

Prevention of *Chlamydia trachomatis* infections: Evaluation of vaccination and post-exposure
prophylactic antibiotic use as population-level strategies

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Abstract

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In 2023, over 1.6 million cases of *Chlamydia trachomatis* (CT) were reported in the United States, making it the most common notifiable sexually transmitted infection (STI). Although CT affects the broader population, young women aged 15 to 24 years and gay, bisexual, and other men who have sex with men (MSM) face disproportionately higher risk of CT acquisition. Prevention of CT and its sequelae from untreated infections requires large-scale public health interventions, including annual screening and health education campaigns. Interest has grown in augmenting current prevention strategies with novel approaches, particularly doxycycline post-exposure prophylaxis (doxy-PEP) and CT vaccination. This dissertation addresses critical knowledge gaps related to these two emerging population-level prevention strategies. Aim 1 (Chapter 2) used data from a prospective cohort of men who have sex with men (MSM) in Seattle, WA to characterize longitudinal antibiotic use, providing a foundation for understanding how doxy-PEP may influence antibiotic consumption and the dissemination of antibiotic resistance in this population. In Aim 2 (Chapter 3), we developed a deterministic,

compartmental model of CT transmission in the United States among males and females aged 15 to 64 years, simulating trends from 2000 to 2075. We then modeled the introduction of a CT vaccine in 2025, estimating its impact on disease burden under a range of implementation strategies and vaccine characteristics. Aim 3 (Chapter 4) builds on this model to evaluate the cost-effectiveness of CT vaccination in the United States from 2025 to 2050 through the incorporation of cost and health utilities data.

In Aim 1, we found that antibiotic consumption among our cohort of MSM was very high, primarily driven by treatment for STIs and other health conditions. Participants with a recent history of bacterial STIs and those aged 25 to 39 years had significantly higher rates of antibiotic initiation. These findings provide a critical foundation for understanding antibiotic use behaviors in MSM and underscore the importance of evaluating how doxy-PEP may influence antibiotic consumption in this already high-using population. In Aims 2 and 3, we found that a partially efficacious vaccine, introduced through routine vaccination of adolescent girls only or adolescent girls and boys, could prevent up to 160 million CT infections and lead to meaningful reductions in CT incidence by 2075. Catch-up vaccination of older, unvaccinated females offered additional gains, but these were relatively modest compared to the impact of sustained routine vaccination. Our findings also suggest that routine CT vaccination has the potential to be a cost-saving or highly cost-effective intervention, even across a range of assumptions about vaccine efficacy, duration of protection, and vaccine coverage. Incremental cost-effectiveness ratios were most influenced by uncertainty in vaccine price per dose and treatment costs for pelvic inflammatory disease, though all results remained cost-effective under the highest accepted willingness-to-pay thresholds in the United States.

We hope this work contributes to a growing body of evidence informing the design, implementation, and scale-up of effective CT prevention strategies, ultimately helping to reduce infections and improve sexual health outcomes.

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Chapter 1

Introduction

1.1 DISEASE BURDEN OF CHLAMYDIA TRACHOMATIS INFECTIONS

According to the 2023 Sexually Transmitted Infections Surveillance Report released by the United States Centers for Disease Control and Prevention (U.S. CDC), *Chlamydia trachomatis* (CT) remains the most common notifiable STI in the United States, with roughly 1.6 million cases diagnosed in 2023 alone.¹ The World Health Organization (WHO) estimated that roughly 128.5 million incident cases of symptomatic and asymptomatic CT occurred among individuals of reproductive age in 2020, highlighting the substantial contributions of CT to global morbidity.² Importantly, accurate reporting of CT is impacted by the asymptomatic presentation of infection. Current estimates show that nearly 70% and 50% of genital CT infections are asymptomatic at the time of diagnosis among women and men, respectively.³⁻⁵ Given the high prevalence of asymptomatic presentation, burden estimates presented by the CDC and other public health organizations likely underrepresent the true number of CT infections.⁶

While active infections can be treated with antibiotics, barriers to healthcare access and the high prevalence of asymptomatic infections can lead to serious short- and long-term sequelae. Among persons with uteri, undiagnosed and untreated infections can lead to pelvic inflammatory disease (PID), tubal factor infertility, ectopic pregnancy, and chronic pelvic pain.⁷ Among persons with penises, testes, or prostates, CT infection can lead to orchitis, epididymitis, and prostatitis.⁸ Although most common among gay, bisexual, and other men who have sex with men (MSM), lymphogranuloma venereum (LGV), an infection caused by the invasive L1, L2 and L3 strains of CT, can also cause severe proctocolitis among all individuals with exposures to the bacteria.^{9,10} Due to the health systems costs associated with treatment of active infection and associated sequelae, CT had an estimated direct lifetime cost of \$691.31 million (2019 USD) from infections acquired in 2018 in the U.S. alone.¹¹ Lifetime costs of CT remain significantly

higher than other bacterial STIs and are comparable to costs associated with vaccine-preventable human papillomavirus. While documented widely across the country, the rates of CT infection vary significantly by age and across specific populations.⁵ Young women aged 15 to 24 years, commercial sex workers (CSWs), and MSM are at a significantly greater risk for acquiring CT when compared to the general population.¹²⁻¹⁴ Disproportionate burden among these populations has been associated with many factors, including social stigma, unstable housing, lower medical insurance coverage, and high burden of other STIs and co-morbidities such as human immunodeficiency virus (HIV) infection.^{15,16}

1.2 ADVENT OF DOXYCYCLINE POST-EXPOSURE PROPHYLAXIS FOR STI PREVENTION

Trends in CT incidence in the United States have prompted increased efforts to identify effective biomedical prevention strategies. The use of antibiotic prophylaxis to reduce the incidence of bacterial STIs has previously been studied, but concerns of antibiotic resistance and poor risk versus benefit outcomes restricted its successful integration as a preventative option.¹⁷ However, interest in the use of doxycycline as a prophylactic prevention measure for CT has grown in recent years, due to its widespread use as a well-tolerated antibiotic for the prevention of numerous infectious diseases, including leptospirosis, malaria, and Lyme disease.¹⁸⁻²⁰

To date, few studies have assessed the impacts of doxycycline when used as pre-exposure prophylaxis (doxy-PrEP) or sexual event-driven post-exposure prophylaxis (doxy-PEP).²¹⁻²⁵ A pilot randomized controlled trial among MSM living with HIV conducted by Bolan et al. (2015) found a 73% reduction (OR: 0.27; 95% CI: 0.09, 0.83) in the odds of CT, syphilis, or *Neisseria gonorrhoea* diagnoses among participants receiving doxy-PrEP for 48 weeks compared to those receiving a financial incentive-based behavioral intervention.²³ Additionally, the IPERGAY HIV-prevention study among MSM and transgender women without HIV on HIV pre-exposure prophylaxis (PrEP), conducted by the French National Agency for Research on AIDS and Viral Hepatitis, studied the impact of doxycycline as post-exposure prophylaxis. It

found a relative reduction of 70-73% for CT and syphilis diagnoses among individuals using doxy-PEP within 24–72 hours of condomless sexual encounters compared to those without prophylactic doxycycline.²² In the United States, Luetkemeyer et al. (2023) also found that, among MSM and transgender women living with HIV or taking HIV PrEP, doxy-PEP was associated with a lower risk of bacterial STIs than the standard of care.²⁴ However, doxycycline prophylaxis has yet to show efficacy in cisgender women. In a randomized, open-label trial comparing doxy-PEP within 72 hours after condomless sex with standard care among Kenyan women 18 to 30 years of age receiving HIV PrEP, researchers found no significant difference in risk of STI acquisition (RR = 0.88; 95% CI: 0.60, 1.29) between intervention arms.²⁵ However, low detection of doxycycline, reflecting low adherence, among participants assigned to receive doxy-PEP may serve as the primary driver for the non-significant results. Further research is needed to assess the efficacy of doxy-PEP among cisgender women and other populations at greatest risk for STI acquisition.

Despite these largely encouraging results, concerns about the use of doxycycline prophylaxis, including poor adherence and the potential for further development of antimicrobial resistance in STIs and other non-target organisms, remain as potential barriers to its feasibility as a CT prevention measure. Tetracycline-resistant *Neisseria gonorrhoea* poses a significant threat to public health and the additional use of doxycycline as prophylaxis may worsen trends of resistance.²⁶⁻²⁸ Researchers from the U.S.-based doxy-PEP study observed more tetracycline-resistant *Neisseria gonorrhoea* cases among participants who used doxy-PEP compared to those who did not (38.5% vs. 12.5%), although the difference was not statistically significant, likely due to small sample sizes.²⁴ Selection and dissemination of doxycycline resistance has not been observed for CT and the risk remains low; however, emergence of resistance after broad, long-term use of doxycycline prophylaxis, alone or in combination with other antibiotic regimens, is plausible.^{17,29,30}

At present, completed studies in this field have not measured receipt of other antibiotics and adherence among study participants receiving doxy-PrEP or doxy-PEP. Additionally, studies assessing broader antibiotic use in MSM and transgender women that would be eligible for doxy-PrEP/PEP have primarily been limited to cross-sectional designs that evaluate previous use rather than longitudinal trends in incidence and prevalence of antibiotic use.³¹⁻³³ Establishing an understanding of antibiotic use behaviors over time is necessary to assess how doxy-PEP implementation impacts antibiotic consumption and risk of dissemination of resistant organisms among MSM.

1.3 CT VACCINE DEVELOPMENT & POTENTIAL IMPACTS

Although the introduction of doxy-PEP in conjunction with annual screening would reduce CT incidence in eligible populations, a safe, effective vaccine is likely required for population-level declines in CT infections. Between the 1940s and now, studies of vaccines protecting against CT have been limited to pre-clinical and Phase I trials.³⁴⁻³⁷ Pre-clinical trials evaluating effective target antigens, adjuvants, and vaccine delivery sites have utilized animal models, including mice, non-human primates, pigs, guinea pigs, and rabbits.^{36,38-40} Through these studies, a purified recombinant outer membrane protein (MOMP) construct has been shown to be immunogenic in non-human primates and mice, thus leading to its development as a front-runner among target antigens. Advancement to Phase 1 trials evaluating safety in small human cohorts has only begun in recent years. A first-in-human, double-blind, randomized, placebo-controlled trial of the MOMP-based fusion antigen CTH522 in a prime-boost immunization schedule was conducted among 35 women between 2016 and 2017 in the United Kingdom.³⁷ Researchers found the antigen CTH522 adjuvanted with either CAF01 or aluminum hydroxide was safe, well tolerated, and immunogenic. Although results from preclinical and Phase 1 testing demonstrate potential for further clinical development in Phase II and Phase III trials, further clinical testing of current candidates has stalled. The unique intracellular biology of CT poses a significant challenge to effective vaccine development. In the face of these

challenges, data on the potential impacts of a vaccine on disease burden could stimulate demand and expand developmental funding; however, these data are limited at this time.⁴¹

Mathematical modeling can provide important estimates of the potential impact of a vaccine prior to its rollout in population-specific or national immunization programs. Developers use public and private data sources to derive model assumptions and collaborate with healthcare providers, epidemiologists, and social scientists on the creation of an appropriate model framework. Through this process, modelers can offer policy and funding decisionmakers with data-driven support for the continued development and testing of vaccines in populations where implementation has not yet begun. While the awareness and use of modeling as a public health tool has seen a dramatic rise over the last two decades, modeling to assess the potential impacts of a CT vaccination has been minimal. Studies modeling the introduction of a CT vaccine have primarily focused on describing its impact on heterosexual transmission of CT to young women between the ages of 15 to 24 years in high-income countries.⁴²⁻⁴⁷ To our knowledge, only one study has assessed the impact of a vaccine on CT burden among the general U.S. population, concluding that a partially effective vaccine could lead to substantial reductions in CT burden.⁴⁸ Additional data are needed to understand how different vaccine characteristics, such as efficacy and duration of protection, and implementation strategies, including sex-specific, sex-neutral, or catch-up campaigns, impact disease burden to improve the accuracy and generalizability of model findings.

1.4 COST-EFFECTIVENESS OF CT VACCINATION

The consideration of economic impact and estimation of accurate costs are vital for the assessment and improvement of health interventions, globally.⁴⁹⁻⁵¹ In resource-limited settings, policymakers are increasingly challenged to allocate scarce financial resources to manage competing health risks. Cost-effectiveness analyses, among other economic evaluation tools, are often used to determine the efficient allocation of healthcare resources to produce the greatest impact on population health, given the competition for limited public health resources.

Limited work has been done to describe the proposed costs or cost-effectiveness of novel CT prevention strategies, including vaccination. In a 2018 study, Dittkowsky et al. found that a U.S.-based vaccination program of all females aged 9 to 26 years would cost an estimated \$710 million over a 17-year period.⁴⁵ Additionally, Owusu-Edusei et al. (2015) determined that a 75% efficacious CT vaccine program for young women in the U.S. was cost-effective when accounting for the costs of a complete vaccine series per person.⁴⁴ To our knowledge, no study has assessed the incremental cost-effectiveness of CT vaccination across the broader U.S. population, accounting for both males, females, and stratification by age.

For public health officials, it is a necessity that economic evaluations are informed by realistic estimates of costs incurred to ensure programmatic success.⁵²⁻⁵⁴ Within sexual and reproductive health, the costs associated with screening and treatment of CT infections have been studied extensively.⁵⁵⁻⁶¹ In the U.S., CT, *Neisseria gonorrhoea*, and syphilis infections accounted for US\$1.1 billion in direct lifetime medical costs each year, with 60% of these costs originating from care among young people aged 15 to 24 years.¹¹ These costs included the lifetime medical care for treatment of acute infections and associated sequelae, for infections acquired in 2018 alone. Although screen-and-treat approaches are critical for CT control and prevention, the observed rise in CT infections globally will drive increases in the resource demands of this approach, further highlighting the need for upstream-prevention strategies. Advocacy for the vaccine development process could be strengthened by using mathematical modeling and health economic evaluations to explore the potential impact and costs of introducing and scaling up CT vaccination.

1.5 SIGNIFICANCE & RESEARCH OBJECTIVES

In summary, CT remains a significant source of morbidity in the United States. While current prevention strategies provide important reductions in disease burden, novel strategies such as doxy-PEP and, eventually, vaccination may offer added benefits for disease control in the future. As such, this dissertation addresses critical knowledge gaps about CT prevention

through the following questions and approach:

- 1.) *Among individuals potentially eligible for doxy-PEP, what is the frequency of, and characteristics associated with, antibiotic use that can inform the utility of doxycycline as a preventative measure?*
- 2.) *What are the impacts of a potential CT vaccine on disease burden in the U.S. with respect to vaccine characteristics such as efficacy and duration of protection? How do vaccine implementation strategies, including female-only, sex-neutral, and catch-up vaccination strategies, differentially impact disease burden in the U.S.?*
- 3.) *Is CT vaccination a cost-effective prevention strategy compared to the current standard of care (screen-and-treat practices) in the U.S.? Are increasingly more inclusive vaccine implementation strategies (e.g. sex-neutral) cost-effective compared to less inclusive strategies (e.g. female-only)?*

First, we characterize the frequency of, and factors associated with, antibiotic use among MSM in Seattle, WA (Chapter 2) using longitudinal data from the ExGen Study, a 48-week prospective, natural history study of extragenital CT and *Neisseria gonorrhoeae*. Second, we develop a mathematical model to predict the 50-year impact of national rollout of a theoretical vaccine on the burden of urogenital CT infections in the U.S. (Chapter 3). Model structure and parameters are sourced from peer-reviewed published literature, publicly available surveillance systems, and vaccine target product profiles. Finally, in Chapter 4, we evaluate the cost-effectiveness of adding CT vaccination to the standard of care (screen-and-treat interventions) in the U.S. compared to the standard of care alone, using the mathematical model developed in Chapter 3 and cost and health utility data from peer-reviewed and public sources over the 2025 to 2050 time horizon.

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Chapter 2

High Incidence and Duration of Antibiotic Use Among a Cohort of Men Who Have Sex with Men in Seattle, WA

This work was originally published in Open Forum Infectious Diseases.¹ Findings were also presented, in part, at the STI Prevention Conference in Atlanta, Georgia, United States, 19 September 2024.

2.1 ABSTRACT

Background: Doxycycline post-exposure prophylaxis (doxy-PEP) effectively prevents bacterial sexually transmitted infections (STIs) but may increase antibiotic pressure. Little is known about longitudinal antibiotic use among men who have sex with men (MSM), a key population for doxy-PEP.

Methods: We analyzed data from a prospective cohort of MSM in Seattle, WA, from 2016-2018, prior to the introduction of doxy-PEP. Antibiotic use and reason for prescription were self-reported in weekly surveys and extracted from medical records. We characterized antibiotic use across 49 weeks of follow-up, stratified by specific antibiotics of interest and reasons for prescription. Incidence rates (IR) were calculated for the number of incident events of antibiotic initiation per 100 person-years (PY) at risk. We assessed factors associated with antibiotic initiation using negative binomial regression to estimate adjusted incidence rate ratios (IRRs).

Results: Among 140 participants, 68.6% (n=96) received at least one antibiotic during follow-up, resulting in an overall IR=264.5 events of antibiotic initiation per 100 PY and 1,696 total days of antibiotic use. STI treatment was the most common reason for antibiotic initiation (IR=153.5 events per 100 PY; 462 days); however, treatment for other conditions contributed most to overall days of antibiotic use (IR=42.6 events per 100 PY; 947 days). An age of 25-39 years (IRR=1.54; 95%CI: 1.02,2.32) and a history of bacterial STIs <12 months prior to enrollment

(IRR=1.81; 95%CI: 1.12,2.93) were significantly associated with higher incidence of antibiotic initiation.

Conclusions: Antibiotic consumption among this population was very high. Our analysis provides a necessary foundation for assessing the potential impacts of doxy-PEP.

2.2 INTRODUCTION

Sexually transmitted infections (STIs), including *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (GC), and syphilis, persist as significant contributors to global morbidity among individuals of reproductive age.^{2,3} In recent years, the incidence of STIs has increased substantially among gay, bisexual, and other men who have sex with men (MSM).^{2,4} This change is likely a result of several factors, including increased uptake of HIV pre-exposure prophylaxis (PrEP), associated increases in STI testing frequency, and reductions in condom use.⁵⁻⁷

In response to rising STI rates, doxycycline post-exposure prophylaxis (doxy-PEP) has emerged as a new biomedical STI prevention strategy involving the use of 200 mg of doxycycline within 72 hours after sex acts.⁸ Doxy-PEP is effective among MSM in preventing syphilis, CT, and to a lesser extent GC, with reductions in the composite incidence of bacterial STIs ranging from 47-82%.⁹⁻¹¹ Organizations, including the United States Centers for Disease Control and Prevention (U.S. CDC), have endorsed doxy-PEP as an STI prevention strategy among eligible MSM and transgender women.^{8,12,13}

However, there are potential drawbacks to widespread doxy-PEP use, including the potential for the development of antibiotic resistance in STIs and non-target organisms.¹⁴⁻¹⁶ Further, the introduction of doxy-PEP may increase or decrease the cumulative use of antibiotics in MSM. At present, antibiotic use patterns among MSM have been underexamined, with available data being cross-sectional.¹⁷ Establishing an understanding of longitudinal antibiotic use behaviors

will allow us to assess how doxy-PEP and changing standards of STI screening and treatment affect antibiotic consumption and risk of resistance dissemination in this population.

Among a cohort of MSM in Seattle, WA observed prior to the popularization of doxy-PEP, we aimed to determine the incidence and correlates of antibiotic initiation, and duration of antibiotic use.

2.3 METHODS

Study Design and Population

We analyzed antibiotic use data collected through the ExGen Study, a 48-week prospective, natural history study of extragenital GC/CT conducted between March 2016 and December 2018.¹⁸ MSM from the Public Health–Seattle & King County Sexual Health Clinic (PHSKC) and the University of Washington’s Center for AIDS Research patient registry were eligible and recruited if they were at least 18 years of age, English-speaking, had access to the internet, reported receptive anal sex in the last 12 months, performed oral sex in the past 2 months, and met at least 1 of the following criteria: 1) had a diagnosis of GC, CT, or syphilis in the past 12 months; 2) reported using methamphetamine or amyl nitrate in the past 12 months; or 3) reported having at least 2 sexual partners in the past 2 months or at least 5 sexual partners in the past 12 months. All enrolled study participants provided written informed consent for participation and medical record extraction. This study was approved by the University of Washington’s Institutional Review Board (no. 50028).

Study Procedures

ExGen study procedures have been previously described.¹⁸⁻²⁰ Briefly, participants attended an in-person enrollment visit where demographic, clinical, and sexual behavior data were collected. Participants were then tested for STIs and HIV; those who tested positive for an STI at enrollment were treated.

During the 48-week follow-up period, each week participants completed a personalized, password-protected electronic survey on the REDCap platform.^{21,22} Weekly survey questions asked participants about hygiene practices, sexual behaviors, symptoms, STI testing, medication, and antibiotic use since their last survey. Participants also self-collected weekly pharyngeal and rectal specimens which were tested for GC/CT after participants completed the study. After completion of follow-up, study personnel extracted data on STI diagnoses and treatments from participants' medical records through PHSKC and the Madison Clinic, an HIV primary care clinic where many of the participants received care. At the final in-person visit, participants completed a final survey and underwent STI testing and treatment. Participants were compensated for completing weekly surveys and shipping self-collected specimens.

Measure of Antibiotic Use

We collected information on antibiotic use in two ways. First, participants were asked in weekly surveys to self-report their antibiotic use in the past week, including the name, route of administration, and reason for use. Second, study personnel collected information on antibiotic use during the duration of the study from participants' medical records, and recorded the type of antibiotic, treatment modality, and clinical indication.

Definitions and Statistical Analyses

Incidence of Antibiotic Initiation

We defined an incident event as the initiation of an antibiotic regimen at enrollment or participant-reported initiation of antibiotics at any point during follow-up, regardless of the length of treatment course. Receipt of antibiotics during follow-up not reported by study participants during weekly surveys but identified in the medical record were also included as incident events. If two or more antibiotics were initiated at the same time, each antibiotic was counted as a separate initiating event. We further stratified initiation by antibiotic type (doxycycline, azithromycin, ceftriaxone, or benzathine-penicillin) and reason for antibiotic use (STI diagnosis, epidemiologic treatment for STI contact, or other reported health conditions). Although additional

antibiotics were reported, the four antibiotics above were selected due to their frequency of use in the cohort (~87.3% of all antibiotics initiated) and their importance in STI treatment. In secondary analyses, we stratified antibiotic initiation by age (<25, 25-39, 40+ years), HIV status and PrEP use at enrollment, and reported STI diagnosis within 12 months prior to enrollment. Study participants were assigned 49 weeks of person-time at risk (1 week pre-enrollment; 48 weeks post-enrollment), as antibiotic initiation could be evaluated through medical records for weeks when individuals did not complete a weekly survey or were lost to follow-up. For stratification by antibiotic type, the time when individuals were receiving the specific antibiotic under consideration was excluded from the denominator (**Supplemental Table A.1**). We also excluded a clinically relevant, antibiotic-specific period post-regimen completion where a study participant would likely not be prescribed the antibiotic again. Incidence rates (IR) were calculated as the number of incident events per 100 person-years (PY) at risk. Exact rate ratio tests evaluated differences in unadjusted IRs across strata.

