Novel partner notification approaches in New York State, and antibiotic resistance in the management of Chlamydia trachomatis infections

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NOVEL PARTNER NOTIFICATION APPROACHES IN NEW YORK STATE, AND ANTIBIOTIC RESISTANCE IN THE MANAGEMENT OF CHLAMYDIA TRACHOMATIS INFECTIONS

By

Christopher F. Davis

A Dissertation
Submitted to the University at Albany, State University of New York
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the Requirements for the Degree of
Doctor of Philosophy

School of Public Health
Department of Epidemiology and Biostatistics
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Abstract

*Chlamydia trachomatis* (chlamydia) is the most frequently reported notifiable disease in the United States. This dissertation provides an evaluation of chlamydia treatment and control through three different lenses: 1) patient views on a novel strategy to facilitate treatment, 2) student perceptions about materials to promote treatment of sexual partners, and 3) evidence regarding recurrent infection etiology.

Recently approved by the New York State legislature, patient delivered partner therapy (PDPT) relies on the index patient to deliver antibiotic prescriptions to treat sexual partner(s) presumptively. The first study evaluates the willingness of chlamydia patients (n=79) to deliver prescriptions to sexual partners and sexual partners’ (n=31) willingness to seek medical evaluation. Half (56.4%) of patients would deliver prescriptions to every partner but approximately one-third (30.7%) report at least one recent sexual partner to whom they would not deliver a prescription. Most partners (63.3%) would seek medical evaluation.

Another strategy to control chlamydia is the provision of informational cards (but not prescriptions) to sexual partners. The information cards (called “card referral”) describe the disease and list local treatment locations. The second investigation describes university students’ (n=543) willingness to provide cards to their partners to facilitate partner notification. Most (66.5%) reported willingness to deliver cards to main partners while half (54.3%) reported willingness to deliver cards to all partners. However, 25.9% indicated there was at least one partner to whom they would not deliver a card.
The third report reviews emerging evidence that first-line chlamydia therapies may be less effective than previously calculated. A systematic review evaluates the evidence for antibiotic resistance and persistence among *Chlamydia trachomatis* (n=97 studies). The data suggest that there is not supportive evidence of antimicrobial resistance but moderate supportive evidence that persistence is the cause of genuine treatment failures. Further research to quantify genuine treatment failures is necessary.

While additional research regarding chlamydia persistence is warranted, effective partner notification that both maximizes the number of partners reached and facilitates follow-through with a medical evaluation should remain the primary focus to reduce incidence and prevalence. Informational cards appear to be a reasonable, low-cost alternative that may be effective among university students.
Chapter 1. Overview

*Chlamydia trachomatis* infection (chlamydia) is the most commonly reported notifiable disease in the United States and has comprised the largest proportion of all incident sexually transmitted infections (STI) reported to the Centers for Disease Control and Prevention (CDC) in the last 15 years. In 2011 there were 1,412,791 cases of chlamydia reported to CDC. In New York State (NYS) 102,460 cases were reported in 2011; 64,966 in the five counties of New York City (NYC) and 37,494 in the remaining 57 counties. Approximately 50% of male cases and 75% of female are asymptomatic resulting in many missed diagnoses. Thus, the estimated true number of cases exceeds three million.

Chlamydia infection being generally asymptomatic often delays both diagnosis and treatment. Untreated cases of chlamydia are at increased risk for serious complications and transmission to others. When untreated in women, the infection may result in sequelae including pelvic inflammatory disease (PID), which can occur in 10-15% of cases, as well as other complications such as ectopic pregnancy, infertility and chronic pelvic pain. In addition, pregnant women infected with chlamydia can infect their newborn infants during birth (vertical transmission). In males, untreated infection can lead to chronic testicular pain and possible sterility. Beyond the consequences that can arise from going untreated, chlamydia infection also facilitates the transmission of human immunodeficiency virus (HIV) as well as other STI.
To stop the chain of infection and subsequent health consequences, reaching all members of a sexual network through partner notification strategies and providing treatment is paramount. There are two main approaches utilized to notify partners of potential infection, patient referral and provider referral.

Patient referral, also known as self-referral or standard referral, is a notification approach in which the individual diagnosed with a STI takes on the responsibility of informing sexual partners of their potential exposure to the STI, and refers them to services for evaluation and treatment. According to the CDC there are several advantages to this approach. One major advantage is that patient referral may result in a more prompt referral to appropriate services because the patient is usually more familiar with the identity and location of the partner relative to alternative methods of partner notification. Another advantage to this method is that few fiscal resources are utilized, including minimal, if any public staff man-hours.\textsuperscript{17} Despite these advantages there are notable limitations to patient referral.

There are several disadvantages associated with traditional patient referral noted by CDC. The first is a “forfeiting of anonymity”, which could result in possible disclosure of a patient’s infection to third parties, such as friends, family and coworkers, potentially leading to subsequent social and emotional distress, or possible workplace discrimination.\textsuperscript{17} There is also the risk for a negative partner reaction including an increased potential for violence. Another issue associated with this approach is the possibility of intentional or unintentional conveyance of incorrect information about the exposure, disease or treatment for the STI by the index patient to their partner(s), which can result in incomplete or ineffective referral and treatment. Finally, it is difficult to
assess partner outcomes and verify treatment when this notification strategy is employed. There is also no guarantee that the index patient will follow through on notifying their partner(s), resulting in an increased possibility of transmission to others, and a chance for recurrent infection of the index patient.\textsuperscript{17, 18} These limitations associated with the use of patient referral are somewhat addressed by provider referral.

Provider referral is a notification approach in which a health provider takes responsibility for confidentially notifying their patient’s sexual partners after receiving consent from the infected index patient. Often, disease intervention specialists (DIS) employed by health departments play a central role in assisting with partner notification with this approach. The DIS will search health department records to determine if the partner has been tested and/or treated, and will further seek extra locating information if necessary. The DIS often play a large role when the health provider in question is a state or locally funded health or STI clinic in a higher incidence locale. Private providers conducting partner notification is rare, but when conducted, they will often contact partners directly to offer evaluation and treatment, generally in areas where there is not assistance from DIS readily available. Research by Macke et al. has shown provider referral in conjunction with DIS or state assisted notification to be among the most effective option for treating partners.\textsuperscript{19}

According to the CDC, advantages of provider referral include the ability to verify partners have been contacted, offered medical evaluation and subsequently treated. Further, provider referral reduces consequences stemming from poor partner reactions (e.g. violence). When DIS assist in partner notification, field specimen collection can occur, along with the provision of on the spot counseling for the partner. The DIS can
also provide immediate referrals and elicit further information regarding other sexual partners who may have been exposed. Despite these advantages, provider referral is limited in two important ways.

Two major disadvantages to provider referral include difficulty identifying and locating partners, as well as increased cost. Compared to the index patient, the provider is often less familiar with the lifestyle and behaviors of partners resulting in difficulty locating and identifying them. Further, CDC cites that this approach utilizes more fiscal resources compared to patient referral, particularly when DIS assist in conducting the notification.17-19

Although costs are high, health department assisted provider referral is often effective in reaching partners.20 Depending on available resources, the preferences of the patient and the health care provider, as well as local policies, either patient and/or provider referral (in some cases with the assistance of health department staff) is generally performed. While each approach has unique strengths and limitations, the number of chlamydia infections continues to rise. With ongoing high chlamydia infection levels, novel approaches to partner notification and treatment are needed.

In NYS the newest approach to partner notification which has been legalized for use is patient delivered partner therapy (PDPT).21 Patient delivered partner therapy is the clinical practice of presumptively treating sexual partners of index patients diagnosed with chlamydia by providing written prescriptions for antibiotics to the patient to be taken to his/her sexual partner(s). The PDPT legislation allows prescriptions to be written for chlamydia antibiotics without the health care provider first examining the partner or the partner receiving prevention counseling.
A lack of medical consultation with the intended prescription recipient raises concern with the use of PDPT as a treatment option. A few obvious concerns include potential for contraindication/side effects of prescribed therapy, the potential for medication not reaching partners, lack of medical evaluation for sexual partners receiving prescriptions, and fears of legal consequences for the prescribing party in the event of complications. Although PDPT is a legal option for partner notification/treatment for chlamydia, it remains unclear to what degree patients will deliver medications to partners, whether patients will deliver prescriptions to all partners and whether partners would seek medical evaluations if they were to receive a prescription.

A second novel partner notification approach for chlamydia is the use of informational cards/booklets to assist patients with directly informing their sexual partners of potential exposure. This approach is an enhanced form of traditional patient referral and can be referred to as booklet enhanced partner referral. In this approach chlamydia patients perform partner notification and referral for treatment using pre-printed cards or booklets provided to them by their health care provider at the time of diagnosis and/or treatment. These cards/booklets generally include a statement informing the recipient that they have been exposed to chlamydia and he/she should seek medical care. The cards may also include information about chlamydia symptoms and potential problems that can arise if the partner is not treated. Finally, there may be additional information regarding locations where the partner can receive examination and treatment. One major advantage of this approach relative to PDPT is that the partner would need to report for a medical examination, including testing for other STIs and assessment for contraindications to prescribed therapy. Evaluation of an individual before prescribing
any antibiotic is important to assess a patient’s allergies or contraindications with other medications he/she may take. Assessment of an individual prior to prescribing chlamydia therapy specifically may be especially critical given newly reported cardiotoxic effects of the standard treatment.

The standard treatment regimen for treating chlamydia is a one gram single dose of azithromycin that is administered orally. A recent development in the literature pertains to potential cardiovascular consequences of azithromycin, in which an analysis demonstrated an increased risk for cardiac events among individuals exposed to azithromycin compared to individuals receiving comparable antibiotics. The Federal Food and Drug Administration (FDA) recently warned the public that azithromycin can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing a fatal heart rhythm after exposure to azithromycin include those with known risk cardiac factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, arrhythmias and other conditions. Assessing patients for these risk factors to prevent potential adverse cardiac events associated with azithromycin treatment is thus recommended. By extension, awareness of cardiac risk factors among those at risk for chlamydia infection, namely those under age 25, may be an important consideration for future treatment protocols and is of specific concern given the option of utilizing PDPT. Under PDPT, patients can bring a prescription for azithromycin to any of their sexual partners. Those partners will not be assessed for any cardiac risk factors, contraindications or allergies. Thus, research into better understanding whether patients know their partner’s cardiac risk factors is
warranted. Further, if azithromycin is to remain the front-line treatment for chlamydia despite its potentially cardio-toxic effects, ensuring it is still effective in clearing infections is critical.

The ability of *Chlamydia trachomatis* to withstand the effects of antimicrobials routinely utilized in treating infection has yet to be established in the literature. Given the increasing incidence of chlamydia and frequent recurrent infections reported,\(^1\)\(^-\)\(^3\) development of resistance to antibiotics that are routinely used in its treatment may be possible. While chlamydia infection does not appear to be clinically resistant to treatment with azithromycin, understanding its current susceptibility to this antibiotic and investigating reasons for reported treatment failures is paramount to developing future treatment protocols, as well as determining the best approach to notifying and subsequently treating sexual partners.

The research presented contributes to the knowledge base of two novel partner notification approaches in NYS; PDPT and enhanced partner referral with informational cards. As the burden of chlamydia infection increases annually, the research assesses whether chlamydia is less susceptible to antimicrobials routinely used in its treatment. Further, it provides insight into STI patients’ and sexual partners’ attitudes and perceptions toward PDPT as well as their willingness to engage in this partner notification practice in NYS. The research helps increase the understanding of college students’ willingness to notify sexual partners of infection with the assistance of information cards. Finally, the research furthers our understanding of college student’s general knowledge of their sexual partners’ cardiac risk factors.
Chapter 2. Background

2.1 Chlamydia trachomatis

2.1.1 Organism description

*Chlamydia trachomatis* is an obligate, intracellular, gram-negative bacterium with 15 defined serovars. The major infectious serovars lead to three conditions; trachoma, chlamydia and lymphogranuloma venereum. Serovar types A-C cause trachoma, a form of chronic conjunctivitis. The sexually transmitted serovars are D-K, which cause chlamydia. Serovars L1-L3 are rare subtypes that cause lymphogranuloma venereum (a form of genital ulcer disease common in tropical countries).

Humans are the only known host of *Chlamydia trachomatis* bacteria. The bacteria is coccoid shaped and is relatively small at 1,042,519 base pairs in length of which there are approximately 894 predicted protein coding sequences. The bacterium has a unique intracellular life cycle (figure 1) and depends on its host cell for adenosine triphosphate (ATP). *Chlamydia* bacteria are incapable of producing ATP and thus cannot survive without viable host cells for this energy source. *Chlamydia* bacteria have a cellular wall structure that enables it to divide and reproduce intracellularly while surviving extracellularly to infect new host cells. *Chlamydia* bacteria exist in two alternating forms; a non-replicating infectious elementary body, found outside the host cells as well as a replicating non-infectious reticulate body, taking form intracelullarly. A direct immuno-fluorescence antibody labeling stain of *Chlamydia trachomatis* in both
elementary and reticulate body forms, infecting and reproducing within mammalian epithelial cell tissue is shown in figure 2.  

### 2.1.2 Transmission and prevention

Elementary bodies, the non-replicating form of the bacteria discharged from host cells, are potentially infectious (figure 3). At the cellular level, *Chlamydia* generally infects columnar epithelial cells but occasionally infects macrophages. When in elementary body form, the bacteria gain entry to host epithelial cells by attaching to a receptor on the surface of the target epithelial cells. The host epithelial cells then ingest the bacteria. Once inside the target host cell *Chlamydia* reverts to the replicating non-infectious reticulate body form.

The spread of infection takes place either by vertical or sexual transmission. Vertical transmission can occur if an infected mother delivers her newborn vaginally and the infant is exposed. Sexual transmission is responsible for nearly all new infections and can occur when an uninfected individual has unprotected sexual contact with an infected partner during vaginal, anal or oral sex. Chlamydia can also be transmitted by sharing sexual toys. Male condoms (latex) are effective in preventing sexual transmission of chlamydia when used both consistently and correctly. Further, routine screening of women, with appropriate treatment where indicated, significantly reduces transmission rates among asymptomatic women and their partners. The asymptomatic nature of chlamydia infection often leads to the transmission of the infection, unbeknownst to the infected individual, to his/her uninfected partner.
2.1.3 Symptomology

Chlamydia is often referred to as a “silent” infection; infected individuals are commonly asymptomatic. Approximately three quarters of cases in women and half in men present with no symptoms. Some evidence suggests even more extreme estimates of asymptomatic cases, as high as 90\%.\(^{38-40}\) When symptoms occur they usually present seven to 21 days after exposure.\(^1\) In females the urethra and the cervix are first infected and can cause mild discomfort or burning during urination. There may also be a discharge from the vagina.\(^{41}\) If left untreated the infection can spread into the fallopian tubes, yet it is possible symptoms may still not occur. Symptoms that could present when infection progresses into the fallopian tubes include pain in the lower abdomen and back, bleeding between menstrual periods, fever and nausea. Infection in the male genital tract may cause burning sensations during urination, a white or cloudy discharge from the penis as well as a persistent itching at the tip of the penis. In some cases an uncommon symptom is pain or swelling of the testicles.\(^{42}\)

In both men and women chlamydia infection can occur in the rectum. Among Men who have sex with men (MSM) screened for rectal chlamydial infection, positivity has ranged from 3.0% to 10.5%.\(^{43,44}\) Among females, rectal infection is less common, but risk of acquiring is comparable among women engaging in receptive anal intercourse.\(^{45}\) Other research has documented infection can spread from the vagina and cervix to the rectum.\(^ {46,47}\) When symptoms of rectal infection present they include rectal pain, bleeding and discharge.\(^{38}\) Chlamydia can also be transmitted via oral sex.

Although oral infection is generally asymptomatic, the most common symptom that
presents is a sore throat.\textsuperscript{44, 47} The asymptomatic nature of the infection leads to many cases going untreated which can result in serious complications.

\textbf{2.1.4 Complications}

Untreated chlamydial infections can result in serious reproductive conditions with both short-term and long-term consequences. In women, untreated infection can lead to a chronic condition of pain known as pelvic inflammatory disease (PID).\textsuperscript{48-50} A large systematic review of the literature conducted by a Centers for Disease Control and Prevention (CDC) expert panel found that approximately 10\% to 15\% of women with cases of untreated chlamydia will develop PID.\textsuperscript{8, 9, 50}

Infection in the upper genital tract can cause permanent damage to the fallopian tubes, uterus and surrounding tissues which can lead not only to chronic pelvic pain, but could also result in infertility. Infection with chlamydia that has spread to the fallopian tubes can lead to ectopic pregnancy, a potentially life threatening condition.\textsuperscript{49}

Complications in men can occur, although this is rare. Infection sometimes spreads to the epididymis in the testicles causing pain, fever, and in some extreme cases, sterility. Untreated infection in both men and women can also result in prostatitis, Reiter’s syndrome (an arthritic like condition accompanied by inflammation of the eyes) and increase the risk for transmitting and/or acquiring human immunodeficiency virus (HIV).\textsuperscript{14-16, 51-52}

Chlamydia infection (as well as infection with other STI) increases the chances of becoming infected with or transmitting the human immunodeficiency virus (HIV) at the cellular level.\textsuperscript{14} Research has shown that susceptibility to HIV infection increases due to genital tract inflammation, which increases the concentration of cells in genital secretions.
that can serve as targets for HIV (e.g. CD4+ cells). Transmission of HIV is more likely if an HIV infected individual is co-infected with chlamydia because he/she is particularly likely to shed HIV in their genital secretions. For example, men who are infected with both chlamydia or gonorrhea and HIV are more than twice as likely to have HIV in genital secretions compared those who are infected only with HIV. Moreover, the median concentration of HIV in semen is also much higher in men who are infected with chlamydia and HIV than in men infected only with HIV. The higher the concentration of HIV in semen or genital fluids, the more likely it is that HIV will be transmitted to a sex partner.\textsuperscript{14-16}

Given the asymptomatic nature of chlamydia and the serious complications that can result from untreated infection, including the increased risk of HIV transmission, the CDC recommends annual chlamydia screening for all sexually active women under 25 years of age. Annual screening is further recommended for women with new or multiple sexual partners as well as for pregnant women to prevent vertical transmission, but is not currently recommended for men.\textsuperscript{37}

\textbf{2.1.5 Screening}

Given the high incidence of new cases each year, the largely asymptomatic nature of the disease and the dangerous sequelae that can result from untreated infection, regular screening for chlamydia is recommended by the CDC and by the United States Preventive Services Task Force (USPSTF).\textsuperscript{37,53} In making their screening recommendations, the USPSTF systematically reviewed the evidence from 57 studies examining the effectiveness and costs of screening tests for chlamydial infection in men.
Given the evidence and noting the high levels of sensitivity of the diagnostic tests, the USPSTF recommends the following:

“screening for chlamydial infection for all sexually active non-pregnant young women aged 24 and younger and for older non-pregnant women who are at increased risk [and] screening for chlamydial infection for all pregnant women aged 24 and younger and for older pregnant women who are at increased risk” 53

The USPSTF also:

“recommends against routinely providing screening for chlamydial infection for women aged 25 and older, whether or not they are pregnant, if they are not at increased risk”. 53, 54

The USPSTF “concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for chlamydial infection” for men.53

Chlamydia screening has also been ranked by the National Committee on Prevention Priorities as a top priority, based on chlamydia’s clinically preventable nature, screening cost effectiveness and the current relatively low rate of use.55

2.1.5.2 Barriers to Screening

Chlamydia screening and subsequent treatment of infection can preserve reproductive health in young women by preventing the aforementioned sequelae (i.e. PID, ectopic pregnancy and sterility).37, 56, 57 There are known barriers that prevent women from receiving screening for chlamydia.

On the part of health providers, barriers to conducting routine screening include a lack of financial reimbursement for the time required to conduct screening tests and
counsel patients, lack of awareness that patients are at risk for STIs, and an incorrect belief that chlamydia screening requires full pelvic examination.\textsuperscript{58, 59}

Barriers to patients undergoing screening include affording the copayment of an office visit, lack of awareness of free services in many areas (eg, STI clinics), lack of knowledge of the asymptomatic nature of the infection, and lack of awareness of the long-term sequelae of chlamydial infection.\textsuperscript{60} The recommendation for routine annual screening has been instrumental in detecting, diagnosing and treating infection therefore concerted efforts to overcome these barriers should be made.

2.1.6 Detection, Diagnosis and Treatment

2.1.6.1 Detection and Diagnosis

Detection of chlamydia infection is accomplished by testing a sample of bodily fluids for the presence of chlamydia bacteria. Infection in females is diagnosed by collecting and testing urine or swab specimens taken from the endocervix or vaginal wall.\textsuperscript{61} Infection in males is identified by urethral swab or urine specimen testing. Rectal infections in both sexes can be detected via rectal swab specimens.\textsuperscript{62} Although urine tests are sufficient, swab specimens may be required for certain test methodologies because of the intracellular nature of chlamydia bacteria. Once swabbed (or urine collected) there are numerous methods available for testing samples for the presence of chlamydia bacteria.

Enzyme immunoassay, direct fluorescent antibody, nucleic acid hybridization tests and nucleic acid amplification tests (NAATs) are commonly utilized for detection of chlamydial infections in female endocervical tissue samples and male urethral swab specimens.\textsuperscript{38, 62} Each test varies in the amount of time required to yield a test result.
Enzyme immunoassay is a rapid test capable of detecting chlamydia antigens that consequently trigger an immune response, typically in less than three hours. A more rapid direct fluorescent antibody test also detects chlamydia antigens and can be completed in 30 minutes. Nucleic acid hybridization tests detect chlamydia DNA and generally are completed in less than 24 hours. Nucleic acid amplification tests, which include ligase chain reaction (LCR) and polymerase chain reaction (PCR), also detect chlamydia DNA in urine and can be completed in less than 24 hours. Cultures, which are swab specimens placed onto special growth media allowing any present bacteria to grow, can help pinpoint a diagnosis.

Culture of chlamydia is difficult to achieve however, and thus is uncommonly performed. Culture is also time consuming relative to the aforementioned methods as it generally takes three to seven days. Despite these difficulties, one reason to attempt culture is when there is treatment failure in a patient. It is important to note that these testing times are averages and will vary by facility, staff, whether testing is on site or at separate labs etc. A separate but critical consideration is the sensitivity and specificity of the tests.

Both sensitivity and specificity vary across diagnostic tests. Culture is considered the gold standard with 100% specificity but has an average sensitivity of 70% to 90%. Many labs have moved away from using culture due to its time consuming and difficult nature relative to the other tests available.

Estimates of sensitivities and specificities of the same types of test vary widely, and also vary by companies that manufacture the tests. For example, in six separate studies of commercial direct fluorescent antibody tests, seven separate sensitivity and
specificity combinations were reported. As shown in table 1, these studies reported direct fluorescent antibody sensitivities ranging from 62% to 85% and specificities ranging from 96% to 100%. One important variable worth noting is that these tests may be affected by the quality and source of the specimens analyzed. For example, in one multi-center study sensitivities of LCR and PCR were slightly lower when performed on urine samples than on endocervical specimens (83.4% vs. 91.4% and 79.5% vs. 84.0%, respectively). Due to the varying results of analyses quantifying each diagnostic test’s sensitivity and specificity, multiple investigations of each diagnostic test have been conducted. As such, a range of each test’s sensitivity and specificity are generally reported. As NAAT’s are widely utilized for chlamydia diagnosis, it is important to have an understanding of the approximate sensitivity and specificity of these tests.

2.1.6.1.1 Investigations of NAAT sensitivity and a comparison to other methods

Comprehensive reviews of diagnostic tests for detecting chlamydia infections indicate that the sensitivities of commercial NAATs (both LCR and PCR) exceed those of other diagnostic tests. A five lab study reported commercial NAATs had sensitivities for endocervical specimens that exceeded the sensitivity of a non-amplified nucleic acid hybridization test by 19.7% [95% CI (12.9%, 26.6%)] for ligase chain reaction (LCR) and 12.4% [95% CI (2.1%, 22.7%)] for polymerase chain reaction (PCR). The sensitivity of LCR exceeded that of culture by 10.8% (85.5% vs. 74.7%, respectively) and that of the hybridization test by 23.6% (85.5% vs. 61.9%, respectively).

For urine specimens the sensitivity of LCR was 80.8%, exceeding the sensitivity of culture and hybridization tests by 18.9% and 6.1%, respectively. Another multi-center study compared LCR and PCR utilized to examine urine samples obtained from
asymptomatic males with culture of intra-urethral swab specimens as an independent reference standard. The reported sensitivities of LCR (84.4%) and PCR (85.4%) in that study were near identical.\textsuperscript{83}

\textbf{2.1.6.1.2 Investigation of NAAT specificity}

Published evaluations of NAATs compared with alternative target NAATs to perform discrepant analysis have reported increased specificities (e.g., exceeding 99.5%) relative to older evaluations.\textsuperscript{84, 85} Published studies, as well as studies described in package inserts using direct fluorescence assays to perform discrepant analysis, have reported NAAT specificities of 94.1\% to 99.5\%.\textsuperscript{86} In 1993 CDC reported a higher range of specificities for non-amplified nucleic acid probe and enzyme immunoassay tests to detect chlamydia bacteria. In general the report indicated all non-culture tests have demonstrated high specificity, often 97\% to 99\%.\textsuperscript{64}

\textbf{2.1.6.1.3 Implications of reported sensitivities and specificities}

Considering the sensitivity and specificity of a diagnostic test is paramount to interpreting test results. Perhaps the more important measure for chlamydia is the sensitivity of the test. For chlamydia, a highly sensitive test is more critical than a highly specific test, as a false negative result could lead to a lack of treatment, dangerous sequelae for the patient and spread of infection to uninfected individuals. Awareness of the sensitivity of a given diagnostic test is thus critical to interpretation of a negative test result. A near 100\% sensitivity suggests the possibility of a false negative is negligible. Thus individuals with a negative test result are likely to be disease free. Given that NAATs are the tests of choice for the diagnosis of chlamydia infection in routine clinical
laboratories, false negative results are uncommon as evaluations reported sensitivities in the range of 76% to 92.5%, with most in the 82.0% to 88.0% range.\textsuperscript{64, 80, 84-86}

### 2.1.6.2 Treatment

The recommended treatment regimen for chlamydia infection is one gram of azithromycin in a single oral dose, or doxycycline 100 milligrams orally twice a day for seven days. Alternative regimens that can be used include erythromycin base 500 milligrams orally four times a day for seven days, erythromycin ethylsuccinate 800 milligrams orally four times a day for seven days, ofloxacin 300 milligrams orally twice a day for seven days or levofloxacin 500 milligrams orally once daily for seven days.\textsuperscript{38, 87}

Overall these regimens were well in clearing infections. Azithromycin and doxycycline have been shown to be equally effective in treating chlamydia, clearing about 98% of infections.\textsuperscript{88} More recent evidence however suggests that the standard treatment may not be as effective as once believed (see section 2.6 ‘Antibiotic resistance’), which is supported by laboratory data, case studies, epidemiological studies and the increasing incidence of chlamydia cases annually.

### 2.2 Descriptive epidemiology

Chlamydia is the most common bacterial STI in the United States and the most commonly reported notifiable infectious disease.\textsuperscript{1} In the last 20 years the number of reported cases has increased four-fold. In 2011, there were over 1.4 million cases of chlamydia reported to CDC in the United States, for an incidence rate of approximately 457.6 cases per 100,000 population, representing over an 8% increase from 2010 alone (figure 4).\textsuperscript{2, 3} Contributing to the increasing incidence of the disease is the number of existing undiagnosed asymptomatic cases. CDC estimates the prevalence of chlamydia
infection to be about 2% among 18 to 26 year olds, Miller et al. estimate actual chlamydia prevalence is much higher. Their calculations suggest that national chlamydia prevalence among adults 18 to 26 years is 4.2%, utilizing data obtained from the National Longitudinal Study of Adolescent Health. Given differing prevalence estimates and taking into account under reported and undiagnosed cases, it is estimated that the true number of incident cases is approximately three million annually.

2.2.1 Age as a risk factor

Rates of chlamydia vary widely among populations, and age is a strong predictor of risk. Until 2010, surveillance data indicated that the 15 to 19 year old population had the highest annual incidence rate. Surveillance data show that 20 to 24 year old women had the highest reported rates of chlamydial infection in 2011 (3,722.5 cases per 100,000 women), closely followed by women ages 15 to 19 (3,416.5 cases per 100,000 women). Rates among older women have also increased in the last few years. In 2011 the chlamydia incidence was 1,343.6 per 100,000 women ages 25 to 29, and 567.7 per 100,000 women ages 30 to 34.

The highest rates among men in 2011 also occurred in those ages 20 to 24 (1,343.3 per 100,000 men) followed by men ages 15 to 19 (803.1 per 100,000 men). Men ages 25 to 29 and 30 to 34 also saw moderate incidence in 2011 (689.7 and 349.8 per 100,000 men, respectively) but much less than the incidence of women of comparable ages. The reported rate of infection in women has historically been higher, and in overall 2011 was nearly three times higher than in men (648.9 cases per 100,000 females, versus 256.9 cases per 100,000 males) and largely reflects the increase in routine screening in women, as discussed above (figure 5).
2.2.2 Race as a risk factor

Race is independently associated with risk for chlamydia (figure 6). In 2011, the incidence among non-Hispanic Blacks (1,194.0 cases per 100,000 population) reported to the CDC was more than seven times the incidence among non-Hispanic Whites (159.0 cases per 100,000 population). Hispanics had an incidence approximately twice that of non-Hispanic whites (383.0 cases per 100,000 population). Among women, the incidence was 232.7 cases per 100,000 women among non-Hispanic White females, compared to 1,563.0 cases per 100,000 women among non-Hispanic Black females. Hispanic females had an incidence more than twice that of non-Hispanic White females (578.2 cases per 100,000 women).

The racial difference in men is even more substantial as the incidence of chlamydia among non-Hispanic Black males was over nine times that of non-Hispanic White males (787.7 per 100,000 population versus 82.3 per 100,000 population, respectively).\(^3\) The incidence among Hispanics was also greater than that of non-Hispanic Whites at 193.8 cases per 100,000 population.

While some of the racial disparities are likely due to variations in reporting, nationally representative studies have substantiated the higher morbidity reported among non-Hispanic Blacks and Hispanic Americans compared to non-Hispanic Whites.\(^89\) For example, an analysis of the National Longitudinal Study of Adolescent Health reported prevalence estimates of 5.9% for Hispanic Americans and 12.5% for non-Hispanic Blacks compared to 1.9% for non-Hispanic Whites, among those participants ages 18 to 26.\(^3,89\) The National Health and Nutrition Examination Survey conducted from 1999 to
2002 also found that among all age groups the prevalence was greater among non-Hispanic Blacks compared to non-Hispanic Whites.\textsuperscript{91}

\textbf{2.2.3 Geographic risk}

There is some geographic variation in the incidence of chlamydia in the United States. Incidence is highest in the South and lowest in the Northeast, but it should be noted that rates are increasing in all areas (figure 7).\textsuperscript{2} The five states with the highest morbidity (per 100,000 population) in 2011 were Alaska (808.0), Mississippi (715.0), Louisiana (697.4), South Carolina (625.5), and Alabama (619.8). New Hampshire, West Virginia and Maine had the lowest incidence (per 100,000 population) of chlamydia in 2011 (228.6, 231.8, and 232.9, respectively). New York State ranked 10\textsuperscript{th} in the nation at with an incidence rate of 533.3 per 100,000 population. This is exceeds the national average for 2011 of 457.6 per 100,000 population.

Not surprisingly, there is also higher morbidity in urban settings relative to rural settings.\textsuperscript{89, 92, 93} As urban settings have a high incidence, the CDC tracks chlamydia in 50 of the largest metropolitan areas. These areas represented 57.2\% of all chlamydia cases reported in 2011. The incidence of chlamydia in many of these cities far exceed the national average of 457.6 cases per 100,000 population, ranging from 324.7 cases per 100,000 population in San Jose-Sunnyvale-Santa Clara, CA to 887.9 cases per 100,000 population in Memphis, TN.

\textbf{2.2.4 Behavioral risk factors}

Despite geographical differences in incidence, behavioral risk factors are prevalent throughout the nation. Behavioral risk factors associated with chlamydial infection include having multiple sexual partners, having a new sexual partner, or having
an infected sexual partner. Other behavioral risk factors include having a history of previous or coexistent STIs including HIV, sex for drugs, alcohol or money, as well as an early age of sexual initiation. Being under the influence of alcohol and drugs during intercourse has also been reported as a risk factor for transmission.

2.3 Partner notification in the management of STI

2.3.1 Patient, contract and provider referral

To prevent the spread of infection it is paramount to locate the sexual partners of infected individuals and provide treatment. Without notifying and treating partners, treated individuals can become re-infected from their regular partner(s). According to the CDC’s program guidelines for STI prevention, there are three major forms of partner notification strategies; patient referral (or self-referral), provider referral with or without state assistance and a combination approach known as contract referral.

2.3.1.1 Patient referral

Patient referral, also called self-referral or standard referral, is a partner notification approach in which an individual diagnosed with STI takes on the responsibility of informing sexual partners of their potential exposure to the STI, and refers them to services for evaluation and treatment. According to CDC there are several advantages to this approach. One major advantage is that patient referral may result in “a more prompt referral to appropriate services because the patient is usually more familiar with the identity and location of the partner” relative to alternative methods of partner notification. Another advantage to this method is that few fiscal resources are utilized.
The CDC also highlights several disadvantages associated with patient referral. The first is a “forfeiting of anonymity”, which can result in possible disclosure of the index patient’s infection to third parties by the partner, leading to subsequent discrimination.\textsuperscript{17, 38} There is also the risk for a negative partner reaction including the increase in the potential for violence.\textsuperscript{19, 106} Another issue associated with this approach is the possibility of intentional or unintentional conveyance of incorrect information about the exposure, disease or treatment for the STI, which can result in incomplete or ineffective referral and treatment. It is also difficult to assess partner outcomes and verify treatment when this notification strategy is employed. Finally, there is also no guarantee that the index patient will follow through on notifying their partner(s), resulting in an increased possibility of transmission to others, and a chance for re-infection of the index patient.\textsuperscript{17, 18}

\textbf{2.3.1.2 Provider referral}

Provider referral is a notification approach in which a health provider takes responsibility for confidentially notifying an index patient’s sexual partners after receiving consent from the patient. Disease intervention specialists (DIS) employed by health departments often play a central role in assisting with partner notification by providers, especially for syphilis, gonorrhea and in some cases chlamydia. The DIS will review health department records to determine if the partner has been tested and/or treated, and will further seek extra locating information if necessary. The DIS play a large role when the health provider is a state or locally funded health or STI clinic in a higher incidence locale. Private providers conducting partner notification may contact partners directly to offer evaluation and treatment, generally in areas where there is not
assistance from DIS readily available. Research by Macke et al. has shown provider referral in conjunction with DIS or state assisted notification to be among the most effective option for treating partners.19

According to the CDC, advantages of provider referral include the ability to verify partners have been contacted, offered medical evaluation and subsequently treated.18 Further, provider referral reduces potential consequences stemming from poor partner reactions (e.g. violence). When DIS assist in partner notification, field specimen collection can occur along with provision of counseling for the partner. The DIS can also provide immediate referrals and elicit further information regarding other sexual partners who may have been exposed. Disadvantages to provider referral include the provider being less familiar with the lifestyle and behaviors of partners compared to the index patient, resulting in difficulty in locating and identifying them. Further, CDC cites that this approach utilizes more fiscal resources compared to patient referral, particularly when DIS assist in conducting the notification.17-19

2.3.1.3 Contract referral

A combination of provider and self-referral partner notification is sometimes utilized known as contract referral. The CDC defines this technique as “a notification strategy in which the provider negotiates a time frame (usually 24-48 hours) for the patient to inform his or her partners of their exposure and to refer them to appropriate services”.18 Under this strategy DIS will collect locating information for all partners, suspects, or associates from the index patient. If the patient is unable or unwilling to inform partners within the negotiated time period, the DIS will notify and refer the partners directly. Advantages to this approach include the provision of assistance from
professionally trained experts in the field of STI control for those patients that choose to notify their own partners. The CDC suggests this can enhance the success of the referral process by decreasing the incidence of incorrect information being given and increasing the probability of an effective referral.\textsuperscript{17, 18} This method also allows for ensuring notification is conducted and that there is prompt follow up with the partner if necessary. One disadvantage to this approach is the potential for more disease transmission if the index patient does not notify their partners in a timely manner, or at all.\textsuperscript{17, 18}

### 2.3.2 Partner services and utilization vary by municipality

The range of partner services and the conditions for which they are offered vary among providers, agencies, states, counties and geographic areas. For example, in NYS there are 62 counties, of which five are served by the New York City (NYC) Department of Health and Mental Hygiene. As of 2009, of the 57 counties outside NYC, 19 allocate resources to employ DIS to conduct partner notification. The remainder refer STI cases to the New York State Department of Health (NYSDOH) Regional Epidemiology Program.\textsuperscript{107}

The CDC recommends municipalities utilize one of the three aforementioned partner notification strategies. Effective partner notification may decrease the overall community exposure to STIs and may have an impact on the incidence and prevalence of STIs in the area.\textsuperscript{18, 19, 108} For decades, public health resources have been directed to partner notification services, but the scholarly evidence of its effectiveness on incidence and transmission prevention is sparse overall.\textsuperscript{108} It is also unknown to what extent health departments in the United States engage in the various types of partner notification approaches.
2.3.2.1 Partner notification in urban areas

Golden et al\textsuperscript{109} quantified public health department attempts at partner notification for common STIs in urban areas in the United States. This paper reported the results of 78 surveyed metropolitan health departments (representing 50 cities in the United States with the highest rates of at least one bacterial STI and AIDS). About three quarters (77\%) of those invited responded. Of 8,492 cases of syphilis reported, in 89\% of cases these health departments attempted to notify and treat sex partners. In stark contrast, they only attempted to identify and contact the partners of 17\% of gonorrhea cases and even less chlamydia cases (12\%).

