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Evaluating Routine Testing and Treatment for Sexually Transmitted Infections among Pregnant  
Women in Southern Africa

A dissertation submitted in partial satisfaction of the  
requirements for the degree Doctor of Philosophy  
in Health Policy and Management

by

Adriane Michelle Wynn

2017



ABSTRACT OF THE DISSERTATION

Evaluating Routine Testing and Treatment for Sexually Transmitted Infections among Pregnant

Women in Southern Africa

by

Adriane Michelle Wynn

Doctor of Philosophy in Health Policy and Management

University of California, Los Angeles, 2017

Professor Roshan Bastani, Chair

*Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* are common sexually transmitted infections (STI) worldwide, which are associated with adverse maternal and infant outcomes. Diagnostic testing accompanied by partner notification and treatment are important strategies for control of STIs. Yet most countries do not provide routine diagnostic testing for pregnant women and partner notification rates are low. While molecular diagnostics are available, the implementation costs are a barrier for many countries. This dissertation examined three aspects of efforts to address the STI burden among pregnant women in Botswana, based on a pilot, point-of-care STI testing and treatment program in Gaborone.

The first study examined the prevalence and correlates of CT, NG, and TV among pregnant women receiving antenatal care and found an infection rate of 14%. HIV infection and being unmarried were associated with having an STI. Self-reported STI-related symptoms were not associated with having an STI.

The second study used qualitative interviews to assess the experiences and preferences related to partner notification among pregnant women who tested positive for an STI. The majority of women had never heard of CT, NG, or TV infections prior to testing. Thirteen out of 15 participants had notified partners about the STI diagnosis. The majority of notified partners received some treatment. Most women expressed a preference for accompanying partners to the clinic for treatment.

The third study determined costs and outcomes associated with CT and NG infection testing and treatment at an antenatal clinic. Data from this single site were modelled to estimate scale-up across Botswana according to three scenarios. Models revealed that point-of-care testing would result in the most of women cured, but at the highest cost. A centralized laboratory scenario was associated with the lowest cost, but fewer women cured. A mixed scenario had the most favorable cost per outcome.

CT, NG, and TV infections remain a significant burden among pregnant women in Botswana. Women are generally receptive to point-of-care STI testing and partner notification. Policy-makers should consider a mixed approach to scaling up STI testing and treatment to maximize population level benefits while controlling associated costs.

The dissertation of Adriane Michelle Wynn is approved.

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2017

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## LIST OF ACRONYMS

Acronym	Definition
STI	Sexually transmitted infection
CT	<i>Chlamydia trachomatis</i>
NG	<i>Neisseria gonorrhoeae</i>
TV	<i>Trichomonas vaginalis</i>
HIV	Human immunodeficiency virus
WHO	World Health Organization
MTR/RIB	<i>Mycobacterium tuberculosis</i> / rifampin

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## CHAPTER 1: Introduction

### 1.1 Introduction to the Dissertation

This dissertation examined efforts to address the burden of sexually transmitted infections (STIs) among pregnant women in Botswana. STIs are extremely common globally and are associated with adverse health outcomes for women and infants.[1] However, because women are not routinely tested for those infections in most countries, the problem is not precisely measured.[1] While new molecular diagnostics for use in clinics have recently become available, the implementation costs continue to be an important system-level barrier to expanding testing. Further, partner notification and treatment rates are low in many settings, which increases the risk of STI reinfection during pregnancy. Clearly, more needs to be done to ensure that STIs are diagnosed, treated, and cured among pregnant women in Southern Africa.

This research addressed the following: 1) examined the prevalence of *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* (TV) and the individual-level correlates of infection among pregnant women in Gaborone, Botswana; 2) explored pregnant woman's experiences with partner notification and treatment of STIs, as well as preferences for future policies; and 3) assessed the costs and outcomes of STI testing at a single antenatal clinic in Gaborone, Botswana and estimated the costs and outcomes of three scenarios for scaling up CT and NG infection testing and treatment to all pregnant women in Botswana. This chapter provides an overview of the burden of common curable STIs in Southern Africa, adverse outcomes associated with infections during pregnancy, current STI management practices in Southern Africa, partner notification and treatment strategies, promising new technologies that could expand testing, and the study setting, Botswana, a

country in Southern Africa. The chapter concludes with a description of the conceptual framework used to guide the dissertation and a brief description of each study.

### **1.2 The burden of curable sexually transmitted infections among pregnant women in Southern Africa is estimated to be large, but has not been measured precisely**

STIs are extremely common globally and disproportionately affect women.[2] A recent systematic review of the literature and global reporting data estimated that there were 78, 131, and 143 million new cases respectively of NG, CT, and TV globally in 2012.[1] This review also determined that the World Health Organization (WHO) Africa region has the highest prevalence of NG and TV of any region, and rates of STIs are higher among women compared to men.[1] For example, in the Africa region in 2012, there were estimated to be 7.8 million cases of incident NG infections among women compared to 3.6 million incident cases among men.[1] Another recent systematic review, which included publications on STI prevalence among pregnant women in low- and middle-income countries, found that the Southern Africa region had the highest adjusted mean prevalence of curable STIs among pregnant women compared to Latin America, East Africa, West Africa, and Asia.[3] The most recent prevalence estimates of CT, NG, and TV infections among pregnant women in Botswana are over 15 years old.[4, 5] In a 2007 study based on 2000/2001 data, Romoren et al. found the prevalence of NG, CT, and TV to be 2%, 8%, and 19%, respectively, among antenatal care attendees in Gaborone, Botswana.[4, 5]

### **1.3 Untreated sexually transmitted infections are associated with adverse health outcomes for women and infants**

Untreated STIs are significant causes of morbidity among women.[2, 6] TV, which is a flagellated protozoan, principally infects the urogenital tract, and the infection can range from



an asymptomatic carrier state to a severe inflammatory disease.[7] Symptoms of acute infection are present in about 50% of infected people and can include purulent, malodorous, thin discharge; burning urination; and/or lower abdominal pain.[8] CT and NG are gram-negative bacterium, which most commonly infect the cervix in women.[9, 10] Greater than 85% of women infected with CT and 70% infected with NG are asymptomatic.[10, 11] Symptoms of CT infection are nonspecific, and may include a change in vaginal discharge and vaginal bleeding.[12] Symptomatic NG infection can include vaginal pruritus, mucopurulent discharge, and vaginal bleeding.[13] The immunologic response to lower genital tract infections can lead to inflammation of the cervico-endometrial tissue, which may result in pelvic inflammatory disease and infertility.[14-19] There is also evidence that CT, NG, and TV can increase the risk of acquisition and transmission of HIV.[20] TV has been associated with more than a 2.7-fold increase in the risk of HIV acquisition [21-23]

CT, NG, and TV infections during pregnancy can increase the risk of adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, low birth weight, and spontaneous abortion.[24-31] TV has been associated with a 1.3-fold increase in preterm labor.[24, 32] Co-infection with HIV and other STIs is associated with an increased risk of mother-to-child transmission of HIV.[33] Further, about 50% of maternal CT and NG infections are transmitted to the neonate during birth.[34-37] Both infections can cause the eye infection ophthalmia neonatorum, presenting as swelling and purulent discharge.[36, 38] Gonococcal eye infections can result in corneal damage and blindness if untreated.[39] One study estimated that globally 4,000 infants are born blind annually due to mother-to-child transmission of CT or

NG.[40] Further, chlamydial infections may be an important cause of neonatal pneumonia as 5-30% of infants born to mothers with CT infections develop this condition.[41-44]

#### **1.4 Most countries use an approach called syndromic management to diagnose and treat STIs**

Despite the clear risks to women and infant health posed by CT, NG, and TV infections, most countries do not offer routine testing during pregnancy.[45] In 2015, only 13 countries had policies recommending that pregnant women be tested for CT and eight promoted screening for NG infections.[45] The United States (U.S.) is one of the few countries that has guidelines recommending routine STI testing for pregnant women.[45] The Centers for Disease Control and Prevention (CDC) recommends CT testing for all pregnant women and NG testing for pregnant women who are at increased risk (e.g., multiple sex partners, exchanging sex for payment, illicit drug use, or a history of STIs) or who live in areas where NG is highly prevalent.[14] Diagnostic testing for TV is recommended for women seeking care for vaginal discharge, receiving care in high-prevalence settings, at high risk for infection, or living with HIV.[46] In Europe, guidelines indicate laboratory testing for those with risk factors for CT infection and/or other STIs (<25 years, new sexual contact or more than one partner in the last year, cervical or vaginal discharge, or have acute pelvic pain and/or symptoms/signs of PID). [47]

The WHO is silent on the issue of testing for CT, NG, and TV infections during pregnancy largely because diagnostics have been unaffordable and inaccessible in low resource settings.[48, 49] The countries without STI testing guidelines rely on an approach called syndromic management, which was included in the WHO's guidelines for the management of STIs beginning in the 1990s.[49] Syndromic management uses algorithms that can be used to

identify STI syndromes (e.g. vaginal discharge syndrome) based on patient symptoms and clinical signs.[50] The algorithms are often converted to flow charts and posted in clinics. Patients are then treated with standardized drug regimens for the possible causes of their syndromes, without testing for specific infections. Syndromic management has a number of benefits, including timely treatment at the point-of-care, and no requirement for laboratory resources. Nevertheless, the syndromic approach lacks sensitivity, which can range from 30-80%, and may fail to identify the large proportion of asymptomatic infections.[5, 50] A recent South African study of 1,480 women found that more than 50% of CT and other STIs were asymptomatic.[51] The Romoren et al. 2007 study in Gaborone, Botswana found that STI symptoms (e.g. vaginal discharge and lower abdominal pain) were not predictive of CT (LR: 1.1; 95% CI: 0.6-1.5).[50] Only 43% of women infected with CT in their sample of pregnant women were identified and treated using syndromic management.[50] The syndromic approach also lacks specificity, potentially unnecessarily exposing pregnant women to antibiotics.[5, 50]

### **1.5 Partner notification and treatment are critical components of sexually transmitted infection management programs, but current rates of partner treatment are estimated to be low**

Partner notification is a process whereby sex partners of an index patient with an STI are identified, notified about their exposure, counselled, and treated if appropriate.[48, 52]

Treating partners reduces the likelihood of re-infecting the index patient, as rates of reinfection of CT and NG from untreated partners are estimated to be high at approximately 55.5%.[53]

Further, notifying and treating partners may also decrease the burden of infection in communities because the partners may be asymptomatic and may not otherwise access STI treatment.[54].

There are three main approaches to partner notification: (1) health professional-oriented methods where healthcare workers contact the partners and counsel them on how to seek treatment and prevent future infections; (2) patient-oriented methods where the index patient notifies their partners and encourages them to seek medical care or provides treatment (i.e., medication) directly to their partner, and (3) mixed approaches involving both the index patient and a healthcare provider.[48]

Partner notification is governed by country-specific laws and policies related to the control of communicable diseases.[55] As such, there is variation between countries in terms of which strategy is used and how the strategy is implemented.[56, 57] Voluntary, patient-based partner notification is the most common method globally; however, some countries place a legal obligation on patients to inform their partners[52, 58] Some countries allow for expedited partner therapy, which is the clinical practice of treating partners by providing medications to the index patient prior to an examination of the partner by a healthcare provider.[59] In the U.S., 38 states expressly allow EPT and four prohibit the practice.[59] Further, new technologies, such as those involving confidential notification over the internet or social media are increasingly being considered for incorporation into partner notification strategies.[58]

Several randomized trials have evaluated partner notification methods; however, no one strategy has been identified as the most effective in terms of increasing notification and/or reducing STI transmission at the population level.[56, 58, 60] A 2007 systematic review and meta-analysis identified 14 trials that examined 16 partner notification interventions involving 12,389 participants in total.[60] This review found that the risk of a persistent or recurrent infection was lower among patients in expedited partner therapy conditions compared to

patients who were assigned to a simple referral condition, where patients were counselled to notify their partners, but partners were not provided with additional information (Summary risk ratio from five trials: 0.73; 95% CIT: 0.57 to 0.93).[60-64] Eight trials compared giving additional information to partners (e.g. written documents or a video) to simple patient referral.[60] Two trials found that providing written information for partners was associated with a lower proportion of persistent or recurrent infections among index patients compared to simple notification.[65] Two trials found no difference between three groups of patients given information either through a structured script or a video compared to provision of a contact card.[66, 67] One trial in South Africa found that more partners were treated when an index patient received verbal education messages and individual counselling compared with those that just received contact cards.[60, 67]

Regardless of the strategy, partner notification rates are often low.[48, 52] Another systematic review, which examined research related to partner notification strategies in low- and middle-income countries, found that the median proportion of partners notified in the 39 included studies was 0.54.[52] The low rates may be related to the complexity of factors that influence the likelihood of partner notification including individual, relationship and community level factors.[52] Prior research has revealed a number of barriers to notifying partners, including fear of rejection, embarrassment, stigma, separation from partner, or long distance relationships.[52] Pregnant women may be more likely to notify their partner than non-pregnant women due to concerns about the baby.[68] Further, even though women often express a willingness to notify their partners about an STI, this willingness does not always result in success in notifying partners.[52] For example, a study in a prenatal clinic in Haiti found

that while 86% of study participants reported wanting to notify their partners about an STI diagnosis, only 30% of partners were determined to have been notified.[69]

Botswana uses patient-oriented partner notification where index patients are provided with contact slips to give to their partners and refer them for treatment.[70, 71] The Botswana Ministry of Health estimates that the national contact notification rate for STIs has been between 8-16% and partner treatment is often delayed as at least 22% of notified partners did not seek treatment for seven days or more following the initial diagnosis of the index patient.[70, 71] Further, there is little research available in Southern Africa that explores whether the partner notification process is working for women.[52]

### **1.6 New technology may present an opportunity to expand sexually transmitted infection testing in low and middle-income countries**

Recent developments in technology have introduced the possibility of testing all pregnant women with highly sensitive, easy to use, rapid tests for STIs. Nucleic acid amplification tests (NAATs), which work by detecting and amplifying bacterial, viral, or parasitic nucleic acid sequences are currently recommended by the CDC for CT, NG, and TV infection testing.[19, 72, 73] These tests initially became available in the 1990s and have several advantages over culture, including ease of specimen collection and transport, and increased sensitivity.[19] However, NAATs are quite expensive and, until recently, required laboratory settings. One NAAT-based platform is available for diagnosis of CT, NG and TV infections at the time of patient care (GeneXpert® system, Cepheid) and additional point-of-care tests are in the pipeline.[17] These new tests are easy to use and patients can receive results and treatment on the same day as testing.[25, 26]. Further, many have multi-plex platforms that enable the detection of several STIs simultaneously. New sample collection methods, such as self-collected

vaginal or urine samples, may reduce personnel costs.[27, 28] Such rapid tests have the potential to dramatically reduce the time between testing, results, and treatment, which may increase the likelihood of treatment and ultimately improve cure rates.[74]

While not widely used, several international studies have found that rapid testing can be feasibly integrated into clinics in low resource settings.[75-78] Further, NAATs are currently being used around the world for the detection of HIV during antenatal care.[79] As a result, an estimated 180,000 infant HIV infections have been averted.[80] Self-collected vaginal swabs used for NAATs have sensitivity and specificity equivalent to provider-administered samples, and acceptability among women has been shown to be high.[75, 76, 81, 82] One study, which took place in a public clinic in Cape Town, South Africa found that most women who provided a self-collected sample for STI testing reported having a good experience, they did not experience pain, and they would choose self-sampling in the future.[83]

### **1.7 Studies have found *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing and treatment to be cost-effective, but more research is needed on the costs and benefits of point-of-care testing in low resource settings**

Previous research shows that appropriate treatment of CT, NG, and TV infections during pregnancy is effective in clearing organisms and improving health outcomes [84-89]; however, only a few studies have evaluated the benefits of point-of-care antenatal testing compared to the costs. Romoren et al. (2007) modeled syndromic management compared to point-of-care testing for CT in a hypothetical cohort of 100,000 antenatal attendees in Southern Africa (using Botswana as the base case).[4] Outcomes were cases cured, magnitude of overtreatment, and successful partner treatment. This study found that STI testing during antenatal care was more effective than syndromic management, but also costlier. Specifically, it found that testing all

ANC attendees on their first visit with a 75% sensitive point-of-care test increased the number of cases cured from 1,500 to 3,500 in a population of 100,000, at a cost of US\$38 per additional case cured, compared to syndromic management.[4] This study faced several limitations, including that it only modelled costs associated with medications, pharmacist time, and the recurrent test costs. It did not estimate differences in capital costs (e.g. the testing system) or the time of health care providers.