Duration of Antibiotic Use

We estimated the duration of antibiotic use as the number of days where antibiotics were prescribed for 1) treatment at enrollment, 2) self-reported use of antibiotics at any point during follow-up, or 3) unreported use of antibiotics at any point during follow-up extracted from medical records. If two or more antibiotics were initiated at the same time, the duration of each antibiotic was counted separately. We stratified days of antibiotic use by antibiotic type and reason for use, as well as by age, HIV status and PrEP use at enrollment, and reported STI diagnosis within 12 months before enrollment. We estimated lower- and upper-bound estimates to account for established ranges in antibiotic course duration (**Supplemental Table A.1**). To account for person-time at risk, we estimated IRs for days of antibiotic use per 100 PY at risk. Study participants each contributed 49 weeks of person-time at risk. However, to estimate IRs stratified by antibiotic type, time was excluded when individuals were either receiving the

specific antibiotic under consideration or were within the clinically relevant time post-regimen where they would not be prescribed the antibiotic again (**Supplemental Table A.1**).

Factors Associated with Antibiotic Initiation

To explore the factors associated with antibiotic initiation, we used negative binomial regression analysis with generalized estimating equations (GEE) with an exchangeable correlation structure to account for within-cluster correlation among observations. In primary analyses, we used overall antibiotic initiation, defined previously, as the primary outcome of interest. We selected the following *a priori* predictor variables: age (<25, 25-39, 40+ years), race/ethnicity, HIV status and PrEP use at enrollment, history of chronic medical conditions, reported methamphetamine use, and STI diagnosis within 12 months of enrollment. To ensure model convergence, we collapsed individuals who reported race/ethnicity as “Non-Hispanic Asian/Pacific Islander”, “Another Race/Ethnicity”, or “Unknown” into a single category of “Another Race/Ethnicity”. Any variables with $p < 0.2$ in univariate analyses were included in the multivariate model. Results of univariate and multivariate regressions are presented as incidence rate ratios (IRRs). In secondary analysis, factors associated with antibiotic initiation for STI treatment alone were explored using the same approach. An $\alpha \leq 0.05$ was considered statistically significant for multivariate analyses. Statistical analyses were performed in R version 4.1.1.

2.4 RESULTS

Between March 2016 and December 2018, 140 MSM were enrolled into ExGen, collectively contributing 131.6 PY of follow-up. The median age was 35 years, 63% reported non-Hispanic White race, and 51% were living with HIV (PWH) (**Table 2.1**). Among those living without HIV (PNWH), 58% reported using HIV PrEP.

Incidence of Antibiotic Initiation

During follow-up, 69% (n=96) of participants received at least one antibiotic, with 16% initiating one regimen, 33% initiating 2-4, and 20% initiating five or more (**Figure 2.1**). Fifty percent, 30%, and 19% of all participants reported at least one antibiotic for the treatment of STIs, presumptive treatment as an STI contact, or for other health conditions, respectively.

In primary analyses, there were 348 unique events of antibiotic initiation, resulting in an overall IR=264.5 events per 100 PY (**Table 2.2; Figure 2.2**). STI treatment yielded the highest rate for antibiotic initiation (153.5 per 100 PY), followed by epidemiologic treatment for an STI contact (68.4 per 100 PY) and other health conditions (42.6 per 100 PY). Azithromycin (97.6 per 100 PY) and ceftriaxone (72.6 per 100 PY) were the most initiated antibiotics (**Figure 2.2**). In secondary analyses (**Supplemental Tables A.2.A – A.2.J**), unadjusted incidence of any antibiotic initiation did not differ in PWH versus PNWH (269.8 vs. 259.1 per 100 PY; p-value=0.71); however, initiation was significantly higher among PrEP versus non-PrEP users (316.6 vs. 179.8 per 100 PY; p-value<0.001).

Duration of Antibiotic Use

Study participants reported using antibiotics during 1,696 total days of follow-up, resulting in an overall IR=1289.1 days (3.53 years) of antibiotic use per 100 PY (**Table 2.2**). STI treatment was reported among 50% of all study participants, yet only accounted for 462 days of total use. Overall, doxycycline (985 days; IR=769.3 days per 100 PY) and azithromycin (146 days; IR=113.1 days per 100 PY) were the most frequently used antibiotics in the cohort (**Table 2.2**). Lower-bound estimates, including those for any antibiotic (1597 days; IR=1213.9 days per 100 PY) or for other health conditions (848 days; IR=644.6 days per 100 PY) were similar to upper-bound estimates. Despite only 19% of individuals reporting antibiotic treatment for other health conditions not specific to STIs, treatment for other conditions contributed most to overall duration of use, accounting for 56% of all days of antibiotic use (947 days; IR=719.8 days per 100 PY). These conditions included acne and chronic skin infections (511 days), respiratory or ear/nose/throat infections (202 days), and acute skin and soft tissue infections (126 days),

among others (**Supplemental Table A.3**). Importantly, two individuals contributed over 500 days of antibiotic use for the treatment of various skin conditions. If these contributions were removed, the IRs for overall use (890.1), treatment of other health conditions (320.8), and doxycycline (437.3) would decrease substantially (**Table 2.2**). Results of secondary analyses are presented in **Supplemental Tables A.2.A – A.2.J**.

Factors Associated with Antibiotic Initiation

In univariate models, HIV status and PrEP use, age, race/ethnicity, and history of bacterial STI <12 months prior to enrollment were associated with antibiotic initiation and included in the multivariate model (**Table 2.3**). In the final multivariate model, age 25-39 years (IRR=1.54; 95% CI: 1.02, 2.32) and a history of bacterial STIs <12 months prior to enrollment (IRR=1.81; 95% CI: 1.12, 2.93) were significantly associated with higher incidence of antibiotic initiation. PWH, PrEP use among PNWH, and non-Hispanic Black/African American race were associated with antibiotic initiation; however, these associations were not significant at $\alpha \leq 0.05$. In secondary analysis assessing antibiotic initiation for STI treatment only, age, race/ethnicity, and history of bacterial STI <12 months prior to enrollment were associated with antibiotic initiation and included in the multivariate model (**Supplemental Table A.4**). In the final model, only a history of bacterial STIs was significantly associated with higher incidence of antibiotic initiation for STI treatment (IRR=2.18; 95% CI: 1.16, 4.11).

2.5 DISCUSSION

To our knowledge, this is the first study to characterize longitudinal antibiotic consumption among a cohort of MSM who would likely be eligible to receive doxy-PEP. We found that initiation of antibiotics during the 49 weeks of follow-up was very high, with 69% of 140 participants taking antibiotics at least once, resulting in 348 unique events of antibiotic initiation and 1,696 days of use. One in five participants initiated 5 or more regimens for any reason during follow-up and half of participants used antibiotics specifically for STI treatment.

The frequency of antibiotic use we observed was higher than results from other published studies. In a Vietnam-based study, 38% of 207 MSM reported using antibiotics in the previous 6 months, including 16% reporting use in the previous month.²³ In Peru, 41% of 386 MSM and transgender women presenting at sexual health clinics reported using any antibiotics in the last 3 months.²⁴ Even among MSM with diagnosed genital, anorectal or pharyngeal GC in Belgium, only 43% of 42 participants reported any antibiotic use in the previous 12 months.²⁵ There are several potential reasons for higher levels of use observed in our cohort. First, study populations likely had differential access to antibiotics and other healthcare services, given substantial variability by geography. ExGen participants had access to frequent STI testing at urogenital and extragenital sites, which would drive increased diagnoses and subsequent treatments. Second, ExGen was designed to enroll participants who were likely to acquire bacterial STIs. Because many of the eligibility criteria are associated with antibiotic consumption, our cohort may have been more predisposed to antibiotic use than the general MSM population. However, this is also reflective of the population recommended to receive doxy-PEP by the CDC.⁸ Third, there is lack of consistency in how antibiotic consumption is defined across studies. Most studies did not specify the reasons for use, which may have resulted in underreporting of antibiotics used to treat health conditions other than STIs.

An important finding in our study was the substantial contributions of other health conditions to the overall number of days of antibiotics used (947 of 1,696 total days). Study participants cited treatment for various respiratory infections, including strep throat and pneumonia, and acute or chronic skin infections. Doxycycline use in our cohort was high (985 days), largely driven by the treatment of acne and other chronic skin conditions (406 days) among two individuals. Long-term systemic use of doxycycline for acne is not clinically recommended, suggesting that this pattern of use may have limited implications at the population level.²⁶ However, MSM, including PWH, have increased risk for several health conditions, including pneumococcal disease, *Staphylococcus aureus*, shigellosis, and giardiasis, and would be more

likely to use antibiotics for the treatment of these conditions.²⁷⁻³⁰ Therefore, a comprehensive approach to characterizing risk of antibiotic resistance among MSM should include considerations beyond treatment for common STIs.

Although determinants of antibiotic use have been well-described among the general population, little is known about the factors associated with increased antibiotic use among MSM.³¹ In multivariate analyses, we found that MSM with a history of bacterial STIs within the previous 12 months and those aged 25-39 years had high rates of antibiotic initiation. Our findings provide important context for informing evidence-based conversations between clinicians and patients, given guidelines on doxy-PEP published by the US CDC in June 2024 which recommend clinician-led counseling on the potential benefits, harms, and risk of antibiotic resistance.⁸

An important consideration surrounding doxy-PEP implementation is the potential for subsequent increases in antibiotic consumption among MSM. The magnitude of this change is likely dependent on several factors, including underlying frequency and reasons for use. Although ~10% of the cohort initiated 5 or more regimens for STI treatment during follow-up, ~50% and ~10% of the study population initiated either 0 or 1 regimen for STI treatment, respectively. As many treatment regimens for STIs use single-dose approaches, doxy-PEP implementation in these individuals with low underlying antibiotic use could lead to increased antibiotic consumption among the broader MSM population. A recent modeling study found that, to balance doxy-PEP consumption with averted doxycycline doses for CT treatment in the U.S., doxy-PEP would need to be restricted to individuals with an incidence of 7.8 infections per person-year.³² One individual in the ExGen cohort met this criterion. Future studies assessing doxy-PEP effectiveness and uptake among MSM should evaluate how doxy-PEP use increases or decreases overall antibiotic consumption and whether any potential increases in antibiotic resistance are primarily influenced by a larger population of individuals using antibiotics or by a smaller group of individuals who use antibiotics frequently.

There are notable strengths to our study. The ExGen Study was a prospective cohort study with 49 weeks of follow-up per participant, allowing us to observe longitudinal antibiotic use behaviors. Additionally, ExGen utilized medical record-based data to supplement and validate self-reported use, ensuring nearly all antibiotic use among study participants was captured.

Our study also has limitations. First, we relied on self-reported antibiotic use, though patient medical records were used to validate and improve accuracy of self-reported measures, when possible. Second, several factors, including methamphetamine use and HIV status, are stigmatized and could be underreported. We attempted to minimize bias by using consistent, inclusive language in weekly surveys that reflected the identities and behaviors of our participants. Third, ExGen enrolled individuals who accessed sexual health services and were at increased risk for acquiring extragenital STIs. Findings from this analysis may not be generalizable to the broader MSM population in the U.S. or other settings. However, this population would be eligible for doxy-PEP and is therefore an important subgroup in which to assess antibiotic use.

In conclusion, most antibiotic regimens were initiated for STI-related conditions, whereas the largest proportion of days of antibiotic use were due to treatment of non-STI conditions. Our analysis provides a necessary foundation for assessing how doxy-PEP and changing standards of STI screening and treatment might affect antibiotic consumption among a target population for doxy-PEP. Future work is needed to understand antibiotic use among broader populations of MSM and surveillance of microorganisms potentially impacted by shifting patterns of STI-related antibiotic use, such as *Staphylococcus aureus*, should also be considered.

2.6 ACKNOWLEDGEMENTS

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2.7 TABLES & FIGURES

Table 2.1. Baseline Demographic & Clinical Characteristics of Study Participants in the ExGen Study, 2016-2018 (N = 140)

Characteristics	Study Participants (N = 140)	Study Participants with ≥1 Antibiotic Regimen Initiation (N = 96)
Age, median (IQR)	35 (28–46)	33 (28.0–44)
Race/ethnicity, n (%)		
Non-Hispanic White/Caucasian	88 (62.9%)	62 (64.6%)
Non-Hispanic Black/African American	15 (10.7%)	9 (9.4%)
Non-Hispanic Asian/Pacific Islander	8 (5.7%)	6 (6.2%)
Hispanic/Latinx	25 (17.9%)	18 (18.8%)
Another Race/Ethnicity	3 (2.1%)	0 (0.0%)
Unknown	1 (0.7%)	1 (1.0%)
Income, n (%)		
<\$14,999	54 (38.6%)	32 (33.3%)
>\$15,000–\$29,999	26 (18.6%)	18 (18.8%)
>\$30,000–\$49,999	28 (20.0%)	22 (22.9%)
>\$50,000–\$99,999	25 (17.9%)	19 (19.8%)
>\$100,000	7 (5.0%)	5 (5.2%)
Educational attainment, n (%)		
Grade school	3 (2.1%)	2 (2.1%)
High school	30 (21.4%)	21 (21.9%)
Some college/associate or technical degree	50 (35.7%)	32 (33.3%)
Bachelor's degree/some graduate school	39 (27.9%)	27 (28.1%)
Graduate degree	18 (12.9%)	14 (14.6%)
HIV Status and PrEP Use, n (%)		
PWH	71 (50.7%)	49 (51.0%)
PNWH, on PrEP	40 (28.6%)	30 (31.3%)
PNWH, not on PrEP	29 (20.7%)	17 (17.7%)
Reported chronic medical condition, n (%)	86 (61.4%)	58 (60.4%)
Criteria for study entry		
Bacterial STI diagnosis, <12 months	104 (74.3%)	77 (80.2%)
Methamphetamine or popper use, <12 months	35 (25%)	21 (21.9%)
Number of sexual partners ^a	117 (83.6%)	86 (89.6%)

^a Reported as at least 2 sexual partners in the past 2 months or at least 5 sex partners in the past 12 months.

Abbreviations: IQR, interquartile range; PWH, people living with HIV; PNWH, people not living with HIV; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection

Table 2.2. Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants in the ExGen Study, 2016-2018 (N = 140)

Outcome	Cumulative Use ^b N (%)	Antibiotic Initiation		Days of Antibiotic Use ^a	
		# of Events	Incidence Rate ^c (95% CI)	# of Days	Incidence Rate ^{c,d} (95% CI)
Any Antibiotic Initiation	96 (69)	348	264.5 (237.5, 293.8)	1696	1289.1 (1228.5, 1352.0)
Reason for Antibiotic Initiation					
STI Treatment	70 (50)	202	153.5 (133.1, 176.2)	462	351.2 (319.9, 384.7)
Epidemiologic Treatment for STI Contact	42 (30)	90	68.4 (55.0, 84.1)	287	218.1 (193.6, 244.9)
Other Health Condition Treatment	26 (19)	56	42.6 (32.2, 55.3)	947	719.8 (674.7, 767.2)
Antibiotic-specific Initiation					
Doxycycline	44 (31)	66	51.5 (39.9, 65.6)	985	769.3 (722.0, 818.9)
Azithromycin	71 (51)	126	97.6 (81.3, 116.2)	146	113.1 (95.5, 133.0)
Ceftriaxone	63 (45)	95	72.6 (58.8, 88.8)	95	72.6 (58.8, 88.8)
Benzathine-penicillin	14 (10)	17	13.0 (7.5, 20.7)	17	13.0 (7.5, 20.7)

^a Reported days of antibiotic use for upper bound only; lower bound estimates provided in Supplemental Tables

^b Cumulative number of study participants reporting antibiotic use, among 140 total participants

^c Incidence per 100 person-years at risk

^d Two study participants contributed over 500 days of antibiotic use (doxycycline and/or minocycline) for the treatment of acne and other chronic skin conditions. If these contributions were removed, the following "Days of Antibiotic Use" estimates would change: *Any Antibiotic Initiation*, 1171 days, IR: 890.1 (839.8, 942.6); *Other Health Condition Treatment*, 422 days, IR: 320.8 (290.9, 352.9); *Doxycycline*, 565 days, IR: 437.3 (402.0, 474.9).

Abbreviations: CI, confidence interval; STI, sexually transmitted infection

Table 2.3. Factors Associated with Antibiotic Initiation in the ExGen Study, 2016-2018

Predictors	Univariate Analysis ^a		Multivariate Analysis ^a	
	IRR (95% CI)	p-value	IRR (95% CI)	p-value
HIV/PrEP Status				
PNWH, not on PrEP	1.00	--	1.00	--
PNWH, on PrEP	1.76 (1.00, 3.09)	0.05	1.65 (0.95, 2.87)	0.08
PWH	1.50 (0.88, 2.57)	0.14	1.68 (0.98, 2.88)	0.06
Age Group				
40+ years	1.00	--	1.00	--
25 – 39 years	1.56 (1.04, 2.35)	0.03	1.54 (1.02, 2.32)	0.04
18 – 24 years	1.09 (0.56, 2.12)	0.80	1.24 (0.62, 2.49)	0.54
History of chronic medical conditions ^b	1.12 (0.77, 1.64)	0.56	--	--
Reported methamphetamine use ^c	0.88 (0.58, 1.33)	0.53	--	--
Race/ethnicity				
Non-Hispanic White/Caucasian	1.00	--	1.00	--
Hispanic/Latinx	0.92 (0.58, 1.46)	0.71	0.83 (0.53, 1.32)	0.43
Non-Hispanic Black/African American	0.61 (0.35, 1.05)	0.08	0.63 (0.36, 1.12)	0.12
Another Race/Ethnicity	0.55 (0.27, 1.11)	0.09	0.63 (0.32, 1.25)	0.19
History of bacterial STI diagnosis, <12 months prior to enrollment ^d	1.84 (1.15, 2.96)	0.01	1.81 (1.12, 2.93)	0.02

^a Implemented negative binomial regression with generalized estimating equations

^b Compared to no history of chronic medical conditions

^c Compared to no reported methamphetamine use

^d Compared to no history of bacterial STI diagnosis, <12 months prior to enrollment

Abbreviations: IRR, incidence rate ratio; CI, confidence interval; PWH, people living with HIV; PNWH, people not living with HIV;

PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection



Figure 2.1: Distribution of antibiotic initiation events during follow-up in the ExGen Study, stratified by: 1A.) any antibiotic initiation, 1B.) treatment reason, or 1C.) antibiotic type.

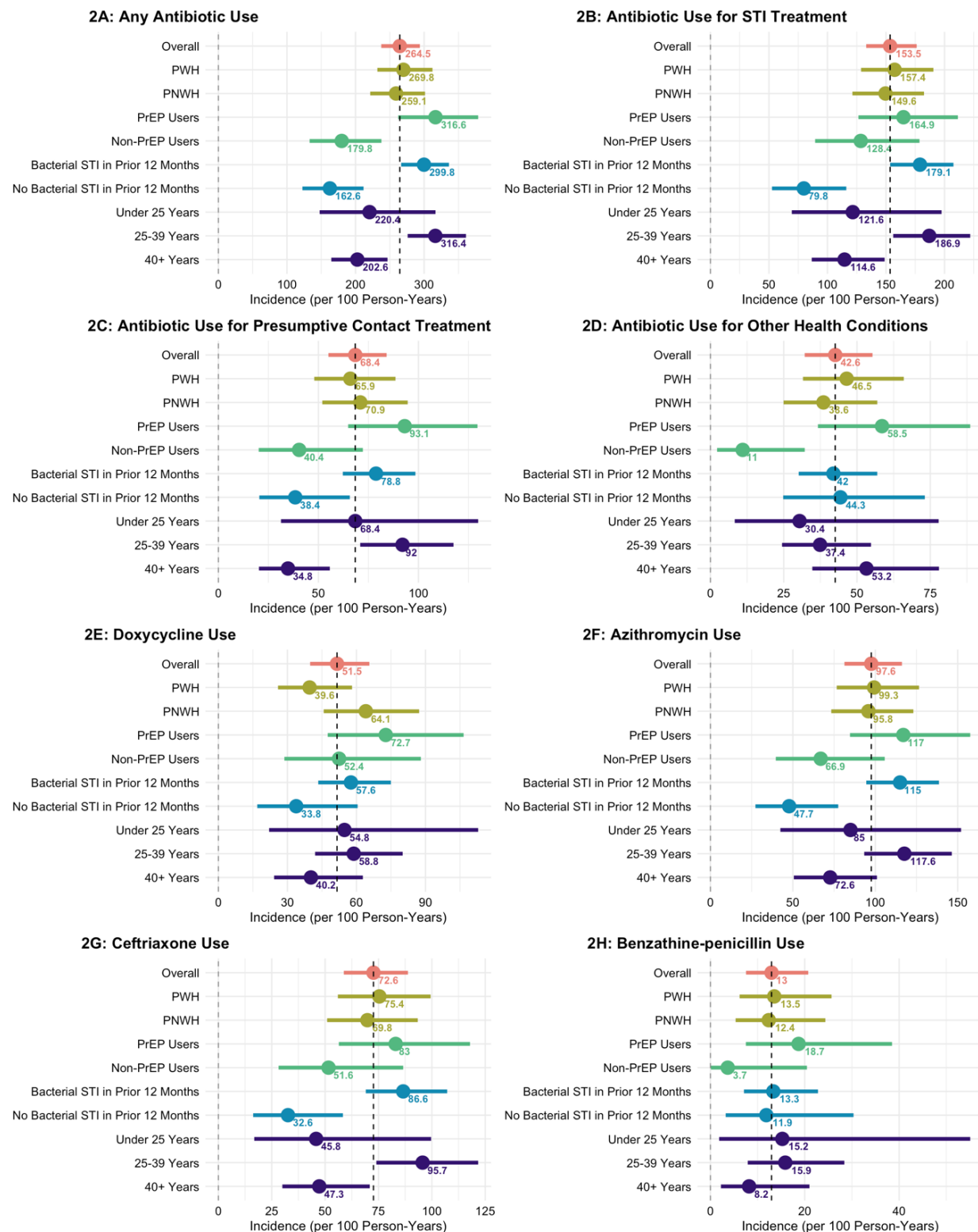


Figure 2.2: Incidence rates of antibiotic initiation overall, by treatment reason, and by antibiotic type in the ExGen Cohort, stratified by HIV status and PrEP use at enrollment, reported STI

diagnosis within 12 months prior to enrollment, and age (<25, 25-39, 40+ years). Abbreviations: HIV, human immunodeficiency virus; PWH, people living with HIV; PNWH, people not living with HIV; PrEP, HIV pre-exposure prophylaxis; STI, sexually transmitted infection.

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Chapter 3

The Potential Impacts of Chlamydia Vaccination on Disease Burden in the United States: A Model-Based Analysis from 2025 to 2075

3.1 ABSTRACT

Background: *Chlamydia trachomatis* (CT) is the most commonly reported sexually transmitted infection in the United States (U.S.). Despite effective treatment, CT can cause severe sequelae if left untreated. Given ongoing transmission and limited prior modeling efforts, mathematical models are critical to evaluate the potential impact of future CT vaccines.

Methods: We developed a deterministic, age- and sex-structured compartmental model of heterosexual CT transmission among U.S. individuals aged 15 to 64 years from 2000 to 2075. The model was calibrated to adjusted annual CT case counts and validated against national prevalence data. We simulated routine vaccination of 15-year-old girls (Scenario A) or sex-neutral vaccination (Scenario B) beginning in 2025, and catch-up campaigns for unvaccinated females aged 15 to 24 years in 2035 (Scenarios C and D), varying vaccine efficacy, duration of protection, and coverage.