In those chlamydia and gonorrhea cases where partner notification was attempted, patient referral was primarily used. Forty-one health departments (68\%) made no attempt to notify or contact the partners of patients treated for gonorrhea outside public health clinics, and 46 (77\%) made no such attempt for the partners of chlamydia patients. Low partner management coverage and ineffective notification was attributed to a lack of adequate personnel and insufficient fiscal resources. In NYS, one study found that in addition to regular screening, provider referral and provider referral in combination with health department assistance is effective in reducing STI incidence. The latter however is only possible in areas with sufficient resources to conduct such notification, in agreement with national findings.\textsuperscript{20} Funding constraints limit health department contact tracing in many areas of the United States and patient referral is often inadequate on its own.\textsuperscript{20, 108-109}

Provider referral when conducted routinely is effective\textsuperscript{18}; but studies have found that patient referral is the most popular approach employed in the United States for
partner notification, particularly in low resource settings, and results in up to half of partners being treated for chlamydia or gonorrhea.\textsuperscript{110-119} Patient referral is limited by several factors, including the patient’s choice in whether to notify a partner, as well as the notified partner’s choice in seeking treatment. Both patient and partner actions are influenced by a host of factors. Asymptomatic partners may fail to seek care because they have no signs or symptoms of infection, and thus may incorrectly assume they are not infected. A problem in low resources settings is that partners may lack health insurance and/or have limited access to medical care, although many jurisdictions likely offer free STI treatment services. These limitations of patient referral demonstrate the necessity for additional strategies to ensure sexual partner treatment. Given the funding constraints limiting the feasibility of conducting DIS assisted provider referral nationwide and the limitations associated with standard patient referral of partners, research into new approaches has been encouraged.\textsuperscript{120}

2.3.3 Calling for new methods of partner notification

Given the lack of concrete evidence on the effectiveness of current partner notification methods in the literature, the rise in anonymous sexual partners reported during contact tracing interviews, and the rise in the incidence of STI in the United States, in 1997 the Institute of Medicine called for creative new methods for the prevention and control of STI.\textsuperscript{120} There have been several novel alternative approaches to partner notification proposed in the past decade. These include notification on the internet, patient delivered partner therapy (as part of expedited partner therapy) and patient distribution of educational materials.\textsuperscript{121-126}
2.3.4 Internet partner notification

The internet has become a tool to meet new people including sexual partners and is often utilized to establish anonymous and/or casual sexual encounters.\textsuperscript{127} There is risk for STI transmission among those who use the internet for meeting sexual partners, not only because arranged sexual encounters are often anonymous, but the internet is also used for erotic services.\textsuperscript{128, 129} This novel way to establish sexual contacts demonstrates the necessity for novel approaches to combating disease transmission and to conducting partner notification.\textsuperscript{96, 127-131} Since many anonymous sex partners are contacted solely online this may be the only form of contact available. Thus, in such cases the internet may be the only possible option for conducting partner notification, but may be a good option for partner notification in general.\textsuperscript{132}

A few studies of internet partner notification have reported that it is possible to use the internet as a tool to notify partners. In a 2000 California study, public health officials used internet screen names belonging to sexual partners provided by index cases to send messages through email to notify them of a potential exposure to STI.\textsuperscript{127} The health department in San Francisco was able to notify 97 individuals of potential exposure and successfully tested 41 (42\%) of them. In Los Angeles 29 of 111 (26\%) sexual partners of a single syphilis case responded to emails sent out by the health department, and another 54\% (7 of 13) of partners of a separate syphilis case responded to index patient e-mails.\textsuperscript{130} In a convenience sample of MSM recruited through the use of public health advertisements on a dating site for meeting casual sexual partners, 92\% reported that they would use the internet in some way to alert potentially infected partners.\textsuperscript{132} In a Texas study of 53 index patients who reported semi-anonymous sexual
encounters, 49.7% of their sexual partners were successfully contacted and told of potential exposure via email. Of those contacted, 40.1% underwent testing. In a recent report evaluating the Washington, DC internet partner notification system for syphilis, the health department found 43% of partners of syphilis cases through their internet notification system. From 361 early syphilis patients, 888 sexual partners were investigated in total. Of these 888 partners identified, 381 (43%) were notified through the internet.

It is likely that the internet will be used increasingly to conduct partner notification, thus it is important to have an understanding of whether utilizing the internet is an effective means to successfully notify and treat sexual partners. The internet is simply a tool for communication and thus notification over the internet is an extension of patient (self) referral, or in the cases of health department assisted internet notification, an extension of health department or DIS assisted provider referral. Further, it is likely that the internet could be used as a part of other partner notification approaches which will be discussed in later sections, such as booklet enhanced patient referral. It is important to note that much like other forms of notification, the responsibility of undergoing testing and/or treatment still rests with the notified partner.

2.3.5 Overview of other novel partner notification approaches

In addition to the traditional forms of partner notification, the method that CDC believes is most promising and has been practiced more each year in the last decade is expedited partner treatment (EPT), which is defined as the treatment of partners prior to any intervening evaluation or assessment by a health provider. There are several approaches to EPT. One is notifying a partner that there is medication ready to pick up at
a designated pharmacy, doctor’s office or public health clinic. Another is having medication be administered by non-medical health workers, such as public health workers (e.g. DIS officers), directly to partners. Finally EPT is most often conducted by treating the partner via the index patient. This process of providing medication or a prescription to the index patient to give to their sexual partners is known as patient delivered partner therapy (PDPT). This approach has been hypothesized to be an efficient method to increase notification and treatment rates of partners, as the partners would not have to be medically evaluated, theoretically expediting the process.

While not specifically “treatment” approaches, other forms of EPT exist. One approach to expedite and make STI testing more tolerable is through home sampling or postal testing kits (PTK). Another approach that has been minimally researched, known as booklet enhanced partner referral, is the provision of educational information about the exposure and illnesses in conjunction with referral cards to local testing and treatment facilities. This dissertation will examine both PDPT and booklet enhanced partner referral.

2.4 Booklet enhanced partner referral

Booklet enhanced partner referral, or simply “booklet referral,” is a method in which the index patient is given booklets of informational referral cards to assist in conducting partner notification of a sexually transmitted infection. The intent is twofold: facilitate notification by the index patient to his or her partners as well as improve access to care by providing information on treatment facilities and a tool to convey potential exposure. In this sense, it is a more comprehensive form of patient referral. When notifying partners, the index patient can tear out a card from the booklet to give to each
sexual partner to aid in conveying information about STI, including symptoms, treatment and prevention methods, as well as contact information for local treatment facilities. The cards can, in turn, be presented to a clinician by the partner to aid in the treatment process as well.

This novel approach to enhancing partner notification was first piloted in a rural Louisiana public health clinic. The results suggested that the number of partners who came in for services increased when the index patients were given booklets with informational tear out cards for their sexual partner(s). To date only two studies (randomized trials) conducted by Kissinger have examined booklet referral. Of the two studies, only one examined chlamydia (as part of male urethritis) whereas the other examined booklet referral for trichomoniasis. These studies also examined PDPT with the goal of comparing the effectiveness of PDPT and booklet referral to a standard patient referral control group.

2.4.1 Booklet referral for male urethritis

In the study by Kissinger, et al., on male urethritis, patients were randomized to one of three study branches: standard referral, booklet referral or PDPT. The study aims were to determine the proportion of sexual partners who received antibiotic treatment under each partner notification method, as well as to determine the rate of recurrence of infection among index patients. Men who visited an STI clinic in New Orleans, Louisiana from 2001 to 2004 were approached to participate if they had received a diagnosis of urethritis with a positive test for chlamydia or gonorrhea, were 16 to 44 years old, and had at least one female sex partner who did not accompany them to the clinic. A total of 977 men participated in the study.
In the standard referral group, men were instructed to tell their partners that they needed to go to either the public STI clinic or a facility of their choice for STI evaluation and treatment. In the booklet referral arm participants were given a “wallet-sized” booklet containing four “tear-out cards” containing information for the partner as well as treatment guidelines for health professionals examining the partners. In the PDPT arm, participants were given up to four packages containing one gram of azithromycin and 400 milligrams of cefixime (later replaced by 500 milligrams ciprofloxacin) to deliver to partners. The medication was accompanied by information about how to take the medication, warnings about side effects, and a nurse's number to call if participants had questions or if the treated partner experienced any problems. A survey was administered (by computer, phone or in the field) to elicit partner information, as well as behavioral and demographic information (one at baseline and one at follow-up). Further, participants were instructed to have a follow-up test four weeks later (no earlier than two weeks later and not more than eight weeks past baseline).

While the rate of retesting at follow-up was very low (38%), the results suggest both booklet referral and PDPT were more effective in preventing recurrent infection among the index patients compared to standard referral alone: infection was present at follow-up in 43% of men in the standard referral group, 14% of men in the booklet group, and 23% of men in the PDPT group. Using standard patient referral as the referent, the odds of being infected at follow-up in the PDPT arm was similar for both chlamydial infection (OR 0.46, 95% CI 0.13-0.87) and gonorrhea (OR 0.34, 95% CI 0.13-0.86). Men in the booklet referral arm were also less likely than those in standard referral and
PDPT arms to test positive again for the same organism as at baseline (10.7%, 23.5%, and 13.8%, respectively; \( p < 0.05 \)).

The study methodology makes it impossible to determine whether the follow-up infections were truly re-infections with strains from original partners, new infections with strains from newly acquired partners, or persistence of the original infection. Most (67.4%) of the participants (16 men with gonorrhea infection and 21 with chlamydia infection) who retested positive for the baseline organism denied having been re-exposed, suggesting either new sexual partnerships with a separate infected partner, treatment failure, resistant organisms or a combination of the three. For both behavioral outcomes and re-infection percentages, booklet referral performed equally to or better than PDPT, and both approaches were reported to lead to better outcomes than standard referral.\(^\text{136}\)

Despite the limitations of the study methodology and the high loss to follow up, this is the only study on booklet referral for the notification of sexual partners potentially exposed to chlamydia. Considering the favorable results of the re-infection proportion among index patients, further study into this method is justified.

### 2.4.2 Contact slips to aid partner notification

Although investigations into booklet referral in the United States are limited, there is research available on a less comprehensive method that is similar to booklet referral in which partners are notified by index patients with the use of “contact slips.” Contact slips are frequently used to conduct partner notification by health providers and STI clinics in some regions of the United States as well as in many areas internationally. Similarly to booklet referral, the contact slips contain information about the suspected disease and local clinic information where a partner can be tested and treated. The
specific information in the cards varies by clinic, region and country. If the partner brings the slip to their health provider and/or local clinic, the information can aid in determining what tests should be administered.

2.4.2.1 Introduction of the contact slip, Potterat et al., 1975.

The concept of the contact slip was first introduced in 1975 by Potterat, et al., who hypothesized more partners could be tested and treated if index patients were able to have an informational aid to assist in notification. Potterat, et al., assigned heterosexual male patients with gonorrhea diagnosed at the El Paso City-County Health Department in Colorado to either a treatment or control group (based on every-other-patient allocation). For the control group, a standard interview was conducted and patients were asked to refer contacts for treatment (standard referral). In the treatment group of the study, researchers administered to the patient contact slips to give to sexual partners and elicited partner information for further follow-up. Compared to those in the standard patient referral group, those patients given contact slips were far more likely to notify their partners directly. A total of 73% (86/116) of partners linked to the index patient were notified directly and given the informational slip, whereas the control group only self-referred 58% (69/119) of all their partners elicited.113

Contact slips were also studied in a randomized trial in Lusaka, Zambia. In this study, individuals diagnosed with an STI were randomized to receive counseling on how to conduct partner notification, or the same counseling combined with informational contact slips about the disease and where to get treatment. Both men and women in the contact slip group were more likely to refer at least one sexual partner to the clinic (100%
vs. 93%, respectively) compared to men and women in the standard referral group (72% vs. 56%, respectively).  

In a United Kingdom study, a slightly more enhanced approach to booklet referral that involves the use of contact slips in addition to informational leaflets about chlamydia and its effect on the number of partners who came in for evaluation and treatment was investigated. The study found that there was a statistically significant increase in the number of sexual contacts who came to the clinic for evaluation and treatment after being given the contact slip and informational pamphlet (84% of partners presented for treatment in response to 190 contact slips issued, 95% CI 79% to 89%), compared to only being given a contact slip (33% of partners responded out of 144 contact slips issued, 95% CI 26% to 43%). The reported findings suggest that the use of information specific to the disease along with a contact slip may significantly increase the proportion of partners who present for treatment.  

2.4.2.2 Comparing contact slip effectiveness with home sampling test kits  

Although contact slips have been shown to be an effective partner notification approach, a few studies have also examined the use of home sampling kits versus contact slips for partner notification. A randomized study in Denmark recruited 96 women with chlamydia infection who were seen in a general practice. The 45 women in the treatment group completed a questionnaire, including the number of male sexual partners they had over the preceding six months, and they were asked to supply their partners with an envelope containing a 10 ml sterile container, information on collecting the first urine sample of the morning, and a prepaid envelope for returning the sample to the laboratory.
Envelopes given to the control group for their partners contained a request for the partner to visit their doctor as well as a contact slip and a prepaid envelope to be given to the doctor for returning a urethral swab sample.

A total of 44 out of 65 (68%) partners were examined in the treatment group compared with 19 out of 68 (28%) in the control group (p<0.01). The researchers also report that partners of women in the treatment group tended to be tested earlier compared to women in the control group, with an average time of 12.6 days and 17.7 days after receiving notification from their partners respectively. The findings of this study suggested that providing a home sampling kit may lead to a higher percentage of women being tested compared to contact slips alone.\textsuperscript{139}

A recent randomized study in the United Kingdom reexamined the effectiveness of contact slips versus home sampling kits to determine which method resulted in a higher proportion of partners who underwent testing. Female index patients diagnosed with genital chlamydial infection were randomized to either receive a home urine sampling kit to provide to their sexual partners or to conduct standard referral with the aid of contact slips. Unlike the study in Denmark, there were no significant differences in the number of partners treated per index case (67% in the contact slip group versus 62% in the urine testing group, p=0.46). There also were no differences in the median number of traceable partners or the number of index patients with at least one partner treated within 28 days. Overall, this study showed that the addition of a urine home sampling testing kit to contact slip notification for male partners of women with genital chlamydial infection did not increase the partner notification rates compared to the use of contact slips alone.\textsuperscript{140} Thus, while contact slips are effective in leading to partners being
notified and treated, they may or may not be improved by providing home sampling kits in addition to the slip. However, they do appear to be more effective when educational materials are provided.\textsuperscript{137, 138}

2.4.3 Section conclusion: contact slips and the more comprehensive booklet referral are more efficient partner notification approaches than standard referral alone.

In summary, contact slips have been found to be an effective approach in promoting notification by index patients to their sexual contacts compared to standard referral alone. Studies suggest the utilization of contact slips by patients to notify their sexual partners may lead to a higher proportion of partners being contacted, tested and treated compared to standard referral alone. However, results are mixed in the two trials that compared partner notification via home sampling kits versus contact slips. While home sampling was found to be a moderately effective approach on its own, it may or may not be a better approach to notification than contact slips. Contact slips that were accompanied by informational pamphlets about the disease (an approach similar to booklet referral) are more effective in achieving partner notification than contact slips alone. Booklet referral, while only being studied in two trials in the United States by Kissinger, et al., one of which was specific to male urethritis and chlamydia, appears to be more effective than standard referral and was reported to be at least as effective as PDPT. Given the limited research on booklet referral and the promising findings of these, and similar, approaches (e.g., utilizing contact slips and informational materials), further investigations into booklet referral as a partner notification approach are warranted.
2.5 Patient delivered partner therapy

Recall that PDPT is the clinical practice of presumptively treating sexual partners of index patients diagnosed with chlamydia, by providing written prescriptions to the patient to be taken to his/her partner without the prescribing health care provider examining the partner or the partner undergoing prevention counseling.\textsuperscript{141} The CDC, American Medical Association and other major health organizations support the use of PDPT as an option to facilitate partner management for chlamydia infections.\textsuperscript{141, 142} In the Sexually Transmitted Diseases Treatment Guidelines, 2006, the CDC for the first time recommended expedited partner therapy (EPT). The rationale cited is that EPT is an evidenced-based option to manage chlamydia and gonorrhea, to effectively notify and treat index patients’ sexual partners, to prevent recurrent infection of the index patients, and to curtail further transmission to uninfected individuals. The CDC again recommended this approach in its 2010 guidelines.\textsuperscript{143} Despite limited evidence in the literature, the use of PDPT is recommended with heterosexual males and females (it is not recommended for homosexual males due to the higher rate of HIV infection in this population).\textsuperscript{144} In NYS, the use of EPT via PDPT was legalized in late 2008 as an option to notify and treat the sexual partners of patients diagnosed with chlamydia.\textsuperscript{21}

2.5.1 Literature regarding PDPT for chlamydia

Although CDC cites PDPT as an evidence-based approach, in most studies PDPT has been shown to be at most equally as effective as traditional partner notification strategies in successfully notifying and treating partners. It is further reported in most but not all studies to be at most equally as effective as other approaches in reducing persistent or recurrent infections.\textsuperscript{145-153}
A recent meta-analysis conducted by Trelle, et al., included five clinical trials involving PDPT. An overall reduced risk (summary risk ratio 0.73, 95% CI 0.57, 0.93) of recurrent infection was reported in patients with chlamydia or gonorrhea who received PDPT, compared with those who received standard partner treatment methods. While this suggests that PDPT is effective in preventing recurrent infection of the index patient, one can conclude from the data that the overall impact is minimal relative to patient referral. The authors acknowledge this and state that when comparing PDPT to patient referral, PDPT was more effective, but “the absolute effects were modest.” This study also examined other methods including home sampling and providing additional information to partners during patient referral.

A key finding that is not highlighted prominently in the manuscript is that PDPT did not reduce persistent or recurrent infections when compared to patient referral with informational supplementation for partners. The study reports that patient referral with the provision of additional informational materials (i.e., booklet referral) was also more effective than patient referral. While this meta-analysis highlights the effectiveness of PDPT and patient referral supplemented with informational materials (i.e., booklet referral), it is important to understand that, like many other meta-analyses, the studies included all contain some methodological weaknesses, which could not only bias the results of those individual studies, but also bias the overall findings from the meta-analysis. Thus, the reported findings must be considered cautiously. A prime example is that the included studies were susceptible to both selection and measurement biases; measurement of the primary outcome could not be obtained in 23% to 70% of index patients in the analyzed studies. The authors conclude that while PDPT may be effective,
“interventions that combine additional information [for partners] may be superior to patient referral alone” and thus we should consider “PDPT, home sampling for partners and providing information for partners” as efficient methods for notifying, testing and treating partners.145

2.5.1.1 Earliest PDPT trial in the United States

One of the earliest studies to examine PDPT effectiveness was conducted in the 1990s by Kissinger, et al. The purpose of the research was to study re-infection among female chlamydia patients who were assigned PDPT or standard referral to treat/notify their sexual partners. Women who returned for a follow-up visit were retested for chlamydia. A total of 256 were eligible, treated and assigned to either PDPT or standard referral for their partners. A total of 178 returned for a follow-up visit, of which 135 were in the standard referral group and 43 in the PDPT group of the observational cohorts.

The researchers reported that the annual recurrent infection rate was found to be lower in the PDPT group compared to the standard patient referral group (11.5% vs. 22.5%, respectively, p<0.05). The authors further reported that women in the PDPT group were also less likely to have an incident chlamydial infection compared to the standard patient referral group (OR 0.37, 95% CI 0.15, 0.97, p<0.05).146

2.5.1.2 PDPT for male urethritis

In a follow-up study to assess PDPT, Kissinger, et al., examined how well it prevented recurrence of male urethritis. As discussed above in section 2.4.1 “Booklet referral for male urethritis,” recall that in this study patients were randomized to standard referral, booklet referral or PDPT. Although booklet referral was reported to be equally, if not more, effective than PDPT, the findings were also positive for PDPT compared to
standard referral. Despite the low rate of retesting at follow-up (38%), the results indicated that PDPT was more effective in preventing recurrent infection compared to standard referral alone (infection was present at follow-up in 43% of men in the standard patient referral group, 14% of men in the booklet group, and 23% of men in the PDPT group). Using standard patient referral as the referent, the proportion of men infected at follow-up in the PDPT arm was similar for both chlamydia infection (OR 0.46, 95% CI 0.13, 0.87) and gonorrhea (OR 0.34, 95% CI 0.13, 0.86). Further, men in the PDPT arm were less likely than those in the standard referral arm to test positive again for the same organism as at baseline (13.8% vs. 23.5%, respectively; p <0.05). For behavioral outcomes and re-infection percentages, PDPT (and booklet referral) was reported to lead to better outcomes than standard referral. The poor rate of retesting however is a significant limitation of this study and thus the findings are subject to selection bias.\textsuperscript{136}

The findings from this study motivated further research in other areas of the country into PDPT as a potential partner notification method for diseases other than chlamydia, including gonorrhea and trichomoniasis.\textsuperscript{135, 136, 147}

2.5.1.3 PDPT research in Washington State

Given the limited yet somewhat positive PDPT data, the bulk of emerging PDPT research was initially conducted in Washington State. The first of such investigations arose from an evaluation of a novel approach to partner notification in King County, Washington. In 1998, public health partner notification services were expanded to private sector patients (those not treated at a county clinic) with chlamydia or gonorrhea. To assess the effectiveness of the expanded program, researchers initiated a trial in which randomly selected patients and their sexual partners were offered expedited treatment at
commercial pharmacies. Participants with at least one untreated sexual partner in the prior 60 days were randomized to either standard patient referral or expedited treatment via PDPT (index patients obtained medication and information packs from local commercial pharmacies to deliver to partners). For standard referral, patients were given a choice to notify partners themselves or have study staff contact partners for patients and notify them of cost free services at the public health clinic.

In the expedited arm of the study, 346 (76%) of 458 study subjects stated they would deliver medication to at least one partner. Among the 266 subjects who arranged to obtain medication for a partner from a commercial pharmacy, 223 (84%) successfully did so. Subjects with more than one sex partner or a partner they did not anticipate seeing again were significantly less likely to obtain medication after agreeing to do so compared to those with just one partner (81% vs. 94%, p<0.001).

While the study indicated that a high number of partners could potentially be notified and treated under PDPT either by the patient or at a commercial pharmacy, two limitations are noteworthy in this paper. First, data was not provided nor collected on the number of partners that were actually contacted by patients in the standard referral group, thus PDPT’s effectiveness relative to standard referral could not be assessed. Another limitation to this study is that a patient merely picking up the medication from a commercial pharmacy is not a guarantee that it was delivered to its intended recipient, or that medication was in fact taken by sexual partners.116

One of the prominent articles often cited to demonstrate the effectiveness of PDPT is a 2005 New England Journal of Medicine study by Golden, et al. This study is a continuation or extension of the study described above in King County, Washington. In
this study, Golden et al., tested whether the use of PDPT could reduce persistent or recurrent infection with gonorrhea or chlamydia compared to standard partner management. The proportions of reported partner notification were not statistically different for PDPT vs. the standard partner management groups (77% partner notification proportion among PDPT-assigned patients vs. 78% among standard referral controls).

Persistent or recurrent gonorrhea or chlamydial infection occurred in 121 of 931 patients (13%) assigned to standard referral and 92 of 929 (10%) assigned to expedited treatment of sexual partners (RR 0.76, 95% CI 0.59, 0.98). Expedited treatment was slightly more effective than standard referral in reducing persistent or recurrent infection among patients with gonorrhea (3% vs. 11%, p=0.01) than in those with chlamydial infection (11% vs. 13%, p=0.17).

For both infections there were slightly fewer patients with recurrent infections in the PDPT group, however the absolute effect is minimal and the 95% confidence interval nearly crosses the null. These findings suggest that expedited treatment is more effective for gonorrhea than chlamydia as it pertains to recurrent infection; however the absolute percentage of partners notified is an important finding to consider. One would reasonably anticipate a greater number of partners notified under PDPT than by standard referral, but in this study the proportion of partners notified under each approach was equivalent. Thus, this oft-cited study to demonstrate the effectiveness of PDPT shows in reality that PDPT may be at most equally effective as standard referral.147

A subset analysis of the Golden, et al., study was recently conducted by Shiely, et al., which claims to show a strong positive effect for PDPT versus standard partner referral. The analysis includes participants from the original study who were retested for
gonorrhea and chlamydial infection at the end of the study or who were diagnosed with gonorrhea or chlamydial infection in the 21 to 133 days following enrollment.

Re-infection risk was found to be lower among the PDPT recipients compared to non-recipients in 21 of 22 subgroups analyzed, with relative risks varying from 0.40 to 0.94. Compared to patients assigned to standard referral, those patients assigned to PDPT were more likely to report that sexual partners were “very likely” to have been treated in 33 of 34 subgroups. In sub-analysis, PDPT was found to have reduced the risk of persistent or recurrent infection somewhat more in men (RR, 0.56; 95% CI 0.30, 1.08) than in women (RR, 0.81; 95% CI 0.61, 1.07), but it must be noted that both of these relative risk confidence intervals cross the null. It was also shown that PDPT led to less re-infection risk in patients with gonorrhea (RR 0.32; 95% CI 0.13, 0.78) compared to those with chlamydia (RR 0.82; 95% CI 0.63, 1.07). These latter findings suggest that PDPT, when accepted and utilized correctly and completely, may be more effective for gonorrhea infections rather than chlamydial infections, similar to the findings of the original study. It is important to note that the findings for chlamydia, while positive for PDPT relative to standard referral were not statistically significant when examining the risk for re-infection. Nevertheless, these moderately positive findings led the Seattle King County public health service to integrate the routine use of PDPT into their partner notification services.

2.5.1.4 PDPT for preventing repeat chlamydia infection in five cities

One of the first studies to document a higher partner notification rate with PDPT versus standard referral was in the 2003 chlamydia repeat infection prevention study by
Schillinger, et al. This was a randomized controlled trial conducted among 1,787 women aged 14 to 34 years with genital chlamydia infection diagnosed at family planning, adolescent and STI clinics/hospitals in five United States cities. Participating women were treated for infection and then randomized to either patient referral or PDPT, in which they were given azithromycin to deliver to each sexual partner. The main outcome measure was infection with chlamydia four months after baseline among the index patients.

The authors reported that 85% of partners were notified among patients assigned PDPT, whereas 75% were notified in the standard referral control group (p=0.01). This is one of the first studies to demonstrate that PDPT may result in more partners being notified, however the absolute difference was only 10%. However, the re-infection proportion of PDPT-assigned patients compared to the standard patient referral re-infection proportion (12% vs. 15% respectively, OR 0.80, 95% CI 0.62-1.05) was essentially equal, suggesting again that PDPT was at most equally effective as standard referral for preventing re-infection with chlamydia. Compliance with the study assignment in the intervention was strong at 82%. Thus, the conclusion that PDPT was no more likely to reduce recurrence of chlamydia among index patients, while prone to some bias, was likely accurate.149

2.5.2 Studies which conclude PDPT is ineffective

2.5.2.1 Comparing PDPT, postal test kits and patient referral, 2009

Other studies have shown PDPT is not more effective than other partner notification methods. In a 2009 United Kingdom study, researchers conducted a randomized trial to determine whether postal testing kits (PTKs) or PDPT to notify
sexual partners of female chlamydia patients could reduce re-infection rates relative to standard patient referral. Only 65% of index patients were retested over one year. They found 32 of 215 women (15%) retested positive; seven women in the standard patient referral group, 15 in the PTK group and 10 in the PDPT group. Using Cox proportional hazards regression, they found there was no significant difference in the hazard ratios (HR) of re-infection between PDPT and standard patient referral (HR 1.32, 95% CI 0.50, 0.56), PTK and standard patient referral (HR 2.35, 95% CI 0.94, 5.88) or PDPT and PTK (HR 0.55, 95% CI 0.24, 1.24). There was also no statistical difference in the proportion of partners who were notified and/or treated between the study groups, however, the PDPT group had the highest proportion of partners treated (34% in standard patient referral vs. 41% in the PTK group and 42% in the PDPT group).

It is important to note that although not significant, the point estimates for the HRs suggest a difference in effectiveness between the three methods, with the group assigned to standard patient referral having the least risk for re-infection. Given the low number of participants in the study coupled with the low number of re-infections, the study does not have enough statistical power to adequately detect important differences, as evidenced by the wide confidence intervals. Despite insufficient power, the study does add to the evidence that PDPT may lead to more partners being notified relative to patient referral. At the same time the study suggests that PDPT is at most equally effective as patient referral in preventing re-infection of the index case.
2.5.2.2 Programmatic audit suggests PDPT causes missed cases—Scotland, UK

A programmatic evaluation of the Sexual Health Services performance in Scotland found that approximately 22% to 28% more chlamydia cases would be missed using PDPT alone, compared to using the clinic-based partner notification assistance program. The evaluation was conducted to estimate the impact of not being able to identify secondary contacts of the index patient (a major limitation of PDPT) on the number of chlamydial infections that would be identified by their services. Although one benefit to the use of PDPT is that more partners of the index case may be notified and treated compared to standard referral, it must be recognized that the index patient’s secondary contacts will frequently be missed because PDPT limits tracing of such contacts. After comparing the number of secondary contacts that tested positive from index patients and their primary sexual partners to the number of partners treated under PDPT, the audit report concludes that an estimated 22% to 28% more cases of chlamydial infection would be identified using the program’s notification service and interview procedures versus PDPT.\textsuperscript{151}

Although PDPT may lead to more primary contacts (that is sexual partners of index cases) being notified compared to standard referral, this programmatic evaluation highlights a major weakness associated with PDPT: secondary contacts of the index patient will be missed at a high rate. Conducting partner interviews and evaluations may elicit further sexual contacts to interrupt the chain of infection. It is plausible that in some cases where an untreated secondary contact exists, an index patient could be re-infected by a sexual partner that was treated under PDPT. By extension, it is possible that most
research finding that PDPT is at most equally effective as standard referral in preventing re-infection is partially attributable to untreated secondary contacts maintaining the chain of infection. Further research is necessary to quantify this possibility.

2.5.2.3 Programmatic evaluation of PDPT effectiveness—San Francisco, CA

In San Francisco, another programmatic evaluation of PDPT effectiveness was conducted at the San Francisco City Clinic. The investigators found that PDPT did not lead to significantly reduced re-infection rates of chlamydia or gonorrhea, further substantiating prior research findings that PDPT is at most equally effective as standard referral in preventing re-infection with chlamydia. In this evaluation, researchers examined re-infection in patients for one year after using PDPT to notify partners. The researchers used propensity score analyses to adjust for selection bias to compare to those index patients who did not receive PDPT. This sizable study had adequate power to detect statistical differences between study groups because it included 4,418 chlamydia cases and 2,115 gonorrhea cases. There was no significant difference between patients who received PDPT and those who did not in the crude cumulative risk estimates for repeat infection with either chlamydia or gonococcal disease. For all patients, 317 (16.3%) were re-infected vs. 399 (15.9%) comparing those who were retested in the PDPT vs. the standard referral group respectively (crude RR 1.04, 95% CI 0.91, 1.19). The propensity score analysis indicated that the adjusted relative risk was found to be essentially null (RR 0.99, 95% CI 0.86, 1.14) for chlamydial re-infection and non-significant (RR 0.90, 95% CI 0.72, 1.11) for gonococcal re-infection.\textsuperscript{152}
2.5.2.4 Conclusions regarding PDPT analyses

The reported findings by Trelle, et al., must be considered cautiously, especially since they reported findings that contradict the majority of PDPT analyses in the literature. They conclude that while PDPT may be effective, “interventions that combine additional information [for partners] may be superior to patient referral alone” and thus we should consider “PDPT, home sampling for partners and providing information for partners” as well as other methods for notifying, testing and treating partners.\textsuperscript{145} Interestingly, in all studies that examine booklet referral or the contact slip coupled with educational information, researchers find these methods of partner notification equally effective to PDPT in notifying partners and may be superior in preventing recurrent infection of the index patient.

That said, the current status of the literature does substantiate the belief that PDPT will lead to more partners of index patients being notified and treated compared to standard patient referral. However, the effects are modest. Further, PDPT is no more effective than patient referral at preventing recurrent infection. Finally, PDPT use prevents the identification of secondary contacts to the index patient, a consequence which may serve to maintain the chain of infection, possibly leading to recurrent infection of the index patient. Under alternative methods, such as health department-assisted notification and patient referral, sexual partners are evaluated medically (if they are found and/or choose to visit a health provider) and thus their sexual contacts can be reached at a higher rate than those partners notified via PDPT.
2.5.3 Professional and patient perspectives on PDPT

2.5.3.1 Australian practitioners partner notification survey

As both health professionals and patients are directly affected by PDPT as a partner management option, some research in the realm of patient and professional viewpoints regarding PDPT use has been conducted, primarily outside of the United States. In a recent Australian study of 40 general practitioners, researchers conducted in-depth telephone interviews about partner notification approaches, including PDPT. They found that those surveyed were divided on the use of PDPT; many felt concerned that it is not the best clinical practice, but many also believed that it is “better than nothing,” meaning better than not treating the partners at all. Not surprisingly, they suggested the ideal would be clinical evaluation of all partners. Nearly all felt partner notification was the patient’s responsibility and not the provider’s. Concerns were raised by respondents regarding PDPT, including lack of taking a health history of the partner thus failing to treat other present infections, as well as legal and ethical issues.

2.5.3.2 Professional and Patient Perspectives—United Kingdom

In the United Kingdom, Shivasankar, et al., sent a mailed questionnaire to health professionals regarding PDPT and found practitioners viewed PDPT more positively than reported in the Australian study, but they also noted more specific legal concerns. The chief concern among health professionals was the overall legal status of utilizing PDPT in the United Kingdom, followed by concerns about being able to ensure treatment of the partner has progressed. Shivasankar, et al., also reported that approximately one-third of the surveyed health professionals were strongly opposed to PDPT. Both physicians and health advisers were cautiously prepared to consider using PDPT, but would do so only if
there is no other option and only if a health professional first made contact with the partner. One of the key findings of the report was that these professionals believed chlamydia was the most appropriate infection for PDPT use, given its asymptomatic nature.\textsuperscript{154}

To refine this preliminary assessment of practitioners’ perspectives on partner notification, Cameron, et al., conducted a study among UK physicians and nurses to identify their preferred strategies for treating the sexual partners of women diagnosed with chlamydia. Respondents were given a choice of standard referral, PTK, PDPT with azithromycin or combined PDPT and PTK. Community pharmacists were also invited to complete a questionnaire regarding their willingness to introduce chlamydia testing and treatment services in the pharmacy environment. Physicians favored either combined PDPT and PTK (30\%) or letting the patient choose how to notify partners (29\%). Standard referral and PDPT alone were least favored (8\% and 9\%, respectively). Nurses had similar preferences, favoring combined PDPT and PTK (23\%) over standard referral (13\%), with PDPT alone being the least favored option (12\%). Physicians reported a perception that combined PDPT and PTK offers improved compliance and increased partner testing rates.

Virtually all pharmacists surveyed (98\%) stated that they would be willing to supply free PTKs for chlamydia testing on their premises. All respondents were willing to dispense azithromycin to women who provided evidence that they were chlamydia-positive. Only 18\% stated that they would not be willing to supply the index woman with a supply of azithromycin to give to her sexual partner(s) for presumptive treatment,
noting concerns of contraindications and lack of receiving adequate information about the medication (i.e., missed opportunity for counseling).¹⁵⁵

This study highlighted an important aspect regarding physician and nurse perspectives of partner notification in that they preferred the most comprehensive approach, which was to combine PDPT with a PTK, essentially allowing the partner to be tested and treated, all without being evaluated in a clinical setting. An interesting finding was that nearly the same percentage of physicians who preferred PDPT and PTK combined preferred to let the patients choose how to notify their partners. Because pharmacists may assume an increasingly active role as PDPT becomes more widely used, it was welcome news that 98% reported being willing to provide home tests for chlamydia. Similar to physician and nurse concerns, 18% of pharmacists reported they would not be comfortable distributing medication to patients (without a prescription) for their partners due to concerns about contraindications and legal consequences.

2.5.3.2.1 Patient perspectives on PDPT

In a follow-up to their practitioner study, Shivasankar, et al., surveyed STI patients in the United Kingdom to determine the partner notification preferences of patients attending a local STI clinic. They surveyed 500 patients and found that traditional patient referral was acceptable to 87%, patient referral with infection-specific information and treatment guidance was acceptable to 82% of respondents and PDPT was acceptable to 81%. Only 71% found PTK an acceptable approach and provider referral was the least popular option at 23%.¹⁵⁶

In another UK study of patient perspectives regarding PDPT, Melvin, et al., reported that of 293 men surveyed regarding partner notification preferences, 70% would
choose standard referral to notify their partners and 53% would prefer to be notified by standard referral. Only 3% reported that they would choose PDPT for notifying, testing and treating partners. Only 6% of men reported they would want to be notified of a potential infection by PDPT.  

