EXAMINING LONG-TERM CHLAMYDIA PREVALENCE AND CASE RATE TRENDS AMONG YOUNG ADULTS IN THE UNITED STATES

Emily Rachel Learner

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology.

Chapel Hill
2017

Approved by:

William C. Miller

Elizabeth A. Torrone

Brian W. Pence

Jason P. Fine

Kimberly A. Powers

ABSTRACT

Emily Rachel Learner: Examining long-term chlamydia prevalence and case rate trends among young adults in the United States
(Under the direction of William C. Miller)

Chlamydia trachomatis (chlamydia) is a sexually transmitted infection that is usually asymptomatic but can result in serious reproductive sequelae if left untreated. Screening and treating sexually active young adults for chlamydia helps prevent transmission and reduces incidence and prevalence. Monitoring prevalence and case rate trends through surveillance is important for assessing screening effectiveness. However, trends from surveillance data are difficult to interpret because they are influenced by important time-varying biases. The purpose of this dissertation was to 1) estimate chlamydia prevalence trends among a sentinel population of young adults, accounting for bias from changing risk profiles (case mix) and imperfect screening tests, and 2) estimate the annual incidence rate of correctly diagnosed chlamydia that would be obtained with perfect screening coverage, screening tests, and case reporting.

For the first objective, we estimated prevalence among young women and men entering the National Job Training Program from 1990 through 2012. We examined the distribution of enrollment by race/ethnicity and region over time to assess case mix, and corrected for time-varying measurement error introduced by increasingly sensitive screening tests. For the second objective, we estimated bias due to screening coverage, screening tests, and reporting, and corrected annual chlamydia case rates from 2000 through 2015 among young women using a series of corrections.

Chlamydia prevalence trends among high-risk young women declined from 20% in 1990 to 12% in 2003, and were relatively stable from 2004 through 2012. Trends among men were

stable over the course of the study at approximately 7%. Prevalence was highest among Black women and men, and in the Southern and Midwestern regions of the US. Counterfactual incidence rates of correctly diagnosed chlamydia among young women were higher than reported case rates, and declined from 12,900 cases per 100,000 person-years in 2000 to 7,100 cases per 100,000 person-years in 2015. Trends declined sharply from 2000 through 2007, and modestly from 2008 through 2015.

Declining chlamydia prevalence and counterfactual incidence rate trends suggest that screening programs may have initially been effective at reducing chlamydia burden, but relatively stable trends in more recent years signal that screening may be losing momentum.

ACKNOWLEDGEMENTS

This dissertation would not have been possible without guidance, mentorship, and support from many individuals. Bill Miller has been an exceptional mentor on both a professional and personal level. You have been instrumental in helping me reach this point, and taught me to always ask questions, consider the bigger picture, and not take things too seriously. I'm very grateful for your kindness, encouragement, and life-advice. I would also like to thank my committee for their guidance and dedication to this research. Kim Powers, thank you for taking the time to work through the nuts of bolts of analyses with me and for challenging me to think more critically. Lizzi Torrone, thank you for sharing you expertise, your boundless enthusiasm, and career advice. Brian Pence, thank you for always being available for questions and providing thoughtful feedback. Jason Fine, thank you for working through analysis strategies with me.

I'm grateful for the support for this dissertation provided by the HIV/STD training grant (T32 5T32AI007001) and Bill Miller, Ada Adimora, and Kathryn Salisbury. I'm also grateful to the staff and participants of the National Job Training Program. Many thanks go to to Nancy Colvin, Valerie Hudock, and Jennifer Moore for always offering a calming perspective and for all of your hard work behind the scenes. I also thank my epidemiology peers who helped me make it through this program.

Lastly, I want to thank my family, who rearranged their lives so I could finish this dissertation, and provided unconditional support and encouragement. Derek, Larry, Marilyn, Zach, and especially Eli, you reminded me to smile and made me laugh. I could not have done this without you.

TABLE OF CONTENTS

LIST OF TABLES viii

LIST OF FIGURES ix

LIST OF ABBREVIATIONS xi

CHAPTER ONE: SPECIFIC AIMS 1

CHAPTER TWO: BACKGROUND AND SIGNIFICANCE 4

CHAPTER THREE: RESEARCH DESIGN AND METHODS 11

3.1 SPECIFIC AIM 1 11

3.2 SPECIFIC AIM 2: 17

CHAPTER FOUR: SPECIFIC AIM 1 RESULTS 25

4.1 INTRODUCTION 25

4.2 MATERIALS AND METHODS 26

4.3 RESULTS 29

4.4 DISCUSSION 32

4.5 TABLES AND FIGURES 35

CHAPTER FIVE: SPECIFIC AIM 2 RESULTS 43

5.1 INTRODUCTION 43

5.2 MATERIALS AND METHODS 44

5.3 RESULTS: 51

5.4 DISCUSSION 53

5.5 FIGURES 56

CHAPTER SIX: CONCLUSIONS 62

APPENDIX 1: AIM 1 SUPPLEMENTAL METHODS 67
APPENDIX 2: AIM 1 SUPPLEMENTAL FIGURES 69
APPENDIX 3: AIM 2 SUPPLEMENTAL FIGURES 79
REFERENCES 81

LIST OF TABLES

Table 4.1: Summary sensitivity and specificity estimates of chlamydia screening tests 36

Table 4.2: Characteristics of National Job Training Program enrollees and unadjusted chlamydia prevalence, 1990-2012 37

LIST OF FIGURES

Figure 4.1: Adjusted and unadjusted chlamydia prevalence among women and men entering the NJTP, 1990-2012 39

Figure 4.2: Adjusted chlamydia prevalence and 95% CIs among women and men entering the NTJP by race/ethnicity, 1990-2012. 40

Figure 4.3: Adjusted chlamydia prevalence and 95% CIs among women and men entering the NTJP by region, 1990-2012. 41

Figure 5.1: Conceptual diagram depicting surveillance data biases in relation to the at-risk population and true chlamydia cases. 56

Figure 5.2: Inputs of reporting fraction, screening test sensitivity and specificity, and screening coverage among young women, 2000-2015. 57

Figure 5.3: Reported chlamydia case rates and counterfactual incidence rates of correctly diagnosed chlamydia among young women, 2000-2015 58

Figure 5.4: Sensitivity analyses of counterfactual incidence rates of correctly diagnosed chlamydia among women, 2000-2015 59

Figure 5.5: Influence analyses of counterfactual incidence rates of correctly diagnosed chlamydia among young women, 2000-2015 60

Figure A1.1: Flow diagram for study selection process for articles included in meta-analyses of sensitivity and specificity estimates for Pathfinder EIA, Gen-Probe PACE 2, or BD ProbeTec ET chlamydia tests. 68

Figure A2.1: Distribution of race/ethnicity of women entering the NJTP (n=350,490), 1990-2012. 69

Figure A2.2: Distribution of region of residence of women entering the NJTP (n=350,490), 1990-2012. 70

Figure A2.3: Distribution of race/ethnicity of men entering the NJTP (n=303,699), 2003-2012. 71

Figure A2.4: Distribution of region of residence of men entering the NJTP (n=303,699), 2003-2012. 72

Figure A2.5: Adjusted and unadjusted prevalence of chlamydia among women entering the NJTP by race/ethnicity, 1990-2012. 73

Figure A2.6: Adjusted and unadjusted chlamydia prevalence among women entering the NJTP by region, 1990-2012. 74

Figure A2.7: Sensitivity analysis of adjusted chlamydia prevalence trends among women entering the NJTP, 1990-2012. 75

Figure A2.8: Adjusted and unadjusted chlamydia prevalence among men entering the NJTP by race/ethnicity, 2003-2012. 76

Figure A2.9: Adjusted and unadjusted chlamydia prevalence among men entering the NJTP by region, 2003-2012. 77

Figure A2.10: Sensitivity analysis of adjusted chlamydia prevalence trends among men entering the NJTP, 2003-2012 78

Figure A3.1: Distribution of chlamydia screening via NAATs, 2000-2015. 79

LIST OF ABBREVIATIONS

AIC	Akaike information criteria
BD	Becton Dickinson
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
EIA	Enzyme immunoassay
EM	Expectation maximization
HEDIS	Healthcare effectiveness data and information set
IPP	Infertility Prevention Project
NAAT	Nucleic acid amplification test
NHANES	National Health and Nutrition Examination Survey
NJTP	National Job Training Program
NSFG	National Survey of Family Growth
PID	Pelvic inflammatory disease
SDA	Strand displacement assay
STD	Sexually transmitted disease
STI	Sexually transmitted infection

CHAPTER ONE: SPECIFIC AIMS

Chlamydia is the most commonly reported sexually transmitted infection (STI) in the US.(1) Since prevalence is highest among young adults age 15 through 24 and infections are often asymptomatic, screening young, sexually active individuals to detect and treat disease is important for reducing the risk of reproductive sequelae.(1–7) Untreated infections may lead to pelvic inflammatory disease, infertility, and ectopic pregnancy in women, and urethritis, prostatitis and infertility in men.(1,6,8–12) Given the severity of sequelae that may result from undetected and untreated infections, federally funded, national screening programs were introduced in the late 1980s with the public health goal of reducing disease prevalence, transmission, and incidence.(13) Monitoring chlamydia prevalence and reported case rate trends using surveillance data is critically important for helping to determine whether large-scale screening programs have been effective in reaching program goals.

Interpreting long-term chlamydia prevalence and case rate trends from surveillance data is challenging because trends can be influenced by multiple biases. Prevalence trends are derived from sentinel surveillance of populations that have universal screening coverage, and are calculated by dividing the number of cases by the total population screened. Case rates trends are derived from population-based surveillance and serve as proxies for incidence rates. Case rates are calculated by dividing the number of nationally reported cases by person time at risk during one year, which is estimated from census data. Both prevalence estimates and case rate estimates are influenced by the use of increasingly sensitive screening tests over time, and by changes in case mix (the proportion of high and low-risk individuals screened in a

population).(1,14–16) Case rates are also influenced by changes in screening coverage (the proportion of the population that is screened) and changes in case reporting compliance (the proportion of cases reported).(1,14,15) These biases may mask the true population prevalence and case rate.

Prevalence and case rate trends that do not properly account for biases may be misleading. Observed chlamydia prevalence trends over the last two decades from sentinel surveillance among the National Job Training Program (NJTP), a national vocational training program for youth, are modestly decreasing, suggesting that screening may have been effective at reducing disease burden.(17–22) But these trends do not sufficiently account for time-varying case mix and measurement error associated with changes in screening tests, and may not reflect true prevalence trends. National chlamydia case rates are also difficult to interpret. Reported case rates have generally been increasing over the past two decades, suggesting that screening has not been effective.(1) However, these rates are influenced by the use of increasingly sensitive screening tests, case mix, expanded screening coverage, and improved reporting compliance. To accurately assess the effectiveness of screening programs on a population level using surveillance data, the effects of multiple biases on prevalence and case rate estimates must be considered.

The goals of the proposed study are to 1) produce less biased chlamydia prevalence trends among a sentinel surveillance population over the past two decades and 2) examine how increased screening coverage, more sensitive screening tests, case mix and improved reporting influence reported national chlamydia case rates. The specific aims of this proposal are to:

Aim 1: Estimate long-term trends of chlamydia prevalence among a national sample of young adults, accounting for time-varying measurement error associated with changes in screening test use and bias due to case mix.

Aim 2: Estimate counterfactual incidence rates of correctly diagnosed chlamydia among young women from 2000 through 2015, accounting for changes in screening coverage, screening tests, case mix, and reporting compliance, and compare counterfactual incidence rates to reported case rates.

To address aim 1, we used annual cross-sectional chlamydia screening data from young adults entering the NJTP collected from 1990-2012. The NJTP is an ideal data source for this research because all NJTP entrants are screened for chlamydia and characteristics of NJTP enrollees have remained relatively stable over time, so prevalence can be easily measured. To address aim 2, we triangulated estimates of biases over time by reviewing published literature and consulting expert opinion. Through a series of corrections that account for multiple biases, we estimated counterfactual incidence rates of correctly diagnosed chlamydia that would be obtained with perfect screening coverage, screening tests, and reporting.

This research produced minimally biased, long-term chlamydia prevalence trends, and demonstrated how reported chlamydia case rates are influenced by multiple biases. These analyses helped us understand whether the national screening efforts implemented over the past two decades have been effective at reducing disease burden. In addition, this research enabled us to more accurately and meaningfully interpret national chlamydia case rate trends.

CHAPTER TWO: BACKGROUND AND SIGNIFICANCE

Chlamydia trachomatis (chlamydia) is the most commonly reported STIs in the US.(1) Approximately 1.5 million cases of chlamydia were reported in the US in 2016, and the burden of infection is highest among young adults age 15 to 24 years, non-Hispanic Blacks, and the Southern region of the US.(1) Most infections are asymptomatic and untreated infections can lead to serious reproductive sequelae, including pelvic inflammatory disease (PID), infertility, and ectopic pregnancy in women, and urethritis, prostatitis, and infertility in men.(1,6,11,12) Untreated infections may also facilitate transmission of HIV.(23,24) Chlamydia can usually be treated easily with antibiotics.(2) Given the high case reporting and clinical features of chlamydia, regular screening of sexually active people to detect and treat infections is important from both an individual and population level perspective. On an individual level, screening allows for detection and treatment of infected individuals, which can reduce their risk of reproductive sequelae.(15,25) On a population level, screening and treating infected individuals may reduce prevalence, which can in turn reduce transmission and incidence.(6,25–27)

Large-scale screening programs for chlamydia have been in place in the US for over 20 years, and evaluating the effectiveness of these screening programs is an important part of gauging return on investment. National chlamydia screening programs were first supported by the Centers for Disease Control and Prevention in the late 1980s, and federally funded national screening was introduced in the 1990s as part of the Infertility Prevention Project (IPP).(13) These programs aimed to increase access to chlamydia screening and treatment services for low-income, sexually active women attending public clinics. Ideally, the effectiveness of these screening programs would be assessed from both individual and population level perspectives.

On an individual level, successful screening programs would result in reduced incidence of PID, infertility, and ectopic pregnancy. However, since reproductive sequelae caused by chlamydia also have other etiologies and are inconsistently reported, evaluating the success of screening programs by monitoring incidence of these sequelae has been challenging.(6,26) On a population level, screening program effectiveness would be indicated by a decline in chlamydia prevalence and incidence over time.

True chlamydia prevalence and incidence on a national scale are difficult to measure, so prevalence estimates are derived from sentinel surveillance or population surveys, and incidence is represented by rates of reported cases from population-based surveillance. Specifically, prevalence can be estimated from sentinel populations with universal screening, such as NJTP(17–22) or military.(28–30) Estimates can also be derived from national population-based surveys such as the National Health and Nutrition Examination Survey (NHANES)(1,3–5) or the National Longitudinal Study of Adolescent to Adult Health (Add Health), although these estimates can be difficult to ascertain given the expense and implementation challenges of large survey studies(1,7) Case rates act as a proxy for incidence rates, and are derived from national population-based surveillance. Annual case rates are calculated from the total number of reported cases in a year (the numerator in the case rate) and person time in one year, which is total number of people in a population, gathered from census data, multiplied by one year (the denominator in a case rate).(15) Trends in prevalence and case rates from surveillance data can be used to evaluate screening programs on a population level.

However, prevalence and case rate trends from surveillance data should be interpreted carefully because both measures can be influenced by biases that can mask true changes in prevalence or case rates. Prevalence and case rates are affected by several biases that

influence the numerators of these measures.(14,15) Both prevalence and case rates are influenced by time-varying case mix (i.e., the relative proportion of high and low risk individuals in a population) and measurement error associated with using increasingly sensitive screening tests over time. Case rates are additionally influenced by screening coverage and reporting practices.

The concept of case mix refers to the relative distribution of high and low risk individuals who are screened in a population, and changes in case mix can bias prevalence and case rate measures by causing the numerator to change while the denominator remains constant.(6) For example, in a population with high and low risk individuals, many cases will be detected if a large proportion of high-risk individuals is screened. If, over time, fewer high-risk individuals are screened and more low-risk individuals are screened, fewer cases will be detected. In this scenario, the number of cases that are identified through screening declines as the composition of high and low-risk individuals being screened changes. The change in the relative proportion of risk levels of individuals being screened does not necessarily reflect true changes in the underlying population disease burden. Changes in case mix over time may produce an artificial increase or decrease in prevalence or case rates. Although difficult to measure, case mix is important to consider when interpreting disease trends.

Changes in screening test can also bias prevalence and case rates, and should be considered jointly with case mix. As screening test technologies improve, tests become better at detecting cases of chlamydia. While all screening tests introduce some measurement error due to imperfect sensitivity (the probability of testing positive given disease is present) and specificity (the probability of testing negative given disease is absent), new technologies typically have improved sensitivity and specificity. For chlamydia in particular, specificity of tests has always been high, but sensitivity has improved dramatically with new technologies. With

improved sensitivity, more cases are detected. But increased case detection due to better screening tests is not necessarily reflective of an increase in the true population disease prevalence.(15,16) Like case mix, changes in screening tests may inflate the numerators of a prevalence or case rate, while the denominators remain constant. Since case counts can be influenced by both case mix and measurement error associated with changes in screening tests, both biases should be accounted for when analyzing and interpreting prevalence and case rate trends.

Case rates are influenced by two additional biases: reporting bias and screening coverage. Reporting bias refers to changes the proportion of cases that are detected and reported through passive surveillance. Chlamydia has been nationally notifiable conditions since 1994, and has been reported by all 50 states and the District of Columbia since 2000. Reporting is imperfect, but has improved due electronic laboratory reporting systems, which enable cases to be reported directly from laboratories and do not rely on physicians' reporting compliance. Electronic systems have become increasingly common since the early 2000s.(1,14) Improved reporting can contribute to the numerator of a case rate, but may not represent a true increase in the caseload. Similarly, screening coverage, or the proportion of the population that is screened, has expanded over time. When a larger proportion of the population is screened, more cases will be detected (contributing to the numerator of a rate). However, the denominator (total person time at risk) is not affected by changes in screening coverage.(15) Interpretation of case rates is exceedingly difficult because rates are influenced not only by changes in incidence, but also by multiple sources of bias.

Because prevalence trends are influenced by fewer biases than rates, prevalence is preferable for examining chlamydia trends over time. One of the most common sources for monitoring chlamydia prevalence trends is the NJTP. The NJTP is administered by the

Department of Labor, and is a no-cost, residential educational and vocational training program for socioeconomically disadvantaged youth between 16 through 24 years old. The Department of Labor began screening NJTP entrants for chlamydia in 1990. Since characteristics of NJTP entrants have remained stable over time and screening coverage is high, it is an optimal data source for measuring prevalence trends. Generally, the annual prevalence of both infections has been high, and modestly decreasing over time. Chlamydia prevalence among women fell from 14.9% to 10.0% from 1990 through 1997(22) and from 11.7% to 10.3% from 1998 through 2004.(17) More recent estimates from 2006 through 2008 showed small declines in annual chlamydia prevalence among women who provided cervical and urine samples for screening (cervical: 16.0% to 15.0%, urine: 13.8% to 11.8% respectively).(19)

While modest decreases in chlamydia prevalence have been reported among NJTP entrants, these trends have two major limitations. First, the trends are short-term and span a maximum of seven years. Some trends are estimated for time periods during which only one screening test was used in order to avoid bias due to changing screening tests.(17,19,22) However, this prohibits direct comparisons of trends across time periods during which different screening tests were used; thus long-term trends cannot be assessed. In addition, a longer time period may be required to observe the effects of screening on annual prevalence trends. Second, trends that span periods when multiple tests were used do not properly account for measurement error associated with changing screening tests.(18,20,21) Estimates incorrectly account for changing screening tests by adjusting for test type in a generalized linear model. Including test type as a covariate in a model holds the effect of test type constant, but does not account for measurement error due to different test sensitivities and specificities.(15) Although some trends do account for case mix by examining the distribution of population characteristics over time, both case mix and changes in screening tests must be properly incorporated into analyses to produce valid, long-term prevalence trends.