Results: Under base-case assumptions (70% efficacy, 10-year protection, 50% coverage), girls-only vaccination reduced cumulative CT infections by 37.4% by 2075, while sex-neutral vaccination reduced infections by 52.3%. In the absence of vaccination, CT incidence increased from 16.9 per 1,000 person-years (PYs) in 2025 to 18.7 by 2075. With girls-only and sex-neutral routine vaccination, incidence declined to 4.0 and 0.4 per 1,000 PYs by 2075, respectively. A single catch-up campaign among unvaccinated females aged 15 to 24 years in 2035 yielded modest additional benefits to girls-only or sex-neutral routine vaccination. Vaccination efficiency, measured as infections averted per 1,000 doses, was highest with longer protection and higher efficacy.

Conclusions: Even partially efficacious vaccines could substantially reduce CT burden when paired with ongoing prevention strategies. Sex-neutral vaccination offers the greatest population-level impact, but girls-only vaccination may be more efficient under resource constraints. These results can guide vaccine development and inform implementation planning.

3.2 INTRODUCTION

Chlamydia trachomatis (CT) remains a significant public health concern and the most common notifiable sexually transmitted infection (STI) in the United States (U.S.), with approximately 1.6 million cases reported in 2023.¹ Although infections can be treated with first-line antibiotics, CT can lead to significant sequelae, including epididymitis, pelvic inflammatory disease (PID), tubal factor infertility (TFI), ectopic pregnancy (EP), and chronic pelvic pain (CPP) if left untreated.^{2,3} The persistence of CT in the U.S. is multifactorial, driven by social stigmatization, fragmented and inequitable access to healthcare services, and high rates of asymptomatic presentation, contributing to missed treatment opportunities and ongoing transmission to sexual partners.^{1,4-6}

Screening remains the primary prevention strategy for CT in the U.S., with annual testing recommended for sexually active women under 25, at-risk women 25 and older, pregnant individuals, and men who have sex with men (MSM) at sites of exposure.⁷ Routine screening is not currently recommended for men who have sex with women (MSW) due to limited evidence of effectiveness in low-risk populations. Despite its importance, coverage remains suboptimal.⁸ In 2022, only ~53% of women aged 16 to 24 years enrolled in Medicaid or commercial insurance were screened for CT.⁹ Emerging strategies, such as doxycycline post-exposure prophylaxis (doxy-PEP), may serve as complements to current screen-and-treat approaches.¹⁰ Clinical trials among MSM and transgender women have demonstrated doxy-PEP's efficacy in preventing bacterial STIs when taken within 72 hours of sexual acts.¹¹⁻¹³ However, concerns of increasing antimicrobial resistance in *Neisseria gonorrhoeae*, a common co-infection, and the

absence of supportive clinical trial data in heterosexual populations limit broader implementation.^{14,15} Therefore, population-level reductions in CT incidence will likely require an efficacious vaccine.

Although clinical trial data on CT vaccine candidates remain limited, early results are encouraging. A Phase 1, double-blind, randomized, placebo-controlled trial in the United Kingdom among healthy women aged 19 to 45 years found that a novel recombinant protein subunit vaccine (CTH522), administered in a prime-boost schedule, was safe, well-tolerated, and immunogenic.¹⁶ Parallel efforts to develop an oral CT vaccine are underway, following promising preclinical studies in mice.^{17,18} In the absence of late-phase clinical trial data, and amid growing concerns about reductions in vaccine research funding in the U.S., mathematical modeling offers a critical tool to assess what the potential population-level impact of vaccine candidates might be if they go on to be licensed.¹⁹ Prior modeling studies suggest that even a partially efficacious vaccine could lead to substantial reductions in CT burden shortly after introduction.²⁰⁻²³ For example, Makhoul et al. (2024) projected that a vaccine with 50% efficacy, introduced in 2025 and reaching 80% coverage among individuals aged 15 to 49 years by 2035, could reduce CT prevalence, incidence, and annual infections within a decade by 36.3%, 38.8%, and 35.8%, respectively.²⁰ To build on these findings, models must utilize knowledge on current biological and social dynamics of CT transmission, incorporate parameters on subsequent sequelae, and include cost data to enable robust cost-effectiveness analyses across the broader U.S. population.

To address limitations of prior models, Chapter 3 presents a compartmental model of CT transmission in the U.S. from 2000 to 2075, used to estimate the impact of vaccination on disease burden under varying implementation strategies and vaccine characteristics, including efficacy and duration of vaccine-conferred immunity. These analyses aim to quantify the potential benefits of CT vaccination, identify optimal strategies for at-risk populations, and inform targets for vaccine design. In Chapter 4, the model is extended to evaluate cost-effectiveness of

vaccination approaches using both cost and quality-adjusted life years (QALYs) data linked to model output.

3.3 METHODS

3.3.a. Mathematical Model

An age- and sex-structured deterministic, compartmental mathematical model using ordinary differential equations (ODEs) was constructed to simulate transmission of CT among individuals aged 15 to 64 years in the U.S. from 2000 to 2075 and assess the impacts of CT vaccination strategies on disease burden from 2025 to 2075 (**Figure 3.1**). The model was structured using a contemporary understanding of disease transmission and natural history, leveraging other published models of sexually transmitted infections.²⁰⁻²⁵

The simulated population was divided into six groups by biological sex at birth and age: males and females aged 15–24, 25–39, and 40–64 years. Age groups were selected *a priori* to reflect the higher burden of CT among individuals aged 15–24 years compared to those 25 years and older.^{26,27} Additional stratification for the 25–39 and 40–64 age groups was included to reflect the age-related decline in acquisition risk, influenced by a complex interplay of decreasing clinical and behavioral risk factors, as well as the potential protective effects of long-lasting partial immunity to reinfection.^{24,28} Partial assortative mixing by age was assumed as individuals preferred to form sexual partnerships within the same age group.^{29,30} Our model does not explicitly account for CT transmission between individuals of the same sex, to focus on the substantial burden of CT among cis-gender, heterosexual women, who subsequently experience the most severe sequelae following infection.^{27,31} Availability of robust, nationally representative data on CT incidence and prevalence among MSM is limited, and including both heterosexual and non-heterosexual mixing would have introduced additional structural complexity and uncertainty in the absence of necessary sexual behavior data. Additionally, a meta-analysis by Bennett et al. (2024) estimated that MSM account for only 3.4% to 4.9% of the

total U.S. male population, representing a relatively small share of sexual partnerships in the general population.³²

The simulated population was further stratified by vaccination status and disease stage: susceptible (S), exposed non-infectious (E), infectious symptomatic infection (I_s), infectious asymptomatic infection (I_A), sequelae-experiencing (Q), or infection-conferred immunity (R). Sequelae were defined as epididymitis for males or PID for females. Infection-conferred immunity occurred among individuals who naturally cleared their infection without treatment. Immunity was assumed to be short in duration and individuals returned to the susceptible population once immunity waned. The force of infection describing the rate at which susceptible individuals acquired CT infection was dependent on the transmission probability per sexual partnership, the annual number of sexual partners, sexual mixing behaviors, and the prevalence of infection among sexual partners. Differential equations, including the force of infection, are provided in Appendix B.

3.3.b. Data Sources & Parameterization

Demographic Data:

Age- and sex-specific demographics from 2000 to 2075 were based on 2024 Revision of World Population Prospects, provided by the Population Division of the Department of Economic and Social Affairs of the United Nations.³³ Rates for model entry, aging, background mortality, and migration were estimated to fit United Nations data by sex and year (**Figure 3.2**).

CT Surveillance Data:

Annual reported age- and sex-specific CT cases between 2000 to 2022 are publicly available through the U.S. Centers for Disease Control and Prevention's (CDC) National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) AtlasPlus tool.³⁴ Reported cases are impacted by several factors, including changes in treatment-seeking behaviors, screening coverage, diagnostic misclassification, and reporting practices, in addition to limitations in the complete capture of asymptomatic infections.^{35,36} Consequently, CT cases in

AtlasPlus underestimate the true number of incident CT infections in a given year. A study by Learner et al. (2020) quantified this underestimation among U.S. women aged 15–24 years from 2000 to 2017.³⁵ They found that accounting for incomplete screening, imperfect diagnostic tests, and under-reporting led to substantially higher estimates of CT burden in young women across the study period when compared to reported estimates. As biases in these factors have diminished over time, the gap between reported and adjusted CT cases has narrowed since 2000.

To use AtlasPlus data for model calibration, we expanded the analytical approach used in Learner et al. (2020) to estimate adjusted annual CT case counts by sex, age group, and year, accounting for parameters including imperfect reporting, diagnostic test misclassification, imperfect screening coverage, reason for CT testing, and uncaptured asymptomatic infections among populations unlikely to receive annual screen-and-treat services (i.e., men who have sex with women).³⁵ Imperfect screening coverage refers to suboptimal uptake of recommended annual screening among eligible populations. Within each year between 2000 to 2022, 200 random draws from triangular distributions were taken to define parameter inputs. Distributions were determined through a combination of assumptions from Learner et al. (2020) and other published sources.^{35,37,38} Using the values in each individual draw, adjusted number of cases were estimated for each year, stratified by the six demographic groups defined in the model (males 15-24 years, males 25-39 years, males 40-64 years, females 15-24 years, females 25-39 years, and females 40-64 years). The median adjusted case count by demographic group and year was estimated across each of the 200 draws and corresponding 95% confidence intervals were calculated. A description of the analytic approach, details on parameter selection, methodological limitations, and results are provided in **Appendix B.3**.

Model Parameters:

Model parameters, including those for CT natural history, sexual behaviors, and treatment, were collected through an assessment of peer-reviewed literature and publicly

available data sources. When significant parameter uncertainty existed, arising from inconsistencies in the literature or lack of empirical data (e.g., CT vaccine efficacy, duration of vaccine-induced immunity), parameter ranges were informed by existing evidence and reference values from analogous STI vaccines, including the human papillomavirus vaccine. Previous mathematical models of CT transmission and other STIs were reviewed for consistency and to update parameters to reflect contemporary evidence. Fixed model parameters and sources are outlined in **Supplemental Table B.1** in **Appendix B**.

3.3.c. Model Calibration & Uncertainty Assessment

To perform model calibration, median adjusted case counts by demographic group and year were used. Although annual CT counts were available from 2000 to 2022, only data from 2013 to 2019 were included, due to uncertainty in early reporting of CT as a notifiable condition in the 2000s, as highlighted by Learner et al. (2020), and the widescale impacts of COVID-19 on disease reporting from 2020 onward.^{35,39} Model parameters subject to significant uncertainty were identified for model calibration and a plausible lower and upper bound were defined based on literature, prior models, and expert input (**Supplemental Table B.2**). The best fitting parameter set was identified by minimizing the sum of squared errors (SSEs) between simulated and observed data for the six demographic groups from 2013-2019. It was identified through an optimization routine using the Levenberg-Marquardt algorithm, a gradient-based method for nonlinear least squares optimization that combines features of both gradient descent and Gauss-Newton methods, which was run for 1000 steps to ensure convergence.⁴⁰ Weighting was applied to prioritize better model fit for younger age groups and females, reflecting the higher CT burden in these populations.^{27,31} The SSE from the optimized parameter set served as a benchmark for evaluating fit in subsequent model runs.

Parameter uncertainty was incorporated into model calibration by generating 2,500 parameter sets uniformly sampled from a narrower sampling distribution informed by the best fitting parameter set from optimization. The model was run for all 2,500 sets, and the

corresponding SSEs were calculated using the same weighting applied in the optimization. Parameter sets with SSE values falling within a predefined error tolerance level (2.75 times the optimized SSE) were retained. This process yielded a distribution of 100 plausible parameter sets that produced simulated outcomes consistent with observed surveillance data, thereby capturing uncertainty in parameter estimates beyond the single best-fitting set (**Figure 3.3**).

Parameter sets from model calibration and uncertainty analyses were further fitted to sex-specific CT prevalence data from the U.S. CDC's National Health and Nutrition Examination Survey (NHANES), collected biannually between 2009 and 2016.⁴¹ Due to lack of publicly available data for individuals aged 15 to 17 years, which requires additional data requests through the National Center for Health Statistics Research Data Center, only data for those aged 18 to 39 years were included in model validation. The model developed for this analysis includes individuals aged 15 to 17 years, who are at lower risk for CT acquisition compared to adults aged 18 years and older. As a result, model-based estimates of CT prevalence are expected to be lower than those observed in NHANES data that do not include 15 to 17-year-olds. To account for this discrepancy, model validation prioritized comparisons of temporal trends in CT prevalence rather than absolute prevalence estimates from 2009 to 2016.

3.3.d. Referent and Intervention Scenarios

The primary referent scenario applied the calibrated model without vaccination, reflecting the current standard of care in the United States that includes screen-and-treat for asymptomatic infections and test-and-treat for symptomatic infections. The impact of vaccination was evaluated through several intervention scenarios, including:

Scenario Group A: Vaccination of 15-year-old girls entering the simulated population, beginning in 2025.

Scenario Group B: Vaccination of 15-year-old girls and boys entering the simulated population, beginning in 2025.

Within each scenario group, we modeled vaccination coverage increasing linearly to 50% by 2035 and remaining fixed at that level through 2075. We varied vaccine efficacy in reducing the risk of CT acquisition (20% to 90%) and duration of vaccine-conferred immunity (0.5 to 20 years) to assess the potential impact of future vaccines with different characteristics. Additional scenarios with coverage levels of 30% and 70% by 2035 were considered to understand the importance of vaccine uptake for the projected results. Next, we assessed the incremental impact of vaccine catch-up campaigns, by simulating the following scenarios:

Scenario Group C: Scenario Group A @ 50% Coverage + catch-up campaign among unvaccinated females aged 15-24 years in 2035

Scenario Group D: Scenario Group B @ 50% Coverage + catch-up campaign among unvaccinated females aged 15-24 years in 2035

We held routine vaccination coverage constant at 50% by 2035 and assumed that a catch-up campaign in 2035 would reach 5%, 10%, or 15% of unvaccinated females living without symptomatic infection or sequelae. Vaccine efficacy (20% to 90%) and duration of vaccine-conferred immunity (0.5 to 20 years) were varied in the same manner as *Scenario Groups A and B*. All vaccination parameters are outlined in **Supplemental Table B.3** in **Appendix B**.

The effectiveness of all *Scenario Groups* were compared to the referent scenario over a 50-year period from 2025 to 2075. Impact was measured as the cumulative number of CT infections prevented by 2075, the proportional reduction in CT infections prevented by 2075, and the reduction in annual CT incidence rates by 2050 and 2075. Additionally, the number of infections prevented per 1,000 vaccination doses by 2075 was used to estimate the efficiency of each implementation strategy. Estimates are reported as the median and interquartile range, when applicable, across all 100 plausible parameter sets selected in model calibration, with values summarized separately for each combination of vaccine efficacy and duration of protection to account for uncertainty within scenarios. For simplicity, the main text presents results on reductions in CT incidence assuming 10 years of vaccine-conferred immunity and

70% vaccine efficacy (base-case), unless stated otherwise. Results for vaccines with different characteristics can be found in **Appendix B**.

3.4 RESULTS

3.4.a. Model Fitting

The model fit was consistent with trends in adjusted CT incidence from CDC AtlasPlus between 2013 and 2019 across sex- and age-specific strata (**Figure 3.4**).³⁴ The model also captured temporal trends in CT prevalence as reported by NHANES among 18 to 39-year-olds, although data for individuals aged 15 to 17 years were not available at the time of analysis due to removal of public-use data from executive orders (**Figure 3.5**).⁴¹ As expected, our estimates of prevalence were lower than those reported by NHANES, except among women captured in the 2015-2016 cycle. Together, these comparisons suggest that the model adequately reproduced key epidemiologic patterns of CT burden in the United States.

3.4.b. Absolute and Relative Reductions in CT Infections by Scenario

Vaccination of 15-year-old girls (Scenario A) led to substantial reductions in cumulative CT infections between 2025 and 2075, with greater impact observed as vaccine coverage, efficacy, and duration of protection increased (**Figure 3.6, Supplemental Table B.5**). For example, under base-case assumptions, a vaccine reaching 50% coverage averted over 104 million infections among males and females by 2075, a 37.4% reduction compared to no vaccination. However, coverage alone was not a strong predictor of success. A poorly performing vaccine (30% efficacy, 0.5-year protection), even at 70% coverage, averted only ~24 million infections (8.6% reduction). Under the best-case scenario (70% coverage, 20-year protection, 90% efficacy), vaccination prevented nearly 55.5% of cumulative infections.

Expanding to sex-neutral vaccination (Scenario B), which included both 15-year-old boys and girls, resulted in substantially greater impact (**Figure 3.6, Supplemental Table B.6**). Under the same base-case assumptions, sex-neutral routine vaccination averted over 145 million

infections, corresponding to a 52.3% reduction compared to no vaccination. The inclusion of vaccinating boys contributed to an additional 41 million infections averted over the 50-year period, of which roughly ~53% were infections among females. Catch-up vaccinations in 2035 among previously unvaccinated females aged 15 to 24 years (Scenarios C and D) modestly increased the number of infections averted when added to routine vaccination of girls (Scenario A) or both sexes (Scenario B) at 50% coverage (**Figure 3.7; Supplemental Tables B.7/B.8**). Under base-case assumptions, the addition of a 5%, 10%, and 15% catch-up campaign to sex-neutral routine vaccination averted approximately 1.2 million, 2.2 million, and 3.2 million additional infections, respectively, from 2025 to 2075.

3.4.c. Reductions in CT Incidence Rates

In the absence of vaccination, the incidence rate of CT among individuals aged 15 to 64 years was projected to reach 16.9 infections per 1,000 person-years (PYs) in 2025, gradually increasing to 18.5 by 2050 and 18.7 per 1,000 PYs by 2075. Following the introduction of girls-only vaccination (Scenario A), the incidence rate of CT declined steadily to 4.0 infections per 1,000 PYs in 2075, a 78.3% reduction compared to no vaccination (**Figure 3.8, Supplemental Table B.9**). When coverage was increased to 70%, the incidence rate by 2075 would be reduced by 91.9% to 1.5 infections per 1,000 PYs in 2075. Notably, girls-only vaccination at 50% coverage achieved slightly greater reductions in incidence among males than females (80.2% vs. 76.4% by 2075, respectively; **Figure 3.8**). Similar trends were observed across all coverage scenarios.

Following the introduction of sex-neutral vaccination (Scenario B), the incidence rate of CT declined to 0.4 infections per 1,000 PYs in 2075, a 97.8% reduction compared to no vaccination (**Figure 3.9, Supplemental Table B.10**). When coverage was increased to 70%, the incidence rate by 2075 was reduced by 99.7% to 0.1 infections per 1,000 PYs. Sex-neutral vaccination at 50% coverage provided comparable benefits in incidence reductions by 2075 to males and females (98.0% vs 97.5%, respectively; **Figure 3.9**), with greater differences

observed in 2050 (81.7% vs 77.5%, respectively; **Figure 3.9**). Similar trends were observed across all coverage scenarios. In addition to reductions in incidence by 2075, the implementation of a sex-neutral strategy also led to more rapid declines in incidence immediately following vaccine introduction. The addition of catch-up campaigns to either girls-only or sex-neutral routine vaccination provided only marginal reductions in CT incidence by 2050 and 2075 (**Supplemental Tables B.11/B.12**).

3.4.d. Vaccination Efficiency

Infections prevented per 1,000 doses administered served as a proxy measure for vaccination efficiency, quantifying the population-level impact of each vaccine dose. Under the base-case assumptions, girls-only vaccination was more efficient than sex-neutral vaccination, preventing over 2,500 infections per 1,000 doses, versus approximately 2,000 infections per 1,000 doses. This greater efficiency reflects better risk-targeted coverage. Across all vaccination scenarios, vaccine duration and efficacy were the most influential determinants of efficiency. In both Scenario A (female-only vaccination) and Scenario B (sex-neutral vaccination), longer durations of protection and higher efficacy substantially increased the number of infections averted per dose (**Figure 3.10; Supplemental Tables B.13/B.14**). Notably, vaccines with greater than 50% efficacy and longer than 5 years of protection consistently prevented more than one infection per dose across coverage levels. While more intensive interventions such as catch-up vaccination campaigns (**Figure 3.11; Supplemental Tables B.15/B.16**) or higher routine coverage levels reached more individuals and averted more total infections, they yielded lower infections prevented per dose, indicating diminishing marginal returns with broader uptake.

3.5 DISCUSSION

We developed a deterministic compartmental model of CT transmission in the United States to estimate the potential impact of CT vaccination through female-only, sex-neutral, and

added catch-up vaccination strategies on disease burden between 2025 and 2075. Vaccinating adolescent boys in addition to girls provided substantial benefits; however, if vaccine supply is limited, targeting girls alone may represent a more efficient strategy. Under both scenarios, vaccination had a greater relative impact on males, likely because they do not routinely receive screening and thus stood to benefit more from an additional prevention strategy. Catch-up vaccination of older, unvaccinated females offered additional gains, but these were relatively modest compared to the impact of sustained routine vaccination. The limited marginal benefit of catch-up campaigns may reflect the indirect protection already conferred through herd immunity.⁴² While catch-up efforts may still hold value from a cost-effectiveness or equity standpoint, their contribution to overall burden reduction appears secondary to achieving high routine vaccination coverage. Importantly, we only modeled a single catch-up campaign in 2035 with coverage up to 15%, so the benefits of broader coverage, the implementation of multi-year campaigns, and catch-up vaccination among males needs to be further assessed.

Across all modeled scenarios, the duration of vaccine-conferred protection emerged as an influential factor in determining cumulative infections averted. For example, assuming 50% coverage by 2035, a sex-neutral vaccine with 70% efficacy conferring 20 years versus 5 years of protection would avert 55.6% versus 44.9% of CT infection by 2075 when compared to no vaccination, respectively. This highlights the importance of developing vaccines that provide long-lasting immunity, even if attainable efficacy is only moderate.

Our results also suggest that a vaccination with efficacy and duration of protection greater than 50% and 5 years, respectively, are well-positioned to prevent more infections than doses administered, serving as a target for vaccine development. While infections prevented per 1,000 doses is a useful proxy for vaccination efficiency, it does not account for the costs associated with vaccine implementation nor does it consider costs averted from reductions in CT infection and subsequent sequelae. As such, apparent diminishing returns in this metric, particularly at higher coverage levels, do not accurately reflect the cost-effectiveness of

vaccination strategies which are investigated in Chapter 4. Without incorporating cost data and health outcomes like quality-adjusted life years (QALYs), these efficiency estimates should be interpreted with caution and not assumed to reflect economic value.

Our findings align with those of Makhoul et al. (2024), who also found that sex-neutral CT vaccination could significantly reduce population-level disease burden.²⁰ However, some key differences stem from the assumptions used by each model in their main analysis. Makhoul et al. assumed 80% coverage by 2035 among individuals aged 15 to 49 years, 50% efficacy, and 20 years of protection, parameters that reflect a highly optimistic implementation environment. In contrast, our base-case scenario was intentionally more conservative, assuming coverage reaches 50% by 2035 among adolescents aged 15 years, 70% efficacy, and 10 years of protection. This was done to reflect a more realistic set of conditions in the current U.S. landscape, where vaccine uptake, particularly for STI-related vaccines, remains suboptimal due to hesitancy, stigma, and access barriers.^{43,44} Despite our conservative implementation assumptions, we observed more pronounced reductions in CT incidence (e.g., 79.6% reduction by 2050 versus 38.8% by 2035, plateauing to 2050 in Makhoul et al.), likely resulting from our higher efficacy values among other model assumptions.