Together, these two studies indicate that standard referral and standard referral with informational materials (i.e., similar to booklet referral), were the most preferred methods of partner notification among patients surveyed. Very few respondents preferred PDPT, and in the Melvin study only 6% would prefer to be notified of an infection by PDPT. Understanding patient perspectives regarding each approach can help direct future studies, as well as inform STI programs regarding the most fruitful approaches to increase evaluation and treatment.

In a smaller study by Coyne, et al., both patients and health professionals were surveyed regarding PDPT at a treatment facility service in the UK. A questionnaire was distributed to 122 medical staff, including doctors, nurses, health advisers and clerical staff. A different questionnaire was given to 525 consecutive patients attending the facility. The majority of staff (81%) thought that PDPT should be combined with written information and a recommendation to attend a clinic. Patients were mostly (59%) in favor of the concept of PDPT, and 94% indicated that after being given antibiotics by a partner, they would attend a clinic for evaluation. Concerns expressed by both staff and patients included possible drug allergies, potential lack of information being provided to partners, management of complicated infection, pregnancy issues and legal implications.

This study highlights two concerns associated with PDPT: properly informing partners as to the nature of their potential exposure and encouraging them to visit a clinic.
or doctor for medical evaluations, as well as quantifying how many patients would actually attend a clinic for testing if they received a prescription or medication from a partner. Over 80% of medical professionals surveyed suggested that informational materials should accompany PDPT prescriptions and nearly all patients (94%) indicated they would seek a medical evaluation if they received a PDPT prescription from a partner.

2.5.3.3 Professional and Patient Perspectives—United States

In the United States, only a few investigations have focused on patient and health professional perspectives regarding novel partner notification methods, and even fewer have delved specifically into PDPT as a partner treatment option for managing chlamydia.

2.5.3.3.1 A survey of 4,223 physicians regarding partner notification

A 1999 to 2000 study on 4,223 physicians regarding case-reporting, patient referral and provider referral found that physicians generally supported standard patient referral over provider referral. Most (83.8%) always asked patients to notify their partners. In contrast, a much smaller number of physicians solely practiced provider referral (4.1%). Respondents also believed case reporting to a health department for contract tracing is a relatively effective means of controlling STI. Most (81.5%) agreed that case reporting presented an opportunity for prevention education, helped prevent the spread of STI (82.7%), and helped patients reduce risky behaviors (40.7%). While recognizing the benefits of case reporting to the health department, most believed (70.1%) that patient referral to be about as effective as case reporting to the health department for controlling STIs. Further, respondents agreed that standard patient referral
presented an opportunity for prevention education (89.7%), helped patients alter their risk behaviors (51.9%), and helped prevent the spread of STIs (83.5%).

In a separate report utilizing this same survey data, Hogben, et al., conducted a sub-analysis of physicians in the study who reported diagnosing at least one STI case (chlamydia or gonorrhea) in the preceding year (about 70% of respondents). Half of the subset reported ever using PDPT (56% for gonorrhea and 49.6% for chlamydia); over 10% reported usually or always doing so (11.3% for gonorrhea, 14.4% chlamydia). It was found that family practice physicians (62%) and obstetricians/gynecologists (65%) used PDPT more so than internists (49%), pediatricians (35%), and emergency department physicians (44%).

Three important findings can be drawn from the main study and sub-analysis. The first is that physicians believed standard referral to be as effective as case reporting to the health department in controlling STI, particularly if time is taken to educate patients on risk reduction as well as the infection they were diagnosed with. Second, physicians believed standard referral to be far more effective than provider referral, and most physicians preferred that patients notify their partners directly. Finally, although at the time of this study PDPT was not expressly legal, it was found that physicians had already begun engaging in this practice, with family practice physicians leading the way. Neither study, however, assessed physician perspectives regarding PDPT.

Both physician and nurse practitioner perspectives on PDPT in treating chlamydia were assessed in a California study conducted December 2001 through March 2002. A questionnaire was mailed to 1,451 physicians and 1,418 nurse practitioners. For a mailed survey, the response rate was very strong: 708 (49%) physicians and 895 (63%) nurse
practitioners responded. About half had utilized PDPT (47% and 48%, physicians and nurse practitioners, respectively) at least once.

The practice of PDPT was met with an overall positive attitude among those returning surveys. Respondents reported that they believed PDPT may help protect their patients from re-infection (95%) and could help provide better overall care for their patients (93% physicians; 95% nurse practitioners). Substantive concerns with PDPT were reported by respondents, similar to those reported by health practitioners in the UK studies, including danger of not knowing allergy history (56% physicians; 55% nurse practitioners), potential for incomplete care for the partners (59% physicians; 61% nurse practitioners) and legal issues (36% physicians; 28% nurse practitioners).161

2.5.3.3.2 Patient perspectives regarding PDPT in the United States.

Three reports in the United States have investigated patient perspectives regarding PDPT. The first was a small qualitative study in which researchers examined the willingness of patients to engage in patient-delivered partner screening and preferences for expedited partner services. The researchers surveyed 40 urban STI clinic patients in the United States about PDPT and patient delivered partner screening (which involved the patient bringing a home test kit to their partner).

Most participants selected patient delivered partner screening and PDPT together as the best approach rather than one over the other. For patient delivered screening, several potentially important barriers and benefits were identified. Perceived benefits included improved sexual health for patients and their sexual partner(s), as well as more privacy, convenience of the method and the potential to increase and build trust between sexual partners. Perceived barriers identified in this study for patient delivered screening
included concerns about the process, most notably the time it would take to receive the result of the test and concerns over the risk of sample contamination, the accuracy of screening test results, stigma and associated blame, lack of trust in a sexual partner, and the packaging/appearance of the screening kit.

This study was small, but highlighted several important issues related to PDPT and the concept of patient delivered partner screening. Overall, while participants seemed to prefer a combination of both screening and PDPT, the concerns associated with screening alone cited by the patients are similar to commonly cited PDPT barriers. The most notable challenge to patient delivered partner screening and PDPT identified in this study was inter-personal relationship dynamics that could affect whether a partner is screened/NOTIFIED, substantiating concerns of health professionals that all partners may not be treated under this approach.¹⁶²

The second published work on patient perspectives regarding PDPT in the United States reported exploratory findings of partner treatment preferences from three urban STI clinics in 2008. A total of 2,887 individuals completed a one question survey which asked participants “how they would like to get their partner(s) treated if [they were] diagnosed with chlamydia.” Half preferred to send their partners to a clinic for treatment (49.7%). Only 20% of respondents (23.5% of females and 15.5% of males) indicated they would prefer to “bring the medicine home for my partner to take.” Thus, most participants did not prefer PDPT.¹⁶⁴

The final study that assessed patient perspectives regarding PDPT was recently conducted by Holloway, et al., in New York. The study specifically examined the perceptions of male STI patients on various partner notification approaches. This study
was a convenience sample of men recruited at a community clinic located in upper Manhattan in 2007. A total of 199 out of 297 (67%) men invited to participate completed the survey which inquired about methods that participants preferred for receiving test results, receiving treatment, past history of STI and use of PDPT.

Most men were willing to use a home sampling kit (71%), or at least go to a clinic to have a urine test (87%). Respondents preferred to be informed of STI test results by phone (67%), but were also willing to receive results via text message (65%) or e-mail (61%). In regards to PDPT, respondents indicated they would be “very willing to take medication brought to them by a sexual partner” for treatment of an STI (83%).165 Thus, in this study in NYC participants were much more accepting of PDPT compared to prior studies examining patient perspectives.

These limited studies on patient preferences for PDPT in the United States suggest that it is an acceptable method to some patients, but most still prefer to have their partners evaluated by medical professionals. Given that PDPT is a legal option in many states, including NYS, important questions remain unanswered. Most notably, it is unclear to what degree patients will deliver medications to partners, whether they will deliver prescriptions to all partners, how long it will take to deliver prescriptions and whether partners would seek medical evaluations if they were to receive a prescription. Answering these questions is critical to placing into context the findings of studies assessing the effectiveness of PDPT as an approach to partner notification and its utility in preventing recurrent infection.

### 2.5.3.3.3 PDPT in New York State
There has been some state-specific research conducted on PDPT in NYS. In a NYC study of 695 health providers, most reported frequent use of patient referral (94%), while about 20% reported also frequently using provider referral. While illegal at the time of this research (NYS law required those receiving prescriptions to be under the care of the prescribing provider), half (49%) of respondents reported ever using PDPT, and 27% reported using this strategy usually or always. Use of PDPT was higher for cases of chlamydia than gonorrhea.

While this study indicated that PDPT was already in use, it did not address concerns of the health providers regarding actual treatment of the partners, nor did it address whether any follow-up was done to ensure treatment. It was also unclear to what degree patients who were given treatment intended for their partners actually delivered the treatment to the intended recipients. Further, given the routine use of PDPT by the surveyed physicians, one questions whether those patients were encouraged to have their partners seek medical evaluation.

Researchers in NYS have also investigated PDPT by conducting in-depth surveys of both NYS county health department STI prevention officials (excluding NYC) and pharmacists in the state. As county health departments in NYS are responsible for diagnosing a large portion of STI cases in the state, particularly in urban counties, researchers conducted telephone interviews of these experts to learn more about their perspectives regarding the approach in NYS. Like many studies of health professionals regarding PDPT conducted in the UK, researchers found county STI control officials were divided about legalizing PDPT, with 45% in favor, 45% against, and 10% undecided. Reasons cited for supporting PDPT were similar to earlier studies and
included the perception that PDPT would result in more infections treated (61%) and improved overall STI control (29%). Reasons for lack of support were also comparable to findings from other studies and included potential contraindications and side effects (28%), potential for prescriptions not reaching partners (28%), and malpractice risk (20%). The lack of a medical evaluation of partners was a serious concern raised by some respondents (18%).

The issues raised in this study are not entirely novel but deserve special consideration as the practice of PDPT is legal in NYS. Specifically, the issue of whether prescriptions would reach partners and whether the partners would seek medical evaluations for other conditions remains unclear. The degree to which partners would seek medical evaluation has not been adequately addressed in the literature. It also remains unclear whether patients would deliver prescriptions to all of their partners and how much time it would take for patients to deliver prescriptions.

It is possible that for partners receiving prescriptions through PDPT, the only contact with the medical community may be at local pharmacies. In these instances pharmacists may have to take on the responsibility of STI counseling and assessment of allergies and other contraindications to a prescribed medication. Research on 193 NYS pharmacists found 63% supported PDPT for chlamydia and that the majority (88%) of pharmacists want prescriptions marked as being issued under PDPT to make the pharmacy aware of special counseling needs for the prescription’s recipient. About half (49%) indicated that the largest barrier they would face in providing counseling for STI treatment and prevention is time, while others indicated a lack of true privacy to conduct adequate prevention counseling for STI.
A separate aspect of the pharmacist study described above identified the need for, and problem of, maintaining a line of confidentiality associated with not only PDPT, but other prescription counseling in general. Researcher observations in the pharmacy noted that conversations at the counter can be overheard over fifteen feet away in 62% of cases. Pharmacy-specific research in NYS also indicates that about 69% of pharmacies have designated counseling areas, many of which are adjacent or within close distance to prescription drop-off or pickup areas. Observations of patient and staff interactions revealed that 28% of interactions occur with another customer within six feet of the conversation.\textsuperscript{167}

This pharmacy-specific research has raised important new questions that have yet to be adequately addressed in the literature specific to PDPT. The findings suggest that confidential counseling for STIs may not be possible in many instances. It remains unclear to what degree patients diagnosed with chlamydia, as well as partners who could potentially receive prescriptions under PDPT, believe they can adequately receive confidential and effective STI counseling from a pharmacist in the commercial pharmacy environment. Further research is warranted to gauge privacy perceptions in the pharmacy as well as to measure whether partners receiving prescriptions feel comfortable discussing a STI with a non-traditional health provider (i.e., their pharmacist).

\textbf{2.6 Antibiotic resistance}

The rising number of incident chlamydia cases annually coupled with increasing recurrent infections among index patients raises the question of whether treatment of chlamydia with recommended antibiotics is as effective as it once was believed.
Recurrent infections among index patients are possible in three ways: re-infection from an untreated sexual partner, treatment failure due to a persistent infection or treatment failure due to antibiotic resistance. While re-infection is straightforward the distinction between persistence and resistance is less clear.

The operational definition of bacterial persistence for this discussion is the ability of the bacteria to survive prolonged exposure to antibiotics, which is not attributable to innate resistance, but rather to a subpopulation of the bacterial infection that is in a morphologically altered, non-growing or slow growing state. Persistence is not due to heritable mutations in the genetic structure, but instead attributable to the slow or non-growing subpopulation present among the ‘normal’ growing bacterial population with altered morphologies that prevent antibiotics from binding to their targets. Antibiotics will still successfully target the normal bacteria and essentially eliminate infection. However, if the aberrant forms of the bacteria that remain post-treatment revert to their normal morphological state the infection process can resume and retreatment will be necessary, which is inherently different than true antibiotic resistance.

In contrast to persistence, resistance is an evolutionary development of the bacteria. Resistance is a property that the organism acquires in its normal life cycle, whether spontaneously, through a genetic mutation, a lateral gene transfer with another bacteria etc. Unlike persistence which is a morphological alternation, resistance is an evolutionary change that confers the ability to naturally evade antimicrobials. The concept of bacteria and other microbes becoming less susceptible to antimicrobials is a growing problem that has developed in the last fifty years.
2.6.1 General information regarding antibiotic resistance

Antimicrobials have been used extensively for the last 70 years to treat patients who have contracted infectious diseases.\textsuperscript{168, 169} Since the 1940’s, illness and death from infectious diseases have significantly declined because of antibiotic use, and when prescribed and taken correctly, are still effective in fighting infections today.\textsuperscript{170, 171} Antibiotics have been used so widely and for so long that many of the bacteria these antibiotics target and eliminate have adapted, making the drugs less effective and causing severe consequences for those infected.\textsuperscript{172-175}

Individuals infected with antimicrobial-resistant organisms are more likely to have longer, more expensive hospital stays, and may be more likely to die as a result of the infection.\textsuperscript{176} When first-line treatments of choice utilized to combat infection are ineffective, patients require treatment with second or possibly even third-line agents. These treatments are usually stronger, generally more costly than first-line treatments, and often have more extensive side effect profiles. There is also no guarantee that these treatments will work and as such a common result is that a patient with an antimicrobial resistant infection has longer morbidity and pays more for treatment.\textsuperscript{177-179} The problem is worsening globally, as a growing cadre of bacteria are exhibiting resistant properties to antibiotics.

2.6.2 Examples of antimicrobial resistant bacteria

A number of bacteria exhibit resistant properties to antibiotics including, but not limited to: \textit{Streptococcus} (group B), \textit{Bacillus anthracis} (anthrax), \textit{Klebsiella pneumoniae}, \textit{Neisseria meningitidis}, \textit{Shigella}, \textit{Salmonella typhi} and \textit{Enterococci} (vancomycin resistant).\textsuperscript{180-193} Some of the most well-known examples of community acquired illnesses
related to microbial resistance include pneumonias, skin and soft tissue infections, and certain STIs. Surveillance data indicates that the prevalence of resistant subtypes of these infections are increasing in the United States. For example, surveillance data for Streptococcus pneumoniae, a common cause of bacterial respiratory tract infections, showed that 24% of isolates were not susceptible to penicillin. In addition, resistance to several other antimicrobials is common among Streptococcus pneumoniae.\textsuperscript{194} Approximately 1.5% of penicillin resistant isolates were resistant to the third-line treatment cefotaxime and some were resistant to newer flouroquinolones.\textsuperscript{195} Penicillin resistance has expanded to many bacteria which were once susceptible, and has long been an issue with Staphylococcus aureus.

Nearly all strains of Staphylococcus aureus in the United States are resistant to penicillin and many are also resistant to the penicillin derivative methicillin. For years vancomycin was the only uniformly effective treatment against these methicillin resistant strains, but over the last decade there have been reported strains of Staphylococcus aureus with decreased susceptibility and isolates that were resistant to vancomycin.\textsuperscript{193} The public health burden of methicillin resistant Staphylococcus aureus (MRSA) is staggering with over 90,000 invasive MRSA infections per year estimated in the United States population.\textsuperscript{183} With vancomycin resistant strains on the rise as well, these infections can require multiple rounds of antibiotics. While MRSA is primarily acquired in the health care setting, many resistant infections are transmitted in the community.

Some common resistant bacteria that are transmitted in the community and are likely better known to the public due to public health educational campaigns or media coverage include Mycobacterium tuberculosis (causing tuberculosis), along with two
STIs, *Treponema pallidum* and *Neisseria gonorrhoeae*, the bacteria that cause syphilis and gonorrhea, respectively. Syphilis and gonorrhea are unique as they are the only resistant organisms spread exclusively through sexual intercourse. Understanding the development of resistance among these STIs provides a foundation for justifying research into the possibility of resistance among *Chlamydia trachomatis* strains.

### 2.6.3 Antibiotic Resistance Among STIs

#### 2.6.3.1 Review of Syphilis Resistance

The discovery and introduction of penicillin in the 1940s revolutionized the treatment of syphilis as it offered an effective method of eliminating the infection and preventing transmission. Penicillin derivatives remain the recommended first-line treatment for all stages of syphilis today.

**2.6.3.1.1 Characteristics of syphilis infection**

Syphilis infection progresses through a series of clinical stages interspersed with a variable period of latency. Interestingly, syphilis infection may often go untreated or be misdiagnosed because of its varying clinical presentation with symptoms mimicking other conditions. Following its early clinical phases, symptoms generally subside without treatment.

Stages of syphilis infection include a primary stage, characterized by the appearance of a single or multiple chancrees that are firm, round and usually painless that occurs at the site of infection. This can last three to six weeks before progressing to the secondary stage in which more generalized skin rashes and/or lesions of the mouth, vagina or anus appear. These secondary symptoms can last weeks to months, but will disappear without treatment as and the patient enters the latent phase. The latent phase
can last for years as the disease slowly progresses into the late stages. Symptoms of late stage syphilis can appear 10 to 20 years after initial infection. Often, symptoms that present are a result of damage to internal organs, the nervous system, blood vessels, eyes and bones. Although uncommon, untreated syphilis can be fatal.\textsuperscript{197}

\subsection*{2.6.3.1.2 Treating syphilis}

For the primary, secondary and early latent stages of syphilis, a single intramuscular injection of 2.4 million units of long acting benzathine penicillin G is effective in clearing infection. For those with late latent syphilis (or latent syphilis of unknown duration) as well as those with late stage syphilis symptoms, a three dose regimen of 2.4 million units of benzathine penicillin G, injected intramuscularly at weekly intervals, will cure the infection. If a patient has signs of neurosyphilis, aqueous crystalline penicillin G at a dose of 18–24 million units per day is recommended, and can be administered as 3.0 to 4.0 million units intravenously every four hours, for 10–14 days.\textsuperscript{143}

\subsection*{2.6.3.1.3 Describing the development of resistance in syphilis, including resistance to therapies utilized for chlamydia treatment}

To date \textit{Treponema pallidum} has not developed resistance to penicillin, although it could become resistant if there was a mutation on certain genes.\textsuperscript{198} What is relevant to the control of syphilis is that \textit{Treponema pallidum} has developed resistance to alternative regimens which were previously thought to be effective, specifically the macrolides which are utilized to treat \textit{Chlamydia trachomatis}.

Shortly after the introduction of erythromycin resistance to this antibiotic was observed in several bacteria.\textsuperscript{199} The first failures of erythromycin treatment for syphilis
were reported in pregnant women who delivered infants with congenital syphilis in the 1960s and 1970s.\textsuperscript{200, 201} In 1977, syphilitic lesions developed in another patient who was receiving erythromycin.\textsuperscript{202} In the 1980s, two additional failures of erythromycin treatment were reported, one in a pregnant woman whose child had congenital syphilis and another in a male patient.\textsuperscript{203, 204} Molecular analyses were later conducted to determine if genetic changes could explain such treatment failures.

Molecular evidence indicated that genetic mutations in certain strains of \textit{Treponema pallidum} conferred resistance to erythromycin. This resistance was demonstrated in a strain which was isolated from the syphilis patient who developed syphilis chancres while undergoing erythromycin treatment in 1977.\textsuperscript{202} Chromosomally mediated resistance in this strain was demonstrated first by an in vitro assay for antibiotic susceptibility and then confirmed by a molecular analysis that revealed the presence of a mutation that prevented erythromycin from binding to the bacteria.\textsuperscript{205-207} Use of penicillin continued to be the treatment of choice with few alternatives until azithromycin was brought to market.

When azithromycin was first approved in the 1990s it appeared to be a viable alternative to penicillin and erythromycin for treating syphilis. Yet just a decade later, in 2002, the San Francisco City Department of health began noting azithromycin treatment failures in syphilis patients.\textsuperscript{218-212} The first of those treatment failures occurred in eight MSM. Three patients were diagnosed with primary syphilis and treated with azithromycin. Five asymptomatic and serologically negative contacts of these syphilis patients were identified and also treated with azithromycin. Symptoms worsened in the three patients who each had received single two gram oral azithromycin doses. The five
partner contacts had received once gram oral azithromycin doses and either became serologically positive or experienced clinical disease. All patients were cleared of infection following treatment with penicillin. Molecular analyses to determine if a genetic change could explain treatment failures with azithromycin were conducted.

Gene sequencing of *Treponema pallidum* specimens from two San Francisco patients who failed to clear infection following azithromycin treatment revealed the presence of the same mutation that led to the earlier erythromycin resistance described above. This mutation was also identified in subsequent specimens obtained and analyzed from four patients from Dublin and two patients from Seattle. To test for the prevalence of this mutation an assay was developed and used to assess a convenience sample of 114 specimens obtained from patients in San Francisco, Seattle, Baltimore, and Dublin. The mutation was present in 12/55 (22%) isolates from San Francisco, 3/23 (13%) isolates from Seattle, 2/19 (11%) isolates from Baltimore, and 15/17 (88%) isolates from Dublin.

This rapid development of resistance to macrolides raises concerns. Macrolides were once promising for syphilis control but they are no longer recommended. In fact, *Treponema pallidum* with mutations conferring macrolide resistance are now present in several areas of the United States, Canada, Europe, and China. Given the possibility for resistance to azithromycin, the CDC cautions against using this antibiotic despite evidence that is has been effective in clearing early infections. While *Treponema pallidum* is a far different bacteria than Chlamydia trachomatis, the history of resistance in the former is important to understand when considering the mechanisms behind which Chlamydia trachomatis might develop resistance to macrolides. Although syphilis has
developed resistance to macrolides, gonorrhea has progressively and rapidly developed resistance to every class of drugs that were once effective.

2.6.3.2 Antibiotic resistance in gonorrhea

The history of gonorrhea treatment demonstrates that it has progressively developed resistance to drugs used to treat it, such as penicillin, tetracycline, and ciprofloxacin. In the 1930s and 1940s, sulfonamides were the primary treatment for infections with gonorrhea. Over the course of a decade, approximately 30% of strains became resistant to treatment with sulfonamides. Their use was discontinued in the 1940s and were eventually replaced by penicillin.\textsuperscript{217}

Penicillin was extremely effective at clearing gonococcal infections when first utilized. Over time however, larger doses of penicillin had to be provided to clear the infection as gonorrhea became less susceptible to the drug. It was discovered that this reduced efficacy was due to mutations in the organism that led to the bacteria producing beta lactamase, which targets and breaks down penicillin.\textsuperscript{218} With an increasing prevalence of these beta lactamase producing organisms, in the 1980s penicillin was discontinued for the treatment of gonorrhea.

During the 1970s and 1980s tetracycline was a front-line drug used for treating penicillin resistant strains. However, in just a few short years, gonorrhea became resistant to the drug and its use was discontinued as a first-line treatment in the 1980s.\textsuperscript{219} Tetracycline was subsequently replaced as a first-line treatment in favor of fluoroquinolones.

While initially incredibly effective, resistance to fluoroquinolones picked up rapidly in the late 1990s. In fact, fluoroquinolone resistant strains in California were less
than 1% prevalent in 1999 and yet became over 20% prevalent in 2003, leading to the 2007 removal of CDC’s recommendation of fluoroquinolones for gonorrhea treatment. Because of the rapid development and widespread prevalence of resistant gonorrhea, continuous monitoring and testing gonorrhea susceptibility to a range of antimicrobials is seen as necessary by the CDC.

2.6.3.2.1 The gonococcal isolate surveillance project

In order to test and monitor for the development of antibiotic resistant gonorrhea, the CDC implemented the Gonococcal Isolate Surveillance Project (GISP) in 1986 in which laboratories from select cities and regions of the United States report susceptibility of gonococcal isolates to various antibiotics. In each city, gonococcal isolates are collected from the first 25 men with urethral gonorrhea attending STI clinics each month. At regional laboratories, the susceptibility of these isolates to penicillin, tetracycline, spectinomycin, ciprofloxacin, ceftriaxone, cefixime, and azithromycin are determined by agar dilution. Minimum inhibitory concentrations (MICs) are measured, and values are interpreted according to criteria recommended by the Clinical and Laboratory Standards Institute. Through this surveillance project, recommendations for gonorrhea treatment have evolved in the last decade to help reduce the burden of resistant strains.

The only class of drugs remaining that are recommended as first-line antibiotics for gonorrhea are the cephalosporins. Susceptibility testing for gonorrhea to the cephalosporin class of antibiotics has been expanded and is currently being conducted by the GISP on ceftriaxone, cefixime, and cefpodoxime. Some of the collected isolates have exhibited a decrease in susceptibility to cephalosporins in the past, but currently none have demonstrated full resistance. Most recently, CDC removed the oral cephalosporin
cefixime from its recommended front-line treatment list as the GISP identified significantly reduced susceptibility among gonococcal isolates. This recent change adds to the long history of changing treatment recommendations to combat resistant gonorrhea.

A plethora of research in the laboratory setting, in the community and in STI clinic patients, as well as the GISP, has demonstrated gonorrhea’s significant resistance profile to the antibiotics utilized to treat infected individuals. Strains of gonorrhea have been developing resistance for years. While some strains are less susceptible to one or two treatments, others are resistant to many classes of antibiotics. Organisms like gonorrhea that are multi-drug resistant are so difficult to treat and the consequences for the patient often so severe that these strains are becoming commonly referred to as “superbugs”.

With a cadre of studies confirming the overwhelming resistance patterns exhibited by gonorrhea “superbug” strains, the CDC now only recommends treatment with 250mg ceftriaxone, an injectable cephalosporin, in combination with either a single 1g azithromycin oral dose or an oral 100mg doxycycline regimen twice a day for seven days as prophylaxis for possible chlamydial coinfection. The GISP and CDC continue to actively monitor gonorrhea susceptibility to currently available antibiotics and stand ready to adjust the treatment protocol in an effort to prevent the spread of resistant gonorrhea while new drugs are being developed to combat the infection.

An understanding of the development of resistance among syphilis and gonorrhea, common bacterial STIs, is important as it highlights the need for monitoring other organisms for the development of resistance. The historical information regarding
syphilis and gonorrhea highlights some of the mechanisms an organism may employ to become resistant. Further, this overview illustrates how rapidly resistance can spread. Considering that STIs, particularly gonorrhea and chlamydia, are on the rise, understanding the implications of resistance is paramount to developing appropriate therapy guidelines. In light of what has occurred with syphilis and gonorrhea, and because treatment failures can lead to dangerous sequelae and facilitate transmission to others, understanding the potential for antibiotic resistance in *Chlamydia trachomatis* is critical to the field of epidemiology.

2.6.4 Antibiotic resistance monitoring among chlamydia

At this time, there is no known laboratory in the world that is conducting active monitoring for the development of antibiotic resistance among chlamydia strains (Robert Kirkcaldy MD, MPH, e-mail communication, June 2012). There are numerous articles in the literature across various scientific specialties, including microbiology, biochemistry, genetics, medicine and epidemiology that could be interpreted as evidence for and against the existence of resistance among *Chlamydia trachomatis*. Despite literature that addresses different components of chlamydia resistance and biological pressures for the bacteria to evolve, there is little consensus among the academic community as to whether resistance is truly a developing problem. However, there is increasing evidence that treatment is becoming less effective. Therefore, it is imperative to have an understanding of whether this phenomenon may be due to bacterial persistence and/or antibiotic resistance.
2.6.4.1 Biological pressure for chlamydia to evolve

An understanding of the selection pressures that induce *Chlamydia trachomatis* to evolve and develop characteristics that enable the organism to evade antibiotics have arisen from studies of concomitant infections. About a quarter (estimates range from 15% to 50%) of gonorrhea cases are co-infected with chlamydia. Concurrent syphilis and chlamydia infections can occur. These co-infections have historically led to therapy complications. A prime example is β-lactam antibiotics, which were historically the recommended drugs for both syphilis and gonorrhea. Treatment of chlamydial infections with these antibiotics may induce morphologic changes in chlamydia that promote persistence. This persistence may exacerbate disease in the genital tract as well as lead to treatment failure of accepted effective therapies increasing the risk for long-term complications.

2.6.5 Accumulating data suggests chlamydial persistence is on the rise

The primary antibiotics utilized in treating chlamydia, tetracyclines and azithromycin, are both highly effective in the treatment of uncomplicated chlamydial infections. Despite historical success in clearing infection, accumulating data suggest that a break in the normal chlamydial developmental cycle can result in persistent, long-term infection that is generally refractory to antibiotic therapy. The increasing frequency of this phenomenon is supported by epidemiologic evidence as it is well documented that there are increasing frequencies of recurrent and persistent infections. Without further genetic testing of chlamydia strains, it is impossible to determine whether recurrent infections are truly new (i.e. re-infections) versus persistent infections or resistant strains.
Stable antibiotic resistance in human chlamydial isolates is nearly non-existent despite significant selective pressures. Further, the lack of chlamydial antimicrobial resistance in clinical settings suggests that *Chlamydia trachomatis* is resistant to alterations of its genetic structure. In contrast, the development of more frequent persistent forms of chlamydia may be an efficient adaptation of the bacteria to evade target antibiotics.

While failure of chlamydia to respond to antibiotic treatment can follow establishment of chlamydial persistence *in vitro*, it may be challenging *in vivo* to differentiate persistence from potential cases of antibiotic resistance. While it is possible that some treatment failures are resistant to prescribed therapy, it is also possible that such failures are a function of poor therapeutic control of morphologically altered, persistent chlamydia in patients.

While uncomplicated infections are quite responsive to antibiotics, isolated cases of unresolved genital, ocular and respiratory infections that fail to respond to antibiotic treatment are documented. Although uncommon, there have been isolated incidences of resistant *Chlamydia* obtained from infected individuals, many of whom failed to respond to treatment.

### 2.6.6 Reports of antibiotic resistant chlamydial isolates

There have been several recent reports describing the isolation of antibiotic resistant chlamydia from patients. About 70% of the resistant isolates were associated with clinical treatment failure. However, all of the isolates screened displayed characteristics of heterotypic resistance, a form of phenotypic resistance in which a small
proportion of the infecting microbe is capable of expressing resistance to treatment at any one time. In each case of clinical resistance reported, a small portion of the population (1% to 10%) expressed true resistance. In one report isolates from patients in Russia contained a small subpopulation with a mutation to the macrolide target site, the 23S rRNA subunit gene, theoretically preventing the growth inhibitory binding of the macrolide and bacteria. The subpopulation containing the mutated genes had very low viability however. It is interesting to note that much of the resistant subpopulations in these reports displayed altered morphology, suggesting persistent forms were also present in these treatment failures. Many of the isolates could not survive long-term exposure to antibiotics in a laboratory setting, or lost their resistance upon long-term passage through antibiotic containing cell cultures. In some cases resistance was observed when a large inoculum was infected on to cells, but a smaller inoculum was not resistant under the same conditions. These characteristics suggest persistence is responsible for the remaining small populations of chlamydia after antibiotic treatment, and this may be an adaptive behavior that influences the survival of bacteria within communities rather than stable genetic resistance mechanisms employed by singular cells. Complicating the assessment of resistance is that accurate and consistent testing for resistance has proved difficult with chlamydia.

2.6.6.1 Difficulties in adequately measuring and quantifying chlamydial antimicrobial resistance

Assays to assess chlamydia susceptibility involve isolating and expanding clinical isolates and then culturing chlamydial progeny in cells with media containing different dilutions of antibiotics. At this time there is no universal testing methodology accepted
for these assays, and the techniques themselves are considered extremely challenging in a technical sense and are very time-consuming.\(^{127,249}\) For example, many different cell lines and techniques are used in different diagnostic laboratories, which presents significant challenges in monitoring and evaluating potential emergence of antibiotic resistance. These issues, combined with the fact that no laboratory is actively conducting surveillance for chlamydia resistance complicates its quantification. Further, potential surveillance is complicated by a number of factors. Primarily, differing methodologies for susceptibility analyses are employed which can impact the reproducibility of the assays and interpretation of findings.

Susceptibility analysis techniques vary widely and a number of factors can complicate the comparability of studies. The outcome of an antibiotic susceptibility analysis can be influenced by the cell line, host cell factors, multiplicity of the chlamydial infection, developmental stage of chlamydia when the antibiotic is added to the infected cells, and presence or absence of cycloheximide (used to slow growth of the host cells).\(^{249}\) Additional attributes of chlamydial growth as well as cellular uptake of antibiotics by host cells can vary substantially in different models.\(^{250-254}\) For example, different cell lines permit variable growth of chlamydia strains when exposed to the same concentration of azithromycin. This issue is exemplified in a report of azithromycin resistant isolates from patients with recurrent infections that were characterized using a cell line permissive to chlamydial growth in the presence of inhibitory concentrations of azithromycin.\(^{255}\) In the report, the minimal bactericidal concentration of azithromycin was lower utilizing polarized cells as opposed to non-polarized cells which were frequently utilized for such analyses (0.125 and 0.5 mg/L, respectively). Polarized cells
also were able to take in more azithromycin over a 24 hour period versus non-polarized cells. The results indicate that the eradication of chlamydial infections may be difficult to prove by antigen detection methods and that results of studies utilizing different methodologies may not be comparable, potentially leading to erroneous interpretations of findings. This example is just one of the interesting challenges that arise when minute differences in methodological approaches are employed which further complicate the interpretation of in vitro resistance investigations and subsequent clinical relevance.

Other difficulties that have arisen preventing consensus on the presence of resistance among Chlamydia trachomatis include difficulty of culturing clinical isolates, slow growth rates of isolates and a high potential for cytotoxicity or persistence. Isolate strains also can be present in very low numbers relative to the reference strains that are used as controls susceptibility assays. Further, although specific percentages vary, there is a significant fraction of NAAT-positive cases that are not detected by culture. Culture recovery rate is especially low when attempted from rectal samples and is only modestly better from urine, cervical, oropharyngeal and other specimen sites. Culture based methods have also become a less attractive tool because of sensitivity issues, as well as the time and technical expertise required for their completion. This means many laboratories are not positioned to perform routine culture and thus are ill-equipped to conduct routine antibiotic susceptibility screening of chlamydial isolates. This may hinder timely and accurate assessment of antibiotic susceptibility of clinical chlamydial isolates, even if resistant isolates are actually present in patients. Nevertheless, laboratory controlled and genetic studies of resistant chlamydia isolates and persistent
forms of the bacteria have been conducted. While there is compelling evidence that treatment is less effective, the literature has yet to be critically evaluated in a comprehensive fashion to inform further research needs and the implications for the field of epidemiology.

2.6.7 Comprehensive research and systematic evaluation of the literature regarding chlamydial resistance/persistence and implications for epidemiology and future research needs is warranted

To date, it remains unclear whether treatments frequently utilized to clear chlamydia infections are as effective as they once were. The increased incidence and prevalence of infections annually raises the question of whether individuals are truly being cleared of infection after taking a course of antibiotics. With the advent of novel approaches to treating sexual partners of index cases without medical evaluation by administering antibiotics presumptively without follow-up to ensure treatment was conducted, comprehensive research into the possibility of antibiotic resistant chlamydia is warranted. This is especially true given the increased proportion of resistant strains of other bacteria once susceptible to antimicrobials, particularly other STIs like syphilis and gonorrhea.

Evidence for the existence of resistance or reduced susceptibility to antibiotics among chlamydia bacteria may emerge from an in-depth look at case studies, epidemiologic data, and information obtained from laboratory investigations. There are numerous articles on chlamydia isolate testing conducted in the laboratory setting throughout the literature, but these studies have not been looked at in tandem or analyzed in a systematic fashion. This information, coupled with epidemiological evidence in the
literature should be analyzed in a more comprehensive fashion. To understand the implications for the field of epidemiology, a critical evaluation of what is known about the presence of antibiotic resistant chlamydia, increasing incidence of persistent infections and decreased efficacy of standard therapies is warranted to identify gaps in the literature and highlight future research needs.

2.7 Azithromycin and the risk of cardiovascular death

The standard treatment regimen for chlamydia infection is a one gram single dose of azithromycin that is administered orally. A recent development in the literature pertains to the potential cardiovascular consequences of azithromycin use. Two independent analyses have demonstrated that the risk of cardiovascular death is increased while using azithromycin.

