjusted incidence for age-sex subgroups identified males 15-19 and 30-39 years old had an increased infection incidence of 60.2% and 9.7% respectively, compared to observed incidence,

suggesting that these cohorts could play a larger role in CT transmission and observed positivity than initially believed.

Across cohorts, higher frequencies of individuals in lower income quintiles and southern, central, or northern health zones were not properly screened for CTNG. Females testing positive for CTNG during pregnancy had an increased likelihood of receiving a screen in their first trimester if in Q3, Q4, and Q5 compared to those in Q1. While those residing in southern health zones had a decreased likelihood of screening in the first trimester compared to those in northern health zones. Other studies have shown an association between lower income quintile and STI infection. For example, a US study found the poorest income quintile had up to 83% increased odds of STI acquisition compared to the richest quintile (27). While a Californian study found in neighbourhoods where 30% of people were below the poverty line, there was a 4.5 times higher odds of NG infection than neighbourhoods where less than 10% of individuals were below the poverty line (28). These results demonstrate factors associated with higher STI risk, yet findings in this chapter show individuals falling in these "higher-risk" categories who are not screened properly for CTNG during their pregnancy.

In 2023, PHAC updated their current CTNG screening recommendations to include universal screening in both the first and the third trimester of pregnancy (29). Though Alberta has yet to update their prenatal screening recommendations to include this second universal screen, studies can be conducted to uncover any potential benefits this new recommendation may have. An additional screen later in pregnancy may be the key to achieving higher CTNG screening values and capturing more cases.

This study was limited by the availability and completeness of the CDOM data and history of STBBI datasets. Any individuals not matched back to the provincial deliveries and

CTNG testing dataset were removed from logistic regression analysis. The decrease in power increases the likelihood of a type 2 error where the association between first trimester screening and these factors are present, however due to low sample size, the observed analysis does not reflect these potential associations.

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Chapter 3 Supplementary Figures

Figure A.1 CT positivity stratified by first performed CTNG test for distinct pregnancies in Alberta from January 1, 2019, to December 31, 2022

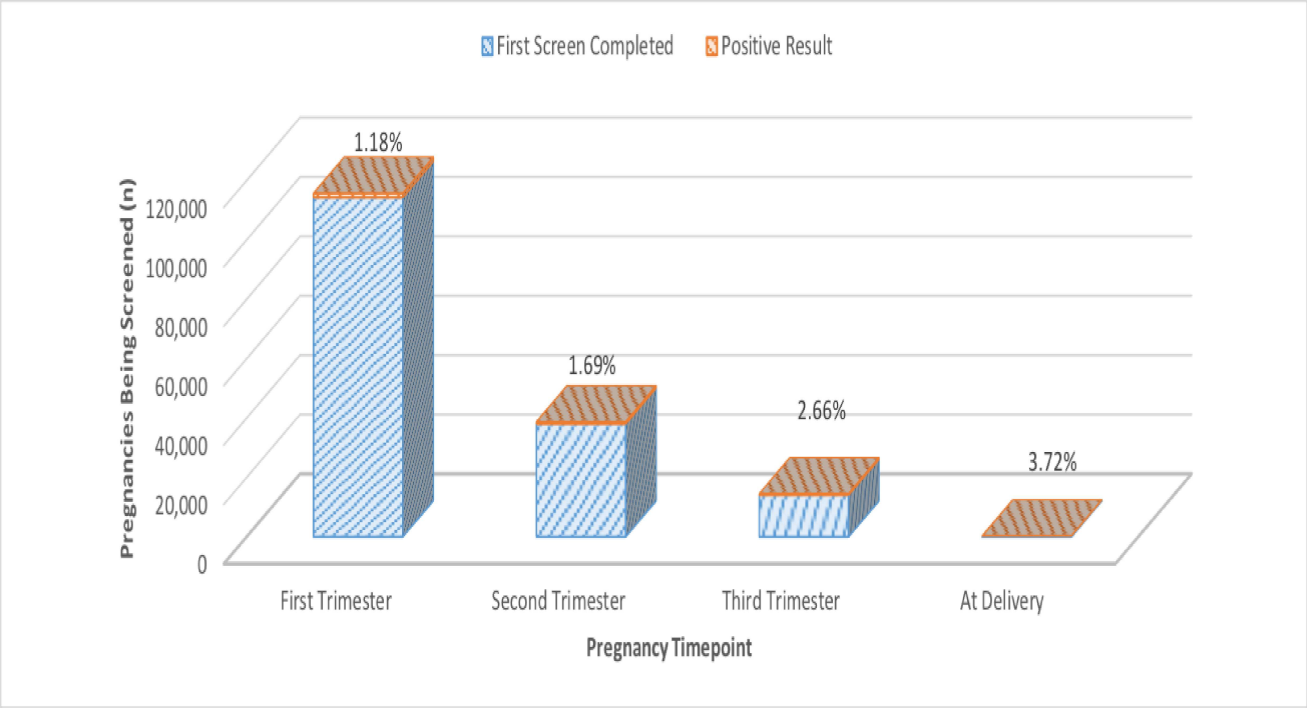


Figure A.2 NG positivity stratified by first performed CTNG test for distinct pregnancies in Alberta from January 1, 2019, to December 31, 2022

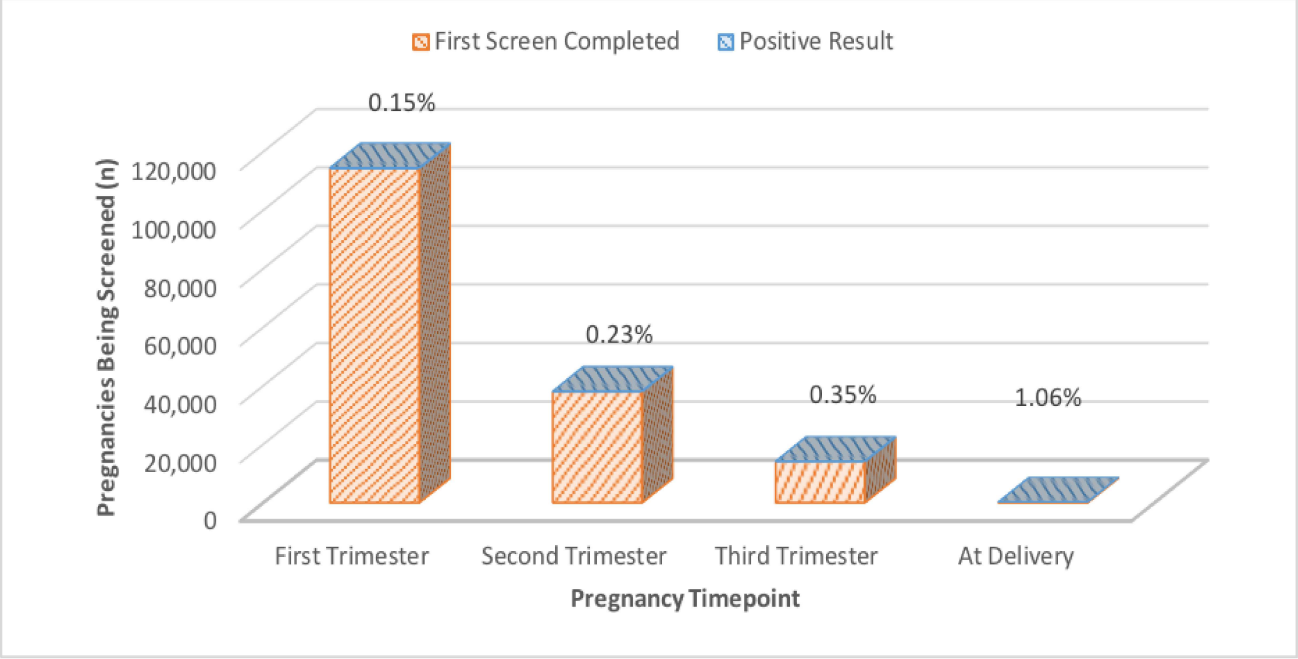


Figure A.3 Annual CT positivity stratified by distinct pregnancies screened for CTNG in Alberta.