Several recent publications have conducted cost analyses of point-of-care diagnostics for CT and NG among women attending STI clinics in high resource settings.[90-92] Turner et al. (2014) conducted a simulation of attendees at England sexual health clinics to compare the use of NAAT testing at the point-of-care with testing and delayed results (within 7 days) for CT and NG infections and found that point-of-care testing was associated with a small increase in quality adjusted life years (derived primarily from reductions in pelvic inflammatory disease) and avoidance of inappropriate treatment.[91] Huang et al. used a simulated population of 10,000 women visiting an STI clinic in Baltimore, Maryland to compare point-of-care NAAT testing with NAAT testing and delayed results.[92] They found that with a test sensitivity of 92.9%, a test cost of \$33.48, and 47.5% of women willing to wait 40 minutes for results, that the point-of-care test saved \$5,050 for each case of pelvic inflammatory disease averted compared to a non-point-of-care NAAT.[92] The results of the above mentioned studies are encouraging, but more comprehensive, context-specific cost studies in low resource settings are needed.

**1.8 Prior to national implementation of an antenatal sexually transmitted infection testing and treatment strategy, more research is needed to understand the system-level factors that can lead to successful scale up**



Scaling up has been defined by the WHO as “deliberate efforts to increase the impact of health service innovations successfully tested in pilot or experimental projects so as to benefit more people and to foster policy and program development on a lasting basis.”[93] Scaling up an innovation is a complex exercise and success depends on the characteristics of the innovation (e.g. based on sound evidence, addresses important problems, has an advantage over standard practice, feasible to implement, acceptable to users, is cost efficient), the user organization (e.g. perceive a need for the innovation, have implementation capacity, timing is right), the environment (e.g. political context, bureaucracy, composition and importance of the health sector, socioeconomic and cultural context), the staff within the implementing organization that ensures integration into program structures and budgets (e.g. effective, motivated, creditable); and strategic choices (e.g. type of scaling, costs, resources, monitoring and evaluation).[93] Strategic choices can involve different approaches to expanding an innovation (e.g. targeting recipients or geographical areas), identifying ways to contain costs (e.g. using economies of scale), and deciding what information to collect to assess the processes, outcomes, and impacts of the innovation.

Cost is a particularly important aspect when making choices about scaling up. Without access to information about potential costs, policy makers are unable to assess the feasibility and sustainability of scaling up.[94] For example, an important aspect of innovative STI diagnostics is the ability to test at the point-of-care by placing the system inside antenatal clinics as opposed to the traditional testing strategy of processing samples in a central laboratory. However, point-of-care testing may run counter to the economic principle of decreasing marginal costs by spreading fixed costs over more people. In other words, point-of-

care testing with same-day results may require more machines that benefit fewer people compared to a strategy where diagnostic machines are centralized and can benefit more people. Further, the placement of testing diagnostics in rural clinics with lower patient volumes may result in diseconomies of scale: costs of testing and treating a patient in a rural area may be higher than in urban areas. The choice between point-of-care and centralized laboratory-based STI testing involves trade-offs between the potential gains in cured infections generated by treating people before they leave the clinic and the increased costs associated with distributing testing platforms to a large number of clinics. Research is needed on the costs and benefits of different approaches to scale-up of STI testing across Southern Africa.

### **1.9 The setting of this dissertation research is Botswana**

Botswana is a landlocked, upper- middle income country in Southern Africa. The population of Botswana is relatively small with just over 2 million people and Gaborone is the country's capital. Botswana provides comprehensive primary health care services to its population across 27 administrative health districts.[95] The Ministry of Health (MOH) is the main public sector health provider and is responsible for formulation of policies, standards, and guidelines for the provision of health services.[96] The MOH has granted authority to district boards to oversee health care services, management, and monitoring and evaluation of referral hospitals.[96] The public sector health system is comprised of six levels: three national referral hospitals, 35 district and primary hospitals, 286 clinics, 342 health posts, and 1,052 mobile stops. Ninety five percent of the population is estimated to live within eight kilometers of a health facility.[97, 98] The national referral hospitals provide tertiary care, including specialist support to primary hospitals and clinics.[96] Primary hospitals serve as general hospitals and

manage most diseases, injuries and immediate health threats.[96] The district hospitals are the principal health facilities in each district, and provide intensive and long term care services as well as outpatient, pediatrics, emergency and urgent care, surgery and intensive care, pharmacy, laboratory, x-ray, dental, eye care, and orthopedic services. Clinics offer most of the primary care and outpatient services, including general consultations, treatment of injuries and minor illnesses. Clinics are staffed by a doctor, nurse, midwife, pharmacist, and sometimes a laboratory technician.[96] Health posts are staffed by a nurse with visits by a midwife, mental health nurse, eye nurse, and doctor.[96] Mobile stops are staffed by nurses, health education assistants, and lay counselors.[96] While most of the population lives near a health facility, the distribution of human resources is skewed with more personnel working in urban areas.[99]

The Government of Botswana has allocated substantial resources to the health sector, with a primary goal of universal coverage of essential health services.[96, 99] Public health spending accounted for 24.7% of total Government expenditure in 2014-2015.[96] Further, healthcare fees for citizens of Botswana are fairly low with general consultations at 5 pula (about 0.5 USD) for adults and free care for children under five years of age and adults over 65 years.[100] However, Botswana's healthcare budget is heavily burdened by the costs of testing and managing HIV. Botswana faces one of the highest HIV prevalence rates in the world with 22% of 15-49 year olds living with HIV.[101] Between 2006 and 2011, funding for HIV programs represented 35% of all government health expenditures.[102] In the face of such a high HIV disease burden, policy-makers must be strategic about funding for other health-related programs.

According to recent census data, the number of women in Botswana (ages 15-65 years) is approximately 635,000 with 47,935 live births annually and a total fertility rate of 2.6.[96] Most births occur in a healthcare facility with less than 1% occurring outside of these settings.[103] Although most pregnant women have at least one antenatal care visit (94%), Botswana faces maternal and infant mortality rates of 169/100,000 and 33/1000 live births respectively.[98] Furthermore, under-five mortality is estimated at 31 per 1,000 live births.[103] Lower respiratory infections and diarrheal diseases contribute to about half of all child mortality.[96] Maternal mortality is driven by complications related to HIV/AIDS, mismanaged abortions, and quality and accessibility of emergency obstetric care.[95, 96] Botswana also has a very high prevalence of HIV among pregnant women (20%) and it has responded aggressively to the epidemic.[101] Botswana provides HIV and syphilis testing during the first antenatal care visit to all women unless they opt out successfully reaching over 95% of mothers.[104] In 2015, the rate of HIV mother-to-child transmission was 3%.[105]

As mentioned above, the burden of STIs, beyond HIV and syphilis, is not well measured in Botswana because guidelines recommend the syndromic approach to manage STIs among pregnant women.[106] The Botswana Ministry of Health's algorithms for identifying and treating STIs are based on WHO guidance and rely on flow charts where syndromes are identified based on patient signs and symptoms and then treated with standard drug regimens. Since 1993, nurses and physicians have received clinic training on the syndromic approach with nurses playing a central role in both the training of health care personnel on this issue and delivery of syndromic management in clinical settings.[106]

### **1.10 Dissertation Aims**

Control of STIs is a public health outcome that is often measured in terms of reduced incidence and prevalence.[107] These outcomes are achieved through multiple synergistic activities, which encompass primary prevention efforts (e.g. education and condom promotion), management strategies (e.g. testing, treatment, and partner notification strategies), and monitoring outcomes over time (e.g. data collection for evaluation or to identify subpopulations for targeting).[107] This dissertation focused on the management aspects of STI control and used a social ecological perspective to conceptualize how individual, interpersonal, and system-level factors affect access, management, costs, and benefits of STI testing and treatment among pregnant women in Botswana. To shed further light on these issues, the dissertation included three distinct studies that utilized primary quantitative, qualitative, and costing data collected from an antenatal CT, NG, and TV testing and treatment pilot program in Gaborone, Botswana. The first study assessed the prevalence of and correlates of STIs among pregnant women seeking care at an antenatal clinic in Gaborone, Botswana. The second study assessed women's experiences and preferences related to partner notification of an STI using semi-structured interviews. The third study estimated the costs associated with antenatal STI testing and treatment in a single antenatal clinic and then modelled the annual costs and outcomes of national scale-up of antenatal STI testing using three scenarios. Data for this dissertation were obtained in the context of an STI testing and treatment program that was conducted from July 2015 to May 2016 in Gaborone, Botswana and tested pregnant women for CT, NG, and TV using the GeneXpert system.

1.10.1 Conceptual framework: based on the social-ecological framework

For this dissertation, the social ecological framework was adapted to focus on the individual, interpersonal, and system-level factors that may be important for improving STI-related outcomes among pregnant women in Botswana.[108,109] The social ecological framework was first developed in the fields of psychology and human development to understand the interactions between individual and environmental factors that affect behavior.[108] The framework has been expanded for use in the public health field for a wide variety of issues, including HIV, obesity, cancer prevention, intimate partner violence among others .[109] The Institute of Medicine has defined the ecological model as "a model of health that emphasizes the linkages and relationships among multiple factors (or determinants) affecting health." [110] The traditional model includes five levels: individual, interpersonal, community, organization, and policy/enabling environment, that are presumed to influence health status as well as enactment of health behaviors.[108] The bottom level includes characteristics of the individual that influence health (biology, knowledge, attitudes, gender, age, socio-economic status, religion, stigma, etc.). The interpersonal level includes social networks and support systems that can influence individual health, including family, friends, peers, co-workers, religious networks, customs, and traditions. The community level represents relationships among organizations, institutions within defined boundaries (e.g. village associations, community leaders, businesses, transportation). Next, the organizational level includes organizations or social institutions with rules and regulations that affect how or how well health or related services are provided to an individual or group. Finally, the policy level includes local, state, national, global policies that affect access to health producing services and resources (e.g. resource allocation, taxes/fees, requirements, and campaigns/advocacy).

For this dissertation, we focused on three levels of influence on STI management in Botswana. Individuals are nested within relationships with sex partners, which are nested within systems. Individual level factors including women's age, marital status, education, HIV infection status, and risk behaviors (e.g. condom use), which are primarily being explored in the first study, "Prevalence and correlates of sexually transmitted infections among pregnant women, Gaborone, Botswana".[76, 111] Relationship characteristics that influence partner notification about an STI include, relationship length, communication, and risk of intimate partner violence; and are explored mainly in the second study, "Partner notification for sexually transmitted infections among pregnant women in Gaborone, Botswana: A qualitative study".[52] System-level factors that may affect the availability of testing services for pregnant women include Ministry of Health guidelines that govern the provision of STI management and patient-based partner notification. Further, it includes system-level characteristics important for the implementation of testing, including infrastructure (e.g. antenatal clinics, water, power), personnel (nurses, doctors), resources (e.g. national budget for health care), and costs (e.g. cost of STI testing). These factors are explored primarily in the third study entitled, "Assessing the costs and estimating scale up of testing pregnant women for curable sexually transmitted infections in Botswana". The three levels also influence each other, for example interpersonal relationships shape individual sexual risk behavior, and partner notification guidelines are associated with how and if a partner is notified.

#### 1.10.2 Prevalence and correlates of sexually transmitted infections among pregnant women, Gaborone, Botswana (Chapter 2)

The first study examined the prevalence of CT, NG, and TV among pregnant women and possible risk factors for infection. The study used individual-level data collected from N=400

pregnant women (ages  $\geq 18$  years) receiving care at an antenatal clinic in Gaborone, Botswana. We assessed socio-demographic factors such as age, education level, and marital status; and health characteristics such as HIV infection status; which were identified in the participant's medical record. Further, we collected information on STI-related symptoms and sexual risk behaviors (e.g. use of condoms) through an interviewer administered survey.

#### 1.10.3 Partner notification for sexually transmitted infections among pregnant women in Gaborone, Botswana: A qualitative study (Chapter 3)

The second study assessed the experiences, including barriers and facilitators, as well as preferences of pregnant women related to notifying their partner(s) about an STI diagnosis and encouraging them to seek treatment.[60] This study utilized qualitative data derived from semi-structured interviews conducted among a sample of 15 women who were diagnosed with an STI during Chapter 2. Results from this study may be used to improve partner notification and STI education policies and programs in order to increase partner treatment and reduce STI reinfection rates.

#### 1.10.4 Assessing the costs and estimating scale-up of testing pregnant women for curable sexually transmitted infections in Botswana (Chapter 4)

The last study explored the costs and outcomes of testing all pregnant women in Botswana for CT and NG during antenatal care. First, it identified the costs and outcomes associated with antenatal CT and NG testing and treatment at a single antenatal clinic in Gaborone, Botswana. Next, it used those data collected from a single testing site to estimate the costs and outcomes of three scale-up scenarios: 1) sample collection and processing at the point-of-care with the potential for same-day results and treatment (point-of-care scenario), 2) sample collection at the point-of-care and processing in laboratories with delayed results and



treatment (reference laboratory scenario), and 3) a combination of the first two scenarios (mixed scenario). Given that one of the primary barriers to STI testing are cost and accessibility, this information will help policy-makers make decisions about increasing STI testing for pregnant women that maximize benefits at the lowest cost.

#### 1.10.5 Innovation and Contributions of this Dissertation Research

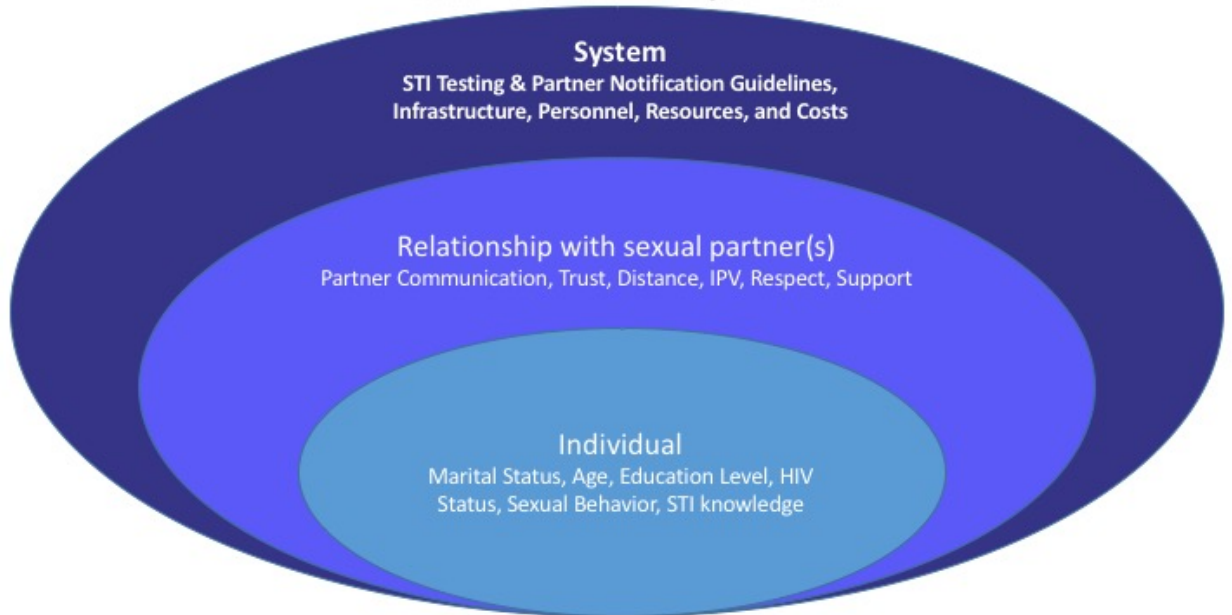
The current literature indicates that CT, NG, and TV infections are extremely common globally and are associated with adverse health outcomes for women and infants. However, because women are not routinely tested for CT, NG, and TV infections, the problem is not precisely measured and few recent studies have estimated the burden among pregnant women in Southern Africa. Further, no single strategy for partner notification has been identified as the gold standard, notification and treatment rates are low globally, and this subject has not been explored qualitatively in Botswana to assess women's experiences or preferences. Further, innovations in testing technology may allow for expanded access to testing, but the costs associated with the new tests have not been well-estimated in low resource settings. Therefore, this dissertation research is unique in several ways that will contribute to our current understanding of STI management among pregnant women. First, the research focused on pregnant women in a low resource setting where testing for infections is not routinely conducted. Second, the research is unique to the STI literature in moving beyond individual level factors to assessing relationship and policy-level factors important for reducing the burden of infections. Lastly, the dissertation employed primary data collection and estimations may be more valid than data derived from the literature or similar settings. The results of this research,

therefore, can inform future STI testing and treatment programs and policies as well as improve the current understanding of this disparity in health care.