The first study conducted by Ray et al in 2012 analyzed individuals who had taken azithromycin, a comparable antibiotic or no antibiotic over ten day periods within a Tennessee Medicaid Cohort. Each individual in the various exposure groups were propensity score matched to another individual in a separate group on 153 characteristics (to balance confounders among exposure groups). The risk of death was compared for those taking a course of azithromycin relative to individuals taking either no antibiotics or a comparable antibiotic. Over the first five days after azithromycin therapy was prescribed compared to those taking no antibiotics, the hazard ratio for cardiovascular death was 2.88 95% CI (1.79, 4.63). Over the first five days after azithromycin therapy was prescribed, compared to those prescribed amoxicillin, the hazard ratio for cardiovascular death was 2.49, 95% CI (1.38, 4.50). A subset analysis also revealed that
those with one or more cardiac risk factors (e.g., hypertension, hyperlipidemia, etc.) were at even greater risk.

It is important to note that this cohort may have been more ill on average relative to a broader population given it consisted of poorer Medicaid participants in the southern United States. Further, there were only several hundred episodes across millions of prescriptions. Despite the limitations of the cohort and the rarity of the outcome overall, these findings suggest that cardiovascular risk of death is increased with azithromycin use.

Noting the limitations of the Ray et al Tennessee Medicaid Cohort study, Svanstrom et al recently conducted their own analysis of the risk of cardiovascular death associated with azithromycin. In this study, Svanstrom et al utilized prescription information over a 13-year period on a Danish cohort of adults aged 18-64 which is much more representative of the general population relative to the Tennessee Medicaid cohort. Svanstrom et al compared the risk of cardiovascular death of those prescribed azithromycin relative to those using no antibiotics and those prescribed penicillin V. Like Ray et al, individuals in the various exposure groups were propensity matched to balance confounders. Unlike the Ray et al study, no significant association was found with cardiovascular death comparing azithromycin to penicillin V (RR 0.93, 95% CI 0.56, 1.55). There was however a significant increase in risk of cardiovascular death comparing azithromycin to no antibiotic use (RR 2.85, 95% CI 1.14, 7.24). It is important to note that this increased risk was driven primarily by those over age 45. Those 18-44 did not have an increase in risk as the RR was 1.12 (95% CI 0.76, 1.64) whereas those 45-64 saw a moderate increase in risk as the RR was 4.87 (95% CI 1.60, 8.90). However,
a subset analysis confirmed that those with multiple cardiac risk factors were at the highest risk of cardiovascular death, including those under age 45. These findings substantiate the sub analysis findings from Ray et al.

Given the findings from Ray et al and Svanstrom et al, future research into cardiotoxic potential of azithromycin is warranted. Further, the risk of a cardiovascular death, while rare (approximately 10-20 additional events per 1,000,000 prescriptions), should give providers pause and consider assessing cardiovascular risk factors prior to administering azithromycin therapy.

The Federal Food and Drug Administration (FDA) recently warned the public that azithromycin can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing a fatal heart rhythm after exposure to azithromycin include those with known risk cardiac factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, arrhythmias and other conditions. Assessing patients for these risk factors to prevent potential adverse cardiac events associated with azithromycin treatment is thus recommended. By extension, awareness of cardiac risk factors among those most at risk for chlamydia infection, namely those under age 25, may be an important consideration for future treatment protocols and is of specific concern given the option of utilizing PDPT. Under PDPT, patients can bring a prescription for azithromycin to any of their sexual partners. Those partners will not be assessed for any cardiac risk factors, contraindications or allergies. Thus, research into better understanding whether patients know their partner’s cardiac risk factors is warranted. Further, if azithromycin is to remain the front-line treatment for
chlamydia despite its potentially cardio-toxic effects, ensuring it is still effective in clearing infections is critical.

Chapter 3. Study Methods

3.1 Rationale for research

In 2011, there were 1,412,791 cases of chlamydia reported to CDC, and given the largely asymptomatic nature of the infection the estimated true number of cases is nearly three million. In NYS, 102,460 cases were reported in 2011. To stop the chain of infection, reaching all members of a sexual network through partner notification strategies and treating them for confirmed or potential infection is paramount. Thus PDPT was legalized in NYS in 2008 to offer patients and providers an additional approach to notifying and treating partners of infected individuals. Gonorrhea has been studied as a candidate for PDPT, and is often co-existent with chlamydia, thus presumptive treatment of chlamydia is often given to sexual partners diagnosed with gonorrhea. In NYS, PDPT is only legal for chlamydia treatment, thus some individuals who do not seek a medical evaluation after receiving a prescription under PDPT could go untreated for a possible gonorrhea infection.

Research is warranted to quantify the likelihood of partners who will seek medical evaluation if notified of potential chlamydia infection under PDPT. Little is known about how patients and partners will accept and react to this approach in NYS. Further, studies have suggested booklet referral may be equally as effective as PDPT in notifying partners
and preventing re-infection of the index patient. Despite these findings, booklet referral has been studied in a limited fashion in the United States and no studies on this approach have been conducted in NYS. As the numbers of chlamydial infections continue to rise, coupled with troubling re-infection rates among index patients, the potential for chlamydia to be less susceptible to treatment, if not antibiotic resistant, should be examined in greater detail. As chlamydia is the most frequently reported bacterial sexually transmitted infection, development of resistant chlamydia strains could become a chief public health concern in future years.

The research contributes to the knowledge base of two novel partner notification approaches in NYS; PDPT and enhanced partner referral with informational cards. As the burden of chlamydia infection increases annually, the proposed research will help assess whether chlamydia is less susceptible to antimicrobials routinely used in its treatment. Further, it provides insight into STI patients’ and sexual partners’ attitudes and perceptions toward PDPT as well as their willingness to engage in this partner notification practice in NYS. The research increases our understanding of college students’ willingness to notify sexual partners of infection with the assistance of information booklets/cards. Finally, the research helps us better understand college student’s knowledge of their sexual partners’ cardiac risk factors. This dissertation addresses the following research questions:

3.2 Research questions, specific aims and hypotheses

3.2.1 Research question one
Research question 1: Is *Chlamydia trachomatis* exhibiting resistance to antibiotics utilized in its treatment?

Specific Aim 1-1: Identify and critically evaluate in vivo and vitro research that investigates resistance, persistence and/or reduced susceptibility to antibiotic utilized in chlamydia treatment.

Hypothesis 1-1: Antibiotic resistance is a growing problem for chlamydia treatment.

Specific Aim 1-2: Identify and critically evaluate epidemiological research that suggests resistance, persistence and/or reduced susceptibility of chlamydia to treatment is increasing.

Hypothesis 1-2: Epidemiological literature will suggest incidence of difficult to treat chlamydia is increasing.

3.2.2 Research question two
Research question 2: Are college students willing to notify their sexual partners of potential infection with the use of informational booklets/cards?

Specific Aim 2-1: Document the willingness of college students to use informational cards to educate sexual partners regarding potential chlamydia infection
Hypothesis 2-1: The majority of college students (>50%) will be willing to utilize informational card to educate sexual partners of potential infection.

Specific Aim 2-2: Document the approach college students would use to notify sexual partners of infection with informational cards.

Hypothesis 2-2: The majority of college students (>50%) will prefer to deliver the informational card in person to their partner(s).

3.2.3 Research question three

Research Question 3: Are STI patients willing to distribute antibiotic prescriptions to all of their sexual partners?

Specific Aim 3-1: Document the willingness of patients to distribute antibiotic prescriptions to sexual partners under PDPT.

Hypothesis 3-1: The majority of patients (>50%) will be willing to deliver prescriptions to all partners.

Specific Aim 3-2: Document the willingness of sexual partners to receive antibiotic prescriptions under PDPT.

Hypothesis 3-2: The majority of partners (>50%) will be willing to receive prescriptions from their partners.

Specific Aim 3-3: Document the reported methods that participants would use to deliver antibiotic prescriptions to their partners.
Hypothesis 3-3: The majority of patients (>50%) will prefer to deliver prescriptions in person.

3.2.4 Research question four

Research Question 4: Do college students know their main sexual partners’ history of cardiac risk factors?

Specific Aim 4-1: Document college students’ knowledge of sexual partner cardiac risk factors.

Hypothesis 4-1: The majority of respondents (>50%) will not know whether their sexual partner has one or more cardiac risk factors.

3.3 Study methodology

3.3.1 Chlamydia antibiotic resistance: a critical review of the literature

The purpose of this study is to critically evaluate the literature for evidence of *Chlamydia trachomatis* exhibiting reduced susceptibility, resistance and/or persistence against antibiotics, as well as to identify gaps in the literature to determine future research needs. Searches of MEDLINE and PubMed electronic databases will be conducted for articles written up through July 1, 2013. Articles will be limited to those written in the English language. Search words/terms to be utilized in searching for potential articles to be reviewed are as follows:
To capture the organism in search results “chlamydia”, “Chlamydia trachomatis”, “C. trachomatis”, “chlamydial infection” and “non-gonococcal urethritis” will be used. To capture resistance/persistence the terms “resistance”, “antibiotic resistance”, “bacterial resistance”, “antimicrobial resistance”, “drug resistant”, “resistant”, “resistant strains”, “persistent infection”, and “persistence” will be utilized. In order to obtain search results containing treatment issues and susceptibility analyses, “azithromycin”, “doxycycline”, “ofloxacin”, “erythromycin”, “treatment”, “treatment failure”, “susceptibility”, “minimum inhibitory concentration (MIC)” and “minimum bactericidal concentration (MBC)”. To capture epidemiological evidence, search terms such as “recurrent”, “re-infection”, “persistent”, “incidence”, “prevalence”, “cases”, and “epidemiology” will be investigated. Terms from each category will be entered in combination with terms from other categories in order to ensure all possible searches are completed.

The number of papers found on the topic will be recorded. Titles and abstracts will be reviewed for appropriateness. Those papers with titles clearly not applicable to this review will not be examined further. Titles of the remainder will be kept on a master list, and duplicates will be removed. Abstracts of the remainder on the list will be reviewed and then selected for further reading and review if they meet one of the following inclusion criteria: research literature that covers 1) antibiotic resistance/susceptibility testing of chlamydia strains, 2) comparisons of effectiveness of multiple anti chlamydia therapies, 3) in vivo or in vitro resistant/persistent strains which survive antimicrobial treatment, 4) case studies of treatment failures or chlamydia infections reported as not cleared through documented routine therapies, 5) documented
increases in prevalence/incidence over time, 6) Studies examining persistent/recurrent infections, 7) studies examining treatment outcomes of chlamydia patients and partners and 8) *Chlamydia* genetics with special focus on difficult to treat strains. If a criterion is not met because not enough information was provided, the abstract will be set aside for further evaluation of the paper to determine appropriateness of inclusion in the review (e.g. studies of chlamydia genetics; potentially relevant if examining a strain with reduced susceptibility).

Final counts of papers found, excluded, reviewed, evaluated and ultimately included in the critical review will be reported. Relevant papers demonstrating resistance and/or reduced susceptibility of *Chlamydia trachomatis* to the various antimicrobials utilized in treating human infections, as well as persistent/recurrent human infections, case studies demonstrating infection not cleared through documented therapies, epidemiological studies showing increased infection over time, and studies conducted in the laboratory in vitro documenting MIC or MBC maybe included as appropriate. A descriptive flow chart figure of the methodology will be created to document the process.

Included articles and the relevant information utilized in the review will be discussed in relation to evidence for and against the development of resistance versus persistence with specific focus on its implications for the field of epidemiology, transmission of the infection and necessary future research. To supplement the literature review, interviews with experts in the field may be conducted.

### 3.3.2 Partner notification via patient delivered partner therapy

The purpose of this study is to survey STI patients and partners to assess their preference in how sexual partners are notified of potential exposure to STI, their
willingness to distribute antibiotic prescriptions, as well as to gauge their perception of privacy associated with PDPT and the pharmacy environment. New York State consists of 62 counties, five of which are served by the NYC Department of Health and Mental Hygiene. Of the 57 counties outside NYC, 19 currently allocate resources to employ DIS to conduct partner notification. The remainder refer STI cases to the NYSDOH Regional Epidemiology Program. Disease Intervention Specialists in the Capital District of the NYSDOH Regional Epidemiology Program and DIS from Dutchess County, a moderately high STI incidence county, will administer the survey. Following a case interview with DIS, potential participants will be asked if they are interested in participating in a brief (10 minute) survey regarding partner notification and treatment services. Those interested will be given informed consent, and the questionnaire will be administered.

The survey covers perspectives on PDPT versus traditional DIS partner notification, contains questions regarding the likelihood of and manner in which one would deliver an antibiotic prescription to a partner, willingness to educate partners on STI and perspectives of privacy in pharmacies. The survey also contains questions regarding if the patient were actually given a prescription to deliver, including likelihood of giving the prescription to their partner, how long they think it would take to give the prescription, the manner in which they would deliver it, as well as their willingness to distribute STI educational materials such as pamphlets and brochures. Among other questions regarding PDPT, we will also inquire about privacy perceptions in the pharmacy environment, including if respondents believe they could talk with their
pharmacists without being overheard by customers and staff and whether they feel comfortable discussing STI with a pharmacist.

The survey will have two near identical versions, one for index patients, and one for partners. Most of the survey is the same, but some questions contain slightly modified language for index patients versus partners. An example of the variation between an index case and a partner question is as follows; if we ask an index patient “how would you most prefer your partner to be notified about a potential exposure [to STI]?” the question for the partner is altered to ask “how would you most like to be notified about a potential exposure to STI?”.

Specifically, to measure index patients’ preference of partner notification methods, we ask “which of the following ways would you most prefer your partner to be notified about their potential exposure to STIs?” with responses of “partner notification where someone like me contacts your recent partner to tell them of their potential exposure,” and “contacting your partner yourself and telling them”. Those who respond with the latter will then be asked “how would you most prefer your partner to receive services for exposure to an STI?,” with responses of “have you tell your partner to go to a clinic or their own doctor to be examined and treated,” and “have your doctor write a prescription for you to give to your partner. Your partner would not have to go to a doctor to receive treatment”. Again, these questions are altered to directly ask partners how they would prefer to be notified and receive treatment. A copy of the survey for both the index patient and the partner can be found in the appendix (appendix I and appendix II).
3.3.2.1 Statistical analysis
The collected survey data will be entered into Epi-Info v.3.3.2. Data will then be imported into SAS (v.9.3, SAS institute, Cary, N.C.) for analyses. Descriptive statistics including frequency counts and proportions will be computed to determine the nature of respondents’ sexual partnerships and to learn about partner notification method preferences, distribution of antibiotic prescriptions and pharmacy privacy perceptions. To further interpret the data, cross-tabulations of demographic characteristics and survey responses will be conducted. Statistical associations will be determined using Chi-Square or Fisher’s exact test, where appropriate.

3.3.2.2 Institutional Review Board approval
The study was approved by the author’s university and the New York State Department of Health Institutional Review Boards. Participants will receive a $10 grocery card as a token for their time.

3.3.3 Partner education and notification via booklet enhanced partner referral among University at Albany students
This purpose of this study is to survey University at Albany students to determine the feasibility and utility of using booklet referral to conduct partner notification for chlamydia infection among college students. A convenience sample of students attending the University at Albany health center will be recruited. To be included in the study potential participants must be at least 18 years old, speak and understand English, and be able to provide informed consent. Recruitment will be conducted in the waiting area of the health center after they check in with health center staff for their appointment.
The survey will cover perspectives on utilizing booklet referral for chlamydia partner notification. Each booklet contains perforated cards containing the following information:

- A statement informing the person that a sexual partner has tested positive for chlamydia.
- A statement instructing the person to seek testing and medical care
- Information about symptoms of chlamydia and potential problems that can arise if it is not treated
- Contact information for a local sexually transmitted diseases clinic.

The survey will contain images of these cards. The survey will include questions to ascertain the manner in which one would deliver a card to a partner, whether respondents would deliver cards to their main sexual partner, whether they would deliver cards to all sexual partners, as well as questions to gauge respondents’ preferred method of partner notification. The survey also contains questions assuming the respondents were given a card by a partner, including willingness to visit a health care provider for medical evaluation.

The survey will have two near identical versions, one for males and one for females. Most of the survey is the same, but some questions contain slightly modified language for males versus females. An example of the variation between a survey question is as follows; if we ask a female “Do you take a birth control pill?”, the survey for the male will not contain this question. Copies of both surveys are included in the appendix.
3.3.3.1 Statistical analysis

The collected survey data will be entered into Epi-Info v.3.3.2. Data will then be imported into SAS (v.9.3, SAS institute, Cary, N.C.) for analyses. Descriptive statistics including frequency counts and proportions will be computed to determine the distribution of sexual and cardiac risk factors and to learn about respondents’ perspectives regarding informational cards, and knowledge of sexual partner cardiac health. To further interpret the data, cross-tabulations of demographic characteristics, sexual risk factors, and cardiac risk factors with survey responses will be conducted. Statistical associations will be determined using Chi-Square or Fisher’s exact test, where appropriate. To determine covariates associated with willingness to utilize informational cards to inform all partners of a potential infection, unconditional logistic regression analyses will be utilized.

3.3.3.2 Institutional Review Board approval

The study will be submitted for approval by the author’s university Institutional Review Board. Participants will receive a small squeeze ball toy as a token for their time.

3.3.4 Knowledge of sexual partner cardiac risk factors among University at Albany students.

The methods for this study are identical to section 3.3.2, partner education and notification via booklet enhanced partner referral among University at Albany students. In addition to PDPT and booklet referral questions, the survey instruments will contain questions to assess the presence of cardiac risk factors among respondents, such as hypertension, hyperlipidemia and diabetes. The survey will also contain questions regarding exercise habits and tobacco use among respondents. Finally, the survey will
inquire about respondent’s knowledge of their main (or most recent) sexual partner’s cardiac risk factors. Questions for this portion of the survey can be found in the appendix.

Chapter 4. Results

The results of research questions 1-3 are presented as three papers. Paper 1, entitled “Antibiotic Resistance Versus Persistence in Sexually Transmitted Chlamydia trachomatis: A Systematic Review of the Literature and Assessment of the Evidence” addresses research question 1 and aims 1-1 and 1-2. This analysis found that the state of the literature suggests there is very low evidence in support of antibiotic resistance while there is moderate evidence for persistence as a cause of suspected treatment failures. It remains unclear what proportion of repeat positive tests are attributable to reinfection versus genuine treatment failures.

Paper 2, entitled “Patient-Delivered Partner Therapy in New York State, Perspectives of Chlamydia Patients and Partners” addresses research question 2 and aims 2-1 and 2-2. This analysis found that chlamydia patients are willing to distribute prescriptions and educational materials to most partners in a timely manner. Most sexual partners would seek medical evaluation if they received a prescription under PDPT. However, patients and partners are uncomfortable discussing STD in the pharmacy environment.
Paper 3, entitled “Utilizing Informational Card-Enhanced Partner Referral For Partner Notification of Chlamydia: Perspectives Of Students Attending A New York University” addressed research question 3 and specific aims 3-1 to 3-3. The results from this analysis show students are willing to deliver informational cards to most partners but those who were unwilling preferred to talk directly to their partners. Given the limited available data and the favorable attitudes expressed toward this approach by university students, further study into this partner notification method is warranted to inform future disease control program recommendations among this at-risk population.


Abstract

Background: The increasing number of recurrent Chlamydia trachomatis infections has called into question the efficacy of recommended first-line antibiotics. This review synthesizes evidence regarding the etiology of recurrent chlamydia infections, which may be due to reinfection, or treatment failure due to either persistent infection or antibiotic resistance.

Methods: Using keywords to identify relevant Medline citations, we systematically reviewed the literature for original research published January 1, 1980 to December 31, 2013 on sexually transmitted C. trachomatis covering susceptibility testing, comparisons of antimicrobial therapies, case studies of treatment failures with persistent/recurrent
infections, and mutations conferring resistance. We rated the quality of evidence for resistant and persistent chlamydia infections using the GRADE criteria.

**Results:** Of the 2,475 studies identified, 97 were included for review. The proportion of repeat positive tests within three months among index patients in these published reports increased over time. Five instances of suspected treatment failures demonstrating decreased antimicrobial susceptibility were reported (23 doxycycline studies, 22 azithromycin studies), one of which was associated with mutations. Mutations conferring resistance are rare, but persistence characteristics were reported in 17 studies.

**Conclusions:** It remains unclear what proportion of repeat positive tests are attributable to reinfection versus genuine treatment failure. We conclude there is limited evidence to support *C. trachomatis* antimicrobial resistance, whereas there is moderate evidence to support persistence causing genuine treatment failures. Future study is needed to understand persistence *in vivo*, to evaluate whether latent persistent forms can reactivate to infectivity, and to assess the plausibility of transmitting persistent variants to sexual partners.

**Key words:** Resistance, persistence, antibiotics, antimicrobials, chlamydia, recurrent, mutations, minimum inhibitory concentration
Introduction

*Chlamydia trachomatis* has a unique intracellular life cycle which has been well described *in vitro*, but less so *in vivo*. The organism is an obligate intracellular bacterium and the infection begins when infectious, metabolically inactive elementary bodies attach to and enter host cells via an inclusion vescicle. Once internalized, the organism differentiates into a metabolically active reticulate body that divides by binary fission. After 8 to 12 rounds of replication reticulate bodies begin to differentiate to progeny elementary bodies which exit the host cell via cytolysis to the extracellular space and a new cycle begins. In total *C. trachomatis* has 15 defined serovars responsible for three clinical conditions: trachoma, genital chlamydia and lymphogranuloma venereum. Serovars D-K cause genital chlamydia. While few evolutionary genetic changes have been documented, a careful inspection of the life cycle is warranted given the recent emergence of recurrent infections.

Recurrent infections among index patients arise from one of three scenarios: reinfection, treatment failure due to a persistent infection or treatment failure due to antibiotic resistance. While reinfection is straightforward, the distinction between persistence and resistance is important to clarify.

Bacterial *persistence* is the ability of bacteria to survive prolonged exposure to antibiotics, a characteristic not attributable to innate resistance, but rather to the ability of a subpopulation of the pathogen to persist in a morphologically altered, latent or slow-growing state. Altered morphologies can prevent antibiotic uptake and a lack of metabolic activity may inhibit drug action. If altered forms of the bacteria are able to enter a “dormant” state during treatment and revert to the “normal” state post-treatment,
the infection process could resume. In contrast to persistence, resistance is an evolutionary change in the bacteria.\textsuperscript{264} The development of resistance to an antibiotic can occur spontaneously, for example, through a genetic mutation or a lateral gene transfer with another bacterium, conferring the ability to evade an antibiotic.

Clinically, it is unclear whether the phenomenon of repeat positive tests after treatment is attributable to resistant or persistent infections. Differentiating between treatment failures and reinfections is difficult as it involves complex and expensive methodologies. As such, most repeat positive tests are simply retreated empirically. Despite this challenge, some early investigations noted tetracycline-resistant subpopulations of infection among suspected treatment failures.\textsuperscript{248} This so-called heterotypic or phenotypic resistance has contributed to evidence suggesting that \textit{C. trachomatis} may persist in an altered subclinical form post-treatment following unresolved infections.\textsuperscript{242} This review summarizes the available evidence from epidemiological literature, laboratory studies and genetic investigations to assess chlamydial persistence and evidence for antimicrobial resistance.

\textbf{Methods}

\textit{Literature search}

The review was conducted in accordance with PRISMA guidelines\textsuperscript{265} in four stages (identification, screening, eligibility assessment, and inclusion). Searches of Medline electronic databases were conducted for English language articles published from January 1, 1980 through December 31, 2013. Multiple search terms were utilized to identify relevant research. Four groups of search terms were employed: (1) organism-related, including “chlamydia,” “\textit{Chlamydia trachomatis},” “\textit{C. trachomatis},” “chlamydial
infection” and “non-gonococcal urethritis”; (2) resistance- or persistence-related, including “resistance,” “antibiotic resistance,” “bacterial resistance,” “antimicrobial resistance,” “drug resistant,” “resistant,” “mutations,” “gene transfer,” “resistant strains,” “persistent infection,” and “persistence”; (3) treatment-related, including “azithromycin,” “doxycycline,” “ofloxacin,” “erythromycin,” “treatment,” “treatment failure,” “susceptibility,” and “minimum inhibitory concentration (MIC)”); and (4) epidemiological evidence, including “recurrent,” “reinfection,” “persistent,” “incidence,” “prevalence,” “cases,” and “epidemiology.” Search terms were drawn from the four categories to ensure all relevant literature was identified.

Inclusion criteria

Abstracts were reviewed and selected for further reading if they included original research on C. trachomatis and potentially met one of the following inclusion criteria: 1) antibiotic resistance/susceptibility testing of strains; 2) comparisons of anti-chlamydia therapies; 3) resistant/persistent strains; 4) case studies of suspected treatment failures; 5) documented increases in prevalence/incidence over time; 6) repeat positive tests; 7) treatment outcomes of infected patients/and or partners with recommended antimicrobials38; or 8) mutations conferring resistance. If the abstract was unclear, the full paper was evaluated to determine appropriateness for inclusion in the review.

Data extraction

We extracted the following data from included studies: publication reference, study period, incidence/prevalence data, the proportion of repeat positive C. trachomatis tests reported in a patient sample, serovars of C. trachomatis tested, reported MICs,
reported mutations, and presence of morphologically- or metabolically-altered subpopulations of *C. trachomatis*.

**Rating the evidence**

We used the GRADE quality rating system as a guide to evaluate the evidence base. We considered treatment failures, elevated MICs, genetic mutations, and mutations that are viable or increase competitive fitness to be evidence of resistance. For persistence, we considered as evidence the following: treatment failures, elevated MICs, morphological or metabolic alterations, and the reactivation of persistent to infectious forms.

**Results**

**Literature identification**

Overall, 2,475 abstracts were reviewed and 338 full-text studies were evaluated; 97 met the inclusion criteria (Figure 1). Reviewed articles included 49 (50.5%) laboratory investigations, 39 epidemiology studies (40.2%) and 9 comprising several categories (9.3%). The 39 epidemiology studies included 14 cohort studies (35.9%), 13 cross-sectional studies (33.3%), 11 randomized trials (28.2%) and one case study (2.6%). Of the 49 laboratory investigations, 25 were *in vitro* susceptibility analyses (51.0%), 9 were genetic studies (18.4%), 8 were multi-component investigations (16.3%) and 7 were studies of biochemistry, immunology or biomarkers (14.3%).

**Epidemiology studies**

The increase in *C. trachomatis* globally was documented in 18 studies. Prevalence estimates increased in China, the United States, Australia, and Europe in the last 15 years, and public health surveillance data support these observations. In one
seminal study, Fine, et al., analyzed 520,512 chlamydia tests from women aged 15 to 24 years who were screened in 125 family planning clinics in the United States. They reported a significant 5% annual increase in prevalence of *C. trachomatis* infection from 1997 to 2004 even after adjusting for individual risk factors, laboratory test characteristics and variability among the clinics (odds ratio 1.05, 95% confidence interval (CI): 1.04, 1.06).

**Repeat positive tests**

It is difficult to determine a genuine treatment failure versus a reinfection. Making this determination requires having a confirmed positive test, monitoring treatment adherence, following the patient to ensure no further sexual activity, retesting, etc. It is not practical outside of a well-defined study protocol. Thus, an imperfect proxy for treatment failures, repeat positive tests, was utilized. In 28 publications, 32 investigations reported data on repeat positive tests within one year of a prior diagnosis (Figure 2). Of these, 15 (46.8%) reported 3% to 10% of participants retested positive. Eleven investigations (34.4%) documented 10% to less than 20% of patients retesting positive. The remaining six investigations reported positive repeat tests in over 20% of those treated; four (80.0%) of these six studies reported that over 30% of participants retested positive.

To assess possible treatment failures and narrow the window of opportunity for a reinfection, 21 investigations were identified containing data on repeat positive tests within 12 weeks (Figure 3). Of these, 14 (66.7%) reported repeat positive tests in 4% to 10% of participants.
and five studies (23.8%) reported 10% to less than 20% of participants retested positive. Two investigations reported over 20% of participants retested positive. All seven studies reporting repeat positive tests among at least 10% of the participants were published after the year 2000. As displayed in Figure 3, the recurrence proportions in recent studies appear to differ substantively from the pre-2000 studies suggesting that repeat positive tests are indeed becoming more common.

**Resistance – in vitro susceptibilities**

In vitro susceptibility data (MIC ranges) for doxycycline was reported in 23 studies and for azithromycin in 22 included studies (Table 1). For doxycycline (Figure 4), no appreciable rise was observed over time; only two studies reported MICs exceeding 2.0 mg/L. Somani, et al., isolated azithromycin and ofloxacin-resistant strains from three patients in the United States. The MIC exceeded 4.0 mg/L in two of the four isolates (serovars E and F). Bhengraj, et al., described 9 isolates from 12 recurrently infected patients in India, 6 of whom (66.7%) showed decreased susceptibility to azithromycin and doxycycline (MIC >2.0 mg/L). Two of these six isolates were resistant to both antimicrobials (MIC >8.0 mg/L), and one was resistant to doxycycline only (MIC > 8.0 mg/L).

Sequential review of 22 studies conducted between 1990 and 2012 suggest that the MICs for azithromycin against *C. trachomatis* have not increased (Figure 5). Only four studies have demonstrated elevated MICs for either first-line agent and only two studies found elevated MICs for azithromycin. Misyurina, *et al.*, tested the in vitro susceptibility of *C. trachomatis* to erythromycin, azithromycin, and josamycin for six clinical isolates from suspected treatment failures in Russia. They reported that four
isolates (serotypes D, G, and I) were resistant to all three macrolides (MIC >5.1 mg/L). Zhu, et al., reported an elevated MIC for azithromycin, but the resistant strains were induced by exposure to sub-inhibitory concentrations of antimicrobials during genetic investigations.\(^{336}\)

**Genetic data**

A number of genetic changes, including lateral gene transfers and mutations, are known to precipitate evolutionary changes in bacteria. The unique intracellular life cycle of *C. trachomatis*, coupled with the absence of genes necessary to survive extracellularly for prolonged periods, generally render the bacterium unable to undergo lateral gene transfer with other bacteria. While further study is required to fully elucidate the role of lateral intra-strain gene transfers in the evolution of *C. trachomatis*, Demars, et al., has demonstrated the possibility of such transfers between *C. trachomatis* serovars which may have facilitated the development of new strains. Although mutations appear to be rare in *C. trachomatis*,\(^{249,318,325,335-345}\) limited evidence suggests they are possible and are almost certainly required to confer resistance.

Azithromycin resistance resulted from mutations in the 23S rRNA peptidyl transferase loop in two studies. The key macrolide resistance mutation is at position 2058 (*E. coli* numbering) and was documented by Misyurina, et al., who also noted a mutation at position 2611 within four resistant isolates obtained from suspected treatment failures. Macrolide resistance also may result from mutations in positions and 2057, 2059 and 2611. All three mutations were noted by Zhu, et al., who induced these mutations through sub-inhibitory exposure to macrolides. Mutations also were documented in position 66 of the L4 ribosomal protein genes.\(^{336}\) Finally, point mutations at position 83 in the *gyrA*
gene, which encodes for the protein DNA gyrase necessary for replication, have been shown to result in ofloxacin resistance. \(^{257,318,341}\) Mutations in positions 103 and 109 of the L4 ribosomal protein genes as well as positions 52, 65 and 77 of the L22 ribosomal protein genes have been noted, but do not appear to confer resistance. \(^{249,335,336,340}\)

Interestingly, mutations in the 23S rRNA subunit were unable to be induced by Binet, *et al.*, in their 2007 paper. \(^{335}\) The work of Binet, *et al.*, in 2005 suggests *C. trachomatis* is less likely to develop 23S rRNA mutations because it harbors two 23S rRNA gene copies and thus selection of spontaneous azithromycin resistant isolates requires the mutation to be dominant over the unmutated copy. \(^{340}\) Furthermore, these mutations are known to impact biological fitness.

**Competitive advantage of mutations**

The resistance conferred by specific mutations is acquired at a cost. Resistant mutants are at a competitive disadvantage relative to wild-type *C. trachomatis* in two respects. First, a stalled growth cycle limits viability as mutants are either delayed in their formation of infectious particles, or do not form them at all. \(^{335,340}\) Second, mutants often occur at a low frequency and are outcompeted by wild-type strains. \(^{249,335,336,339,340-341}\) When resistance occurs it is accompanied by signs of clinical persistence.

**Persistence**

Persistent *C. trachomatis* has been isolated in suspected treatment failures at a higher frequency than resistant strains, and unlike resistance, persistence is easily induced \(^{245,252,293,333,343,346-356}\) by exposure to antibiotics (n=6 studies), or interferon gamma (n=6 studies). When subpopulations display persistence (n=9 studies), they may contribute to suspected treatment failures (n=5 studies). Consistent with these
observations, Somani, et al., Misyurina, et al., and Bhengraj, et al., each noted that a small subpopulation of the bacterial population was refractory to treatment and contained altered morphologies and metabolic activity.250,324,336

There is ample evidence from multiple studies that persistence is associated with altered morphology and/or altered metabolic activity. However, altered morphologies, consisting of altered, enlarged inclusion counts, were noted more often (n=13)245,250,252,393,342,345,346,349-355 compared to metabolic changes (n=9)342,345,346,349-353,356, most frequently characterized by alterations in various proteins expressed. It is important to note that most studies documenting altered morphologies also noted altered metabolic activities, implying that these alterations are concomitant. Finally, seven studies245,252,333,349,353-355 noted that in the absence of a stressor (e.g., antibiotic or cytokine exposure), persistent forms resume growth and presumably infectivity on par with the wild-type strains. This is evidenced by the presence of typical inclusion size and count as well as the development of elementary bodies, but the data is sparse and limited to in vitro observations.

*Rating the evidence*

The GRADE criteria specifies four categories (high, moderate, low, and very low) that are applied to a body of literature, not individual studies, to rate the quality of evidence. We employed the GRADE criteria to assess the quality of the evidence supporting antibiotic resistance and persistence (Table 2). We conclude there is low evidence for increasing repeat positive tests, mutations in *C. trachomatis*, and reactivation of latent forms; moderate evidence for metabolic alterations; moderate evidence against a longitudinal increase in MICs and a competitive advantage of
mutations; and high evidence of morphological alterations. Collectively, the literature suggests very low evidence in support of antibiotic resistance and moderate evidence in support of persistence.

**Discussion**

This systematic review presents four major findings. First, *C. trachomatis* infection appears to be increasing globally with a concomitant increase in the proportion of repeat positive tests.\(^{136,147,262,269-307}\) Second, with few exceptions, the MICs of azithromycin and doxycycline have not risen over the last 20 years.\(^{245,247,249,250,308-336}\) Among the few exceptional elevated MICs, only one report was of a suspected treatment failure with resistant *C. trachomatis* infection caused by a 23S rRNA subunit mutation.\(^{249}\) Third, mutations conferring resistance are exceptionally rare and inhibit fitness of the organism by stalling the growth cycle.\(^{249,318,335,337-341}\) Fourth, persistence can be readily induced and persistent forms have been isolated from suspected treatment failures.\(^{43,65,89,99,103-114}\) Therefore, genuine treatment failures are likely due to persistence rather than antibiotic resistance.

The literature has not yet reached consensus on a key question: do latent persistent cells reactivate and return to an infectious state? Our literature search indicates that persistent forms are reversible *in vitro*.\(^{245,252,333,349,353-355}\) The studies noted that after removal of a stressor inducing persistence (e.g. antibiotic exposures or immune cytokines), within several days growth resumed to levels on par with untreated *C. trachomatis* strains. Production of elementary bodies occurred in most cases, suggesting infectivity returned to levels in line with pre-treatment levels. However, the degree to which persistent forms occur and reactivate in humans to produce active infection
remains unclear. Further, while tests of RNA are more clear, it is uncertain whether detection of chlamydial DNA is consistent with an active infection, or an inactive persistent infection. Most repeat positive tests in studies included in the present review measured the presence of chlamydial DNA.

In most cases of repeat positive tests, a clinician will suspect reinfection and prescribe standard therapy. Unless the patient is enrolled in a research study, infection is rarely assessed further to differentiate between treatment failure and reinfection. To inform this vital issue, Hocking, et al., is prospectively following women diagnosed with chlamydia post-treatment. The primary outcome will be the proportion of women with treatment failure by 28, 42 or 56 days after recruitment. Investigators will conduct PCR amplification for chlamydial DNA to detect possible reinfections or treatment failures. To differentiate chlamydia reinfection vs. treatment failure, the investigators plan to use sexual behavior data, the detection of Y chromosome DNA, and chlamydial genotyping. Culture and MIC assays will further characterize the infections to distinguish persistent versus antibiotic-resistant infections. Further, genetic analyses will be conducted to look for mutations.

The existing literature suggests that mutations do not confer a competitive advantage over wild-type C. trachomatis. Mutations in the 23S rRNA subunit lead to resistance against azithromycin but reduce infectivity and viability. The impact of mutations in the L22 and L4 genes is unclear, but they do not appear to promote resistance. Because C. trachomatis has two rrn operons, a mutation would have to be dominant over the wild-type operon to successfully promote this mutation and subsequent resistance in progeny. In other Chlamydia species with only
one rrn operon, point mutations do not need to be superior to the wild type and are more likely to proliferate in progeny and lead to resistance. The work of Gomes, et al., in 2004 Demars, et al., in 2007 and 2008 suggests that new serotypes may have formed by intra-strain lateral gene transfer.\textsuperscript{337,338,358} Theoretically, lateral gene transfer could occur between serovars of \textit{C. trachomatis} that are replicating intracellularly as reticulate bodies within the same cells; multiple serovars have been isolated from a single patient. While data to support this hypothesis are lacking, it is an intriguing possibility. As genetic recombination methodologies improve over time new research will critically improve the evidence base.