Vaccination should be viewed as a complementary tool rather than a replacement for existing CT prevention and treatment strategies. Our model assumed that screening, diagnostic testing, and access to care would continue at current levels following vaccine introduction, reflecting a scenario in which vaccination is integrated into existing public health infrastructure. Even with substantial reductions in CT burden through vaccination, routine screening remains essential for identifying ongoing transmission and detecting potential disparities in vaccine impact across subpopulations.⁷ Continued screening can help identify at-risk groups, including MSM, transgender women, and historically marginalized communities, who may benefit from tailored implementation strategies, such as adapted outreach, messaging, and delivery settings, if early declines in CT burden are not equitably distributed. For example, a 2023 systematic

review of influenza, pertussis, tetanus, diphtheria, meningitis and hepatitis vaccination found that tailored, multi-component interventions were often successful at increasing vaccine uptake among ethnic minority populations across diverse geographic settings.⁴⁵ Furthermore, other novel biomedical prevention strategies, such as doxy-PEP, may serve as important tools, particularly for vaccine-hesitant individuals and those not eligible for, or not covered by, vaccination efforts.¹⁰ A multipronged approach that combines vaccination with robust screening programs and emerging prevention strategies will be critical to achieve sustained, equitable reductions in CT transmission.

Our model has important limitations, some resulting from the quality and availability of data necessary to parameterize and calibrate the model. Unlike previous models, we did not explicitly stratify by sexual risk, which may underestimate the impact of vaccination among individuals with higher-risk behaviors, including frequent sexual partner changes.^{20,21} Given the uncertainty in sexual transmission parameters across age, sex, and risk groups, additional stratification may have introduced further complexity without improving accuracy. Instead, our age- and sex-stratified model assumed younger individuals experienced more frequent sexual partner changes, thus serving as a proxy for heterogeneity in sexual risk across the general population and aligning with observed patterns of partner change frequency.⁴⁶⁻⁴⁸

Next, the model focused exclusively on heterosexual, urogenital transmission of CT and did not incorporate extragenital infections at rectal or pharyngeal sites. While extragenital infections occur in heterosexual populations, they are more frequently diagnosed and may play a larger role in CT transmission among MSM.⁴⁹⁻⁵² In Rahman et al. (2023), researchers found urogenital-only screening would have missed 34.5% of CT infections among MSM, compared to 4.4% and 1% among women and MSW, respectively.⁴⁹ While we excluded MSM and non-heterosexual mixing from the model due to limited data on extragenital screening, test performance by anatomical site, and sexual network structure, cases among MSM were still included in our calibration targets from AtlasPlus, which do not differentiate infections by

anatomical site or sexual orientation.³⁴ As a result, while MSM cases are technically captured in the observed case counts, they are not explicitly modeled as contributors to transmission. Given their smaller contribution to total infections, MSM-attributed cases likely have limited influence on model outcomes. Nonetheless, MSM represent a population with a disproportionate burden of CT and would likely benefit from targeted vaccination strategies.¹ Future modeling efforts should explicitly incorporate MSM and account for both urogenital and extragenital transmission pathways to more comprehensively estimate the population-level impact of a CT vaccine. These efforts would be strengthened by additional research on CT natural history, site-specific transmissibility, and clearance rates.

A key limitation of our model is the absence of stratification by race and ethnicity. CT incidence in the United States is known to vary substantially across racial and ethnic groups, with Black individuals, and particularly Black women, experiencing consistently higher rates of infection across all ages.⁵³ By not incorporating race and ethnicity into the model structure, we were unable to assess potential disparities in vaccine impact or quantify how vaccination may reduce inequities in CT burden. Future modeling efforts should seek to include race and ethnicity to more accurately capture heterogeneity in disease transmission and inform equitable vaccination strategies.

Our model offers several notable strengths. To our knowledge, this is the first modeling study of CT vaccination to incorporate both CT annual cases from CDC AtlasPlus and prevalence data from NHANES during model calibration. While prior studies have relied exclusively on CT prevalence, due to known underreporting of cases, we built on the approach by Learner et al. (2020) to adjust reported case counts for several important limitations, including imperfect screening in recommended populations, diagnostic misclassification, and undetected infections arising from asymptomatic disease.³⁵ This dual calibration approach strengthened the model's validity by ensuring alignment with both key measures of disease frequency. Second, we included all individuals aged 15 to 64 years within our simulated

population, capturing the majority of time during which individuals are most at-risk for CT infection. While CT burden is highest in younger populations and generally declines with age, recent CDC AtlasPlus data show notable increases in reported CT cases among adults aged 55 and older.³⁴ By incorporating both younger individuals who benefit directly from vaccination and older individuals who may gain protection through herd effects, the model provides a more comprehensive assessment of population-level vaccination impacts. Third, our analysis explored a range of plausible vaccination strategies, including routine vaccination of adolescents, sex-neutral approaches, and catch-up campaigns, that align with public health planning considerations. We also explored a broad set of vaccine characteristics, such as varying levels of efficacy, duration of protection, and coverage. These parameters were selected to reflect potential attributes of a future CT vaccine candidate as it progresses through clinical trials. Notably, we included scenarios with lower coverage, efficacy, and shorter duration of protection to realistically capture the potential population-level impact of vaccines under less-than-ideal conditions. This approach acknowledges the challenges historically associated with uptake of STI-specific vaccines, as illustrated by HPV vaccination. In 2023, only ~60% of U.S. adolescents aged 13 to 17 years were up to date on HPV vaccination, with substantial variation reported by geography and sex.⁵⁴

Ultimately, the modeled reductions in incidence suggest that even a partially efficacious vaccine could meaningfully advance national efforts to reduce CT burden. However, vaccination should be viewed as a complement, not a replacement, for ongoing screening and treatment programs. Future modeling studies should explore how targeted implementation strategies in other high-risk populations affect disease dynamics and incorporate emerging data on CT transmission and natural history to strengthen model validity. Building on the current findings, Chapter 4 integrates cost and QALY estimates to evaluate the cost-effectiveness of these vaccination strategies.

3.6 FIGURES & TABLES

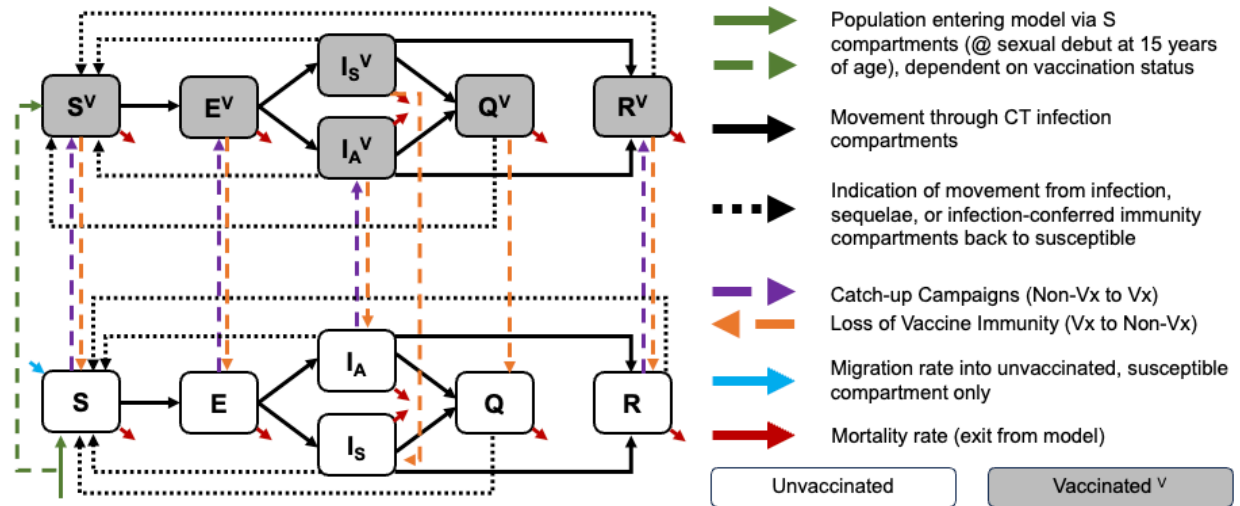


Figure 3.1: Schematic of compartmental model. Compartments represented by the following: susceptible (S), exposed non-infectious (E), infectious symptomatic infection (I_S), infectious asymptomatic infection (I_A), sequelae-experiencing (Q), or infection-conferred immunity (R)

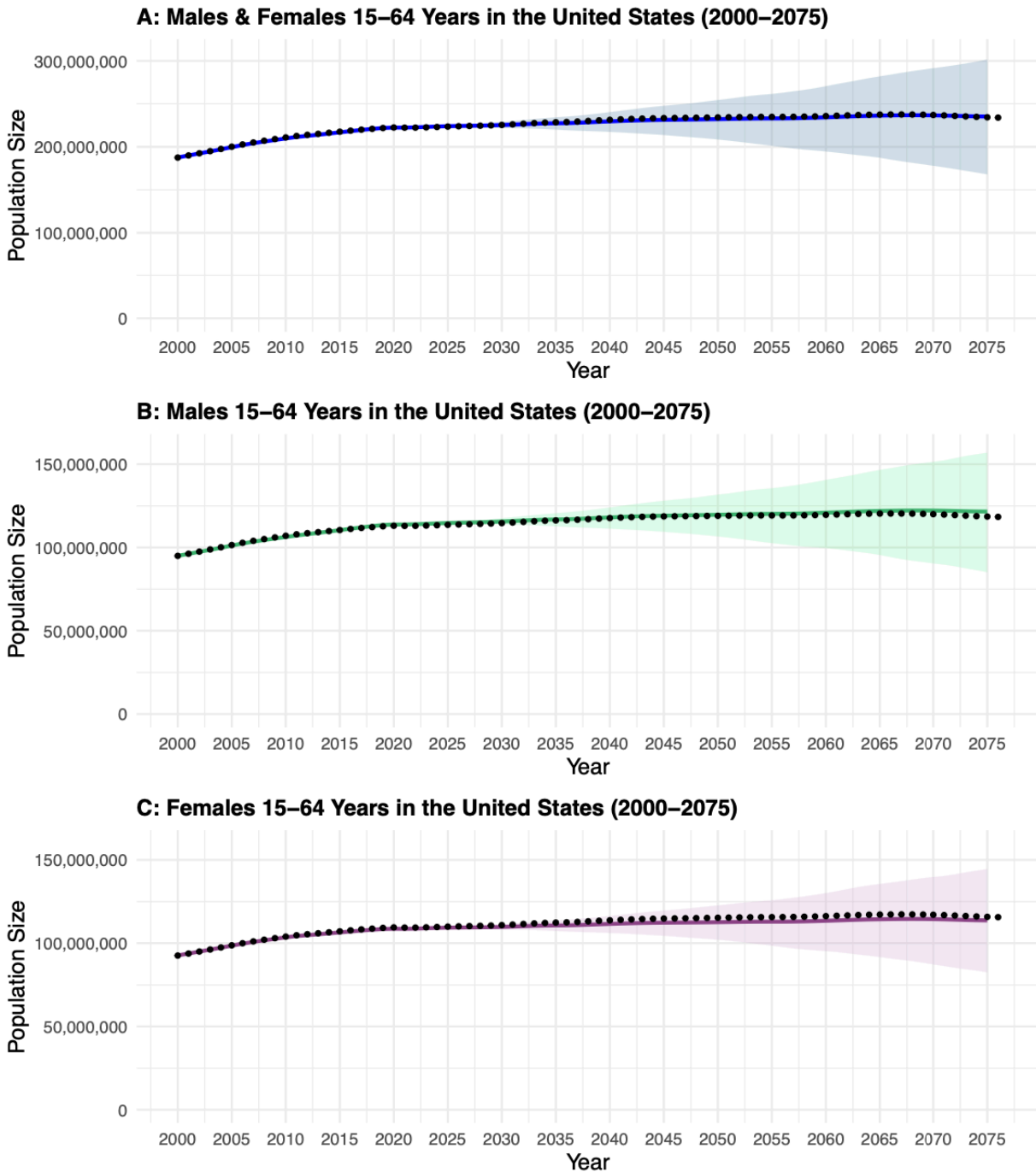


Figure 3.2: Comparison of United Nations population projections of the United States (solid lines; confidence intervals) from 2000 to 2075 versus model-generated annual demographic estimates (dotted lines)

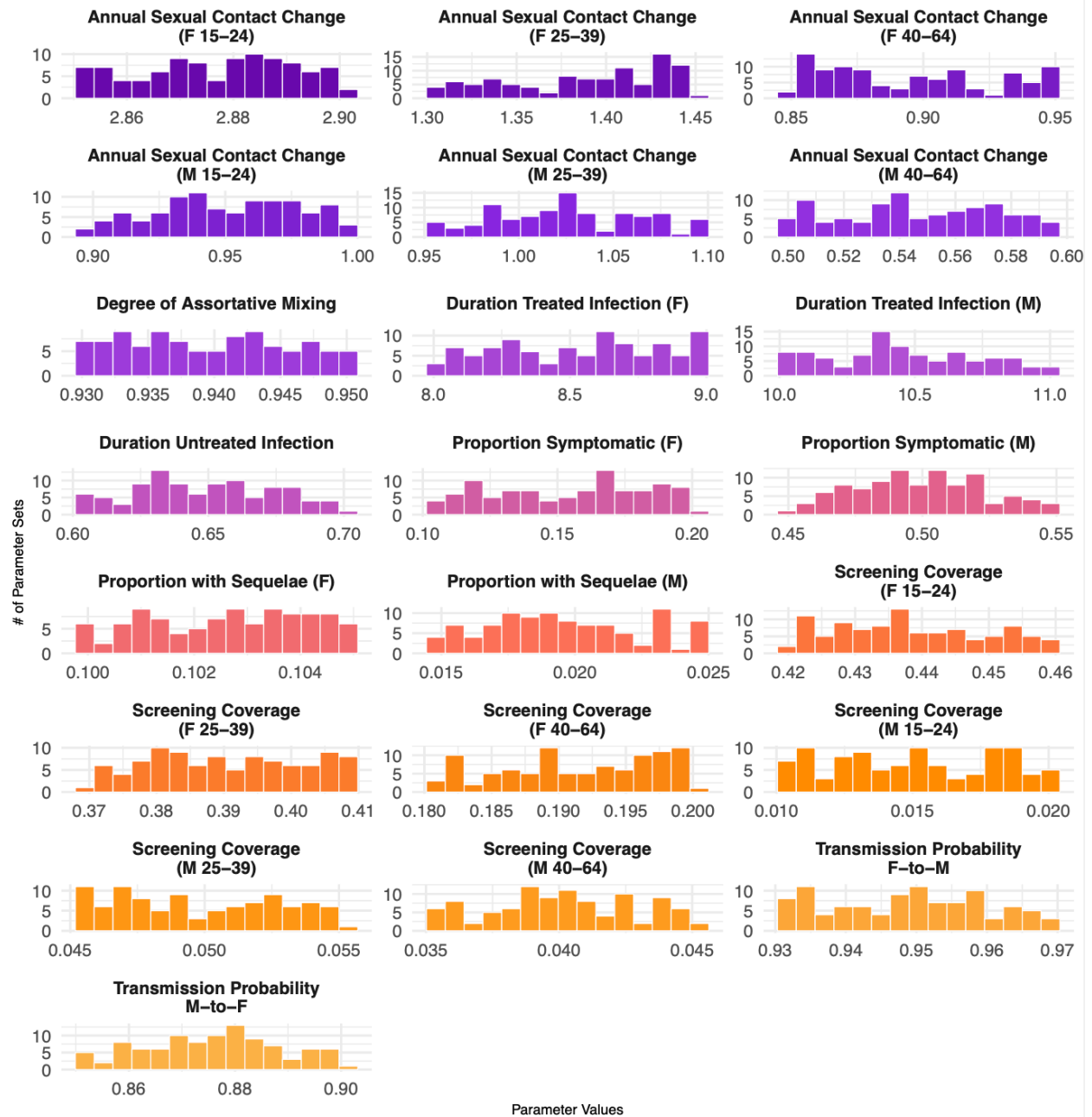


Figure 3.3: Distribution of uncertain parameter values based on parameter sets accepted from model calibration (N = 100)

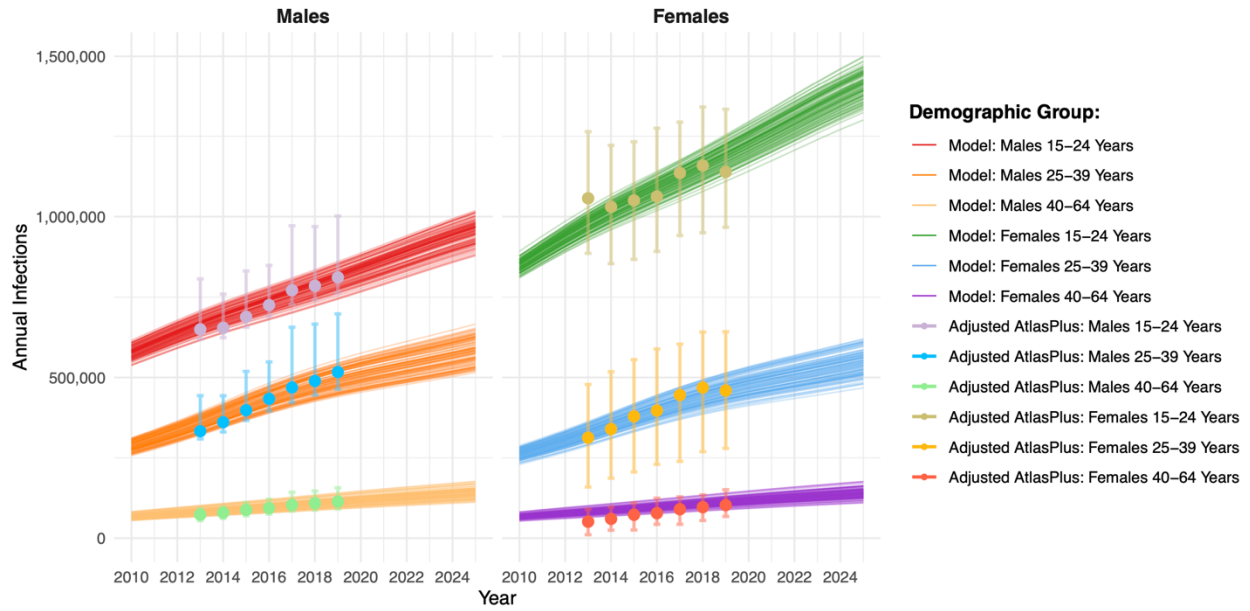


Figure 3.4: Assessment of model fit, comparing annual incident cases of CT from model simulations using 100 parameter sets accepted from model calibration (solid lines) vs. adjusted AtlasPlus incident cases of CT (dots and confidence intervals), by demographic group and year

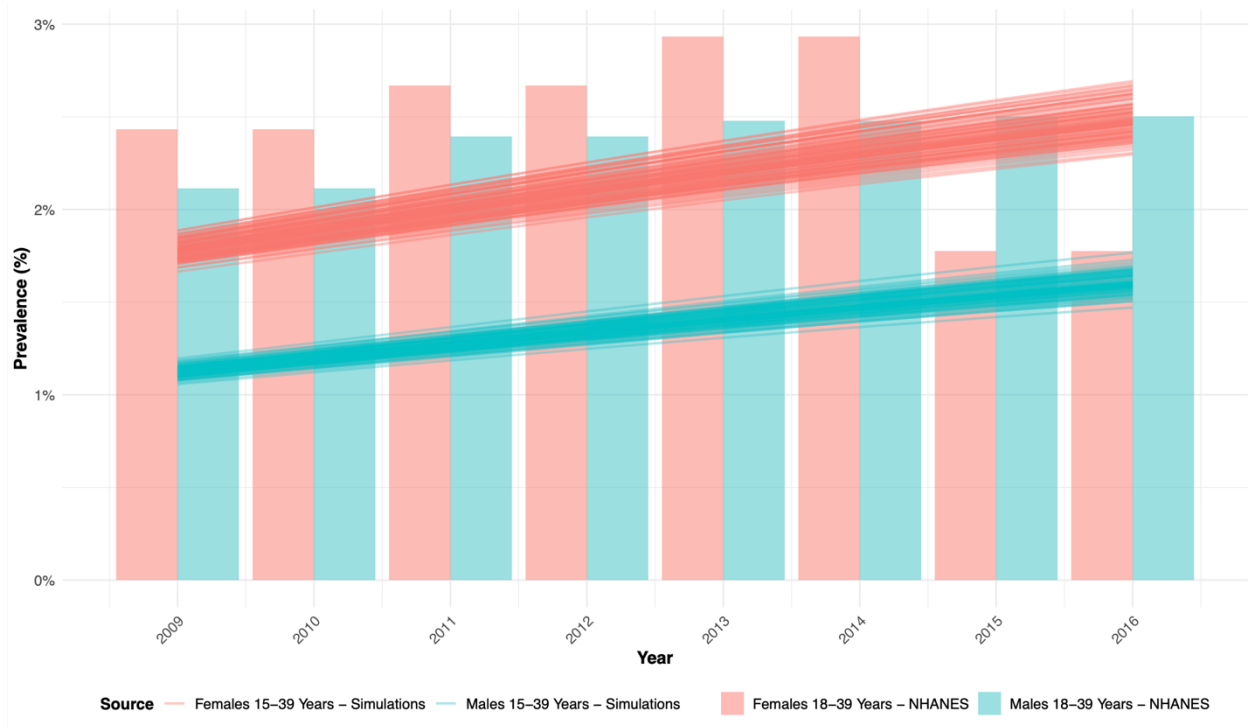


Figure 3.5: Assessment of model fit, comparing annual CT prevalence estimates from model simulations (solid lines; ages 15–39 years) vs. NHANES data (bars; ages 18–39 years), by biological sex and year

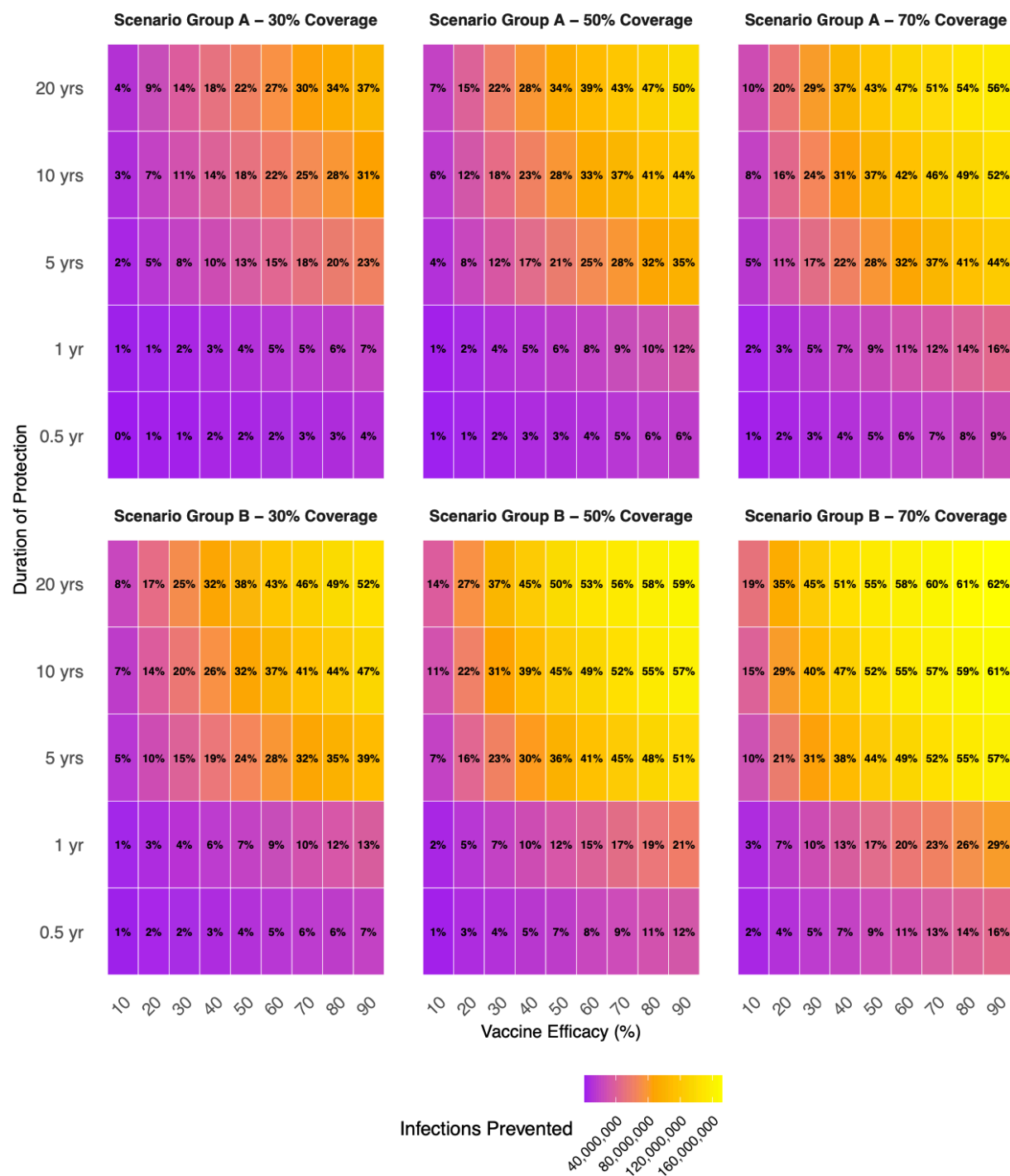


Figure 3.6: Cumulative CT infections prevented among males and females between 2025-2075, across combinations of vaccine coverage, efficacy, and duration of protection, for Scenario Groups A and B compared to no vaccination (referent scenario). Heatmap: Cumulative infections prevented represented by colors. Text Values: Relative reduction in CT infections.