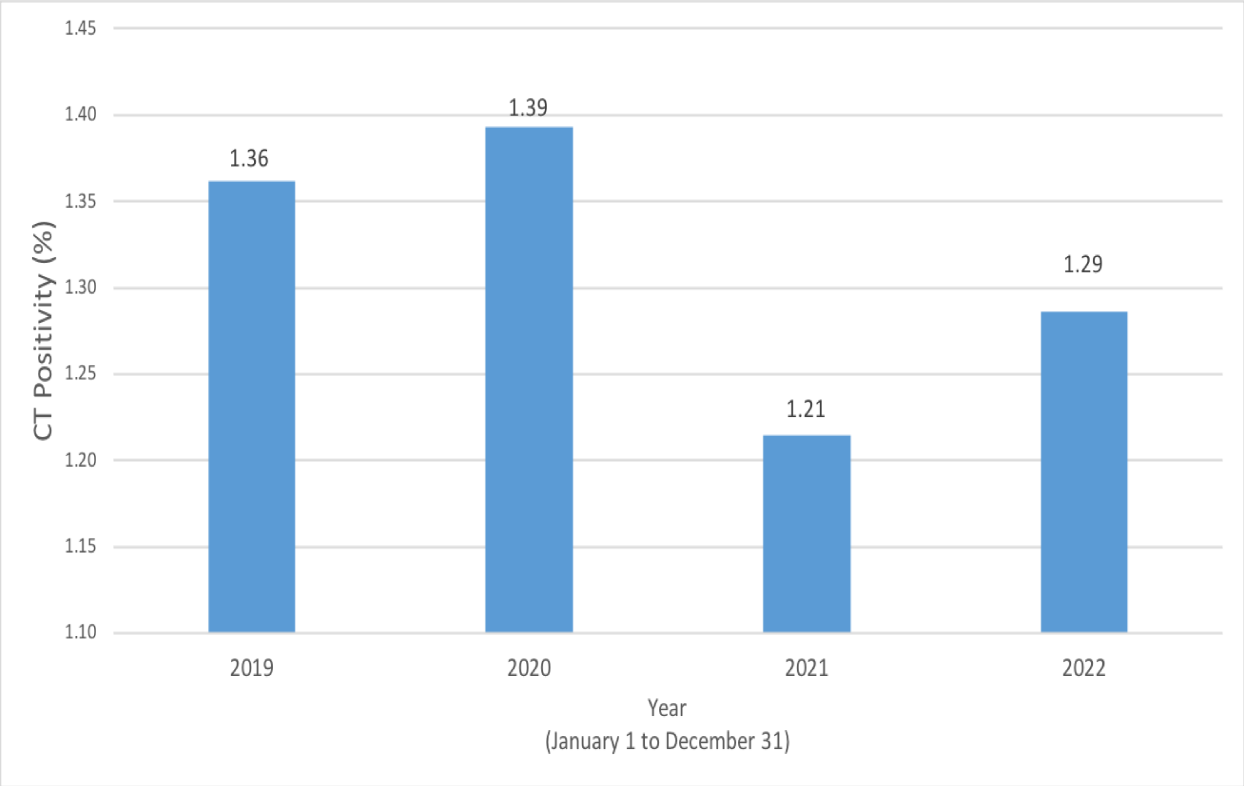
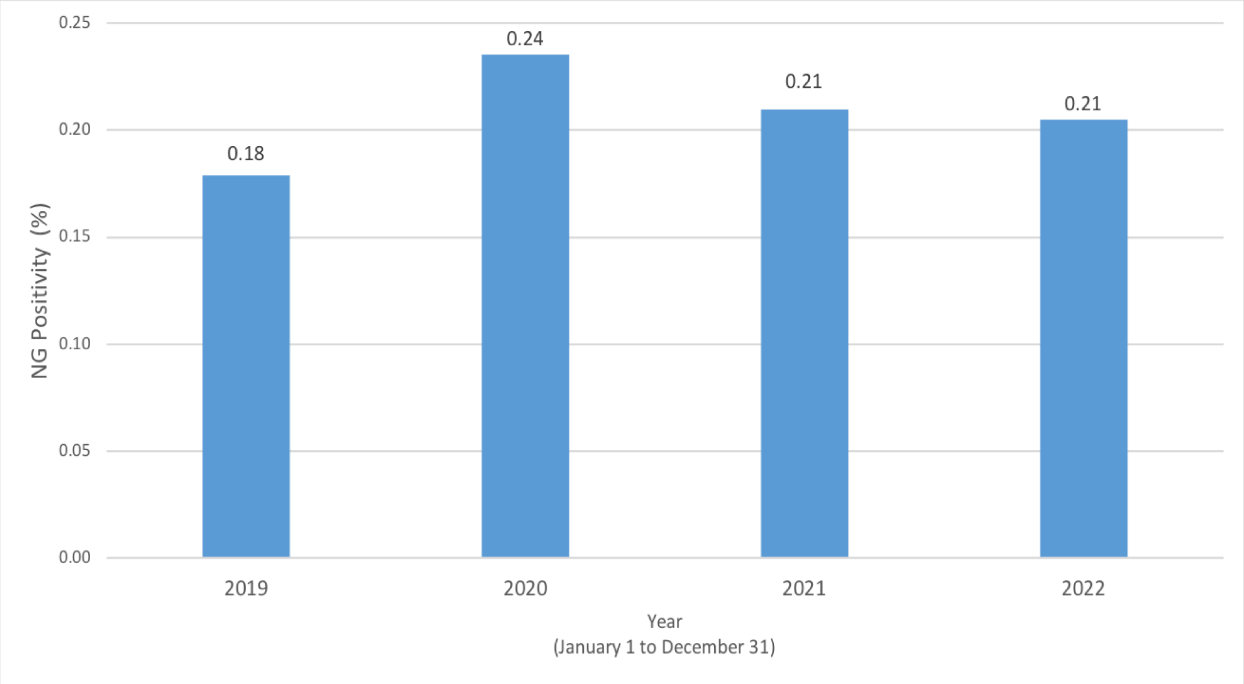


Figure A.4 Annual NG positivity stratified by distinct pregnancies screened for CTNG in Alberta



Chapter 4 Universally screening for chlamydia and gonorrhea in a post-natal population at a single hospital site in Edmonton, Alberta

4.1 Introduction

CTNG are bacteria that can cause STIs in both males and females (1,2). Vertical transmission can occur during delivery if a pregnant woman has an active infection leading to newborn health complications, such as ophthalmia neonatorum (1,2). Prenatal screening programs are in place to prevent transmission of infection from mom to infant (3). The PHAC prenatal screening recommendations for CTNG includes a universal first and third trimester screen while in Alberta, the first trimester screen is universal while a third trimester screen is recommended for high-risk or late-to-care individuals only (3,4). Little research has been conducted to determine if an additional universal screen later in pregnancy is beneficial in preventing CTNG transmission to the infant. One such study in Montréal, Canada, found that 11.4% of prenatal females < 25 years old who initially tested negative, tested positive when screened again at a later pregnancy timepoint (5). In an adolescent prenatal cohort in Toronto, Canada 28.3% of individuals were diagnosed with an STI in the third trimester (6). Finally, a study conducted in New Orleans found that 3.9% of females who tested negative for CT in the first trimester tested positive when re-screened in the third trimester, while 13.3% of females who were initially positive remained positive when re-screened, reflecting improper treatment or reinfection (7). Based on the trends observed in the literature, an additional screen for CTNG during pregnancy is shown to capture cases that may have otherwise been missed, suggesting potential benefits to implementing a second universal screen later in pregnancy.