### 1.11 Tables and Figures

**Figure 1.1: Conceptual Framework**

**Conceptual Model of Sexually Transmitted Infection Management**  
Based on the Socio-Ecological Model



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## CHAPTER 2: Prevalence and correlates of sexually transmitted infections among pregnant women, Gaborone, Botswana

### 2.1 Chapter Introduction

*Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* (TV) infections during pregnancy increase the risk of adverse pregnancy, birth, and infant outcomes, including preterm birth, low birth weight, and spontaneous abortion.[1-8] Co-infection with human immunodeficiency virus (HIV) and CT and NG has also been found to be associated with an increased risk of mother-to-child transmission of HIV.[9, 10] Infection with TV is associated with increased risk for acquisition [11-13] and shedding of HIV. [14-16] Further, about 50% of maternal CT and NG infections are transmitted to the neonate during birth.[17-20] Both infections can cause the eye infection, ophthalmia neonatorum, and untreated gonococcal eye infections can cause blindness.[19, 21, 22] Chlamydial infections are an important cause of neonatal pneumonia as 5- 30% of infants born to mothers with CT infection can develop this condition.[23-26] Infants of mothers infected with TV may contract the infection during delivery, which could result in fever, respiratory problems, and urinary tract infections.[27-30]

Despite the serious risks to maternal and infant health, there is little data on the prevalence and risk factors for these infections in Southern Africa (including Angola, Botswana, Lesotho, Madagascar, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia, and Zimbabwe).[31]. A recent systematic review on STI prevalence among pregnant women in low- and middle-income countries identified only 15 studies based in Southern Africa.[31] These studies found that the Southern Africa region had the highest adjusted mean prevalence of curable STIs among pregnant women compared to Latin America, East Africa, West Africa, and Asia.[31]

The lack of evidence for the burden of STIs during pregnancy in Southern Africa may be due to the absence of diagnostic testing during antenatal care regardless of symptoms, age, and other risk factors. In 2015, only 13 (Australia, The Bahamas, Bulgaria, Canada, Democratic People's Republic of Korea, Estonia, Germany, Japan, Latvia, Romania, Sweden, the United Kingdom, and the United States) and 8 (Australia, The Bahamas, Canada, Democratic People's Republic of Korea, Germany, New Zealand, the United Kingdom, and the United States) countries worldwide had policies to provide laboratory testing for CT and NG, respectively, among pregnant women.[32] Other countries rely on syndromic management, which has been included in the World Health Organization (WHO)'s guidelines for the management of STIs beginning in the 1990s. Syndromic management was developed for use in countries where laboratory diagnosis was not accessible.[33, 34] The approach uses algorithms to classify symptoms into STI syndromes, which are treated with standardized drug regimens. [35] Diagnosis based on symptoms lacks sensitivity, which ranges from 30-80%, and may fail to identify a large proportion of asymptomatic infections.[35, 36] A recent South African study of 1,480 women found that more than 50% of CT and other STIs were asymptomatic.[37] Syndromic management also lacks specificity, leading to unnecessary exposure to antibiotic in pregnancy.[35, 36]

Botswana has achieved high levels of antenatal care coverage with over 94% of pregnant women receiving at least one visit, and universal screening for HIV infection and syphilis are integrated into antenatal care.[38, 39] Nevertheless, Botswana continues to face high rates of adverse birth outcomes, including preterm birth (15/100 live births) and infant mortality (36/1,000 live births).[40, 41] The burden of CT, NG, and TV among pregnant women is unknown as prevalence estimates in Botswana are over 15 years old.[36, 42] The absence of diagnostic testing for curable STIs during pregnancy may represent a missed opportunity to reduce the burden of infection and poor maternal

outcomes. Our study assessed the prevalence and correlates of CT, NG, and TV infections in a high volume antenatal care clinic in Gaborone, Botswana.

## **2.2 Methods**

### **2.2.1 Data Source**

We conducted a prospective cross-sectional study among 400 consecutively enrolled pregnant women in the antenatal clinic in Princess Marina Hospital in Gaborone, Botswana. Pregnant women attending the antenatal clinic between July 2015 and May 2016, who were over age 18 years, less than 35 weeks of gestation (to ensure the possibility of a test of cure after four weeks prior to birth), and planning to return to the clinic for a follow-up visit were offered screening for CT, NG, and TV infections. With a sample size of 400, a two-sided 95% confidence interval using normal approximation for the assumed prevalence of 13% ranges from 9.9% to 16.7%, which should be narrow enough to give sufficient precision for the estimate of prevalence. Princess Marina Hospital is located in Botswana's capital city, and is the main referral hospital for southern Botswana. Participants who gave written informed consent provided self-collected vaginal swab specimens after receiving verbal instructions from study staff. Samples were collected in the clinic washroom by participants. Following sample collection, participants responded to an interviewer-administered questionnaire conducted in English or Setswana (the language spoken by the majority of people in Botswana), which collected sociodemographic (e.g. age, marital status, and education level) and behavioral information (e.g. condom use). We also asked if participants were experiencing any symptoms that could be related to having an STI, including abnormal vaginal discharge, painful urination, and/or lower abdominal pain. We chose these symptoms because they are currently used in Botswana's syndromic management algorithm to identify STIs.[43] We also abstracted obstetric and historical health information from

medical records. Testing and treatment were free of charge and participants were not offered incentives for enrollment in the study.

Testing was conducted by trained study staff using the U.S. Food and Drug Administration-approved Xpert® CT/NG and Xpert® TV nucleic acid amplification assays (Cepheid, Sunnyvale, CA). Xpert allows for 90-minute detection for CT and NG infections and 59 minutes for TV infection.

The goal of the study was to provide participants with results in person on the same day as testing. If a participant left prior to receipt of results, they were to be called and advised to return to the clinic for treatment. Those who tested positive for CT, NG, and/or TV were offered directly observed treatment. We followed U.S. Centers for Disease Control and Prevention (CDC) treatment guidelines, which included directly observed therapy of 1g oral azithromycin for chlamydial infection, a 250 mg intramuscular injection of ceftriaxone and 1g oral azithromycin for gonococcal infection, and 2g oral metronidazole for trichomonal infection.[44] Participants who were HIV infected were given 400mg of metronidazole twice per day for 7 days.[45] Participants who tested positive were counseled to tell their partner(s), given the option of bringing their partner(s) into the study clinic for treatment, and provided with a contact sheet with instructions for their partners to receive treatment at a clinic of their choosing. Finally, those who tested positive were encouraged to return to the clinic for a follow-up visit, but no sooner than four weeks, for a test of cure. The test of cure is needed to assess persistent infection despite treatment, and the CDC guidelines recommend the test of cure take place 3-4 weeks after treatment completion for pregnant women.[45]

### 2.2.2 Data Analysis

Descriptive statistics were used to characterize socio-demographics and obstetric and medical characteristics of participants. Bivariate comparisons, including chi-square tests of proportions, Fisher's exact test, Student's t-tests, and Mann-Whitney U tests were used to examine the relationships

between participant characteristics and STI diagnosis. Finally, multivariable logistic regression was used to identify characteristics independently associated with having an STI, adjusting for other factors. Variables were included based on results of stepwise selection for logistic regression analyses, and covariates with a significance level of  $\leq 0.2$  were included in the model. Statistical significance of variables in the final model was assessed at the 0.05 level. Stata 13 (StataCorp, College Station, TX) was used for all analyses.

### 2.2.3 Ethics

The institutional review boards at the University of Botswana (URB/IRB/1547), the Botswana Ministry of Health, Health Research Development Committee (PPME 13/18/1 IX(434)); and Princess Marina Hospital (PMH 5/79(223-3-2016)) approved the study protocol. The University of California, Los Angeles (15-000692), approved analyses using de-identified data.

## 2.3 Results

Between July 2015 and May 2016, we enrolled 400 (86%) of the 466 eligible women (Figure 2.1). The most common reason for refusal was concern about the time it would take to collect the sample (24%). The ages and gestational ages of women who enrolled and those who declined did not differ (data not shown). We were able to provide results to 99% of participants either in person (61%) on the same day as testing or by phone (39%) within a week.

As displayed in Table 2.1, the median age of our sample was 30 years, the median gestational age was 26 weeks at enrollment, most women (77%) were unmarried, and 40% had some post-secondary level of education. The HIV prevalence was 23%. Twenty-seven percent of participants reported never using a condom during the year prior to pregnancy; and 47% reported never using condoms during pregnancy. The median number of previous pregnancies was two and 65% had a prior birth. Among those who had given birth, 76 (29%) had experienced at least one prior preterm birth,

which is 19% of the total sample. In terms of current symptoms, 41% reported that they were experiencing at least one STI-related symptom, including vaginal discharge (27%), lower abdominal pain (22%), and/or painful urination (4%). Symptoms related to herpes simplex virus infections such as genital ulcers (1%), and human papillomavirus infections such as warts (4.5%) were rare. Over 12% had been treated syndromically for an STI (other than HIV or syphilis) previously during the current pregnancy. Prior treatment did not differ by HIV infection status.

As seen in Table 2.1, we found the prevalence of CT, NG, and/or TV, hereafter referred to collectively as *any STI* to be 13.5% (54/400). The prevalence of CT was 7.8% (31/400), NG was 1.3% (5/400) and TV was 5% (21/400). Two participants were dually infected with CT and NG, and one was infected with CT and TV. Among the women who tested positive for any STI, 74% received results in person prior to leaving the clinic, and all were treated on the same day (Figure 2.1). Eight women were called and provided results on the same day; however, while all were treated, the treatment was not provided on the same day. Six women received delayed results (e.g. we were not able to reach them on the same day), and 4 (67%) were treated. In total, 52 (96%) were treated, and 77% were treated on the same day. Further, 41 of the 52 participants treated for an STI returned for a test of cure. Among the 41, four (9.8%) retested positive, including three with CT and one with TV.

Bivariate comparisons revealed that marital status (Chi-squared p-value=0.01) and HIV infection status (Chi-squared p-value=0.002) were significantly associated with having any STI. Unmarried participants were more likely to have any STI (16%) than those who were married (5.6%) and those living with HIV infection were more likely to have any STI (23.3%) than those who were HIV uninfected (10.5%). Age was also not associated with having an STI. Among women who had previously given birth, those who experienced a prior preterm birth were more likely to be diagnosed with CT (16%), compared to those with no history of preterm birth (5%). Self-reported STI-related symptoms

(abnormal vaginal discharge, lower abdominal pain, and/or painful urination) were not associated with a positive STI diagnosis (Chi-squared p-value=0.89). Among those diagnosed with any STI, 41% (22/54) reported having a symptom related to CT, NG, or TV (28% (15/54) had abnormal vaginal discharge, 17% (9/54) had lower abdominal pain, and 4% (2/54) had painful urination). Among those without an STI, 42% reported having a symptom related to CT, NG, or TV (27% (92/343) had abnormal vaginal discharge, 23% (79/343) had lower abdominal pain, and 4% (14/343) had painful urination).

The stepwise regression analysis was performed using eight predictor variables, including participant age, marital status, HIV infection status, education level, condom use before and after pregnancy, prior births, and STI-related symptoms (abnormal vaginal discharge, lower abdominal pain, and painful urination). Table 2.2 provides the results from a multivariable logistic regression model with the five independent variables listed in the order in which they were selected by the stepwise procedure. Marital and HIV status were independently and significantly associated with a positive STI diagnosis, after adjustment for age, education, and condom use during pregnancy.

## **2.4 Discussion**

We provided testing and treatment for three curable STIs to 400 pregnant women at a large antenatal clinic in Gaborone, Botswana. The prevalence of one or more STIs was 13.5%. The CT and NG prevalences were high compared to global pooled prevalence estimates among women, with regional values ranging from 1.8-7.6% for CT and 0.3-1.7% for NG.[46] Being unmarried and HIV-infected were significantly associated with testing positive for an STI. Further, self-reported STI symptoms were not associated with testing positive for an STI.

The only prior study conducted among pregnant women in Botswana described similar prevalence estimates for CT (8%) and NG (3%).[35] However, our estimate of TV prevalence was almost four times lower than the 19% identified by Romoren et al. in their sample from 2000/2001.[36] These



results may be partially explained by differences in our samples. For example, Romoren et al. did not exclude those under 18 years of age, and our participants have a median age that is five years older. Romoren et al. found that age was the strongest predictor of cervical infection, and the prevalence of infection was highest among teenagers.[35, 36] More research is needed to understand whether these differences in prevalence estimates are due to sample differences, variation in diagnostics tests used, or a change in the prevalence of TV in Gaborone, Botswana over time.[47, 48] In comparison to other prevalence studies among women in Africa, our estimates are similar to a recent review, which found a pooled prevalence of 3.7% (2.7-5.2) for CT, 1.7% (1.1-2.6) for NG, and 11.5% (9.0-14.6) for TV.[46]

Our study assessed the association between CT, NG, and TV infections and HIV infection among pregnant women in Gaborone, Botswana. We found that HIV-infected participants were much more likely to test positive for an STI. The relationship between HIV infection and STIs is complex and likely bidirectional.[49] STIs are recognized cofactors in the transmission of HIV, increasing both susceptibility and transmissibility.[50-52] Given the increased risks of HIV transmission and the large proportion of participants who were co-infected with HIV and an STI, those infected with HIV may be appropriate to target for STI laboratory diagnostics during antenatal care.

The lack of an association between self-reported STI symptoms provides further evidence that syndromic management may not adequately identify STIs in pregnant women. In Botswana, guidelines indicate a speculum exam during the first antenatal visit to identify infections.[43] However, the speculum exam is rarely performed due to lack of equipment (i.e. speculums), and clinicians base their diagnosis on the patient's self-reported symptoms, using questions similar to those asked in our study.[53] It is important to also note that speculum exams do not greatly increase the sensitivity of syndromic management as the majority of women with CT, NG, and TV infections are asymptomatic.[37] While syndromic management has the benefit of low costs and resource

requirements, it is likely that pregnant women are being unnecessarily exposed to antibiotics, which is particularly concerning given the expansion of drug resistant NG.[54] Further, true infections are likely being missed, which may be contributing to the high rate of adverse birth outcomes in Botswana, including preterm birth.[55]

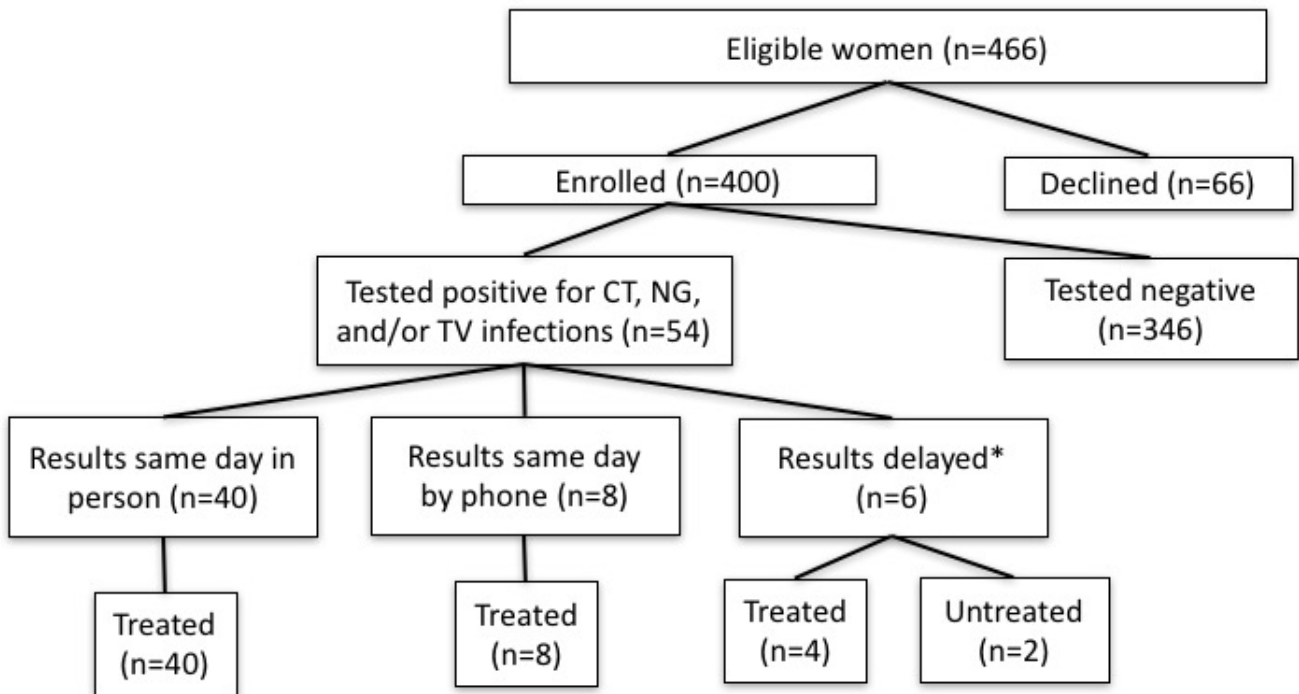
Our study has some limitations. First, women were recruited from a single site, Princess Marina Hospital antenatal clinic, which provides antenatal care, and also serves as a referral clinic for women with high-risk pregnancies. However, close to a quarter of our sample (17%) reported that their appointment was a routine check-up, and the remainder was referred for a high-risk condition. While our sample may be different from the population of pregnant women in Gaborone, the most common referral condition was high-blood pressure (22%), followed by having a history of miscarriages (7%), rhesus disease (6%), the need for a cesarean section (3%), and diabetes (3%); which are likely not associated with an STI. It is encouraging to note that the characteristics of our sample do not differ greatly from the population of women in Botswana. The 2007 Botswana Family Health Survey IV Report, which identifies and surveys a representative sample of the population of Botswana on topics related to family planning awareness and basic maternal and child health indicators, also found that very few women were married (18%), 70% reached at least a secondary level of education, and the highest proportion of pregnancies occurred among women between the ages of 30-34.[56] Further, the Botswana AIDS Impact Survey IV Report, which provides HIV infection incidence and prevalence estimates among the population aged six to 64 years, found that the HIV infection prevalence among pregnant women was 20.5%. This is similar to our HIV prevalence estimate of 22.5%. The high proportion of preterm births among women who had previously given birth is expected given that Botswana is one of 11 countries with a national preterm birth rate higher than 15%.[41]

Additionally, our sample represents women who agreed to participate and may be more likely to include women who believe they are at greater risk for infection. However, this concern is mitigated by the large proportion of women who accepted (86%) out of all those eligible.