Finally, although case rates are influenced by more biases than prevalence, rates are still important to examine. Rates are conveniently and easily derived from national case report data and census data, and can be useful for describing chlamydia epidemiology on a national scale. As discussed earlier, several biases influence reported case rates, and the influence of biases can be clearly seen in national chlamydia case rate trends. National chlamydia case rates reported by the CDC have been generally increasing from 2000 through 2010 overall and among young women age 15 through 24 years, suggesting that disease burden is also growing.(1,31) However, during this same time period, use of more sensitive screening tests became increasingly common, screening coverage generally expanded, and reporting compliance among states and clinics improved.(1) Additionally, as screening became more accessible and was offered routinely in both private and public clinics, the proportion of high and low-risk individuals being screened likely fluctuated over time. The upward trend in chlamydia case rates has been attributed to expanded screening coverage and transitioning to screening test with near perfect sensitivity and specificity, but the effects of multiple biases on national rates have not been rigorously examined.(1,14,16,27,32) From 2010 through 2013, case rates began to decline, but it is unknown if the decline is due to changes in screening coverage or to a true decline in incidence.(1) Disentangling the effect of multiple biases on observed population chlamydia case rates is important for better understanding true population rates and the effectiveness of screening programs.

The goals of this research were to generate minimally biased chlamydia prevalence trends over the past two decades, and to examine the influence of multiple time-varying biases on national chlamydia case rates. First, this research generated valid chlamydia prevalence trends among NJTP entrants over the past 20 years, accounting for measurement error associated with changing screening tests and bias due to case mix. Understanding whether

prevalence of chlamydia is truly decreasing and quantifying changes in prevalence over time is important for understanding whether screening efforts over the past two decades have achieved their goal of reducing population disease burden. Second, this research examined how screening- and reported-related biases influence chlamydia case rates. By estimating counterfactual incidence rates of correctly diagnosed, we were able to assess the extent to which biases influence and limit interpretability of case rate trends.

CHAPTER THREE: RESEARCH DESIGN AND METHODS

3.1 SPECIFIC AIM 1

Estimate long-term trends of chlamydia prevalence among a national sample of young adults, accounting for time-varying measurement error associated with changes in screening test use and bias due to case mix.

Specific Aim 1 Study Description

Description of NJTP Population

We analyzed annual cross-sectional chlamydia screening data from young women and men enrolled in the NJTP from 1990 through 2012. The NJTP is a national educational and vocational training program for economically disadvantaged youths administered by the Department of Labor (33,34). Approximately 20,000 to 60,000 young adults are trained annually at residential centers nationwide. Men and women age 16 through 24 are eligible to enroll in the NJTP if they are legal US residents, meet low-income criteria, and face barriers to employment, such as needing additional training or education required to get and hold a job. Eligibility criteria for NJTP were consistent throughout the study period.

All NJTP enrollees are required to have a physical exam and STI screening within 48 hours of entering the NJTP. Chlamydia screening has been required of all women since 1990, and of all men since 2003. Biological samples for screening were collected at NJTP center health services departments. Samples were collected either by a healthcare provider (cervical

swabs) or self-collected (vaginal swabs or urine). Most NJTP sites sent samples for chlamydia testing to one national contract laboratory. The national contract laboratory reports the sample type, screening test type, and the screening test results (positive or negative) to the CDC Division of STD Prevention.

Outcome Assessment

The outcome of interest for Aim 1 was laboratory-confirmed chlamydial infection. Several screening tests were used to identify a positive chlamydia case throughout the study period. From 1990 through 1997, chlamydia screening was performed via Pathfinder Enzyme Immunoassays (EIA) (Sanofi Diagnostics Pasteur, Inc, Redmond, Washington) of cervical specimens. From March 2000 through 2006, the Gen-Probe Pace2 assay (Gen-Probe Inc., San Diego, California), a DNA hybridization probe test, of cervical swabs (women) or urine samples (men) was used. From 2000 through 2012, BD ProbeTec ET test (Becton-Dickinson, Sparks, Maryland), a strand displacement assay test (nucleic acid amplification test NAAT) was used. From March 2000 through 2006, only urine (men and women) was screened with BD ProbeTec ET. After 2006, both urine and cervical or vaginal swabs were screened with BD ProbeTec ET. The screening test used from 1998 through February 2000 was not recorded. Since missing data were only associated with study year, test type during this period could not be imputed and was considered missing.

Covariates

We included several demographic variables in our analyses. Variables included sex, age, race/ethnicity (self-reported non-Hispanic, Black, Hispanic, Native American), region of residence (Northeast, Midwest, South and West), and self-report of any STI symptoms at the time of screening.

Study Sample

Eligible participants for these analyses were defined as non-Hispanic White, Black, Hispanic, or American Indian women and men entering the NJTP from 1990 through 2012 who had a positive or negative chlamydia screening test result. Enrollees were excluded if their chlamydia test result, race/ethnicity, region of residence at the time of enrollment, or type of chlamydia screening test were unknown or missing.

Specific Aim 1 Analysis

Meta-Analyses for Screening Test Sensitivity and Specificity

Sensitivity and specificity of screening tests vary by population, and the precise sensitivity and specificity for the NJTP population is unknown. To generate estimates for the NJTP population, we conducted a targeted meta-analysis of peer-reviewed literature to generate sensitivity and specificity estimates for the different tests used for screening of NJTP enrollees. Inclusion and exclusion criteria of peer-reviewed publications and assessment of publication validity were guided by the Quality Assessment of Studies of Diagnostic Accuracy tool.(35) Only studies that evaluated the same brand of chlamydia screening tests as those used for NJTP screening were considered.

The following data were abstracted:

- Study characteristics: First author's name, year of publication, journal, study period, study design
- Study sample characteristics: age, sex, race/ethnicity, geography, place of recruitment and screening, sample size
- Screening tests data: number of true positives, true negatives, false positives, and false negatives, and number of missing

Bivariate generalized linear mixed effects models with a logit link were used to calculate summary sensitivity and specificity estimates and corresponding 95% confidence intervals.

Case Mix Assessment

We evaluated case mix by examining the distribution of enrollment by race/ethnicity (non-Hispanic White, Black, Hispanic, and American Indian) and enrollment by region (Midwest, South, Northeast, and West) for women and men throughout the study period. Race/ethnicity and region served as proxies for chlamydia risk since the prevalence and case rates of chlamydial infection vary by race/ethnicity and region, with Blacks and the Southern region of the US having the highest burden (1,4,7). We visualized the distribution of race and region over time using stacked bar charts and modeled enrollment using logistic regression. In all models, race/ethnicity or region was the dependent variable. Various functional forms of study year (continuous) were included as the independent variable(s). Akaike information criteria (AIC) and visual inspection were used to determine model fit.

Modeling Chlamydia Prevalence

To account for time-varying measurement error associated with changing screening tests, the annual prevalence of chlamydia was modeled using an expectation maximization (EM) algorithm based maximum likelihood approach first described by Magder and Hughes (1997).(36) This approach uses EM to estimate a maximum-likelihood regression model when the outcome is measured with imperfect sensitivity and specificity, and allows the sensitivity and specificity of disease classification to vary across observations.

This approach incorporates a correction for outcome misclassification into logistic regression. First, using arbitrary regression parameters and Bayes theorem, the predicted

probability of being truly diseased for each observation is calculated based on the probability of being classified as diseased (the probability of a true positive or a false negative) given screening test sensitivity and specificity, and covariate values. The data are then duplicated and each observation included twice, once with the outcome variable set as diseased and another with the outcome set as non-diseased. A weighted logistic regression model is fitted with weights equal to the probability of being truly diseased and probability of being truly not diseased, respectively. The new regression parameters from the weighted logistic regression are then used to calculate new probabilities of being truly diseased. This process continues until convergence. The algorithm can be implemented using the LogitEM command in Stata.

Our models accounted for sensitivity and specificity estimates that were generated from our meta-analyses. Laboratory-confirmed chlamydial infection (positive or negative screening test result) was the dependent variable in all models and study year (continuous) was the independent variable. The functional form of year was assessed using AIC and visual inspection. Estimated coefficients from the model output (i.e. $p_x = 1/(1+(e^{-(\beta_o + \beta_1 X_1)})$ were used to calculate the predicted probability (prevalence) of chlamydia across study years. Ninety-five percent CIs were obtained by bootstrapping (n=200). Prevalence trends were modeled separately for women and men. We also stratified by race/ethnicity and region to examine differences in trends for each subgroup.

Sensitivity Analyses

We conducted two sensitivity analyses to examine uncertainty around sensitivity and specificity estimates that were used to model prevalence. To account for random error, we modeled prevalence trends using the upper and lower bounds of the 95% CI around sensitivity and specificity estimates. To account for systematic error, we re-estimated test sensitivity and

specificity using more selective inclusion/exclusion criteria for the meta-analyses. We used these new estimates to model adjusted prevalence trends.

Limitations

This research has several limitations. First, although the NJTP is a national sample of young adults, chlamydia trends are only generalizable to socio-economically disadvantaged young adults entering a job-training program. Trends may not reflect disease trends of young adults on a broader national scale. However, prevalence estimates of chlamydia from this population are still relevant and important because NJTP is comprised of individuals who are at typically highest risk of chlamydia and likely targets of screening programs.

Second, trends may be biased due to case mix and population characteristics that cannot be accounted for with the measured variables. This analysis used the best available covariates to represent case mix (race/ethnicity and residence). However, these variables may not fully capture changing risk profiles or characteristics of the NJTP population over time.

Third, we could not account for other factors, such as sexual behaviors, condom use, or sexual debut, which may have changed over time and influenced chlamydia prevalence trends.

3.2 SPECIFIC AIM 2:

Estimate counterfactual incidence rates of correctly diagnosed chlamydia among young women from 2000 through 2015, accounting for changes in screening coverage, screening tests, case mix, and reporting compliance, and compare counterfactual incidence rates to reported case rates.

Specific Aim 2 Study Description

Conceptual Framework

Our estimation approach was based on a conceptual diagram of relationship between the at-risk population and surveillance-related biases. In our conceptualization, the true chlamydia caseload is systematically reduced by these biases. We start with a dynamic population of at-risk women in steady-state. Within this population are true chlamydia cases, as well as the proportion of the population that is screened for chlamydia, the proportion diagnosed with chlamydia, and the proportion reported as chlamydia cases. Reported chlamydia cases are an underestimate of true chlamydia cases in the population as a result of partial screening coverage, misclassification due to imperfect screening tests, and under-reporting.

We implemented a series of corrections that addressed each bias successively, and calculated the counterfactual incidence of correctly diagnosed chlamydia that would have been observed in the absence of screening- and reporting-related biases. Specifically, we corrected annual case rates for under-reporting, case misclassification, and partial screening coverage. We corrected case rates among all women aged 15 through 24, and stratified case rates by age group (15 through 19 years, and 20 through 24 years) to examine variation in trends among younger and older women. Our approach allowed for temporal variation in biases to reflect improvements over time in screening coverage, screening tests, and reporting.

Description of National Chlamydia Case Rates

Reported chlamydia case rates for women in our target age groups (ages 15 through 24, 15 through 19, and 20 through 24) in the US from 2000 through 2015 were obtained from the CDC's National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention AtlasPlus tool (37). Case rate numerators represent the total number of chlamydia cases (diagnoses) reported to the CDC in one year by STI control programs and health departments in all 50 states and the District of Columbia. Case rate denominators are calculated as the US census population of women of the target ages in a given year.

Specific Aim 2 Analysis

We made a series of simple corrections to annual reported chlamydia case rates to account for under-reporting, imperfect screening tests, and partial screening coverage.

For a given year, we defined the following:

C = number of reported cases (case rate numerator)

N = total at-risk population (case rate denominator)

R = proportion of chlamydia diagnoses that were reported to CDC through national notifiable disease surveillance (reporting fraction)

Se= screening test sensitivity

Sp = screening test specificity

Sc = proportion of the at-risk population screened for chlamydia (screening coverage)

In each study year, we took 200 random draws from distributions describing reporting, screening tests, and screening coverage (see "Bias Parameter Inputs" below) to define values for the inputs R, Se, Sp, and Sc above. With the values in each draw, we performed the calculations described below to estimate the counterfactual incidence of correctly diagnosed chlamydia in a given year. We then compared the annual medians of these corrected rates to the reported chlamydia case rates from 2000 through 2015 to assess the impact of these biases on reported trends.

Correcting for under-reporting

To correct for under-reporting of chlamydia cases, we divided reported chlamydia cases [C] by the reporting fraction [R]. This step generated the counterfactual count of chlamydia diagnoses (both true and false positives) among women screened that we would expect to be included in case rate estimates under perfect reporting.

Correcting for misclassification due to imperfect screening tests

To calculate the number of true chlamydia cases among women who were screened in a given year, which we will call *A*, we corrected for misclassification of chlamydia cases due to imperfect screening test sensitivity and specificity following Greenland,1996 (38),

$$A = \frac{\frac{C}{R} - FrT}{Se}, \qquad \text{Equation 1}$$

where FrT is the number of false positive diagnoses per unit person-time among women screened. If we assume that each individual in a given annual case rate denominator (N) contributes, on average, one year of person time during which he or she is at risk of chlamydia diagnosis that year, FrT can be calculated as

$$FrT = (1 - Sp) * (1 - P) * ScN, \qquad \text{Equation 2}$$

where P is the underlying true prevalence of chlamydia in the screened population. This assumption is valid if 1) the at-risk population is dynamic and in steady-state (39), 2) person-time contributed by unidentified true cases is relatively small, and 3) identified cases are treated and promptly return to the pool of at-risk women.

We derived annual prevalence as follows: In a steady-state population with non-differential screening according to true chlamydial infection, the cumulative number of diagnosed cases among women screened [C/R] in a given year should equal the number of new diagnoses that would be observed in a one-time screening process conducted in the population that year. This number, in turn, is equal to the total number of true and false positives that would be observed in that screening process, which can be calculated as $ScN(SeP + (1 - Sp)(1 - P))$. Setting this expression equal to C/R and solving for P, we obtain:

$$P = \frac{\frac{C}{R} - ScN(1-Sp)}{ScN(Se+Sp-1)}, \qquad \text{Equation 3}$$

Substituting this expression for prevalence into Equation 2 above allowed us to calculate FrT, which we entered into Equation 1 to generate the counterfactual number of diagnosed true chlamydia cases that would have been observed among women screened under perfect reporting and screening test performance [A].

Correcting for partial screening coverage

To correct for screening coverage, we divided the number of diagnoses of true chlamydia cases among women screened [A] by the screening coverage [Sc]. This step gave us the counterfactual number of correctly diagnosed chlamydia cases in the total at-risk population over one year that would be observed with perfect reporting, screening tests, and screening coverage. Under our assumption that each person in the case-rate denominator (N) contributes an average of one year of person-time at risk, we calculated the counterfactual incidence of correctly diagnosed chlamydia by dividing A by N person-years.

Bias Parameter Inputs:

We incorporated sampling distributions for each bias into our calculations to account for random error in bias estimates. We conducted literature reviews and sought expert opinion to create the sampling distributions. Unless specified otherwise, we created triangular distributions to describe the range of plausible bias inputs for each study year. The sampling distributions for each bias parameter over the course of the study period are shown in figure 5.

Reporting Fraction: By 2000, all 50 states and the District of Columbia reported chlamydia cases as part of national surveillance (STD disease surveillance). A fraction of cases go unreported due to imperfect reporting compliance, but compliance has improved over time with the implementation of electronic laboratory reporting systems, which enable cases to be reported directly from laboratories. Based on CDC expert opinion, we assumed reporting fraction for all age groups increased from approximately 70% to 95% over the study period (40).

Misclassification Due To Imperfect Screening Tests: We incorporated time-varying misclassification due to the use of increasingly sensitive screening tests by considering test use and test performance over the study period. Chlamydia screening gradually transitioned from

low-sensitivity, high-specificity tests, which we refer to as non-nucleic acid amplification tests (non-NAATs), to high-sensitivity, high-specificity tests (NAATs). We selected sensitivity and specificity values for non-NAATs and NAATs that were consistent with estimates reported in previous literature (41–44). We set sensitivity to be 75% and 92% for non-NAATs and NAATs, respectively, and specificity to be 99.5% for both test types. We also estimated the proportion of screening via non-NAATs and NAATs each year based from regional screening data collected as part of the Infertility Prevention Project from 2000 through 2011 (13). We attached lognormal distributions to these test use estimates (Figure A3.1). We used these annual test use estimates to calculate weighted-average sensitivity and specificity estimates for screening tests each year.

Screening Coverage: Inputs for screening coverage were based upon coverage reported by the Healthcare Effectiveness Data and Information Set (HEDIS), and CDC expert opinion(40,45). Annual coverage estimates from HEDIS are derived from women enrolled in commercial healthcare plans or Medicaid, and calculated as the women screened for chlamydia out of all sexually active women who saw a healthcare provider. HEDIS provides screening coverage estimates for women aged 15 through 24, as well as women aged 15 through 20 and aged 21 through 24 because screening coverage among younger women is typically lower than coverage among older women. For study each year and each age group, we considered the screening coverage estimate among women enrolled in commercial insurance plans and Medicaid, and calculated the midpoint of these estimates. Based on these midpoints and CDC expert opinion, we selected plausible screening coverage estimates for 2000 through 2015. Estimates for all women age 15 through 24 increased from 30% in 2000 to 50% in 2015. Estimates for women age 20 through 24 increased from 30% to 55%. Estimates for women age 15 through 19 increased from 30% to 45%.

Sensitivity and Influence Analyses:

We conducted several sensitivity analyses for case rate corrections among women aged 15 through 24 to address potential systematic error in literature reporting estimates screening test sensitivity and screening coverage. Screening test sensitivity estimates in literature are variable, so we incorporated sensitivity estimates of non-NAATs and NAATs that were reasonable lower and upper bounds of our initial inputs. These new sensitivity estimates were selected based on approximate upper and lower bounds of sensitivity reported in literature. We specified low non-NAAT and NAAT sensitivities of 70% and 85%, and high non-NAAT and NAAT sensitivities of 85% and 97% (42,44).

We also incorporated a range of screening coverage estimates to account for limitations of HEDIS coverage estimates. Estimates from HEDIS capture only women who are enrolled in a commercial health plan or Medicaid and have an indicator of sexually activity, and may not be representative of screening coverage in the underlying population. Therefore, we incorporated estimates of screening coverage that we considered to be the plausible lower bound of coverage for women age 15 through 24 over the study period, and estimates that we considered to be the plausible upper bound of coverage. We selected coverage that increased from 20% to 40% over time (lower bounds), and coverage that increased from 40% to 60% over time (upper bounds).

Finally, to understand whether one bias or set of biases was particularly influential, we examined scenarios in which reported case rates were corrected for only under-reporting, only imperfect screening tests, or only coverage. We also examine a scenario in which reported case rates were corrected for reporting fraction and imperfect screening tests only.

Limitations

Limitations for Aim 2 stem from concerns about the validity of estimates used to generate bias parameters, and a paucity of data informing some bias parameters. Individual estimates of reporting, test sensitivity and specificity, or coverage may be influenced by internal biases and may have limited external validity. Incorporating uncertainty into the estimates of biases helped mitigate these concerns.

We did not have enough data to properly account for bias due to case mix. To account for case mix, analyses should be completed separately for sub-population with similar chlamydia risk factors and therefore similar chlamydia risk. We did not have about data to conduct analyses among subgroups and were unable to account for case mix.