Scenario A: Vaccinating 15-year-old girls entering the model between 2025-2075. Scenario B:
Vaccinating 15-year-old girls and boys entering the model between 2025-2075.

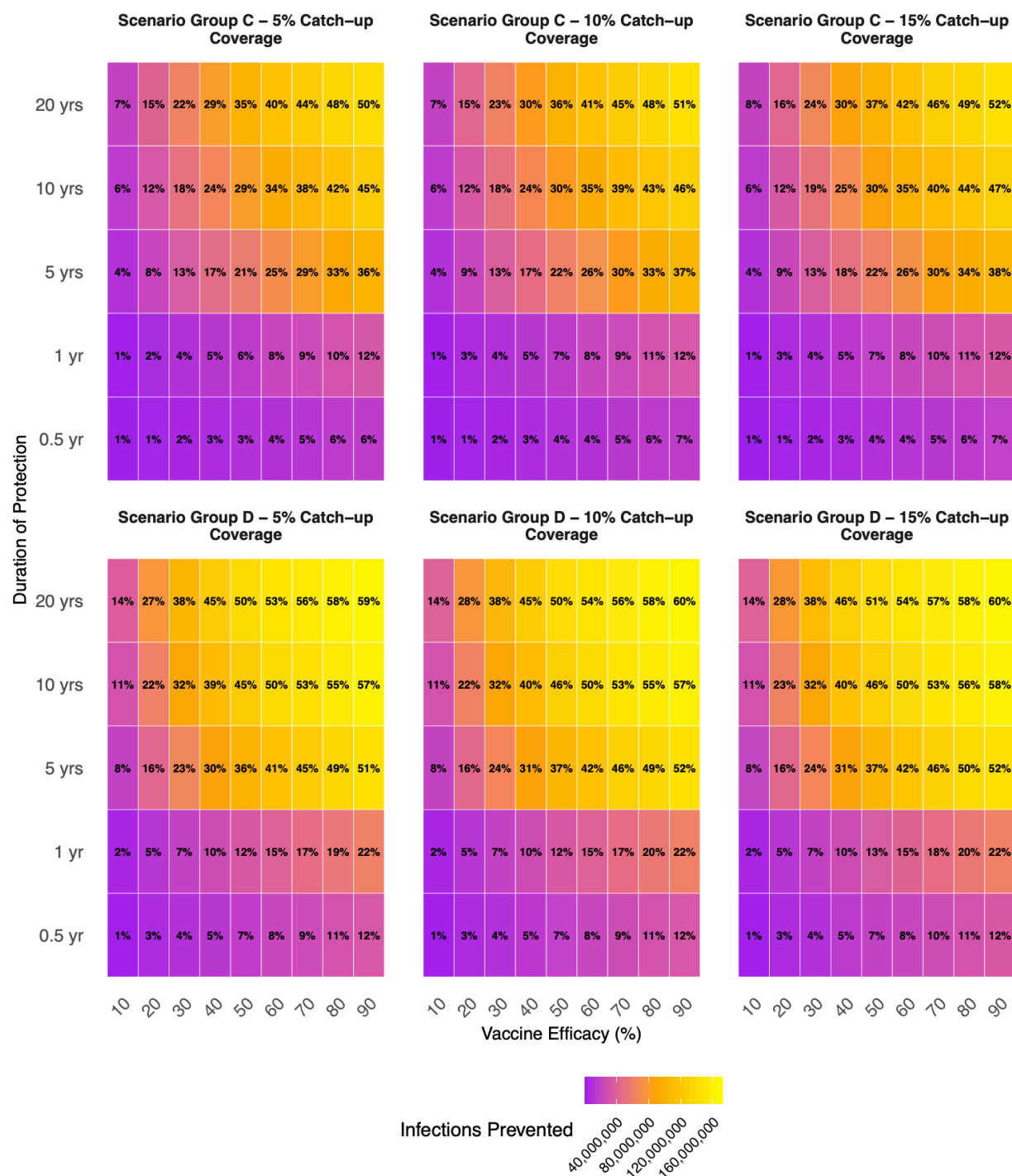
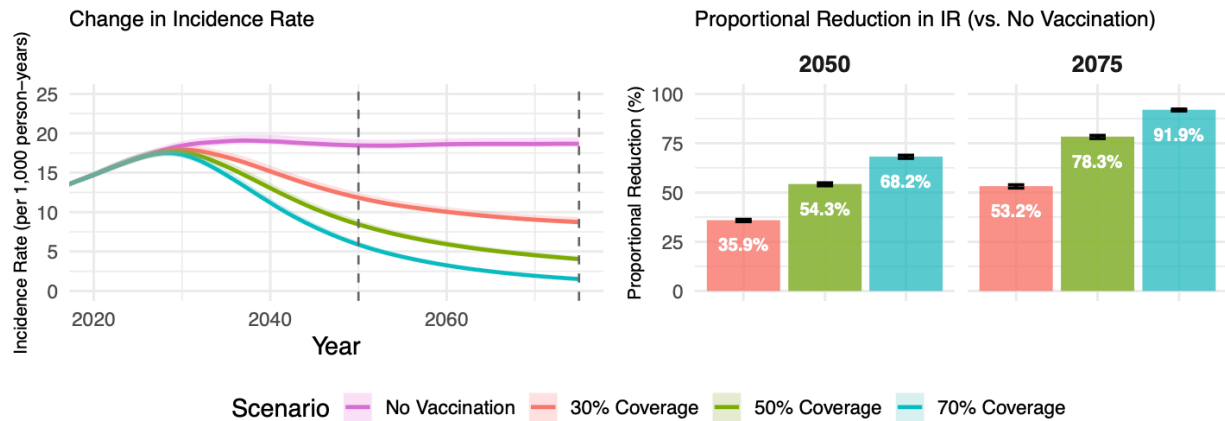


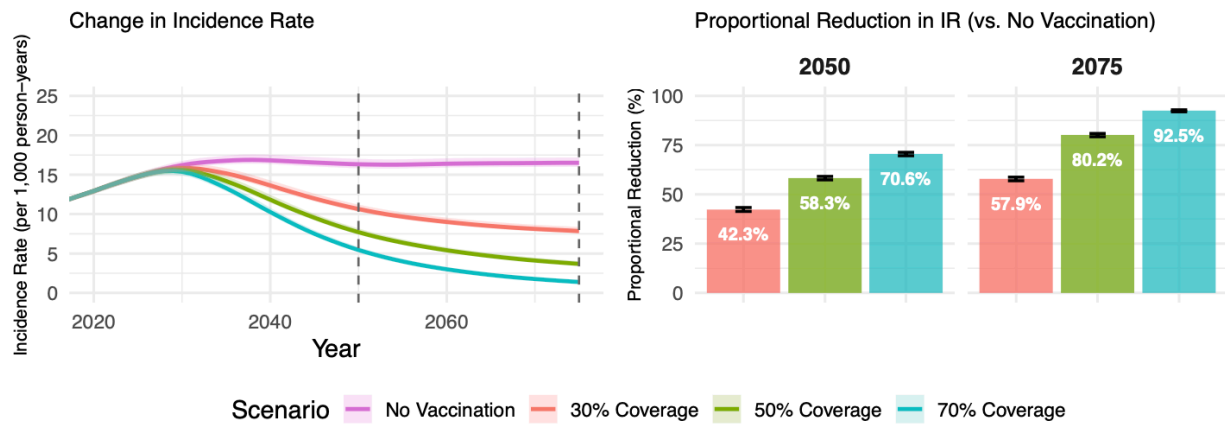
Figure 3.7: Cumulative CT infections prevented among males and females between 2025-2075, across combinations of catch-up vaccination coverage, efficacy, and duration of protection, for Scenario Groups C and D compared to no vaccination (referent scenario). Heatmap: Cumulative infections prevented represented by colors. Text Values: Relative

reduction in CT infections. Scenario C: Scenario A at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035. Scenario D: Scenario B at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035.

A. Scenario A: 70% VE & 10-year Duration of Protection (Total Population)



B. Scenario A: 70% VE & 10-year Duration of Protection (Male Population)



C. Scenario A: 70% VE & 10-year Duration of Protection (Female Population)

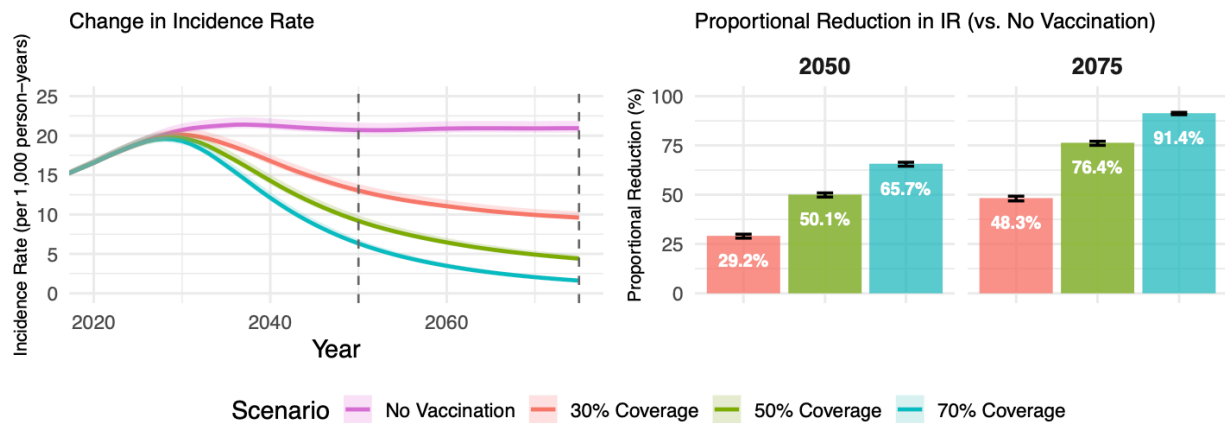
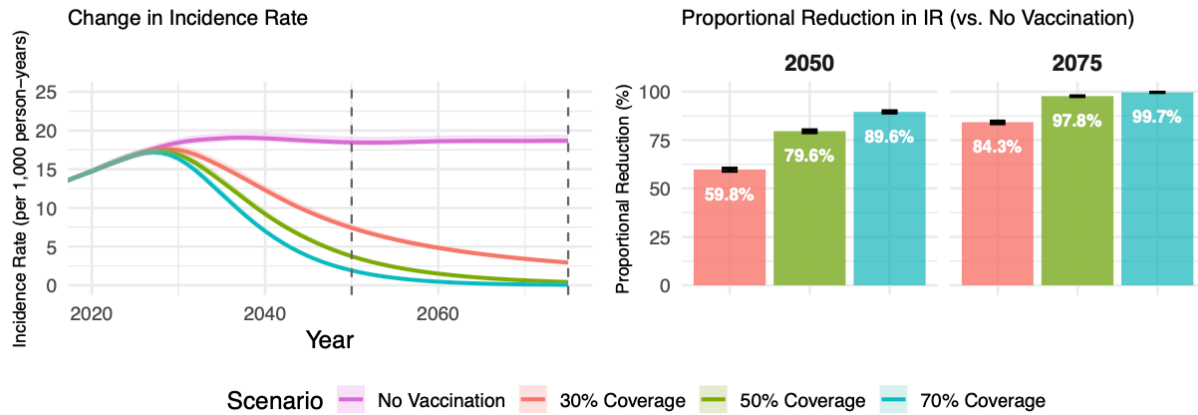


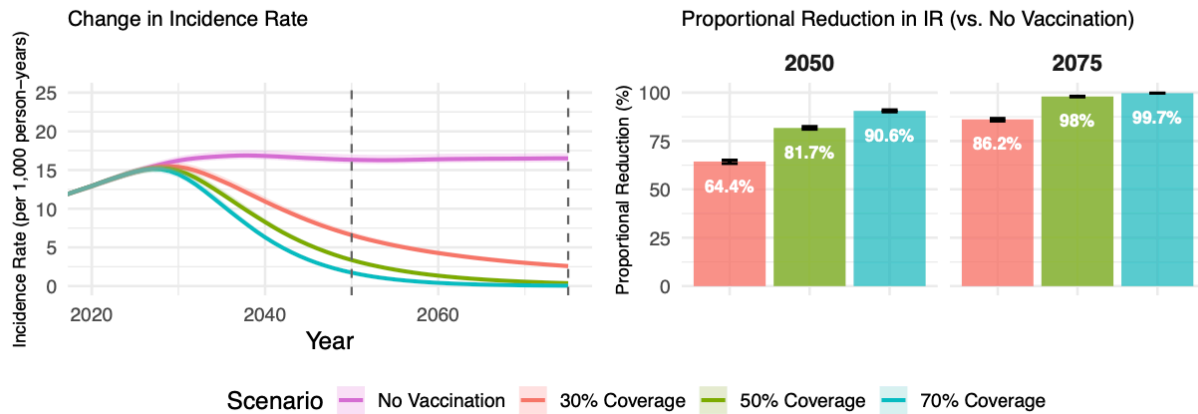
Figure 3.8: The absolute and proportional reduction in CT incidence rates for Scenario A in 2050 and 2075 when compared to the Referent Scenario (no vaccination), assuming 10-year

duration of vaccine-conferred immunity and 70% VE (base-case assumption). Results are presented by vaccine coverage attained by 2035 and biological sex.

A. Scenario B: 70% VE & 10-year Duration of Protection (Total Population)



B. Scenario B: 70% VE & 10-year Duration of Protection (Male Population)



C. Scenario B: 70% VE & 10-year Duration of Protection (Female Population)

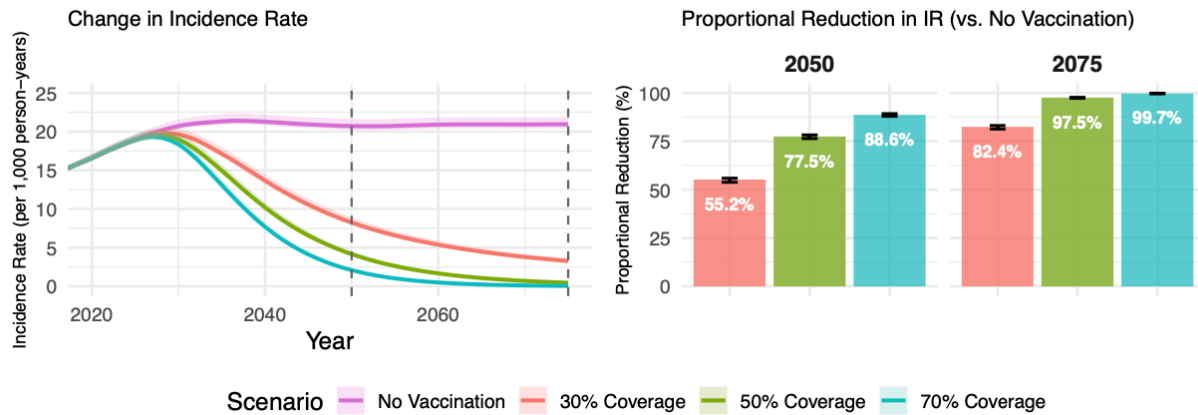


Figure 3.9: The absolute and proportional reduction in CT incidence rates for Scenario B in 2050 and 2075 when compared to the Referent Scenario (no vaccination), assuming 10-year

duration of vaccine-conferred immunity and 70% VE (base-case assumption). Results are presented by vaccine coverage attained by 2035 and biological sex.

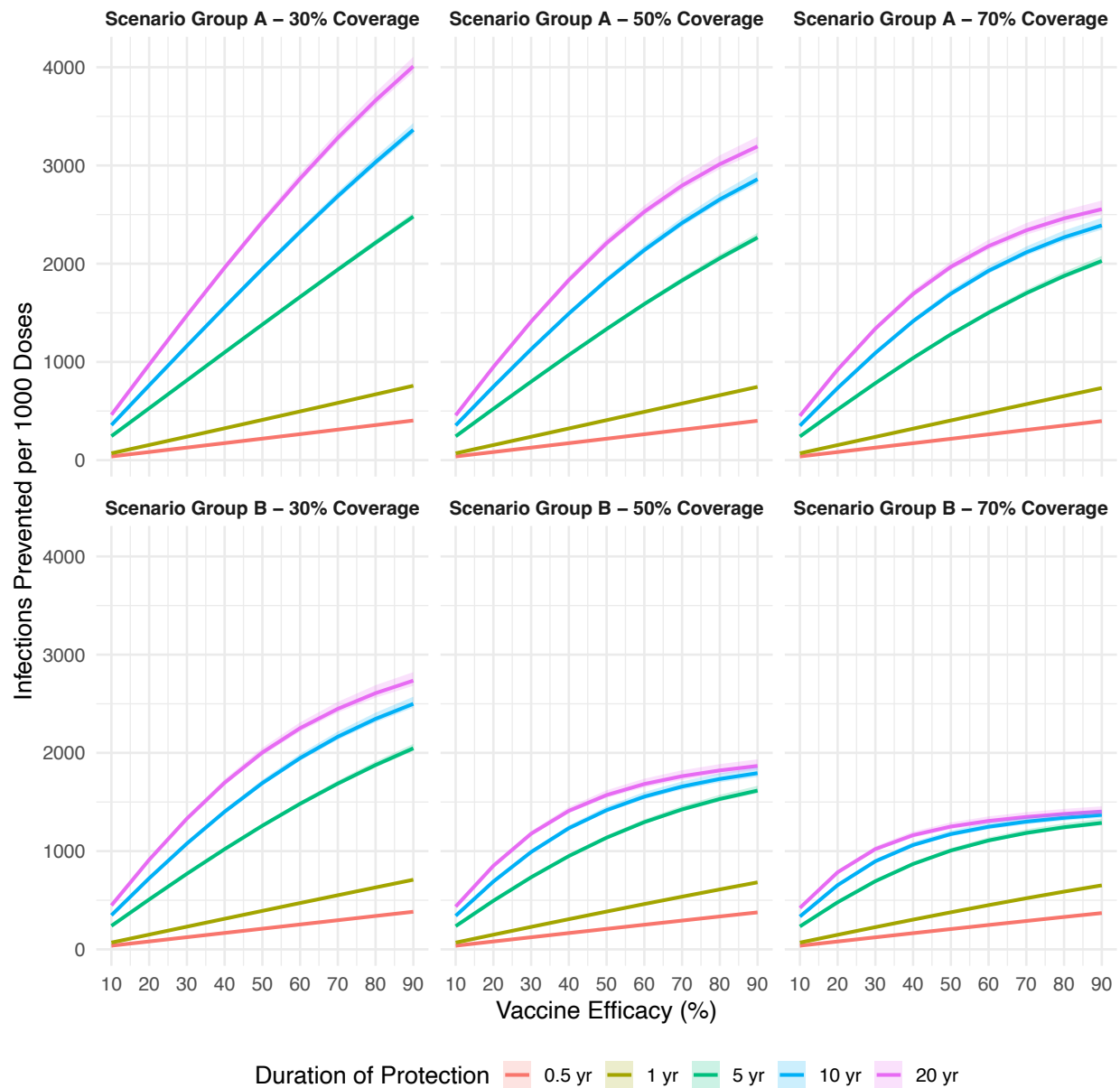


Figure 3.10: Infections prevented per 1,000 doses of vaccine given, by vaccine efficacy and duration of protection for Scenario Group A and Scenario Group B (vs. No Vaccination).