In conclusion, providing testing and treatment for curable STIs to pregnant women in an antenatal clinic in Gaborone, Botswana revealed a high STI prevalence. Participant HIV infection and marital status were significantly associated with testing positive for an STI and self-reported STI symptoms were not associated with testing positive. The absence of diagnostic tests for STIs during antenatal care represents a missed opportunity to improve pregnancy and birth outcomes in Southern Africa. As highly sensitive, point-of-care testing assays become more widely available, it is important for Health Ministers and other policy makers to assess the short term and long-term cost and benefits of offering STI screening during antenatal care.

## **2.5 Tables and Figures**

**Figure 2.1: Flow of eligible women and participants in a *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* testing and treatment study in Gaborone, Botswana.**



Note: \* Delayed results includes one participant who did not receive results.

**Table 2.1: Characteristics of study participants and associations with *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* infection testing and treatment study in Gaborone, Botswana. (N=400)**

	Total sample (n=400)		An STI* (n=54)			CT (n=31)			NG (n=5)			TV (n=21)		
	n	%	n	%	p	n	%	p	n	%	p	n	%	p
<b>Age, Median [range]</b>	30	[19-45]	29	[19-43]		28	[19-40]	†	22	[21-39]		31	[21-43]	
18-25 years	95	(24)	17	(18)		12	(13)		3	(3)		4	(4)	
26-35 years	221	(55)	25	(11)		14	(6)		1	(0.5)		11	(5)	
>35 years	84	(21)	12	(14)		5	(6)		1	(1)		6	(7)	
<b>Marital Status (n=396)</b>					‡									‡
Unmarried	307	(77)	49	(16)		27	(9)		5	(2)		20	(7)	
Married	89	(22)	5	(6)		4	(4)		0	(0)		1	(1)	
<b>Education (n=392)</b>					†									‡
Junior secondary or less	118	(30)	22	(19)		9	(8)		2	(2)		12	(10)	
Senior secondary	114	(29)	17	(15)		12	(11)		0	(0)		5	(4)	
Tertiary	160	(40)	15	(9)		10	(6)		3	(2)		4	(3)	
<b>Gestational Age weeks (LNMP), Median [range]</b>	26	[5-36]	28	[8-35]		28	[8-35]		22	[11-32]		29	[14-34]	
<b>Prior pregnancies, Median [range]</b>	1	[0-10]	1	[0-5]		1	[0-5]		1	[0-1]		2	[0-5]	
<b>Prior births, Median [range]</b>	1	[0-7]	1	[0-5]		1	[0-5]		1	[0-1]		2	[0-5]	
<b>1 or more births</b>	261	(65)	37	(14)		20	(8)		3	(1)		16	(6)	
Prior preterm birth	64	(25)	12	(19)		10	(16)	‡	1	(2)		3	(5)	
No prior preterm birth	192	(74)	25	(13)		10	(5)		2	(1)		13	(7)	
<b>Current CT/NG/TV symptoms</b>	165	(41)	22	(13)		10	(6)		3	(2)		10	(6)	
Vaginal discharge	107	(27)	15	(14)		8	(7)		2	(2)		6	(6)	
lower abdominal pain	88	(22)	9	(10)		2	(2)		1	(1)		6	(7)	
Painful urination	16	(4)	2	(13)		2	(13)		0	(0)		0	(0)	
<b>Treated syndromicly during pregnancy</b>	48	(12)	8	(17)		5	(16)		1	(20)		2	(10)	

<b>Condom use before pregnancy**</b>										
Never	110	(28)	14	(13)	8	(7)	1	(1)	5	(5)
Sometimes	185	(47)	28	(15)	17	(9)	2	(1)	10	(5)
Always	98	(25)	12	(12)	6	(6)	2	(2)	6	(6)
<b>Condom use during pregnancy</b>										
Never	188	(47)	30	(16)	16	(9)	4	(2)	13	(7)
Sometimes	83	(21)	9	(11)	6	(7)	0	(0)	3	(4)
Always	75	(19)	12	(16)	7	(9)	1	(1)	4	(5)
<b>HIV infection status</b>										
Infected	90	(23)	21	(23)	10	(11)	2	(2)	9	(10)
Uninfected	305	(76)	32	10)	20	(7)	3	(1)	12	(4)

Notes: \*Any STI means diagnosed with CT, NG, and/or TV infection. LNMP stands for last normal menstrual period. \*\*Women were asked about condom use during the 3 months prior to the pregnancy or trying for the pregnancy. Ranges are in brackets. Percentages are in parentheses, may not add up to 100 due to rounding, and the denominators are derived from the row value in the Total sample column. ‡ represent  $p \leq 0.05$  and † represents  $p < 0.1$ , which resulted from Student's T-test, Chi-squared test, Fisher's exact test, or Wilcoxon-Mann-Whitney test. CT, NG, and/or TV symptoms include vaginal discharge, lower abdominal pain and painful urination.

**Table 2.2 Results of a multivariable logistic regression model assessing participant characteristics associated with *Chlamydia trachomatis*, *Neisseria gonorrhoea* and *Trichomonas vaginalis* infection (n=376)**

Characteristics	Positive for CT, NG and/or TV	
	OR (95%CI)	P-value
Age ≤ 25 years	1.67 (0.84-3.29)	0.14
Unmarried	2.89 (1.09-7.67)	0.03
High school education or less	1.69 (0.85-3.37)	0.14
Never used a condom during current pregnancy	1.59 (0.86-2.96)	0.14
HIV infected	2.72 (1.45-5.10)	0.002

Notes: Independent variables (age, marital status, education level, condom use during pregnancy, and HIV infection status.) were included based on a stepwise regression model. Odds ratios reflect increased or decreased likelihood of women with this characteristic being diagnosed with CT, NG, and/or TV.

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## CHAPTER 3: Partner notification for sexually transmitted infections among pregnant women in Botswana: A qualitative study

### 3.1 Chapter Introduction

*Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* (TV) are curable sexually transmitted infections (STI), but are major causes of morbidity among women and are associated with adverse birth and infant outcomes, including preterm birth, low birth weight, spontaneous abortion, and mother-to-child transmission of HIV.[1-7] Partner notification is an essential component of STI management, and is the process where sex partners are identified, notified about their exposure, counselled, and treated if appropriate.[8, 9] Treating partners reduces the likelihood of re-infecting a treated index patient, as per-partnership transmission probabilities are estimated to be high, based on prior research.[10] Further, notifying and treating the partners of pregnant women may also decrease the burden of infection in communities because the partners may be asymptomatic and otherwise unlikely to access the healthcare system for treatment.[7, 11-13] Thus, if a pregnant woman is identified as having an STI, she should be treated and advised to notify sex partner(s) about the infection.[14]

There are three main approaches to partner notification: (1) health professional-oriented methods where healthcare workers contact the partners and advise them on how to seek treatment and prevent future infections; (2) patient-oriented methods where the index patient notifies their partners and encourages them to seek medical care or provides treatment directly to their partner, and (3) mixed approaches involving both the index patient and a healthcare provider. For example, an index patient could sign a contract to notify a partner

within a certain timeframe after which the provider may contact the partner.[8] Regardless of the strategy utilized, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommends that partner notification for HIV and other STIs be conducted on a voluntary basis.[15]

Among the above-mentioned strategies, none has been identified as the gold standard and partner notification rates are often low regardless of the strategy used.[8, 9] A systematic review, which examined research related to partner notification strategies in low- and middle-income countries, found that just over half of partners were notified in the 39 included studies.[9] In order to improve rates of partner notification and treatment and subsequently reduce rates of re-infection, more research is needed to understand barriers and facilitators to notification.

This study seeks to explore the experiences and preferences related to partner notification among women who were diagnosed with an STI during pregnancy. The study was conducted in Botswana, a country in Southern Africa that is heavily burdened by HIV infection. This qualitative study aims to inform partner notification guidelines in Southern Africa as well as future research with a deeper understanding of partner notification.

## **3.2 Methods**

### **3.2.1 Study setting and participant selection and recruitment**

Between August 2016-February 2017, a sample of women who tested positive for CT, NG, or TV at the Princess Marina Hospital antenatal clinic in Gaborone, Botswana were recruited by phone for participation in the qualitative study by a female, Setswana and English-speaking researcher. Per the standard of care in Botswana, after testing positive for an STI,

women received a partner contact slip with information about the STI they were diagnosed with, the treatment provided, and space for a partner's healthcare provider to sign to confirm that the partner was treated. Further, women were counselled to notify partners, encourage partners to get treatment, and avoid sex for seven days after treatment.[16] Women were advised to return for a test of cure after four weeks. In order to understand a variety of perspectives, we aimed to recruit participants diagnosed with different STIs (e.g. CT, NG, or TV), with and without HIV coinfection, and who did and did not tell their partners about their STI diagnosis. All women were pregnant (<35 weeks of gestation), at least 18 years of age, and receiving care at Princess Marina at the time of the STI diagnosis. Those who agreed to participate in this study were scheduled for an in-person, 30 min to 1-hour interview in a private office on the University of Botswana campus or a location of their choosing. Participants were given a 30 pula (~3 USD) reimbursement for their time. Prior to the interview, participants were provided with informed consent and given the opportunity to ask any questions or voice concerns to the interviewer.

The interviews were guided by an outline of open-ended questions and probes that explored the following domains: participant's general well-being, sexual relationship status and history, HIV infection status, experiences with STI testing, partner notification experiences, barriers and facilitators to notifying their partners, partner reaction and treatment outcomes, and preferences related to partner notification. The guide (See Appendix A) was pilot tested on two participants and revised to improve understanding. The study was also temporarily paused after seven interviews, and transcripts were reviewed to ensure the guide was understood and facilitated collection of detailed and candid information. Each transcript also included a brief

fieldnotes section where the interviewer could describe the setting and any other thoughts relevant to the interview.

### **3.2.2 Data collection**

One-on-one interviews were conducted in Setswana or English by a female researcher who had a University degree, training in qualitative methods, and extensive experience in interviewing on women's reproductive health issues. Referrals to health organizations and community-based services for depression, domestic violence, or health concerns were offered as needed.

Interviews were digitally recorded, transcribed verbatim, and translated to English. A sample of transcriptions was translated by another member of the study team, the translations were discussed, and only minor changes were made.

### **3.2.3 Data analysis**

To develop a codebook, four transcripts were selected at random and codes were extracted by two study team members based on themes included in the interview guide while also allowing for new codes to emerge inductively from the unique data.[17] The codes were then compared and aggregated into a master codebook with codes and definitions. All transcripts were read and coded using this codebook in Microsoft Word and Excel. Coded transcripts were assessed for frequently used codes and patterns associated with women's experiences related to partner notification of an STI. Illustrative quotations were extracted for dominant themes. Divergent or minority views were also noted. Narratives and themes were compared between participants to understand similarities and differences. Reporting was based on the consolidated criteria for reporting qualitative research (COREQ).[18]

### **3.2.4 Ethics**

The institutional review boards at the University of Botswana, the Botswana Ministry of Health, Health Research Development Committee, and Princess Marina Hospital approved the study protocol. The University of California, Los Angeles, approved analyses using deidentified data. All data from the interviews were kept confidential and stored in secured locations. During transcription personal identifiers were removed and documents were labeled with a study ID. Once transcription was complete, audio files were destroyed.

## **3.3 Results**

### **3.3.1 Participant characteristics**

A total of 22 women were contacted and 15 were enrolled in the study. Of the seven who were not enrolled, four initially agreed and then continually postponed, two people moved away from Gaborone, and in one instance, the study interviewer declined to stay for an interview due to safety concerns. Characteristics collected at the time of STI testing, including demographic and relationship characteristics, HIV infection status, STI-related symptoms, and self-reported partner notification outcomes, were compared between those who refused and enrolled. Nonparametric tests, including Wilcoxon rank sum and Fisher's exact test, did not reveal appreciable differences between those who participated and those who did not enroll. However, those who did not enroll had an older median age (31 compared to 29 years), and one person was married whereas all participants were unmarried. Among the seven who did not enroll, five reported that they told their partners about the STI diagnosis and one partner was not treated (results not shown).



Table 3.1 describes the age, marital status, highest education level, HIV infection status, self-reported STI symptoms, partner notification outcomes, and test of cure results for the study sample. The mean age was 29 years, all were single and most women had achieved a tertiary level of education. The prevalence of HIV infection was 40% (6) and almost a third (4) reported having abnormal vaginal discharge at time of STI testing. Thirteen women notified their partners about their positive STI diagnosis, and seven reported that their partners were treated, four said that their partners were not treated, and four said that they weren't sure if their partners were treated. Three women in the sample retested positive for an STI at test of cure, which took place four weeks after initial testing.

Table 3.2 describes each participant's STI diagnosis, HIV infection and partner status, self-reported partner notification and partner treatment outcomes, and test of cure outcome. Most women in our qualitative sample were infected with CT-only (9) and still in a relationship with the baby's father (10). The two women, who did not tell partners about the STI diagnosis, were no longer in a relationship with the baby's father. Four women reported that their partners were not treated, including two who were not treated despite being notified. Four women were unsure if their partners were treated because they did not have proof (e.g. by accompanying him to the clinic or being provided with a contact slip signed by a doctor/nurse). Among the three women who retested positive for CT at follow-up, one was unsure if her partner was treated. The time between initial STI test and interview ranged from 5 to 20 months.

### 3.3.2 Qualitative Themes

#### ***Knowledge about CT, NG, or TV infections***

Ten women had never heard of CT, NG, or TV infections prior to testing, three women said that she had heard about the infections, and two reported only hearing about gonorrhea.

### ***Reasons for testing for CT, NG, or TV infections***

When asked about their motivation for STI testing during their pregnancy, seven women mentioned that they wanted to test in order to know if they had infections and expressed an understanding that they could be infected without knowing.

*Because most of the time, we will be living with infections, but not knowing, so I wanted to see.* (Participant 3, age 27)

\*\*\*

*I felt that it was important to do that [test] because you never know, maybe some things stay in you, you can have them without symptoms you see.*  
(Participant 4, age 33)

Two women said that they tested to protect the baby from infections. *"... for the sake of my baby, so that's why I wanted to."* (Participant 2, age 28) Two women said that it was an opportunity to test that they would not normally have. Two women reported that they had symptoms they thought may be a result of an STI or had been previously treated for an STI and wanted to see if it they were still infected.