CHAPTER FOUR: SPECIFIC AIM 1 RESULTS

4.1 INTRODUCTION

Chlamydia trachomatis (chlamydia) infection is usually asymptomatic, but can result in serious reproductive sequelae if left untreated. In response to the high burden of chlamydia among young women, the Centers for Disease Control and Prevention introduced a regional federally funded chlamydia screening program in 1988. By 1995, screening programs were implemented in all regions of the US as part of the Infertility Prevention Project (13,46). The screening programs strengthened clinical, educational, laboratory, and surveillance operations related to chlamydia and supported screening and treatment services for low-income, sexually active women attending public clinics. The goals were to identify and treat infections, which in turn prevents transmission and reduces incidence and prevalence (14).

At the population level, a reduction in chlamydia prevalence should be observable in sentinel populations if national screening programs achieve sufficiently high penetration (26). A primary source for sentinel surveillance of chlamydia in the U.S. is the National Job Training Program (NJTP), a vocational training program for socioeconomically disadvantaged adolescents and young adults administered by the Department of Labor (1,33,34). The NJTP has maintained consistent eligibility criteria over time and screens all entrants for chlamydia, making it a stable, high-risk population ideal for monitoring chlamydia prevalence. Among NJTP enrollees, chlamydia prevalence trends spanning short periods have shown modest decreases since the early 1990s, suggesting that national screening programs may have had an effect on chlamydia prevalence, as measured in this sentinel population (19–22).

Observed prevalence trends from sentinel surveillance should be interpreted cautiously because of potential biases. Two of the most important sources of bias that can affect prevalence trend estimates are time-varying measurement error from changing screening tests and sentinel population risk profiles. Changes in measurement error can bias prevalence trend estimates when new screening technologies with different sensitivities and specificities are used (14,16). Changes in population risk profiles, which we refer to as "case mix," can bias prevalence trend estimates when the relative proportion of high and low-risk individuals screened in a sentinel population fluctuates (14). These biases may mask changes in prevalence over time, and trend estimates that do not properly account for changes in measurement error and case mix may be misleading.

We examined chlamydia prevalence trends over 23 years among NJTP enrollees, while accounting for potential biases associated with changing screening tests and case mix to understand whether national chlamydia screening programs may have contributed to declining chlamydia prevalence trends among high-risk youth.

4.2 MATERIALS AND METHODS

Study Population

We analyzed annual cross-sectional chlamydia screening data from NJTP enrollees from 1990 through 2012. US residents age 16 through 24 who meet low-income criteria and face barriers to employment can enroll in the NJTP. Universal chlamydia screening of NJTP entrants began in 1990 for women and 2003 for men. Screening was performed by a national contract laboratory that used several tests. From 1990 through 1997, cervical or vaginal swabs were tested by Pathfinder Enzyme Immunoassays (EIA) (Sanofi Diagnostics Pasteur, Inc, Redmond, Washington). Screening tests used from 1998 through February 2000 are unknown.

From March 2000 through December 2006, screening was done with Gen-Probe PACE 2 DNA hybridization probe (Gen-Probe Inc., San Diego, California) of swabs from women or urine from men, or BD ProbeTec ET strand displacement assay (SDA) (Becton-Dickinson, Sparks, Maryland) of urine. After December 2006, screening was done by BD ProbeTec ET of swabs or urine.

Eligible participants for these analyses were non-Hispanic White, Black, Hispanic, or American Indian women and men entering the NJTP who had a recorded chlamydia screening test result. Enrollees were excluded if their chlamydia test result, race/ethnicity, region of residence, or screening test type were unknown.

Screening Test Sensitivity and Specificity

Pairs of sensitivity and specificity estimates for each screening test and sample type were generated through targeted meta-analyses of existing literature. We searched PubMed and Scopus using medical subject heading terms and keywords related to chlamydia screening and diagnostic accuracy (Appendix 1). We included studies conducted in North America or Europe that reported the diagnostic accuracy of the Pathfinder EIA, Gen-Probe PACE 2, and BD ProbeTec ET, and from which counts of true positive, true negative, false positive, and false negative tests could be extracted or calculated (47–65). Bivariate generalized linear mixed effects models with a logit link were used to generate summary sensitivity and specificity estimates and corresponding 95% confidence intervals (CI) (Table 1).

Case mix

Chlamydia prevalence and case rates are associated with race/ethnicity and geography, with Blacks and the South having the highest burden (1,4,7). To assess potential bias from longitudinal changes in the demographics of NJTP enrollees, we examined the racial/ethnic and

geographical distributions of enrollees over time. We visualized the distribution of race/ethnicity and enrollment by region using stacked bar charts, and observed a uniform distribution over time for both factors (Figures A2.1-A2.4). We also examined temporal trends in enrollment by these factors using logistic regression, with race/ethnicity or region as the dependent variable, and study year (continuous) as the independent variable(s). No meaningful variation in the relative proportion of race/ethnicity and region over time was observed, and additional results are not reported. These analyses provided evidence that no meaningful case mix variation occurred.

Prevalence Trends

We modeled chlamydia prevalence trends using an expectation-maximization (EM)-based maximum-likelihood approach that accounts for measurement error due to imperfect screening test sensitivity and specificity (36). This approach uses EM to estimate a maximum-likelihood regression model when the outcome is measured with uncertainty, and allows the sensitivity and specificity of screening tests to vary across observations. Our models accounted for sensitivity and specificity estimates generated from our meta-analyses. Chlamydial infection (positive or negative) was the dependent variable in all models and study year (continuous) was the independent variable. The functional form of year was assessed using Akaike information criteria and visual inspection, and included quadratic spline terms with three knots in models for women and a quadratic term in models for men. Estimated coefficients from the model output were used to calculate the probability (prevalence) of chlamydia across study years. Ninety-five percent CIs were obtained by bootstrapping (n=200). We compared trends from the EM maximum-likelihood regression model (adjusted trends that account for time-varying measurement error) to trends from a logistic regression model (unadjusted trends that do not account for time-varying measurement error) to assess the impact of changing screening tests

on prevalence trend estimates. We also stratified by race/ethnicity and region to examine subgroup differences.

Sensitivity Analyses

We conducted sensitivity analyses to account for random and systematic error in the estimates of test sensitivity and specificity that were used to model prevalence. To account for random error, we modeled prevalence using the upper and lower bounds of the 95% CI around our summary sensitivity and specificity estimates. To account for systematic error, we re-estimated test sensitivity and specificity using more selective inclusion/exclusion criteria for the meta-analyses. We excluded studies that used the test of interest in their reference test definition (reference test bias) or performed repeat testing. We used these new estimates to model adjusted prevalence.

Analyses were performed in Stata version 14.1 (66).

4.3 RESULTS

Screening Test Sensitivity and Specificity

Sensitivity increased over the study period. The estimated sensitivity of EIA, DNA probe, and SDA for women was 73%, 80%, and 87% respectively (Table 4.1). Among men, sensitivity of DNA probe and SDA was 72% and 95% respectively. All tests had specificities >98%.

Women:

From 1990 through 2012, 439,992 women were screened for chlamydia. Relatively few women had an uninterpretable screening test result (n=3,466). Due to administrative changes in reporting, race/ethnicity could not be determined for approximately 30% of women in 2001 and 2002. Because missing race/ethnicity in these years was large and associated only with study

year, all women in 2001 and 2002 were excluded (n=21,021). Across other years, relatively few women had missing race/ethnicity (n=19,703) or region (n=15,613). Chlamydia screening test type was unknown for women enrolled between January 1998 and February 2000 (n=26,730) and a small number of women in other study years (n=2,969), and these data were considered missing. After excluding women with uninterpretable test results or missing data, 350,490 women (80% of women screened for chlamydia) were included in analyses.

Most women were Black (58%) and approximately half lived in the South (45%) (Table 4.2). Two thirds were age 16 through 19 (69%), and few reported symptoms (3%). Approximately 40% of women were tested for chlamydia via EIA, 15% were tested by DNA probe, and the remainder was tested via SDA of swabs (14%) or urine (30%).

Unadjusted chlamydia prevalence was high overall, ranging between 15% and 10%. Prevalence declined modestly from 1990 through 2003, before rising slightly through 2009 (Figure 1). After accounting for measurement error associated with different screening tests, we observed a higher burden of chlamydia across all years and a sharper decline in prevalence in the first half of the study, relative to unadjusted estimates (Figure 4.1). Prevalence was highest in 1990 at approximately 20%, and steadily decreased to 12% by 2003. Between 2004 and 2012, prevalence was relatively steady and rose slightly to 14% before dropping to 12%.

Black women had the highest burden of chlamydia throughout the study, followed by American Indian, Hispanic, and White women (Figure 4.2). For all race/ethnicities, prevalence declined early on, with the sharpest decline occurring among American Indian women (24% to 12%) and Black women (23% to 14%). Among Hispanic and White women, prevalence declined from approximately 15% to 10% and 13% to 7% respectively. Adjusting for time-varying measurement error revealed a larger decline in prevalence for all race/ethnicities early in the

study, relative to unadjusted trends (Figure A2.5). In the second half of the study, chlamydia prevalence remained relatively steady among White and Hispanic women. Prevalence in Black women rose modestly from 14% to 17% between 2003 and 2008, before beginning to drop. American Indian women experienced a slight uptick in prevalence from 2008 through 2012 (12% to 16%).

Chlamydia prevalence was highest throughout the study in the South, followed by the Midwest, Northeast, and West. In all regions, prevalence was high in 1990, ranging between 16% in the West to 21% in the South (Figures 4.3 and A2.6). Prevalence declined in the first half of the study in all regions, and leveled out in the second half in the West and Northeast. Modest increases in prevalence occurred in the South and Midwest between 2004 and 2009.

In sensitivity analyses, neither the magnitude nor shape of the overall prevalence trend was substantially altered by using the lower and upper bounds of the 95% CI around test sensitivity and specificity estimates (Figure A2.7). Modeling trends with re-estimated test sensitivity and specificity also had minimal influence on the overall trend (results not shown).

Men:

From 2003 through 2012, 370,047 men were screened for chlamydia. Few men had an uninterpretable test result (n=1,288), or were missing race/ethnicity (n=21,976). Region and chlamydia screening test type were missing for 7,486 men and 35,598 men respectively. Overall, 303,699 men (82% of men screened for chlamydia) were included in analyses.

Half of men were Black (51%) and lived in the South (49%) (Table 4.2). Two thirds were age 16 through 19 (67%). Few men reported sexually transmitted infection symptoms (1%).

Almost all men were screened with SDA (99%). Unadjusted chlamydia prevalence remained stable throughout the study, and fluctuated between 8% and 9% (Figure 4.1).

After accounting for measurement error, the prevalence of chlamydia among men decreased slightly in all years relative to unadjusted estimates but remained steady over time at approximately 7% (Figure 1). Black men had the highest prevalence across all years (approximately 11%), followed by American Indian (approximately 5%), Hispanic (approximately 4%), and White men (approximately 1%) (Figures 4.2 and A2.8). Prevalence was consistently highest in the South, followed by the Midwest, Northeast, and West (Figure 4.3 and A2.9). Prevalence estimates generated from the upper and lower bounds of the 95% CI around test sensitivity and specificity did not substantially alter trends (Figure A2.10).

4.4 DISCUSSION

Chlamydia remains one of the most commonly reported sexually transmitted infections in the US despite long-standing national screening and treatment programs (1). Sentinel surveillance of chlamydia among NJTP enrollees provides a unique opportunity to evaluate the impact of national chlamydia screening programs on prevalence among high-risk youth. After ruling out bias due to case mix and adjusting for time-varying measurement error associated with changing screening tests, chlamydia prevalence among women declined from 20% to 12% during the first 14 years of the study, and hovered between 12% and 14% through 2012. Adjusted chlamydia prevalence among men was stable from 2003 through 2012 (approximately 7%). For women and men, prevalence was highest among Black and American Indian youth, and the South and Midwest throughout the study.

The decline in chlamydia prevalence among women entering the NJTP during the 1990s provides support for the early success of screening programs in reducing chlamydia burden.

Women in the NJTP are a surrogate for high-risk young women in the general population, and falling trends within the NJTP suggest that national screening programs initially may have led to a reduction in chlamydia among high-risk young women. After 2003, prevalence stopped declining, suggesting that on-going screening efforts targeting high-risk young women were ineffective at continuing to reduce prevalence. Current screening efforts may be sufficient to stabilize chlamydia prevalence in high-risk populations, but are unlikely to drive any further decline.

Chlamydia prevalence among men was steady throughout the study. Screening for men started in 2003, when the prevalence among women began to stabilize. Prevalence among men may have declined similarly to women prior to 2003 since men are a reservoir for chlamydia. The flat trend signals that ongoing prevention efforts have been ineffective at reducing chlamydia among men.

We observed large disparities in chlamydia prevalence by race/ethnicity and region, with Blacks, American Indians, and the South having consistently higher prevalence compared to other races/ethnicities and regions. Prevalence in these groups also increased modestly during the latter half of the study. Similar racial and regional disparities have been observed among large population-based surveys and public high school students (4,5,7,67,68). The NJTP population consists of socioeconomically disadvantaged youth and our results cannot be generalized to all youth. However, consideration of targeted chlamydia prevention efforts for these groups is warranted since racial and regional disparities exist in multiple populations.

Our findings differ from previously reported chlamydia prevalence trends among NJTP enrollees with respect to trend direction, duration, and validity. Previously reported trends are decreasing but estimated only over the short-term. (19–22) While focusing on shorter periods

may avoid bias from changing tests, it prohibits trend comparisons across periods with different tests. Additionally, time spans may be too short to observe the impact of screening on a population level. We examined 23-year prevalence trends to generate a comprehensive picture of chlamydia burden over time, and observed no substantial decline after 2003.

We also used robust methods to account for measurement error due to changing screening tests. In previous trend estimates, measurement error was addressed by controlling for screening tests in generalized linear models or restricting by test type (20,21). These methods do not account for differing test sensitivities and specificities (15). To generate more valid prevalence estimates that correctly account for measurement error, we estimated screening tests' diagnostic accuracy through meta-analyses, and used EM-based maximum-likelihood regression to incorporate sensitivities and specificities into prevalence trend estimation. We examined several sensitivity and specificity estimates to account for random and systematic error that may have influenced our diagnostic accuracy estimates. Sensitivity analyses showed that adjusted prevalence trend estimates were generally unaffected by a range of plausible screening test sensitivity and specificity values.

Additionally, we evaluated the need to account for case mix by examining characteristics of NJTP enrollees over time. NJTP entrance criteria for socioeconomic status, education, and age were constant throughout the study (34), and we did not observe meaningful variation in race/ethnicity or region over time. We could not assess whether characteristics of individuals meeting NJTP entrance criteria changed over time, so although entrance criteria were consistent, risk profiles of enrollees, such as sexual behavior, could have changed. Still, unchanged criteria helped ensure that the relative proportion of major risk factors for chlamydial infection (socioeconomic status, age, race/ethnicity, and region) was stable.

We acknowledge that factors other than screening program effectiveness or biases in surveillance data could have influenced chlamydia prevalence trends. Two such factors are changes in sexual behaviors and increased condom use. These factors drove falling teen pregnancy trends (69), which declined similarly to chlamydia in the 1990s but continued to drop steadily through 2012 while chlamydia trends plateaued or rose, suggesting that multiple factors played a role in the early decline of chlamydia. We cannot evaluate whether additional factors influenced chlamydia trends for this study. However, in the absence of more complete data about the impact of screening programs or potential influential factors, sentinel surveillance data are uniquely informative for chlamydia screening program effectiveness. Our study addresses two of the most important biases that can impact prevalence (measurement error and case mix) and was not subject to biases from changes in healthcare seeking behaviors, coverage, or reporting. Thus, we believe that chlamydia screening programs contributed to the decline in chlamydia prevalence in the 1990s.

Our study is the first to generate long-term chlamydia prevalence trend estimates among NJTP enrollees while properly accounting for biases that influence observed prevalence in sentinel populations. We observed an initial decline in chlamydia prevalence among women, followed by a period of stagnation. The trend is evidence that chlamydia screening programs were initially effective on a population level, but screening later lost momentum in reducing chlamydia prevalence, which remained high despite the initial decline. Although screening programs may have impacted related outcomes, such as reproductive sequelae or HIV transmission, evaluating programs' success by monitoring the incidence of related outcomes is difficult since these outcomes have multiple etiologies. Therefore, monitoring chlamydia prevalence is an important part of chlamydia control. Chlamydia prevalence among high-risk youth remains alarmingly high, and expanded screening and prevention efforts are needed for any further reduction.

4.5 TABLES AND FIGURES

Table 4.1: Summary sensitivity and specificity estimates of chlamydia screening tests

Screening Test (sample type)	No. of Studies[Ref]	Sensitivity (95% CI)	Specificity (95% CI)
Women			
Pathfinder EIA (Swab)[1]	2[47,48]	72.92 (39.07, 91.88)	99.64 (98.14, 99.93)
Gen-Probe PACE 2 DNA Probe (Swab)[2]	11[47,49–58]	80.07 (76.66, 83.08)	99.21 (98.43, 99.60)
BD ProbeTec ET SDA (Urine)[3]	4[60,62–64]	87.82 (83.74, 90.99)	99.10 (97.66, 99.66)
BD ProbeTec ET SDA (Swab)[4]	6[59–64]	87.49 (81.27, 91.86)	99.47 (98.69, 99.79)
Men			
Gen-Probe PACE 2 DNA Probe (Urine)[2]	3[51,55,65]	72.09 (60.07, 81.61)	99.17 (97.04, 99.77)
BD ProbeTec ET SDA (Urine)[3]	3[60,62,63]	94.04 (91.54, 95.83)	98.21 (91.32, 99.65)

[1]Used for screening from 1990 through 1997

[2]Used for screening from March 2000 through 2006 for women, and 2003 through 2006 for men

[3]Used for screening from 2000 through 2012 for women, and 2003 through 2012 for men

[4]Used for screening from 2007 through 2012

Table 4.2: Characteristics of National Job Training Program enrollees and unadjusted chlamydia prevalence, 1990-2012[1]

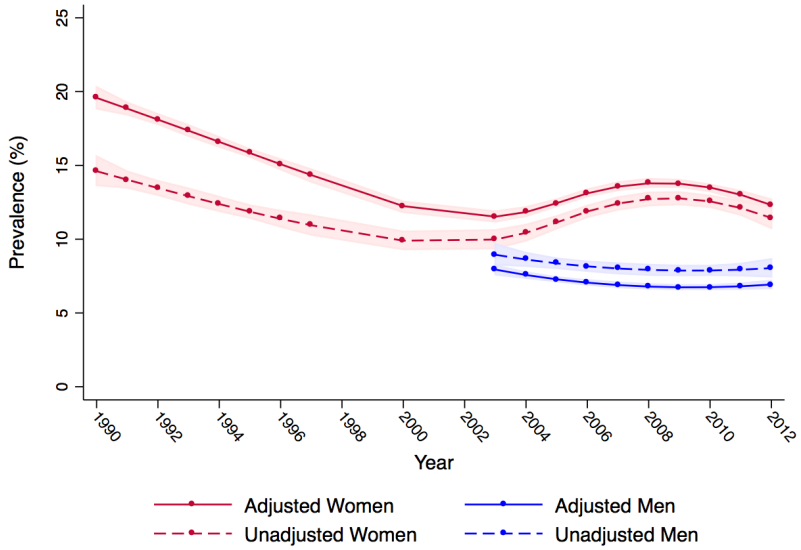
	Women (n=350,490)				Men (n=303,699)			
Characteristic	**No. Tested**	**(Col %)**	**No. Positive**	**Unadjusted Prevalence (%)[2,3]**	**No. Tested**	**(Col %)**	**No. Positive**	**Unadjusted Prevalence (%)[2]**
Age (yrs)								
16-19	242,330	(69.1)	32,631	13.5	204,778	(67.4)	16,147	7.9
20-24	108,160	(30.9)	9,743	9.0	98,921	(32.6)	8,567	8.7
Race/Ethnicity								
Black	202,707	(57.8)	29,445	14.5	155,045	(51.1)	19,031	12.3
White	82,366	(23.5)	6,116	7.4	95,994	(31.6)	2,761	2.9
Hispanic	54,799	(15.6)	5,527	10.1	44,822	(14.8)	2,713	6.1
American Indian	10,618	(3.0)	1,286	12.1	7,838	(2.6)	507	6.5
Region								
Midwest	64,153	(18.3)	7,911	12.3	51,361	(16.9)	4,423	8.6
Northeast	60,654	(17.3)	6,321	10.4	45,730	(15.1)	2,893	6.3
South	157,294	(44.9)	22,047	14.0	149,464	(49.2)	14,983	10.0
West	68,389	(19.5)	6,095	8.9	57,144	(18.8)	2,415	4.2
Symptoms at Entrance								
Yes	10,365	(3.0)	1,556	15.0	3,707	(1.2)	673	18.2
No	340,125	(97.0)	40,818	12.0	299,992	(98.8)	24,041	8.0
Test (sample type)								
EIA (swab)	141,932	(40.5)	17,811	12.5	--	--	--	--
DNA Probe (swab)	53,812	(15.4)	5,139	9.5	--	--	--	--
DNA Probe (urine)	--	--	--	--	954	(0.3)	83	8.7
SDA (swab)	47,690	(13.6)	6,779	14.2	--	--	--	--
SDA (urine)	107,056	(30.5)	12,645	11.8	302,745	(99.7)	24,631	8.1