Universal first and third trimester screening was adopted from May 1, 2016 to April 30, 2017 in a hospital in Toronto, Canada and outcomes were assessed (8). Authors noted low protocol compliance by healthcare providers as a potential explanation for missed screening

(10.1% not screened) and found overall positivity to be 1.04%. Third trimester positivity was low; however, it was observed that many testing positive lacked traditional high-risk factors associated with CTNG infection. In Alberta, where third trimester screening is based on high-risk factors alone (3), these individuals may have been missed in the absence of a second later universal screen.

The aim of chapter 4 is to: (1) assess protocol compliance of universal CTNG screening at labour/delivery at a single hospital site in Edmonton, Alberta; (2) determine if additional cases are captured from this program by comparing screening and positivity proportions to provincial high-risk third trimester screening from the year prior; and (3) determine motivations behind opting out of perinatal CTNG screening to improve inclusion if universal screening strategies should be more widely adopted.

4.2 Methods

4.2.1 Project Execution

The Royal Alexandra Hospital (RAH), a high-risk perinatal hospital in northern Alberta, was the sampling site for this study. Between March 20, 2023 and October 17, 2023, females delivering at the RAH were approached by healthcare staff to participate in universal CTNG screening. Individuals opting out of universal screening were asked for specific motivation to withdraw, which was documented in opt out binders at each participating unit by the responsible nurse (**Figure 4.2.1**). I attended change of shift meetings where nursing staff shared feedback on patient responses, leading to project modifications.

Initially, the labour and delivery unit was responsible for collecting patient samples. Due to staff feedback and low sampling numbers, collection moved to the 2nd and 3rd floor post-

partum units. 97% of females admitted for delivery at the RAH were transferred to post-partum units following delivery, providing a representative population for sampling.

A script was developed for nursing staff to use when discussing project aims to patients. This script was altered to reflect feedback from patient responses to the study.

A pizza party incentive for nursing staff was developed on a recommendation from a staff member to encourage increased sampling collection. The post-partum unit with the highest numbers received a pizza lunch.

Figure 4.2.1 Opt-out binders provided to each participating unit

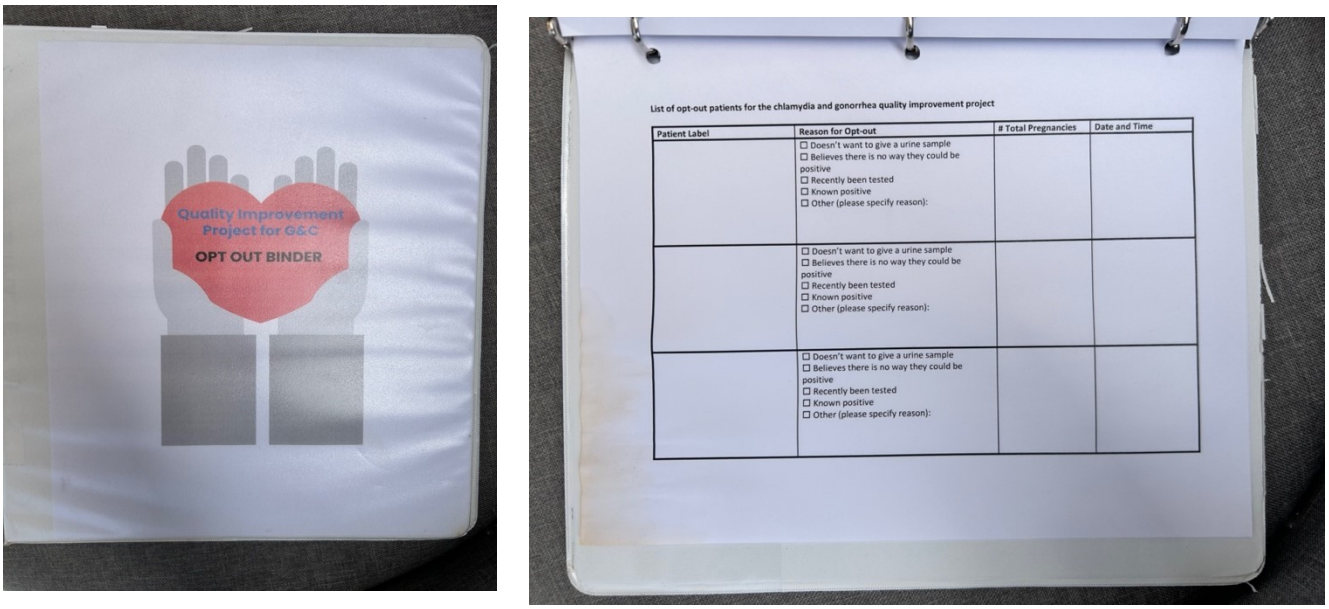


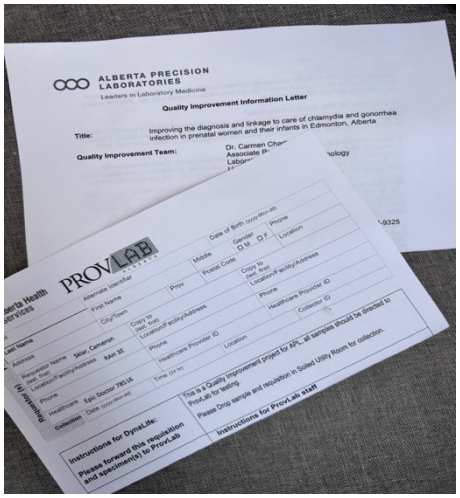
Figure 4.2.1 Legend. Opt-out binders provided to participating units. Nurses responsible for printing off a patient label, selecting opt-out reason from provided list, recording number of previous pregnancies, along with date and time of individual opting out.

4.2.2 Project Specifics

CTNG test kits were created at the University of Alberta Hospital and included a paper requisition form, a printout summary of the project (Supplementary **Figure A.5**), a urine collection cup, and an APTIMA urine collection kit (APTIMA Combo 2 Assay, Panther, Hologic) (**Figure 4.2.2**). In collaboration with Alberta Precision Labs distribution center Edmonton (ProvLab, North), test kits were transported to the RAH and collected samples were transported daily to ProvLab for NAAT.

Figure 4.2.2 Test kit components: urine collection for individuals presenting to the RAH at delivery

A



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C

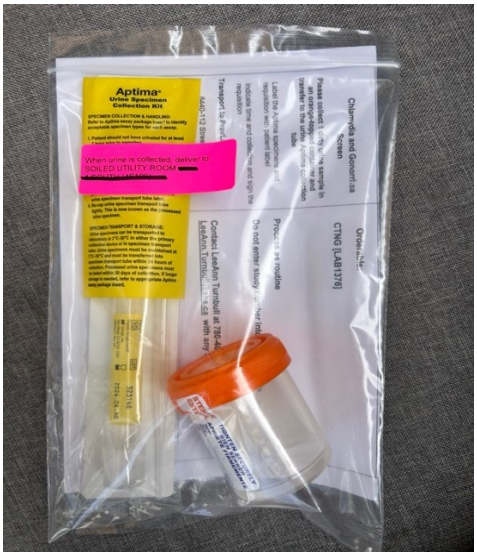


Figure 4.2.2 Legend. A) Study information letter and CTNG requisition form, B) APTIMA urine collection kit along with urine collection cup, and C) Completed test kit sent to the RAH.

4.2.3 Data Collation

Data from opt-out binders were transcribed into Excel 2013 (Microsoft Corporation, Redmond, Washington) and imported into STATA v. 17.0 (StataCorp, College Station, Texas, USA) for analysis. The proportion of opt-out from testing was calculated by dividing the number of individuals opting out by the total number of individuals participating in the study.