Another consideration is that there may be an underlying mechanism in \textit{C. trachomatis} allowing for selective induction of a persistent phenotype, for example, through membrane alterations which alter drug intake. Although data is not available for the frequency of persistence by serovar, it is possible that persistence could develop at varying rates across serovars. Future study is necessary to describe differences in persistence frequency by serovar. Finally, if persistent infections are truly increasing in prevalence, it is important to study the transmissibility of these persistent infections.

To date, scant evidence exists to suggest that persistent \textit{C. trachomatis} is transmissible. One study identified \textit{C. trachomatis} with altered reticulate bodies in the ejaculate and prostatic secretions of patients with chronic chlamydial prostatitis.\textsuperscript{359} It is possible these altered forms are the same as those observed \textit{in vitro}. More evidence is needed to connect the findings—whether the morphologically altered \textit{C. trachomatis} found in ejaculate is somehow infectious and is the same as persistent forms noted \textit{in vitro}. Another question which should be explored \textit{in vivo} is the degree to which antibiotic
treatment with CDC recommended regimens, as well as exposure to general antibiotics (e.g. penicillin, amoxicillin etc.) induces persistence, potentially leading to treatment failure.

Our review noted that azithromycin was more frequently associated with suspected treatment failure relative to doxycycline. Although there is no evidence yet that mutations in *C. trachomatis* confer resistance to doxycycline, some mutations have been found to be resistant to azithromycin and recent evidence from two clinical trials is concerning. Stamm, *et al.*, and Schwebke, *et al.*, noted the reduced ability of azithromycin to clear *C. trachomatis* infection in males with non-gonococcal urethritis after five weeks. Only 63.0% of infections were cleared in the Stamm, *et al* study and 77.3% were cleared in the Schwebke, *et al* study. No studies demonstrating a dramatic reduction in efficacy for doxycycline were identified. These studies suggest that the efficacy of azithromycin has either diminished with time or that advances in testing are able to produce a more accurate picture of effectiveness today. Azithromycin was declared 97% to 98% effective prior to the widespread introduction of the much more sensitive nucleic acid amplification tests. It is important to note that detection of chlamydial DNA may be inferior as a test of cure relative to the detection of chlamydial RNA because some data suggests chlamydial DNA is detectable more often than chlamydial RNA after effective treatment. Further study is needed to better understand the benefits of detecting DNA versus RNA and the implications for treatment, however with the availability of more sensitive tests and the increasing prevalence of repeat infections, further study is justified to quantify the efficacy of azithromycin in clearing *C. trachomatis*.
Limitations

Several limitations are noteworthy. Repeat positive tests were used as an imperfect proxy for treatment failures as there is scant literature defining genuine treatment failures. Although there appears to be a rise in repeat positive tests, as a proxy for treatment failures, the measure is confounded by the unknown proportion of reinfections as well as later studies relying on more sensitive tests thus this proxy should be interpreted with caution. The epidemiological evidence presented was a mix of observational and trial data which each carry their own limitations. One such limitation to note is that aside from some of the earliest studies conducted, included studies did not use culture as a confirmatory test to ensure *C. trachomatis* that could lead to active infection was eradicated. Instead these studies relied on nucleic acid amplification tests which, despite strong sensitivity and specificity, cannot distinguish active infection from the presence of chlamydial DNA or RNA. Further, with the exception of the studies by Batteiger, *et al.* and Walker, *et al.*, no studies isolated strains after repeat positive tests and conducted genetic analyses to determine possible reinfections with another serovar. Thus, these studies are inherently limited as a proxy for treatment failures.

Care should also be taken in interpreting the findings from the reported laboratory data as their direct comparability is unclear for several reasons. Assays to assess chlamydia susceptibility involve isolating and expanding clinical isolates and then culturing chlamydial progeny in cells with media containing different dilutions of antibiotics. At this time, there is no universal testing methodology accepted for these assays, and the techniques are considered very technically challenging and time-consuming. Laboratory results are influenced by a wide variety of factors, such as the cell
line used, host cell characteristics, multiplicity of the chlamydial infection, developmental stage of chlamydia when the antibiotic is added to the infected cells, and the presence or absence additives that slow the growth of the host cells. Further, the rate of chlamydial growth, as well as cellular uptake of antibiotics by host cells, can vary substantially in different models. The differing methodologies directly affect the reproducibility of the assays and, thus, the interpretation and comparability of findings, particularly surrounding the reporting of the MIC data.

There are inherit limitations to utilizing MIC as a marker for antimicrobial effectiveness. Standard MIC definitions for *C. trachomatis* varied slightly across all of the studies but all examined the lowest concentration at which there were no apparent inclusions formed. In contrast the minimum chlamydicidal concentration (MCC) was reported far less frequently. Somani, *et al.*, who isolated strains from suspected treatment failures, employed MCC in addition to MIC. The MCC is defined as the lowest concentration required to prevent formation of any inclusions after passage on antibiotic free medium. This is likely superior as this approach better ensures that all forms have been eliminated (including persistent forms). Thus, papers reporting MIC only potentially may miss cases of persistence.

There are also inherent limitations in utilizing the GRADE criteria to assess the evidence presented in this review. The GRADE system was initially developed to address questions about alternative management strategies, interventions and policies, and to score the collective quality of evidence. It has been utilized more liberally in the literature in recent years, but to our knowledge this is the first time GRADE has been employed to assess antibiotic resistance. While the GRADE criteria adds another layer of objectivity,
it does not fully eliminate the subjective nature of classifying and rating an evidence base.

**Conclusion**

The evidence suggests that antibiotic resistance is of little significance to treatment considerations regarding *C. trachomatis*. While rare mutations of the organism have been associated with resistance to azithromycin, such mutations do not appear to be compatible with viability. The exact proportion of repeat positive tests that are due to genuine treatment failures or reinfections is unclear. Further study is necessary to quantify and properly attribute these cases. Among true treatment failures, persistence is likely responsible and this is supported by a body of evidence of moderate quality, characterized by numerous reports each yielding similar findings with regards to the presence of persistence characteristics. As such, future study is warranted to determine how often infections become persistent, under what conditions persistent infections revert to the infectious state *in vivo*, and if persistent infections are transmissible.
Figure 1. Flow chart of reported study identification, inclusion and exclusion.
Figure 2. Proportion And 95 Percent Confidence Intervals of Patients With Repeat Positive Tests For Chlamydia trachomatis Infections Within One Year of Treatment, Studies Published 1988-2012.
Figure 3. Proportion And 95 Percent Confidence Intervals of Patients With Repeat Positive Tests For *Chlamydia trachomatis* Infections Within 12 Weeks of Treatment, Studies Published 1988-2012.
Figure 4. Reported MIC Ranges Of Doxycycline For Various *Chlamydia trachomatis* Serovars, By Publication and Study Year, 1986-2013.

Lead Author, Publication Year and (Study Period)

*Max MIC 4.0 mg/L
**Max MIC 8.0 mg/L
£Associated with treatment failure
Figure 5. Reported MIC Ranges Of Azithromycin For Various Chlamydia trachomatis Serovars, By Publication and Study Year 1990-2013.

**Lead Author And Publication Year**
*Associated with treatment failure
*Max MIC > 8.0 mg/L
Table 1. Studies examining MIC of the Centers for Disease Control and Prevention recommended treatments against *C. trachomatis*, serovars tested, values reported and main findings.

<table>
<thead>
<tr>
<th>Study</th>
<th>Serovars Tested</th>
<th>Recommended Antimicrobials Tested And Reported Minimum Inhibitory Concentration(s) Ranges (mg/L)</th>
<th>Special Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirai, et al., 1986</td>
<td>A, B, D, E, L2</td>
<td>Doxycycline (0.10) Ofloxacin (0.10-0.39)</td>
<td>Doxycycline only tested on L2 Strain. Ofloxacin lowest for most A strains, L2, and B. One A strain 0.39. Both D and E strains 0.19.</td>
</tr>
<tr>
<td>Christensen, et al., 1986</td>
<td>E</td>
<td>Doxycycline (0.03-0.06) Erythromycin (0.5-2.0)</td>
<td>Eleven isolates of <em>C. trachomatis</em> found in a Danish hospital were examined for susceptibility.</td>
</tr>
<tr>
<td>Bowie, et al., 1987</td>
<td>Unspecified</td>
<td>Doxycycline (0.016-0.032) Erythromycin (0.06-0.13)</td>
<td></td>
</tr>
<tr>
<td>Bianchi, et al., 1988</td>
<td>Unspecified</td>
<td>Doxycycline (0.032-0.064) Erythromycin (0.016-0.064) Ofloxacin (0.50)</td>
<td></td>
</tr>
<tr>
<td>Segreti, et al., 1989</td>
<td>D, L2 and 11 clinical isolates of unknown serovar</td>
<td>Doxycycline (0.015-0.125)</td>
<td>MIC’s determined for 13 clinical isolates. 0.125 MIC was for L2.</td>
</tr>
<tr>
<td>Borsum, et al., 1990</td>
<td>Unspecified, 8 isolates from neonatal infections</td>
<td>Azithromycin (0.06-0.25) Erythromycin (0.125-0.50) Ofloxacin (0.5-1.0)</td>
<td></td>
</tr>
<tr>
<td>Jones, et al., 1990</td>
<td>D, E, F, I</td>
<td>Doxycycline (0.03-0.06) Erythromycin (0.50-1.0)</td>
<td>Only tetracycline resistant isolates were tested for susceptibility to other antimicrobials</td>
</tr>
<tr>
<td>Welsh, et al., 1992</td>
<td>D, E, F, J, K, L2</td>
<td>Azithromycin (0.125-0.5) Erythromycin (0.25-1.0)</td>
<td>Eleven clinical isolates from uncomplicated urogenital chlamydia infections were assayed. Highest for serovar K.</td>
</tr>
<tr>
<td>Rumpianesi, et al., 1993</td>
<td>Unspecified, all genital isolates</td>
<td>Azithromycin(0.06-0.5) Erythromycin (0.06-0.5)</td>
<td></td>
</tr>
<tr>
<td>Agacfidan, et al., 1999</td>
<td>B, D, E, F, H, J, K</td>
<td>Azithromycin (≤0.06-1.0)</td>
<td>Serovar J had the highest reported MICs</td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Serovars</td>
<td>Antimicrobial Agents</td>
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<tr>
<td>1993</td>
<td>Martens, et al., 1993</td>
<td>Unspecified</td>
<td>Doxycycline (0.015-0.06)</td>
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<td></td>
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<td></td>
<td>Doxycycline (&lt;2.0)</td>
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<td></td>
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<td>Erythromycin (&lt;4.0)</td>
</tr>
<tr>
<td>1993</td>
<td>Wise, et al., 1994</td>
<td>Unspecified</td>
<td>Erythromycin (0.25-0.5)</td>
</tr>
<tr>
<td></td>
<td>Rice, et al., 1995</td>
<td>B, D, E, F, I, K, J</td>
<td>Azithromycin (0.125-1.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Doxycycline (0.015-&gt;0.125)</td>
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<td></td>
<td></td>
<td></td>
<td>Ofloxacin (0.25-1.0)</td>
</tr>
<tr>
<td>1996</td>
<td>Zanetti, et al., 1996</td>
<td>Unspecified, 20 isolates taken from STD patients</td>
<td>Erythromycin (0.125-0.5)</td>
</tr>
<tr>
<td>1997</td>
<td>Jones, et al., 1997</td>
<td>D, E, F, I, L1, L2</td>
<td>Doxycycline (0.063-0.125)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erythromycin (0.063-0.25)</td>
</tr>
<tr>
<td>1998</td>
<td>Dessus-Barbus, et al., 1998</td>
<td>L2 and 14 unspecified genital isolates.</td>
<td>Doxycycline (0.05-1.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erythromycin (0.4-0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ofloxacin (1.0-2.0)</td>
</tr>
<tr>
<td>1998</td>
<td>Dessus-Barbus, et al., 1998</td>
<td>L2 reference strain and two L2 fluoroquinolone resistant mutants</td>
<td>Reference strain: Doxycycline (0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erythromycin (0.4)</td>
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<td></td>
<td></td>
<td></td>
<td>Ofloxacin (1.0)</td>
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<tr>
<td></td>
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<td></td>
<td>For Ofloxacin Induced Resistant strain: Doxycycline (0.05)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Erythromycin (0.4)</td>
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<td></td>
<td></td>
<td></td>
<td>Ofloxacin (&gt;64.0)</td>
</tr>
<tr>
<td>1998</td>
<td>Lefevre, et al., 1998</td>
<td>Unspecified, 35 total strains from chlamydia patients, 1 of</td>
<td>Azithromycin (0.06-&gt;0.125)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erythromycin (0.06-0.25)</td>
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<td></td>
<td></td>
<td></td>
<td>Ofloxacin (0.5-1.0)</td>
</tr>
<tr>
<td>Study</td>
<td>Organisms</td>
<td>MIC Range</td>
<td></td>
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<tr>
<td>-------------------------------------------</td>
<td>------------------------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Pudjatmoko, et al., 1998</td>
<td>tetracycline resistance</td>
<td>Doxycycline (0.031) Erythromycin (0.125) Ofloxacin (0.25)</td>
<td></td>
</tr>
<tr>
<td>Andrews, et al., 2000</td>
<td>Chlamydia pecorum</td>
<td>Erythromycin (0.25)</td>
<td></td>
</tr>
<tr>
<td>Somani, et al., 2000</td>
<td>Chlamydia trachomatis L2</td>
<td>Azithromycin (0.5-4.0) Doxycycline (0.125-4.0) Ofloxacin (2.0-4.0)</td>
<td></td>
</tr>
<tr>
<td>Roblin, et al., 2000</td>
<td>Chlamydia trachomatis</td>
<td>Doxycycline (0.25) Ofloxacin (0.25-0.50)</td>
<td></td>
</tr>
<tr>
<td>Samra, et al., 2001</td>
<td>Chlamydia trachomatis</td>
<td>Azithromycin (0.06-0.125) Doxycycline (0.125-0.25) Erythromycin (0.06-0.25)</td>
<td></td>
</tr>
<tr>
<td>Dreses-werringloer, et al., 2001</td>
<td>Chlamydia trachomatis</td>
<td>Azithromycin (0.25)</td>
<td></td>
</tr>
</tbody>
</table>

Unspecified, three strains from genital isolates. Erythromycin (0.25) Chlamydia trachomatis was one of a number of organisms tested for susceptibility against a novel compound, in addition to standard therapies. Urogenital isolates of *Chlamydia trachomatis* were taken from 3 patients, 2 of whom showed evidence of clinical treatment failure with azithromycin and one of whom was the wife of a patient. All 3 isolates demonstrated multidrug resistance to doxycycline, azithromycin, and ofloxacin. Recurrent disease due to relapsing infection with the same resistant isolate was documented on the basis of identical genotypes of both organisms. Patient 2 and 3 had resistant strains of serovar F to doxycycline, azithromycin, and ofloxacin. Patient 1 with strain serovar D had resistance to ofloxacin but susceptibility to doxycycline, azithromycin.

MIC’s determined for 50 clinical isolates
<table>
<thead>
<tr>
<th>Study</th>
<th>Strains</th>
<th>Drug and Concentration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morrissey, et al., 2002</td>
<td>L2</td>
<td>Ofloxacin (0.25) for first 8 passages at which point MIC began to rise</td>
<td>Ofloxacin resistant strain (induced after 30 passages)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ofloxacin (&gt;64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluoroquinolone resistance didn’t take until 10\textsuperscript{th}-12\textsuperscript{th} passage through subinhibitory concentrations; at which point it developed rapidly.</td>
</tr>
<tr>
<td>Speciale, et al., 2002</td>
<td>Unspecified</td>
<td>Doxycycline (0.03-0.12)</td>
<td>Unspecified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin (0.06-0.25)</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Suchland, et al., 2003</td>
<td>B, D, E, F, G, H, I, Ia, H, J, K, L2.</td>
<td>Azithromycin (0.125)</td>
<td>No differences between strains noted for MICs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxycycline (0.064)</td>
<td>No differences between strains noted for MICs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ofloxacin (0.5)</td>
<td>No differences between strains noted for MICs</td>
</tr>
<tr>
<td>Misyurina, et al., 2004</td>
<td>B, D, G, I</td>
<td>Wild Type and unmutated isolates.</td>
<td>In vitro susceptibility to erythromycin, azithromycin among 6 clinical isolates, four from patients at a clinic in Russia and reference strains. The observed resistance was heterotypic; i.e., the inclusions observed were small and their number in the presence of antibiotics was much lower. Resistant isolates could be visually distinguished from sensitive ones, which showed no inclusions at the drug concentrations defined as the MIC and MBC. This study also found mutations in the peptidyl transferase region of the 23S rRNA gene have been found in macrolide-resistant C. trachomatis. Only strain B did not display the 23S mutation (and had a low MIC).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin (0.08)</td>
<td>Mutations in 23S rRNA gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin (0.16)</td>
<td>Mutations in 23S rRNA gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutations in 23S rRNA gene</td>
<td>Mutations in 23S rRNA gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin (&gt;5.12)</td>
<td>Mutations in 23S rRNA gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin (&gt;5.12)</td>
<td>Mutations in 23S rRNA gene</td>
</tr>
<tr>
<td>Smelov, et al., 2004</td>
<td>Unspecified</td>
<td>Azithromycin (2.0)</td>
<td>Antibacterial susceptibility of <em>Chlamydia trachomatis</em> was done on strains in 138 patients with chronic prostatitis; azithromycin may not be best treatment for those with chronic prostatitis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxycycline (0.06)</td>
<td>Antibacterial susceptibility of <em>Chlamydia trachomatis</em> was done on strains in 138 patients with chronic prostatitis; azithromycin may not be best treatment for those with chronic prostatitis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ofloxacin (1.0)</td>
<td>Antibacterial susceptibility of <em>Chlamydia trachomatis</em> was done on strains in 138 patients with chronic prostatitis; azithromycin may not be best treatment for those with chronic prostatitis.</td>
</tr>
<tr>
<td>Binet, et al., 2007</td>
<td>L2</td>
<td>Wild Type:</td>
<td>A mutation in the L4 protein from a Q\textsubscript{66}K amino acid substitution results in higher MIC, but clinically not relevant and mutation is</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin (0.1)</td>
<td>A mutation in the L4 protein from a Q\textsubscript{66}K amino acid substitution results in higher MIC, but clinically not relevant and mutation is</td>
</tr>
<tr>
<td>Authors, Year</td>
<td>Strains</td>
<td>Antibiotics &amp; Concentrations</td>
<td>Remarks</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Bebear, et al., 2008</td>
<td>D, E, F, H (reference strains) and 40 urogenital strains (unspecified serotype)</td>
<td>Azithromycin (≤0.015-0.5) Doxycycline (0.015-0.5) Erythromycin (≤0.015-1.0) Ofloxacin (0.25-4.0)</td>
<td>Over 44 isolates of <em>Chlamydia trachomatis</em> tested; doxycycline most potent tested.</td>
</tr>
<tr>
<td>Donati, et al., 2010</td>
<td>D, E, F, G, H, I, J, K</td>
<td>Azithromycin (0.25-0.50) Doxycycline (0.03-0.06) Erythromycin (0.50-1.0) Levofloxacin (0.25-0.50)</td>
<td>Researchers examined <em>Chlamydia trachomatis</em> strains D-K. Very little difference between strains reported.</td>
</tr>
<tr>
<td>Zhu, et al., 2010</td>
<td>E</td>
<td>Azithromycin (0.5-1.0) Erythromycin (0.5-1.0)</td>
<td>Thirteen strains of <em>Chlamydia trachomatis</em> were exposed to subinhibitory concentrations of erythromycin, azithromycin, and josamycin to select macrolide-resistant mutants with serial passages. The ribosomal protein L4 and 23S rRNA genes of the susceptible and resistant strains of <em>C. trachomatis</em> were partially sequenced. A double mutation was found in ribosomal protein L4 of the mutants, but these mutations were also found in parent strains. An investigation into the sequences of 23S rRNAs in the mutants revealed point mutations of A2057G, A2059G and T2611C. These results suggest that point mutations located in 23S rRNA were associated with macrolide resistance in <em>C. trachomatis</em>.</td>
</tr>
<tr>
<td>Bhengraj, et al., 2010</td>
<td>D for reference strain, then 21 Unspecified clinical isolates</td>
<td>Azithromycin (≤0.125) Doxycycline (≤0.25) Azithromycin (0.25-4.0)</td>
<td>In vitro susceptibility assay was performed for azithromycin and doxycycline using the cell culture technique against 21 clinical isolates obtained from <em>C. trachomatis</em>-positive patients including those who were recurrently infected. Decreased antibiotic susceptibility to the current first-line drugs</td>
</tr>
<tr>
<td>Reference</td>
<td>Strains/Genotypes</td>
<td>Antimicrobials Concentrations</td>
<td>Treatment Notes</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------------------</td>
<td>--------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Peuchant, et al., 2011</td>
<td>D, L2</td>
<td>Azithromycin (0.03-0.06)</td>
<td>Doxycycline (0.007-0.015) Ofloxacin (0.50)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>This paper also showed that while MIC is achieved at these levels, MUCH higher concentrations for each antimicrobial required to limit gene transcription (1.0-≥8.0, depending on gene examined). Thus, clinically medications may truly only be bacteriostatic in many cases.</td>
</tr>
<tr>
<td>Shima, et al., 2011</td>
<td>L2</td>
<td>Under normal oxygen conditions (20% O₂) Azithromycin (0.04) Doxycycline (0.05)</td>
<td>Under Hypoxic conditions (2% O₂) Azithromycin (0.08) Doxycycline (0.05)</td>
</tr>
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<td>While low oxygen availability only moderately decreased the antichlamydial activity of azithromycin in conventional MIC testing (0.08 mg/L versus 0.04 mg/L; P&lt;0.05), TKC analyses revealed profound divergences for antibiotic efficacies between the two conditions. Thus, C. trachomatis was significantly less rapidly killed by doxycycline and azithromycin under hypoxia. MIC’s thus are not the best predictor of therapeuitic efficacy in vivo.</td>
</tr>
<tr>
<td>Chotikanatis, et al., 2013</td>
<td>Reference strains; D, E, F, H, I, J, L2 as well as two unspecified genital isolates and one conjunctival isolate</td>
<td>Azithromycin( 0.25-0.50)</td>
<td>Doxycycline (0.03-0.06) Levofloxacin (0.25-0.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(azithromycin and doxycycline) for chlamydial infection treatment was observed in isolates obtained from recurrently infected patients.</td>
</tr>
</tbody>
</table>
Table 2. Assessment of the quality of evidence in support of antibiotic resistance and persistence among genital *Chlamydia trachomatis* infections utilizing GRADE criteria.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Study references contributing evidence to criteria</th>
<th>Notes regarding GRADE assessment</th>
<th>Evidence rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resistance factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure (repeat positive tests as proxy)</td>
<td>136,137,262,270,274,252, 253, 285,287-307</td>
<td>Evidence rating based on large number of studies, varying methodologies, the presence of an apparent time trend, consistency across studies, general risk for confounding/bias given more sensitive tests employed over time, some degree of imprecision in the estimates, and indirectness of repeat positive tests as a proxy for treatment failure and no clear publication bias.</td>
<td>Low supportive evidence</td>
</tr>
<tr>
<td>Elevated minimum inhibitory concentrations</td>
<td>245,247,249,250,257, 308-335</td>
<td>Evidence rating based on moderate number of studies, widely varying methodologies, a very slight rising overtime, but not clinically meaningful, some degree of consistency across studies, generally low risk for bias with some degree of imprecision in the estimates, directness of findings no clear publication bias.</td>
<td>Moderate evidence against</td>
</tr>
<tr>
<td>Genetic changes: horizontal gene transfer</td>
<td>337,338,358</td>
<td>Evidence rating based primarily on clear lack of studies, inability to assess generally unknown risk for bias and imprecision in the estimates and employed methodologies. The results are seemingly direct, but and there may be a publication bias given lack of publications refuting horizontal gene transfers.</td>
<td>Very low evidence</td>
</tr>
<tr>
<td>Genetic changes: mutations</td>
<td>249,318,335,336,339-341,345</td>
<td>Evidence rating based primarily low number of studies, generally unknown risk for bias and imprecision in the estimates and employed methodologies. The</td>
<td>Low evidence</td>
</tr>
</tbody>
</table>
results are seemingly direct, but there is no apparent publication bias given publications reporting mutations and those reporting lack thereof.

<table>
<thead>
<tr>
<th>Viability of mutations</th>
<th>249,318,335,336,339-341,345</th>
<th>Evidence rating based primarily on the strong consistency of findings despite a generally low number of studies, a probable lack of the risk for bias or imprecision in the estimates and employed methodologies. The results are seemingly direct, but there is no apparent publication bias.</th>
<th>Moderate evidence against</th>
</tr>
</thead>
</table>

**Persistence factors**

<table>
<thead>
<tr>
<th>Treatment failures (repeat positive tests as proxy)</th>
<th>136,137,262,270,274,252, 253,285,287-307</th>
<th>Evidence rating based on large number of studies, varying methodologies, the presence of an apparent time trend, consistency across studies, general risk for confounding/bias given more sensitive tests employed over time, some degree of imprecision in the estimates, and indirectness of repeat positive tests as a proxy for treatment failure and no clear publication bias.</th>
<th>Low supportive evidence</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Elevated minimum inhibitory concentrations</th>
<th>245,247,249,250,257, 308-335</th>
<th>Evidence rating based on moderate number of studies, widely varying methodologies, a very slight rising overtime, but not clinically meaningful, some degree of consistency across studies, generally low risk for bias with some degree of imprecision in the estimates, directness of findings no clear publication bias.</th>
<th>Moderate evidence against</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Altered morphologies</th>
<th>245,250,252,293,342,345, 346,349-352,354,355</th>
<th>Evidence rating based on moderate number of studies, from both in vitro only and in vivo sources, the strong consistency of findings, very low risk for bias with little potential for imprecision, directness of results and no clear publication bias.</th>
<th>High evidence</th>
</tr>
</thead>
</table>
Altered metabolic activity 342,345-347,350-353,356 Evidence rating based on moderate number of studies, from both in vitro only and in vivo sources, general consistency of findings, but unknown risk for bias and imprecision among the varying methodologies, directness of results and no clear publication bias. Moderate evidence

Reactivation of altered forms 245,252,349,351,353-355 Evidence rating based on low number of studies limited to in vitro experimental observations only with consistency of findings, but unknown risk for bias and imprecision among the varying methodologies, directness of results and unknown publication bias. Low evidence
ABSTRACT

Objectives: The following perceptions of patient-delivered partner therapy (PDPT) for sexually transmitted disease (STD) were evaluated: patient willingness to distribute antibiotic prescriptions and educational materials to sexual partners, preferred method of prescription delivery, time estimated to deliver prescriptions, sexual partner likelihood of seeking medical evaluation, and perception of privacy in pharmacies.

Methods: We performed bivariate analyses of responses to a cross-sectional survey administered between November 2007 and August 2008 among New York State STD patients and partner(s).

Results: Of the 110 respondents, 79 were index patients (71.8%) and 31 were partners (28.2%). Most index patients reported they would deliver prescriptions in three days or less (85.5%), in person (65.8%). Approximately one-third (30.7%) of index patients indicated there was at least one recent sexual partner to whom they would not deliver a prescription. Fewer than half of patients and partners (45.6%, 40.0%, respectively) feel comfortable discussing STD with a pharmacist. If given a prescription under PDPT, only 13.3% of partners indicate they would not seek a medical evaluation.
**Conclusions:** Patients reported willingness to distribute prescriptions and educational materials to most partners in a timely manner. Most partners interviewed stated they would seek medical evaluation if they received a prescription under PDPT. Patients and partners are uncomfortable discussing STD in the pharmacy environment. Given that approximately 30% of patients would not distribute prescriptions to every sexual partner, further research to identify factors associated with patient willingness to deliver prescriptions to all sexual partners is warranted to maximize effectiveness of PDPT.
The burden of sexually transmitted disease (STD) continues to be a major public health concern, affecting millions of people annually. Over the last decade, declining financial resources have hindered STD control activities, most notably by causing a severe reduction in the number of disease intervention specialists (DIS), the public health workforce tasked with interviewing patients and providing comprehensive partner notification (PN) services. As such, DIS PN is prioritized for HIV, syphilis and gonorrhea; it is rarely conducted for chlamydia. To reach more sexual partners of index patients, several alternative PN approaches have been considered, including patient-delivered partner therapy (PDPT), as part of a broader expedited partner therapy (EPT) approach. The Centers for Disease Control and Prevention (CDC) recommends states allow the use of PDPT to reduce the incidence of chlamydia and PDPT is now legally permissible in many states.

In late 2008, New York State (NYS) legalized PDPT for chlamydia. Experts in STD treatment in NYS, when surveyed about PDPT, recognized the potential value of another treatment and notification approach, but noted specific concerns, including fear that prescriptions will not reach partners, the potential for side effects of medication, and a lack of medical evaluation of sexual partners. Research among medical personnel documented similar concerns. The effectiveness of PDPT for disease control hinges on both patient and partner factors related to the delivery of pharmaceuticals and compliance with treatment. Patient factors include willingness to deliver antibiotic prescriptions to all partners, the method in which prescriptions would be delivered, and the time it would take prescriptions to reach partners. Partner factors include willingness
to take antibiotic prescriptions brought to them by an index patient and the partner’s likelihood of seeking medical evaluation. To date, research is limited about these issues, and more broadly about perceptions of PDPT.

Research on patient PN preferences when PDPT is included as an option suggests that individuals may wish to be notified by their partner directly about the risk for infection and may or may not prefer to use PDPT. One study conducted in three STD clinics found that only 20% of respondents would choose to take medicine to a partner for treatment; half preferred to send their partner to a clinic for evaluation and treatment. Another study measured patient preferences for EPT versus standard patient referral and found that 55% preferred to use standard referral over EPT (45%) to notify partners. A small qualitative study further suggests patients who are willing to engage in PDPT may not deliver prescriptions to all partners. Studies examining partner perspectives are even more limited. One small study among men who have sex with men (MSM) suggested that partners who hypothetically received a prescription under PDPT would be very likely to seek medical evaluation, but would be less likely to if they were asymptomatic. Thus, important considerations regarding PDPT use and its effectiveness as an alternative disease control strategy remain unaddressed or understudied.

There are two key questions related to the patient side of the equation which we will explore. First, are patients willing to distribute prescriptions to all of their sexual partners? And second, how long it will take prescriptions to be delivered? With respect to
partners, neither their willingness to accept PDPT prescriptions nor their likelihood of seeking medical evaluation/screening for co-infection has been well documented.

This study adds to the PDPT literature by surveying STD index patients and sexual partners to assess their preferences regarding how sexual partners are notified of potential exposures to STD and to assess their willingness to distribute or accept antibiotic prescriptions. We also investigated how long it would take patients to deliver prescriptions to their partners and whether partners would seek a medical evaluation if given a prescription under PDPT.

METHODS

New York State is comprised of 57 counties outside New York City (NYC). Nineteen counties employ DIS to conduct PN; the remaining 38 counties refer STD cases to the New York State Department of Health (NYSDOH) Regional Epidemiology Program. We partnered with the Northeastern (Capital Region) section of the NYSDOH Regional Epidemiology Program (237.2 chlamydia cases per 100,000 population, 2008) and the STD control program in Dutchess County (217.0 chlamydia cases per 100,000 population, 2008) to conduct our study. Two DIS and a student intern from the Regional Epidemiology Program, as well as two DIS personnel from Dutchess County recruited study participants and administered our surveys from November 2007 to August 2008.

Recruitment
Study participants were recruited following a standard DIS interview comprised of disease-related prevention counseling and partner elicitation. Following the interview, potential participants were asked if they would complete a 10 minute survey regarding PN and treatment services. To be eligible, potential participants had to be 18 years of age or older, English speaking and diagnosed with chlamydia, gonorrhea, or both, as well as have completed their DIS interview. Recruited partners were not necessarily contacts of surveyed index patients, but partners were identified as sexual contacts by individuals diagnosed with chlamydia, gonorrhea or both. With the exception of age and language requirements, no further inclusion criteria existed related to demographic characteristics for recruiting participants. Rather, DIS invited consecutive individuals until the study period ended. Those interested and eligible were provided informed consent, and the DIS administered the survey by interview conducted in person in a private space (generally where the field interview was conducted). The completed de-identified questionnaire was placed in an unmarked envelope and sealed. Sealed envelopes were delivered by hand to research staff biweekly.

Survey Instrument

Our survey was developed using modified questions from prior PDPT surveys conducted with county STD supervisors and pharmacists in NYS. Two near-identical versions of the survey were employed, one for index patients and one for partners. Most survey questions were the same, however some questions contained slightly modified language for index patients versus partners. An example of the
variation is as follows: if we asked an index patient “how would you most prefer your partner to be notified about a potential exposure to STD?” the question for the partner was altered to ask “how would you most like to be notified about a potential exposure to STD?” For prescription delivery inquiries among partners, participants were asked to assume they were diagnosed with an STD. The survey covered perspectives on PDPT, questions regarding prescription delivery, willingness to educate partners about STD, and perspectives of privacy in pharmacies. The survey questions primarily had categorical responses. We allowed respondents to comment in an open-ended fashion any time during the survey and recorded their comments.

**Statistical analysis**

Survey data were entered into Epi-Info (v.3.3.2, CDC, Atlanta GA) and imported into SAS (v.9.1.3, SAS institute, Cary, N.C.) for analysis. Descriptive statistics including frequency counts and proportions were computed to quantify respondents’ sexual partnerships and to learn about PN method preferences, including attitudes toward PDPT, preferred method of antibiotic prescription delivery and pharmacy privacy perceptions. Cross-tabulations of demographic characteristics and survey responses were also conducted. Statistical associations were determined using Chi-square or Fisher’s exact test (0.05 significance level), as appropriate.

**Institutional Review Board approval**
The study was approved by the authors’ university and the New York State Department of Health Institutional Review Boards. Participants were given a $10 grocery card for completing the interview.

RESULTS

A total of 110 individuals participated in the study. Of these, 79 (71.8%) were index patients and 31 (28.2%) were partners for an estimated response proportion of 60.0%. Respondents were primarily African American/Black (68.4% index patients, 46.4% partners), less than 25 years of age (53.9% index patients, 53.4% partners) and most (75.5% index patients, 56.7% partners) had at least a high school diploma or equivalent (table 1). The majority reported two or fewer sexual partners in the last year (56.4% index patients, 58.6% partners) and resided in urban areas of the Capital District of NYS (53.2% index patients, 67.9% partners).

When questioned about knowledge of STD, approximately one-fourth (26.9%) of index patients reported they believed their sexual partners knew “a lot” about STD (table 2). About 30% of surveyed partners reported they knew “a lot” about STD. Index patients were willing to educate their partners: 80.0% reported they were willing to inform their partners through pamphlets or brochures. Partners were open to being educated regarding potential infections: 90.0% reported they are willing to receive education via pamphlets/brochures delivered by index patients.

Respondents were evenly divided on their attitudes toward PDPT (table 3). When asked if they believed “it is ok for a doctor to give someone with an STD a written
prescription for his/her sexual partner” to receive treatment, 44.3% of index patients agreed, while 44.3% disagreed. A similar dichotomy was seen for partners, as 40.0% agreed and 40.0% disagreed. Most (72.1%) index patients reported it was 100% likely they would deliver the prescription to their most recent partner. Respondents who would not give a prescription to a sexual partner (27.9%) said they would not do so mostly because of shame or relationship dynamics, evidenced by participant comments such as “do not want to admit having an STD” or “do not want to see [the partner] again.”

With respect to delivery of prescriptions, most index patients reported they would deliver the prescription to their most recent partner within three days (85.5%), primarily by directly handing the prescription to the partner (65.8%). Approximately one-third of index patients (30.4%) and half of partners (53.3%) reported that there was at least one partner to whom they would not give a prescription. Partners reported that they would be more likely to give their main partner a prescription (78.6%), compared to a casual sexual partner (33.3%) ($p=0.039$). Finally, if they were to receive a prescription from a sexual partner under PDPT, most partners (63.3%) reported they would still seek a medical evaluation; only 13.3% of partners reported they would not seek medical evaluation. Bivariate analysis did not show statistically significant differences in responses by demographic variables, including diagnosis type, race or number of partners.

Both index patients and partners reported a lack of comfort discussing STD in the pharmacy environment. When asked if they felt comfortable discussing STD with their pharmacist, fewer than half of index patients (45.6%) and partners (40.0%) answered affirmatively. Further, while the vast majority of participants want private discussions
with their pharmacist (90.2%), 52.5% of index patients and 43.0% of partners believed discussions would be overheard by other pharmacy staff and customers. We stratified pharmacy privacy perspectives by number of sexual partners in the last year. Among partners who reported two or fewer sexual partners in the last year, 64.7% believed they could discuss issues with their pharmacist without other customers overhearing, versus 9.1% for those reporting more than two partners ($p=0.007$). Similarly, 58.8% of those with two or fewer partners perceived that other staff members cannot overhear their conversations, versus 9.1% for those with more than two sexual partners ($p=0.024$).