Table 4.2 (Continued): Characteristics of National Job Training Program enrollees and unadjusted chlamydia prevalence, 1990-2012[1]

	Women (n=350,490)				Men (n=303,699)			
Characteristic	**No. Tested (Col %)**		**No. Positive**	**Unadjusted Prevalence (%)[2,3]**	**No. Tested (Col %)**		**No. Positive**	**Unadjusted Prevalence (%)[2]**
Year of Test								
1990	10,143	(2.9)	1,518	15.0	--	--	--	--
1991	18,086	(5.2)	2,588	14.3	--	--	--	--
1992	18,922	(5.4)	2,380	12.6	--	--	--	--
1993	20,132	(5.7)	2,484	12.3	--	--	--	--
1994	19,994	(5.7)	2,722	13.6	--	--	--	--
1995	18,151	(5.2)	2,276	12.5	--	--	--	--
1996	21,115	(6.0)	2,235	10.6	--	--	--	--
1997	15,389	(4.4)	1,608	10.4	--	--	--	--
2000	8,274	(2.4)	938	11.3	--	--	--	--
2003	16,095	(4.6)	1,598	9.9	16,206	(5.3)	1,447	8.9
2004	17,936	(5.1)	1,862	10.4	32,593	(10.7)	2,766	8.5
2005	19,114	(5.5)	1,758	9.2	33,637	(11.1)	2,849	8.5
2006	19,339	(5.5)	2,611	13.5	32,652	(10.8)	2,699	8.3
2007	20,825	(5.9)	2,811	13.5	33,147	(10.9)	2,683	8.1
2008	21,494	(6.1)	2,743	12.8	33,158	(10.9)	2,624	7.9
2009	21,288	(6.1)	2,518	11.8	31,435	(10.4)	2,411	7.7
2010	21,948	(6.3)	2,669	12.2	30,421	(10.0)	2,346	7.7
2011	22,162	(6.3)	2,646	11.9	31,661	(10.4)	2,581	8.2
2012	20,083	(5.7)	2,409	12.0	28,789	(9.5)	2,308	8.0

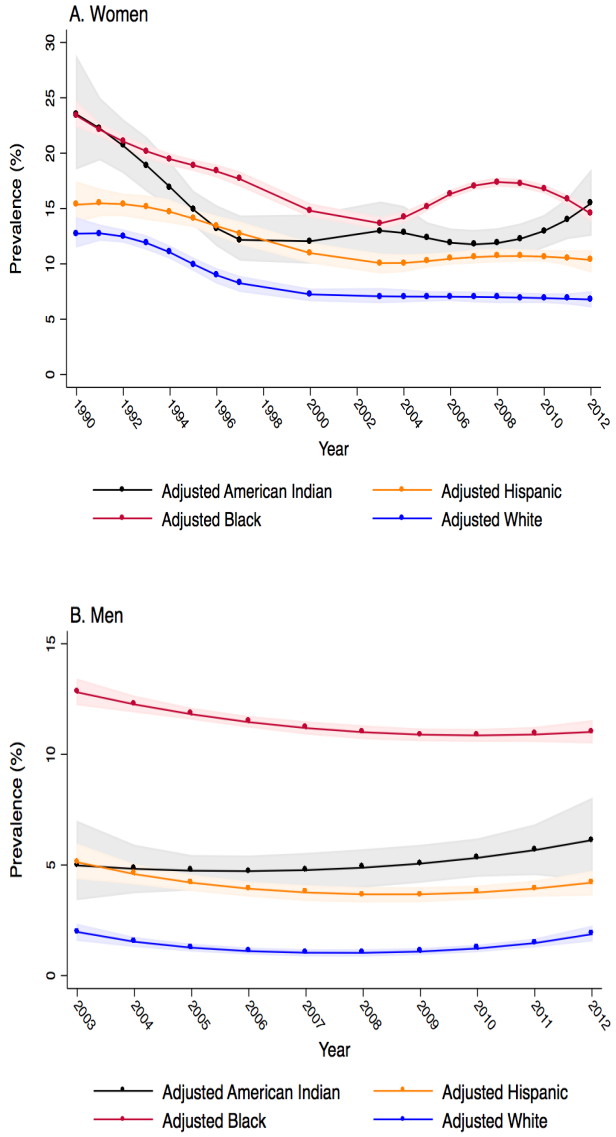
[1]Data from 1998-March 2000 were excluded due to missing chlamydia screening test type. Data from 2001-2002 were excluded due to missing race/ethnicity.
[2]Unadjusted prevalence was calculated as the total number of positive tests divided by the total number tested. Estimates differ slightly from estimates derived from logistic regression models.
[3]Unadjusted prevalence estimates among women in years excluded from analyses are as follows: 1998: 11.8%; 1999: 11.5%; 2000 (all months): 11.2%; 2001: 10.8%; 2002: 10.5%.

Figure 4.1: Adjusted and unadjusted chlamydia prevalence among women and men entering the NJTP, 1990-2012



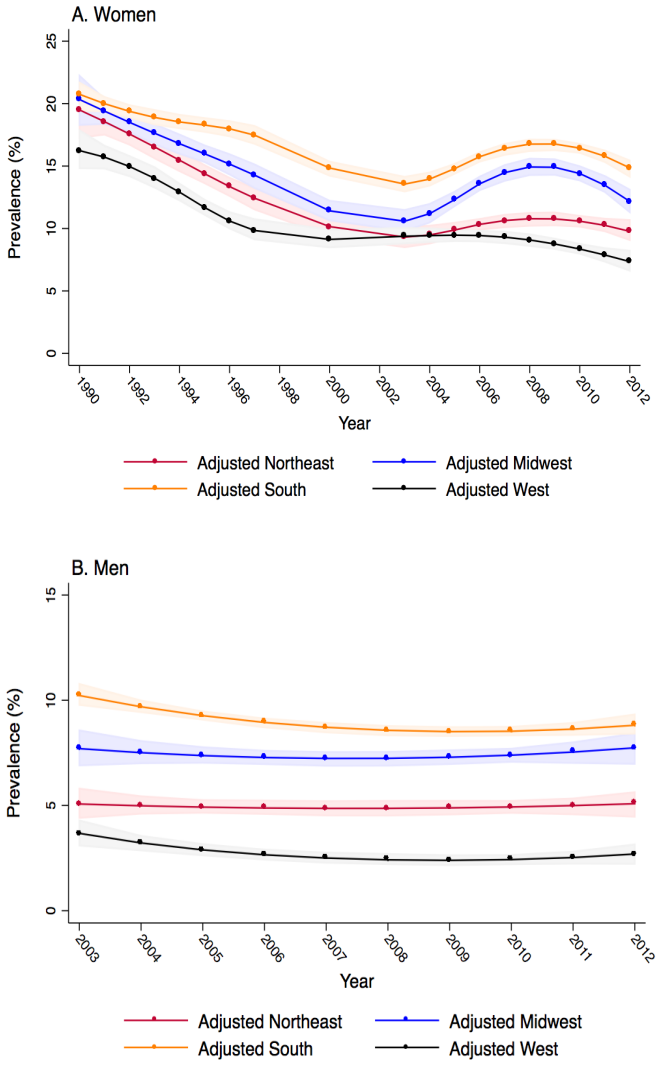
Adjusted and unadjusted chlamydia prevalence among women entering the NJTP (n=350,490) from 1990-2012 and men entering the NJTP (n= 303,699) from 2003-2012. Adjusted prevalence estimates and 95% CIs account for measurement error associated with use of increasingly sensitive chlamydia screening tests over time (Pathfinder EIA of swabs [1990-1997], Gen-Probe PACE 2 DNA hybridization probe of urine or swabs [2000-2006], and BD ProbeTec ET SDA of urine [2000-2012] or swabs [2007-2012]). Adjusted estimates were modeled using an EM algorithm incorporated into logistic regression. Unadjusted estimates were generated from a logistic regression model, and do not account for changes in the diagnostic accuracy of tests. Note: Women enrolled in January 1998-February 2000 and 2001-2002 were excluded from analyses due to missing data on test type and race/ethnicity, respectively.

Figure 4.2: Adjusted chlamydia prevalence and 95% CIs among women and men entering the NTJP by race/ethnicity, 1990-2012.



Adjusted chlamydia prevalence and 95% CIs among Hispanic (n=54,799), Black (n=202,707), White (n=82,366), and American Indian (n=10,618) women entering the NJTP, 1990-2012 (Panel A) and Hispanic (n=44,822), Black (n=155,045), White (n=95,994), and American Indian (n=7,838) men entering the NJTP, 2003-2012 (Panel B). Adjusted prevalence was modelled using an EM algorithm incorporated into logistic regression to account for measurement error due to changes in the diagnostic accuracy of chlamydia screening tests over the study period.

Figure 4.3: Adjusted chlamydia prevalence and 95% CIs among women and men entering the NTJP by region, 1990-2012.



Adjusted chlamydia prevalence and 95% CIs among women entering the NJTP in four regions of the US, 1990-2012 (Midwest: n=64,153; South: n=157,294; West: n=68,389; Northeast: n=60,654) (Panel A) and men entering the NJTP in four regions of the US, 2003-2012 (Midwest: n=51,361; South: n=149,464; West: n=57,144; Northeast: n=45,730) (Panel B). Adjusted prevalence was modelled using an EM algorithm incorporated into logistic regression

to account for measurement error due to changes in the diagnostic accuracy of chlamydia screening tests.

CHAPTER FIVE: SPECIFIC AIM 2 RESULTS

5.1 INTRODUCTION

Chlamydia is the most commonly reported sexually transmitted disease (STD) in the US (1). Because infections are often asymptomatic, routine screening of young, sexually active women to detect and treat disease is important for preventing reproductive sequelae and reducing chlamydia incidence (1–7). Nationally notifiable STD surveillance data collected by the Centers for Disease Control and Prevention (CDC) show annual chlamydia case rates among young women aged 15 through 24 years climbed from 2000 through 2011, and then shifted to a downward trend through 2014(1). At first glance, the downward shift may suggest chlamydia incidence is decreasing; however, interpreting trends in reported chlamydia case rates is challenging.

Case rates, which are calculated by dividing the number of reported chlamydia cases in a given year by the size of the at-risk population (estimated using census data), may be influenced not only by changes in true incidence of infection, but also by several time-varying biases, such as changes in screening coverage, diagnostic technologies, and reporting practices. The observed increase in chlamydia case rates during 2000 through 2011 may be a result of expanded screening coverage, the use of increasingly sensitive diagnostic tests, and improvements in reporting practices over that period. (1,8–11) In the current era of widespread use of highly sensitive tests and electronic reporting systems which ensure most positive tests are reported to local health authorities, falling case rates may reflect a true decline in incidence or changes in screening coverage. The time-varying roles of each of these forces must be

carefully considered in interpreting case rate trends, but to date no study has quantified biases and examined their joint influence on reported case rates trends.

The goal of this study was to account for these time-varying biases in calculating the annual incidence of diagnosed and reported chlamydia that would have been observed with perfect screening coverage, diagnostic tests, and case reporting among young women in the US from 2000 through 2015.

5.2 MATERIALS AND METHODS

Our estimation approach was based on a conceptual diagram of relationship between the at-risk population and surveillance-related biases (Figure 5.1). We start with a dynamic population of at-risk women in steady-state. Within this population are all chlamydial infections ("true cases"), as well as the proportion of this population is screened for chlamydia. Some proportion of the population is diagnosed with chlamydia, and some proportion of women diagnosed with chlamydia is reported as chlamydia cases ("reported cases"). Reported chlamydia cases are an underestimate of true chlamydia cases in the population as a result of partial screening coverage (i.e., not all at-risk women are screened), misclassification due to imperfect diagnostic tests (i.e., diagnostic tests are <100% sensitive), and under-reporting (i.e., some diagnosed infections are not reported).

We implemented a series of corrections that addressed each bias successively, and calculated an annual counterfactual incidence rate of correctly diagnosed chlamydia that would be observed with perfect screening coverage, diagnostic tests, and reporting. This counterfactual incidence rate of diagnosis represents the case rate that we would expect if every at-risk individual were screened once annually using perfect diagnostic tests, and if every chlamydia diagnosis was reported. To calculate the counterfactual incidence rate of correctly

diagnosed chlamydia we corrected annual case rates for under-reporting, case misclassification due to imperfect diagnostic tests, and partial screening coverage, respectively. We corrected reported case rates among all women aged 15 through 24 years, and stratified case rates by age group (15 through 19 years, and 20 through 24 years) to examine variation in trends among younger and older women. Our approach allowed for temporal variation in biases to reflect improvements over time in screening coverage, use of more sensitive diagnostic tests, and reporting completeness.

Case Rate Inputs

Reported chlamydia case rates for women in our target age groups (ages 15 through 24 years, 15 through 19 years, and 20 through 24 years) in the US from 2000 through 2015 were obtained from the CDC's National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention AtlasPlus tool. (12) Case rate numerators represent the total number of chlamydia cases (diagnoses) reported to the CDC in one year by state and local health authorities in all 50 states and the District of Columbia. Case rate denominators are calculated as the US census population of women of the target ages in a given year.

Corrections for Biases:

We made a series of simple corrections to annual reported chlamydia case rates to account for under-reporting, imperfect diagnostic tests, and partial screening coverage. For a given year, we defined the following:

C = number of reported cases (case rate numerator)

N = total at-risk population (case rate denominator)

R = proportion of chlamydia diagnoses that were reported to CDC through national notifiable disease surveillance (reporting fraction)

Se= diagnostic test sensitivity

Sp = diagnostic test specificity

Sc = proportion of the at-risk population screened for chlamydia (screening coverage)

In each study year, we took 200 random draws from distributions describing reporting, diagnostic tests, and screening coverage (see "Bias Parameter Inputs" below) to define values for the inputs R, Se, Sp, and Sc above. With the values in each draw, we performed the calculations described below to estimate the counterfactual incidence of correctly diagnosed chlamydia in a given year. We then compared the annual medians of these corrected rates to the reported chlamydia case rates from 2000 through 2015 to assess the impact of these biases on reported trends.

Correcting for under-reporting

To correct for under-reporting of chlamydia cases, we divided reported chlamydia cases [C] by the reporting fraction [R]. This step generated the counterfactual count of chlamydia diagnoses (both true and false positives) among women screened that we would expect to be included in case rate estimates under perfect reporting.

Correcting for misclassification due to imperfect diagnostic tests

To calculate the number of true chlamydia cases among women who were screened in a given year, which we will call *A*, we corrected for misclassification of chlamydia cases due to imperfect diagnostic test sensitivity and specificity following Greenland,1996 (38),

$$A = \frac{\frac{C}{R} - FrT}{Se}, \qquad \text{Equation 1}$$

where FrT is the number of false positive diagnoses per unit person-time among women screened. If we assume that each individual in a given annual case rate denominator (N) contributes, on average, one year of person time during which he or she is at risk of chlamydia diagnosis that year, FrT can be calculated as

$$FrT = (1 - Sp) * (1 - P) * ScN, \qquad \text{Equation 2}$$

where P is the underlying true prevalence of chlamydia in the screened population. This assumption is valid if 1) the at-risk population is dynamic and in steady-state (39), 2) person-time contributed by unidentified true cases is relatively small, and 3) identified cases are treated and promptly return to the pool of at-risk women.

We derived annual prevalence as follows: In a steady-state population with non-differential screening according to true chlamydial infection, the cumulative number of diagnosed cases among women screened [C/R] in a given year should equal the number of new diagnoses that would be observed in a one-time screening process conducted in the population that year. This number, in turn, is equal to the total number of true and false positives that would be observed in that screening process, which can be calculated as $ScN(SeP + (1 - Sp)(1 - P))$. Setting this expression equal to C/R and solving for P, we obtain:

$$P = \frac{\frac{C}{R} - ScN(1-Sp)}{ScN(Se+Sp-1)}, \qquad \text{Equation 3}$$

Substituting this expression for prevalence into Equation 2 above allowed us to calculate FrT, which we entered into Equation 1 to generate the counterfactual number of diagnosed true

chlamydia cases that would have been observed among women screened under perfect reporting and diagnostic test performance [A].

Correcting for partial screening coverage

To correct for screening coverage, we divided the number of diagnoses of true chlamydia cases among women screened [A] by the screening coverage [Sc]. This step gave us the counterfactual number of correctly diagnosed chlamydia cases in the total at-risk population over one year that would be observed with perfect reporting, diagnostic tests, and screening coverage. Under our assumption that each person in the case-rate denominator (N) contributes an average of one year of person-time at risk, we calculated the counterfactual incidence of correctly diagnosed chlamydia by dividing A by N person-years.

Bias Parameter Inputs:

We incorporated sampling distributions for each bias into our calculations to account for random error in bias estimates. We conducted literature reviews and sought expert opinion to create the sampling distributions. Unless specified otherwise, we created triangular distributions to describe the range of plausible bias inputs for each study year, and describe the modes of distributions below. Sampling distributions for each bias parameter over the course of the study period are shown in Figure 5.2.

Reporting Fraction: By 2000, all 50 states and the District of Columbia reported chlamydia cases as part of national surveillance (STD disease surveillance). A fraction of cases go unreported due to imperfect reporting compliance, but compliance has improved over time with the implementation of electronic laboratory reporting systems, which enable cases to be reported directly from laboratories. Based on CDC expert opinion, we assumed reporting fraction for all age groups increased from approximately 70% to 95% over the study period (40).

Misclassification Due To Imperfect Diagnostic Tests: We incorporated time-varying misclassification due to the use of increasingly sensitive diagnostic tests by considering test use and test performance over the study period. Chlamydia screening gradually transitioned from low-sensitivity, high-specificity tests, which we refer to as non-nucleic acid amplification tests (non-NAATs), to high-sensitivity, high-specificity tests (NAATs). We selected sensitivity and specificity values for non-NAATs and NAATs that were consistent with estimates reported in previous literature. (41–44) We set sensitivity to be 75% and 92% for non-NAATs and NAATs, respectively, and specificity to be 99.5% for both test types. We also estimated the proportion of screening via non-NAATs and NAATs each year based from regional screening data collected as part of the Infertility Prevention Project from 2000 through 2011. (13) We attached lognormal distributions to these test use estimates (Figure A3.1). We used these annual test use estimates to calculate weighted-average sensitivity and specificity estimates for diagnostic tests each year.