Proportions for study participation were determined by dividing the number of females approached to participate in the study by total deliveries at the RAH during the defined period. CTNG post-partum screening study results were extracted from ProvLab LIS databases. Any samples for CTNG testing routed through DynaLife Base Laboratory for testing were extracted from the DynaLife LIS and were included in the total number of samples screened. The total number of individuals admitted for delivery at the RAH during the study period was determined using DAD where discharges from acute care institutions in Alberta, including the RAH, are recorded. The proportion of females screened in the pilot was calculated by dividing the number of individuals screened for CTNG at post-partum by the total number of individuals delivering at the RAH during the study period. CTNG positivity was calculated by dividing the number of positive CTNG results by total number of individuals screened. Postal code data from the 2021 Alberta census estimates provided income quintile and geographic region (rural, urban, or metropolitan) which was merged to the screening results dataset using maternal postal codes. A screening result variable was created where all positive test results; whether CT, NG, or CTNG

positive, were defined as positive, and negative results were defined as negative and a test result variable was created to define an individual as NG positive, CT positive, or CTNG positive.

A provincial comparison dataset was created by examining CTNG screening for individuals from the prior year within the same date range (March 20, 2022 to October 17, 2022) who received a third trimester CTNG screen or an "At Delivery" screen (up to 2 days after delivery). An individual was considered "screened" if they received a valid test result. Duplicates were dropped and the earliest valid result was analyzed for individuals screened multiple times during the defined period. The provincial proportion of individuals who were screened in the third trimester or at delivery was determined by dividing the number of screened individuals by total deliveries. Positivity was calculated by dividing positive CTNG results by the number of individuals screened.

4.2.4 Statistical Analysis

Data was collated using STATA v. 17.0 (StataCorp, College Station, Texas, USA), figures were produced using Microsoft Word 2013 (Microsoft Corporation, Redmond, Washington), and tables were produced using Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, Washington). Screening proportion and positivity were compared between 2023 RAH outcomes and 2022 provincial outcomes using two-sample z-tests. Chi^2 or Fisher's Exact test for small cell counts to assess associations between screening results and demographic variables.

4.2.5 Ethical Statement

Ethics was approved by the University of Alberta Research Ethics Board Pro00106321.

4.3 Results

4.3.1 Study Summary

3,761 females were admitted to the RAH for delivery between March 20, 2023 and October 17, 2023. 667 (17.73%) were approached to participate in universal CTNG screening. 77 (11.54%) opted-out of CTNG screening after being approached (**Figure 4.3.1**).

Figure 4.3.1 RAH study summary with inclusion and opt out proportions

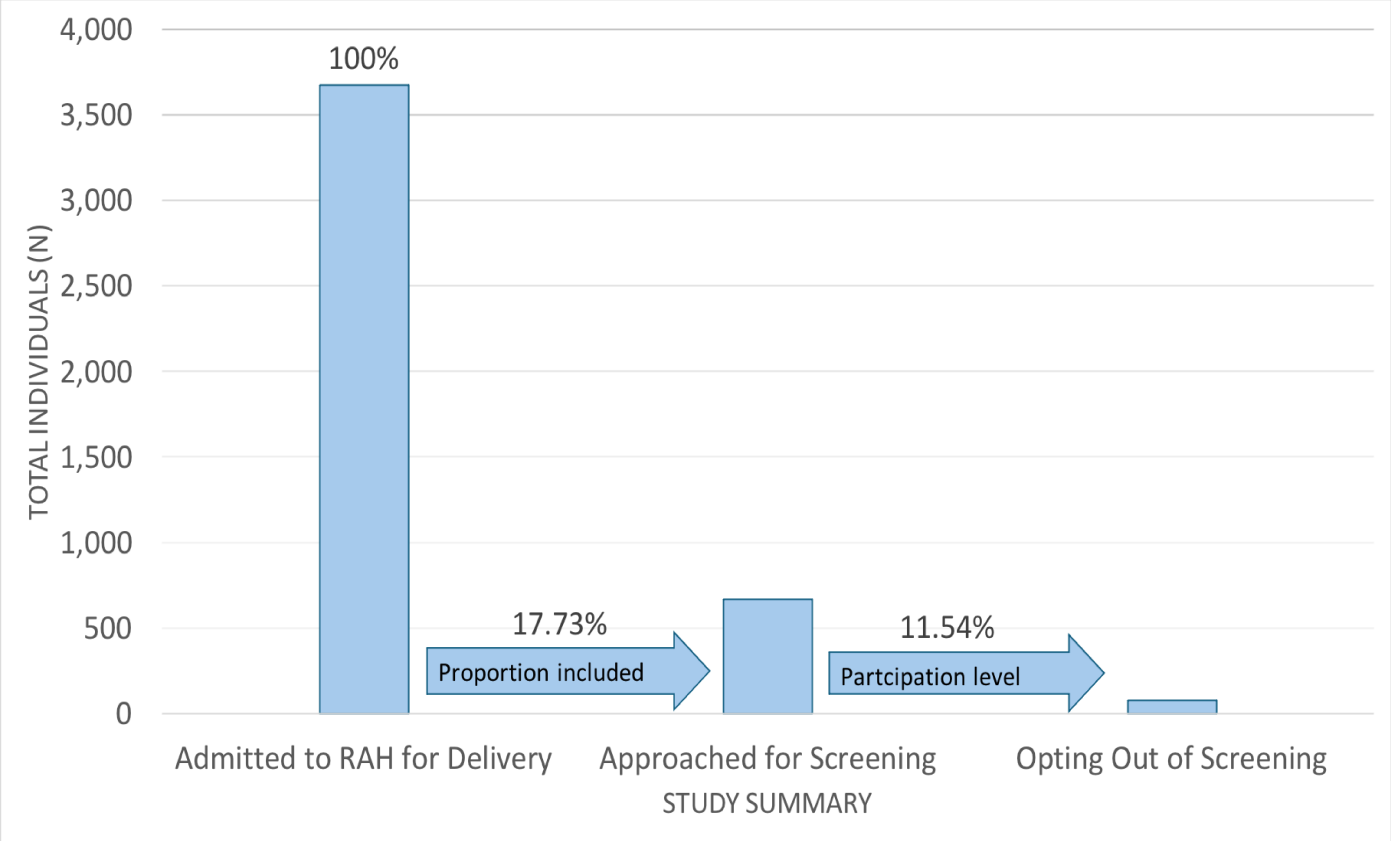


Figure 4.3.1 Legend. Proportions above blue arrow calculated using previous value as denominator. 667 individuals approached for screening, out of 3,761 deliveries (17.73%). 77 individuals opted out of the current study, out of 667 individuals approached to participate (11.54%).

4.3.2 Motivations for Opting Out

77 individuals approached to participate opted out of the current study and 76 (98.7%) individuals provided a reason. 54 (71.1%) chose not to give a sample, 7 (9.21%) individuals chose not to give a sample and cited a low likelihood of positivity, 3 (3.95%) individuals cited a low likelihood of positivity, 3 (3.95%) provided no reason for opting out, and 3 (3.95%) cited too much discomfort or anxiety. 2 (2.63%) individuals were recently tested, and 1 (1.32%) individual has been with one partner thus seeing screening as unnecessary, 1 (1.32%) individual withdrew, citing "disbelief in research", 1 (1.32%) left before a sample could be taken, and finally, 1 (1.32%) individual was recently tested, cited low likelihood of positivity, and chose not to give a sample (**Figure 4.3.2**).

Figure 4.3.2 Motivation behind opting out of universal third trimester or post-partum CTNG urine-based screening.