**DISCUSSION**

In this cross-sectional survey, STD index patients and partners were evenly divided in their support for PDPT. Non-delivery of prescriptions is a primary concern for physicians and STD treatment experts queried about PDPT.\textsuperscript{107,366,367} Data that address this concern are limited but our results indicated most index patients, while divided on support for PDPT, are willing to deliver a prescription to their most recent partner, and more than half would give prescriptions to every recent partner. Our findings substantiate prior research reporting that approximately half or more of those queried about PDPT would deliver prescriptions to most sexual partners.\textsuperscript{371,374}

The amount of time that elapses between an index patient being treated and their sexual partners ultimately being notified is critical to interrupting disease transmission.
The majority of index patients in our study reported they would deliver prescriptions to their most recent partner within three days (85.5%) and nearly all would do so within one week (97.4%). The method of delivery also affects the time to receipt. Index patients reported they would deliver prescriptions primarily in person, similar to the findings of Gurshaney, et al. While most index patients reported that they would deliver the prescription in person within a week, nearly one in three would not deliver prescriptions to at least one sexual partner. Our findings are similar to those of Temkin, et al., who noted that EPT was declined for 17 of 58 partners, or 29% of reported partners. Participant comments such as “[I] do not want to admit having STD” or “[I] do not want to see [the partner] again” illustrate the perceived stigma and underlying relationship dynamics that provide plausible and/or possible reasons for our findings. Further, preferences for different methods of PN and subsequent health seeking behavior of the partner may vary by such relationship dynamics.

A remaining concern regarding successfully delivered PDPT prescriptions is the lack of medical evaluation for partners. The CDC recommends that the prescribing health care practitioner encourage the intended recipient to seek medical care in addition to taking the medication. Our study found that 63.3% of partners reported they would seek medical evaluation from a physician after receiving a prescription. More importantly, only 13.3% of partners explicitly report that they would not seek medical evaluation. One approach to encourage partners to seek medical evaluation is to couple educational materials with PDPT prescriptions.
In our study, 80% of index patients reported willingness to educate partners through pamphlets or brochures and 90% of partners reported they would be willing to receive such education. These findings are encouraging. The CDC recommends that educational materials including treatment instructions, appropriate warnings about taking medications, general health counseling, and the necessity for partners to seek medical evaluation.\textsuperscript{143} In practice, it remains unclear how often physicians combine informational materials with PDPT prescriptions. For those partners who do not seek medical evaluation but fill the prescription, the pharmacist might play a central role in providing care and counseling partners.

Our research has shown that pharmacists are willing to counsel STD patients, however, pharmacists receive little training in STD treatment and counseling.\textsuperscript{166} While prevention counseling is a critical facet of effective PN, in this study only one in three partners reported they were comfortable discussing STD with a pharmacist. Privacy is an issue for our respondents, half of whom reported a perception that their conversations could be overheard in the pharmacy environment. These perceptions are not unfounded. Research on pharmacy interactions in NYS indicate that nearly 60% of pharmacy patient and staff discussions could be discerned at a distance of greater than 15 feet.\textsuperscript{167} A lack of privacy coupled with an expressed lack of comfort discussing STD with pharmacists suggests the opportunity for effective STD counseling may be missed in typical pharmacy settings.

Our study has several strengths. It is the first NYS study to quantify both patient and partner perspectives regarding PDPT. We successfully interviewed both index
patients and partners from diverse backgrounds; participants encompassed a wide demographic mix of ages, race/ethnicities, educational levels and sexual practices. Our study addresses several gaps in the literature because we assessed whether respondents would deliver prescriptions to all partners, how long delivery would take, how delivery would be conducted, and whether partners would seek medical evaluations after receiving PDPT prescriptions. We further evaluated respondents’ willingness to educate partners regarding STD and opinions regarding STD educational counseling in the pharmacy environment.

The following limitations are noteworthy. Our sampling method was one of convenience. All participants were DIS-interviewed, therefore, our sample may not be representative of all potential recipients of PDPT in NYS. While sufficient to gauge important trends in the perceptions of interest, our study’s sample size was small especially for partners, reducing statistical power for stratified analyses. Further, not all refusals were documented by DIS staff, thus an accurate response proportion could not be calculated. Based on those refusals tracked, the number of completed surveys, and number of daily DIS interviews, we estimate the response proportion to be 60.0%. Further, the present study involved interviewing participants during a stress-associated experience and we surmise that many potential respondents likely wanted to complete the DIS contact tracing interview and prevention counseling and then depart. Finally, we were not given permission to interview minors until close to the study period completion. Given the substantial proportion of chlamydia infections among those younger than 18 years of age, their opinions regarding PDPT should be ascertained.
These limitations notwithstanding, this study contributes to the PN discussion and provides insights to inform future program enhancement efforts by presenting perspectives of those most impacted by PDPT in NYS. Our results, coupled with prior research on PDPT, suggest there are intra- and inter-individual conflicting attitudes which must be addressed in order to maximize the effectiveness of PDPT. On the positive side we found that most index patients were willing to deliver prescriptions and educational materials to partners in a timely fashion. Partners overwhelmingly indicated that they were comfortable receiving prescriptions and most would seek medical evaluation. However, respondents expressed some important negative attitudes and beliefs that potentially undermine the effectiveness of PDPT in interrupting the spread of infection. In this context, we identified the following areas as important for future research and program enhancement: 1) assessment of factors impacting recipient support for the use of PDPT, in general; 2) methods to promote and assure the delivery of prescriptions and educational materials to all sexual partners; 3) strategies that promote optimal recipient health-care seeking behavior (the medical evaluation) and; 4) methods for enhancing acceptability of STD education and prevention counseling in pharmacies.
Table 1. Demographic Characteristics of Sexually Transmitted Disease Patients and Partners, New York State Capital District and Dutchess County, 2008.

<table>
<thead>
<tr>
<th></th>
<th>Index</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Most recent partner type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main</td>
<td>44</td>
<td>55.7</td>
</tr>
<tr>
<td>Casual</td>
<td>35</td>
<td>44.3</td>
</tr>
<tr>
<td>Where most recent partner was met</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through a friend</td>
<td>27</td>
<td>34.2</td>
</tr>
<tr>
<td>Other</td>
<td>24</td>
<td>30.4</td>
</tr>
<tr>
<td>Party</td>
<td>9</td>
<td>11.4</td>
</tr>
<tr>
<td>At school</td>
<td>7</td>
<td>8.9</td>
</tr>
<tr>
<td>At work</td>
<td>6</td>
<td>7.6</td>
</tr>
<tr>
<td>Bar or Club</td>
<td>5</td>
<td>6.3</td>
</tr>
<tr>
<td>On the internet</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Self-reported overall health status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>19</td>
<td>24.1</td>
</tr>
<tr>
<td>Very good</td>
<td>27</td>
<td>34.1</td>
</tr>
<tr>
<td>Good</td>
<td>19</td>
<td>24.1</td>
</tr>
<tr>
<td>Fair</td>
<td>12</td>
<td>15.2</td>
</tr>
<tr>
<td>Poor</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Number of sexual partners in the last year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or less</td>
<td>44</td>
<td>56.4</td>
</tr>
<tr>
<td>3-5</td>
<td>24</td>
<td>30.8</td>
</tr>
<tr>
<td>6-9</td>
<td>6</td>
<td>7.7</td>
</tr>
<tr>
<td>10 or more</td>
<td>3</td>
<td>3.8</td>
</tr>
<tr>
<td>Refused</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Have health insurance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54</td>
<td>68.4</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>31.6</td>
</tr>
<tr>
<td>Refused</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Have a primary doctor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, only one</td>
<td>38</td>
<td>48.1</td>
</tr>
<tr>
<td>No, no one doctor</td>
<td>26</td>
<td>32.9</td>
</tr>
<tr>
<td>More than one</td>
<td>15</td>
<td>19.0</td>
</tr>
<tr>
<td>Refused</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Could afford doctor cost out of pocket</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17</td>
<td>21.5</td>
</tr>
<tr>
<td>No</td>
<td>61</td>
<td>77.2</td>
</tr>
<tr>
<td>Don’t know / Not sure</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Refused</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
## Last general health checkup

<table>
<thead>
<tr>
<th>Interval</th>
<th>Count</th>
<th>Percentage</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within the past year</td>
<td>69</td>
<td>87.3</td>
<td>21</td>
<td>70.1</td>
</tr>
<tr>
<td>One to two years ago</td>
<td>7</td>
<td>8.8</td>
<td>7</td>
<td>23.3</td>
</tr>
<tr>
<td>Two to five years ago</td>
<td>1</td>
<td>1.3</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Over 5 years ago</td>
<td>1</td>
<td>1.3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Refused</td>
<td>1</td>
<td>1.3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

## Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Count</th>
<th>Percentage</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-20</td>
<td>22</td>
<td>28.2</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>21-25</td>
<td>20</td>
<td>25.7</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>26-30</td>
<td>15</td>
<td>19.2</td>
<td>6</td>
<td>20.0</td>
</tr>
<tr>
<td>31-35</td>
<td>9</td>
<td>11.5</td>
<td>4</td>
<td>13.3</td>
</tr>
<tr>
<td>36-40</td>
<td>9</td>
<td>11.5</td>
<td>3</td>
<td>10.0</td>
</tr>
<tr>
<td>41+</td>
<td>3</td>
<td>3.9</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Missing</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

## Hispanic or Latino

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>9</td>
<td>11.4</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>No</td>
<td>70</td>
<td>88.6</td>
<td>21</td>
<td>70.0</td>
</tr>
<tr>
<td>Refused</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

## Race

<table>
<thead>
<tr>
<th>Race Category</th>
<th>Count</th>
<th>Percentage</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black or African American</td>
<td>62</td>
<td>68.4</td>
<td>13</td>
<td>46.4</td>
</tr>
<tr>
<td>White</td>
<td>15</td>
<td>19.8</td>
<td>12</td>
<td>42.9</td>
</tr>
<tr>
<td>Some other race</td>
<td>6</td>
<td>7.9</td>
<td>2</td>
<td>7.2</td>
</tr>
<tr>
<td>Don’t know / Not sure</td>
<td>1</td>
<td>1.3</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Refused</td>
<td>2</td>
<td>2.6</td>
<td>1</td>
<td>3.5</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

## Marital status

<table>
<thead>
<tr>
<th>Marital Status</th>
<th>Count</th>
<th>Percentage</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never married</td>
<td>61</td>
<td>77.2</td>
<td>23</td>
<td>76.7</td>
</tr>
<tr>
<td>Separated</td>
<td>6</td>
<td>7.6</td>
<td>3</td>
<td>10.0</td>
</tr>
<tr>
<td>Divorced</td>
<td>5</td>
<td>6.3</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>A member of unmarried couple</td>
<td>3</td>
<td>3.8</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>Married</td>
<td>3</td>
<td>3.8</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Refused</td>
<td>1</td>
<td>1.3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

## Education level

<table>
<thead>
<tr>
<th>Education Level</th>
<th>Count</th>
<th>Percentage</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 1 through 8</td>
<td>1</td>
<td>1.3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Grades 9 through 11</td>
<td>16</td>
<td>20.2</td>
<td>11</td>
<td>36.7</td>
</tr>
<tr>
<td>Grade 12 or GED</td>
<td>34</td>
<td>43.0</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>College 1 year to 3 years</td>
<td>22</td>
<td>27.9</td>
<td>7</td>
<td>23.3</td>
</tr>
<tr>
<td>College 4 years or more</td>
<td>6</td>
<td>7.6</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>Refused</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

## Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
<th>Percentage</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhea</td>
<td>43</td>
<td>54.4</td>
<td>12</td>
<td>38.7</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>31</td>
<td>39.2</td>
<td>15</td>
<td>48.4</td>
</tr>
<tr>
<td>Don’t want to disclose</td>
<td>2</td>
<td>2.6</td>
<td>3</td>
<td>10.0</td>
</tr>
<tr>
<td>Multiple or additional STDs</td>
<td>2</td>
<td>2.6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Capital District urban area</td>
<td>42</td>
<td>53.2</td>
<td>19</td>
<td>67.9</td>
</tr>
<tr>
<td>Dutchess county</td>
<td>19</td>
<td>24.0</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>Capital District rural area</td>
<td>11</td>
<td>13.9</td>
<td>1</td>
<td>3.5</td>
</tr>
<tr>
<td>Capital District suburban area</td>
<td>7</td>
<td>8.9</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
Table 2. Patient and Partner Perspectives Regarding Partner Notification and Education Methods, New York State Capital District and Dutchess County, 2008.

<table>
<thead>
<tr>
<th>Index: How would you most prefer your partner receive partner notification?</th>
<th>Partner: How would you most prefer to receive partner notification?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Talk directly with partner about exposure to STD (patient referral)</strong></td>
<td>45</td>
</tr>
<tr>
<td><strong>Partner notification by health department representatives</strong></td>
<td>33</td>
</tr>
<tr>
<td><strong>No preference</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Index: How much do you think your partner knows about STD?</strong></td>
<td><strong>Partner: How much do you know about STD?</strong></td>
</tr>
<tr>
<td><strong>Some</strong></td>
<td>25</td>
</tr>
<tr>
<td><strong>A lot</strong></td>
<td>21</td>
</tr>
<tr>
<td><strong>A little</strong></td>
<td>13</td>
</tr>
<tr>
<td><strong>Don’t know</strong></td>
<td>11</td>
</tr>
<tr>
<td><strong>Nothing</strong></td>
<td>8</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Index: Willing to educate partners about STD through pamphlets or brochures? Partner: Willing to receive education from partners through pamphlets or brochures?</strong></td>
<td><strong>Yes, absolutely</strong></td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>11</td>
</tr>
<tr>
<td><strong>Probably</strong></td>
<td>10</td>
</tr>
<tr>
<td><strong>probably not</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Being diagnosed with a STD will make me more likely to engage in safe sex</strong></td>
<td><strong>Strongly agree</strong></td>
</tr>
<tr>
<td><strong>Agree</strong></td>
<td>25</td>
</tr>
<tr>
<td><strong>Neither agree or disagree</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Disagree</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Strongly disagree</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>It is OK for a health provider to give a written prescription to their patient to give to their sexual partners to treat STD</strong></td>
<td><strong>Strongly agree</strong></td>
</tr>
<tr>
<td><strong>Agree</strong></td>
<td>25</td>
</tr>
<tr>
<td><strong>Neither agree or disagree</strong></td>
<td>9</td>
</tr>
<tr>
<td><strong>Disagree</strong></td>
<td>26</td>
</tr>
<tr>
<td><strong>Strongly disagree</strong></td>
<td>9</td>
</tr>
<tr>
<td><strong>Refused</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>1</td>
</tr>
</tbody>
</table>
Table 3. Patient and Partner Perspectives Regarding Delivery of Antibiotic Prescriptions to Sexual Partners Under Patient Delivered Partner Therapy, New York State Capital District and Dutchess County.

<table>
<thead>
<tr>
<th>Index: If given a prescription for your most recent partner under PDPT, how likely is it that you would give it to your partner. Partner: if your most recent partner was given a prescription, how likely is it they would give it to you?</th>
<th>Partner</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 %</td>
<td>57</td>
<td>72.1</td>
<td>16</td>
</tr>
<tr>
<td>Around 80 %</td>
<td>7</td>
<td>8.9</td>
<td>2</td>
</tr>
<tr>
<td>Around 50 %</td>
<td>7</td>
<td>8.9</td>
<td>7</td>
</tr>
<tr>
<td>Less than 50 %</td>
<td>4</td>
<td>5.0</td>
<td>3</td>
</tr>
<tr>
<td>0 %</td>
<td>3</td>
<td>3.8</td>
<td>1</td>
</tr>
<tr>
<td>Refused</td>
<td>1</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How long will it take to give partner their prescription</th>
<th>Partner</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>One day or less</td>
<td>53</td>
<td>69.7</td>
<td>12</td>
</tr>
<tr>
<td>Two to three days</td>
<td>12</td>
<td>15.8</td>
<td>12</td>
</tr>
<tr>
<td>Four to six days</td>
<td>6</td>
<td>7.9</td>
<td>1</td>
</tr>
<tr>
<td>Refused</td>
<td>3</td>
<td>4.0</td>
<td>0</td>
</tr>
<tr>
<td>A week or more</td>
<td>1</td>
<td>1.3</td>
<td>2</td>
</tr>
<tr>
<td>Don’t know</td>
<td>1</td>
<td>1.3</td>
<td>2</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How the prescription would be delivered to their partner</th>
<th>Partner</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand in to them in person</td>
<td>50</td>
<td>65.8</td>
<td>19</td>
</tr>
<tr>
<td>Mail the prescription</td>
<td>7</td>
<td>9.2</td>
<td>3</td>
</tr>
<tr>
<td>Get the prescription filled and give it directly to them in person</td>
<td>5</td>
<td>6.6</td>
<td>0</td>
</tr>
<tr>
<td>Drop it off at a pharmacy for the partner to pickup</td>
<td>4</td>
<td>5.3</td>
<td>1</td>
</tr>
<tr>
<td>Refused</td>
<td>4</td>
<td>5.3</td>
<td>0</td>
</tr>
<tr>
<td>Telephone the partner telling them where to pick up the prescription</td>
<td>3</td>
<td>3.9</td>
<td>4</td>
</tr>
<tr>
<td>Don’t know</td>
<td>2</td>
<td>2.6</td>
<td>1</td>
</tr>
<tr>
<td>Do it some other way</td>
<td>1</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If you did bring the prescription to a pharmacy, which pharmacy would it be?</th>
<th>Partner</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where the partner usually fills their prescriptions</td>
<td>33</td>
<td>43.4</td>
<td>10</td>
</tr>
<tr>
<td>Don’t know</td>
<td>14</td>
<td>18.4</td>
<td>13</td>
</tr>
<tr>
<td>Another pharmacy other than the partner usually uses</td>
<td>26</td>
<td>34.2</td>
<td>6</td>
</tr>
<tr>
<td>Refused</td>
<td>3</td>
<td>4.0</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At least one person in the past year would not get the prescription</th>
<th>Partner</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly Agree</td>
<td>8</td>
<td>10.1</td>
<td>5</td>
</tr>
<tr>
<td>Agree</td>
<td>16</td>
<td>20.3</td>
<td>11</td>
</tr>
<tr>
<td>Neither agree or disagree</td>
<td>1</td>
<td>1.3</td>
<td>2</td>
</tr>
<tr>
<td>Disagree</td>
<td>28</td>
<td>35.4</td>
<td>8</td>
</tr>
<tr>
<td>Strongly Disagree</td>
<td>24</td>
<td>30.4</td>
<td>3</td>
</tr>
<tr>
<td>Refused</td>
<td>2</td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
There is at least one partner I would not trust to give me a prescription

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
<th>Percentage</th>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly agree</td>
<td>17</td>
<td>21.5</td>
<td>3</td>
<td>10.0</td>
</tr>
<tr>
<td>Agree</td>
<td>25</td>
<td>31.6</td>
<td>6</td>
<td>20.0</td>
</tr>
<tr>
<td>Neither agree or disagree</td>
<td>6</td>
<td>7.6</td>
<td>10</td>
<td>33.3</td>
</tr>
<tr>
<td>Disagree</td>
<td>20</td>
<td>25.3</td>
<td>9</td>
<td>30.0</td>
</tr>
<tr>
<td>Strongly disagree</td>
<td>10</td>
<td>12.7</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Refused</td>
<td>1</td>
<td>1.3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

If given an antibiotic prescription by my partner, I would still see a doctor

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
<th>Percentage</th>
<th>Median</th>
<th>Mean</th>
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<td>40</td>
<td>50.6</td>
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<tr>
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<tr>
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</table>

I would give a prescription to every recent partner

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<th>Median</th>
<th>Mean</th>
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<td>26.7</td>
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<tr>
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**Paper 3: Utilizing Informational Card-Enhanced Partner Referral For Partner Notification of Chlamydia: Perspectives Of Students Attending A New York University**

**Abstract**

**Background:** Partner notification for *Chlamydia trachomatis* may be enhanced with patient-delivered information cards which include contact information for treatment clinics. We assessed university student perceptions about using this form of partner notification.

**Methods:** A self-administered survey of consecutive students attending a University health center was conducted from February 2013 to March 2013 to determine student willingness to notify sexual partners of potential chlamydia exposure by distributing informational cards to their partner(s). We also asked about the preferred method of card delivery and reasons for not wanting to deliver cards. Bivariate analyses and log binomial regression were conducted to identify predictors of student willingness to deliver notification cards to partners.

**Results:** Data from 543 surveyed students, 334 females (61.5%) and 209 males (38.5%), was analyzed. Most reported a willingness to deliver cards to main partners (65.8%) and would do so in person (77.2%). Half of respondents would deliver cards to all partners (54.3%). Often those who reported they would not deliver cards to all partners cited a negative reason, including being unable/unwilling to contact their partner (20.2%) or embarrassment to admit having a sexually transmitted infection (15.1%). Being in a steady relationship and participant race/ethnicity were predictive of willingness to deliver cards to all partners.
Conclusions: Participants reported a willingness to deliver informational cards to most partners. Given the limited available data and the generally favorable attitudes expressed toward this approach by University students, further study into card referral is warranted to inform future disease control program recommendations among this at-risk population.

Keywords: Sexually transmitted diseases, patient delivered partner therapy, informational cards, partner notification, chlamydia, University, treatment.

Introduction

Chlamydia is the most common bacterial sexually transmitted infection (STI) with an estimated three million new infections annually in the United States; 63% occur in those under age 25. Partner notification leading to testing and treatment of all sexual partners is an important means of disease control. Research suggests that health department-assisted partner notification is the most effective partner notification approach, but given the competition for the scarce public health resources allocated to STI control, chlamydia is often a low priority.120,362

Patient self-referral or “standard” referral is the most common method of partner notification for chlamydia. With standard referral, the infected patient directly notifies their sexual partner(s) of potential exposure and refers them to treatment. While this method is less resource and labor intensive compared to other approaches, prior studies suggest about half of sexual partners are successfully referred using this approach.146,176,379-381 To reach more sexual partners of index patients, several alternative partner notification approaches have been considered and implemented in the last decade.121-123,141,364 One alternative approach which has been studied in limited fashion is
the concept of providing informational cards to index patients to facilitate partner referral (i.e., “booklet enhanced partner referral”).\textsuperscript{135,136}

Informational cards enhance standard patient referral by allowing the index patient to inform and refer partners for treatment using pre-printed cards given to them by their health care provider. These cards inform the recipient that he or she has been exposed to chlamydia and should seek medical care. The cards also may include information regarding symptoms, potential sequelae of untreated infection, and information about local treatment facilities. The intent of the informational card is twofold: facilitate notification of potential exposure by the index patient to his or her partners, and improve access to care by providing information on treatment facilities. The cards can also be presented to a clinician by the partner to aid in the treatment process.

Research on the effectiveness of informational cards (hereafter referred to as “card referral”), limited to date, suggests augmenting the standard referral process with local treatment clinic information and/or educational materials may be more effective than standard referral alone.\textsuperscript{113,137,138} Use of informational cards was investigated in two studies by Kissinger, \textit{et al.}, but the two studies produced conflicting findings. In a male urethritis study, card referral was more effective in preventing recurrent infection among index patients compared to standard referral: infection was present at follow-up in 43\% in the standard referral group and 14\% in the card referral group.\textsuperscript{135} However, in a study of women being treated for \textit{Trichomonas vaginalis}, women receiving card referral were slightly more likely to be infected with \textit{Trichomonas vaginalis} at follow-up compared to women using standard referral (9\% vs. 6\%, respectively).\textsuperscript{136}
With chlamydia prevalence generally high among college students, novel approaches to combat the disease burden are worthy targets for research. However, the literature on partner notification remains relatively scant for this population despite the high prevalence of chlamydia. Given the encouragingly low reinfection proportion in the male urethritis study, we were interested in evaluating willingness of college students to use informational cards for partner notification. We also describe the approaches that students would utilize to deliver these informational cards.

**Materials and Methods**

Consecutive students visiting a University health center during defined study periods were recruited to participate in this cross-sectional study. To be eligible, participants had to be a currently registered student, at least 18 years old, speak and understand English, and be able to provide informed consent. Participants were recruited from February to March 2013. We also recruited eligible students accompanying ill students visiting the health center. The study procedures were explained and students were administered informed consent prior to enrollment. Participants were seated a minimum of six feet apart in sections of the waiting area designated for research. Participants were given a copy of the informed consent, a survey, and a large envelope in which to seal the completed survey. This study was approved by the Institutional Review Board of the authors’ University. Participants were given a small gift as a token for their time.

The survey assessed participant sexual risk factors, such as number of partners in the last year, relationship status and condom use frequency. Further, the survey covered participants’ perspectives on card referral, including willingness to utilize an
informational card to help notify partners, the likelihood of delivering cards to all partners, and the methods participants would employ to deliver cards to their most recent sexual partner(s). The survey questions were primarily categorical in nature, but an open-ended comments section was included at the end of the survey to capture more qualitative information.

The survey data were entered into Epi-Info v.3.3.2. Data were imported into SAS (v.9.3, SAS institute, Cary, N.C.) for analyses. Descriptive statistics, including frequency counts and proportions, were computed to ascertain respondents’ perspectives on the informational cards. Cross-tabulations of participant demographic characteristics with survey responses were conducted. Statistical associations were determined using Fisher’s exact test. Utilizing a stepwise backward elimination process, a multivariable log-binomial regression model was constructed to determine covariates predictive of participant willingness to utilize informational cards to inform both main sexual partners, as well as all sexual partners, of potential exposure to chlamydia. Confounding variables were identified by adding back into the model all covariates and assessing the change in effect estimates. Any covariate which changed the effect estimates by more than 10% was retained in the full model.

**Results**

Of the 628 eligible recruits, 600 university students agreed to participate, yielding a 95.5% response proportion. We limited the analysis to the 543 participants reporting at least one sexual partner in the last year (90.5%). These participants were 61.5% female.
(n=334), predominantly White/non-Hispanic (58.6%), and 18 to 20 years of age (53.6%). Most (56.2%) were not in a current, steady relationship. (Table 1)

The majority of participants reported having one main sexual partner (63.8%), while nearly a quarter reported having current casual sexual partners (24.3%). Many (63.9%) of the respondents reported not always utilizing condoms during sexual activity and 12.9% of all respondents reported never using condoms. (Table 2) We further stratified sexual behavior by sex. Males were significantly more likely than females to report currently having casual sexual partners (31.6% versus 19.8%, respectively, p<0.001). Males also were more likely than females to report having multiple sexual partners in the last year (62.5% versus 56.8%, respectively, p=0.091).

The majority of participants with a main sexual partner reported that they would “probably” or “definitely” deliver informational cards to their primary partner to facilitate partner notification for chlamydia (65.8%). (Table 3) When asked how they would notify their main sexual partner with this card, 77.2% reported they would do so in person, while another 11.1% indicated they would do so electronically by text/email if this option was available. When asked if they would prefer to bring a prescription directly to their partner rather than utilizing a card, only 24.2% responded affirmatively. Of those who are unlikely to deliver cards to main partners (34.2%), the majority wanted to conduct notification directly, without using cards (88.1%).

About half of respondents reported they would give cards to all of their sexual partners (54.3%). Of the remaining 45.7% of those who reported unwillingness to deliver cards to all partners, almost half cited a negative reason, such as being unable/unwilling
to contact their partner (20.2%), being embarrassed to admit having an STI (15.1%) and fear of a partner’s reaction (7.3%).

We also stratified card referral perspectives by the number of sexual partners in the last year (one versus two or more) as shown in Table 3. Having fewer sexual partners increased the likelihood of delivering cards to both main partners and all partners. Those with one sexual partner in the last year reported greater willingness to deliver cards to their main partners compared to those with two or more sexual partners in the last year (67.9% versus 63.0%, respectively, p<0.001). Furthermore, those with only one sexual partner reported greater willingness to deliver cards to all partners compared to those reporting two or more partners (65.6% versus 46.1%, respectively, p=0.003).

Being in a steady relationship also influenced the likelihood of reporting willingness to deliver cards. We found that those who were in steady relationships reported greater willingness to distribute cards to all partners compared to those not in steady relationships (65.1% versus 44.3%, respectively, p=0.011). Those not in a steady relationship also were less willing to “definitely” give cards to their main sexual partner versus those respondents in a steady relationship (29.2% versus 35.8%, respectively, p=0.011). Among those with two or more sexual partners in the last year, being in a steady relationship increased the likelihood of reporting willingness to deliver cards to all partners compared to those not in a steady relationship (58.2% versus 41.8%, respectively, p=0.034). Again, for those reporting only one sexual partner in the last year, those in a steady relationship were more willing to deliver cards than those who were not (69.9% versus 54.3%, respectively, p=0.088).
Multivariable log binomial regressions identified few factors associated with willingness to give informational cards to partners. (Table 4) In a model including all participants with at least one sexual partner in the last year, participant race/ethnicity and self-reported use of condoms during every sexual encounter were significant predictors of willingness to give a card to a main partner. In this model, despite the association of number of sexual partners in the last year and relationship status with willingness to deliver cards to main partners, neither covariate was predictive, when including an interaction variable. However, in a model restricted to those reporting two or more sexual partners in the last year, being in a steady relationship, as well as participant race ethnicity (Black-non Hispanic) were significant predictors of willingness to give a card to all sexual partners. Condom use was not a significant predictor in the restricted model but was a borderline confounder and thus retained in the model.

**Discussion**

University students were generally willing to deliver cards to their sexual partners. It is encouraging that over half of respondents would give cards to all partners, while over two-thirds reported they would definitely or probably give cards to their main partners. While the findings in our study are positive, they are offset somewhat by the fact that almost half of those who reported they would not deliver cards to all partners cited a negative reason, such as being unable/unwilling to contact their partner (20.2%), embarrassment to admit having an STI (15.1%) and fear of a partner’s reaction (7.3%). This is important, as it is unclear whether any of the patient driven expedited partner notification approaches (i.e. PDPT, card referral etc.) would result in these partners being notified. While health department assisted partner notification, in which investigators
work with patients to identify partners then conduct notification on the patient’s behalf, has been the most effective partner notification approach and could potentially circumvent these obstacles, resources are inadequate in most areas to implement this strategy for chlamydia, which is a lower programmatic priority versus HIV, syphilis and gonorrhea. Given this reality, our findings for card referral as another option to reach partners suggest that this outreach method may be worth developing. While health providers often counsel patients on how to inform partners of the need for evaluation and treatment under standard patient referral, limited data suggests that the provision of disease specific information and/or treatment center location to assist partner notification is more effective over standard patient referral alone.

While novel approaches to improve effective partner notification are needed, very few have been studied intensively in the past decade, and none are as effective as health department assisted notification. Research suggests that the more sexual partners, the less likely the person with an STI is to conduct partner notification of any kind with all partners. However, there is evidence that those who are in long-term relationships, including marriages, are more likely to initiate partner notification for STI compared to those who are single. Our findings were consistent with this prior research.

As the internet is an avenue for meeting new partners, use of electronic partner notification is being studied and shows some promise in achieving notification. Surprisingly, few students (11.1%) reported they would use electronic mailing services (e.g., email, Facebook) as a means of notifying partners with informational cards.
Unfortunately, our data also buttress the notion that participants who are not in a steady relationship would not be willing to deliver a card to all recent partners. These individuals may have lost contact with prior partners or have had more anonymous or one-time encounters. In our study, while most respondents in a steady relationship reported having only one sexual partner, a large percentage (35.7%) reported having two or more partners. Yet the tendency to be more willing to deliver cards persisted—75% of those in a steady relationship who also had casual partners would deliver cards to all partners compared to just 34% of those who were not in a steady relationship.

Our findings regarding condom use and willingness to deliver a card to a main partner may be partially explained by the notion that positive sexual behaviors correlate. Controlling for race/ethnicity, those reporting always using condoms during sexual activity were 17% more likely to report willingness to give a card to their main partner compared to those who reported not always using condoms. There are two possible explanations. First, these respondents may be more health conscious and, consequently, also value sexual health. In our sample, those who used condoms every time were also less likely to smoke (data not shown). A second explanation could be that these respondents’ answers were influenced by a social desirability bias, however, other reported health behaviors did not predict willingness to deliver cards nor confound the final model.

Perhaps more importantly, we were interested in quantifying covariates predictive of delivering cards to all partners. Interestingly, in this case, even among those reporting two or more sexual partners in the last year, relationship status was predictive of willingness to deliver cards to all partners. Controlling for race/ethnicity and condom use,
those reporting they were in a steady relationship were 53% more likely to deliver cards to all partners compared to those who were not in a steady relationship. An explanation for this observation is unclear, but in our sample, it was not a function of the number of sexual partners in the last year, health seeking or health conscious behavior, or other demographic characteristics. Our data do indicate that those not in a steady relationship more frequently reported they preferred to talk to partners directly regarding a possible infection versus those who were in a steady relationship, however this variable was not predictive in the model.

We found Black/non-Hispanics students were most likely to be willing to deliver cards to all partners. Given that Black/non-Hispanics within this age group have a high burden of chlamydia, we find their willingness to deliver cards to all partners encouraging. It would be helpful to understand what interventions potentially caused this difference and if they can be expanded.

Our study has several strengths. It is the first study in the United States that we are aware of to quantify willingness of a University-aged sample to engage in partner notification for chlamydia with the use of informational cards. We successfully surveyed students with diverse backgrounds; participants encompassed a wide demographic mix of age, racial/ethnic groups, health and sexual practices. We also attempted to add details to our understanding of this population, such as whether respondents would utilize cards to notify both main and casual sexual partners, the mode of delivery, and reasons for opting out of partner notification in this manner.

Several limitations are noteworthy. Our sampling method was one of convenience. Students visiting the University health center may not be representative of...
all University students. Those visiting the health center may, on average, have been more ill than the general University population, or more health seeking than the general University population. This may have influenced the observations noted in this study. Our sample was mostly female primarily due to women seeking preventive care at the health center. However, with the exception of number of casual sexual partners, there were no statistical differences in responses by gender. We relied on self-report to assess sexual history which may introduce recall or social desirability bias, potentially impacting the associations identified in the analysis. Further, our sample was not restricted to patients diagnosed with chlamydia but rather those in a subpopulation at risk for chlamydia, thus, our findings may not be generalizable to all potential chlamydia patients of similar age/education. We did not anticipate the high proportion of University students that would report no sexual partners in the least year (nearly 10%). This limited the available data for analysis and thus statistical precision. Our protocol also excluded minors who represent a group equally at risk for chlamydia (however, minors are a small proportion of the overall University population). Given the substantial proportion of chlamydia infections among those younger than 18 years of age, their opinions regarding card referral should be ascertained.

These limitations notwithstanding, this study contributes to the partner notification discussion by presenting perspectives of those vulnerable to chlamydia infection—young adults attending a local University. Our results suggest that University students are willing to engage in this modified partner notification approach which has been shown to be at least equally likely to result in successful partner notification versus
standard referral. Given the limited body of literature regarding card referral, our positive findings indicate further research into card referral is justified.
Table 1: Demographic characteristics of participants*, University Health Center patient survey, New York State, 2013.