Screening Coverage: Inputs for screening coverage were based upon coverage reported by the Healthcare Effectiveness Data and Information Set (HEDIS), and CDC expert opinion. (40,45) Annual coverage estimates from HEDIS are derived from women enrolled in commercial healthcare plans or Medicaid, and calculated as the women screened for chlamydia out of all sexually active women who saw a healthcare provider. HEDIS provides screening coverage estimates for women aged 15 through 24 years, as well as women aged 15 through 20 years and aged 21 through 24 years because screening coverage among younger women is typically lower than coverage among older women. For study each year and each age group, we considered the screening coverage estimate among women enrolled in commercial insurance plans and Medicaid, and calculated the midpoint of these estimates. Based on these midpoints and CDC expert opinion, we selected plausible screening coverage estimates for 2000 through

2015. Estimates for all women aged 15 through 24 years increased from 30% in 2000 to 50% in 2015. Estimates for women age 20 through 24 years increased from 30% to 55%. Estimates for women aged 15 through 19 years increased from 30% to 45%.

Sensitivity and Influence Analyses:

We conducted several sensitivity analyses for case rate corrections among women aged 15 through 24 years to address potential systematic error in literature reporting estimates diagnostic test sensitivity and screening coverage. Diagnostic test sensitivity estimates in literature are variable, so we incorporated sensitivity estimates of non-NAATs and NAATs that were reasonable lower and upper bounds of sensitivity estimates. These new sensitivity estimates were selected based on approximate upper and lower bounds of sensitivity reported in literature. We specified low non-NAAT and NAAT sensitivities of 70% and 85%, and high non-NAAT and NAAT sensitivities of 85% and 97%. (42,44)

We also incorporated a range of screening coverage estimates to account for limitations of HEDIS coverage estimates. Estimates from HEDIS capture only women who are enrolled in a commercial health plan or Medicaid and have an indicator of sexually activity, and may not be representative of screening coverage in the underlying population. Therefore, we incorporated estimates of screening coverage that we considered to be the plausible lower bound of coverage for women aged 15 through 24 years over the study period, and estimates that we considered to be the plausible upper bound of coverage. We selected coverage that increased from 20% to 40% over time (lower bounds), and coverage that increased from 40% to 60% over time (upper bounds).

Finally, to understand whether one bias or set of biases was particularly influential, we examined scenarios in which reported case rates were corrected for only reporting fraction, only

imperfect diagnostic tests, or only coverage. We also examined a scenario in which reported case rates were corrected for reporting fraction and imperfect diagnostic tests.

5.3 RESULTS:

Reported chlamydia case rates among women 15 through 24 years generally increased over the study period. Case rates rose from approximately 2,200 cases per 100,000 person-years in 2000 to 3,600 cases per 100,000 person-years in 2011. Between 2011 and 2014, case rates modestly declined from 3,300 cases per 100,000 person-years before increasing to 3,400 cases per 100,000 person-years in 2015 (figure 5.3A).

After correcting reported case rates among women aged 15 through 24 years for time-varying reporting fraction, diagnostic tests, and screening coverage, counterfactual incidence rates of correctly diagnosed chlamydia, which we will refer to as incidence rates, were higher than reported case rates, but incidence rate trends declined substantially over time (figure 5.3A). Incidence rates of correctly diagnosed chlamydia fell sharply between 2000 and 2007 (approximately 12,900 cases per 100,000 person-years to 7,900 cases per 100,000 person-years). Between 2008 and 2015, incidence rates were fairly steady, but rose modestly to 8,000 cases per 100,000 person-years in 2008 before dropping to 7,100 cases per 100,000 person-years in 2015.

Stratifying by age group showed that reported case rates among younger women and older women also rose from 2000 through 2011 (figure 5.3B). Reported case rates among women in both age groups were nearly identical from 2000 through 2011, and case rates increased from approximately 2,100 cases per 100,000 person-years to 3,500 cases per 100,000 person-years. After 2011, case rates among older women continued rising to 3,700

cases per 100,000 person-years by 2015, while case rates among younger women dropped to 3,000 cases per 100,000 person-years by 2015.

Incidence rate trends of correctly diagnosed chlamydia among younger and older women declined, but the shape of the trends differed between the two age groups (figure 5.3B). Younger women experienced a more dramatic decline in incidence rates trends compared to older women. In 2000, incidence rates among younger women were higher than incidence rates among older women (13,700 cases per 100,000 person-years versus 12,100 cases per 100,000 person-years, respectively). Incidence rates for both age groups were equal by 2015 (7,000 cases per 100,000 person-years). In addition, incidence rates among older women held steady at approximately 7,000 cases per 100,000 person-years from 2009 through 2015, while incidence rates among younger women during the same time period dropped from 9,600 cases per 100,000 person-years to 7,000 cases per 100,000 person-years.

In sensitivity analyses, we examined different estimates of diagnostic test sensitivity and screening coverage. Scenarios with the lower bound of coverage estimates produced sharper declines in incidence rates compared to scenarios with the upper bound of coverage estimates (figure 5.4). Incorporating upper and lower bounds of plausible diagnostic test sensitivities influenced the magnitude but not shape of incidence rate trends, with lower sensitivities resulting in higher incidence rates and vice versa.

In our influence analysis, the impact of correcting for reporting and imperfect diagnostic tests individually (figure 5.5A) or jointly (figure 5.5B) was small. Incidence rates corrected for these biases were only slightly larger than reported case rates, and trends followed roughly the same shape as report case rate trends. Correcting for screening coverage has a noticeable impact. Compared to reported case rates, incidence rates corrected for only for screening

coverage were higher, and trends were relatively stable (approximately 7,900 cases per 100,000 person-years).

5.4 DISCUSSION

We estimated counterfactual incidence rates of correctly diagnosed chlamydia among young women that would be obtained in the absence of bias from partial screening coverage, imperfect diagnostic tests and under-reporting. Counterfactual incidence rates represent the chlamydia case rate that would be observed if the total at-risk population was screened once per year using perfect diagnostic tests, and if all cases were reported. After correcting chlamydia case rates for time-varying biases, we observed that counterfactual incidence rate trends among women aged 15 through 24 years declined over the study period. Trends declined sharply in the first half of the study period and modestly in the second half of the study period. When stratified by age, incidence rate trends among women aged 15 through 19 years and 20 through 24 years also declined, but incidence rates among younger women were higher and generally declined for most of the study period, while incidence rates among older women were fairly steady after 2009.

Our results suggest that the increase in reported chlamydia case rates among young women may be due to time-varying biases. Chlamydia screening programs have been in place since the early 1990s, and should lead to a decrease in incidence, as screening and treatment shorten disease duration and help prevent ongoing transmission.(20) Biases in surveillance data may mask declining incidence trends that are expected to occur with widespread screening. By correcting case rates for time-varying biases, we attempted to disentangle the influence of biases on incidence rate trends. The downward trend in counterfactual incidence rates of correctly diagnosed chlamydia suggests that, in the absence of bias related to

screening coverage, diagnostic tests and reporting, chlamydia incidence rates among young women may be substantially higher than reported case rates but may be declining over time.

We also observed differences in the counterfactual incidence rates trends of correctly diagnosed chlamydia among women aged 15 through 19 years and women aged 20 through 24 years. Trends among younger women generally declined throughout the study period, while trends among older women leveled off in the later half of the study period. The difference in trends may be due to differences in sexual risk behaviors and healthcare access among younger and older women over time. Determining if changes in behavior or healthcare access are contributing to trends among younger and older women is an important area for future research.

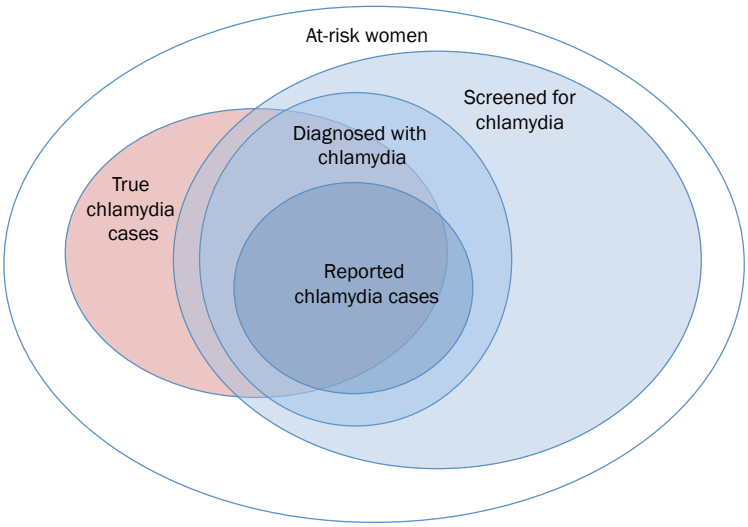
Declining counterfactual incidence rates of correctly diagnosed chlamydia are suggestive of a decrease in chlamydia burden over time, but incidence rates of diagnosis differ from incidence rates of infection. Chlamydia case rates are flawed measures of incidence rates of diagnosis, and we estimated counterfactual incidence rates of diagnosis to understand what surveillance systems would capture if screening coverage, diagnostic tests, and reporting were perfect. From a public health perspective, incidence of infection may be a more informative measure of chlamydia burden. The incidence of infection may be higher or lower than the incidence of diagnosis in a given year depending on infection duration and when screening occurs. Surveillance systems cannot capture the incidence of infection and instead provide an estimate of the incidence of diagnosis, but with increasing screening coverage and test sensitivity, and declining steady-state chlamydia prevalence, we would expect incidence rates of infection to be declining over time, similarly to incidence rates of diagnosis.

In influence analyses, bias from screening coverage, more so than bias from reporting and diagnostic tests, had a substantial impact on the shape of counterfactual incidence rate trends. Counterfactual incidence rate trends were predominately driven by changes in coverage. Our results suggest that understanding the relationship between coverage and incidence rates is critical for interpreting incidence rate trends, and highlight the need for accurate estimates of coverage. Existing estimates have significant limitations. Estimates from HEDIS or other claims data are derived from women presenting to care who are sexually active and receive screening. These estimates may over-estimate coverage and lack generalizability because they fail to capture women who seek care at out-of-plan facilities. They are also affected by healthcare access. (22–29) Estimates are also derived from the self-report data collected by the National Survey for Family Growth (NSFG). NSFG may more accurately capture sexual activity among women and therefore be a better indicator of who should be screened, but may less accurately capture actual screening due to recall bias or social desirability bias. (30) Further, estimates from claims data and self-report data generally have poor concordance. (30,31) More valid estimates of coverage are important for understanding whether screening targets are met, and for a more valid interpretation of chlamydia case rate trends derived from surveillance data.

Our study demonstrates how biases present in surveillance data limit interpretability of reported chlamydia case rate trends. After correcting for time-varying reporting, diagnostic tests, and screening coverage, we observed that counterfactual incidence rates of correctly diagnosed chlamydia among young women were higher than reported case rates and decreased over the study period. Our results suggest that reported case rates from 2000 through 2011 may have increased due to the influence of time-varying biases, and that the incidence of diagnosis of chlamydia may be declining.

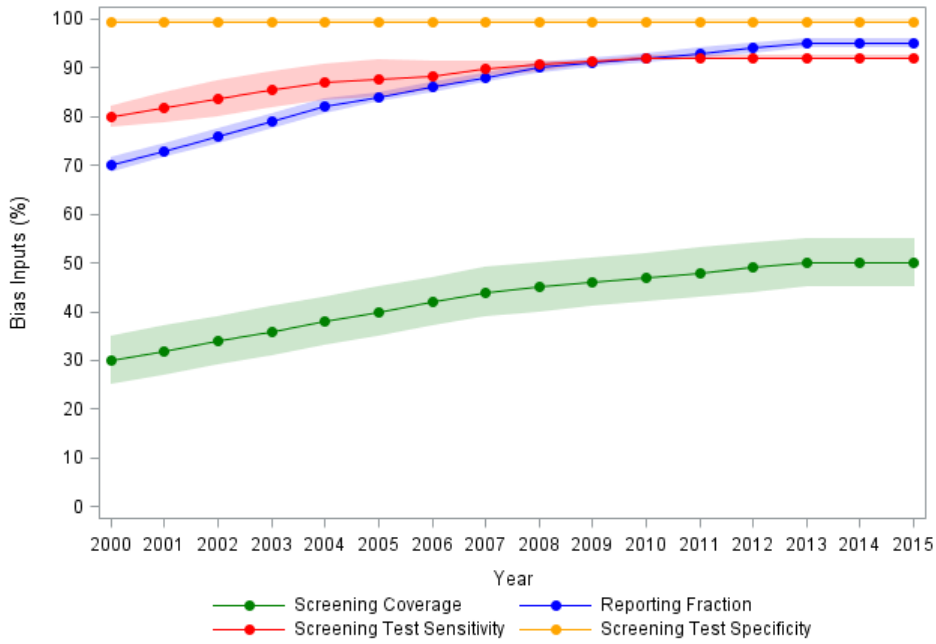
5.5 FIGURES

Figure 5.1: Conceptual diagram depicting surveillance data biases in relation to the at-risk population and true chlamydia cases.



True chlamydia cases exist within a dynamic, steady state population of at-risk young women. A proportion of chlamydia cases and non-cases are screened, classified as cases, and reported as cases. The three inner ellipses represent bias due partial screening coverage, imperfect diagnostic tests, and under-reporting. The extent to which biases influence reported case rates varies over time as reporting practices, diagnostic tests, and screening coverage change.

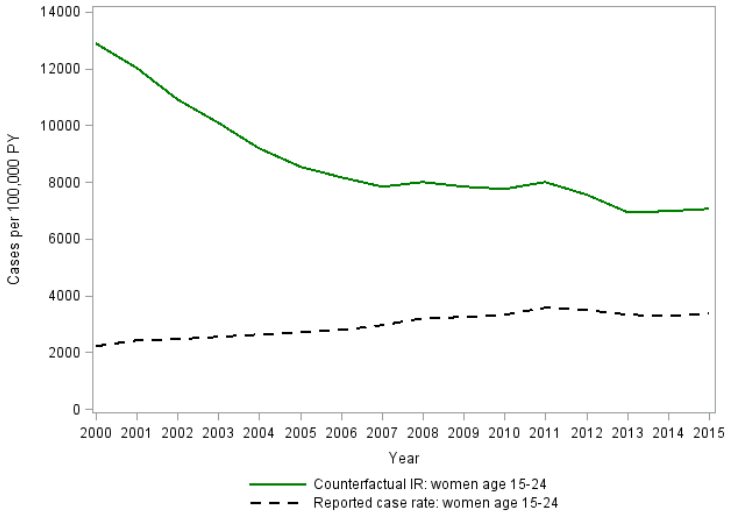
Figure 5.2: Inputs of reporting fraction, diagnostic test sensitivity and specificity, and screening coverage among young women, 2000-2015.



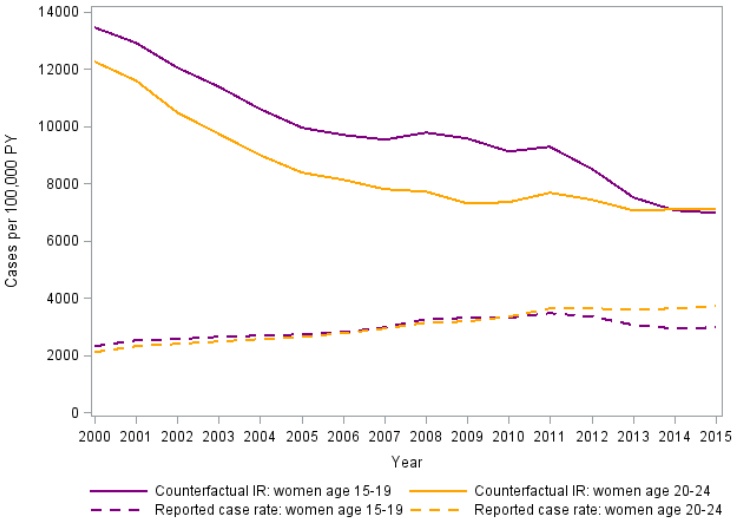
Solid lines represent the mode of triangular distributions and shaded areas cover the range between the lower and upper limits of distributions. Coverage estimates for age-stratified analyses are not depicted, but were as follows: for women aged 15 through 19 years, coverage increased from 30% to 45% (increasing one percentage point per year from 2000 through 2015). For women aged 20 through 24 years, coverage increased from 30% to 55% (increasing two percentage points per year from 2000 through 2010 and one percentage point per year from 2011 through 2015). Note: Test sensitivity was a weighted-average of non-NAAT and NAAT sensitivity based on annual test use (figure A3.1). The shaded area above is the approximate range from which sensitivity values were drawn.

Figure 5.3: Reported chlamydia case rates and counterfactual incidence rates of correctly diagnosed chlamydia among young women, 2000-2015

A.

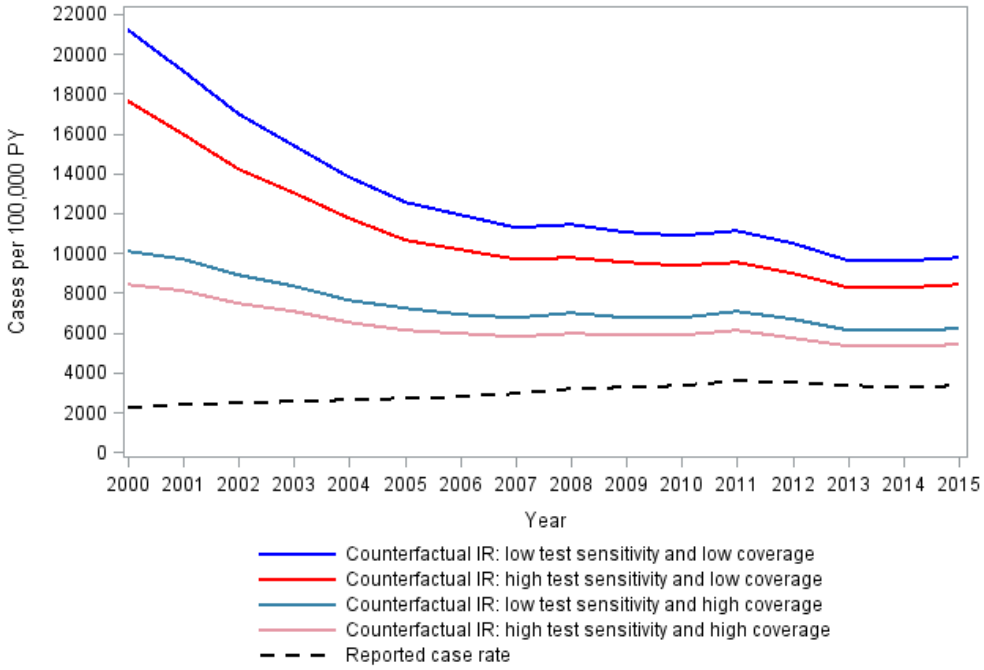


B.



Reported chlamydia case rates and counterfactual incidence rates of correctly diagnosed chlamydia from 2000 through 2015 among young women aged 15 through 24 (panel A) and among women stratified into two age groups (panel B). Counterfactual incidence rates were generated by correcting reported case rates for time-varying reporting fraction, diagnostic tests, and screening coverage.