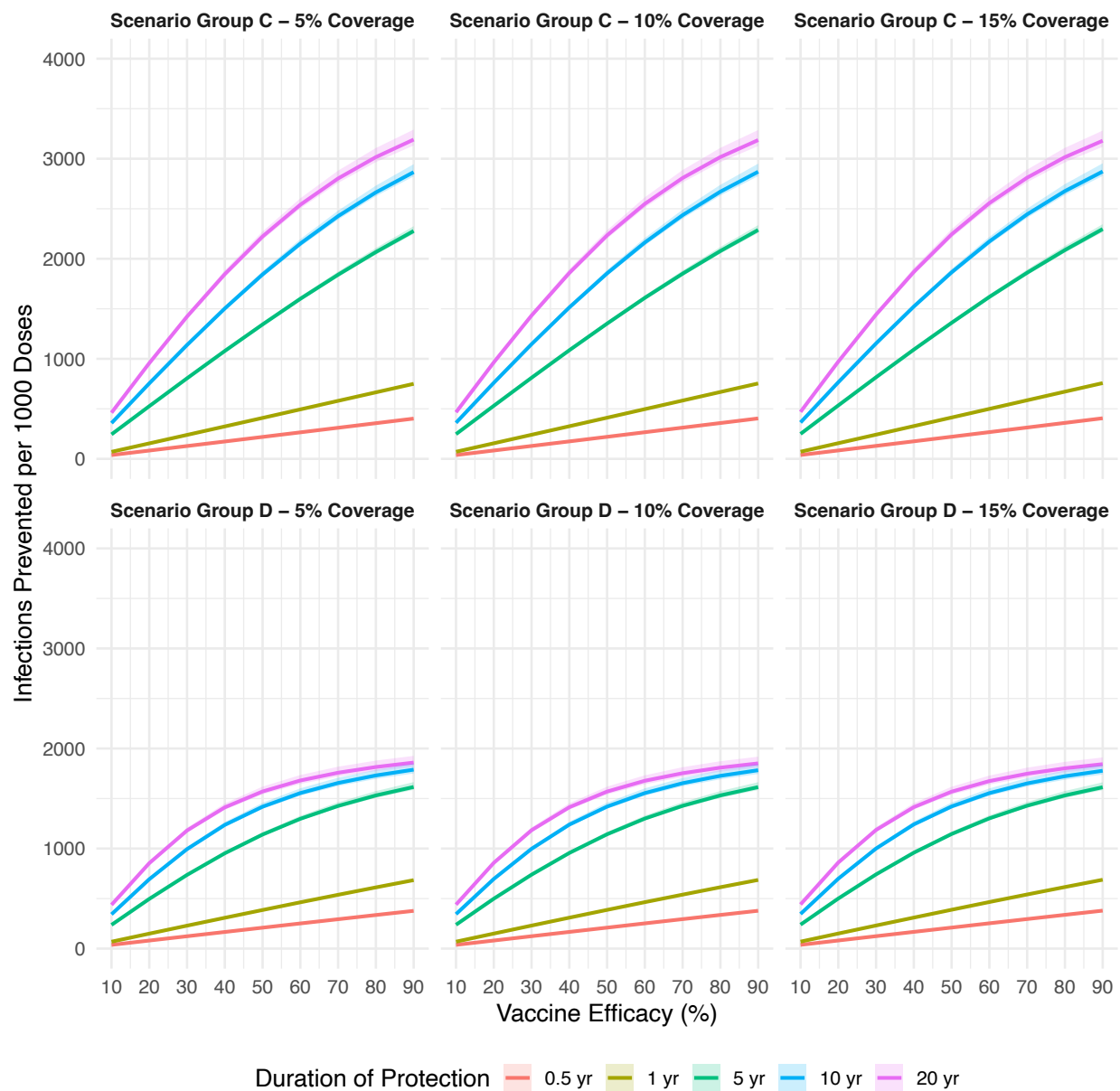


Figure 3.11: Infections prevented per 1,000 doses of vaccine given, by vaccine efficacy and duration of protection for Scenario Group C and Scenario Group D (vs. No Vaccination).

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Chapter 4

Cost-Effectiveness of Chlamydia Vaccination Strategies in the United States: A 2025 to 2050 Modeling Analysis

4.1 ABSTRACT

Background: *Chlamydia trachomatis* (CT) remains the most commonly reported sexually transmitted infection in the United States (U.S.), disproportionately affecting young women and generating substantial costs. While routine screening remains a cost-effective strategy, annual screening is not recommended for all sexually active individuals, limiting its population-level impact. CT vaccination has emerged as a promising complement to existing prevention strategies, but its potential cost-effectiveness at the national level remains understudied.

Methods: We extended a deterministic, age- and sex-stratified compartmental model of CT transmission in the U.S. to evaluate the cost-effectiveness of hypothetical CT vaccination strategies from 2025 to 2050. Strategies included routine vaccination of adolescent girls or sex-neutral vaccination starting in 2025, along with the incremental addition of a catch-up campaign for unvaccinated females aged 15 to 24 years in 2035. Health outcomes were measured in quality-adjusted life years (QALYs), and costs were estimated from a societal perspective, incorporating direct medical costs and productivity losses. We calculated incremental cost-effectiveness ratios (ICERs) and conducted extensive scenario and sensitivity analyses to assess robustness of ICER estimates.

Results: Under base-case assumptions (50% coverage, 70% vaccine efficacy, 10-year protection), all vaccination strategies were considered cost-saving in sequential analysis, whether compared to no vaccination or to a less extensive vaccination strategy. Introduction of routine vaccination of girls at age 15 beginning in 2025 yielded 254,841 QALYs and saved \$1.97 billion compared to current standards of care. Adding vaccination for boys yielded 145,943 additional QALYs and \$354 million in savings compared to girls-only vaccination.

Catch-up campaigns further improved outcomes when added incrementally to girls-only or sex-neutral routine vaccination. Results remained cost-saving or highly cost-effective across variations in vaccine efficacy (30-90%), coverage (30-70%), and duration of protection (5-20 years). ICERs were most sensitive to vaccine price-per-dose and treatment costs for pelvic inflammatory disease; however, all ICER estimates were still below the upper-limit of the willingness-to-pay threshold for the United States.

Conclusions: CT vaccination is likely to be a cost-saving or highly cost-effective intervention in the United States, particularly when implemented through female-only or sex-neutral adolescent programs. These findings support continued investment in CT vaccine development.

4.2 INTRODUCTION

Chlamydia trachomatis (CT) is one of the most commonly reported notifiable diseases in the United States (U.S.), with approximately 1.6 million cases reported to the U.S. Centers for Disease Control and Prevention (CDC) in 2023.¹ CT disproportionately affects women and individuals aged ≤ 25 years and is the most costly non-viral sexually transmitted infection (STI) in the U.S.¹⁻⁵ The lifetime direct medical and productivity costs of CT infections acquired in 2018 were estimated at ~\$870 million and \$560 million, respectively (2025 USD).^{3,5} Women bear a disproportionate share of these costs due to the high burden of pelvic inflammatory disease (PID), tubal factor infertility (TFI), ectopic pregnancy (EP), and chronic pelvic pain (CPP) from untreated infections.³⁻⁵

CT prevention in the U.S. centers on routine annual screening, recommended for all sexually active women under 25 years old, at-risk women 25 years and older, and men who have sex with men (MSM).⁶ Despite increasing short-term healthcare costs, screening remains cost-effective due to its role in reducing transmission and CT-associated sequelae.⁷⁻⁹ For example, Rönn et al. (2023) estimated that CT screening and partner notification from 2000 to 2015 cost \$9,700 (2020 USD) per QALY gained, which is well below U.S. willingness-to-pay

thresholds, even when coverage was expanded to reflect national screening targets for young women.⁸

The asymptomatic presentation of most infections limits the effectiveness of screening as a stand-alone strategy for reducing incidence.¹ Consequently, vaccination has emerged as a promising complementary strategy, with pre-clinical and early-stage clinical trials showing encouraging results.^{10,11} Cost-effectiveness analyses can be essential for assessing the value of vaccination relative to the current standard of care, even when based on projected health benefits and costs of currently unlicensed vaccines. While a few studies have evaluated the potential economic impact of CT vaccination, existing models remain limited in scope.^{12,13} For example, Owusu-Edusei et al. (2015) modeled a simplified, non-age-structured population of 100,000 individuals aged 15 to 24 years, while Ditkowsky et al. (2018) focused exclusively on a cohort of U.S. females aged 9 to 26 years and used a cost-benefit framework rather than a formal cost-effectiveness approach.^{12,13} To date, no study has assessed the incremental cost-effectiveness of CT vaccination across the broader U.S. population, accounting for both males, females, and stratification by age. Furthermore, no prior study has evaluated the relative value of female-only, sex-neutral, and catch-up vaccination strategies within the same cost-effectiveness framework at the national level. Although some analyses have explored these approaches individually, or outside of a formal economic evaluation, none have assessed them in combination using an integrated modeling approach.¹²⁻¹⁴

To address this gap, in Chapter 4 we extended the modeling framework developed in Chapter 3 by incorporating direct medical costs, productivity losses, and health utility data to estimate the incremental cost-effectiveness of multiple vaccination strategies to reduce the burden of disease, measured by quality-adjusted life years (QALYs) from CT. We estimated incremental cost-effectiveness ratios (ICERs) for routine vaccination of adolescent girls, sex-neutral routine vaccination of adolescents, and catch-up campaigns for unvaccinated women aged 15 to 24 years, compared to the current standard of care (screen-and-treat for

asymptomatic infections and test-and-treat for symptomatic infections). These analyses provide a comprehensive assessment of CT vaccination cost-effectiveness in the U.S. over a 25-year time horizon (2025-2050), linking disease burden reductions with economic outcomes to inform policy and program planning.

4.3 METHODS

4.3.a. Mathematical Model

An in-depth description of the model, parameter sources, and calibration process are provided in **Chapter 3**. In summary, we developed a deterministic, compartmental model using ordinary differential equations to simulate CT transmission among individuals aged 15 to 64 years in the U.S. from 2000 to 2075. The population was stratified by biological sex (male/female), age group (15 to 24 years, 25 to 39 years, 40 to 64 years), vaccination status, and disease stage (susceptible, exposed non-infectious, infectious symptomatic infection, infectious asymptomatic infection, sequelae-experiencing, or recovered with short-term infection-conferred immunity). The model incorporated age-related heterogeneity in risk and assumed partial assortative mixing within age groups.¹⁵⁻¹⁸ Transmission was modeled as a function of partnership formation, infection prevalence among partners, and disease-specific transmission probabilities. Same-sex transmission was not explicitly modeled in order to focus on heterosexual transmission dynamics and associated burden among cis-gender, heterosexual women.^{16,19}

Model inputs included demographic data from the 2024 UN World Population Prospects and age- and sex-specific CT case counts from CDC AtlasPlus data.^{20,21} Parameters related to natural history, sexual behavior, treatment, and immunity were informed by peer-reviewed literature and prior STI models. Scenarios, based on different vaccine-related parameters (e.g., efficacy, duration of protection), were created borrowing data from previous modeling studies and analogous STI vaccines, including the human papillomavirus vaccine. When parameter

uncertainty existed, plausible ranges were defined using published data and expert-informed assumptions. A full list of parameter values and sources is available in **Appendix B.2**. Model calibration used reported CT case counts from 2013 to 2019 and targeted key parameters with substantial uncertainty. Details on calibration procedures, including data sources, parameter sampling, and validation against NHANES prevalence data, are described in **Chapter 3**.

4.3.b. Referent and Intervention Scenarios: Base Case

The primary referent scenario applied the calibrated model without vaccination-specific parameters, reflecting the current standard of care in the United States with screen-and-treat for asymptomatic infections and test-and-treat for symptomatic infections. Female-only routine vaccination was initially evaluated through the following intervention scenario:

Scenario Group A: Vaccination of only 15-year-old girls entering the simulated population, beginning in 2025.

Within Scenario Group A, we modeled vaccination coverage increasing linearly to 50% by 2035. We assumed the duration of vaccine-conferred immunity was 10 years and vaccine efficacy was 70%. Next, we assessed the incremental benefits of implementing sex-neutral vaccination under the same coverage, duration of protection, and efficacy assumptions:

Scenario Group B: Vaccination of 15-year-old girls and boys entering the simulated population, beginning in 2025.

Finally, we estimated the incremental benefits of implementing catch-up vaccination campaigns as follows:

Scenario Group C: Scenario Group A @ 50% Coverage + catch-up campaign among unvaccinated females aged 15-24 years in 2035

Scenario Group D: Scenario Group B @ 50% Coverage + catch-up campaign among unvaccinated females aged 15-24 years in 2035

We held vaccination coverage among 15-year-olds constant at 50% by 2035 and assumed that a catch-up campaign in 2035 would reach 10% of unvaccinated females 15-24 years living

without symptomatic infection or sequelae. Vaccine efficacy (70%) and duration of vaccine-conferred immunity (10 years) were the same as *Scenario Groups A and B*. All vaccination parameters are outlined in **Table 4.1**.

4.3.c. Health Outcomes Approach

We estimated health outcomes in quality-adjusted life years (QALYs), a summary measure that captures both gains in life expectancy and improvements in health-related quality of life.²² QALYs combine the quantity and quality of life into a single metric, using health utility weights that represent the relative desirability or burden of different health states. Utility losses were applied to acute symptomatic and asymptomatic CT infections and associated sequelae, including PID in females and epididymitis in males (**Table 4.2**). For PID, the utility weight represented a weighted average based on the probabilities of experiencing downstream sequelae, including TFI, EP, and CPP.^{13,23,24} Cumulative QALYs for each intervention scenario were estimated from 2025 to 2050 and discounted at 3% annually. Incremental QALYs gained were calculated as the difference in total QALYs between an intervention and its comparator scenario (**Appendix C.2**). Details on model parameters and sources can also be found in **Table 4.1**.

4.3.d. Costing Approach

We used ingredient-based costing methods to estimate the costs of CT prevention and treatment using unit costs derived from published studies. Cost components included screening, diagnostic testing and treatment for acute infection, management of sequelae (PID and epididymitis), and vaccination (price per dose and implementation costs). To reflect the societal perspective, direct medical costs and productivity losses (indirect costs) were collected separately. Direct medical costs included labor, cost of diagnostic tests, medical supplies, and medications for treatment, among other relevant costs. Treatment costs associated with PID incorporated both acute care and the expected value of downstream sequelae, including TFI, EP, and CPP. Productivity losses captured the value of time lost due to travel, waiting, and

receipt of CT-related services.⁵ Rather than modeling each complication separately, we applied average per-case estimates of direct medical costs and productivity losses from published sources that accounted for the likelihood and timing of these outcomes. This approach allowed us to reflect the full burden of PID, without requiring explicit tracking of long-term sequelae within the model. In the absence of publicly available pricing data for a CT vaccine, we assumed a base-case price of \$100 USD per dose. We also examined a price-per-dose range of \$25 to \$1,000 in sensitivity analyses, informed by the costs of analogous vaccines.²⁵ These included STI-related vaccines (e.g., MenB for protection against GC, hepatitis B, Mpox, and HPV) as well as vaccines typically administered outside of routine early childhood immunization (COVID-19, influenza, HPV). For all costs of CT prevention and treatment, we identified a primary cost estimate along with plausible lower and upper bounds for use in sensitivity analyses, as to account for uncertainty in the published literature. All values were adjusted to 2025 U.S. dollars using the Consumer Price Index.²⁶ After adjustment, direct medical costs and productivity losses were combined to generate total unit costs.

Unit costs were then applied to model-projected numbers of individuals screened, treated, vaccinated, or experiencing sequelae, to estimate total costs for each scenario. Costs were assigned to corresponding outflows in the compartmental model and estimated annually from 2025 to 2050. To ensure inclusion of diagnostic misclassification and missed treatments after a positive test, we included model parameters on test sensitivity, specificity, and the probability of treatment following positive test results to ensure appropriate tracking of costs dependent on screening and treatment outcomes. A 3% annual discount rate was applied to future costs, and final cost outcomes were presented in 2025 USD. This approach allowed for consistent integration of health and economic outcomes over the model's 25-year time horizon. Costs and corresponding sources are available in **Table 4.3**. Detailed model equations used to estimate total costs can be found in **Appendix C.2**. Details on model parameters and sources can also be found in **Table 4.1**.

4.3.e. Cost-Effectiveness Estimation

We calculated ICERs as the additional cost per additional QALY gained when moving from one vaccination strategy to a more extensive strategy:

$$ICER = \frac{Cost_{Intervention} - Cost_{Referent}}{QALYs_{Intervention} - QALYs_{Referent}}$$

Depending on the comparison, the ICER either reflects the incremental cost-effectiveness of introducing vaccination compared to the current standard of care (screen-and-treat and test-and-treat) or the incremental cost-effectiveness of expanding vaccination beyond a simpler program (see **Supplemental Table C.1**). We evaluated ICERs over a time horizon from 2025 to 2050 and interpreted ICERs to be very cost-effective if they fell below the willingness-to-pay threshold (WTP) of \$50,000 to \$100,000 USD per QALY gained (\$/QALY).²⁷ Although WTP values for the U.S. have been cited up to \$150,000 USD, we have taken a conservative approach to reflect potential bias against sexual and reproductive health services.²⁸ As our primary approach, we conducted a sequential analysis separately for the female-only and sex-neutral routine vaccination pathways to assess overall efficiency and identify any dominated strategies. A strategy was considered dominated if it was both more costly and less effective than another strategy. Although some scenarios may be dominated in sequential analysis, we retained them in our results to illustrate the full range of implementation options, recognizing that programmatic decisions are often constrained by budget or logistical considerations.

4.3.f. Scenario Analysis

The base-case scenario for Groups A, B, C, and D assumed 50% vaccine coverage, attained linearly by 2035 among 15-year-olds, 10-year duration of protection, and 70% VE. The base-case scenario for Groups C and D also assumed 10% of the unvaccinated 15-24-year-old female population was vaccinated via catch-up campaigns in 2035. We conducted an extensive scenario analysis, in which we simulated variations of Scenario Groups A and B to assess the impacts of varying relevant vaccination parameters on reported results as follows:

- 1.) To evaluate how VE estimates influence ICERs across the time horizon, we applied the base-case scenario and varied VE at 30%, 50%, or 90%, respectively.
- 2.) To evaluate how vaccination uptake influenced ICERs across the time horizon, we applied the base-case scenario and varied vaccination coverage among 15-year-olds at lower (30%) or higher (70%) coverage levels by 2035, respectively.
- 3.) To evaluate how vaccine-conferred immunity influenced ICERs across the time horizon, we applied the base-case scenario and varied duration of protection at 5 or 20 years, respectively.

A similar approach was used for Scenario Groups C and D with coverage among 15-year-olds fixed at 50% by 2035 and focusing on varying coverage from catch-up campaigns (base-case = 10% vs. 5% or 15%). A descriptive summary of all scenarios can be found in **Supplemental Table C.2.**

4.3.g. Sensitivity Analysis

To further examine the robustness of our findings, we conducted one-way sensitivity analyses by individually varying the price per vaccine dose, treatment and prevention costs, QALY estimates, and discounting rates using feasible ranges informed by published studies. Model calibration incorporated key epidemiological uncertainties for several parameters, including the probability of symptomatic presentation and likelihood of sequelae development. As such, these parameters were not separately varied in one-way sensitivity analyses. All sensitivity analyses assume the base-case scenario (Scenarios A-D: 50% coverage by 2035, 10-year duration of protection, and 70% VE; Scenarios C/D: 10% catch-up campaign coverage in 2035).

4.4 RESULTS

4.4.a. Cost-Effectiveness

In the base-case scenario, assuming 50% vaccine coverage by 2035 among 15-year-olds, 10-year duration of protection, and 70% VE, the introduction of CT vaccination among girls at age 15 years (Scenario A) led to substantial health and economic benefits compared to current standards of care (**Table 4.4**). This strategy was dominant, with 254,841 QALYs gained and \$1.97 billion USD in cost savings between 2025 and 2050. Adding a catch-up campaign for unvaccinated females aged 15 to 24 years in 2035 (Scenario C) was dominant over routine vaccination of girls only, yielding an additional 23,836 QALYs and \$210 million in cost savings compared to Scenario A.

When considering sex-neutral vaccination strategies, the addition of vaccinating boys at age 15 (Scenario B) to the female-only strategy (Scenario A) was dominant, resulting in 145,943 QALYs gained and \$354 million in cost savings. Further expanding Scenario B with the addition of catch-up campaigns for unvaccinated females aged 15 to 24 years in 2035 (Scenario D) led to an additional 14,883 QALYs and \$55 million in cost savings. Although Scenario B provided meaningful benefits, it was dominated by Scenario D, which achieved greater health gains at lower cost. All evaluated strategies under the base-case assumption were cost-saving and well below the conservative U.S. WTP threshold of \$50,000/QALY gained (**Figure 4.1**).

4.4.b. Scenario Analysis

Across all VE assumptions (30%, 50%, 70%, 90%), vaccination strategies were either cost-effective or cost-saving (**Figure C.1; Supplemental Table C.3**). When vaccinating girls only, Scenario A was cost-effective at 30% VE (ICER = \$5,065/QALY gained) and became cost-saving at 50% VE and above. The addition of a catch-up campaign for unvaccinated females (Scenario C) further improved outcomes and remained cost-saving across all VE levels. When adding vaccination for boys to vaccination for girls, Scenario B was cost-effective at 30% VE (ICER = \$7,945/QALY gained) and cost-saving by 70% VE. The addition of a catch-up campaign for unvaccinated females (Scenario D) also improved outcomes and was cost-saving at or above 50% VE.

Across both female-only and sex-neutral routine vaccination strategies, longer duration of protection consistently improved cost-effectiveness of CT vaccination (**Figure C.2; Supplemental Table C.4**). A 5-year duration resulted in more modest health gains and cost savings, while a 20-year duration produced the largest QALY gains and cost reductions, underscoring the robustness of vaccination benefits across a range of duration assumptions. The impact of duration was less pronounced on ICERs for Scenarios C and D; however, there were still improvements in cost savings with longer duration. Additionally, changes to vaccine coverage by 2035 among 15-year-olds led to cost-effective results (**Figure C.3; Supplemental Table C.5**). At 70% coverage, female-only routine vaccination (Scenario A) led to 331,661 QALYs gained and over \$2.3 billion in cost savings compared to no vaccination. Sex-neutral vaccination at 70% coverage through the addition of vaccination for boys (Scenario B) produced 155,553 additional QALYs gained but incurred added costs, resulting in an ICER of \$2,313/QALY gained. Although this was no longer considered cost-saving, the addition of sex-neutral vaccination was still well below the WTP threshold for the U.S. All scenarios with coverage at 30% or 50% were cost-saving, respectively.

These findings demonstrate that, even under uncertain VE, coverage, and duration of protection assumptions, CT vaccination remains a cost-effective or cost-saving intervention across all evaluated scenarios. Detailed results from all scenario analyses, including varying coverage from catch-up campaigns (**Supplemental Table C.6**), can be found in **Appendix C.4**.

4.4.c. Sensitivity Analysis

Figures C.4-C.7 in **Appendix C.5** display results from one-way sensitivity analyses on base-case ICERs, comparing 1.) Scenario A vs No Vaccination, 2.) Scenario C vs Scenario A, 3.) Scenario B vs Scenario A, and 4.) Scenario D vs Scenario B. For comparison of female-only routine vaccination (Scenario A) versus no vaccination, ICERs were sensitive to the vaccine price-per-dose (ICER range: cost-saving to \$37,809/QALY gained) and assumptions of treatment costs for PID (ICER range: all cost-saving). For Scenario A, vaccination was no longer

cost-saving once price-per-dose went above \$250 USD. Screening, infection treatment, and vaccination visit costs, PID-related QALY estimates, and discounting also notably influenced results, though the intervention remained cost-saving under these parameter variations. Similar findings were seen with the addition of catch-up vaccination (Scenario C), as results were most sensitive to vaccine price-per-dose (ICER range: cost-saving to \$35,219/QALY gained). All parameter variations led to cost-saving or cost-effective ICERs.

With the introduction of vaccinating boys (Scenario B vs. Scenario A), sensitivity to vaccine price-per-dose was pronounced, with ICERs ranging from cost-saving at \$25 per dose to non-cost-effective at \$1,000 per dose (\$79,876/QALY). Specifically, vaccination was no longer cost-saving once price-per-dose went above ~\$125. Several parameters, including PID treatment costs and vaccination visit costs, shifted the ICER to no longer be cost-saving, highlighting greater uncertainty in the incremental benefits of expanding to a sex-neutral strategy. Similar results were seen with the addition of catch-up vaccination (Scenario D), with vaccine price-per-dose ranging ICERs from cost-saving to values above the low end of the WTP threshold (\$66,887/QALY). Variability in PID treatment costs was the only other parameter that led to a cost-effective, but not cost-saving, estimate (ICER range: cost-saving to \$624/QALY). Importantly, even when considering vaccine price-per-dose at \$1000, ICERs fell below other accepted WTP thresholds of \$100,000 and \$150,000, respectively. Therefore, female-only and sex-neutral routine vaccination strategies, with or without catch-up vaccination for 15 to 24 year-old unvaccinated females, remained a cost-saving or cost-effective approach in nearly all scenarios evaluated.