<table>
<thead>
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<th></th>
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<td>21-25</td>
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<td>1.7</td>
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*Limited to the 543 participants reporting at least one sexual partner in the last year
**Many participants accompanied their friends to routine appointments, had post-surgical follow-ups, and were picking up prescriptions, among other reasons.
<table>
<thead>
<tr>
<th>Current has one main sexual partner</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
<th>p-value</th>
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<tr>
<td>Yes</td>
<td>346</td>
<td>127</td>
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<td>196</td>
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<td>1</td>
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<table>
<thead>
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<th>Currently has casual sexual partners</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
<th>p-value</th>
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<td>Yes</td>
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<td>66</td>
<td>66</td>
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<td>No</td>
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<td>143</td>
<td>268</td>
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</table>

<table>
<thead>
<tr>
<th>Number of sexual partners in the last year</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
<th>p-value</th>
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<tr>
<td>1</td>
<td>225</td>
<td>78</td>
<td>147</td>
<td>0.091</td>
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<tr>
<td>2</td>
<td>128</td>
<td>48</td>
<td>80</td>
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<tr>
<td>3-5</td>
<td>134</td>
<td>54</td>
<td>80</td>
<td></td>
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<tr>
<td>6+</td>
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<td>1</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency of condom use during sexual activity</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
<th>p-value</th>
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<td>Every time</td>
<td>196</td>
<td>80</td>
<td>116</td>
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<td>Most times</td>
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<td>62</td>
<td>100</td>
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<td>About half the time</td>
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<td>8</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>88</td>
<td>26</td>
<td>62</td>
<td></td>
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<tr>
<td>Never</td>
<td>70</td>
<td>33</td>
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<tr>
<td>Missing</td>
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</tbody>
</table>

Table 2: Basic sexual behavior of participants in the University Health Center patient survey, by gender, University at Albany, New York, 2013.
<table>
<thead>
<tr>
<th>Would give card to main sexual partner</th>
<th>n</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th><strong>p-value</strong></th>
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</thead>
<tbody>
<tr>
<td>Definitely</td>
<td>152</td>
<td>32.5</td>
<td>73</td>
<td>36.5</td>
<td>79</td>
<td>29.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Probably</td>
<td>156</td>
<td>33.3</td>
<td>53</td>
<td>26.5</td>
<td>103</td>
<td>38.4</td>
<td></td>
</tr>
<tr>
<td>Probably not</td>
<td>111</td>
<td>23.7</td>
<td>42</td>
<td>21.0</td>
<td>69</td>
<td>25.8</td>
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<tr>
<td>Definitely not</td>
<td>49</td>
<td>10.5</td>
<td>32</td>
<td>16.0</td>
<td>17</td>
<td>6.3</td>
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<tr>
<td>Not applicable/missing</td>
<td>75</td>
<td>10.5</td>
<td>25</td>
<td>12.5</td>
<td>50</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td><strong>Would give card to all sexual partners</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Yes, all partners</td>
<td>166</td>
<td>54.3</td>
<td>82</td>
<td>65.6</td>
<td>84</td>
<td>46.1</td>
<td></td>
</tr>
<tr>
<td>Some, but not all partners</td>
<td>125</td>
<td>40.8</td>
<td>37</td>
<td>30.5</td>
<td>88</td>
<td>48.4</td>
<td></td>
</tr>
<tr>
<td>No, none of them</td>
<td>15</td>
<td>4.9</td>
<td>5</td>
<td>3.9</td>
<td>10</td>
<td>5.5</td>
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<td>100</td>
<td></td>
<td>136</td>
<td></td>
<td></td>
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<td><strong>Would not give main partner card because</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.251</td>
</tr>
<tr>
<td>Would tell partner directly</td>
<td>141</td>
<td>88.1</td>
<td>66</td>
<td>89.2</td>
<td>75</td>
<td>87.2</td>
<td></td>
</tr>
<tr>
<td>Anger/would not want to see them</td>
<td>3</td>
<td>1.9</td>
<td>3</td>
<td>4.0</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Embarrassed to admit having STI</td>
<td>6</td>
<td>3.8</td>
<td>2</td>
<td>2.7</td>
<td>4</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Fear of partner’s reaction</td>
<td>5</td>
<td>3.1</td>
<td>1</td>
<td>1.4</td>
<td>4</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Other reason</td>
<td>5</td>
<td>3.1</td>
<td>2</td>
<td>2.7</td>
<td>3</td>
<td>3.4</td>
<td></td>
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<tr>
<td>Not applicable/missing</td>
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<td></td>
<td>151</td>
<td></td>
<td>232</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reason would not give card to all partners</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.211</td>
</tr>
<tr>
<td>Would tell partners directly</td>
<td>59</td>
<td>42.3</td>
<td>20</td>
<td>48.8</td>
<td>39</td>
<td>39.8</td>
<td></td>
</tr>
<tr>
<td>Anger/not want to see them</td>
<td>6</td>
<td>4.4</td>
<td>3</td>
<td>7.3</td>
<td>4</td>
<td>3.1</td>
<td></td>
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<tr>
<td>Embarrassed to admit having STI</td>
<td>21</td>
<td>15.1</td>
<td>6</td>
<td>14.6</td>
<td>18</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>Fear of partner’s reaction</td>
<td>10</td>
<td>7.3</td>
<td>2</td>
<td>4.9</td>
<td>14</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Unable to contact some recent partners</td>
<td>22</td>
<td>15.8</td>
<td>4</td>
<td>9.8</td>
<td>24</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>Other reason</td>
<td>21</td>
<td>15.1</td>
<td>6</td>
<td>14.6</td>
<td>19</td>
<td>15.3</td>
<td></td>
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<tr>
<td>Missing/Not applicable</td>
<td>405</td>
<td>185</td>
<td>220</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>-----</td>
<td>-----</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Would not give card to at least one partner</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongly agree</td>
<td>80</td>
<td>14.9</td>
<td>27</td>
<td>12.3</td>
<td>53</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>59</td>
<td>11.0</td>
<td>10</td>
<td>4.6</td>
<td>49</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td>Neither agree nor disagree</td>
<td>65</td>
<td>12.2</td>
<td>21</td>
<td>9.5</td>
<td>44</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>Disagree</td>
<td>103</td>
<td>19.2</td>
<td>38</td>
<td>17.3</td>
<td>65</td>
<td>20.6</td>
<td></td>
</tr>
<tr>
<td>Strongly disagree</td>
<td>229</td>
<td>42.7</td>
<td>124</td>
<td>56.3</td>
<td>105</td>
<td>33.2</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td></td>
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</tr>
</tbody>
</table>
Table 4: Final log binomial regression results showing covariates predictive of participant willingness to notify main sexual partners of potential chlamydia exposure with the use of informational cards, University Health Center patient survey, New York State, 2013.

<table>
<thead>
<tr>
<th>Willing to deliver card to main partner (vs. not willing)</th>
<th>RR</th>
<th>95% CI</th>
<th>aRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condom use during sexual activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not always</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Always</td>
<td>1.20</td>
<td>1.05, 1.36</td>
<td>1.17</td>
<td>1.04, 1.32</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>1.06</td>
<td>0.98, 1.17</td>
<td>1.11</td>
<td>0.93, 1.33</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.10</td>
<td>1.01, 1.21</td>
<td>1.18</td>
<td>1.00, 1.40</td>
</tr>
<tr>
<td>Asian</td>
<td>1.07</td>
<td>1.01, 1.15</td>
<td>1.24</td>
<td>1.02, 1.51</td>
</tr>
<tr>
<td>Other</td>
<td>1.02</td>
<td>0.92, 1.19</td>
<td>1.04</td>
<td>0.76, 1.43</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Willing to deliver card to all partners (vs. not willing)*</th>
<th>RR</th>
<th>95% CI</th>
<th>aRR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td><strong>Relationship status</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not in a steady relationship</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>In a steady relationship</td>
<td>1.41</td>
<td>1.04, 1.81</td>
<td>1.55</td>
<td>1.18, 2.03</td>
</tr>
</tbody>
</table>
### Race/ethnicity

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>RR</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>White non-Hispanic</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>1.30</td>
<td>1.01, 1.62</td>
<td>1.45</td>
<td>1.10, 1.92</td>
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<tr>
<td>Hispanic</td>
<td>0.90</td>
<td>0.69, 1.27</td>
<td>0.94</td>
<td>0.57, 1.52</td>
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<tr>
<td>Asian</td>
<td>1.11</td>
<td>0.71, 1.92</td>
<td>1.08</td>
<td>0.48, 2.42</td>
</tr>
<tr>
<td>Other</td>
<td>1.22</td>
<td>0.65, 2.02</td>
<td>1.14</td>
<td>0.58, 2.22</td>
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</tbody>
</table>

### Condom use during sexual activity

<table>
<thead>
<tr>
<th>Condom use during sexual activity</th>
<th>RR</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not always</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Always</td>
<td>1.11</td>
<td>0.88, 1.41</td>
<td>1.12</td>
<td>0.86, 1.45</td>
</tr>
</tbody>
</table>

*Limited to those reporting two or more sexual partners in the last year

Multivariable (adjusted) results control for condom use during sexual activity and race/ethnicity.

RR, (unadjusted) relative risk; ARR, adjusted relative risk
Chapter 5. Conclusions

The burden of *Chlamydia trachomatis* infection continues to rise globally, largely due to more effective screening, but the increased incidence and prevalence seen over the last two decades is unlikely attributable entirely to better detection. The data from this study suggests that repeat positive infections are also on the rise, ranging on average from 5%-20% of previously treated patients retesting positive within three months. There are three possible reasons for this phenomenon which the research presented in this dissertation addressed. First, antibiotic-resistant chlamydia infections, while exceptionally rare, have been documented. Second, the evidence suggests that a significant portion of the genuine treatment failures might be attributable to persistent infections. Third, patients may be reinfected by untreated sexual partners, underscoring the importance of notifying and treating these individuals. This dissertation augments the existing literature in these three areas and identifies additional research questions which merit further investigation.

For instance, the respective proportions of repeat positive tests attributable to resistance, persistence, and reinfection are currently unknown. Given the paucity of research in this area, it remains difficult to draw any firm conclusions regarding antibiotic-resistant strains. The limited data available suggests that for the small fraction of repeat positives which are true treatment failures, antibiotic resistance is not likely to be the root cause. While the body of evidence is limited, comprising fewer than 10 studies, it appears that mutations do not generally increase competitiveness. As such, the
data do not support funding public health monitoring for antibiotic resistance for *C. trachomatis*.

On the other hand, persistence is likely responsible for most cases of true treatment failures; there is a moderate quality body of evidence characterized by numerous reports each yielding consistent findings with regards to the presence of persistence characteristics. With evidence supporting persistence occurring in *C. trachomatis*, future study is justified to determine how often infections become persistent, under what conditions the persistent infection reverts to the infectious state in vivo, and if persistent infections are transmissible. Despite the evidence for persistence as a cause of genuine treatment failures, the primary public health concern should remain focused on preventing reinfection from an untreated partner.

With novel partner notification approaches, such as PDPT and informational card referral, more choices are available for infected patients to get their sexual partners treated. This dissertation adds meaningfully to the PDPT literature as it is among the first studies to quantify the perspectives of patients and sexual partners regarding PDPT. Patients were sharply divided on their attitudes toward PDPT: 44.3% of index patients believed it was “ok for a doctor to give someone with an STD a written prescription for his/her sexual partner” while 44.3% disagreed. A similar dichotomy was seen for partners, as 40.0% agreed and 40.0% disagreed. An important finding is that most (72.1%) index patients reported they would deliver the prescription to their most recent partner and the majority would do so within three days (85.5%), which is very favorable. However, this generally positive stance toward PDPT was offset by the fact that approximately one-third of index patients (30.4%) and half of partners (53.3%) reported
that there was at least one partner to whom they would not give a prescription. This finding is troubling as it opens the door for the chain of infection to continue. Interestingly, surveyed students were far less likely to support PDPT and preferred information card referral.

The data suggests that card referral is worthy of further research as most (66.5%) students reported that they would probably or definitely deliver informational cards to their main partner. A critical caveat to these findings is that among those who would not utilize card referral, 88.2% preferred to notify their partners directly (i.e., standard referral). Most students reported they would give cards to all of their sexual partners (54.3%) but this positive finding was offset by the fact that nearly half (42.3%) cited they would not do so because they preferred to notify partners directly, making it less likely that these partners would be reached. While PDPT and card referral can be useful in reaching partners who otherwise would not seek treatment, to break the chain of infection, partner notification needs to occur in 100% of cases. Health department notification may be the most effective way to reach most partners, but is simply not currently feasible in most regions. Of the two novel partner notification approaches studied, the advantage of card referral is clear: partners need to present for evaluation and treatment. Encouragingly, most partners reached by PDPT (63.3%) indicated they would seek a medical evaluation, and nearly all students (96%) would seek medical evaluation if they received an informational card from a sexual partner.

It should be noted that this dissertation sought to quantify college student knowledge of their sexual partner’s cardiac risk factors. This study was undertaken in response to findings published by Ray, et al. showing an increased risk of cardiovascular
death among those using azithromycin\textsuperscript{22}, prompting an FDA warning for physicians to consider cardiac risk factors prior to prescribing azithromycin.\textsuperscript{23} The study was stopped because Svanstrom, \textit{et al.} published a population-based study demonstrating there was little to no risk whatsoever among the college age population and instead was limited to those over age 45 or with significant cardiovascular health issues.\textsuperscript{259} As such, findings regarding knowledge of sexual partner cardiac risk factors, while interesting and a possible area worthy of further behavioral research, became somewhat irrelevant to the treatment of chlamydia.

In conclusion, it appears that azithromycin will remain the first-line agent for chlamydia. Despite evidence that bacterial persistence is responsible for some treatment failures, azithromycin was implicated in exceptionally rare cases of resistance, as were other antimicrobials. This dissertation has identified several promising areas worthy of additional research. Strategies to improve effective partner notification should be evaluated and refined by robust studies. Effective notification and treatment should include maximizing the number of partners who are medically evaluated after receiving a PDPT prescription. Finally, the findings from the card referral study offer compelling evidence that this approach should be evaluated in a larger population, particularly when considered in tandem with the findings of Kissinger, \textit{et al.}\textsuperscript{135,136} An informational card which includes contact information for a local treatment center is a reasonable, low-cost enhancement that warrants further study in New York State where standard referral is the most prevalent outreach strategy at present.
6. References


21. Prescriptions. Title 8 of the New York State Education Law, Article 137, §6810.


Available at


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40. Eng T, Butler WT. The Hidden Epidemic: Confronting Sexually Transmitted Diseases. Washington, DC: Committee on Prevention and Control of Sexually Transmitted Diseases, Institute of Medicine, National Academy Press; 1997


165. Rogers ME, Opdyke KM, Blank S, Schillinger JA. Patient-delivered partner treatment and other partner management strategies for sexually transmitted


206. Stamm LV, Bergen HL. A point mutation associated with bacterial macrolide resistance is present in both 23S rRNA genes of an erythromycin resistant


200


365. Untitled act—“Authorizes a health care practitioner diagnosing a sexually transmitted chlamydia trachomatis infection to provide antibiotic drugs to such patient's partner”, A8730-C, Chapter 577, Pub. L. no. 2312 (September 25, 2008).


7. Additional Tables and Figures

Table 1. Results of Seven Studies Conducted to Quantify the Sensitivities and Specificities of a Direct Fluorescent Antibody Test to Detect Chlamydia Demonstrating the Variability in Reported Findings.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Sample Source Population</th>
<th>Reported Sensitivity (%)</th>
<th>Reported Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarke et al., 1993</td>
<td>217 females</td>
<td>78</td>
<td>98.8</td>
</tr>
<tr>
<td>Warren et al., 1993</td>
<td>1,037 females</td>
<td>80</td>
<td>99.3</td>
</tr>
<tr>
<td>Altaie et al., 1992</td>
<td>1,240 females</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Genc et al., 1991</td>
<td>245 females</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td>Genc et al., 1991</td>
<td>196 males</td>
<td>62</td>
<td>96</td>
</tr>
<tr>
<td>Gaydos et al., 1990</td>
<td>307 males and females</td>
<td>77</td>
<td>98</td>
</tr>
<tr>
<td>Moncada et al., 1990</td>
<td>2,891 females</td>
<td>81</td>
<td>99</td>
</tr>
</tbody>
</table>
### Table 2. Table of Patient Delivered Partner Therapy Studies and Their Main Findings.

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Participant characteristics</th>
<th>Study Characteristics, interventions etc.</th>
<th>Sample size</th>
<th>Primary findings, results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatski et al, 2010.</td>
<td>Women with HIV and Trichomonas vaginalis (TV)</td>
<td>Purpose: evaluate adherence to PDPT and investigate causes of repeat infection with TV among HIV infected women. Women were treated and given treatment to deliver to all reported sex partners. Test of cure conducted 1 to 2 weeks later.</td>
<td>252</td>
<td>Of 183 women with sex partners at baseline, 75.4% gave PDPT to all partners, 61.7% report partner surely took medicine. 10.3% retested TV positive</td>
</tr>
<tr>
<td>Stephens et al. 2010</td>
<td>Chlamydia cases and gonorrhea cases in San Francisco STI Clinics, diagnosed October 2005 to March 2008</td>
<td>Purpose: examine the association between receiving PDPT and Chlamydia/Gonorrhea reinfection within 1 year. Patients were given either PDPT or standard referral for PN, and followed for 1 year to evaluate reinfection status; propensity score modeling used to control differences between two PN methods</td>
<td>6533 cases; 4418 Chlamydia, 2115 gonorrhea</td>
<td>No significant difference between patients PDPT and those that did not in crude cumulative risk for repeat infection of either disease. Adjusted relative risk was 0.99 (0.86, 1.14) for Chlamydial reinfection and 0.90 (0.72–1.11) for gonococcal reinfection.</td>
</tr>
<tr>
<td>Schwebke et al. 2010</td>
<td>Women age 19+ attending Jefferson county clinic in Birmingham, AL with positive test for Trichomonas vaginalis.</td>
<td>Purpose: to conduct randomized trial to evaluate effectiveness of PDPT, DIS-PN and standard referral on prevention of repeat infection at 1 and 3 months of follow up. The proportion of women who exhibit repeat infection was calculated across the 3 groups with pairwise comparisons using the chisquare test or Fisher exact test, and 95% confidence intervals were computed</td>
<td>484 women randomized, 160 standard referral, 162 PDPT, 162 DIS-PN.</td>
<td>At 1 month follow up, 61% were retested and re-infection difference between DIS-PN and standard referral group was not significant [15% DIS group, 9.8% standard referral group, RR 1.24, (0.88, 1.74)]. The re-infection difference between the PDPT group and the standard group was also not significant [5.8% PDPT group vs. 9.8% standard referral group, RR 0.74, (0.39, 1.39)]. The difference between the DIS group and the referent referral group was then not significant, the DIS re-infection rate was 7.8%, the referent 5.0% [tRR 1.23, 0.70,</td>
</tr>
<tr>
<td>Year</td>
<td>Study Title</td>
<td>Study Type</td>
<td>Methods</td>
<td>Results</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>2010</td>
<td>Shiely et al.</td>
<td>Gonorrhea and Chlamydia patients from the Golden et al. 2005 study</td>
<td>Purpose: Subgroup analysis of the data/study conducted by Golden et al. 2005, to detect differences in re-infection rates in demographic subgroup (defined by race, age, partner type etc.)</td>
<td>1860 patients, 931 in the standard referral group, 929 in the PDPT group. Re-infection risk lower among the PDPT recipients compared to the non-recipients in 21 of 22 subgroups, with relative risks varying from 0.40 to 0.94. PDPT was reported to have reduced the risk of recurrent infection somewhat more in men (RR, 0.56; 95% CI, 0.3-1.08) than in women (RR, 0.81; 95% CI, 0.61-1.07), but it must be noted these findings cross the null. It was also shown that PDPT led to less re-infection risk in patients with gonorrhea (RR, 0.32; 95% CI, 0.13-0.78) compared to those with Chlamydia (RR, 0.82; 95% CI, 0.63-1.07).</td>
</tr>
<tr>
<td>2009</td>
<td>Forbes et al.</td>
<td>Chlamydia patients diagnosed in Scotland sexual health services clinic</td>
<td>Purpose: To theoretically establish the number of cases that would be missed by missing secondary contacts of index patients through use of PDPT, estimated by the number of secondary contacts found through the health services clinic during a programmatic evaluation</td>
<td>127 index cases with Chlamydia, 189 partners found. Of the 100 partners tested, 64 were Chlamydia positive, and 36 new contacts (secondary contacts of original patient were identified), of which 14 (36%) were infected. The audit report concludes that an estimated 22-28% more cases of chlamydial infection would be indentified in their service using their notification and interview procedures versus giving treatment to partners alone (via 2.16), and the difference between the PDPT group and the standard group was reported as “not significant” 14.3% in PDPT versus 5.0% in referent [RR 1.50, (1.06, 2.12)], but the CI does not cross the null.</td>
</tr>
</tbody>
</table>

Forbes et al. 2009

- Chlamydia patients diagnosed in Scotland sexual health services clinic
- Purpose: To theoretically establish the number of cases that would be missed by missing secondary contacts of index patients through use of PDPT, estimated by the number of secondary contacts found through the health services clinic during a programmatic evaluation
- Results: 127 index cases with Chlamydia, 189 partners found. Of the 100 partners tested, 64 were Chlamydia positive, and 36 new contacts (secondary contacts of original patient were identified), of which 14 (36%) were infected. The audit report concludes that an estimated 22-28% more cases of chlamydial infection would be identified in their service using their notification and interview procedures versus giving treatment to partners alone (via 2.16), and the difference between the PDPT group and the standard group was reported as “not significant” 14.3% in PDPT versus 5.0% in referent [RR 1.50, (1.06, 2.12)], but the CI does not cross the null. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Purpose</th>
<th>Sample Size</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameron et al. 2009</td>
<td>Women diagnosed with Chlamydia in the United Kingdom (Edinburgh), age 16-45 from May 2004 to Dec 2006.</td>
<td>Conduct a randomized trial of partner notification methods (PDPT, Postal Test Kit [PTK], standard referral) and evaluate their effects on reinfection with Chlamydia.</td>
<td>330 women (110 randomized to each trial arm)</td>
<td>215 (65%) were retested. 32 women retested positive (7 in standard referral, 15 in PTK and 10 in PDPT.) There was no significant difference in reinfection between PDPT vs. standard referral (HR 1.32, 95% CI 0.50–3.56), PTK versus standard referral (HR 2.35, 95% CI 0.94–5.88) or PDPT versus PTK (HR 0.55, 95% CI 0.24–1.24). The low sample size of reinfections reduced power.</td>
</tr>
<tr>
<td>Young et al. 2007</td>
<td>Women with an STI in South Africa, diagnosed during a community based screening initiative</td>
<td>To allow women to choose method of PN (PDPT or standard referral) to examine women’s preferences and proportion of partners treated (PDPT) or came for evaluation (standard referral).</td>
<td>106 women</td>
<td>Most (93%) women chose PDPT over standard referral. Women report 94% of partners took medicine (89% did so in front of woman), and 92% of standard referral came in for evaluation at clinic.</td>
</tr>
<tr>
<td>Golden et al. 2007</td>
<td>Gonorrhea and/or Chlamydia patients diagnosed may 2004 to August 2005, historical cases data utilized from 1998-2003 for comparison.</td>
<td>To evaluate a partner notification program for gonorrhea and chlamydial infection that involves communitywide access to PDPT pre and post initiation of the program. They evaluated program components in randomly selected cases and compared outcomes before and after program institution by interviewing patients and comparing to patients interviewed for a prior study.</td>
<td>N=1,757</td>
<td>Following institution of the program, the percentage of cases who received PDPT from their diagnosing clinician increased from 5.6% to 16% (adjusted OR 3.2, 95% CI, 2.5,4.1). The percentage of cases classified as having all of their partners treated increased from 39% to 65% concurrent with institution of the program.</td>
</tr>
<tr>
<td>Trelle et al. 2007</td>
<td>Meta analysis of partner notification studies that included men and women</td>
<td>To examine the effectiveness of methods to improve partner notification by patient referral through systematic review of any randomized</td>
<td>14 trials were included with 12,389 participants. 6 trials of PDPT (6,719</td>
<td>PDPT meta analyses result in finding reduced risk of persistent or recurrent infection in patients with Chlamydia or gonorrhea (summary)</td>
</tr>
<tr>
<td>Kissinger et al. 2006</td>
<td>Women diagnosed with <em>Trichomonas vaginalis</em> between December 2001 and August 2004.</td>
<td>Purpose: conduct a randomized controlled trial to evaluate two interventions (PDPT and booklet referral) compared to a control standard referral group on prevention of re-infection.</td>
<td>463 women (155 in standard referral, 154 in booklet referral and 154 in PDPT arms of study)</td>
<td>Persistent or recurrent infection occurred in 9.4% of women in PDPT arm, 9.0% of women in the booklet referral arm, and only 6.0% in the standard referral arm (p=0.64). PDPT, booklet referral not statistically different than standard referral in this study.</td>
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<tr>
<td>Kissinger et al. 2005</td>
<td>Men diagnosed with Chlamydia or gonorrhea (urethritis causing organisms) between Dec 2001 and Mar 2004 in New Orleans, L.A.</td>
<td>Purpose: Conduct randomized trial to determine whether PDPT is better than booklet referral or standard referral of partners in treating sexual partners and prevent re-infection with Chlamydia or gonorrhea in index men.</td>
<td>977 men (348 in booklet referral, 344 in PDPT and 285 in standard referral arms of the study)</td>
<td>Men in PDPT arm more likely than those in booklet referral arm and standard referral arm to report seeing their partners, talking to them, giving the intervention and being told by the partner that the antibiotic treatment was taken (55.8%, 45.6% and 35.0%, respectively). Among the 37.5% of men who were retested, men in the booklet referral and PDPT arms less likely to be reinfected than standard referral group (14.3%, 23.0% and 35.0% respectively)</td>
</tr>
<tr>
<td>Golden et al. 2005</td>
<td>Men and women with gonorrhoea or Chlamydia between Sep 1998 and March 2003 in King County, WA</td>
<td>Purpose: Conduct randomized trial of expedited partner therapy (through PPDT) compared to standard patient referral of partners and its effect on persistent or recurrent Chlamydia or gonorrhoea infections among women and heterosexual men.</td>
<td>2751 randomized, 1376 PDPT, 1375 standard referral, after loss to follow up, 931 in PDPT and 929 in standard referral control group</td>
<td>Persistent or recurrent gonorrhoea or Chlamydia infection occurred in 121 (13%) patients in the standard partner referral group and 92 (10%) of those assigned to the PDPT group, RR 0.76, 95% CI 0.59 to 0.98. PDPT was more effective in reducing persistent/recurrent infection.</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Purpose</td>
<td>Participants</td>
<td>Results</td>
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<td>-----------------------------------------</td>
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<tr>
<td>Schillinger et al. 2003</td>
<td>Women ages 14-34 years old diagnosed with uncomplicated Chlamydia in five United States cities between September 1996 and June 2000.</td>
<td>Purpose: To conduct a multicenter randomized trial to study whether giving medication (azithromycin) to female patients to deliver to their partners (PDPT) can reduce repeated infections with Chlamydia compared to a standard self-referral of patients approach.</td>
<td>1889 enrolled, 946 assigned to PDPT, 943 to standard referral. Some women ineligible after randomization. A total of 1454 of 1787 eligible women returned for ≥ 1 follow up visit. PDPT 728/887 and standard referral 726/900. Final n=1454</td>
<td>85% of partners were notified among patients assigned PDPT, where as 75% were notified in the standard referral control group (p=0.01). The re-infection rates of PDPT assigned patients were slightly less (not statistically different) compared to the standard patient referral re-infection rates. (12% vs. 15% respectively, OR 0.80 (0.62-1.05).</td>
</tr>
<tr>
<td>Golden et al. 2001</td>
<td>Women and heterosexual men diagnosed with Chlamydia or gonorrhea in King County, WA from Sep 1998 to Jul 1999</td>
<td>To assess the feasibility of expanding partner notification services in King County, WA and evaluate the feasibility of treating sexual partners through PDPT where treatment packs for partners are distributed through local commercial pharmacies.</td>
<td>N=1693</td>
<td>In the PDPT arm of the study, 346(76%) of the 458 participants stated they would deliver medication to at least one partner. Of the 266 patients who arranged to obtain medication under PDPT from a commercial pharmacy (84%) successfully did so. Those with more than one sex partner or a partner they did not anticipate seeing again were less likely to obtain medication after agreeing to do so (81% vs. 94%, p&lt;0.001)</td>
</tr>
<tr>
<td>Nuwaha et al. 2001</td>
<td>Men and women with syndromic sexually transmitted infections diagnosed from Nov 1999 to Jan 2000 in Ugandan STI clinic</td>
<td>Purpose: Compare standard patient based partner referral with patient delivery of medications to their partners (PDPT) in a randomized trial to see the effect on the number of partners that reportedly</td>
<td>383 patients randomized (192 total in the PDPT arm and 191 in the standard referral arm)</td>
<td>According to self report of index patients, 176/237 partners of the PDPT group patients took the medicine (74%). In the self-referral group with contact slips 79/234 partners were referred</td>
</tr>
<tr>
<td>Kissinger et al. 1998</td>
<td>Women ages 14-39 years old attending a family planning clinic in New Orleans, LA from Oct 1993 to Dec 1994, diagnosed with Chlamydia</td>
<td>Purpose: Conduct and observational cohort study of female Chlamydia patients followed after receiving treatment and given PDPT or standard referral with cards (contact slips to be treated at STI clinic) to treat/notify partners. Women who returned for a follow up visit before study end (1996) were retested for Chlamydia</td>
<td>256 women eligible, 178 returned for a follow up visit. 135 were in the standard referral group and 43 in the PDPT group of the observational cohorts.</td>
<td>Women who received PDPT were less likely than women who received standard referral with partners cards to be re-infected with Chlamydia (11.5% vs. 22.1%, p&lt;0.05).</td>
</tr>
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</table>
Table 3. Summary of Health Professional and Patient Perspectives of Partner Notification Via Patient Delivered Partner Therapy.

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Participant characteristics</th>
<th>Study Design / Characteristics</th>
<th>Sample Size</th>
<th>Primary Findings/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard et al., 2011</td>
<td>Attendees at three STI clinics (New Orleans, LA; Jackson, MS; St. Louis, MO) from June to Sep 2008</td>
<td>Cross sectional; a one question survey (with demographics questions) administered. Inquired how they would want partners treated if they were diagnosed with Chlamydia</td>
<td>2887</td>
<td>Half preferred to send sexual partners to clinic (49.7%). 80% preferred other methods over PDPT</td>
</tr>
<tr>
<td>Mohamed et al., 2010</td>
<td>Participants from Kissinger et al. 2006 and Kissinger et al. 2005 study reanalyzed</td>
<td>Objective was to determine the factors associated with disclosure of STI to sexual partners. Data were obtained and reanalyzed from the Kissinger et al. 2006 and Kissinger et al. 2005 studies.</td>
<td>977 men and 463 women, reported information on disclosure to 1991 and 521 sexual partners, respectively</td>
<td>Disclosure of STI to partners was 57.8% for men and 87.3% for women. The provision of PDPT was associated with increased disclosure among men but not women.</td>
</tr>
<tr>
<td>Pavlin et al., 2010</td>
<td>General practitioners from rural, regional and urban Australia from Nov 2006 to Mar 2007</td>
<td>Cross sectional; In depth, structured telephone interviews covering current practice, partner notification, barriers, supports and views of PDPT. Qualitative study, statistics of responses not given.</td>
<td>40</td>
<td>Those surveyed were divided on the use of PDPT; many felt concerned that it is not the best clinical practice, but many also felt that it is “better than nothing,” meaning “better than not treating the partners at all”. They felt the ideal is clinical evaluation of all partners. Nearly all felt partner notification was the patients’ responsibility not the providers. Legal and ethical concerns were raised, lack of taking a health history of the partner and potential for other present infections to be missed were identified as issues regarding PDPT</td>
</tr>
<tr>
<td>Source</td>
<td>Setting/Participants</td>
<td>Methodology</td>
<td>Sample Size</td>
<td>Summary</td>
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<tr>
<td>Mcbride et al., 2010</td>
<td>Urban (Indianapolis, IN) STI clinic patients, age 18-40.</td>
<td>A qualitative mixed methods interview exploring views on expedited partner screening and willingness to engage in patient delivered partner screening (PDPS) and PDPT. Perceived benefits and barriers were investigated</td>
<td>40</td>
<td>Most believed PDPS and PDPT together was an effective approach. Uptake would vary by relationship characteristics. Perceived benefits of PDPS include improved sexual health as well as convenience, privacy and potential to enhance trust between partners. Perceived barriers include concerns about PDPS processes (time, appearance of screening kit, risk of sample contamination), accuracy of test, stigma, and other PDPT barriers.</td>
</tr>
<tr>
<td>Mcbride et al., 2009</td>
<td>Patients from an urban (Indianapolis, IN) STI clinic, ages 17-40.</td>
<td>To evaluate willingness to partake in PDPT, and to elicit attitudes about materials related to PDPT packaging via a cross sectional survey</td>
<td>64</td>
<td>Prior to review of PDPT kits and treatment information, participants were more willing to deliver (87.5%) than receive (57.0%) PDPT materials. Participants were less willing to deliver (48.1%) than receive PDPT (88.1%) after the prototype PDPT informational and treatment kit review.</td>
</tr>
<tr>
<td>Melvin et al., 2009</td>
<td>Women (age 16-45) infected with Chlamydia who were participating in a randomized study assigning partners to standard referral, postal test kits or PDPT. Men (age 16-45) attending genitorurinary or family planning clinics in Edinburh.</td>
<td>Cross sectional questionnaires regarding preferred intervention of patients for diagnosing and testing Chlamydia for partners and themselves. Reported preferences for men and women was the main</td>
<td>293 men, 174 women</td>
<td>Of the 174 women surveyed, 67% preferred PDPT for partners and 57% prefer PDPT for themselves. Of 293 men surveyed, 70% preferred standard referral for partners and 53% chose standard referral for themselves. Only 3% of women and 9% of men preferred postal testing kits for partners.</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Participants</td>
<td>Study Design</td>
<td>Sample Size</td>
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<td>Goldsworthy et al., 2009</td>
<td>United Kingdom</td>
<td>Individuals age 18-47, geographically distributed in 11 localities in the United States in Aug 2007. A time-space sampling technique used, persons who were not clearly children were approached in public places, screened for age and invited to participate</td>
<td>Cross sectional study with two surveys, given randomly to participants. One for patient-delivery perspectives and one for partner-use perspectives. Descriptive statistics calculated.</td>
<td>505 (260 for patient delivery survey and 247 for partner use survey)</td>
</tr>
<tr>
<td>Davis et al., 2009</td>
<td>County STI program supervisors in New York State exclusive of New York City surveyed from Jan 2007 to Mar 2007.</td>
<td>Cross sectional study conducted telephone interviews of County STI programs to determine conditions that were diagnosed and treated, current partner notification practices, and to assess perspectives on PDPT and alternative interventions.</td>
<td>55 (out of 57, 97% response proportion)</td>
<td>Respondents were divided about legalizing PDPT, with 45% in favor, 45% against and 10% undecided. Those that supported legalization of PDPT gave reasons such as belief more infections would be treated (61%) and improved STI control (29%). Reasons for lack of support included potential side effects (28%), medication not reaching partners (28%), and malpractice risk (20%). The least preferred strategy was PDPT</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Methodology</td>
<td>Participants</td>
<td>Findings</td>
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<tr>
<td>McNutt et al., 2009</td>
<td>In 16 counties of New York State, community pharmacists were surveyed from April 2007 to August 2007.</td>
<td>Cross sectional study; surveyed to determine pharmacists perceptions about PDPT, education on STIs, potential barriers that need to be addressed in pharmacies for successful implementation of PDPT.</td>
<td>193</td>
<td>Out of the 193 pharmacists surveyed, 63% supported PDPT for Chlamydia. When asked about a potential behind the counter status for Chlamydia antibiotics, 78% were opposed. Most (88%) want prescriptions written under PDPT to marked as such. The most common barrier cited to counseling STI patients was time (49%).</td>
</tr>
<tr>
<td>Shivasankar et al., 2008</td>
<td>Physicians working in genitourinary medicine and health advisers in the United Kingdom.</td>
<td>Cross sectional study; postal questionnaires mailed, to assess whether professionals had given PDPT in the past, whether they might consider future PDPT use, which infections and antibiotics might be suitable for PDPT.</td>
<td>359 (206 physicians, 153 health advisers)</td>
<td>206 (65%) physician questionnaires and 153 (77%) health-adviser questionnaires were returned. One hundred and three (50%) physicians and 31 (22%) health advisers reported ever having used PDPT. Approximately 1/3 of professionals are strongly opposed to PDPT. The majority of both professional groups are cautiously prepared to consider PDPT, but only if there is no other option and only if a health professional first makes contact with the partner. The legal status of PDPT in the United Kingdom was main concern.</td>
</tr>
<tr>
<td>Shivasankar et al., 2008</td>
<td>Patients attending the Plymouth medical clinic in the United Kingdom</td>
<td>Cross sectional design; self administered questionnaire that covered general demographics, symptomology and various methods of partner notification they would find acceptable</td>
<td>500</td>
<td>500/512 (98% response proportion) participated. Traditional standard referral was more popular than PDPT but not significant. Acceptability of traditional partner referral was 87% (435/500), partner referral with infection.</td>
</tr>
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</table>
Cameron et al., 2007

**Between May and December 2005, surveys conducted among three groups of health professionals: (1) doctors, GPs, gynecologists/ doctors in family planning (2) practice nurses and (3) community pharmacists in clinical meetings throughout the United Kingdom and Scotland**

Cross sectional design; Anonymous, self-administered regarding novel testing/ treatment options for partners of women with Chlamydia, indicating their preferred strategy for testing/ treating sexual partners of women with Chlamydia if given choice of partner notification, postal testing kit, PDPT with azithromycin or combined PDPT and postal kit. Pharmacists asked about willingness to do testing and treatment.

| 334 (211 physicians, 73 nurses, 50 pharmacists) | The most popular choice of physicians (30%) and nurses (23%) was a combination of PDPT and postal kit with standard referral the least popular (8 and 3%, respectively). About 25% of physicians had previously used PDPT for treating partners. Most pharmacists were willing to supply free postal testing kits (98%), offer testing (75%) and treatment services (100%), and give women PDPM for partners (80%) |

Coyne et al., 2007

**Medical staff at the genitourinary center across the Chelsea and Westminster Healthcare National Trust (physicians, nurses, health advisers and clerical staff). Patients (consecutive attendees) of the clinics were administered patient survey.**

Cross sectional design. Two separate surveys, one for patients and one for professionals. All staff was invited to participate, and 525 consecutive patients were approached. The goal was to assess attitudes and beliefs of staff and patients about PDPT.

| 88 staff, 473 patients | For staff, 81% (71) felt PDPT would be acceptable to patients, and 61% (54) to sexual contacts. Ninety percent (79) thought partners should be given written information about the specific infection diagnosed. Eighty-nine percent (78) thought that a recommendation to attend a clinic for a full sexual health screen was |
Patients were mostly (59%) in favor of PDPT, 87% thought it would make it easier to abstain from sex during treatment, and 94% indicated that after being given antibiotics by a partner, they would attend a clinic for tests.

Apoola et al., 2007

<table>
<thead>
<tr>
<th>Method of Partner Notification</th>
<th>Rating</th>
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<tbody>
<tr>
<td>Patient referral</td>
<td>65.8%</td>
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<tr>
<td>Letter</td>
<td></td>
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<tr>
<td>Phone</td>
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<td>Text message</td>
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<td>Email</td>
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Respondents with access to mobile phones, private emails, and private letters were more likely to rate a method of partner notification using that mode of communication as “good” compared to those without.