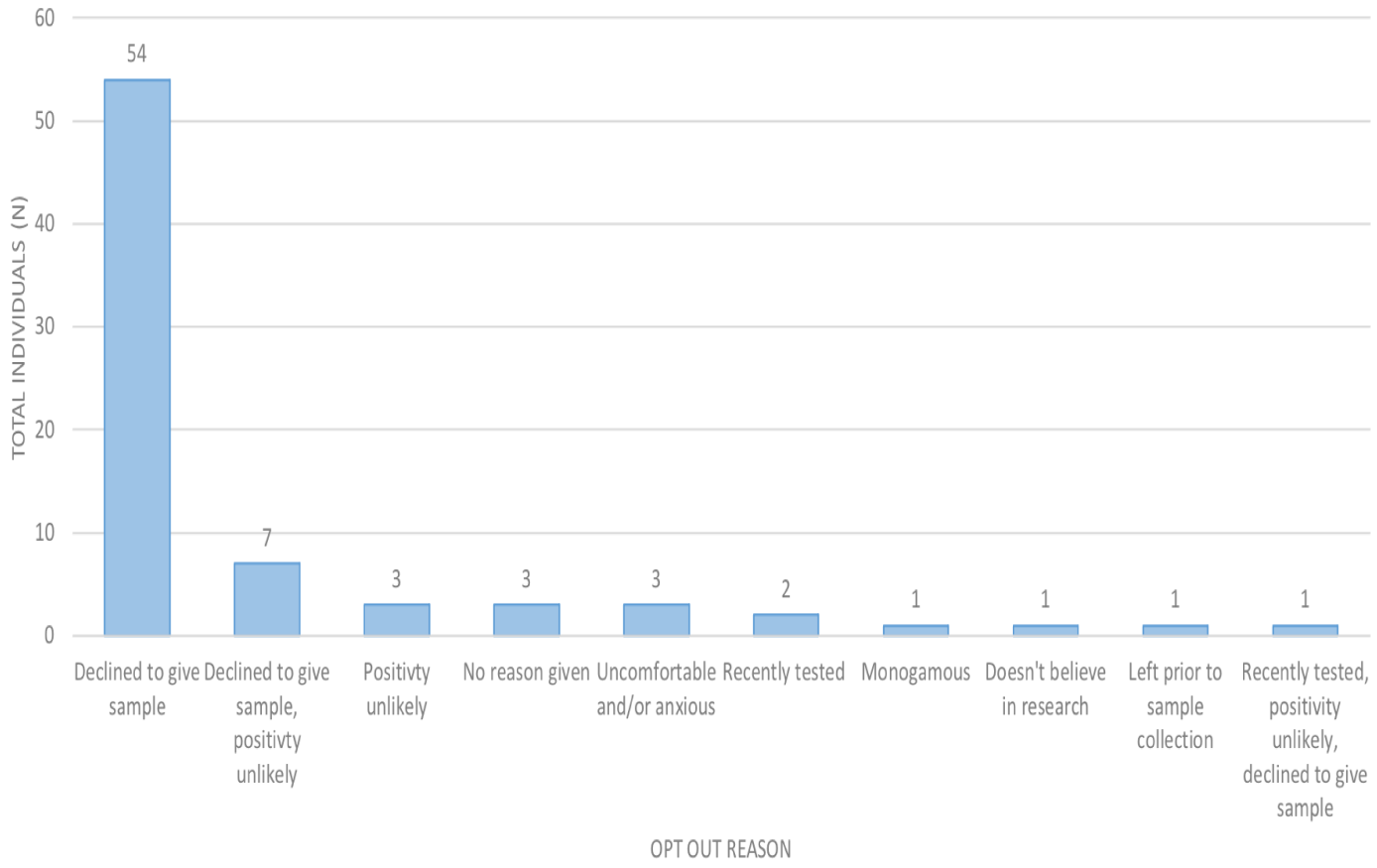


Figure 4.3.2 Legend. Numbers above the bar represent number of individuals selecting reason for opting out of the study as recorded in the opt-out binders.

4.3.3 Screening and Positivity Proportions

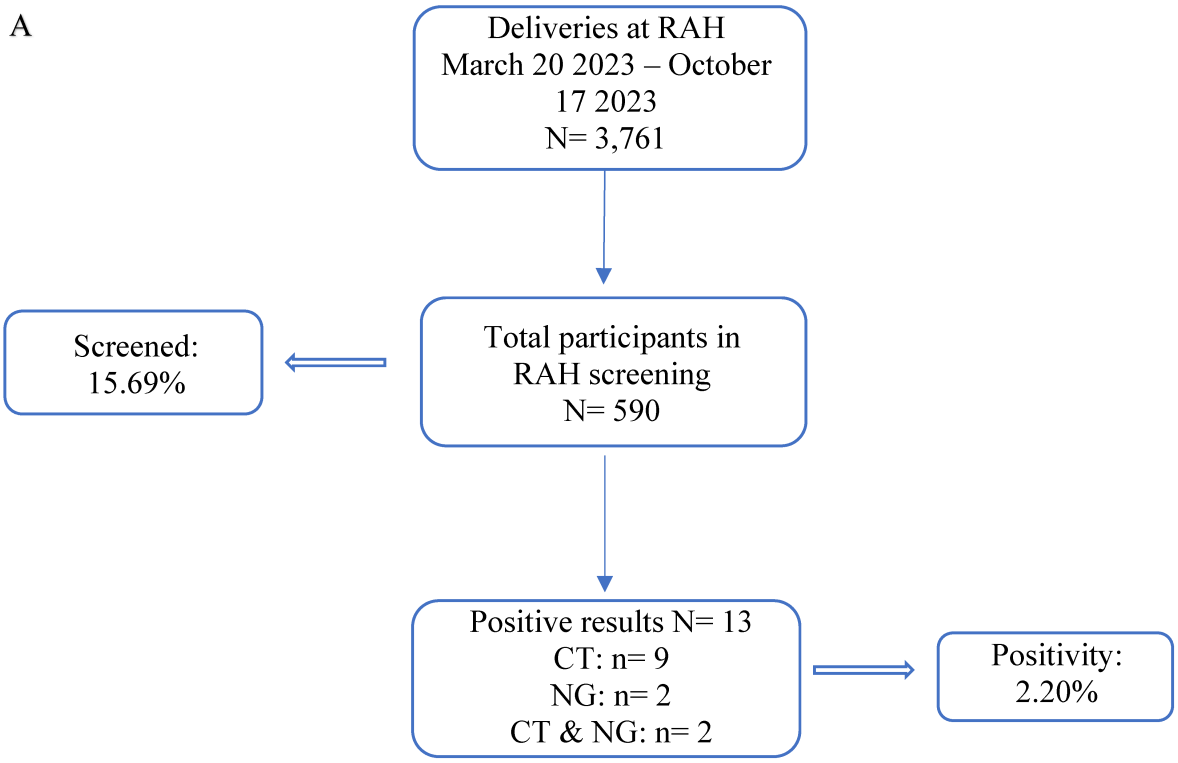
Among the 3,761 females admitted to the RAH for delivery, 590 (15.69%) individuals were screened for CTNG at least once during their post-partum period. 13 (2.20%) test results were positive, with 9 individuals testing positive for CT, 2 for NG, and 2 with a coinfection (both CT and NG positive; **Figure 4.3.3 A**). No demographic variables were significantly associated

with screening results, though a higher frequency of those testing positive were from the lowest income quintiles, Q1 and Q2, compared to those testing negative. (**Table 4.3.1**).

In comparison, 27,548 provincial deliveries were recorded between March 20, 2022 and October 17, 2022. 3,916 (14.22%) individuals were screened at least once during the third trimester or at delivery, following high-risk screening protocol. Provincial screening proportions in 2022 were significantly lower than screening proportions seen at the RAH in 2023 during the pilot project period ($p= 0.016$).

Among the 3,916 individuals screened provincially following high-risk protocol in 2022, 94 (2.40%) individuals tested positive; with 79 individuals testing positive for CT, 11 for NG, and 4 with a coinfection (both CT and NG positive). There was no significant difference in positivity between 2022 provincial and 2023 RAH results ($p = 0.766$; **Figure 4.3.3 B**). Geographic region and income quintile were significantly associated with screening in provincial analysis ($p= 0.011$ and $p < 0.001$, respectively). A higher proportion of those testing positive were from the lowest income quintile compared to those testing negative (54.22% and 25.76%, respectively). Similarly, those testing positive had a higher frequency of residing in urban or rural geographic regions compared to those testing negative (11.83% vs. 6.78% and 31.18% vs. 22.33%, respectively) (**Table 4.3.2**).