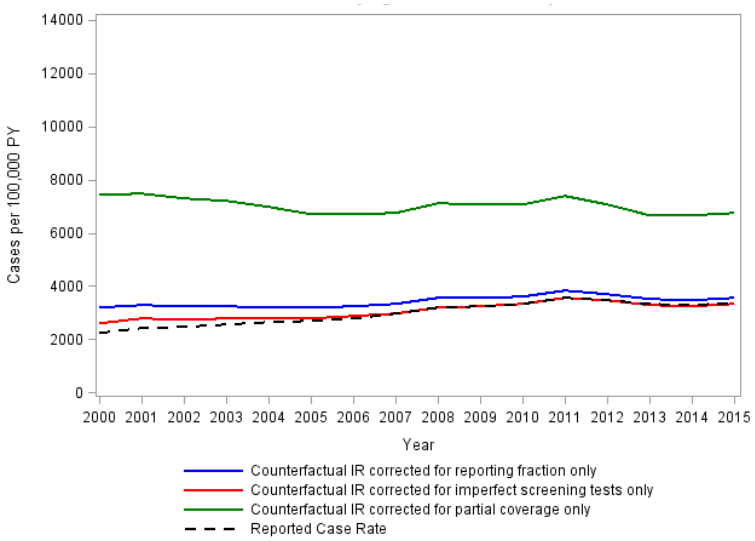
Figure 5.4: Sensitivity analyses of counterfactual incidence rates of correctly diagnosed chlamydia among women, 2000-2015



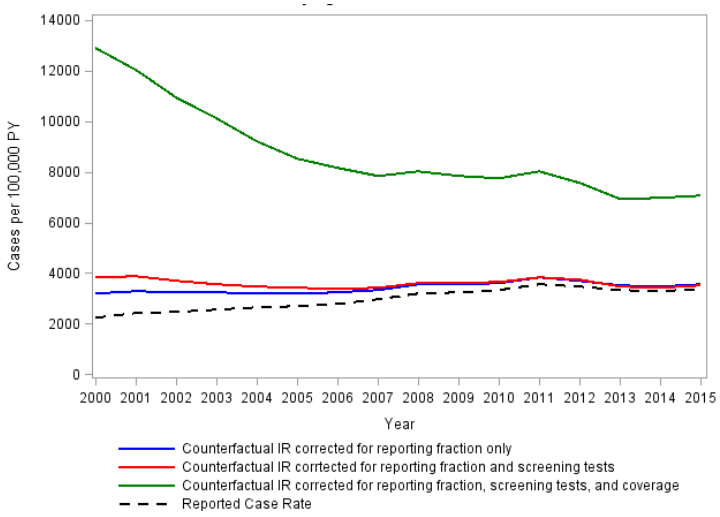
The upper bound of screening coverage ranged from 40% to 60% over the study period and lower bound ranged from 20% to 40% over the study period. Low non-NAAT and NAAT sensitivity was 70% and 85%, respectively. High non-NAAT and NAAT sensitivity was 85% and 97% respectively. Coverage was more influential on the shape of trends than diagnostic test sensitivity.

Figure 5.5: Influence analyses of counterfactual incidence rates of correctly diagnosed chlamydia among young women, 2000-2015

A.



B.



Influence analyses of counterfactual incidence rates of correctly diagnosed chlamydia among young women from 2000 through 2015 after correcting for individual biases (panel A) or sets of biases (panel B). In panel A, correcting for only reporting fraction (blue) or only diagnostic tests (red) resulted in counterfactual incidence rates that closely mirrored reported case rate trends. Correcting for coverage (green) resulted in counterfactual incidence rates that were substantially higher than reported case rates and relatively stable over time. In panel B, correcting for only reporting fraction (blue) or correcting for reporting fraction and imperfect

diagnostic tests (red) did not substantially alter the shape of the trends. Correcting for all three biases (reporting fraction, diagnostic tests, and coverage) resulted in trends that declined over time (green).

CHAPTER SIX: CONCLUSIONS

Valid interpretations of chlamydia prevalence and case rate trends are important for assessing screening program effectiveness and understanding chlamydia epidemiology on a national scale. Sentinel surveillance of chlamydia and national notifiable disease surveillance of chlamydia are convenient sources for estimating prevalence and case rates, but prevalence and case rate trends can be difficult to interpret due to time-varying biases. The overall goal of this dissertation was to estimate chlamydia prevalence and case rate trends accounting for multiple time-varying biases, in order to gauge the success of national screening programs at reducing chlamydia burden and more accurately interpret chlamydia trends from surveillance data.

We estimated minimally-biased chlamydia prevalence trends among a sentinel surveillance population of high-risk young adults enrolled in the NJTP. Evaluating chlamydia prevalence trends from sentinel surveillance allowed us to assess the success national chlamydia screening programs in the US, which were rolled out in the late 1980s and early 1990s to reduce population burden. After ruling out bias due to case mix and correcting for time varying measurement error due to changing screening tests, chlamydia prevalence among women was high throughout the study period, but fell from 20% in 1990 to 12% in 2003, and hovered between 12% and 14% through 2012. Prevalence among men was steady throughout the study period at approximately 7%. For both women and men, prevalence was highest among Black and American Indian youth, and the Southern and Midwestern regions of the US throughout the study. Our trend estimates provide support for the early success of national chlamydia screening programs in reducing chlamydia burden among high-risk youth. The

relatively steady prevalence trend among women and men from 2003 through 2012 suggests that screening programs had no further impact for this sentinel population.

We also estimated counterfactual incidence of correctly diagnosed chlamydia among young women from 2000 through 2015. We corrected reported annual chlamydia case rates for screening- and reporting-related biases, and generated counterfactual incidence rates of correctly diagnosed chlamydia that would have been observed with perfect screening coverage, screening tests, and reporting. Counterfactual incidence rates among all young women age 15 through 24 years were higher than reported case rates and declined over the study period from 12,900 cases per 100,000 person-years in 2000 to 7,100 cases per 100,000 person-years in 2015. Rates declined more sharply in the first half of the study period compared to the second. When stratified by age group, incidences rate trends declined relatively steadily among women aged through 15 through 19 years over the study period, while incidence rate trends among women aged 20 through 24 years declined relatively steadily until 2009 before beginning to stabilize. These results suggest that bias due to screening coverage, imperfect screening tests and reporting contribute to the rising trends of chlamydia case rates from 2000 through 2015, and that in the absence of biases, case rates may be declining.

Our studies are the first to thoroughly examine the influence of multiple time-varying biases on chlamydia prevalence and case rate trends derived from surveillance data. Our prevalence estimates stand apart from other estimates of prevalence in the NJTP with respect to duration and validity. Our study is the first to estimate prevalence among women across 23 years and prevalence among men across 10 years. Our study is also the first to consider the influence of case mix and account for time-varying measurement error introduced by changes in screening test technologies during the study period. Long-term prevalence trends that address

two of the most important biases in data from sentinel surveillance programs allow us to consider the influence of national screening programs on chlamydia prevalence trends.

In addition, our estimation of counterfactual incidence rate of correctly diagnosed chlamydia cases is the first attempt to correct reported chlamydia case rates the most commonly discussed biases in surveillance data. Reported case rates trends are published with the caveat that trends are difficult to interpret due to the potential influence of biases.(1) While the relationship between biases and incidence rates has been examined previously,(14) our study is the first derive estimates the magnitude of bias due to screening coverage, screening tests, and under-reporting, and to correct reported case rate data for biases. Estimated counterfactual incidence of diagnosis trends provide a picture of what incidence trends from surveillance data might look like in the absence of biases.

Trends of prevalence and incidence rates of correctly diagnosed chlamydia declined but gradually leveled off, suggesting that although screening initially may have been effective at reducing chlamydia, on a population level, it may be losing momentum. Understanding why trends may be beginning to stabilize is important for policy makers as they consider screening policies and programs for the future. Our results may be evidence that screening is becoming less effective, but other factors that can influence trends must also be considered. Two of the most important factors are changes in sexual behaviors and healthcare access. Changes in sexual behaviors (sexual activity, condom use, and age of sexual debut) may change an individuals' likelihood of becoming infected with chlamydia, and an increase in chlamydia prevalence and incidence would be expected with riskier sexual behaviors. Shifts in health care access, and changes in access to STD clinics in particular, are also important to consider. With budget constraints forcing state and local STD programs to close STD clinics, screening responsibilities shift to primary care clinics, which may be less likely than public clinics to

conduct routine screening. Understanding changes in sexual behaviors and changes in access to care in combination with screening will be important for understanding what is driving disease trends.

Although prevalence and counterfactual incidence rates of correctly diagnosed chlamydia trends were similar with respect to shape, time periods during which prevalence trends and incidence rates trends declined did not overlap. From 2000 through 2012, young women in the NJTP had a fairly small absolute increase in prevalence, while incidence rates of diagnosis among young women in the US declined. The differences in trends' direction are potentially explained by differences in the populations giving rise to the trends. Young adults in the NJTP meet several important risk factors for chlamydia (low-socioeconomic status, predominantly Black and residing in the South, low educational attainment), and are a higher-risk population than the total US population giving rise to incidence rates trends. Changes in healthcare access, possibly resulting in poorer screening of higher-risk population, could result in an increase in prevalence, but the change may not be substantial enough to influence incidence rates of diagnosis in the general population. Changes in behavior in higher-risk populations could also result in changes in prevalence trends that are not reflected in incidence rates of diagnosis trends.

Our results also highlight the need for more valid screening coverage estimates. Incidence rates are directly affected by screening coverage, and we observed that screening coverage, more so than bias from reporting and screening tests, was particularly influential on the shape of incidence rates of correctly diagnosed chlamydia trends. Coverage is not directly incorporated into estimates of prevalence, but estimation of prevalence from sentinel surveillance rests on an assumption that screening is sufficiently high in the underlying population. Accurate estimates of screening coverage are crucial for interpreting chlamydia

trends, but current estimates of coverage have significant limitations. Estimates from claims data are derived from women who present to care. (70–77) These estimates are affected by healthcare access and may lack generalizability because they do not capture women who seek care at out-of-plan facilities. Estimates from self-reported data collected by national surveys may be more generalizable, but may also be subject to recall bias. (78,79) Estimates from self-report data and estimates from claims data generally have poor concordance. (79,80) More valid estimates of coverage that include a denominator that is generalizable to all sexually active women and a well measured numerator are important for understanding whether screening targets are met, and for a more valid interpretation and understanding of chlamydia trends derived from surveillance data.

In conclusion, declining prevalence and incidence rate trends suggest that screening programs may have been successful in driving down population burden of chlamydia, but the slope of trends over time also suggest that screening may be losing momentum. Whether screening programs should be expanded in an attempt to drive further decline is an important question to consider. Policy makers will need to weigh factors that influence disease trends, including surveillance data biases, sexual behavior, healthcare access, and screening of men, as well as the cost of screening and impact of screening on reproductive sequelae and related outcomes. Continued surveillance of prevalence trends and case rate trends in the current era of highly sensitive and specific screening tests and electronic reporting will be important for helping shape future chlamydia screening programs.

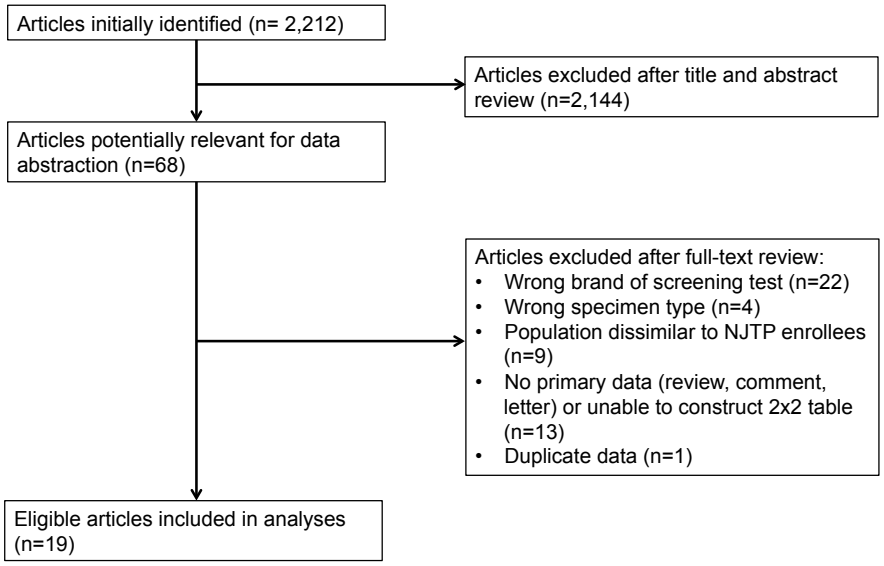
APPENDIX 1: AIM 1 SUPPLEMENTAL METHODS

Screening Test Sensitivity and Specificity Meta-Analyses

We searched PubMed and Scopus using medical subject headings and keywords related to chlamydial infection (chlamydia, sexually transmitted infection, STI, sexually transmitted disease, STD, urogenital, genitourinary) and diagnostic accuracy of screening tests (diagnostic, diagnosis, mass screening, screening, sensitivity, specificity, predictive value, accuracy). Studies were limited to humans and English. The last search was performed on March 3, 2016.

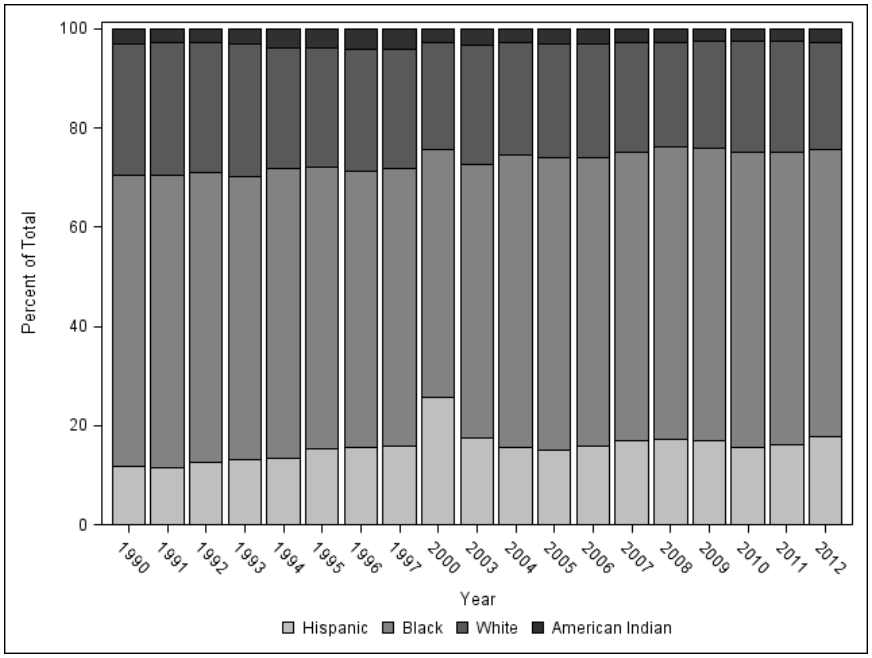
A total of 2,212 articles were initially identified. Nineteen studies were selected for inclusion after reviewing titles, abstracts, and full text (Appendix 1, Figure S1). Studies conducted outside of North America or Europe and studies of populations dissimilar to the NJTP (e.g. sex workers, or older/younger populations) were excluded. We included studies that reported the diagnostic accuracy of the Pathfinder EIA, Gen-Probe PACE 2 DNA probe, or BD ProbeTec ET SDA of cervical or vaginal swabs or urine. We used a standardized spreadsheet to abstract data. The following information was documented for each article: author(s), study location, study period, characteristics of sample screened (e.g. clinic patients, type of clinic, etc.), age, gender, sample size, specimen type, reference test definition, prevalence, sensitivity, specificity and potential sources of bias (e.g. discrepant analysis performed or composite reference test definition used). Numbers of true positives, true negatives, false positives and false negatives were either abstracted or calculated.

Figure A1.1: Flow diagram for study selection process for articles included in meta-analyses of sensitivity and specificity estimates for Pathfinder EIA, Gen-Probe PACE 2, or BD ProbeTec ET chlamydia tests.



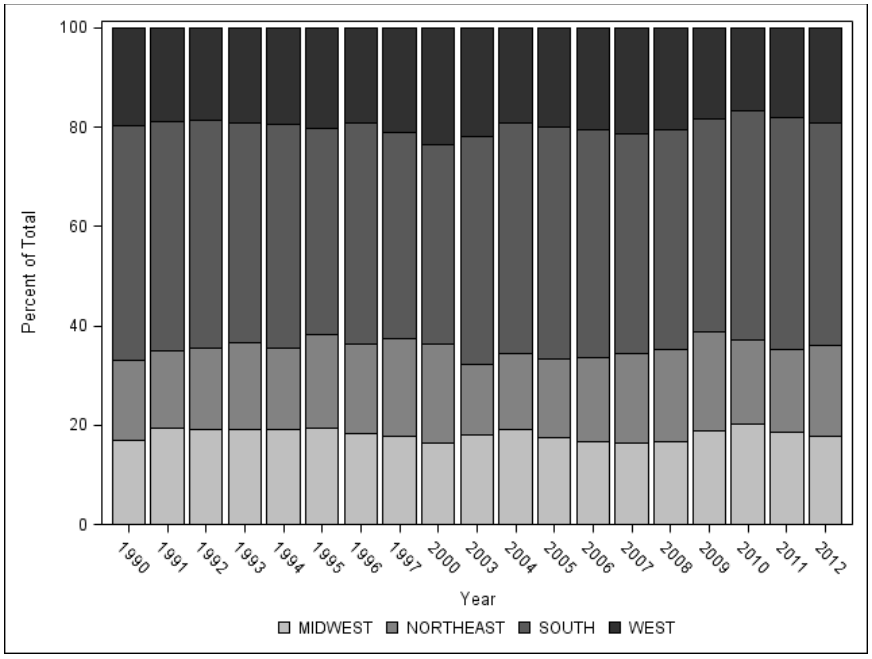
APPENDIX 2: AIM 1 SUPPLEMENTAL FIGURES

Figure A2.1: Distribution of race/ethnicity of women entering the NJTP (n=350,490), 1990-2012.



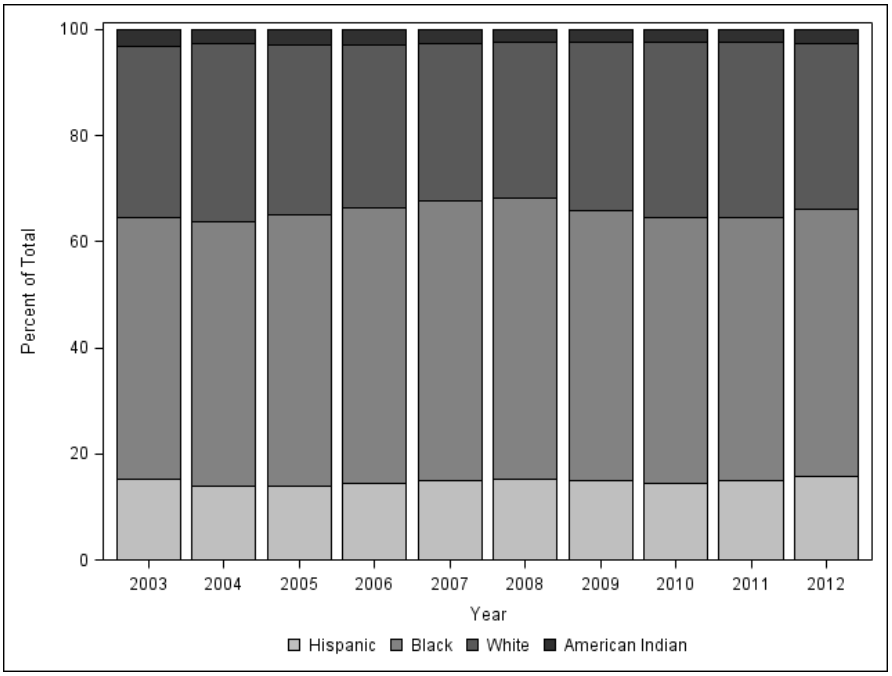
The relative proportion of race/ethnicity of newly enrolled women did not vary substantially over time.

Figure A2.2: Distribution of region of residence of women entering the NJTP (n=350,490), 1990-2012.