*I had challenges of, for two months I used to get itchy down there and I'd ask myself why, you see.* (Participant 6, age 31)

While only one woman mentioned partner infidelity as a reason for testing, seven women reported that their partners were likely having sex with other women and one woman said *"...he is all over the place. There's no one that doesn't know him."* (Participant 12, age 25) Two women broke up with their partners because they impregnated other women. Alcohol use was discussed as a contributor to infidelity. *"Yes, when I ask him, he says he was drunk and didn't know what he was doing."* (Participant 1, age 24)

### ***Women's reaction to STI diagnosis***

Four of the 15 women reported that they were “okay” with the results or “accepted” them and did not choose to elaborate further upon probing. Only a few reported that they were very surprised to be infected and the remainder expressed relief or an appreciation for being able to receive treatment for an infection.

*Now, when I was told, I just accepted that, yes, maybe they'll help me. I just really wanted help. (Participant 11, age 21)*

\*\*\*

*That's why I accepted because even if I had received wrong results [testing positive], I knew I would be helped, and the baby. (Participant 9, age 28)*

### ***Partner notification experiences***

Among the 13 women who told their partners about the STI results, three had recently separated from their partners and the remainder were still with the partner who they had been with for one year or longer at the time of notification. In notifying their partners, most women told them in person, without much delay from time of diagnosis and were straightforward in sharing the news. All but a few women reported using the contact slip to help inform their partners about the STI results.

*I told him that “Mr. I was told that we have STI's.” ...And again I showed him the clinic card, because you had marked it somewhere. (Participant 1, age 24)*

\*\*\*

*Yes. I didn't go around in circles, I got in and said, I was in [the clinic] and there were people testing for sexually transmitted diseases so I also tested, but came back positive. The disease is called Chlamydia now you can read these papers and see what kind of disease it is. (Participant 5, age 35)*

The only barrier to notification identified by women who told their partners was distance, when the partner lived in another city, which caused delays in notification. Those who waited did not want to share this information over the phone.

*“Hey, [this news is] sensitive and can’t be said over the phone.”* (Participant 7, age 33)

One person shared the results through an image of her medical record on Whatsapp.

Reasons for telling partners were generally multi-faceted and included wanting to protect the partner’s health, prevent reinfection, and not wanting to keep a secret from the partner.

*Because we are together, we sleep together. So obviously, what I have I must share with him. So that if he also needs help he may get it.* (Participant 4, age 33)

Finally, one woman said that counselling provided in the clinic encouraged her to ensure that her partner was treated.

*The advice that [clinic staff] gave me is the one that gave me that courage to tell them. [They] told me it's safe to get treated for that and my boyfriend to get treated...Because there will be no point of me getting treated and him not.* (Participant 11, age 21)

The two women who did not notify their partners were no longer in a relationship with the baby’s father at the time that they received the STI results. One woman did not know how to get in contact with the partner and one was reluctant to communicate after the breakup.

Women living with HIV infection did not report different experiences with partner notification compared to those who were uninfected. Five notified their partners about the STI diagnosis and one woman did not because they were no longer together. Five women in our sample, including three women living with HIV, did not know their partners’ HIV infection status, and reported that their partners were likely *“testing through me.”* Several women mentioned that their partner was unwilling to get tested because he could check his status when she got tested.

*Yes, because when I said go and test, I tested myself, he asked me “are you ok” and I said “I’m fine” then he said “yes that means I’m fine.” Do you see the issue?* (Participant 12, age 25)

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*He is very difficult when it comes to testing. When I go and test and then show him he believes he is also ok.* (Participant 5, age 35)

### **Partner’s reactions to STI diagnosis**

Among participants who notified their partners, the majority reported that their partners reacted well to being informed about the STI results. Six women reported that their partners said “it’s okay” or “it will be fine” after being told about the diagnosis. Two partners were reported to be scared, one for the baby’s safety and the other about getting an injection. One partner made a joke.

*“...Then they found that I have this infection.” (Starts laughing) Then he just said “it’s loving sex, that’s the only problem.”* (Participant 7, age 33)

One participant reported that her partner reacted in anger and she had sex with him to calm him down.

*I said “I went to [the clinic] for a checkup and then I checked myself [tested].” Now he is shouting at me for checking myself... “What did you check for?” saying “you like testing yourself for so many things!” This and that. “So you think I sleep around with girls, am I sick?” Right then we had sex again because he was shouting right... Yes, I was calming him down.* (Participant 12, age 25)

Some partners asked questions and participants didn’t have enough information to answer.

*I said, “Don’t bother me with too many questions I don’t want questions, you will ask for yourself. There’s a lot of time, they give you time to ask.”* (Participant 8, age 31)

*He just asked what it was. I said, “I don’t know I’m asking you, let’s go.”* (Participant 1, age 24)

### **Partner treatment experiences**

Women encouraged partners to seek treatment in a variety of ways. One woman said that she wouldn't sleep with him until he received treatment, "*We are not going to have sex until you're tested*", another woman said, "*if you want a child again let's go check again for STI's*" (Participant 5, age 35), and one woman said that she's protecting him by telling him to get treated for the STI, "*dude, do you see how much I protect you?*" (Participant 2, age 28) A few partners did not seek treatment until contacted by clinic staff, at the participant's request, to encourage treatment uptake.

*So they [partners] come with us. Because when we tell them they refuse. You see that I asked him and then after [clinic staff] called that's when he came.*  
(Participant 12, age 25)

The two un-notified partners were assumed to be untreated. Among the two notified partners that were not treated, one participant reported that his work schedule was a barrier to receiving care at a clinic. Another woman, who was no longer together with the baby's father reported, "*it was just laziness,*" (Participant 10, age 32) that prevented her ex-partner from seeking care. Several women reported that their partners may not have been treated if the treatment was injection. Several women reported having problems getting the partner treated when they didn't have the contact slip. One partner was confused about what to say when he arrived at the clinic without a contact slip.

*He told me that, when he gets to the hospital what should he say. And I told him "no when you get to the hospital, there's no evidence that I can give you, when you get to the hospital you tell them my partner was tested and she was found with STI's."* (Participant 5, age 35)

Among those treated, half of the women accompanied their partners to the clinic. When partners went to the clinic on their own, some participants had doubts that they were treated.

*I'll just have to believe I can't dispute it. [Interviewer: He hasn't shown you his card or anything?] No, he hasn't shown me. (Participant 9, age 28)*

While most women were cured when tested approximately 4 weeks after STI diagnosis and treatment, three women retested positive for CT at the first test of cure. One of these women did not notify her partner after the first diagnosis and had sex without a condom. Thereafter, she notified him, he was treated, and her second test of cure was negative. Similarly, the remaining two women's partners were treated only after the first test of cure was positive, and in both cases clinic staff called to encourage the partners to seek treatment.

### ***Preferences for notifying partners in the future***

Participants were asked questions about how they might want to notify a partner in the future and different options were described to them. When asked, in general, how they would prefer to notify partners in the future, most women preferred to tell their partner themselves in person and generally thought the way they told him went well. Only the woman whose partner shouted at her upon notification preferred to have a healthcare provider notify.

*Me as a woman, I can tell him. If it's a problem and he can't understand, that's when I can take him to you [clinic staff] so you explain what we are talking about. (Participant 6, age 31)*

We also asked how women preferred that partners get treatment, and described possible options, which included: bringing treatment home to partners (e.g. women would bring information and treatment home for their partners to take prior to him being examined by a healthcare provider), have partners go to the clinic alone (with probing questions on whether a contact slip was sufficient or if a provider should call), or accompany partners to the clinic. Most participants said that they would like to accompany their partners to the clinic for treatment because many said that otherwise he may not go.

*But if you give me the paper [contact slip] I'm going to need to go with him because if I don't he won't do it [get treated]. (Participant 10, age 32)*

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*I would need me to come with him. If you call him and say he should come, he is going to agree and not come. It needs me to say let's go, they called you. (493)*

No women preferred to bring treatment home to their partners. Two women explained that they would not want to bring treatment home because the partner would have many questions or would refuse the treatment.

*Ah, it wasn't going to be good. He was going to refuse... He was going to ask himself what pills I was giving to him that he hasn't been told about. (Participant 1, age 24)*

### **3.4 Discussion**

We assessed women's experiences and preferences associated with partner notification of an STI diagnosed during pregnancy by conducting semi-structured interviews with a convenience sample of 15 women who had tested positive for a CT, NG, or TV infection. Most of the participants had never heard of CT, NG, or TV infections before testing. All but two notified their partners and among those who notified, distance (e.g. when the partner lived in another city) was described as a barrier. Most women used the contact slip to notify their partners and encourage them to get treatment. Women who didn't notify their partners were no longer in relationships. Just under half of women reported that their partners were definitely treated, and the remainder said their partners were not treated or they weren't certain that their partners were treated. Women who tested positive for an STI at the test of cure reported that partners delayed receiving treatment. Several women needed to have a healthcare provider call to encourage the partner to get treatment. Reported barriers to treatment were the partner's work schedule and a fear of injections. Many women reported



concerns that their partners were having sex with other women. In terms of future preferences, all but one woman reported that they would want to tell their partner about an STI diagnosis themselves. Most women would want to accompany their partners to the clinic for treatment and none would prefer to take medication home to the partner.

Similar to previous research, we found that even though women were willing to notify their partners about an STI, this willingness did not always result in partners being treated.[9] Previous qualitative research in Southern Africa found that women were motivated to tell partners about an STI diagnosis because they thought sex partners were the source of infection and needed treatment, or to protect a child from infection.[19] However, barriers to telling partners also included: partners lived far away, embarrassment, and fearing losing support.[19, 20] A study among pregnant women in Haiti found that while 86% of participants wanted to notify their partners about an STI diagnosis, only 30% of partners accessed healthcare for treatment.[21]

Additionally, even when partners were notified, several received delayed treatment, which may have put pregnant women at risk for reinfection. Delays in treatment may reduce the effectiveness of antenatal STI testing and treatment. A recent modelling study found that reducing partner treatment from fourteen to one or two days substantially reduced the risk of CT and NG reinfection of an index patient.[10] Further, delays in partner treatment have been previously identified as a concern in Botswana. A 2013 study assessed contact slips of partners treated for an STI from approximately 285 health facilities in Botswana to identify any delays between index patient and partner treatment. This study found that, among partners who reported for treatment, 22.1% were treated a week or more after the index patient.[22]

In order to improve and expedite partner treatment rates, several new strategies have been proposed and implemented in other settings, such as the United States.[23] One strategy is expedited partner therapy, where an index patient brings medication home to a partner prior to the partner's evaluation by a healthcare provider.[23] Several randomized controlled trials have shown that expedited partner treatment can reduce reinfection rates compared to simple patient referral (patient tells sex partners they need to be treated).[24] One study involving men and women in the United States, who were randomized to expedited partner treatment or simple partner referral, found that 13% of index patients in the simple referral group had a persistent or recurrent gonococcal or chlamydial infection compared to only 10% in the expedited partner treatment group.[25]

Decisions about future partner notification strategies should also consider enhanced patient notification activities, such as providing additional information about STIs for the index patient and partner. Study participants expressed concern that they would not be able to answer all of their partners' questions, and this lack of knowledge was cited as a reason for not preferring to bring treatment to their partners above accompanying them to the clinic for treatment. The participants in our sample also demonstrated a low level of basic knowledge about curable STIs, which has been identified as a barrier to partner notification and treatment in other settings.[26] Many study participants valued the contact slip and information provided by clinic staff on the importance of partner treatment. Further, a recent systematic review found that there was no statistical evidence of a difference in STI reinfection rates between expedited partner therapy and enhanced patient referral, which included home sampling kits

for partners, educational information for patients to give to partners, and disease-specific websites.[24]

Participants in our study were unwilling or unable to notify previous partners about an STI diagnosis, which is a finding similar to previous research in Southern Africa.[19, 20] While women are not at risk of reinfection from ex-partners, not notifying a likely STI case may represent a missed opportunity to reduce infections in the community. Studies have estimated that 70–80% of partners of index cases with NG are infected and 60–70% of partners of index cases with CT are infected.[27, 28]

In circumstances where women are unable or unwilling to notify their former partners themselves, it may be possible for electronic communication technologies to play a role, such as SMS, or web-based notification. Although little research has taken place in sub-Saharan Africa, there is growing research on the acceptability and utilization of these technologies for STI notification.[29] Further, many participants expressed concerns that their partners may have other casual sex partners who could potentially also be reached through electronic communication if their partners are unwilling to tell them in person. Previous studies found that referral strategies requiring less interaction, were preferred for notifying ex-partners or casual partners.[10]

The study has some limitations. First, our sample was small and was derived from a single site. As previously reported, the sample of women tested for CT, NG, and TV infections from which women were recruited for this study had characteristics similar to the population of pregnant women in Botswana in terms of age, and marital and HIV status.[30, 31] Second, participants who consented to participate in the qualitative study may be different than women

who declined. For example, our sample may include those more willing to discuss partner notification because they were more successful in notifying their partners. However, as described above, self-reported partner notification and treatment outcomes were similar between those groups. Third, response bias is almost always a limitation when participants are asked sensitive questions. However, it was encouraging to read in the transcript field notes sections that our trained interviewer interpreted most women's responses to be honest and open. Finally, our study included only pregnant women, and findings are not generalizable to non-pregnant women diagnosed with an STI in Botswana. Previous research has found that pregnant women may be more likely to be in long term relationships and to notify their partners due to concerns about the baby compared to non-pregnant women.[32]

In conclusion, the aim of our study was to gain a more detailed understanding about the experiences and preferences of pregnant women related to notifying partners about an STI diagnosis. In order to improve rates of partner notification and treatment, reduce rates of re-infection during pregnancy, and subsequently reduce adverse maternal and infant outcomes due to antenatal STIs; more research is needed to identify effective and appropriate strategies for partner treatment, and to improve knowledge and understanding about STIs among pregnant women.

### 3.5 Tables and Figures

**Table 3.1: Characteristics of women participants in the sexually transmitted infection partner notification study at Princess Marina Hospital in Gaborone, Botswana (N=15)**

	Study Sample N (%)
Age in years, Mean (SD)	29 (4.7)
Unmarried	15 (100%)
Education	
Junior secondary or less	6 (40%)
Senior secondary	3 (20%)
Tertiary	6 (40%)
Living with HIV infection	6 (40%)
Self-reported STI-related symptoms at time of STI testing	
Vaginal discharge	4 (27%)
Painful urination	2 (13%)
Lower abdominal pain	3 (20%)
Told partner about STI diagnosis	13 (87%)
Partner treatment	
Yes	7 (47%)
No (includes those who were not notified)	4 (27%)
Unsure	4 (27%)
STI cured in index participant at follow-up	12 (80%)

Note: Percentages may not add up to 100 due to rounding.

**Table 3.2: Characteristics of women included in the qualitative interview sample.**

Pseudonym	STI	HIV Infection Status	Partner status*	Partner notified	Partner treated	STI cured**
Dimpho	TV	Infected	No partner	No	No	Yes
Lesego	TV	Uninfected	New partner	No	No	Yes
Tshepho	CT	Infected	Baby's father	Yes	No	Yes
Nametso	CT	Infected	No partner	Yes	No	Yes
Kgomotso	NG	Infected	Baby's father	Yes	Unsure	Yes
Otsile	CT	Uninfected	Baby's father	Yes	Unsure	No
Lorato	TV	Uninfected	Baby's father	Yes	Unsure	Yes
Patricia	CT	Uninfected	No partner	Yes	Unsure	Yes
Tumelo	CT	Uninfected	Baby's father	Yes	Yes	Yes
Lesedi	CT	Uninfected	Baby's father	Yes	Yes	No
Precious	CT	Uninfected	Baby's father	Yes	Yes	No
Naledi	CT	Infected	Baby's father	Yes	Yes	Yes
Bonolo	TV	Uninfected	Baby's father	Yes	Yes	Yes
Keomogetse	TV	Uninfected	Baby's father	Yes	Yes	Yes
Kefilwe	CT	Infected	No partner	Yes	Yes	Yes

Note: \*Partner status at time of interview. \*\*Participant retested at four weeks for cure.