4.5 DISCUSSION

We developed a deterministic compartmental model of CT transmission in the United States to estimate the potential cost-effectiveness of CT vaccination through female-only, sex-neutral, and added catch-up vaccination strategies. We found that, under base-case

assumptions, adding routine vaccination of 15-year-old girls to current screening practices was cost-saving. When incrementally extending vaccination to 15-year-old boys, we found this approach to also be cost-saving. The additional inclusion of catch-up campaigns for unvaccinated females aged 15 to 24 years to either female-only or sex-neutral strategies were also subsequently cost-saving. Findings remained consistent when parameters for VE, duration of protection, and vaccine coverage by 2035 were individually varied from the base-case, with all scenarios estimating ICERs at cost-saving or cost-effective levels under a WTP threshold of \$50,000-\$100,000 USD.

One-way sensitivity analyses demonstrated that both female-only and sex-neutral CT vaccination strategies were generally cost-saving or cost-effective across a wide range of parameter values. ICERs were most sensitive to vaccine price-per-dose and assumptions about PID treatment costs, with additional influence from QALY estimates, discounting, and visit costs. While female-only strategies remained cost-saving under nearly all parameter values, sex-neutral strategies showed greater uncertainty, with ICERs ranging from cost-saving to above the \$50,000/QALY threshold at high vaccine prices. Nonetheless, at \$1,000 per dose, ICERs for sex-neutral vaccination remained below commonly accepted thresholds of \$100,000 to \$150,000/QALY, supporting the robustness of vaccination as a cost-effective intervention.

To our knowledge, our findings are the first to estimate cost-effectiveness of CT vaccination at the national level. A recent modeling study by Makhoul et al. (2024) evaluating CT vaccination nationally in the United States found that a partially effective vaccine could substantially reduce infection rates, associated health outcomes, and be cost-effective under realistic scenarios.¹⁴ However, their study did not formally incorporate QALYs or cost data, so direct comparisons with our study are not possible. The best comparison to our analysis is the modeling study by Owusu-Edusei et al. (2015), who found that a vaccination program targeting 14-year-old girls, with or without catch-up vaccination for women aged 15-24 years, would be cost-effective at \$35,300/QALY gained and \$53,200/QALY gained, respectively.¹³ Our model

showed greater potential for cost-savings, likely as a result of differences in model development. While both studies used dynamic, compartmental transmission models and adopted a societal cost perspective, our model included greater structural complexity and broader population stratification, incorporating age- and sex-structured compartments for those aged 15-24, 25-39, and 40-64 years. In contrast, Owusu-Edusei et al. modeled a simplified population of 100,000 individuals aged 15-24 years, without accounting for contributions to transmission from older age groups or heterogeneity in age-based sexual mixing. As a result, their model is not nationally representative and does not capture the full age range at risk for CT infection, which may underestimate both the transmission dynamics and potential benefits of vaccination across the broader population. However, our models align that CT vaccinations may be well-positioned to be cost-effective prevention strategies in the United States.

Additionally, our findings broadly differ from the cost-benefit analysis by Ditkowsky et al. (2018), who concluded that CT vaccination would reduce CT morbidity but increase healthcare costs by \$41.77 million (2015 USD).¹² This discrepancy is also primarily due to methodological differences. First, we used a dynamic transmission model that captures herd effects and long-term reductions in transmission, while Ditkowsky et al. used a static Markov model. Our analysis also included costs averted among males and applied a societal perspective by incorporating indirect costs, whereas Ditkowsky et al. focused solely on direct healthcare costs incurred by the simulated population. Additionally, we used a longer time horizon, broader age and sex stratification, and more flexible assumptions around vaccine efficacy, duration, and coverage. These differences allowed our model to capture greater long-term benefits of vaccination, leading to findings of cost savings under certain scenarios.

We focused specifically on heterosexual transmission of urogenital CT and were not able to capture changes in disease burden and societal costs among other subpopulations. While the findings provide meaningful insights into the potential benefits of routine vaccination in the general adolescent population, they may not be generalizable to groups experiencing a

disproportionate burden of CT, such as MSM and transgender women.^{1,29} Given rising vaccine hesitancy and persistent stigma surrounding sexual and reproductive health in the United States, cost-saving findings for a routine CT vaccine may not be enough to garner necessary support.^{30,31} Future studies should therefore evaluate the cost-effectiveness of target CT vaccination in subpopulations at greatest risk through model expansion. It would also be important for modeling studies among MSM to incorporate parameters on extragenital infections, particularly at rectal and pharyngeal sites, to fully assess the spectrum of health and economic outcomes.

Our study has several important limitations. First, considerable uncertainty in parameter values exist for vaccination costs and vaccine-specific characteristics in the absence of a viable candidate in late-stage clinical development. Significant data gaps also persist in our understanding of CT natural history and sexual transmission. Therefore, findings from this cost-effectiveness analysis should be interpreted with caution. To address this, we used a multi-step approach, whereby model calibration was performed using 100 parameter sets fit to CT annual cases and prevalence data.^{20,32} Median base-case ICERs were estimated across these sets, with additional scenario analyses varying realistic vaccine characteristics. We also conducted one-way sensitivity analyses to assess the impact of other parameters on ICER estimates. The reliability of future CT transmission models hinges on the continued collection of high-quality observational data to mitigate uncertainty in key parameters.

Next, we did not model potential vaccine effects on CT infectiousness, duration, or symptom presentation. However, such effects would likely enhance cost-saving potential by further reducing infections and complications with minimal change to vaccination costs. Makhoul et al. (2024) incorporated vaccine-derived impacts on infectiousness and infection-duration among vaccinated individuals, but these impacts have yet to be incorporated in cost-effectiveness analyses at the national level.¹⁴ Importantly, our study is generalizable only to the United States, as underlying epidemiological burden of CT, direct and indirect costs, and sexual

transmission patterns are heavily dependent on the geographical setting under review. Additional studies are needed to assess whether the cost-saving results from our model are realistic in settings outside the United States. Next, while our cost estimates for PID incorporated the average case, accounting for the probability of subsequent complications, they may underestimate the true burden of infertility.^{33,34} In particular, our analysis may not fully capture the acute and long-term mental health impacts associated with infertility.³⁵ As a result, the cost savings attributable to vaccination may be underestimated. Finally, our study did not account for multi-dose vaccination series or the implementation of periodic boosters following waned vaccine-conferred immunity. As with other vaccinations for bacterial infections, multiple doses may be required to confer long-term protection.³⁶ Routine pneumococcal conjugate vaccination for all children younger than 5 years are administered at four time points, with additional boosters recommended for higher-risk children and adults.³⁷ As such, our findings of cost-savings or cost-effectiveness may change with the inclusion of product and delivery costs for additional doses.

Our study has several important strengths. Our model incorporated CT prevention and treatment unit costs derived from contemporary published studies. The inclusion of this data provided updated cost estimates incorporating both direct medical costs and the productivity losses tied to accessing treatment and prevention services. Therefore, we were able to take a societal perspective for our cost-effectiveness analysis. Next, model calibration incorporated both adjusted CT annual cases from CDC AtlasPlus data and CT prevalence data from NHANES, ensuring our model adequately fit established data from two separate sources.^{20,32} Finally, our model was sufficiently complex to inform vaccination policy recommendations at the population-level as we incorporated sex- and age-based sexual mixing, allowing for more realistic representation of transmission dynamics across age groups. While we did not explicitly model individual-level partnership dynamics or reinfection from untreated partners, we provided a robust framework for assessing vaccination impact and cost-effectiveness.

Our findings suggest that CT vaccination, particularly when implemented in adolescent girls or through broader, sex-neutral strategies, has the potential to be a cost-saving or highly cost-effective intervention across a range of realistic scenarios. By using a dynamic, age- and sex-stratified transmission model, we captured both direct and indirect benefits of vaccination while addressing key uncertainties in disease burden and vaccine performance. As vaccine development advances, these results underscore the importance of continued investment in CT vaccine research, the need for additional research on CT natural history, and the further refinement of mathematical models to understand implementation strategies among other populations.

4.6 TABLES & FIGURES

Table 4.1. Outline of Vaccination Parameters & QALY- and Cost-Associated Parameters ^A

A. Vaccination Parameters			
Parameter Description	Group	Value/Range	Sources
Vaccination coverage in 2035 (increasing linearly beginning in 2025), among individuals entering model @ 15 years (Vx_{ij})	Females	30%, 50%, 70%	Assumption
	Males	0%, 30%, 50%, 70%	Assumption
Vaccination coverage via catch-up campaigns in 2035, among 15-24-year-olds only ($\beta_{j,k}$)	Females	5%, 10%, 15%	Assumption
Duration of vaccine-conferred immunity (θ_k)	All groups	5, 10, or 20 years	Assumption
Vaccine efficacy, defined as the proportional reduction in susceptibility to infection, comparing vaccinated to unvaccinated individuals (VE_s)	All groups	30%, 50%, 70%, 90%	Assumption
B. QALY- and Cost-associated Parameters			
Parameter Description	Group	Value/Range	Sources
Discount rate per year (d)	All groups	3%	Assumption
Probability of symptomatic infection (ζ_j)	Females	0.1 – 0.3	13,14,19,38,39
	Males	0.4 – 0.6	13,14,19,38,39
Incubation period (φ)	All groups	14 days	13,18
Duration of untreated infection (to natural resolution; ι)	All groups	1.25 – 2.0 years	13,18,40,41
Probability of sequelae, given untreated infection (κ_j)	Females	0.10 – 0.14	13,42,43
	Males	0.01 – 0.03	13,24,44
Probability of annual screening for CT ($r_{j,k}$)	Females, 15-24 years	0.35 – 0.48	13,45-49
	Females, 25-39 years	0.35 – 0.41	
	Females, 40-64 years	0.18 – 0.25	
	Males, 15-24 years	0.01 – 0.02	
	Males, 25-39 years	0.04 – 0.06	13,50-52
	Males, 40-64 years	0.03 – 0.05	

Sensitivity of CT diagnostic test (ε)	All groups	0.96	53-55
Specificity of CT diagnostic test ($spec$)	All groups	0.99	53-55
Post-screening treatment probability (ν)	All groups	0.80	13,56
Probability of treatment, symptomatic (p_{txt})	All groups	0.89	13,57
Duration of treated symptomatic infection (dur_{tx_i})	Females	35 – 49 days	14,18,19
	Males	28 – 42 days	14,18,19
Sequelae resolution (ϖ_i)	Females	60 days	13,58
	Males	21 days	13
“Birth” rate (η)	Females/Males	Year-dependent	21

^A Parameter values necessary for cost-effectiveness analyses are provided above, with additional detail on remaining model parameters available in Appendix B.2 of Chapter 3.
Abbreviations: CT, *Chlamydia trachomatis*.

Table 4.2. Outline of Health Utilities (QALYs) ^A

Category	Females	Males	Sources
Acute Symptomatic CT Infection	0.010 (0.005, 0.015)	0.006 (0.003, 0.009)	9,13,24
Acute Asymptomatic CT Infection ^B	0	0	8,13,23
Epididymitis	--	0.010 (0.005, 0.015)	9,13,24
PID & Complications ^C	0.4144 (0.2072, 0.6216)	--	13,23,24

^A Health utilities represent average QALYs lost per incident event.

^B Asymptomatic CT infection assumed to have no impact on QALYs

^C QALYs lost for PID accounts for the 'average' case of PID, based on probability of further development of chronic pelvic pain, ectopic pregnancy, infertility, or no other complications

Abbreviations: QALYs, quality-adjusted life-years; CT, *Chlamydia trachomatis*; PID, pelvic inflammatory disease

Table 4.3. Outline of Cost Estimates

A. Females				
Category	Direct Costs ^A (USD 2025)	Indirect Costs ^B (USD 2025)	Total Costs ^C (2025 USD)	Sources
Vaccination (Clinical Visit)	\$35.17 (\$26.38, \$43.96)	\$35.17 (\$15.35, \$69.11)	\$70.34 (\$41.73, \$113.07)	5,13,25,59- 62
Vaccination (Price Per Dose)	\$ per dose (\$25 - \$1000)	N/A	\$ per dose (\$25 - \$1000)	25
Treatment of Acute Infection	\$187.00 (\$164.00, \$210.00)	\$68.48 (\$29.30, \$135.66)	\$255.48 (\$193.30, \$345.66)	4,5,63
Screening without Treatment	\$147.00 (\$98.00, \$196.00)	\$35.17 (\$15.35, \$69.11)	\$182.17 (\$113.35, \$265.11)	5,8,13,63-65
Treatment of PID ^D	\$3,049.26 (\$2,377.03, \$4,568.92)	\$740.22 (\$279.41, \$1,532.57)	\$5,314.75 (\$3230.89, \$9259.41)	4,5
B. Males				
Category	Direct Costs ^A (USD 2025)	Indirect Costs ^B (USD 2025)	Total Costs ^C (2025 USD)	Sources
Vaccination (Clinical Visit)	\$35.17 (\$26.38, \$43.96)	\$35.17 (\$15.35, \$69.11)	\$70.34 (\$41.73, \$113.07)	5,13,25,59- 62
Vaccination (Price Per Dose)	\$ per dose (\$25 - \$1000)	N/A	\$ per dose (\$25 - \$1000)	25
Treatment of Acute Infection	\$194.00 (\$160.00, \$228.00)	\$68.48 (\$29.30, \$135.66)	\$262.48 (\$189.30, \$363.66)	4,5,63
Screening without Treatment	\$147.00 (\$98.00, \$196.00)	\$35.17 (\$15.35, \$69.11)	\$182.17 (\$113.35, \$265.11)	5,8,13,63-65
Treatment of Epididymitis	\$465.96 (\$288.28, \$643.65)	\$2,265.49 (\$853.86, \$4,690.49)	\$1,206.18 (\$567.69, \$2,176.22)	4,5

^A Direct costs include all medical costs (supplies, diagnostics, provider salaries, etc.) for one unit of the corresponding category.

^B Indirect costs represent productivity losses for one unit of the corresponding category, capturing the value of time lost due to travel, waiting, and receipt of CT-related services.

^C Total costs include the total direct and indirect costs for one unit of the corresponding category.

^D Costs for PID were estimated by combining the probability and discounted cost of each PID-related outcome (outpatient and inpatient treatment, ectopic pregnancy, tubal factor infertility, chronic pelvic pain), using a 3% annual discount rate and assuming the time from infection to PID onset was under one year.

Costs are presented as main unit cost (lower bound, upper bound). Abbreviations: PID, pelvic inflammatory disease; CT, *Chlamydia trachomatis*.

Table 4.4. Sequential cost-effectiveness analysis for female-only, sex-neutral, and catch-up vaccination strategies, under base-case assumptions¹ (2025 - 2050)

A. Female-only Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	145,948.52	1,002,268	-1,973.42	254,841	Cost Saving
3	Scenario C	Scenario A	145,738.31	978,432	-210.20	23,836	Cost Saving
B. Sex-neutral Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD)	Total QALY Decrements	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	145,948.52	1,002,268	-1,973.42	254,841	Cost Saving
3	Scenario B	Scenario A	145,594.28	856,325	-354.23	145,943	Cost Saving
4	Scenario D	Scenario B	145,539.70	841,442	-54.59	14,883	Cost Saving

¹ Base-case assumptions include Scenarios A-D: 50% coverage by 2035, 10-year duration of protection, and 70% VE; Scenarios C/D: 10% catch-up campaign coverage in 2035.

² Costs and QALYs are discounted at 3% annually.

³ Costs are in 2025 USD

Scenario A: Vaccinating 15-year-old girls entering the model between 2025-2075. Scenario B: Vaccinating 15-year-old girls and boys entering the model between 2025-2075. Scenario C: Scenario A at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035. Scenario D: Scenario B at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035.

Abbreviations: USD, United States Dollar, QALY, quality-adjusted life years; VE, vaccine efficacy

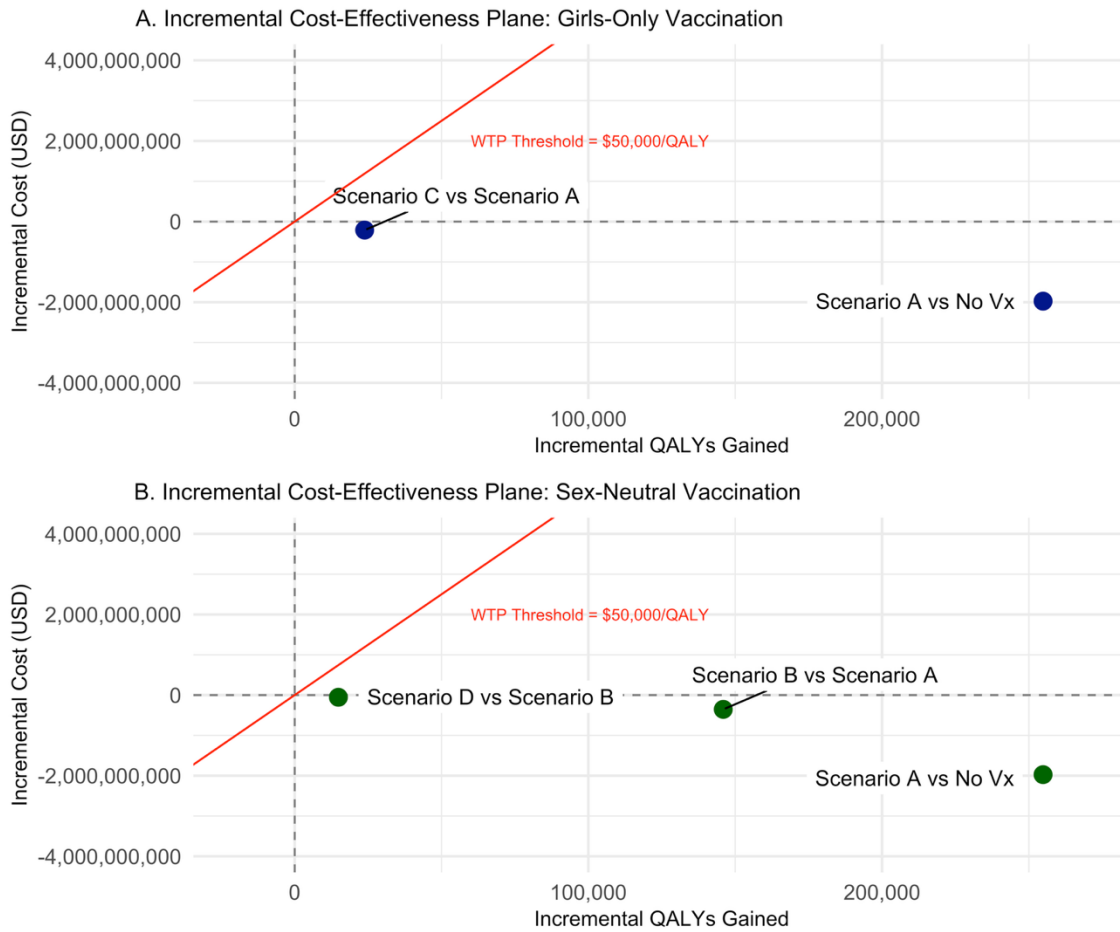


Figure 4.1: Cost-effectiveness planes for female-only, sex-neutral, and catch-up CT vaccination strategies under base-case assumptions (2025 - 2050)

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Chapter 5

Conclusions

The three studies discussed in this dissertation aim to advance population-level prevention strategies for CT infection in the United States, with specific focus on doxy-PEP and CT vaccination among sexually active individuals.

In Chapter 2, we examined patterns of antibiotic consumption among a cohort of MSM in Seattle, WA prior to the introduction of doxy-PEP. Nearly 70% of participants initiated antibiotics during 49 weeks of follow-up, with an overall incidence of 264.5 initiation events per 100 person-years. While STI treatment was the most common reason for initiating antibiotics, treatment for other health conditions, particularly chronic skin and respiratory conditions, significantly contributed to the total days of antibiotic use. Younger age (25 to 39 years) and a recent history of bacterial STIs were significantly associated with higher rates of antibiotic initiation. These findings demonstrate that antibiotic use was already high in this population prior to the implementation of doxy-PEP, and that antibiotic consumption extends beyond STI treatment alone. As such, concerns about resistance development with doxy-PEP rollout must be contextualized within a broader landscape of antibiotic exposure, particularly among MSM who may frequently use antibiotics for non-STI-related infections. Importantly, a small number of individuals in the cohort contributed disproportionately to total days of antibiotic use, suggesting that heterogeneity in risk and use patterns should inform more tailored recommendations for doxy-PEP use amongst MSM and transgender women.

Looking forward, these results lay essential groundwork for evaluating how doxy-PEP introduction might alter antibiotic use patterns and resistance risk in this key population. Future research should 1.) explore population-level antibiotic use behaviors post-doxy-PEP uptake among MSM, 2.) characterize antibiotic use among cis-gender women prior to any future doxy-PEP recommendations, 3.) continue examining resistance patterns in both STI and non-STI

pathogens relevant to MSM, and 4.) support surveillance systems that can monitor how changing standards of STI prevention impact antibiotic exposure. These insights are critical to ensuring that antimicrobial stewardship efforts are balanced with the urgent need for effective STI prevention.

In Chapter 3, we used a dynamic, compartmental model to evaluate the impact of various CT vaccination strategies on disease burden in the United States. The model projected that, under base-case assumptions (70% vaccine efficacy, 50% coverage, 10-year protection), sex-neutral vaccination of adolescents at age 15 could reduce incidence to just 0.4 infections per 1,000 person-years by 2075, compared to 4.0 and 18.7 infections per 1,000 person-years with girls-only routine vaccination and no vaccination, respectively. Cumulative infections averted and vaccination efficiency varied by strategy, but routine vaccination of adolescents, especially in a sex-neutral framework, consistently yielded the greatest impact. These findings underscore the strong potential of CT vaccination to meaningfully reduce transmission over the long term. Importantly, sex-neutral vaccination strategies offer greater population-level protection and could promote gender equity in prevention, especially in the absence of universal screening.

Future modeling studies should continue to address how real-world barriers, including vaccine hesitancy, incomplete coverage, and waning protection, may affect the effectiveness of CT vaccination strategies. Modeling efforts must also account for heterogeneity in risk and access, including disparities by race and ethnicity, to ensure that vaccination is responsive to populations most affected by CT. This includes explicitly incorporating MSM, a key population in whom extragenital infections are common. Future studies should also reflect more realistic rollout scenarios, including geographic variation in vaccine delivery and coverage attainment. As our understanding of CT natural history, such as the role of reinfection and progression to sequelae, continues to evolve, models must remain adaptable to integrate empirical evidence. Moreover, dynamic modeling frameworks should continue to evolve, incorporating emerging

behavioral trends, antimicrobial resistance patterns, and novel technologies that may shape the future CT prevention landscape.