Packel et al., 2006

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross sectional</td>
<td>1603 (708 physicians and 895 nurse practitioners)</td>
</tr>
</tbody>
</table>
2002, they mailed a self-administered survey. However, providers reported concerns that PDPT may result in incomplete care for the partner, may be dangerous without knowing the partner’s medical or allergy history, is an activity the practice may not be reimbursed for, and may result in legal consequences.

| Hogben et al, 2005 | Physicians drawn from the 1999-2000 AMA master list. | Using a nationally representative cross sectional survey of physicians that specialize in areas with frequent diagnoses of STI, the survey sought to assess how many United States physicians practice PDPT | 4223 (of which 3011 diagnosed at least one STI (gonorrhea or Chlamydia) in the preceding year) | For gonorrhea and chlamydial infection, 50% to 56% reported ever using PDPT; 11% to 14% reported usually or always doing so. Obstetricians and gynecologists and family practice physicians more often used PDPT than internists, pediatricians, and emergency department physicians. Clinicians who collected sex partner information, as well as those who saw more female and white patients, used PDPT most often. |
Figure 1. Life Cycle of Chlamydia trachomatis bacteria.

This diagram represents the usual productive life cycle of Chlamydia trachomatis with adequate nutritional sources (i.e., an infected host cell). The red dots are the infectious elementary bodies that leave an infected cell to bind to and infect new host cells. The larger beige oval represents the reticulate body, which is the form of the bacteria that is intracellular and replicates.

Figure 2. Direct immuno-fluorescence antibody labeling stain of Chlamydia trachomatis.

This image shows healthy mammalian cells (green) and cells infected by Chlamydia trachomatis (red). Image achieved through direct immune fluorescence antibody labeling stain techniques.

Figure 3. *Chlamydia trachomatis* elementary bodies exiting an infected host cell.

This image is of an electron micrograph taken by researchers showing the extrusion based exit of elementary bodies of *Chlamydia trachomatis* from an infected host cell. The bacteria can be seen extruding through the cell wall.

Figure 4. Chlamydia rates, total and by sex, United States, 1991-2011.

This image (modified from original for clarity) shows the increasing number of Chlamydia cases reported to the CDC in the United States in the last 20 years. It shows that women are affected approximately three times as much as men are.

Figure 5. Chlamydia rates, by age sex, United States, 2011.

This image (modified from original for clarity) shows the increasing number of Chlamydia cases reported to the CDC in the United States in the last 20 years. It shows that women are affected approximately three times as much as men are.

Figure 6. Chlamydia rates, by Race/Ethnicity, United States, 2002-2012.

This image (modified from original for clarity) shows the increasing number of Chlamydia cases reported to the CDC in the United States in the last 10 years by race/ethnicity. It shows that rates reported are increasing in all regions, and are highest in Blacks, while lowest in Asian/pacific islanders.

**Figure 7. Chlamydia rates, by region, United States, 2002-2012.**

This image (modified from original for clarity) shows the increasing number of Chlamydia cases reported to the CDC in the United States in the last 10 years by region of the country. It shows that rates reported are increasing in all regions, and are highest in the south, while lowest in the northeast.

8. Appendices

8.1 Appendix I. Survey to be administered to index patients that participate in the proposed patient delivered partner therapy study.

Most of the questions on this survey have to do with the way we contact partners of individuals with sexually transmitted diseases and provide treatment. The New York State Legislature is being asked to consider changing the way your partner(s) are notified about exposure to a sexually transmitted disease and treated. The researchers want your perspective included in the decision-making regarding treatment approaches.

First, think about your most recent sexual partner.

1. Was this partner a:
   a) main partner
   b) casual partner

2. Where did you meet this partner?
   a) at a party
   b) at a bar or club
   c) through a friend
   d) at work
   e) at school
   f) on the internet
   g) other: specify: ____________________________
   h) refused
The researchers know this may or may not be the person related to your current exposure to a sexually transmitted disease. Think about having been exposed to a sexually transmitted disease. Now think about how comfortable you would be talking directly to your most recent partner, compared to a State representative contacting your most recent partner.

3. With those thoughts in mind, which of the following ways would you most prefer your partner to be notified about their potential exposure to sexually transmitted diseases?

a) Partner notification where someone like me contacts your recent partner to tell them of their potential exposure.

3a) Why? (then go to \( \rightarrow 6 \))

b) Contacting your partner yourself and telling them.

3b) Why? (then go to \( \rightarrow 4 \))

4. How would you most prefer your partner to receive services for exposure to an STI?

a) Have you tell your partner to go to a clinic or their own doctor to be examined and treated. (go to question 6)

b) Have your doctor write a prescription for you to give to your partner. Your partner would not go to the doctor to receive treatment. (Go to question 5)
IF Answered “b” to question 4

5. Which would you be more likely to do: Give a prescription to this partner, give it to someone to give to this partner, or take it to the pharmacy to get it filled?

a) Give the prescription to my partner directly
b) Give the prescription to someone else to give to my partner
c) Take the prescription to the pharmacy to be filled
d) Don’t know, specify: ________________________________
e) Other, specify: ________________________________
f) Refused

6. Do you know if your most recent partner has insurance for prescription medication?

a) Yes
b) No
c) Don’t know, reason: ________________________________

d) Refused

7. Do you know if your partner can afford the cost of the medication, it costs:

(if not insured) about $35?
(if insured) your generic drug co-pay?

a) Yes
b) No
c) Don’t know, why? ________________________________

d) Refused
8. If you were given a prescription for your partner, how likely is it that you would give it to him/her?

   a) 100% → go to question 9
   b) Around 80% → go to question 9
   c) Around 50% → go to question 9
   d) Less than 50% → go to question 9 (and 10, 11) then 12 also
   e) 0% - I would not do it → go to question 12
   f) Don’t know → “Let’s assume you would for these next questions.” go to question 9
   g) Refused → go to question 9

“YES (a-d, f)”

9. How long do you think it would take you to give the prescription to your partner?

   Would you say …

   a) One day or less
   b) Two to three days
   c) Four to six days
   d) A week or more
   e) Don’t know, reason: ________________________________
   f) Refuse

10. How do you think you would most likely give your partner the prescription?

   Would you say you would…

   a) Hand him/her the prescription in person
   b) Telephone your partner and tell him/her where to pick up the prescription
   c) Mail him/her the prescription
   d) Drop the prescription off at a pharmacy for him/her to pick up
   e) Get the prescription filled and give them the medicine directly
   f) Do it some other way, specify: ________________________________
   g) Don’t know, reason: ________________________________
   h) Refused

11a. Do you know where your partner takes prescriptions to be filled?
11b. **If you took the prescription to a pharmacy for your partner, what pharmacy would you take the prescription to?**

*Would you say …*

- a) Where your partner usually fills his/her prescriptions
- b) A pharmacy other than the one your partner usually uses
- c) Don’t know
- d) Other, specify: ________________________________
- e) Refused

**YES END** Go to question 13 unless “less than 50%” on question 8, then ask 12 also

**“NO” (Skip if answered “yes” to question 8)**

12. **Why would you not give the prescription to your partner?**

*NOTE: Circle all that apply.*

- a) You don’t want to admit you had a sexually transmitted disease
- b) You wouldn’t know how to find or contact your partner
- c) You don’t see him/her anymore
- d) He/she would be angry
- e) To punish them because I think he/she may have given me the disease
- f) Other, specify: ________________________________
- g) Don’t know, reason: ________________________________
- h) Refused

13. **If your partner received the prescription, do you think they would still go to a clinic or doctor for an examination and treatment?** *Would you say …*

- a) Yes, absolutely
- b) Probably
- c) Probably not
- d) No
- e) Don’t know
- f) Refused

14. **Some prescriptions for STIs are so specific, pharmacists may be able to identify the particular disease by the medicine prescribed. How comfortable would you feel if your most recent partner was given a prescription with your name on it?** *Would you say …*
15. If you got a prescription for your most recent partner, he/she would not have to talk to a doctor or someone like me. How much do you think your partner knows about STIs? Would you say…

   a) A lot   c) A little   e) Don’t Know
   b) Some   d) Nothing   f) Refused

16. Would you be willing to educate your partners on STIs by giving them pamphlets or brochures? Would you say…

   a) Yes, absolutely   c) Probably not   e) Don’t Know
   b) Probably   d) No   f) Refused

17. How strongly do you agree or disagree with the following statements?

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree nor disagree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
<th>Refused</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Being diagnosed with an STI will make me more likely to engage in safer sex.</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>b) It’s OK for a doctor to give someone with an STI a written prescription for his/her sexual partner (with the partner’s name on it).</td>
<td>1</td>
<td>2</td>
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<tr>
<td>c) There is at least one partner in the past year that I wouldn’t give a prescription to</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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</table>
d) There is at least one partner I had in the past year that I would not trust to give me a prescription with my name on it. Would you say you...  

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</table>

e) If a partner gave me a prescription with my name on it, I would take it to the pharmacy, get the medicine and take it. Would you say you...  

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f) If I were given a prescription by a partner, I would go see a doctor anyway to get examined and treated. Would you say you...  

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</table>

g) If I were offered prescriptions for all my partners in the past year, I would take the prescriptions to every partner. Would you say you...  

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</table>

h) When I pick up medicine at the pharmacy, I feel comfortable asking the pharmacist questions about sexually transmitted diseases. Would you say you...  

<table>
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</table>

i) I can talk with my pharmacist without other customers hearing us. Would you say you...  

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j) I can talk with my pharmacist without other staff members hearing us. Would you say you...  

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k) I don’t want other people to overhear my conversation when I talk to a pharmacist. Would you say you...  

<table>
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<th></th>
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</thead>
</table>

DEMOGRAPHICS AND GENERAL HEALTH AND HEALTH CARE
18. Would you say that in general your health is:
   a) Excellent
   b) Very good
   c) Good
   d) Fair
   e) Poor
   f) Refused

19. How many sexual partners have you had in the last year?
   a) 2 or less
   b) 3-5
   c) 6-9
   d) 10 or more……specify________
   e) Refused

20. Please circle the participant’s sex (Male   Female) Which of the following best explains your usual sexual encounters?

   Would you say your encounters are…
   a) Just men (go to 21)
   b) Just women (go to 21)
   c) A mix of women and men (go to 20a)

20a. Ask only if answered mix of men and women-Are your sexual encounters…
   a) Mostly men
   b) Mostly women
   c) 50/50 split between men and women
21. Do you have any kind of health care coverage, including health insurance, prepaid plans such as HMOs, or government plans such as Medicaid?
   a) Yes
   b) No
   c) Don’t know / Not sure
   d) Refused

22. Do you have one person you think of as your personal doctor or health care provider?
   If “No,” ask: “Is there more than one, or is there no person who you think of as your personal doctor or health care provider?”
   a) Yes, only one
   b) More than one
   c) No, no one doctor
   d) Don’t know / Not sure
   e) Refused
23. Was there a time in the past 12 months when you needed to see a doctor but could not because of cost?
   a) Yes
   b) No
   c) Don’t know / Not sure
   d) Refused

24. About how long has it been since you last visited a doctor for a routine checkup? A routine checkup is a general physical exam, not an exam for a specific injury, illness, or condition.
   a) Within the past year (anytime less than 12 months ago)
   b) Within the past 2 years (1 year but less than 2 years ago)
   c) Within the past 5 years (2 years but less than 5 years ago)
   d) 5 or more years ago
   e) Don’t know / Not sure
   f) Never
   g) Refused

25. What is your age?
   a) 18-20    d) 31-35    g) Refused
   b) 21-25    e) 36-40
   c) 26-30    f) 41 +

26. Are you Hispanic or Latino?
   a) Yes
   b) No
   c) Don’t know / Not sure
   d) Refused
27. Which of the following would you say is your race? (select all that apply)
   a) White
   b) Black or African American
   c) Asian
   d) Native Hawaiian or Other Pacific Islander
   e) American Indian or Alaska Native or
   f) Some other race [specify] ________________________________
   g) Don’t know / Not sure
   h) Refused

28. Are you…?
   a) Married
   b) Divorced
   c) Widowed
   d) Separated
   e) Never married or
   f) A member of an unmarried couple
   g) Refused

29. What is the highest grade or year of school you completed? Read only if necessary:
   a) Never attended school or only attended kindergarten
   b) Grades 1 through 8 (Elementary)
   c) Grades 9 through 11 (Some high school)
   d) Grade 12 or GED (High school graduate)
   e) College 1 year to 3 years (Some college or technical school)
   f) College 4 years or more (College graduate)
   g) Refused
30. The researchers would like to know which STIs you have been diagnosed with today. May I circle them here? *If yes, circle all that apply.*

a) No, please do not disclose specific information on this.  
b) Chlamydia  
c) Gonorrhea  
d) One or more additional STIs.  
e) Refused

31. That is all the questions. Is there anything else you would like to tell the researchers?

a) No  
b) Yes (record comments in space below)

32. Interview occurred in:  
a) August
b) September  

c) October  

d) November  

e) December  

33. County or residence:

a) Capital District urban area  
b) Capital District suburban area  
c) Capital District rural area  
d) Syracuse region urban area  
e) Syracuse region suburban area  
f) Syracuse region rural area  
g) Dutchess  

The Researchers Thank You for participating. The information will be provided to policy makers so that your voice is heard in the discussion.
8.2 Appendix II. Survey to be administered to partners that participate in the proposed patient delivered partner therapy study.

Most of the questions on this survey have to do with the way we contact the partners of people with sexually transmitted diseases and provide treatment. The New York State Legislature is being asked to consider changing the way you are notified about exposure to sexually transmitted diseases and treated. The researchers want your perspective included in the decision-making regarding treatment approaches.

First, think about your most recent sexual partner.

1. Was this partner a:
   a) Main partner
   b) Casual partner

2. Where did you meet this partner?
   i) At a party
   j) At a bar or club
   k) Through a friend
   l) At work
   m) At school
   n) On the internet
   o) Other: specify: _____________________________
   h) Refused

The researchers know this may or may not be the person who exposed you to a sexually transmitted disease. Think about having been exposed to a sexually transmitted disease and then how comfortable you would be talking directly to your most recent partner as compared to how we discussed things today.

3. With those thoughts in mind, which of the following ways would you most prefer to be notified about a potential exposure to sexually transmitted diseases?
a) Partner notification where someone like me contacts you to tell you about the potential exposure.

3a) Why? (then go to → 6)

b) Having your partner contact you and tell you directly.

3b) Why? (then go to → 4)

4. How would you most prefer to receive services for exposure to an STI?

a) Have your partner tell you to go to a clinic or your own doctor to be examined and treated. (Go to question 6)

b) Have your partner’s doctor write a prescription for you that your partner would give to you. You would not go to the doctor to receive treatment. (Go to question 5)
IF Answered “b” to question 4

5. Which would your partner be more likely to do: Give the prescription to you, give it to someone to give to you, or take it to the pharmacy to get it filled?

   a) Give the prescription to me directly
   b) Give the prescription to someone else to give to me
   c) Take the prescription to the pharmacy to be filled
   d) Don’t know, specify: ______________________________
   e) Other, specify: ______________________________
   f) Refused

6. Do you have insurance for prescription medication?

   a) Yes
   b) No
   c) Don’t know, reason: ______________________________

   __________________________________________________
   d) Refused

7. Can you afford the cost of the medication, it costs:

   (if not insured) about $35?
   (if insured) your generic drug co-pay?

   a) Yes
   b) No
   c) Don’t know, why? ______________________________
8. If a prescription was given to your partner for you, how likely is it that he/she would give it to you? Would you say...

h) 100% → go to question 9
i) Around 80% → go to question 9
j) Around 50% → go to question 9
k) Less than 50% → go to question 9 (and 10, 11) then 12 also
l) 0% - I would not do it → go to question 12
m) Don’t know → “Let’s assume they would for these next questions.” go to question 9

YES a-d, f

9. How long do you think it would take for your partner to give you the prescription? Would you say...

a) One day or less
b) Two to three days
c) Four to six days
d) A week or more
e) Don’t know, reason:__________________________________________________________
f) Refused

10. How do you think your partner would give you the prescription? Would you say....

b) Hand you the prescription in person
b) Telephone you and tell you where to pick up the prescription
c) Mail you the prescription
d) Drop the prescription off at a pharmacy for you to pick up
e) Get the prescription filled and give you the medicine directly
f) Do it some other way, specify: ______________________________

g) Don’t know, reason: ______________________________

h) Refused

11a. Do you think your partner knows where you fill your prescriptions

   a) Yes   b) no

11b. If your partner took the prescription to a pharmacy for you, what pharmacy would they likely take the prescription to?

   Would you say …

   e) Where your partner usually fills his/her prescriptions
   f) A pharmacy other than the one your partner usually uses
   g) Don’t know
   h) Other, specify: ______________________________
   e) Refused

YES END, Go to question 13, unless “less than 50%” on question 8, then ask 12 also

“NO” (Skip if answered “yes” to question 8)

12. Why do you think your partner would not give you the prescription? Would you say…

NOTE: Circle all that apply.

   i) Partner would never admit he/she had a sexually transmitted disease
   j) Wouldn’t know how to find or contact me
   k) Don’t see him/her anymore
   l) He/she knows I would be angry
   m) To punish me because he/she will think I gave them the disease
   n) Other, specify: ______________________________
   o) Don’t know, reason: ______________________________
   p) Refused

13. If you received the prescription, do you think you would still go to a clinic or doctor for examination and treatment? Would you say…

   a) Yes, absolutely
b) Probably

c) Probably Not

d) No

e) Don’t know, reason: ________________________________

f) Refused

14. Some prescriptions for STIs are so specific, pharmacists may be able to identify the particular disease by the medicine prescribed. How comfortable would you feel if your most recent partner was given a prescription with your name on it? Would you say …

   a) Very comfortable
   b) Somewhat comfortable
   c) Somewhat uncomfortable
   d) Very uncomfortable
   e) Don’t know. Why? ________________________________
   f) Refused

15. Would you get a medical exam if you were told your most recent partner had a sexually transmitted disease but you were not given medication or a prescription?

   a) Yes absolutely
   b) Probably
   c) Probably not
   d) No
16. Today, during your notification you were able to ask questions about STIs and received education about how to reduce your chances of being exposed to infections in the future. If you were to be given a prescription by your most recent partner, you would not meet with a person like me to discuss these things or ask questions. Prior to today’s notification, how much did you know about STIs? Would you say...

a) A lot
b) Some
c) A little
d) Nothing
e) Don’t know

17. Would you be willing to receive education on STIs from your partner in the form of a pamphlet or brochure?

a) Yes absolutely
b) Probably
c) Probably not
d) No
e) Don’t know, reason?______________________________________________________________.
f) Refused
18) How strongly do you agree or disagree with the following statements?

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree nor disagree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
<th>Refused [don't read]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Being notified that I may have been exposed to an STI will make me more likely to engage in safer sex. Would you say you...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>b) It’s OK for a doctor to give someone with an STI a written prescription for his/her sexual partner (with the partner’s name on it). Would you say you...</td>
<td>1</td>
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<td>3</td>
<td>4</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>c) There is at least one recent partner that I wouldn’t trust to give me the prescription... Would you say you...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>d) If a partner gave me a prescription with my name on it, I would take it to the pharmacy, get the medicine and take it. Would you say you...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>e) I feel comfortable with a partner being given a prescription with my name on it. Would you say you...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>f) I’m not comfortable taking medicine for an STI unless it’s confirmed by a test that I’m actually</td>
<td>1</td>
<td>2</td>
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infected. *Would you say you...*

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<tr>
<th>g) If I were offered prescriptions for all my recent partners, I would take the prescriptions to every partner. <em>Would you say you...</em></th>
<th>1</th>
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<tr>
<td>h) When I pick up medicine at the pharmacy, I feel comfortable asking the pharmacist questions about sexually transmitted diseases. <em>Would you say you...</em></td>
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<td>i) I can talk with my pharmacist without other customers hearing us. <em>Would you say you...</em></td>
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<td>j) I can talk with my pharmacist without other staff members hearing us. <em>Would you say you...</em></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td>8</td>
</tr>
<tr>
<td>k) I don’t want other people to overhear my conversation when I talk to the pharmacist. <em>Would you say you...</em></td>
<td>1</td>
<td>2</td>
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</table>
DEMOGRAPHICS AND GENERAL HEALTH AND HEALTH CARE

19. In general, would you say that your health is:
   a) Excellent
   b) Very good
   c) Good
   d) Fair
   e) Poor
   f) Refused

20. How many sexual partners have you had in the last year?
   a) 2 or less
   b) 3-5
   c) 6-9
   d) 10 or more……specify________
   e) Refused

21. Please circle the participant’s sex (Male   Female)Which of the following best describes your usual sexual encounters?
   Would you say your encounters are with…
   a) Just men
   b) Just women
   c) Mix of men and women

21a. Ask only if answered mix of men and women-Are your sexual encounters…
   d) Mostly men
   e) Mostly women
22. Do you have any kind of health care coverage, including health insurance, prepaid plans such as HMOs, or government plans such as Medicaid?
   a) Yes
   b) No
   c) Don’t know / Not sure
   d) Refused

23. Do you have one person you think of as your personal doctor or health care provider?
   If “No,” ask: “Is there more than one, or is there no person who you think of as your personal doctor or health care provider?”
   a) Yes, only one
   b) More than one
   c) No, no one doctor
   d) Don’t know / Not sure
   e) Refused

24. Was there a time in the past 12 months when you needed to see a doctor but could not because of cost?
   a) Yes
   b) No
   c) Don’t know / Not sure
   d) Refused

25. About how long has it been since you last visited a doctor for a routine checkup? A routine checkup is a general physical exam, not an exam for a specific injury, illness, or condition.
26. What is your age?
   a) 18-20    d) 31-35    g) Refused
   b) 21-25    e) 36-40
   c) 26-30    f) 41 +

27. Are you Hispanic or Latino?
   a) Yes
   b) No
   c) Don’t know / Not sure
   d) Refused

28. Which one or more of the following would you say is your race?
   a) White
   b) Black or African American
   c) Asian
   d) Native Hawaiian or Other Pacific Islander
   e) American Indian or Alaska Native or
   f) Some other race [specify] _________________________________________________________
   g) Don’t know / Not sure
29. Are you…?
   a) Married
   b) Divorced
   c) Widowed
   d) Separated
   e) Never married or
   f) A member of an unmarried couple
   g) Refused

30. What is the highest grade or year of school you completed? Read only if necessary:
   a) Never attended school or only attended kindergarten
   b) Grades 1 through 8 (Elementary)
   c) Grades 9 through 11 (Some high school)
   d) Grade 12 or GED (High school graduate)
   e) College 1 year to 3 years (Some college or technical school)
   f) College 4 years or more (College graduate)
   g) Refused

31. The researchers would like to know which STIs you have been diagnosed with or potentially exposed today. May I circle them here? If yes, circle all that apply.
   f) No, please do not disclose specific information on this.
   g) Chlamydia
   h) Gonorrhea
i) One or more additional STIs.

32. Is there anything else you would like the researchers to know?

   a) No
   b) Yes
   c) No
   d) Yes (record comments in space below)

33. Interview occurred in:

   f) August
   g) September
   h) October
   i) November
   j) December

34. County or residence:

   h) Capital District urban area
   i) Capital District suburban area
   j) Capital District rural area
   k) Syracuse region urban area
   l) Syracuse region suburban area
   m) Syracuse region rural area
   n) Dutchess

The Researchers Thank You for participating. The information will be provided to policy makers so that your voice is heard in the discussion.

8.3 Appendix III. Draft of survey to be administered to female participants in proposed booklet referral, cardiac risk factor study at the University Health Center, 2013.
Thank you for agreeing to give us information about your basic health history and about your opinions regarding a new STI treatment method. The following questions will help the researchers understand these issues better.

*First, the researchers would like to know about your general health*

1. Why are you here at the clinic today?
   a) General check-up/physical  
   b) Routine Ob-Gyn appointment (e.g. annual exam)  
   c) Special Ob-Gyn appointment (e.g. symptoms of pain, burning, etc.)  
   d) Injury  
   e) Flu/cold like symptoms (eg. fever, cough/sore throat, chills, runny stuff nose)  
   f) Stomach symptoms (stomach ache, vomiting, diarrhea, etc.)  
   g) Fatigue/tiredness  
   h) Anxiety/nervousness  
   i) Some other reason

2. Do you smoke cigarettes every day, some days, or not at all?
   a) Every day  
   b) Some days  
   c) Not at all  
   d) Don’t know

3. How often do you exercise for at least 20 minutes at a time causing your breathing rate to become heavy?
   a) at least once a day  
   b) 5-6 days a week  
   c) 3-4 days a week  
   d) 1-2 days a week  
   e) Less than once per week

*Now just a few questions to better understand your health history*

4. Before today, when was the last time you had your blood pressure taken?
   a) Within the past 6 months  
   b) More than 6 months ago but within the past year  
   c) Over a year ago, but less than two years ago  
   d) More than two years ago  
   e) Don’t Know

5. Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?
   a) Yes  
   b) No  
   c) Don’t know

6. Because of high blood pressure, have you ever been told to take prescribed medicine to lower it?
   a) Yes  
   b) No  
   c) Don’t know
7. Have you ever been told by a doctor or other health professional that your blood cholesterol was high?
   a) Yes        b) No        c) Don’t know

8. Because of high cholesterol, have you ever been told to take prescribed medicine to lower it?
   a) Yes        b) No        c) Don’t know

9. Have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?
   a) Yes        b) No        c) Don’t know

10. Have you ever been told by a doctor or other health professional that you have PRE-diabetes or PRE-sugar diabetes?
    a) Yes        b) No        c) Don’t know

11. About how tall are you without shoes? (Feet, Inches)
    __________________feet   ________________inches

12. About how much do you weigh without shoes (LBS)?
    ___________LBS

Now the researchers have a few basic questions about your sexual history. Remember your responses are anonymous.

13. Do you currently have one main sexual partner?
    a) Yes        b) No

14. Do you currently have casual sexual partners?
    a) Yes        b) No

15. How many sexual partners have you had in the last year?
    a) 0        b) 1        c) 2        d) 3-5        e) 6-9        f) 10 or more

16. Do you take a routine birth control pill?
    a) Yes
    b) No
    c) I use another form of birth control (specify) ________________________________
17. Have you ever used emergency contraception (e.g. morning after pill)?
   a) Yes
   b) No
   c) Don’t Know

18. How often do you use condoms during sexual activity?
   a) Every time
   b) Most times
   c) About half the time
   d) Sometimes
   e) Never

19. If you were diagnosed with chlamydia, an STI, how would you most prefer your sexual partner(s) be told about possible infection?
   a) Tell them myself directly
   b) Tell them myself with the use of a card containing information about the disease and where to go for testing and treatment
   c) Have the health department tell them
   d) Bring an antibiotic prescription to them directly
   e) Have my doctor/nurse contact them
   f) Some other way
      (specify):_______________________________________________
   g) Don’t know

Thinking now about your main sexual partner (if you do not have main sexual partner, please think of your most recent sexual partner)…

20. Do you know if your main sexual partner has hypertension also called high blood pressure?
   a) Yes, my partner has hypertension/high blood pressure
   b) No, my partner does not have hypertension/high blood pressure
   c) I do not know if my partner has hypertension/high blood pressure or not

21. Do you know if your main sexual partner has high cholesterol?
   a) Yes, my partner has high cholesterol
   b) No, my partner does not have high cholesterol
   c) I do not know if my partner has high cholesterol or not

22. Do you know if your main sexual partner has diabetes/sugar diabetes?
   a) Yes, my partner has diabetes
b) No, my partner does not have diabetes  
c) I do not know if my partner has diabetes or not

23. **Would you say your main sexual partner is...**  
   a) Obese (very overweight)  
   b) Overweight  
   c) Normal weight  
   d) Underweight  
   e) Don’t know

*Next the researchers would like to know just a little more about you*

24. **What is your age?**  
   a) 18-20  
   b) 21-25  
   c) 26-30  
   d) 31-35  
   e) 36-40  
   f) 41 +

25. **Which of the following would best describes your race? (select all that apply)**  
   a) White  
   b) Black or African American  
   c) Asian  
   d) Native Hawaiian or Other Pacific Islander  
   e) American Indian or Alaska Native  
   f) Some other race [specify] ________________________________  
   g) Don’t know / Not sure

26. **Are you Hispanic or Latino?**  
   a) Yes  
   b) No  
   c) Don’t know / Not sure

27. **Are you...?**  
   a) Never married and single  
   b) In a steady relationship (but unmarried)  
   c) Married  
   d) Separated/Divorced  
   e) Widowed

28. **What year are you in at UAlbany?**  
   a) Freshman  
   b) Sophomore  
   c) Junior  
   d) Senior  
   e) Graduate School  
   f) Other

29. **What type of health insurance do you have?**  
   a) University insurance  
   b) I’m on my parent’s insurance plan  
   c) Other (please specify):__________________________________________________
We’d like your opinion on these information cards. These cards have information that can help someone tell their sexual partner that they may have an STI. We would like to know if people think these cards could help in the difficult process of telling their partner about a possible STI, and where they can go to get tested. Please take a minute to look at the card below:

<table>
<thead>
<tr>
<th>Someone who says they had sex with you has been treated for Chlamydia, a sexually transmitted disease (STD). Chlamydia can be spread through oral, vaginal or anal sex.</th>
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</thead>
<tbody>
<tr>
<td><strong>You may be infected but not have any symptoms. In fact, most infected people don’t know it.</strong></td>
</tr>
<tr>
<td>If you have symptoms, they can include:</td>
</tr>
<tr>
<td>• Vaginal or penile discharge</td>
</tr>
<tr>
<td>• Pain or burning during urination (when you pee)</td>
</tr>
<tr>
<td>• Pain or discharge in the rectum, if you had anal sex</td>
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<tr>
<td>Chlamydia can be treated with antibiotics. If you don’t get treated, you could become sterile or develop painful symptoms.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th><strong>You need to get tested and treated.</strong> You can go to your doctors office, an STD clinic or an urgent care medical clinic.</th>
</tr>
</thead>
<tbody>
<tr>
<td>You should also be tested for other STDs and HIV.</td>
</tr>
<tr>
<td>Condoms can prevent the spread of Chlamydia if you use them correctly every time you have sex. You may be able to get condoms at your local health department STD clinic.</td>
</tr>
</tbody>
</table>
For the next few questions, please consider if YOU became infected with Chlamydia, an STI.
These questions are about the image of the card on the last page. Please carefully follow the arrows based on your answers

30. Would you give a card to your main sexual partner?

a) Definitely
b) Probably
c) Probably not
d) Definitely not

31. Would you give a card to ALL of your sexual partners?

a) Yes, all
b) Some, but not all
c) No, none of them

30A. Why would you probably or definitely NOT give a card to your main sexual partner?

a) I prefer to tell them about infection directly
b) I would be angry with my partner and not want to see him
c) I would be too embarrassed to admit to my partner I had an STD
d) I would be afraid of my partner’s reaction

e) Some other reason (please specify):
   ____________________________
   ____________________________
   ____________________________

31A. Why wouldn’t you give a card to all of your sexual partners?

a) I prefer to tell them about infection directly
b) I would be angry with a partner and not want to see him
c) I would be too embarrassed to admit to my partners I had an STD
d) I would be afraid of my partners’ reactions
e) I wouldn’t know how to contact some recent partner(s)
f) Some other reason (please specify): ____________________________
   ____________________________
   ____________________________
   ____________________________
32. How would you most prefer the card be given to your partner(s)?
   a) Give them the card myself
   b) I’d mail the card to them (old fashioned ‘snail mail’)
   c) I’d call them and read the info on the card rather than handing it to them
   d) Electronically (If available electronically, I would E-Mail or Text it to them)
   e) I would put it in their mailbox or under their door
   f) I’d give it to someone else to bring to my partner(s)
   g) I would want it given to them some other way
      (specify)______________________________________________________________
      ________________________________________________________________
   h) Don’t know
      (reason)______________________________________________________________
      ________________________________________________________________

33. If your partner received the card, do you think they would go to a clinic or doctor for an examination and treatment?
   a) Definitely b) Probably c) Probably not d) Definitely not
      e) Don’t know

34. Instead of telling your partner about possible infection with the aid of these cards, would you prefer to bring a prescription to your partner to treat the infection?
   a) Yes b) No c) Don’t Know

35. The researchers would like to know if you agree or disagree with the following statements.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree nor disagree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) There is at least one partner in the past 2 months that I wouldn’t give the card to</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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We’d like to know more about your thoughts regarding the influenza (‘the flu’) vaccine.

36. Did you get a flu vaccine this season (between September 2012 and now)?
   a) No
   b) Yes, at the University Flu Vaccination Program
   c) Yes, at the University Health Center
   d) Yes, at a pharmacy
   e) Yes, at private doctor’s office
   f) Yes, at my place of employment
   g) Yes, at another place (please specify)__________________________________

37. If you did not receive the flu vaccine, why? Circle all that apply
   a) The cost was too much ($30 on campus and many pharmacies)
   b) It was available at inconvenient locations
   c) It was available at inconvenient times
   d) Don’t need it because I’m healthy
   e) To lazy to bother getting it
   f) I’m afraid of vaccines
   g) I’m afraid of needles
   h) I had a prior bad reaction to a flu vaccine
   i) I had a prior bad reaction to a different vaccine so I don’t want a flu vaccine
   g) Another reason (please specify)___________________________________________
38. Did you know you could receive a flu vaccine on campus? If yes, circle all that apply.
   a) No, I did not know I could receive the flu vaccine on campus
   b) Yes, from signs on campus
   c) Yes, from E-mails
   d) Yes, from campus newsletters
   e) Yes, from University website
   f) Yes, by word of mouth
   g) Yes, some other reason (please specify) ________________________________

39. What is the most you would pay to receive a flu vaccine?
   Amount $___________    OR    No amount matters, I will not get the vaccine

40. Did you see any of the following people over the holidays?
   i) Infants under one year of age?
      a) Yes    b) No
   ii) Elderly individual over age 65?
      a) Yes    b) No
   iii) Seriously ill family members (for example, heart disease, cancer)
      a) Yes    b) No

41. A major reason to vaccinate healthy, young individuals is that it helps protect those under age one (who can’t be vaccinated) as well as the elderly and the very ill (where vaccine is less effective). Before today, have you ever been told this?
   a) Yes    b) No

42. Learning that vaccinating healthy young adults helps those most at risk for severe flu (including death) makes me more willing to be vaccinated?
   a) Strongly agree    b) agree    c) disagree    d) strongly disagree

43. Do you know if your health insurance covers the cost of the flu vaccine?
   a) Yes, it is covered
   b) No, it is not covered
   c) I do not know if it is covered or not

Thank you for taking the time to complete the survey. That is all the questions the researchers have. If you have any comments or anything you would like the researchers to know, please use the space below.
8.4 Appendix IV. Draft of survey to be administered to male participants in proposed booklet referral, cardiac risk factor study at the University Health Center, 2013.

Thank you for agreeing to give us information about your basic health history and about your opinions regarding a new STI treatment method. The following questions will help the researchers understand these issues better.

*First, the researchers would like to know about your general health*

2. Why are you here at the clinic today?
   a) General check-up/physical
   b) Injury
   c) Flu/cold like symptoms (eg. fever, cough/sore throat, chills, runny stuff nose)
   d) Stomach symptoms (stomach ache, vomiting, diarrhea, etc.)
   e) Fatigue/tiredness
   f) Anxiety/nervousness
   g) Some other reason

2. Do you smoke cigarettes every day, some days, or not at all?
   a) Every day
   b) Some days
   c) Not at all
   d) Don’t know

3. How often do you exercise for at least 20 minutes at a time causing your breathing rate to become heavy?
   a) at least once a day
   b) 5-6 days a week
   c) 3-4 days a week
   d) 1-2 days a week
   e) Less than once per week

*Now just a few questions to better understand your health history*

4. Before today, when was the last time you had your blood pressure taken?
   a) Within the past 6 months
   b) More than 6 months ago but within the past year
   c) Over a year ago, but less than two years ago
   d) More than two years ago
   e) Don’t Know

5. Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?
   a) Yes
   b) No
   c) Don’t know
6. Because of high blood pressure, have you ever been told to take prescribed medicine to lower it?
   a) Yes  b) No  c) Don’t know

7. Have you ever been told by a doctor or other health professional that your blood cholesterol was high?
   a) Yes  b) No  c) Don’t know

8. Because of high cholesterol, have you ever been told to take prescribed medicine to lower it?
   a) Yes  b) No  c) Don’t know

9. Have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?
   a) Yes  b) No  c) Don’t know

10. Have you ever been told by a doctor or other health professional that you have PRE-diabetes or PRE-sugar diabetes?
    a) Yes  b) No  c) Don’t know

11. About how tall are you without shoes? (Feet, Inches)
    __________________ feet  ____________ inches

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Now the researchers have a few basic questions about your sexual history. Remember your responses are anonymous.

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    a) 0  b) 1  c) 2  d) 3-5  e) 6-9  f) 10 or more

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a) Every time  
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26. What year are you in at UAlbany?
   a) Freshman   b) Sophomore   c) Junior   d) Senior   e) Graduate School   f) Other

27. What type of health insurance do you have?
   a) University insurance
   b) I’m on my parent’s insurance plan
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Please proceed to the next page
We’d like your opinion on these information cards. These cards have information that can help someone tell their sexual partner that they may have an STI. We would like to know if people think these cards could help in the difficult process of telling their partner about a possible STI, and where they can go to get tested. Please take a minute to look at the card below:

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b) Probably
c) Probably not
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   ________________________________

28 A. Why would you probably or definitely NOT give a card to your main sexual partner?

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      (specify)______________________________________________________________
      ________________________________________________________________
   p) Don’t know
      (reason)____________________________________________________________
      ________________________________________________________________

31. If your partner received the card, do you think they would go to a clinic or doctor for an examination and treatment?
   b) Definitely b) Probably c) Probably not d) Definitely not e) Don’t know

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