Figure 4.3.3 RAH screening results in comparison to provincial high-risk screening results



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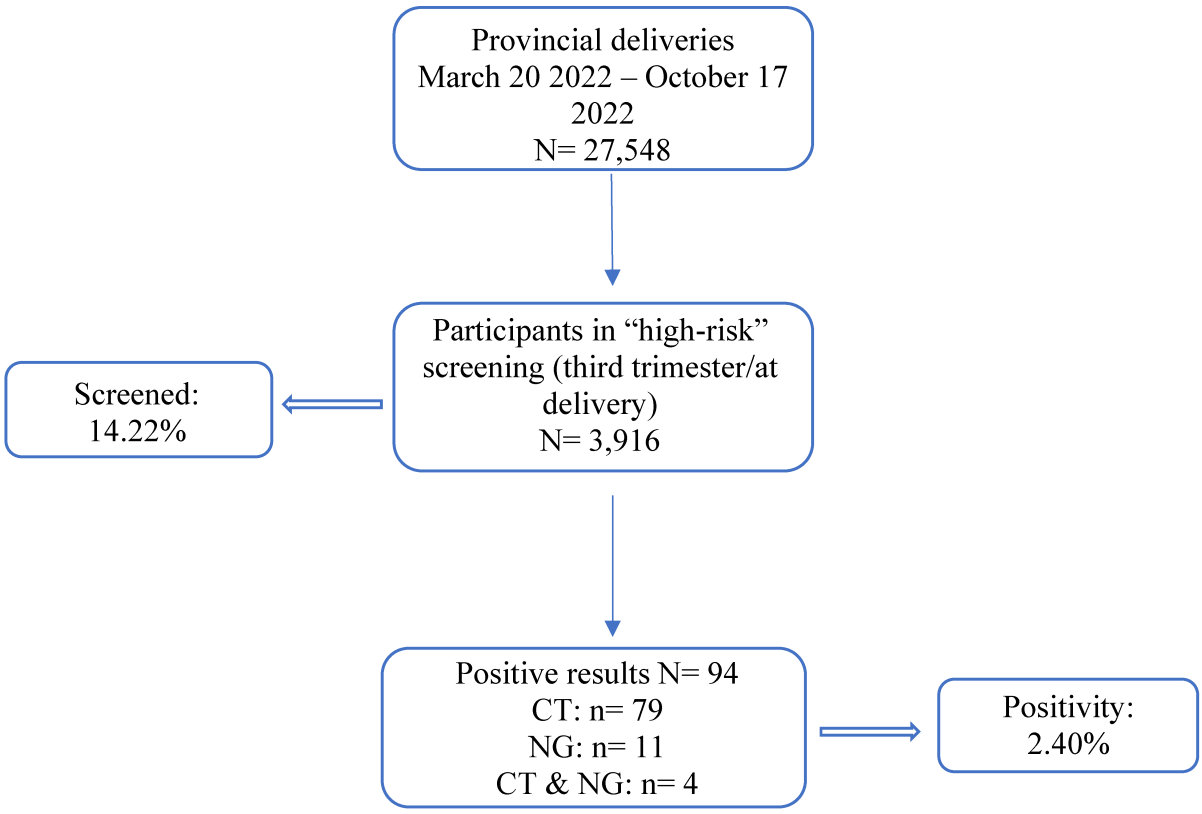

Figure 4.3.3 Legend. A) CTNG screening proportion and positivity from the RAH between March 20, 2023 and October 17, 2023, B) CTNG screening proportion and positivity from province for those receiving a third trimester or At Delivery screen from March 20, 2022 to October 17, 2022.

Table 4.3.1. Descriptive statistics for perinatal patients screened for CTNG at the RAH from March 20, 2023 to October 17, 2023.

	Negative n (%) N= 360	Positive n (%) N= 8	p-value*
Geographic Region (n=368)			1.00
Metro (n=316)	309 (85.83)	7 (87.50)	
Urban (n=0)	0	0	
Rural (n=52)	51 (14.17)	1 (12.50)	
Income Quintile (n=368)			0.279
Q1 lowest (n=103)	99 (27.50)	4 (50.00)	
Q2 (n=86)	83 (20.17)	3 (37.50)	
Q3 (n=47)	46 (12.78)	1 (12.50)	
Q4 (n=82)	82 (22.78)	0 (0)	
Q5 highest (n=50)	50 (13.89)	0 (0)	

n: sample size, %: frequency of column totals
*: p-value based on Fisher's Exact test with significance at p-value at ≤ 0.05

Table 4.3.2. Descriptive statistics for provincial patients screened for CTNG from March 20, 2022 to October 17, 2022.

	Negative n (%)	Positive n (%)	p-value*
Geographic Region (n=3,900)	**N= 3,807**	**N= 93**	0.011*
Metro (n=2,752)	2,699 (70.90)	53 (56.99)	
Urban (n=269)	258 (6.78)	11 (11.83)	
Rural (n=879)	850 (22.33)	29 (31.18)	
Income Quintile (n=3,421)	**N= 3,338**	**N= 83**	< 0.001
Q1 lowest (n=905)	860 (25.76)	45 (54.22)	
Q2 (n=646)	636 (19.05)	10 (12.05)	
Q3 (n=630)	625 (18.72)	5 (6.02)	
Q4 (n=655)	638 (19.11)	17 (20.48)	
Q5 highest (n=585)	579 (17.35)	6 (7.23)	

n: sample size, %: frequency of column totals
*: p-value based on Chi2 test with significant p-value at ≤ 0.05

4.4 Discussion

PHAC guidelines now recommend a third trimester screen for all pregnant females (4). If no third trimester screening occurs, one during labour will ensure successful capture and treatment of cases in mom and baby (4). The current study sought to establish a universal CTNG perinatal screening program at a single hospital site in Edmonton, Alberta. However, less than 20% of females presenting for delivery at the RAH were approached to participate in this universal screening study. Low protocol compliance by healthcare staff may contribute to these suboptimal levels, however, more research is required to determine why so few females were approached. Alterations made to the patient script and the pizza party incentive led to an increase in sampling numbers; however, levels continued to remain suboptimal. The RAH CTNG pilot study had a significantly higher proportion of screened individuals than comparable provincial screening in the previous year; however, the total proportions screened were similar (14.22% vs. 15.69%). CTNG positivity was not significantly different between the RAH pilot project and provincial screening from the previous year. This pilot study was unsuccessful at establishing a universal screening program and instead reflected results similar to current risk-based screening protocol. However, it should be noted, with over 80% of females not approached for the pilot study, screening proportions and positivity results likely do not reflect true RAH population findings.

However, 88.46% of individuals approached agreed to be screened for CTNG. This number reflects considerable willingness to participate in CTNG screening following delivery. By increasing target population participation, future studies could be successful in establishing another universal screening program.

The benefits of an additional CTNG screen at a later timepoint in pregnancy is evident in the literature. A national retrospective review was conducted in the US where authors determined 6.04% and 3.83% of females initially testing positive for CT and NG, respectively, were positive at their last perinatal test, possibly due to lack of treatment or reinfection (9). Another retrospective study found factors associated with a higher likelihood of CTNG infection in pregnancy included initiating prenatal care late or not receiving any prenatal care (10). These studies confirm that universal screening for CTNG later in pregnancy could capture cases that may have otherwise been missed.