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## CHAPTER 4: Assessing the costs and estimating scale-up of testing pregnant women for curable sexually transmitted infections in Botswana

### 4.1 Chapter Introduction

*Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) are among the most common sexually transmitted infections (STI) worldwide.(1) CT and NG infections during pregnancy are associated with increased risk for adverse outcomes, including preterm birth, low birth weight, spontaneous abortion, and mother-to-child transmission of infection during delivery.(2-12)

Despite clear risks to women and infants' health, most countries do not promote routine testing for CT and NG during pregnancy.(13) Instead, countries rely on syndromic management, whereby patients are treated with standardized drug regimens based on their symptoms and clinical signs, and which has been included in the World Health Organization's STI management guidelines since the 1990s.(14, 15) This approach has low sensitivity since many infections may be asymptomatic (16-18), and it lacks specificity, potentially exposing women to unnecessary antibiotics.(16, 17)

Recent developments in technology have introduced the possibility of antenatal testing with highly sensitive, easy to use, rapid tests for CT and NG. A nucleic acid amplification testing (NAAT)-based platform is available for diagnosis of CT and NG (GeneXpert® system, Cepheid) at the point-of-care.(19) Several studies have piloted point-of-care CT and NG testing during antenatal care in low-resource settings, and have shown that these diagnostics can achieve high treatment rates.(20, 21) However, more research is needed to understand the costs of scaling up antenatal CT and NG testing and treatment to the national level.

This study assessed the costs and outcomes of three approaches for scaling up antenatal CT and NG testing in Botswana. We used a new system simulation model, with data from a CT and NG testing and treatment program as well as newly-collected cost information, to compare strategies for CT and NG testing and treatment at-scale: 1) sample processing at the point-of-care with same-day results and treatment (point-of-care scenario), 2) sample processing in centralized laboratories with delayed results and treatment (centralized laboratory scenario) and 3) a combination approach (mixed scenario) that offers point-of-care testing at high-volume sites and pools samples across lower-volume sites for testing at centralized sites. Given that a system-level barrier to scaling up STI testing may be cost and accessibility, information from this study may inform policy-makers' decisions about approaches to maximize the number of STI infections cured among pregnant women, at the lowest cost.

## **4.2 Methods**

First, we discuss the study setting and primary data from the pilot program. Next, we describe the analysis approach of simulating three scenarios of scaling up CT and NG testing in Botswana.

### **4.2.1 Pilot CT and NG testing and treatment program**

We collected primary cost data and information about point-of-care test uptake and treatment rates, from a pilot program to test and treat pregnant women for CT and NG infections in an antenatal clinic in Gaborone, Botswana. Testing was conducted using a GeneXpert® CT/NG [Cepheid, Sunnyvale, CA] system with two 4-module machines, which provided a 90-minute time to result. Those who tested positive were given directly observed antibiotic therapy, counselled to notify their partners, and asked to return for a test of cure in

four weeks. Characteristics of women recruited at this single site were similar to the population of pregnant women in Botswana. (22)

#### **4.2.2 Primary cost data collection**

Economic and financial costs of the CT and NG pilot program were collected retrospectively from programmatic expenditures and invoices. We took a health system perspective when considering relevant costs. Market prices and actual salaries were used to estimate the economic costs of donated items and time. All costs were collected in Botswana Pula and converted to USD using the average exchange rate between July 2015 and May 2016.(23)

The cost components considered were: new equipment (capital), training, personnel, and supplies. Capital costs were the Xpert system, which ranges in size. The costs associated with different sizes of the Xpert machines were obtained from the manufacturer and are based on high-burden low-income country negotiated prices. The acquisition costs were converted to annual costs, based on a useful life of 5 years and a discount rate of 3%.(24) The machine package included the modules, desktop computer, barcode scanner, printer, uninterruptible power source (5-10 minute run-time), and a fan. Further, to ensure the 2-year warranty the system must be calibrated at a cost of \$450 after the first year. Training consisted of a 3.5 hour, hands-on seminar with the Xpert manufacturer. Observations of personnel time and supplies needed to provide counseling (e.g. pre-test counselling, sample collection instruction, results, treatment, and counselling to notify sex partners) and to process the samples and complete paperwork, were conducted on a random sample of testing days. Personnel included two research assistants, a program manager, a physician, and a nurse midwife. Supplies included

the CT/NG cartridges, sample collection tubes, CT and NG treatment for women and partners who tested positive, gloves, disinfectant, paper towels, and office supplies. Costs incurred from research activities were not included.

#### **4.2.3 Scale-up Simulations**

##### **Overview**

We developed an Excel-based model that represented all public hospitals, clinics, and health posts in Botswana; distributed annual antenatal patient volume across these sites, and extrapolated per test costs (based on the pilot program data) to estimate the one-year costs and outcomes of national scale-up of CT and NG testing and treatment according to three scenarios: 1) sample processing at the point-of-care (point-of-care scenario), 2) sample processing in laboratories (centralized laboratory scenario), and 3) a combination of the first two scenarios (mixed scenario) that would offer point-of-care testing and treatment at high-volume sites and pool samples across lower-volume sites for testing at the high volume sites.

##### **Outcomes**

For the pilot program and each of the three simulated scenarios, we totaled cost elements and estimated the average cost per: 1) pregnant woman tested, 2) infection treated, and 3) infection cured. The cost per woman tested and treated was calculated as  $C/(Va)$ , where  $C$ =total annual cost at a site,  $V$ = annual number of antenatal visits at the site, and  $A$ =% of patients accepting testing. Cost per infected patient treated was  $C/(Vait)$ , where  $i$ =% of all patients infected and  $t$ =% of infected patients treated. Cost of curing an infected patient was  $C/(Vaitp)$ , where  $p$ =% not reinfected by their partners. Costs and treatment rates vary by scenario.

## Model Assumptions & Parameter Values

Figure 4.1 shows how certain model parameters differed by each of the three scale-up scenarios, including percentages of women who received results and treatment, and were cured. These parameters were based on findings from the pilot program.(22) Based on results from the pilot, we assumed that, among pregnant women tested in point-of-care facilities, 74% would receive results in-person on the day of testing, and 95% of those diagnosed with an STI would receive treatment. Among those who received delayed results, 67% would receive treatment and the remainder would be lost to follow-up. Also, among those treated, 90% would be cured at the test of cure. For the centralized laboratory scenario, we assumed that 100% of pregnant women tested would receive delayed results and that the proportion of women treated would be the same as those who received delayed results in the pilot program.

Table 4.1 outlines the variables used to parameterize the scale-up models. The Botswana Health Statistics Report(25) provided volume of antenatal visits at individual hospitals. However, volume at individual lower level facilities (e.g. clinics, health posts) was summed by type of facility, so we distributed the volume equally across clinics and health posts within each region. We assumed 220 business days per year to account for weekends, holidays, and possible power or water outages at clinics.(26) CT and NG prevalences and partner treatment rates were derived from the pilot program.(22, 27, 28) The capital and calibration costs were informed by the manufacturer and the World Health Organization's Xpert MTB/RIF implementation manual and represent high burden low income countries.(29)

In addition to the capital costs of the Xpert machines, we projected costs of personnel, supplies (e.g. CT and NG treatment and CT/NG testing cartridges), training, and sample shipping when necessary. Staff salaries, provided by the Botswana Ministry of Health (unpublished data),

were multiplied by the staff time for CT and NG testing as determined by a time-use study in the pilot program. (Table 4.1). Staff time included training, pre-test counselling, sample collection instruction, sample processing, reporting results, providing treatment, providing information for partners, and record keeping. We assumed that medical auxiliary staff and nurses were available at all sites, and that doctors were not available except at health posts. Supply costs were derived from invoices from the pilot program or quotes from distributors. The cost of temperature-controlled storage and shipping was estimated to be 5% of the cost of the CT/NG testing cartridges, which was based on a cost analysis from South Africa.(24)

We estimated the numbers of Xpert machines that would be needed at each site based on expected daily testing volume, uptake rate and the length of the work day at health facilities.(22) Each Xpert module can process one CT/NG cartridge at a time, which takes 90 minutes. For example, one machine with two modules could process eight samples a day, assuming a six-hour clinic day. For this analysis, a two-module machine would need to be added for every additional eight tests conducted per clinic day. For example, if a busy clinic saw 24 new antenatal patients a day, it would need at least 6 modules to complete testing by the end of the day. Table 4.2 summarizes assumptions and structure of the three scenarios, each of which is described below.

### **Scenario 1: Universal point-of-care testing**

For the point-of-care scenario, we allocated at least one Xpert machine (with two modules, which is the smallest system currently available) to all clinics and hospitals that provided antenatal care in Botswana. Health posts were not included in this scenario due to a lack of trained personnel and infrastructure for point-of-care testing.

We assumed that each clinic operated 6 hours a day. Since this scenario assumed that results and treatment could be provided on the same day as testing, there were no additional shipping or storage costs in this scenario. Medical auxiliary staff were assumed to be able to process samples using the Xpert system.

The costs of curing an infected patient were calculated as  $C_{poc}/(V_{ait_{poc}} p)$ .

### **Scenario 2: Centralized laboratory testing**

For the centralized laboratory scenario, at least one 2-module Xpert was placed in each of Botswana's 27 health districts. Samples collected in hospitals, clinics, and health posts would be stored on-site in sample collection tubes and shipped twice per month to these Xperts in each health district. The size (and cost) of each centralized machine was determined based on summed patient volume across each of the 27 health districts.

Personnel included medical auxiliary staff, pharmacists, nurses, doctors, and laboratory technicians to process the samples. Laboratories were assumed to operate 8 hours per day. Training costs were included for one laboratory technician per district.

Thus, the costs of curing an infected patient were calculated as  $(C+S)_{lab}/V_{ait_{lab}} p$ , where  $S$ =total storage and shipping costs (shipping costs\* $V_a$ ).

### **Scenario 3: Mixed point-of-care and centralized laboratory testing**

For this scenario, we assessed whether, based on each health district's antenatal volume, it would require more than two Xpert modules. If the district's volume was not large enough to require more than two modules, we placed an Xpert at the largest facility in the district, which would offer point-of-care testing to its patients and serve as a central lab for samples from smaller facilities in that district – including health posts – within the clinic's 6-hour working day. If the district's antenatal volume was large enough to warrant more than two

modules, we utilized a “constrained optimization” (30) approach: point-of-care testing and treatment would be provided at every facility up until the cost per outcome ratio was greater than the ratio produced in the laboratory scenario; thereafter, facilities would ship samples for processing at a central lab.

$$\text{Maximize: } \quad \Sigma \text{ Vaitp}$$

$$\text{Subject to: } \quad \Sigma x [C_{\text{poc}}/(\text{Vait}_{\text{poc}} p)] \leq (C+S)_{\text{lab}}/(\text{Vait}_{\text{lab}} p)$$

$$0 \leq x \leq 1 \text{ (for all poc)}$$

In the equation above adapted from Holtgrave, 1998; Vaitp (described above) is the effectiveness of each strategy implemented for all antenatal care attendees in Botswana. The ratio  $C_{\text{poc}}/(\text{Vait}_{\text{poc}} p)$  represents the cost per cure experienced by the point-of-care scenario,  $(C+S)_{\text{lab}}/(\text{Vait}_{\text{lab}} p)$  represents the cost per cure in the laboratory scenario, and x represents the proportion of antenatal attendees able to receive point-of-care results and treatment under the constraints.

To implement this strategy in high volume districts, we placed Xpert machines with enough modules to provide point-of-care testing for all patients at the facility with the largest antenatal volume in the district. If the Xpert’s capacity was not maximized by the facility’s antenatal volume, that facility could accept samples from smaller clinics and health posts that would be processed according to the laboratory assumption parameters. Next, we placed another Xpert at the second largest facility in the district to provide point-of-care CT and NG testing. If the machine’s capacity wasn’t maximized with facility volume, again, the facility could accept samples from smaller clinics for processing. This process was continued until there was capacity for all antenatal attendees to be tested in the district. Finally, we assessed the volume



and capacity of each of the machines and made adjustments so that testing volume at each site was at or just below the threshold where another machine would need to be added.

#### **4.2.4 Sensitivity analyses**

To assess the impact of the uncertainties associated with model parameters, univariate sensitivity analyses were performed to test the robustness of the outcomes of the analysis. We varied the following variables: clinic operating hours, Xpert module costs, Xpert CT/NG cartridges costs, and additional shipping costs, which were calculated as a percentage of the CT/NG cartridges. We also varied the proportion of women who received point-of-care results, point-of-care treatment, delayed treatment, and who had their infections cured. Most parameters were either halved or doubled for these sensitivity tests, with the exception of: the high and low CT and NG prevalence estimates were derived from a systematic review of STIs among pregnant women in the Southern Africa region, and the Botswana AIDS Impact Survey, 2013;(22, 27, 28) and test sensitivity and specificity ranges came from validation research.(31) We also conducted a variant of scenario 1 that included health posts as point-of-care sites; even though this may not be realistic, since health posts provide antenatal care for many women, it is important to consider their role in scaling up STI testing.

#### **4.2.5 Ethics**

The Institutional Review Boards at the University of Botswana, the Botswana Ministry of Health, Health Research Development Committee, and Princess Marina Hospital approved the study protocol. The University of California, Los Angeles, approved analyses using deidentified data.

## **4.3 Results**

### **4.3.1 Pilot Program**

Between July 2015 and May 2016, the antenatal CT and NG testing pilot in Gaborone, Botswana tested 400 pregnant women, treated 34 CT and NG infections, tested 24 women with CT/NG infections for cure, and cured 22 CT/NG infections, at a total cost of \$19,857 (Table 4.4). The pilot program received donated equipment, supplies, and personnel time; thus, the financial costs (\$703) of the program were very low compared to the economic costs (\$19,154). The main drivers of the total (financial and economic) costs were supplies (\$8,127; 41% of the total), which included CT/NG cartridges, treatment, and consumables; and equipment (\$8,487; 43% of the total), which included the amortized costs of two 4-module Xpert machines, and accessories (e.g. desktop computer, barcode reader, short-term power supply unit, and a fan). Start-up costs included installation/calibration, and training.

Table 4.5 displays the average cost per program outcome. Financial costs were \$1.76 per test, \$20.67 per infection identified, and \$31.95 per infection cured. After combining financial and economic costs, the average cost per test was \$49.64, the average cost per infection identified was \$584.01, and the average cost per infection cured was \$902.57.

### **4.3.2 Scale-up Scenarios**

The annual costs and outcomes of scaling up antenatal CT and NG testing according to the point-of-care, centralized laboratory, and mixed scenarios are outlined in Table 4.6. The columns represent capital/start-up (e.g. Xpert & training), shipping, personnel, and supply costs (e.g. treatment, CT/NG cartridges, and consumables). The components of each program are further broken down by row to delineate the costs associated with training, testing, CT and NG

management, partner management, and test of cure. The point-of-care scenario placed 314 2-module Xperts at 28 hospitals and 286 clinics. The laboratory scenario placed 74 modules in the 27 health districts across Botswana, which included two 8-module machines, four 4-module machines, and 21 2-module machines. The mixed scenario placed 2-module machines in 20 districts with low antenatal patient volume. Seven health districts received a combination of Xpert sizes with the goal of maximizing the cost per infection cured ratio in the district (Francistown received a 2 and a 4-module; Gaborone: 4 & 4; Kgatleng: 4; Kweneng East: 4 & 2, Mahalapye: 4; Ngamiland: 4; South East: 4; Tutume: 4). are outlined in Exhibit 6. The columns represent capital/start-up (e.g. Xpert & training), shipping, personnel, and supply costs (e.g. treatment, CT/NG cartridges, and consumables).

The point-of-care scenario was the most expensive overall (\$1,654,928), and the capital (Xperts) were the largest cost driver (\$821,336), followed by the supplies required for testing (\$707,141), which were largely composed of the cost of the CT/NG cartridges. The mixed scenario was the second most expensive scenario (\$1,100,461), while the central laboratory scenario had the lowest cost at \$1,100,089. This lab scenario had lower Xpert costs but higher personnel and shipping costs compared to the mixed and point-of-care scenarios. In each of the scenarios, activities and supplies for testing made up more than 95% of the cost, while less than 5% of the total cost was for treatment and partner management.

Table 4.7 shows the estimated outcomes and cost per outcome ratios of the three scenarios. The laboratory and mixed scenarios were able to test the same number of women and identify the same number of infections (43,187 and 3,436 respectively). The point-of-care scenario tested fewer women (36,225) because it did not include health posts – but treated the

largest proportion of diagnosed infections (88%); and resulted in the largest number of infections cured. The point-of-care scenario had the highest cost per test (\$46), per person treated (\$400), and per infection cured (\$728). The mixed scenario's cost per test was similar to the laboratory scenario (\$25); however, the cost per person treated (\$281), and per infection cured (\$512) were lower.