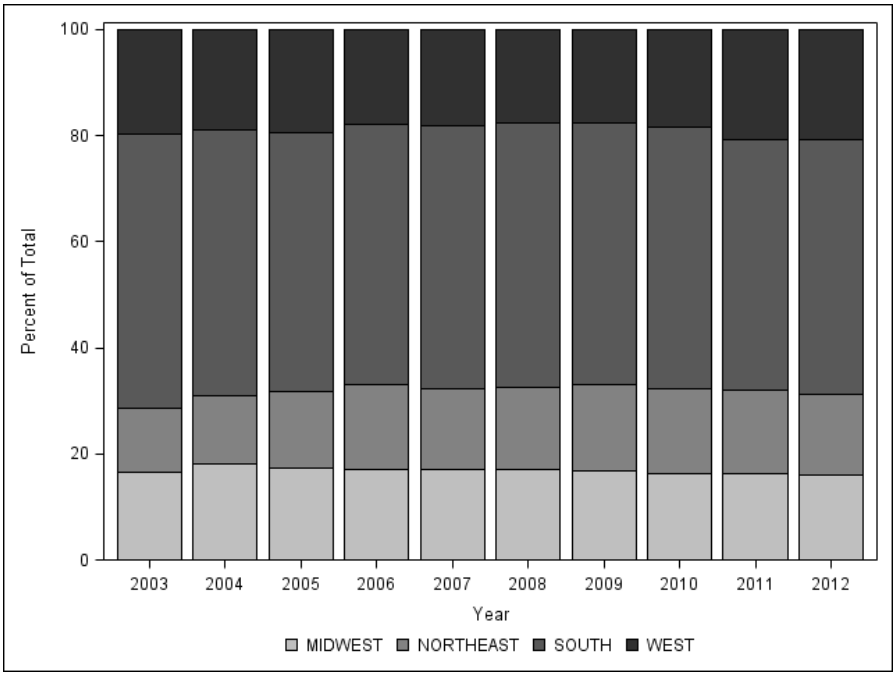
The relative proportion of region (Midwest, Northeast, South, and West) did not vary substantially over time.

Figure A2.3: Distribution of race/ethnicity of men entering the NJTP (n=303,699), 2003-2012.



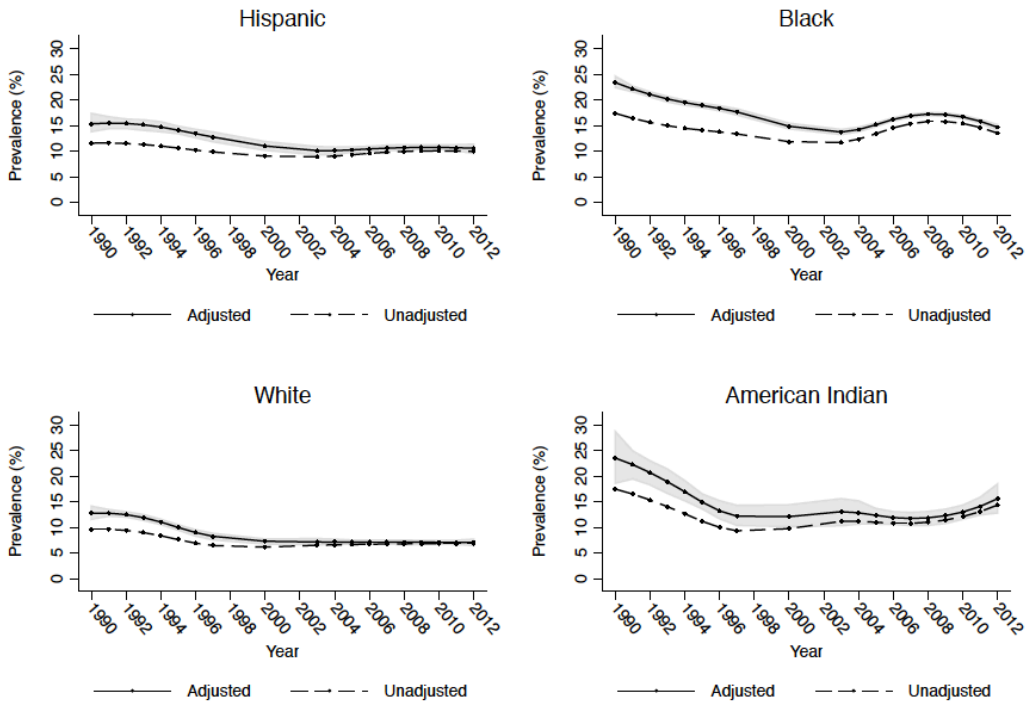
The relative proportion of race/ethnicity of newly enrolled men was consistent over time.

Figure A2.4: Distribution of region of residence of men entering the NJTP (n=303,699), 2003-2012.



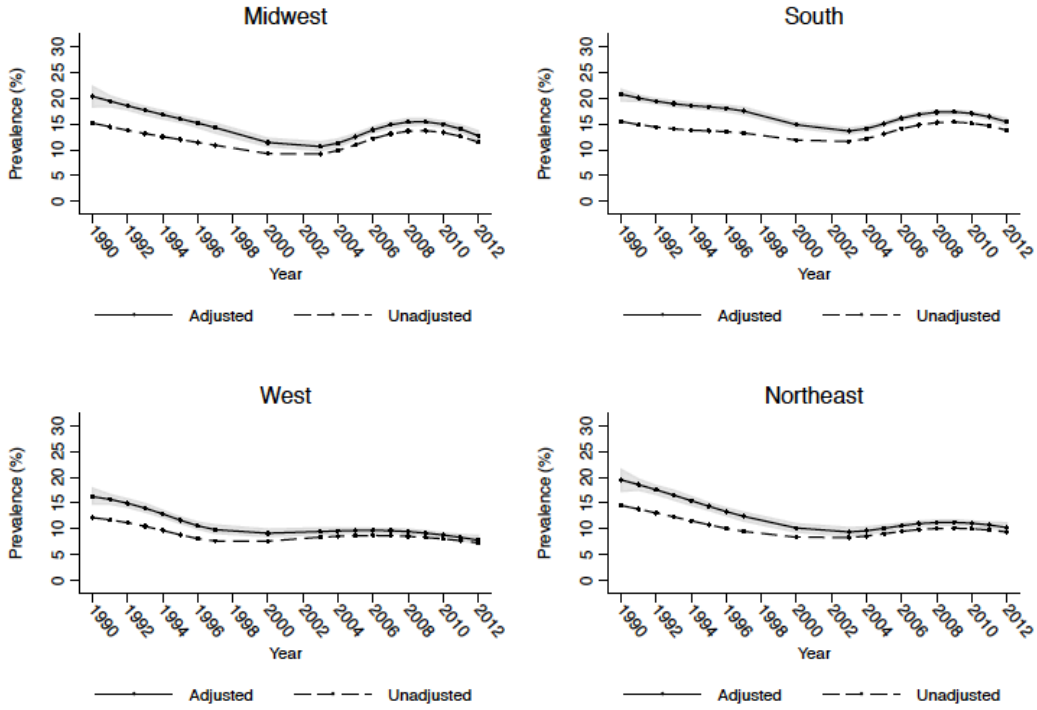
The relative proportion of region (Midwest, Northeast, South, and West) was consistent over time.

Figure A2.5: Adjusted and unadjusted prevalence of chlamydia among women entering the NJTP by race/ethnicity, 1990-2012.



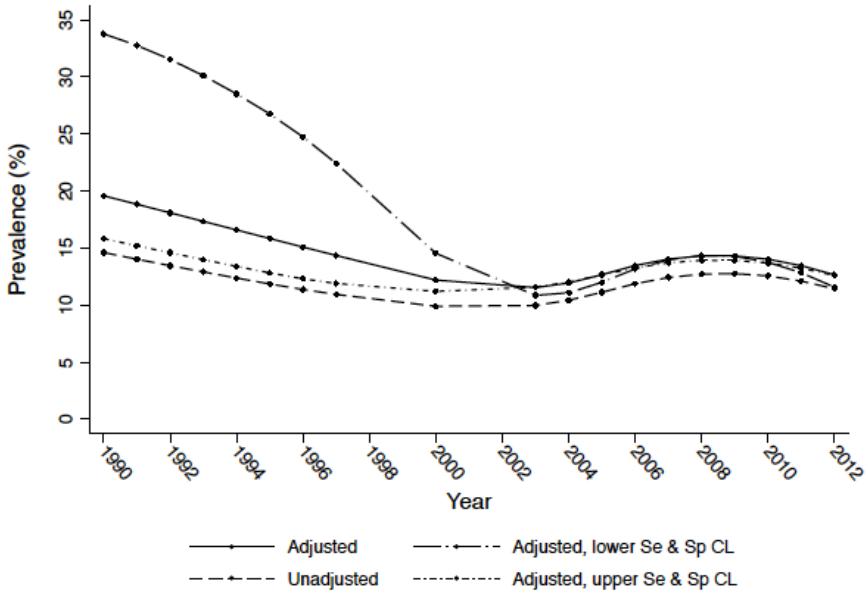
Adjusted and unadjusted prevalence of chlamydia among Hispanic (n=54,799), Black (n=202,707), White (n=82,366), and American Indian (n=10,618) women entering the NJTP, 1990-2012. Adjusted estimates and 95% CIs account for measurement error associated with changes in the diagnostic accuracy of chlamydia screening tests over time. Unadjusted estimates do not account for measurement error.

Figure A2.6: Adjusted and unadjusted chlamydia prevalence among women entering the NJTP by region, 1990-2012.



Adjusted and unadjusted chlamydia prevalence among women entering the NJTP in four regions of the US, 1990-2012 (Midwest: n=64,153; South: n=157,294; West: n=68,389; Northeast: n=60,654). Adjusted estimates account for measurement error associated with changes in the diagnostic accuracy of chlamydia screening tests over time. Unadjusted estimates do not account for measurement error.

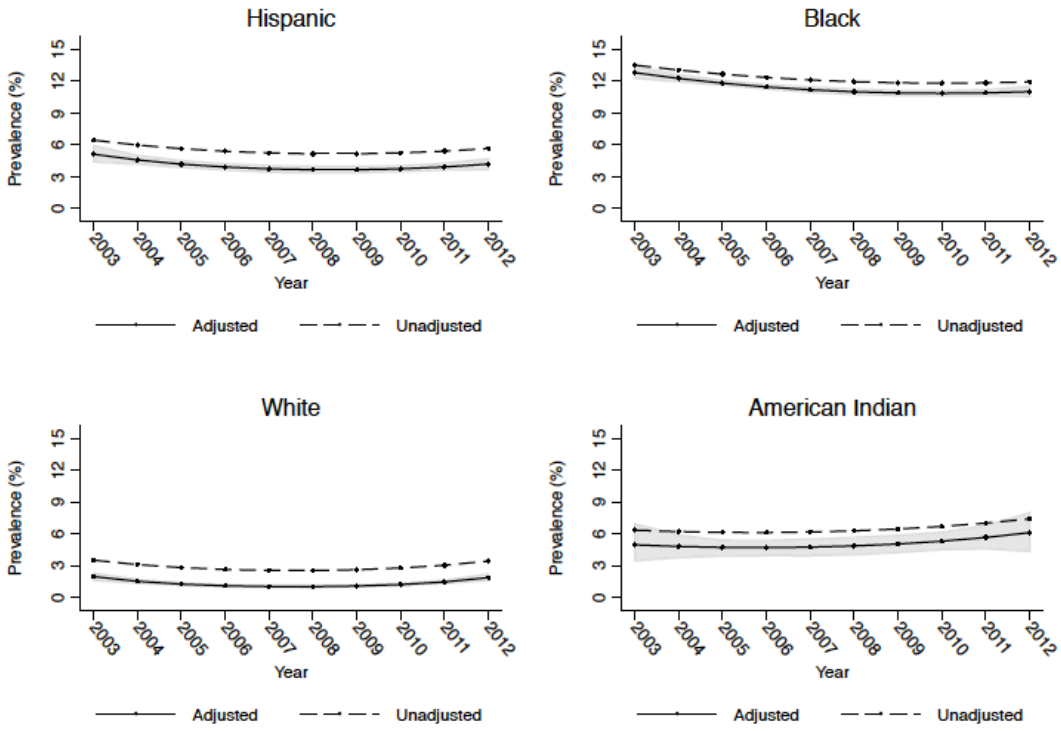
Figure A2.7: Sensitivity analysis of adjusted chlamydia prevalence trends among women entering the NJTP, 1990-2012.



Adjusted chlamydia prevalence trends among women entering the NJTP (n=350,490) modelled using the main sensitivity and specificity estimates for each test, as well as the upper and lower limits of the 95% CI around the sensitivity and specificity estimates. Adjusted prevalence estimates account for measurement error associated with the use of increasingly sensitive chlamydia screening tests over time. The unadjusted prevalence trend, which does not account for measurement error, is shown for comparison.

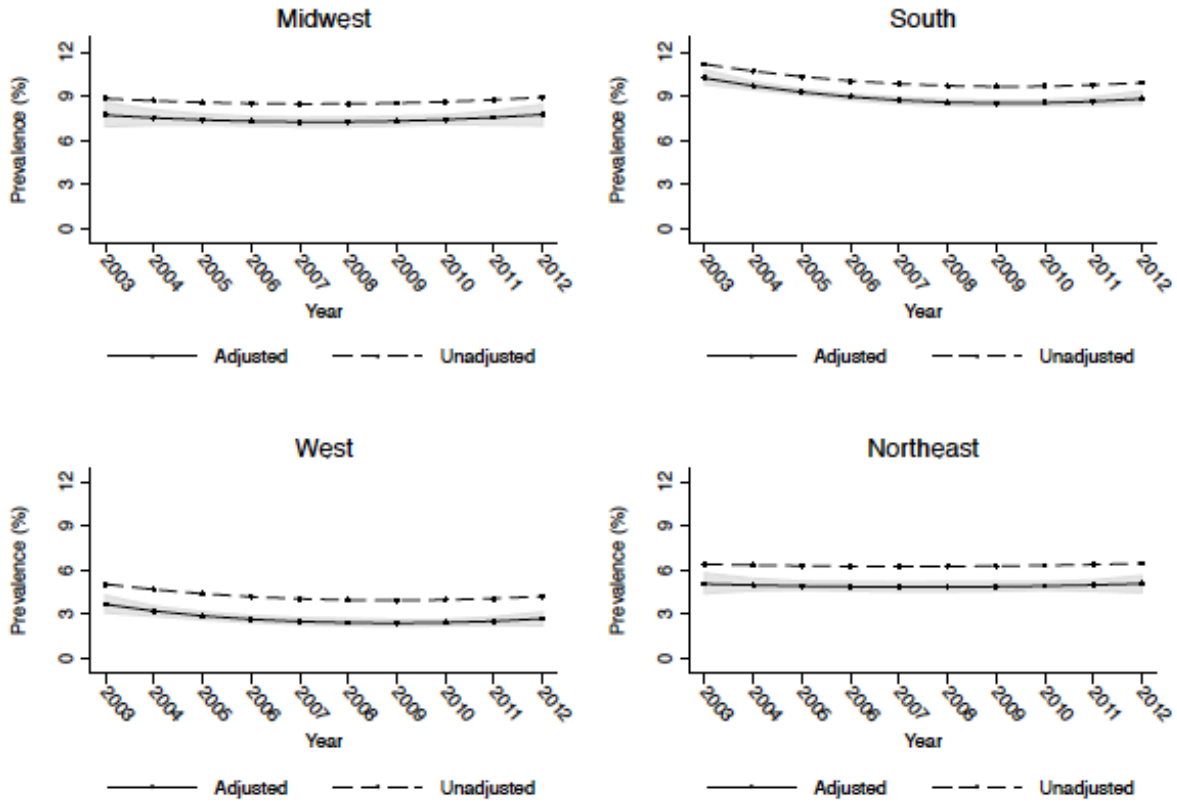
Se = sensitivity; Sp = specificity; CL = confidence limit

Figure A2.8: Adjusted and unadjusted chlamydia prevalence among men entering the NJTP by race/ethnicity, 2003-2012.



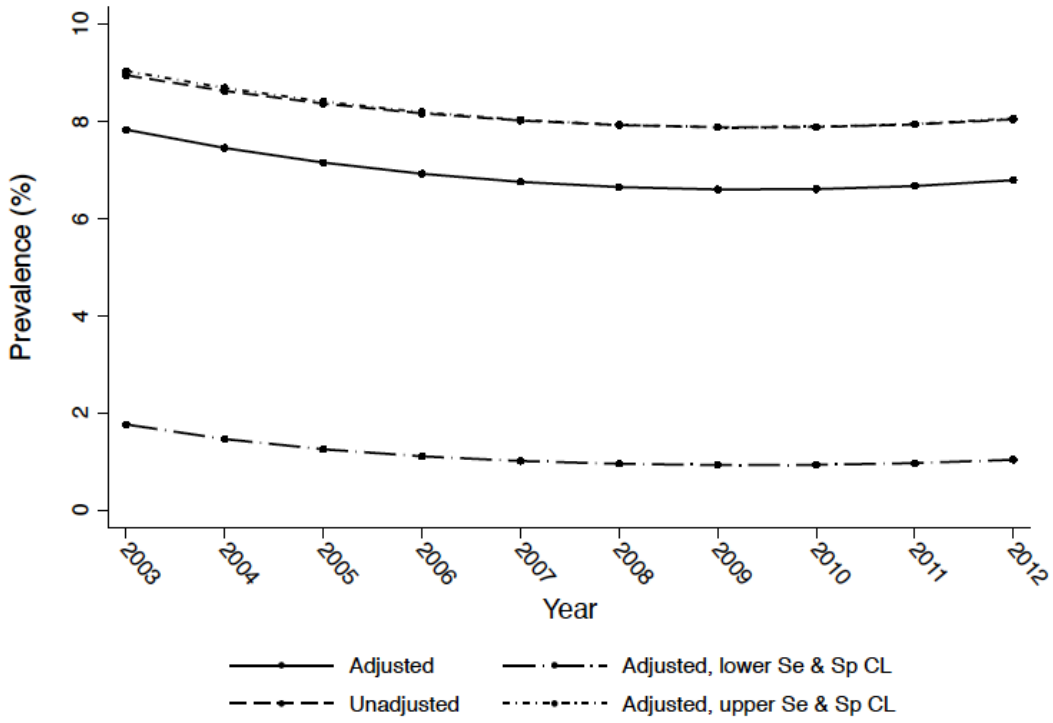
Adjusted and unadjusted chlamydia prevalence among Hispanic (n=44,822), Black (n=155,045), White (n=95,994), and American Indian (n=7,838) men entering the NJTP, 2003-2012. Adjusted estimates and 95% CIs account for measurement error associated with changes in the diagnostic accuracy of chlamydia screening tests over time. Unadjusted estimates do not account for measurement error.

Figure A2.9: Adjusted and unadjusted chlamydia prevalence among men entering the NJTP by region, 2003-2012.



Adjusted and unadjusted chlamydia prevalence among men entering the NJTP in four regions of the US, 2003-2012 (Midwest: n=51,361; South: n=149,464; West: n=57,144; Northeast: n=45,730). Adjusted estimates account for measurement error associated with changes in the diagnostic accuracy of chlamydia screening tests over time. Unadjusted estimates do not account for measurement error.