Motivations on why individuals chose to opt out of this study were primarily due to the reluctance of giving a sample. Understanding why individuals choose to participate in prenatal STI screening programs can improve future studies. In one example, pregnant females seeing a midwife and their partners were asked to provide a sample for CT testing, and then complete a questionnaire (11). The majority of individuals in the study (54%) believed that all females should be tested during pregnancy and the majority of females (56.2%) and their partners (59.2%) felt satisfied about being offered the test, while less than 2% of females and 4% of partners felt stigmatized by the screening offer (11). In another study, prenatal females in Vietnam were approached to provide a self-collected vaginal swab or urine sample for CTNG testing; 99.5% of females consented to being tested (12). Those who refused, remarked being too tired, having no interest, not having enough time, or being tested elsewhere, while 97% of females agreed that STI screening during pregnancy is very or somewhat important (12). In a separate study, a cohort of prenatal females were highly supportive of routine CT screening during pregnancy (13). During conducted interviews, all females supported testing for chlamydia as part of routine perinatal care with overall themes of being “no big deal” given all other routine

testing done during pregnancy. The biggest motivator behind supporting a CT screen was to improve the safety and health of the baby. As individuals learned about the risks of CT infection in their infants, they were more supportive of having a CT screen during pregnancy to prevent transmission (13). Overall, these studies support the acceptance that most pregnant females tend to have towards screening for STI's, specifically CTNG, during their pregnancy. If Alberta were to establish another prenatal universal CTNG screen, the acceptability may be high, based on the literature and the high number of females from the RAH accepting screening when approached (88.46%).

The cost benefit analysis of implementing universal prenatal screening programs is evident in the literature. A model was developed in one study to estimate costs and health effects of screening pregnant females for CT in a high burden setting in New York (14). If CT prevalence was above 16.9% in pregnant females aged 15-24 years old, a net cost savings would result from each individual being screened during pregnancy compared with no screening (14). An Australian study found universal screening was cost-effective if the CT prevalence in pregnant females aged 16-25 years was 3% or greater compared to no screening with a $50,000 per quality-adjusted life-years (QALY) threshold (15). If this population prevalence increased to greater than 5% with a $50,000 QALY threshold, universal screening was superior to selective screening (15). A study conducted in the Netherlands showed there was a net cost-saving outcome if all prenatal females were screened for CT during pregnancy with a prevalence equal to or greater than 3.2% (16). This was found to be especially true in females aged 30 years old or younger and females with their first pregnancy. Overall, these studies show there is a cost-effectiveness gain when universal prenatal STI screening programs are implemented. As CT and NG are highly asymptomatic and have high reinfection proportions in females, another universal

screen may be the most effective means in capturing and treating cases prenatally before infection is transmitted to the infant (17–19).

There are several limitations to the project conducted in this chapter. Firstly, potential biases from nursing staff may have led health care workers to approach individuals to participate who were already considered higher risk for infection as opposed to universally screening all individuals regardless of risk factors. This may have led to an inflation of positive results and not be reflective of true positivity from the RAH population. Another potential bias is language barriers present between healthcare staff and participating individuals. If individuals approached to participate were unable to fully communicate their questions or did not wish to engage in a conversation, non-participation or agreement to participate to appease the healthcare staff may have resulted. These biases may have had a direct impact on the results observed in the current study such as overrepresentation of social and demographic factors that may be present in this sub-population. Additional research is required to determine if universal third trimester screening is superior to current testing.

In summary, this chapter reports the findings of the attempt to establish a universal screen at the RAH. This study was unsuccessful in establishing a universal screening program with screening levels instead reflective of high-risk screening protocol. Additionally, the main motivator behind opting out of universal CTNG screening was an individual's choice to not give a sample.

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Chapter 4 Supplementary Figures

A.5 Quality Improvement Information Letter

Quality Improvement Information Letter

Title: Improving the diagnosis and linkage to care of chlamydia and gonorrhea infection in prenatal women and their infants in Edmonton, Alberta

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What is the Quality Improvement Project?
Chlamydia and gonorrhea cause infection in both women and men. Often people have no symptoms so do not know that they have these infections unless they are tested. If infection is not treated when a woman is pregnant, the baby can get chlamydia or gonorrhea at birth. The baby may then get eye infection or pneumonia.

To prevent these problems in the baby, all pregnant women in Alberta are supposed to be tested for chlamydia and gonorrhea at least once during the pregnancy. However, not all doctors or mid-wives order the test. Sometimes women develop chlamydia or gonorrhea without knowing it between when they are tested and when they deliver.

The reasons for this quality improvement project is to see how many chlamydia and gonorrhea infections are being missed in pregnant women. If many infections are being missed, then we may decide in the future to test all women for chlamydia and gonorrhea at about 35 weeks gestation when they are being tested for group B Strep.

What do I need to do?
A a urine sample will be collected and sent to the lab. This can be done before or after you deliver. The results will be sent to your doctor.

If you tell your nurse or doctor that you do not want to participate in the quality improvement project, the urine will not be sent to the lab. No one will be annoyed with you. You will receive the same care that you otherwise would.

What are the benefits to me and my baby?
Treatment of chlamydia and gonorrhea prevents complications and prevents spread to other people. If you are positive for gonorrhea, you and your baby will be given antibiotics. If you are positive for chlamydia, you will be given antibiotics and told what to watch for in your baby.

What are the risks to me and my baby?
There are no risks to participate in this quality improvement project. If you are positive for chlamydia or gonorrhea, you will be asked to name your sexual contacts if you are willing to do so. They will then be advised to be tested but will not be told that it was you who named them as a contact.

What if I change my mind?
You can change your mind at any time. If you agreed to participate in the quality improvement project but no longer want to, let your nurse or doctor know. We will not run the tests on your urine if they have not already been run. If you did not want to participate at first but now do, please let your nurse or doctor know before you go home.

Who will be able to find out my results?
Your results will be kept confidential. Only the laboratory technicians, the quality improvement team (the three people listed on the first page) and your doctor will see your results. They know that they are not allowed to share your results with anybody else.

Where will results be stored?
The results will be entered into your electronic healthcare record, just as any other laboratory test would be. Only your doctors or clinical care team, and the quality improvement team will have access to these files.

What if I have questions?
If you have any questions regarding the quality improvement project, you can contact your doctor or the quality improvement team listed on the front of this letter.

If you do not want your urine sample to be tested, please simply tell the nurse or doctor. Unless you state otherwise, we will assume that you consent to the collection and use of your samples for the purposes described above.

Chapter 5 Discussion, Significance, and Future Directions

5.1 Discussion

CTNG infections have steadily been on the rise throughout Canada since 2012, and prenatal females are a targeted population for screening (1). Nationally, NG resistance has been monitored for growing AMR (2). The rise of NG strains with resistance to commonly deployed antimicrobials has occurred since the beginning of the antibiotic age (3). AST is utilised to identify isolates with non-susceptibility to antimicrobials. In 2001, Alberta began examining AMR of NG strains isolated from the province (4). Results of provincial AST on all antimicrobials have not been updated since 2016 (4). In **Chapter 2**, 4,056 isolates from 3,617 individuals were cultured for NG in the province between 2016 and 2022. The lowest proportion of susceptibility was observed for penicillin, tetracycline, and ciprofloxacin (**Figure 2.3.1 & Figure 2.3.2**). This is consistent with findings in the literature, where susceptibility is lowest for antimicrobials no longer in use (2,4). Cefixime and ceftriaxone remained 100% susceptible for all isolates in females of childbearing age (**Figure 2.3.2**). In 2018, one isolate from a 32-year-old male showed resistance to cefixime and ceftriaxone. Azithromycin susceptibility remained high, though never reached 100% (**Figure 2.3.1**). These outcomes are reflected in recent provincial reports (5), where AMR trends show levels of decreased susceptibility to currently deployed antimicrobials. The rise of strains with resistance to azithromycin has been identified nationally and globally (6–8). NG isolates with resistance to azithromycin is steadily rising in the EU (6); while *mtr* mutations are being identified as a major source of azithromycin resistance in strains identified from North America (7,8). In chapter 2, a higher frequency of isolates with resistance to azithromycin was found in males (81.16% vs. 91.77%) and in those residing in the Edmonton health zone (36.71% vs. 51.90%) (**Table 2.3.1 B**). The major finding of **Chapter 2** is that current

provincial AST results show high level susceptibility against the antimicrobials in current first-line treatments (azithromycin and ceftriaxone/azithromycin and cefixime); however, azithromycin susceptibility remains below 100% and higher concentrations of cephalosporins (cefixime, ceftriaxone) are beginning to be needed for NG clearance, emphasizing the need for alternative treatment options.