Figure 4.2 depicts the relationship between cost and the number of women treated and infections cured for the three scenarios. While the laboratory scenario is the lowest cost, the mixed scenario appears to be the optimal strategy for maximizing the cost per infections cured.

When we integrated health posts into the point-of-care scenario in an additional analysis, the number of infections cured increased (to 2,878) but annual costs were very high (\$2,712,641) and the ratio of cost to infections cured was \$932. Given the high cost and challenges associated with personnel capacity and infrastructure, this scenario may not be viable despite reaching a larger number of women and curing more infections.

Figure 4.3 reflects the results of the univariate sensitivity analysis, which assessed the impact of altering model parameter values on the main outcome variable: number of infections cured. Varying the Xpert module costs had the largest impact on the point-of-care scenario and the cost per infection cured ranged from \$554 to \$1,076 when the costs were halved or doubled. CT/NG cartridges had the biggest impact in the laboratory and mixed scenarios, which ranged from \$320 to \$966 per infection cured in the centralized lab scenario and \$306 to \$925 in the mixed scenario. Varying the proportion of patients who received treatment and the proportion of patients whose infections were cured was important for all scenarios.

#### **4.4 Discussion**

We used data from a pilot antenatal CT and NG testing and treatment program to estimate the costs and outcomes associated with national scale-up of CT and NG testing and treatment across Botswana according to three scenarios. Our models revealed that point-of-care testing would result in the greatest number of women tested and cured, but at the highest cost. A centralized laboratory scenario was associated with the lowest overall cost, but fewer women were treated due to loss to follow-up. The mixed scenario, involving both point-of-care and centralized testing, had the most favorable cost per outcome ratios. The sensitivity analysis demonstrated that the point-of-care scenario was most sensitive to the costs of the Xperts compared to the other scenarios. The cost of the CT/NG cartridges was influential in the centralized lab and mixed scenarios.

The sensitivity analysis also revealed that improving treatment rates is important for optimizing the costs per infection cured in all scenarios. Loss to follow-up continues to be a barrier associated with STI and tuberculosis testing globally.(32, 33) A study comparing antenatal point-of-care syphilis testing with laboratory testing in South Africa showed that 20% of women who received delayed results did not initiate treatment.(33) These findings are similar to those identified in tuberculosis testing research in Southern Africa.(32, 34) A study in Mozambique showed that, among patients receiving CD4 cell count monitoring with delayed staging results, 64% were lost to follow-up before antiretroviral therapy.(35) Further, partner treatment rates are often low. A systematic review, which examined research related to partner notification strategies in low- and middle-income countries, found that the just over half of partners were notified in the 39 included studies.(36) Thus, in order for a national

antenatal CT and NG testing program to be successful, attention must be paid to ensuring that pregnant women and sex partners are treated for infections.

Although it is beyond the scope of this study to compare CT and NG testing with other programs aimed at improving maternal and child health, the per-test CT and NG costs identified in the pilot and all three scale-up scenarios are comparable to or lower than other testing programs in Southern Africa. An assessment of HIV testing and counselling (HTC) costs in Botswana found that the direct cost of antenatal HTC, including human resources, consumables and equipment, and test kits; was \$34.51 per test (2012 USD).(26) Further, a cost analysis of national scale-up of point-of-care pulmonary tuberculosis testing in South Africa estimated costs to be \$38.91 (USD 2014) per test. Further, those previously mentioned tests were used for a single infection while this study assessed the costs of testing for two targets, CT and NG.

Additionally, this study provides a methodology that takes findings from pilot research to estimate potential impact at scale. Pilot programs have much greater value when put in the context of wider policy or program endeavors. According to the WHO, there is limited practical guidance on how to implement scale-up, and many successful pilot programs have failed to expand beyond the pilot stage.(37) This study developed an innovative method that can be adapted to estimate the costs and outcomes of scaling up testing and treatment programs targeting a variety of care models in many different settings.

Our analysis has several limitations. First, some parameter estimates were based on data from a single pilot study and may not reflect variation across health facilities. However, we compared our parameter estimates with other STI testing studies and found the personnel time and supply estimations were similar.(38) The results also may have limited generalizability

outside Botswana – but since many sub-Saharan African countries have an antenatal care attendance rate of 70% or higher and deliver opt-out antenatal HIV testing, this could provide a framework for integrating CT and NG testing.(39, 40) Also, the primary cost drivers in the model (Xpert modules and cartridges) were based on high burden low income country prices so would be similar across the region.

Second, we could not disaggregate antenatal volume statistics to the clinics or health post level and instead averaged these across all facilities in each region. This method does not allow for any variation in volume and/or geographic distance, and thus results should not be used for specific decisions about individual facilities. We did not include facility overhead costs in our analysis (e.g. building costs, utilities), as we assumed this CT and NG testing would be integrated into already-occurring antenatal visits, and the space required for the Xpert machines is very small. Similarly, although we did not consider any patient-borne costs such as transport or opportunity costs associated with waiting for results or returning for results, such costs may be low as many women attend antenatal care regardless of STI results. Lastly, a key assumption that undergirds these simulated scenarios is that testing could reach scale immediately. These models do not take into account the political advocacy and leadership that would be required to implement expanded testing. This might affect both time/delay in attaining at-scale implementation, as well as possible costs (e.g., training, lobbying, communications, etc.)(37)

Xpert capacity can be used for many other infections -- such as early detection of HIV, viral load testing and diagnosis of human papilloma virus, or multi-drug resistant tuberculosis. This analysis did not include these possible additional benefits. Multi-indication use would have

important clinical and public health implications and would spread costs across multiple diseases. For example, viral load testing is critical for provision of antiretroviral therapy, but access to testing is limited in many countries due to equipment costs and personnel needs.(41) It may also be possible to leverage capacity of the existing 34 Xperts already in place in Botswana (for TB testing) to expand antenatal CT and NG testing. Other countries may similarly be equipped to begin scale-up.

Further, while each scenario was associated with a large number of cured antenatal CT and NG infections, this study does not attempt to estimate subsequent improvements in health outcomes, such as decreased rates of preterm birth or mother-to-child transmission of CT and/or NG. Several critical parameters for such an analysis are currently unavailable for pregnant women in Southern Africa.(42) Thus, more rigorous research on the impact of antenatal CT and NG testing on pregnancy and birth outcomes is needed.

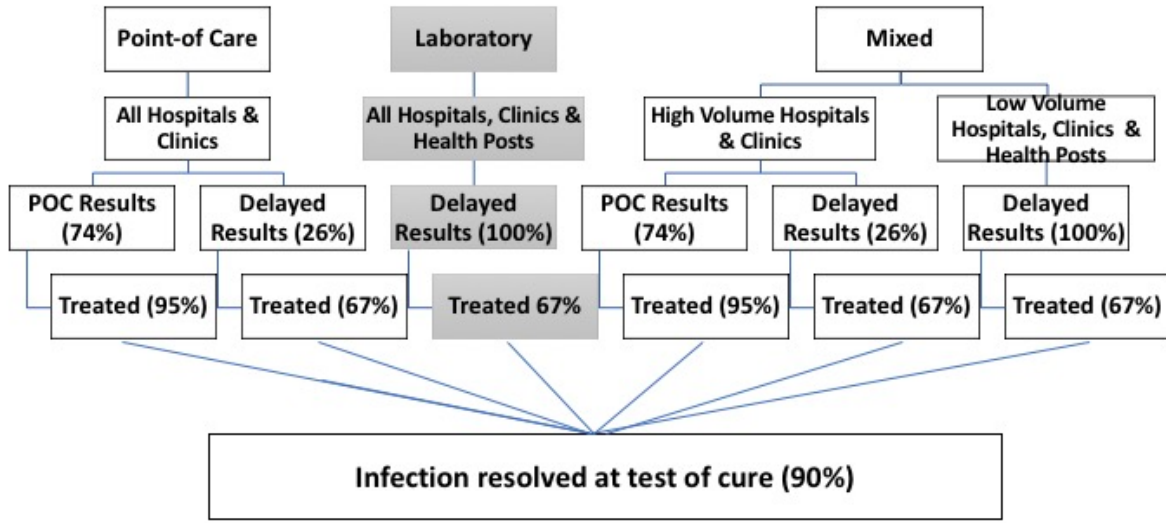
In conclusion, national scale-up of a mixed point-of-care and centralized antenatal CT and NG testing and treatment program has the potential to cure a large number of infections at the lowest cost of the scale-up strategies explored here. While CT and NG testing costs are low compared to other testing programs, it is essential for policy-makers and administrators to consider strategies for improving treatment rates among pregnant women and partners in order to maximize the effectiveness of the program. The results of this study are intended to inform decisions about whether and how to expand CT and NG testing and treatment services to pregnant women. While the short-term outcome of infections cured is not ideal for making policy decisions, this study provides information on scenarios that would maximize outcomes following resource allocation, which is highly relevant to health policy makers. The scale-up



models developed for this study can be adapted for a variety of infections in different settings and can be used to generate evidence to help policymakers extrapolate findings from pilot studies and plan for scale-up within health system and budgetary constraints.

#### **4.5 Tables and Figures**

**Figure 4.1: Results, treatment, and cure parameters for the three antenatal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* scale-up models**



**Table 4.1: Variables used to parameterize antenatal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing scale-up models**

Parameter	Value	Source
Total annual first antenatal visit volume (2009)	50,218	(25)
All hospital volume	5,562	(25)
All clinic volume	36,758	(25)
All health post volume	7,998	(25)
Annual number of business days per year in Botswana	220	(26)
Average exchange rate (Pula to USD July 2015-May 2016)	0.094	(23)
<b>Epidemiology</b>		
Prevalence of <i>C. trachomatis</i>	7.3%	(22, 27)
Prevalence of <i>N. gonorrhoeae</i>	0.8%	(22, 27)
Prevalence of dual infection	0.5	(22, 27)
Partner treatment rate (among treated women)	59%	(22)
<b>Testing</b>		
Testing uptake	0.860	(12, 22, 43, 44)
Xpert CT sensitivity	0.987	(45)
Xpert NG sensitivity	1	(45)
Xpert CT specificity	0.994	(45)
Xpert NG specificity	0.999	(45)
Error rate	0.03	(22, 24, 45)
<b>Costs</b>		
Xpert CT/NG cartridge	\$16.20	Cepheid/Find
Azithromycin (1 course of treatment-1g)	\$0.54	(46)
Ceftriaxone (1 course of treatment-250mg)	\$0.27	(46)
GeneXpert instrument (installation, uninterrupted power unit, 2-year warranty)		
GeneXpert II (2-modules with desktop computer)	\$11,530	Cepheid/Find
GeneXpert IV (4-modules with desktop computer)	\$17,000	Cepheid/Find
Calibration kit after 1st year	\$450	(29)
Useful life of GeneXpert instrument (years)	5	(24)
import tax, clearance and last-mile shipping charges	13%	Invoice
<b>Results, treatment, and cure probabilities</b>		
Receive same-day results	74%	(22)
If received same-day results: Treated on same-day	95%	(22)
Receive delayed results	26%	(22)
If received delayed results: Treated ever	67%	(22)
If treated: Cured	90%	(22)

**Table 4.2: Assumptions for three antenatal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing and treatment scale-up scenarios**

Assumptions	Point-of-Care (POC)	Laboratory	Mixed
Testing location	All samples tested on-site	All samples sent to 1 lab per district	Samples tested on-site at POC sites, remainder are shipped
Treatment timing	Same-day	2-week delay	Same-day at POC sites, remainder 2-week delay
Xpert quantity needed	≥1 per hospital & clinic (n=628)	≥1 per health district (n=74)	≥1 per health district (n=76)
Testing population	ANC at hospital or clinic (n= 36,225)	ANC at hospital, clinic, or health post (n=43,187)	
Personnel: Counseling and treatment	Medical auxiliary, pharmacist, nurse, physician	Medical auxiliary, pharmacist, nurse, physician	Medical auxiliary, pharmacist, nurse, physician
Personnel: Testing	Medical auxiliary	Laboratory technician	Medical auxiliary
Testing hours daily	6	8	6
Shipping & storage costs	None	5% added to all tests	5% added to shipped tests None for on-site tests

**Table 4.3: Costs of the antenatal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing and treatment pilot program in Gaborone, Botswana (2016 USD)**

CT/NG Testing Cost Category	Economic Costs	Financial Costs	Overall Costs
<b>Start-up</b>			
Training	\$264	\$70	\$335
<b>Total Start-up Costs</b>	<b>\$264</b>	<b>\$70</b>	<b>\$335</b>
<b>Capital</b>			
Equipment	\$8,487	\$0	\$8,487
<b>Total Capital Costs</b>	<b>\$8,487</b>	<b>\$0</b>	<b>\$8,487</b>
<b>Recurrent</b>			
Personnel	\$293	\$514	\$807
Supplies	\$8,109	\$18	\$8,127
Other	\$0	\$100	\$100
<b>Total Recurrent Costs</b>	<b>\$8,402</b>	<b>\$632</b>	<b>\$9,035</b>
<b>TOTAL COSTS</b>	<b>\$17,154</b>	<b>\$703</b>	<b>\$17,857</b>

**Table 4.4: Average costs of the antenatal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing and treatment program per output (2016 USD)**

Output measure	N	Economic Costs	Financial Costs Per Output	Total Cost
Pregnant women tested	400	\$42.88	\$1.76	\$44.64
Infections identified	34	\$504.52	\$20.67	\$525.19
Infections cured	22	\$779.71	\$31.95	\$811.66

**Table 4.5: Estimated one year costs of three scale-up strategies for antenatal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing and treatment (2016 USD)**

	Capital/ Start-up	Shipping	Personnel	Supplies	Total
<b><u>Point-of-Care Scenario</u></b>					
Training	\$32,419				\$32,419
Testing	\$821,336		\$43,274	\$707,141	\$1,571,751
CT management			\$2,930	\$1,763	\$4,693
NG/Dual management			\$695	\$421	\$1,116
Partner CT management			\$2,143	\$968	\$3,111
Partner NG management			\$458	\$240	\$698
Test of Cure			\$1,644	\$39,496	\$41,140
<b>Total 1-year costs</b>	<b>\$853,756</b>		<b>\$51,144</b>	<b>\$750,029</b>	<b>\$1,654,928</b>
<b><u>Laboratory Scenario</u></b>					
Training	\$22,770				\$22,770
Testing	\$85,214	\$34,982	\$66,305	\$843,059	\$1,029,560
CT management			\$2,299	\$1,600	\$3,899
NG/Dual management			\$641	\$382	\$1,023
Partner CT management			\$1,858	\$878	\$2,737
Partner NG management			\$445	\$218	\$662
Test of Cure		\$1,487	\$2,117	\$35,836	\$39,440
<b>Total 1-year costs</b>	<b>\$107,984</b>	<b>\$36,469</b>	<b>\$73,665</b>	<b>\$881,972</b>	<b>\$1,100,089</b>
<b><u>Mixed Scenario</u></b>					
Training	\$38,227				\$38,227
Testing	\$88,026	\$30,363	\$51,592	\$843,065	\$1,013,046
CT management			\$2,738	\$1,666	\$4,404
NG/Dual management			\$649	\$397	\$1,047
Partner CT management			\$2,007	\$915	\$2,921
Partner NG management			\$429	\$227	\$655
Test of Cure		\$1,291	\$1,553	\$37,318	\$40,161
<b>Total 1-year costs</b>	<b>\$126,253</b>	<b>\$31,654</b>	<b>\$58,967</b>	<b>\$883,587</b>	<b>\$1,100,461</b>

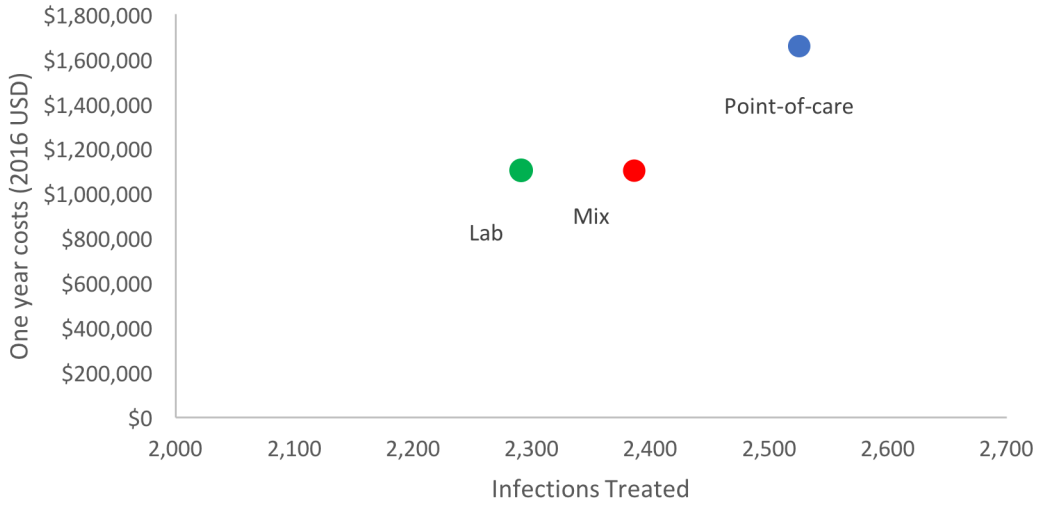
Notes: Columns: Capital/Start-up includes the Xpert system and training. Shipping is a 5% increase on cartridge costs. Personnel include medical auxiliary staff, nurses, pharmacists, physicians, and the lab scenario includes a lab technician. Supplies include treatment, CT/NG cartridges, and consumables. Rows: Training is self-explanatory. Testing includes the activities and supplies involved in explaining sample collection, processing the sample (e.g. cartridges), providing results for uninfected patients, and completing paperwork. CT/NG management include providing results, counselling, and treatment for infected patients. Partner management includes providing counselling and treatment for partners. Test of cure includes testing and providing results for a test of cure.