Figure A2.10: Sensitivity analysis of adjusted chlamydia prevalence trends among men entering the NJTP, 2003-2012



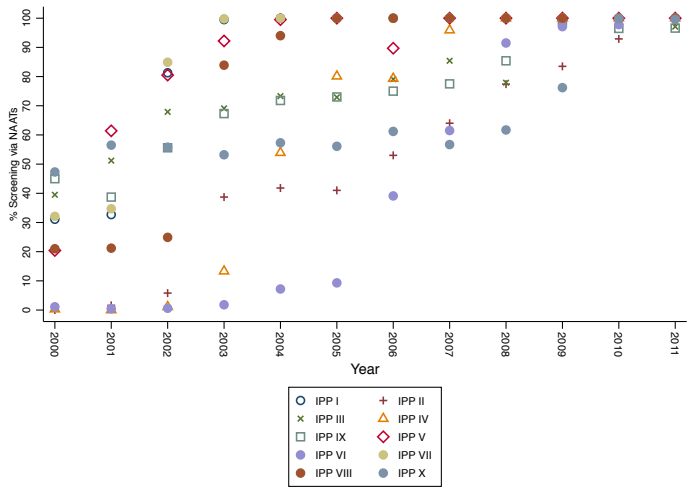
Adjusted chlamydia prevalence trends among men entering the NJTP (n=303,699) modelled using the main sensitivity and specificity estimates for each test, as well as the upper and lower limits of the 95% CI around the sensitivity and specificity estimates. Adjusted prevalence estimates account for measurement error associated with the use of increasingly sensitive chlamydia screening tests over time. The unadjusted prevalence trend, which does not account for measurement error, is shown for comparison. The unadjusted prevalence trend and the adjusted prevalence trend modelled using the upper sensitivity and specificity confidence limits follow a similar trajectory and overlap.

Se = sensitivity; Sp = specificity; CL = confidence limit

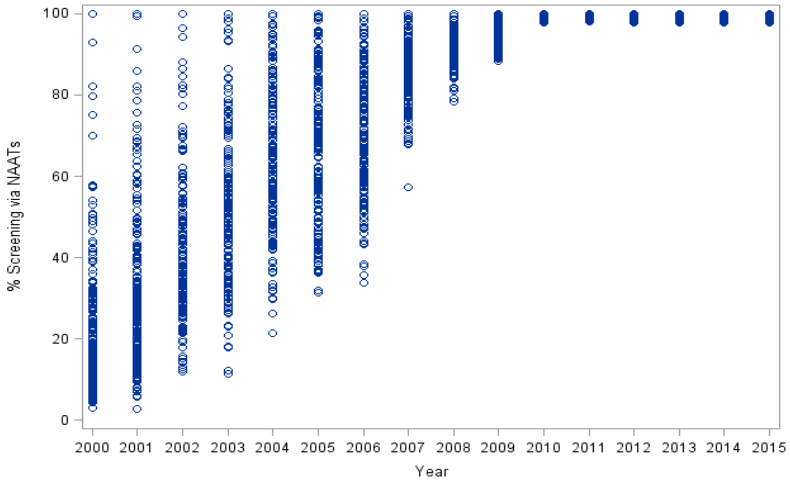
APPENDIX 3: AIM 2 SUPPLEMENTAL FIGURES

Figure A3.1: Distribution of chlamydia screening via NAATs, 2000-2015.

A.



B.



Panel A) Percentage of chlamydia screening via NAATs by ten regions of the Infertility Prevention Project from 2000 through 2011. Panel B) Lognormal distributions of the percentage of chlamydia screening via NAATs from 2000 through 2015. We created lognormal distributions of the percentage of screening via NAATs in an attempt to mimic the distribution of screening via NAATs in the Infertility Prevention Project. Distributions of the percentage of screening via NAATs (and percentage of screening via non-NAATs, calculated as 1-% screening via NAATs)

were used in the main analyses to calculate a weighted-average of non-NAAT and NAAT sensitivity.

REFERENCES

1. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2016. Atlanta: US Department of Health and Human Services; 2017.

2. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. MMWR. 2010;59(RR-12):8–12, 44–55.

3. Datta SD, Torrone E, Kruszon-Moran D, Berman S, Johnson R, Satterwhite CL, et al. Chlamydia trachomatis trends in the United States among persons 14 to 39 years of age, 1999-2008. Sex Transm Dis. 2012;39(2):92–6.

4. Torrone E, Papp J, Weinstock H. Prevalence of Chlamydia trachomatis Genital Infection Among Persons Aged 14–39 Years — United States, 2007–2012. MMWR. 2014;63(38):2011–3.

5. Torrone EA, Johnson RE, Tian LH, Papp JR, Datta SD, Weinstock HS. Prevalence of Neisseria gonorrhoeae among persons 14 to 39 years of age, United States, 1999 to 2008. Sex Transm Dis. 2013 Mar;40(3):202–5.

6. Nelson K, Masters Williams C. Infectious Disease Epidemiology: Theory and Practice. Third Edit. Burlington, MA: Learning, Jones & Bartlett; 2014. 782-786 p.

7. Miller WC, Ford CA, Morris M, Handcock MS, Schmitz JL, Hobbs MM, et al. Prevalence of chlamydial and gonococcal infections among young adults in the United States. JAMA. 2004;291(18):2229–36.

8. Hillis SD, Owens LM, Marchbanks PA, Amsterdam LF, Mac Kenzie WR. Recurrent chlamydial infections increase the risks of hospitalization for ectopic pregnancy and pelvic inflammatory disease. Am J Obstet Gynecol. 1997 Jan;176(1):103–7.

9. Weström L, Joesoef R, Reynolds G, Hagdu A, Thompson SE. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. Sex Transm Dis. Jan;19(4):185–92.

10. Gottlieb SL, Xu F, Brunham RC. Screening and treating Chlamydia trachomatis genital infection to prevent pelvic inflammatory disease: interpretation of findings from randomized controlled trials. Sex Transm Dis. 2013 Feb;40(2):97–102.

11. Oakeshott P, Kerry S, Aghaizu A, Atherton H, Hay S, Taylor-Robinson D, et al. Randomised controlled trial of screening for Chlamydia trachomatis to prevent pelvic inflammatory disease: the POPI (prevention of pelvic infection) trial. BMJ. 2010;340:c1642.

12. Scholes D, Stergachis A, Heidrich FE, Andrilla H, Holmes KK, Stamm WE. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. N Engl J Med. 1996;334(21):1362–6.

13. Centers for Disease Control and Prevention. Infertility Prevention Project [Internet]. 2013 [cited 2015 Dec 10]. Available from: http://www.cdc.gov/std/infertility/ipp-archive.htm

14. Miller WC. Epidemiology of chlamydial infection: are we losing ground? Sex Transm Infect. 2008;84(2):82–6.

15. Rothman K, Greenland S, Lash T. Modern Epidemiology. Third Edit. Philadelphia, PA: Lippincott, Williams, & Wilkins; 2008.

16. Dicker LW, Mosure DJ, Levine WC, Black CM, Berman SM. Impact of switching laboratory tests on reported trends in Chlamydia trachomatis infections. Am J Epidemiol. 2000;151(4):430–5.

17. Joesoef MR, Mosure DJ. Prevalence of Chlamydia in Young Men in the United States From Newly Implemented Universal Screening in a National Job Training Program. 2006;33(10):636–9.

18. Bradley H, Satterwhite CL. Prevalence of neisseria gonorrhoeae infections among men and women entering the National Job Training Program—United States, 2004–2009. Sex Transm Dis. 2012;39(1):49–54.

19. Tian L, Satterwhite C, Braxton J, Groseclose S. Application of the Time-Series Approach to Assess the Temporal Trend of Racial Disparity in Chlamydia Prevalence in the US National Job Training Program. Am J Epidemiol. 2011;173(2):217–24.

20. Satterwhite CL, Tian LH, Braxton J, Weinstock H. Chlamydia prevalence among women and men entering the National Job Training Program: United States, 2003-2007. Sex Transm Dis. 2010 Feb;37(2):63–7.

21. Joesoef MR, Mosure DJ. Prevalence trends in chlamydial infections among young women entering the National Job Training Program, 1998-2004. Sex Transm Dis. 2006 Sep;33(9):571–5.

22. Mertz KJ, Ransom RL, St. Louis ME, Groseclose SL, Hadgu A, Levine WC, et al. Prevalence of genital chlamydial infection in young women entering a National Job Training Program, 1990-1997. Am J Public Health. 2001;91(8):1287–90.

23. Cohen MS. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. Lancet. 1998;351 Suppl:5–7.

24. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75(1):3–17.

25. Low N. Screening programmes for chlamydial infection: when will we ever learn? BMJ. 2007;334(7596):725–8.

26. Miller WC. Screening for chlamydial infection: are we doing enough? Lancet. 2005;365(9458):456–8.

27. Chow JM, Bauer HM. What Data Are Really Needed to Evaluate the Population Impact of Chlamydia Screening Programs? Sex Transm Dis. 2016 Jan;43(1):9–11.

28. Gaydos C a, Howell MR, Pare B, Clark KL, Ellis D a, Hendrix RM, et al. Chlamydia trachomatis infections in female military recruits. N Engl J Med. 1998;339(11):739–44.

29. Lechner BL, Baker JA, Chastain DO, Cuda SE, Lynch J. The prevalence of asymptomatic Chlamydia trachomatis in military dependent adolescents. Mil Med. 2002;167(7):600–1.

30. Stary A, Steyrer K, Heller-Vitouch C, Muller I, Mardh PA. Screening for Chlamydia trachomatis in military personnel by urine testing. Infection. 1991;19(4):205–7.

31. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for HIV, STD and TB Prevention (NCHSTP), Division of STD/HIV Prevention . Sexually Transmitted Disease Morbidity for selected STDs by age, race/ethnicity and gender 1996-2013. CDC WONDER Online Database. [cited 2015 Jan 3]. Available from: http://wonder.cdc.gov/std-v2013-race-age.html

32. Vickers DM, Osgood ND. Current crisis or artifact of surveillance: insights into rebound chlamydia rates from dynamic modelling. BMC Infect Dis. 2010;10:70.

33. US Department of Labor. US Department of Labor Job Corps Annual Report. 2009.

34. U.S. Department of Labor Office of Job Corps. Policy and Handbook Requirements. 2015.

35. Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25.

36. Magder LS, Hughes JP. Logistic regression when the outcome is measured with uncertainty. Am J Epidemiol. 1997;146(2):195–203.

37. Centers for Disease Control Prevention. NCHHSTP AtlasPlus. Updated 2017. [cited 2017 May 2]. Available from: https://www.cdc.gov/nchhstp/atlas/index.htm

38. Greenland S. Basic methods for sensitivity analysis of biases. Int J Epidemiol. 1996;25(6):1107–16.

39. Szklo M, Nieto J. Epidemiology: Beyond the Basics. Edition 2. Sudbury, Mass: Jones & Bartlett Publishers; 2007. 58-59 p.

40. Torrone E. Personal communication. October 2017.

41. Satterwhite CL, Grier L, Patzer R, Weinstock H, Howards PP, Kleinbaum D. Chlamydia positivity trends among women attending family planning clinics: United States, 2004-2008. Sex Transm Dis; 2011;38(11):989–94.

42. Wiesenfeld HC. Screening for *Chlamydia trachomatis* Infections in Women. N Engl J Med. 2017;376(8):765–73.

43. Turner CF. Untreated Gonococcal and Chlamydial Infection in a Probability Sample of Adults. Jama. 2002;287(6):726.

44. Zakher B, Cantor AAG, Pappas M, Daeges M, Nelson HD. Screening for Gonorrhea and Chlamydia: A Systematic Review for the US Preventive Services Task Force. Ann Intern Med. 2014;161(12):884-U81.

45. National Committee for Quality Assurance. Chlamydia Screening in Women. Healthcare Effectiveness Data and Information Set. 2017.

46. Centers for Disease Control and Prevention. Recommendations for the prevention and management of Chlamydia trachomatis infections. MMWR. 1993;42(No. RR-12).

47. Hadgu A, Qu Y. A biomedical application of latent class models with random effects. Appl Stat. 1998;47(4):603–16.

48. LeBar W, Schubiner H, Jemal C, Herschman B, Criswell K, Curtin N, et al. Comparison of the Kallested Pathfinder EIA, cytocentrifuged direct fluorescent antibody, and cell culture for the detection of Chlamydia trachomatis. Diagn Microbiol Infect Dis. 1991;14(1):17–20.

49. Black CM, Marrazzo J, Johnson RE, Hook III EW, Jones RB, Green TA, et al. Head-to-head multicenter comparison of DNA probe and nucleic acid amplification tests for Chlamydia trachomatis infection in women performed with an improved reference standard. J Clin Microbiol. 2002;40(10):3757–63.

50. Blanding J, Hirsch L, Stranton N, Wright T, Aarnaes S, de la Maza L, et al. Comparison of the Clearview Chlamydia, the PACE 2 assay, and culture for detection of Chlamydia trachomatis from cervical specimens in a low-prevalence population. J Clin Microbiol. 1993;31(6):1622–5.

51. Carroll KC, Aldeen WE, Morrison M, Anderson R, Lee D, Mottice S. Evaluation of the Abbott LCx ligase chain reaction assay for detection of Chlamydia trachomatis and Neisseria gonorrhoeae in urine and genital swab specimens from a sexually transmitted disease clinic population. J Clin Microbiol. 1998;36(6):1630–3.

52. Clarke LM, Sierra MF, Daidone BJ, Lopez N, Covino JM, McCormack WM. Comparison of the Syva MicroTrak enzyme immunoassay and Gen-Probe PACE 2 with cell culture for diagnosis of cervical Chlamydia trachomatis infection in a high-prevalence female population. J Clin Microbiol. 1993;31(4):968–71.

53. Hsuih TCH, Guichon A, Diaz A, Bottone EJ, Sperling R, Zhang DY. Chlamydial infection in a high-risk population: Comparison of Amplicor PCR and Gen-Probe PACE II for diagnosis. Adolesc Pediatr Gynecol. 1995;8(2):71–6.

54. Iwen PC, Blair TM, Woods GL. Comparison of the Gen-Probe PACE 2 system, direct fluorescent-antibody, and cell culture for detecting Chlamydia trachomatis in cervical specimens. Am J Clin Pathol. 1991;95(4):578–82.

55. Kluytmans JA, Niesters HG, Mouton JW, Quint WG, Ijpelaar JA, Van Rijsoort-Vos JH, et al. Performance of a nonisotopic DNA probe for detection of Chlamydia trachomatis in urogenital specimens. J Clin Microbiol. 1991;29(12):2685–9.

56. Lauderdale T-L, Landers L, Thorneycroft I, Chapin K. Comparison of the PACE 2 assay, two amplification assays, and clearview EIA for detection of Chlamydia trachomatis in female endocervical and urine specimens. J Clin Microbiol. 1999;37(7):2223–9.

57. Semeniuk H, Zentner A, Read R, Church D. Evaluation of sequential testing strategies using non-amplified and amplified methods for detection of Chlamydia trachomatis in endocervical and urine specimens from women. Diagn Microbiol Infect Dis. 2002;42(1):43–51.

58. Wylie JL, Moses S, Babcock R, Jolly A, Giercke S, Hammond G. Comparative evaluation of chlamydiazyme, PACE 2, and AMP-CT assays for detection of Chlamydia trachomatis in endocervical specimens. J Clin Microbiol. 1998;36(12):3488–91.

59. Cosentino LA, Landers D V, Hillier SL. Detection of Chlamydia trachomatis and Neisseria gonorrhoeae by strand displacement amplification and relevance of the amplification control for use with vaginal swab specimens. J Clin Microbiol. 2003;41(8):3592–6.

60. Gaydos CA, Cartwright CP, Colaninno P, Welsch J, Holden J, Ho SY, et al. Performance of the Abbott RealTime CT/NG for detection of Chlamydia trachomatis and Neisseria gonorrhoeae. J Clin Microbiol. 2010;48(9):3236–43.

61. Masek BJ, Arora N, Quinn N, Aumakhan B, Holden J, Hardick A, et al. Performance of three nucleic acid amplification tests for detection of Chlamydia trachomatis and Neisseria gonorrhoeae by use of self-collected vaginal swabs obtained via an Internet-based screening program. J Clin Microbiol. 2009;47(6):1663–7.

62. Taylor SN, Van Der Pol B, Lillis R, Hook EW, Lebar W, Davis T, et al. Clinical evaluation of the BD probetec™ chlamydia trachomatis Qx amplified DNA assay on the BD viper™ system with XTR™ technology. Sex Transm Dis. 2011 Jul;38(7):603–9.

63. Van der Pol B, Ferrero D V., Buck-Barrington L, Hook E, Lenderman C, Quinn T, et al. Multicenter evaluation of the BDProbeTec ET System for detection of Chlamydia trachomatis and Neisseria gonorrhoeae in urine specimens, female endocervical swabs, and male urethral swabs. J Clin Microbiol. 2001;39(3):1008–16.

64. Haugland S, Thune T, Fosse B, Wentzel-Larsen T, Hjelmevoll SO, Myrmel H. Comparing urine samples and cervical swabs for Chlamydia testing in a female population by means of Strand Displacement Assay (SDA). BMC. 2010;10.

65. Beltrami JF, Farley TA, Hamrick JT, Cohen DA, Martin DH. Evaluation of the Gen-Probe PACE 2 assay for the detection of asymptomatic chlamydia trachomatis and neisseria gonorrhoeae infections in male arrestees. Sex Transm Dis. 1998;25(10):501–4.

66. StataCorp. Stata statistical software: release 14.1. College Station, TX: StataCorp LP; 2016.

67. Nsuami MJ, Nsa M, Brennan C, Cammarata CL, Martin DH, Taylor SN. Chlamydia positivity in New Orleans public high schools, 1996-2005: implications for clinical and public health practices. Acad Pediatr. 2013;13(4):308–15.

68. Asbel LE, Newbern EC, Salmon M, Spain CV, Goldberg M. School-based screening for Chlamydia trachomatis and Neisseria gonorrhoeae among Philadelphia public high school students. Sex Transm Dis. 2006;33(10):614–20.

69. Santelli JS, Lindberg LD, Finer LB, Singh S. Explaining recent declines in adolescent pregnancy in the United States: The contribution of abstinence and improved contraceptive use. Am J Public Health. 2007;97(1):150–6.

70. Christiansen-Lindquist L, Tao G, Hoover K, Frank R, Kent C. Chlamydia screening of young sexually active, Medicaid-insured women by race and ethnicity, 2002-2005. Sex Transm Dis. 2009;36(10):642–6.

71. Nguyen TQ, Ford CA, Kaufman JS, Leone PA, Suchindran C, Miller WC. Infrequent chlamydial testing among young adults: financial and regional differences. Sex Transm Dis. 2008;35(8):725–30.

72. Ahmed K, Baasiri H, Hoover K, Kent C. Chlamydia Screening Among Sexually Active Young Female Enrollees of Health Plans --- United States , 1999--2001. MMWR. 2009;53(42):4–7.

73. Heijne JCM, Tao G, Kent CK, Low N. Uptake of regular chlamydia testing by U.S. women: a longitudinal study. Am J Prev Med. 2010 Sep;39(3):243–50.

74. Khosropour CM, Broad JM, Scholes D, Saint-Johnson J, Manhart LE, Golden MR. Estimating Chlamydia Screening Coverage. Sex Transm Dis. 2014;41(11):665–70.

75. Patel CG, Tao G. The Significant Impact of Different Insurance Enrollment Criteria on the HEDIS Chlamydia Screening Measure for Young Women Enrolled in Medicaid and Commercial Insurance Plans. Sex Transm Dis. 2015;42(10):575–9.

76. Tao G, Hoover KW, Kent CK. Chlamydia testing patterns for commercially insured women, 2008. Am J Prev Med. 2012;42(4):337–41.

77. Centers for Disease Control and Prevention. Chlamydia Screening Among Sexually Active Young Female Enrollees of Health Plans --- United States , 1999--2001. MMWR. 2004;53(42):983–5.

78. Tao G, Hoover KW, Leichliter JS, Peterman TA, Kent CK. Self-reported Chlamydia testing rates of sexually active women aged 15-25 years in the United States, 2006-2008. Sex Transm Dis. 2012;39(8):605–7.

79. Tao G, Tian LH, Peterman T. Estimating Chlamydia screening rates by using reported sexually transmitted disease tests for sexually active women aged 16 to 25 years in the United States. Sex Transm Dis. 2007;34(3):180–2.

80. Tao G, Hoover KW, Leichliter JS, Peterman TA, Kent CK. Self-reported chlamydia testing rates of sexually active women aged 15-25 years in the United States, 2006-2008. Sex Transm Dis. 2012;39(8).