Since the establishment of a CTNG prenatal screening program in Alberta in 2018, only one retrospective review has been conducted to assess implementation success (9). In **Chapter 3** further analysis on screening guideline adherence and population positivity was completed with the inclusion of additional demographics. Between 2019-2022, 194,386 deliveries were recorded; 86% were screened for CTNG at least once during pregnancy (**Figure 3.3.1**). 67% of individuals who received CTNG testing were screened during the first trimester, which is adherent to the universal first trimester screening guidelines (**Figure 3.3.1**). From 2018, first trimester CTNG screening gradually increased each year, until 2022, where a slight decrease was observed (**Figure 3.3.2**). These suboptimal levels are similar to what has been observed in other provinces (10–12). First trimester guideline adherence was lowest in southern, central, and northern health zones, respectively, and in lowest income quintiles (**Table 3.3.2**). Logistic regression analysis identified individuals in higher income quintiles (Q3, Q4, and Q5), had a higher odds of being screened in their first trimester compared to those in the lowest income quintile (Q1) when testing positive for CTNG during their pregnancy; while those in southern health zones had a decreased odds of being screened in their first trimester compared to those in northern health zones. (**Table 3.3.4**). Other research has identified prenatal STI screening adherence was lowest in lower income quintiles and non-metropolitan residences (13), similar to results found in **Chapter 3**.

Prenatal CTNG screening practices differ globally. As of 2008, New Zealand recommends universal CT screening for pregnant females, while no recommendations are in place for NG (14). In New Zealand, authors performed a retrospective analysis to determine CT prenatal screening adherence and identified suboptimal CT screening (<62%) across 4 different cities despite universal recommendations (15). The US Preventive Services Task Force and CDC recommend screening all pregnant individuals aged 24 or younger and screening again in the third trimester for those at high risk (16,17). Retrospective analysis conducted in the US from 2010-2018 analyzed the pregnant population to uncover trends in CTNG testing and prevalence (18). Authors identified over 30% of females aged 20-24 remained unscreened and higher screening levels were observed in Black non-Hispanic or Hispanic persons, suggesting screening occurred based on perceived risk despite universal recommendations (18). There are currently no CTNG prenatal screening recommendations in place in the UK, though CT screening is offered opportunistically for all sexually active females younger than 25 accessing sexual health care (19,20). An identified barrier to successful establishment of prenatal CTNG screening programs includes inconsistent evidence in the literature for the benefits of universal CT and NG screening compared to risk-based screening (21). The major conclusions of **Chapter 3** are that suboptimal prenatal CTNG screening is occurring in the province despite established universal screening recommendations and that high frequencies of individuals who are considered high risk for STIs are not being screened according to guidelines. Potential improvements could be made by establishing an additional universal screen at a later perinatal timepoint to ensure the capture of individuals late to care and those not being screened in their first trimester.

To determine if an additional universal CTNG screen at a later perinatal timepoint would be beneficial, all females were to be offered CTNG testing to mimic a universal program at the

RAH between March 20 to October 17 in 2023 (**Chapter 4**). A total of 3,761 females were admitted for delivery at the RAH as the target population for universal screening. 17% (667) of females were approached to participate in the study, and over 88% (590) provided a sample for CTNG testing (**Figure 4.3.1**). Choosing to not provide a specimen for testing was the primary (82.9%) motivator behind opting out of the current study (**Figure 4.3.2**). A 2022 dataset was analyzed to compare results of this program to the current provincial risk-based program for individuals receiving a CTNG screen in their third trimester or at delivery. More females were screened at this perinatal timepoint compared to provincial proportions from the previous year; however, the proportion of cases captured from screening remained the same (**Figure 4.3.3 A/B**). Understanding patient perspectives on STI screening could be a factor in improving the establishment of future screening programs in the prenatal population. In Australia, females in the general population were asked of their experiences receiving a CT screen and perspectives were compared between those with positive or negative test results (22). Surprisingly, authors found individuals testing positive were pleased to be tested, less anxious about a positive result than females testing negative, and reported they would be more likely to change their sexual behaviour in the future compared to those testing negative (22). Authors found that supports such as informative websites, access to one-on-one telephone consultations with sexual health physicians, and sensitive management of results, increase the degree of comfort experienced with testing (22). In the UK, authors uncovered the perspectives of males and females testing for CT during their study (23). Overall, it was found that discomfort and anxiety was present when individuals were approached to participate in CT screening, and that females were more concerned with stigma surrounding a positive result (23). Authors found that the fear of stigma was more prevalent than actual concrete judgements individuals faced. And despite negative

connotations with CT testing, females testing positive cited a sense of relief at capturing cases to combat further complications from untreated infections (23). Finally, young females in Australia were asked their opinion on CT screening implementation in general practice (24). Predominant responses were the preference of screening all females as opposed to targeting high-risk individuals based on a sexual history assessment. Most females did not want to be asked about their sexual history and some reported they would most likely lie if asked (24). Patient perspectives identified in these studies can be applied to prenatal populations to increase acceptance and comfort of future prenatal STI screening programs.

5.2 Significance

The findings in this thesis are significant in numerous respects. **Chapter 2** describes current AMR trends in NG strains isolated across the province and includes descriptive statistics to identify population-level patterns. While other studies have analyzed prenatal CTNG screening implementation success in the province (9), novel findings in **Chapter 3** include an in-depth assessment of individuals testing positive for CTNG at least once during their pregnancy. Factors affecting the odds of being screened following CTNG first trimester screening guidelines has not been conducted for Alberta's prenatal population before, providing a clear picture of where the province is missing the mark for prenatal CTNG screening. And finally, attempting to establish a universal third trimester/post-partum CTNG screening program for females in **Chapter 4** has not, until now, been conducted in the province. This program helped identify barriers and perspectives on universal prenatal CTNG screening at a later perinatal timepoint to aid in the future establishment of universal STI screening programs.

5.3 Future Directions

Interesting findings have been uncovered from provincial NG AST results and CTNG prenatal screening results; however, there are avenues that can be explored further. Sequence typing (ST) is a beneficial tool that can be used to determine the genotype of bacterial strains. The NML in Manitoba is responsible for sequencing gonorrhea isolates throughout Canada (25). The NML uses NG multi-antigen sequence typing (NG-MAST) on gonorrhea positive samples to determine genotype (26). It would be beneficial to analyze NG-MAST results from Alberta isolates with azithromycin resistance and decreased cefixime and ceftriaxone susceptibility. Results will help identify strains present in the province and the mechanisms of AMR in these strains. This further aids decision makers on treatment options.

The Alberta prenatal CTNG screening program was established in 2018 (27), and while this thesis did not have access to results prior to 2019, it would be beneficial to include analysis from years prior to guideline implementation. This will assess improvements resulting from the prenatal CTNG screening program. Previous research in the US identified delays from time of diagnosis to treatment, with over half of CTNG positive prenatal females treated after more than 7 days (28). The most common reasoning for treatment delay was the lack of health care provider recognition of the result, followed by difficulty contacting patients (28). The research conducted in this thesis identified 431 pregnancies with multiple positive test results at different time points within the same pregnancy. Analyzing treatment data can uncover treatment delays or occurrences of reinfection in the prenatal population and help educate health care staff on the importance of quick and effective treatment of females testing positive for CTNG.

And finally, due to the failure of establishing universal CTNG screening at the RAH, future studies can seek to establish a universal program at another site to determine benefits of an additional universal CTNG screen at the third trimester as recommended by the PHAC (29).

In conclusion, prenatal CTNG screening ensures successful treatment during pregnancy to prevent transmission to the infant (30), yet suboptimal screening levels are occurring in Alberta. Since 2023, the PHAC recommends the inclusion of a second universal screen in the third trimester (29) while Alberta has yet to respond to this update. Incorporating another universal screen in the province may prove essential in improving prenatal care outcomes for mothers and infants due to the already suboptimal screening taking place.

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