**Table 4.6: Estimated outcomes and cost per outcome ratios of three antenatal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing scale-up strategies**

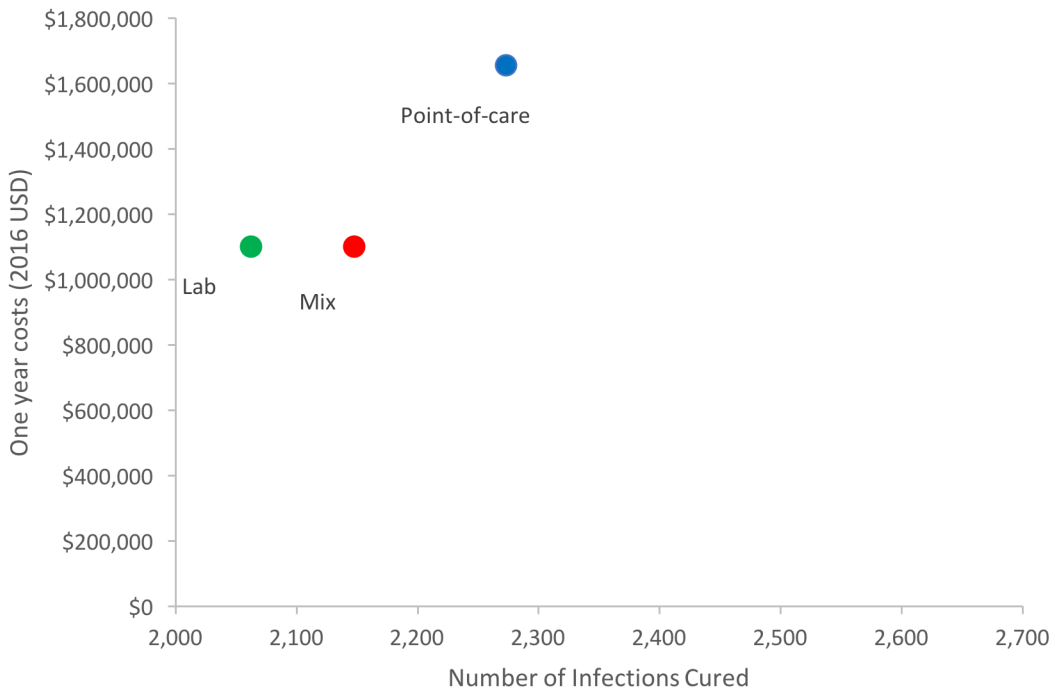
<b>Outcome</b>	<b>Point-of-Care</b>	<b>Laboratory</b>	<b>Mixed</b>
Xpert modules needed	628	74	76
Pregnant Women tested	36,225	43,187	43,187
Infections diagnosed	2,882	3,436	3,436
Pregnant women treated	2,526	2,292	2,386
Partners treated	1,613	1,464	1,524
Tests of cure	2,023	1,836	1,912
Pregnant women cured	2,273	2,063	2,148
<b>Average cost per outcome</b>	<b>Total</b>	<b>Total</b>	<b>Total</b>
Initial test	\$45.69	\$25.57	\$25.48
Women & partners treated	\$399.85	\$292.94	\$281.40
Infections cured	\$728.02	\$533.36	\$512.36

**Figure 4.2: Cost per infection treated and cured, by three scale-up strategies for antenatal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing**

Cost per infection treated



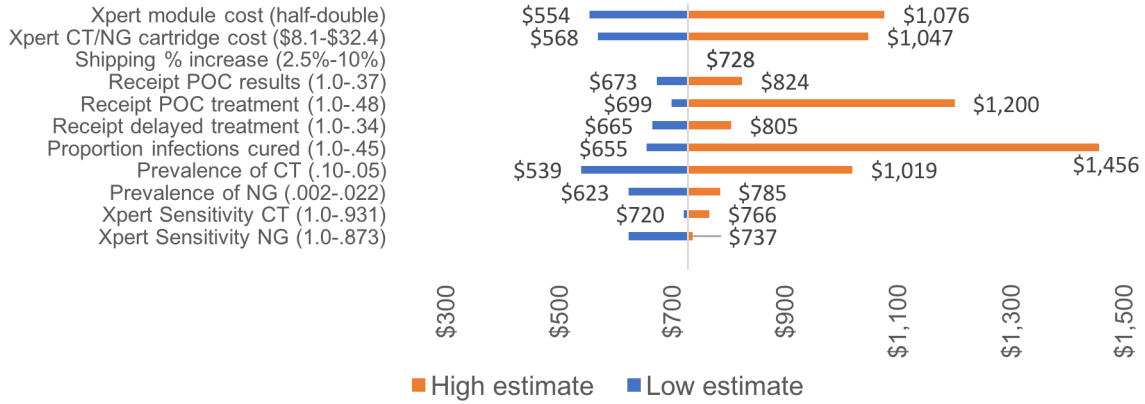
Cost per infection cured



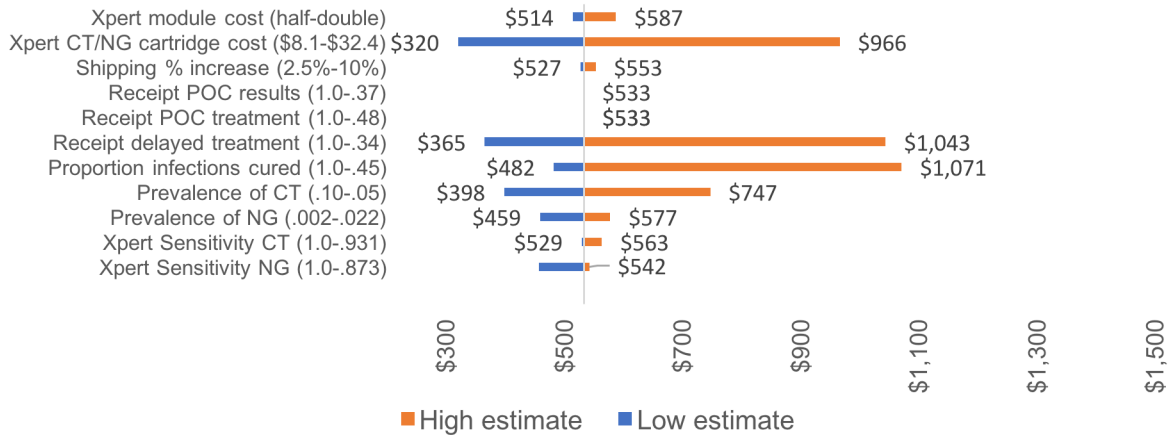


**Figure 4.3: Univariate sensitivity analysis by antenatal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* testing scale-up scenarios**

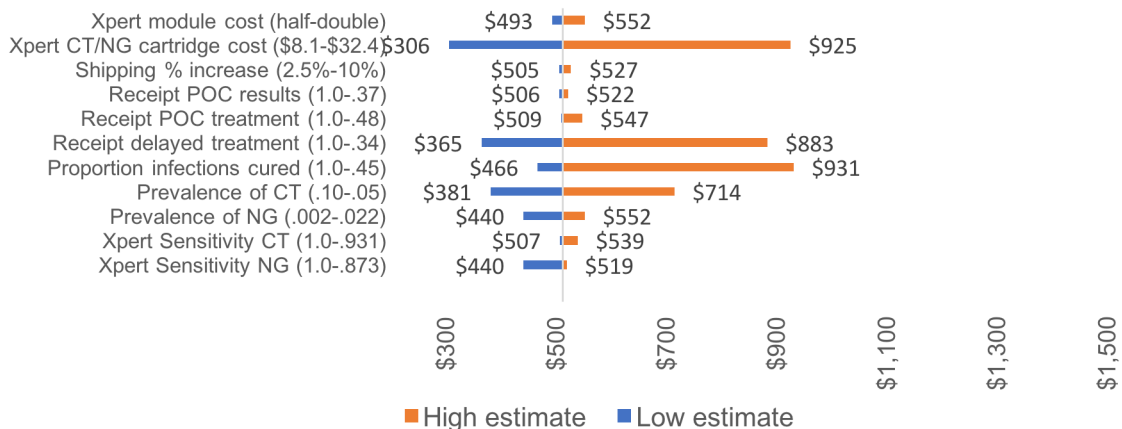
**Point-of-Care**



**Centralized Laboratory (Base: \$533)**



**Mixed (Base: \$512)**



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## CHAPTER 5: Conclusion

### 5.1 Discussion

Improved strategies to diagnose and treat STIs and prevent reinfection during pregnancy are needed. CT, NG, and TV infections are extremely common globally and are associated with adverse health outcomes for women and infants. However, because women are not routinely tested for those infections in most countries, the burden of infection is not precisely measured. Further, partner notification and treatment rates are low in many settings, which increases the risk of STI reinfection during pregnancy. While new molecular diagnostics for use in clinics have recently become available, the implementation costs continue to be an important system-level barrier to expanding testing. This dissertation employed a mixed-methods approach and collected primary data to examine three aspects of STI management among pregnant women in Botswana: 1) prevalence and correlates of antenatal CT, NG, and TV infections in Gaborone, Botswana, 2) women's experiences and preferences with notifying sex partners about an STI and encouraging treatment, and 3) costs associated with three scenarios for scaling up STI testing and treatment nationally across Botswana.

#### 5.1.1 Key Findings

Given the limited recent research on the burden of STIs in Southern Africa, the first study estimated the prevalence of CT, NG, and TV infections in a sample of pregnant women attending a busy antenatal clinic in Gaborone, Botswana. We found that 14% of women had one or more of the above mentioned STIs. We also assessed the correlates of infection using bivariate comparisons and a multivariable logistic regression model and found that living with

HIV and being unmarried were associated with being diagnosed with an STI. Further, self-reported STI-related symptoms were not associated with an infection.

The second study used qualitative interviews to assess women's experiences and preferences related to partner notification of an STI diagnosed during pregnancy. Interviews were conducted with women who tested positive for an STI while seeking antenatal care at a clinic in Gaborone, Botswana. The study found that 13 out of 15 participants had notified their partners and most did this in person and used the contact slip provided by the clinic. Those who did not notify their partners were no longer in relationships with their baby's father at the time of testing. Four partners were not treated (including two that were not notified) and four reported that they were treated, but provided no evidence. We also learned that most women had never heard of CT, NG, or TV infections prior to testing; and many were unable to answer all of their partners' questions about these STIs. In terms of future preferences, most woman reported that they would want to accompany their partners to the clinic, compared to bringing medication home or having healthcare providers conduct notification.

Chapter 4 determined the costs and outcomes associated with a CT and NG infection testing and treatment program at an antenatal clinic in Gaborone, Botswana. Data from this single site were then modelled to estimate the costs and outcomes of national scale-up across Botswana according to three scenarios: 1) sample processing at the point-of-care, 2) samples sent for processing at centralized laboratories, and 3) a combination approach – point-of-care testing at high-volume sites plus pooled sample testing across lower-volume sites. Our models revealed that point-of-care testing would result in the greatest number of women tested and cured, but at the highest cost. A centralized laboratory scenario was associated with the lowest

overall cost, but fewer women were treated due to loss to follow-up. The mixed scenario, involving both point-of-care and centralized testing, had the most favorable cost per outcome ratios. The sensitivity analysis also revealed that improving treatment rates is important for optimizing the costs per infection cured.

## **5.2 Limitations**

This dissertation used three forms of primary data, including quantitative data collected from test results, medical record review, and a questionnaire; qualitative data collected from semi-structured interviews; and cost data collected from programmatic documents, time-and-motion observations, and the literature. Each dataset and corresponding study presented unique challenges, but they all suffer from potential limits on generalizability. Each study included data derived from a single site in Gaborone, Botswana. While the sample of participants in the first study is similar to the population of pregnant women in Botswana on characteristics such as age, education, and marital and HIV status; it is likely that the prevalence of STIs among pregnant women varies by antenatal site and region. Nonetheless, given the limited recent research available, the study provided an estimate of STI prevalence at a busy antenatal site in Botswana's most populous city, and it highlighted that the burden of STIs among pregnant women continues to be significant, particularly among those living with HIV.

The qualitative study's main limitation was sampling. As only 15 women were interviewed, it is possible that participants who were more likely to have successfully notified their partners were oversampled. However, it is encouraging that we enrolled women with a range of STIs, HIV statuses, and partner notification outcomes; and the sample was generally representative of the group of women who tested positive for an STI in the first study. Further,



the proportions of partners that were notified and treated were similar between participants and those that did not enroll.

Finally, many of the cost analysis parameters in study three were derived from an STI testing program at a single site in Gaborone, Botswana. Without facility-specific data on personnel and infrastructure, it's not possible to reflect variation across facilities. However, we did vary personnel based on the type of facility. Further, the antenatal site from which data was derived was generally representative of how antenatal care is administered throughout Botswana as guidelines are set by the Ministry of Health. Thus, the cost study may inform national decisions about whether and how to expand STI testing and treatment for pregnant women.

### **5.3 Implications & Future Directions**

This dissertation found that STIs continue to be a burden among pregnant women in Botswana, particularly those living with HIV infections. Most women in our study had notified their partners about their STI diagnosis, however, more efforts are needed to ensure that partners are treated. Policy-makers should consider a mixed point-of-care and centralized laboratory approach if STI testing is to be scaled-up nationally and efforts should be made to increase treatment uptake. This dissertation also identified the need for additional research, including: 1) Larger studies to estimate regional variation in STI prevalence among pregnant women in Botswana. STI surveillance using a representative sample of pregnant women in Botswana would improve knowledge about the burden of infection and inform decisions about where to allocate testing and treatment resources in the future. 2) Research exploring the relationship between STI-related knowledge and partner notification and treatment. This

dissertation found that many women in the sample had low levels of knowledge, which may have decreased their ability to answer partner questions and encourage partners to get treatment. STI-related knowledge would also be important if Botswana implemented a strategy where women bring home medication to their partners because this strategy would depend on women's ability to communicate the need for and importance of STI treatment. 3) Impact studies to determine the efficacy of antenatal STI testing and treatment on adverse maternal and infant outcomes. While this dissertation estimated the costs and numbers of infections diagnosed, treated, and cured associated with scale-up of antenatal STI testing and treatment, it would be helpful for policy-makers to know the impact that testing and treatment would have on averting outcomes such as preterm birth and mother-to-child transmission of CT, NG, and HIV. This information would help policy-makers compare STI testing and treatment to other interventions and would provide an estimate of cost savings associated with averting potentially costly, long-lasting health outcomes.

In conclusion, this dissertation utilized unique, primary data to address a broad range of issues related to the management of STIs during pregnancy. Further, it addressed many of the components identified by the WHO as necessary for making decisions about guidelines, including need, feasibility, and cost. While the data are derived from STI testing and treatment at a single site in Gaborone, Botswana, this dissertation demonstrated that more should be done to diagnose, treat, prevent reinfection, and cure STIs during pregnancy in Southern Africa. Finally, given the rapid introduction of innovative diagnostics aimed at improving maternal and child health and reducing infectious diseases, this dissertation is timely, and it takes a

comprehensive look at programmatic components that will be essential to the successful implementation of new antenatal STI testing and treatment strategies globally.