Building on the previous chapter, Chapter 4 further assessed the cost-effectiveness of CT vaccination under a range of coverage, efficacy, and duration assumptions. Under base-case assumptions (70% efficacy, 10-year protection, 50% coverage attained by 2035), all modeled vaccination strategies were incrementally cost-saving. Sex-neutral vaccination was the most impactful and cost-saving approach when compared sequentially to girls-only vaccination. Sensitivity analyses showed that results were most influenced by vaccine price and assumptions around treatment costs for PID but remained cost-effective under current willingness-to-pay thresholds in the United States. These findings bolster the economic case for vaccine development and support early investments in implementation planning, especially if long-term protection and moderate coverage can be achieved. However, benefits would accumulate slowly while programmatic costs are frontloaded, potentially limiting short-term political or financial support.

While this work shows strong promise for CT vaccination in the United States, several areas warrant further investigation to strengthen the robustness and real-world applicability of our findings. Our model assumed a simplified single-dose vaccine schedule with a single catch-up campaign for unvaccinated females; however, it is unlikely that implementation will follow this streamlined approach. Future modeling studies should evaluate the implications of multi-dose schedules, age-specific boosters, and more complex catch-up strategies, particularly among individuals at higher risk or with waning vaccine-induced immunity over time. Cost-effectiveness analyses should also be expanded to incorporate a wider range of outcomes, including direct non-medical costs, other indirect costs, and considerations for the contributions of acute and chronic mental health outcomes related to CT infection and reproductive complications. Given the global burden of CT, complementary cost-effectiveness analyses in contexts outside the

United States will be critical to assess the generalizability of our findings and support continued advancement of vaccine candidates.

Together, these chapters highlight both the immense promise and critical complexities of emerging CT prevention strategies, underscoring the continued need for research to guide policy and investment. They also serve as a reminder that scientific progress does not occur in isolation. In the United States, a shifting political landscape has increasingly vilified sexual and reproductive health, threatening access to essential services, including doxy-PEP prescription, and weakening public health infrastructure. Although our findings provide strong evidence that CT vaccination could be a cost-saving and impactful tool, evidence alone may not be sufficient to secure the support necessary to bring this intervention to scale. As we look to the future, developing new tools is not enough. We must also protect the prevention and treatment strategies we already have and ensure they remain responsive to the evolving needs of the communities most affected. This requires a commitment to health equity and scientific integrity in the face of politicization. Our work must not only envision what is possible, but also defend what is essential today.

Appendix A

Supplementary Materials for Chapter 2

Supplemental Table A.1. Reported Antibiotic Regimens: Durations & Clinically Relevant Buffer Periods Post-Regimen Completion^a

Reported Clinical Diagnosis (Antibiotic)	Regimen Duration ^b	Buffer Period ^c
<i>Chlamydia trachomatis</i>		
Azithromycin	1 Day	+ 6 Days
Doxycycline	7 Days	+ 5 Days
<i>Neisseria gonorrhoeae</i>		
Cefixime, Ceftriaxone, Gentamicin	1 Day	+ 2 Days
Azithromycin	1 Day	+ 6 Days
Syphilis		
Benzathine-penicillin ^d , Penicillin	1 Day (per shot)	+ 6 Days
Doxycycline	14 Days	+ 5 Days
Non-Gonococcal Urethritis		
Doxycycline	7 Days	+ 5 Days
Urinary Tract Infection		
Ciprofloxacin	3 – 7 Days	+ 2 Days
Moxifloxacin	5 – 7 Days	+ 2 Days
Epididymitis		
Doxycycline, Ofloxacin	10 Days	+ 2 Days
Proctitis		
Doxycycline	21 Days	+ 5 Days
Anal Fissure		
Doxycycline	7 Days	+ 2 Days
Respiratory Infection		
Azithromycin	3 – 5 Days	+ 2 Days
Doxycycline, Levofloxacin	5 Days	+ 2 Days
Bactrim	21 Days	+ 0 Days
Strep Throat		
Amoxicillin, Cephalexin	10 Days	+ 2 Days
Pneumonia		
Cephalexin	5 – 7 Days	+ 2 Days

Bronchitis		
Ciprofloxacin	5 – 7 Days	+ 2 Days
Skin Infection or Abscess (Acute)		
Vancomycin	3 – 7 Days	+ 0 Days
Bactrim, Cephalexin, Mupirocin	5 – 7 Days	+ 2 Days
Doxycycline	5 – 14 Days	+ 2 Days
Skin Infection or Acne (Chronic)		
Doxycycline, Minocycline Hydrochloride	Duration of Reporting	NA
Shigella		
Ciprofloxacin	3 – 7 Days	+ 2 Days
Giardia		
Tinidazole	1 Day	+ 7 Days
Tooth Abscess		
Penicillin	7 – 14 Days	+ 0 Days

^a Antibiotic regimens for non-STI specific conditions were most often patient reported and may not align with standard treatment practices. In instances where non-standard use was reported, we estimated potential duration and buffer periods informed by clinical practice and patient reported information.

^b Duration of antibiotic regimen, dependent on clinical diagnosis. Upper and lower bounds provided for antibiotics regimens with potential ranges in duration.

^c Clinically relevant time period post-regimen where study participants would not be prescribed the antibiotic again. Time excluded from antibiotic-specific person-time at risk.

^d Also referred to as Bicillin L-A.

Supplemental Tables A.2.A. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among All Study Participants in the ExGen Study, 2016-2018 (N = 140)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d,e} (95% CI)
Any Antibiotic Initiation	96 (69)	348	UB: 264.5 (237.5, 293.8) LB: NA	UB: 1696 LB: 1597	UB: 1289.1 (1228.5, 1352.0) LB: 1213.9 (1155.1, 1274.9)
Reason for Antibiotic Initiation					
STI Treatment	70 (50)	202	UB: 153.5 (133.1, 176.2) LB: NA	UB: 462 LB: NA	UB: 351.2 (319.9, 384.7) LB: NA
Epidemiologic Treatment for STI Contact	42 (30)	90	UB: 68.4 (55.0, 84.1) LB: NA	UB: 287 LB: NA	UB: 218.1 (193.6, 244.9) LB: NA
Other Health Condition Treatment	26 (19)	56	UB: 42.6 (32.2, 55.3) LB: NA	UB: 947 LB: 848	UB: 719.8 (674.7, 767.2) LB: 644.6 (601.9, 689.4)
Antibiotic-specific Initiation					
Doxycycline	44 (31)	66	UB: 51.5 (39.9, 65.6) LB: 51.5 (39.8, 65.5)	UB: 985 LB: 956	UB: 769.3 (722.0, 818.9) LB: 746.2 (699.6, 795.0)
Azithromycin	71 (51)	126	UB: 97.6 (81.3, 116.2) LB: 97.6 (81.3, 116.2)	UB: 146 LB: 140	UB: 113.1 (95.5, 133.0) LB: 108.4 (91.2, 127.9)
Ceftriaxone	63 (45)	95	UB: 72.6 (58.8, 88.8) LB: NA	UB: 95 LB: NA	UB: 72.6 (58.8, 88.8) LB: NA
Benzathine-penicillin	14 (10)	17	UB: 13.0 (7.5, 20.7) LB: NA	UB: 17 LB: NA	UB: 13.0 (7.5, 20.7) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 140 total participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

^e Two study participants contributed over 500 days of antibiotic use (doxycycline and/or minocycline) for the treatment of acne and other chronic skin conditions. If these contributions were removed, the following "Days of Antibiotic Use" estimates would change: Upper Bound - *Any Antibiotic Initiation*, 1171 days, IR: 890.1 (839.8, 942.6); Other Health Condition Treatment, 422 days, IR: 320.8 (290.9, 352.9); Doxycycline, 565 days, IR: 437.3 (402.0, 474.9). Lower Bound - *Any Antibiotic Initiation*, 1081 days, IR: 821.7 (773.4, 872.1); Other Health Condition Treatment, 332 days, IR: 252.4 (225.9, 281.0); Doxycycline, 545 days, IR: 421.7 (387.0, 458.6)
Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Tables A.2.B. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants Living with HIV in the ExGen Study, 2016-2018 (N = 71)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d} (95% CI)
Any Antibiotic Initiation	49 (69)	180	UB: 269.8 (231.8, 312.2) LB: NA	UB: 747 LB: 677	UB: 1119.6 (1040.7, 1202.8) LB: 1014.7 (939.7, 1094.1)
Reason for Antibiotic Initiation					
STI Treatment	37 (52)	105	UB: 157.4 (128.7, 190.5) LB: NA	UB: 216 LB: NA	UB: 323.7 (282.0, 369.9) LB: NA
Epidemiologic Treatment for STI Contact	19 (27)	44	UB: 65.9 (47.9, 88.5) LB: NA	UB: 113 LB: NA	UB: 169.4 (139.6, 203.6) LB: NA
Other Health Condition Treatment	12 (17)	31	UB: 46.5 (31.6, 65.9) LB: NA	UB: 418 LB: 348	UB: 626.5 (567.9, 689.5) LB: 521.6 (468.2, 579.4)
Antibiotic-specific Initiation					
Doxycycline	20 (28)	26	UB: 39.6 (25.9, 58.1) LB: 39.6 (25.9, 58.0)	UB: 294 LB: 276	UB: = 448.2 (398.5, 502.5) LB: = 420.5 (372.3, 473.1)
Azithromycin	38 (54)	65	UB: 99.3 (76.6, 126.5) LB: 99.3 (76.6, 126.5)	UB: 73 LB: 69	UB: 111.5 (87.4, 140.2) LB: 105.4 (82.0, 133.3)
Ceftriaxone	32 (45)	50	UB: 75.4 (56.0, 99.4) LB: NA	UB: 50 LB: NA	UB: 75.4 (56.0, 99.4) LB: NA
Benzathine-penicillin	8 (11)	9	UB: 13.5 (6.2, 25.7) LB: NA	UB: 9 LB: NA	UB: 13.5 (6.2, 25.7) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 71 participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Tables A.2.C. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants Not Living with HIV in the ExGen Study, 2016-2018 (N = 69)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d} (95% CI)
Any Antibiotic Initiation	47 (68)	168	UB: 259.1 (221.4, 301.4) LB: NA	UB: 949 LB: 920	UB: 1463.6 (1371.9, 1559.7) LB: 1418.9 (1328.6, 1513.6)
Reason for Antibiotic Initiation					
STI Treatment	33 (48)	97	UB: 149.6 (121.3, 182.5) LB: NA	UB: 246 LB: NA	UB: 379.4 (333.5, 429.9) LB: NA
Epidemiologic Treatment for STI Contact	23 (33)	46	UB: 70.9 (51.9, 94.6) LB: NA	UB: 174 LB: NA	UB: 268.3 (230.0, 311.3) LB: NA
Other Health Condition Treatment	14 (20)	25	UB: 38.6 (25.0, 56.9) LB: NA	UB: 529 LB: 500	UB: 815.8 (747.8, 888.4) LB: 771.1 (705.0, 841.8)
Antibiotic-specific Initiation					
Doxycycline	24 (35)	40	UB: 64.1 (45.8, 87.2) LB: 64.0 (45.7, 87.2)	UB: 691 LB: 680	UB: 1106.5 (1025.6, 1192.2) LB: 1088.4 (1008.1, 1173.4)
Azithromycin	33 (48)	61	UB: 95.8 (73.3, 123.1) LB: 95.8 (73.3, 123.1)	UB: 73 LB: 71	UB: 114.7 (89.9, 144.2) LB: 111.5 (87.1, 140.7)
Ceftriaxone	31 (45)	45	UB: 69.8 (50.9, 93.4) LB: NA	UB: 45 LB: NA	UB: 69.8 (50.9, 93.4) LB: NA
Benzathine-penicillin	6 (9)	8	UB: 12.4 (5.3, 24.4) LB: NA	UB: 8 LB: NA	UB: 12.4 (5.3, 24.4) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 69 total participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Tables A.2.D. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants on PrEP in the ExGen Study, 2016-2018 (N = 40)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d} (95% CI)
Any Antibiotic Initiation	30 (75)	119	UB: 316.6 (262.3, 378.8) LB: NA	UB: 769 LB: 746	UB: 2045.8 (1903.8, 2195.7) LB: 1984.6 (1844.7, 2132.3)
Reason for Antibiotic Initiation					
STI Treatment	20 (50)	62	UB: 164.9 (126.5, 211.4) LB: NA	UB: 143 LB: NA	UB: 380.4 (320.6, 448.1) LB: NA
Epidemiologic Treatment for STI Contact	17 (43)	35	UB: 93.1 (64.9, 129.5) LB: NA	UB: 118 LB: NA	UB: 313.9 (259.8, 375.9) LB: NA
Other Health Condition Treatment	11 (28)	22	UB: 58.5 (36.7, 88.6) LB: NA	UB: 508 LB: 485	UB: 1351.5 (1236.5, 1474.3) LB: 1290.3 (1178.0, 1410.4)
Antibiotic-specific Initiation					
Doxycycline	15 (38)	26	UB: 72.7 (47.5, 106.6) LB: 72.7 (47.5, 106.5)	UB: 558 LB: 547	UB: 1560.8 (1434.0, 1695.9) LB: 1528.8 (1403.3, 1662.4)
Azithromycin	23 (58)	43	UB: 117.0 (84.7, 157.6) LB: 117.0 (84.7, 157.6)	UB: 55 LB: 53	UB: 149.6 (112.7, 194.8) LB: 144.2 (108.0, 188.6)
Ceftriaxone	22 (55)	31	UB: 83.0 (56.4, 117.9) LB: NA	UB: 31 LB: NA	UB: 83.0 (56.4, 117.9) LB: NA
Benzathine-penicillin	5 (13)	7	UB: 18.7 (7.5, 38.5) LB: NA	UB: 7 LB: NA	UB: 18.7 (7.5, 38.5) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 40 total participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Tables A.2.E. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants Not Living with HIV, Not on PrEP in the ExGen Study, 2016-2018 (N = 29)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d} (95% CI)
Any Antibiotic Initiation	17 (59)	49	UB: 179.8 (133.0, 237.7) LB: NA	UB: 180 LB: 174	UB: 660.5 (567.5, 764.4) LB: 638.5 (547.1, 740.7)
Reason for Antibiotic Initiation					
STI Treatment	13 (45)	35	UB: 128.4 (89.5, 178.6) LB: NA	UB: 103 LB: NA	UB: 378.0 (308.5, 458.4) LB: NA
Epidemiologic Treatment for STI Contact	6 (21)	11	UB: 40.4 (20.1, 72.2) LB: NA	UB: 56 LB: NA	UB: 205.5 (155.2, 266.8) LB: NA
Other Health Condition Treatment	3 (10)	3	UB: 11.0 (2.3, 32.2) LB: NA	UB: 21 LB: 15	UB: 77.1 (47.7, 117.8) LB: 55.0 (30.8, 90.8)
Antibiotic-specific Initiation					
Doxycycline	9 (31)	14	UB: 52.4 (28.7, 88.0) LB: 52.4 (28.7, 88.0)	UB: 133 LB: 133	UB: 498.2 (417.1, 590.4) LB: 498.2 (417.1, 590.4)
Azithromycin	10 (34)	18	UB: 66.9 (39.6, 105.7) LB: 66.9 (39.6, 105.7)	UB: 18 LB: 18	UB: 66.9 (39.6, 105.7) LB: 66.9 (39.6, 105.7)
Ceftriaxone	9 (31)	14	UB: 51.6 (28.2, 86.6) LB: NA	UB: 14 LB: NA	UB: 51.6 (28.2, 86.6) LB: NA
Benzathine-penicillin	1 (3)	1	UB: 3.7 (0.1, 20.5) LB: NA	UB: 1 LB: NA	UB: 3.7 (0.1, 20.5) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 29 total participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Tables A.2.F. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants with a Bacterial STI Diagnosis 12 Months Prior to Enrollment in the ExGen Study, 2016-2018 (N = 104)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d} (95% CI)
Any Antibiotic Initiation	77 (74)	293	UB: 299.8 (266.5, 336.2) LB: NA	UB: 1111 LB: 1050	UB: 1136.8 (1070.9, 1205.7) LB: 1074.4 (1010.4, 1141.4)
Reason for Antibiotic Initiation					
STI Treatment	58 (56)	175	UB: 179.1 (153.5, 207.6) LB: NA	UB: 389 LB: NA	UB: 398.0 (359.5, 439.6) LB: NA
Epidemiologic Treatment for STI Contact	36 (35)	77	UB: 78.8 (62.2, 98.5) LB: NA	UB: 255 LB: NA	UB: 260.9 (229.9, 295.0) LB: NA
Other Health Condition Treatment	20 (19)	41	UB: 42.0 (30.1, 56.9) LB: NA	UB: 467 LB: 406	UB: 477.8 (435.5, 523.2) LB: 415.4 (376.0, 457.9)
Antibiotic-specific Initiation					
Doxycycline	36 (35)	55	UB: 57.6 (43.4, 75.0) LB: 57.6 (43.4, 74.9)	UB: 558 LB: 538	UB: 584.3 (536.8, 634.8) LB: 563.0 (516.4, 612.7)
Azithromycin	60 (58)	110	UB: 115.0 (94.5, 138.7) LB: 115.0 (94.5, 138.6)	UB: 126 LB: 120	UB: 131.8 (109.8, 156.9) LB: 125.5 (104.0, 150.0)
Ceftriaxone	55 (53)	84	UB: 86.6 (69.0, 107.2) LB: NA	UB: 84 LB: NA	UB: 86.6 (69.0, 107.2) LB: NA
Benzathine-penicillin	11 (11)	13	UB: 13.3 (7.1, 22.8) LB: NA	UB: 13 LB: NA	UB: 13.3 (7.1, 22.8) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 104 total participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Tables A.2.G. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants without a Bacterial STI Diagnosis 12 Months Prior to Enrollment in the ExGen Study, 2016-2018 (N = 36)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d} (95% CI)
Any Antibiotic Initiation	19 (53)	55	UB: 162.6 (122.5, 211.6) LB: NA	UB: 585 LB: 547	UB: 1729.2 (1591.9, 1875.2) LB: 1616.9 (1484.2, 1758.3)
Reason for Antibiotic Initiation					
STI Treatment	12 (33)	27	UB: 79.8 (52.6, 116.1) LB: NA	UB: 73 LB: NA	UB: 215.8 (169.1, 271.3) LB: NA
Epidemiologic Treatment for STI Contact	6 (17)	13	UB: 38.4 (20.5, 65.7) LB: NA	UB: 32 LB: NA	UB: 94.6 (64.7, 133.5) LB: NA
Other Health Condition Treatment	6 (17)	15	UB: 44.3 (24.8, 73.1) LB: NA	UB: 480 LB: 442	UB: 1418.9 (1294.7, 1551.6) LB: 1306.5 (1187.5, 1434.2)
Antibiotic-specific Initiation					
Doxycycline	8 (22)	11	UB: 33.8 (16.9, 60.5) LB: 33.8 (16.9, 60.5)	UB: 427 LB: 418	UB: 1312.6 (1191.0, 1443.2) LB: 1283.9 (1163.8, 1413.1)
Azithromycin	11 (31)	16	UB: 47.7 (27.3, 77.5) LB: 47.7 (27.3, 77.5)	UB: 20 LB: 20	UB: 59.7 (36.5, 92.2) LB: 59.7 (36.5, 92.2)
Ceftriaxone	8 (22)	11	UB: 32.6 (16.3, 58.3) LB: NA	UB: 11 LB: NA	UB: 32.6 (16.3, 58.3) LB: NA
Benzathine-penicillin	3 (8)	4	UB: 11.9 (3.2, 30.3) LB: NA	UB: 4 LB: NA	UB: 11.9 (3.2, 30.3) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 36 total participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Tables A.2.H. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants Under 25 Years of Age in the ExGen Study, 2016-2018 (N = 14)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d} (95% CI)
Any Antibiotic Initiation	10 (71)	29	UB: 220.4 (147.6, 316.6) LB: NA	UB: 238 LB: 229	UB: 1809.0 (1586.5, 2054.1) LB: 1740.6 (1522.5, 1981.3)
Reason for Antibiotic Initiation					
STI Treatment	7 (50)	16	UB: 121.6 (69.5, 197.5) LB: NA	UB: 34 LB: NA	UB: 258.4 (179.0, 361.1) LB: NA
Epidemiologic Treatment for STI Contact	4 (29)	9	UB: 68.4 (31.3, 129.9) LB: NA	UB: 21 LB: NA	UB: 159.6 (98.8, 244.0) LB: NA
Other Health Condition Treatment	2 (14)	4	UB: 30.4 (8.3, 77.8) LB: NA	UB: 183 LB: 174	UB: 1391.0 (1196.7, 1607.8) LB: 1322.6 (1133.4, 1534.4)
Antibiotic-specific Initiation					
Doxycycline	4 (29)	7	UB: 54.8 (22.0, 112.9) LB: 54.7 (22.0, 112.7)	UB: 112 LB: 103	UB: 876.7 (721.9, 1054.9) LB: 804.7 (656.8, 975.9)
Azithromycin	7 (50)	11	UB: 85.0 (42.4, 152.0) LB: 85.0 (42.4, 152.0)	UB: 11 LB: 11	UB: 85.0 (42.4, 152.0) LB: 85.0 (42.4, 152.0)
Ceftriaxone	4 (29)	6	UB: 45.8 (16.8, 99.6) LB: NA	UB: 6 LB: NA	UB: 45.8 (16.8, 99.6) LB: NA
Benzathine-penicillin	2 (14)	2	UB: 15.2 (1.8, 55.1) LB: NA	UB: 2 LB: NA	UB: 15.2 (1.8, 55.1) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 14 total participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Tables A.2.I. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants 25 – 39 Years of Age in the ExGen Study, 2016-2018 (N = 74)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d} (95% CI)
Any Antibiotic Initiation	55 (74)	220	UB: 316.4 (275.9, 361.0) LB: NA	UB: 683 LB: 640	UB: 982.2 (909.9, 1058.7) LB: 920.3 (850.4, 994.5)
Reason for Antibiotic Initiation					
STI Treatment	42 (57)	130	UB: 186.9 (156.2, 222.0) LB: NA	UB: 300 LB: NA	UB: 431.4 (384.0, 483.1) LB: NA
Epidemiologic Treatment for STI Contact	29 (39)	64	UB: 92.0 (70.9, 117.5) LB: NA	UB: 198 LB: NA	UB: 284.7 (246.4, 327.3) LB: NA
Other Health Condition Treatment	11 (15)	26	UB: 37.4 (24.4, 54.8) LB: NA	UB: 185 LB: 142	UB: 266.0 (229.1, 307.3) LB: 204.2 (172.0, 240.7)
Antibiotic-specific Initiation					
Doxycycline	28 (38)	40	UB: 58.8 (42.0, 80.1) LB: 58.8 (42.0, 80.1)	UB: 364 LB: 353	UB: 535.2 (481.6, 593.1) LB: 518.8 (466.1, 575.8)
Azithromycin	41 (55)	80	UB: 117.6 (93.3, 146.4) LB: 117.6 (93.3, 146.4)	UB: 84 LB: 82	UB: 123.5 (98.5, 152.9) LB: 120.6 (95.9, 149.7)
Ceftriaxone	41 (55)	66	UB: 95.7 (74.0, 121.7) LB: NA	UB: 66 LB: NA	UB: 95.7 (74.0, 121.7) LB: NA
Benzathine-penicillin	8 (11)	11	UB: 15.9 (7.9, 28.4) LB: NA	UB: 11 LB: NA	UB: 15.9 (7.9, 28.4) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 74 total participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Tables A.2.J. Secondary Analysis - Incidence of Antibiotic Initiation & Days of Antibiotic Use Among Study Participants 40+ Years of Age in the ExGen Study, 2016-2018 (N = 52)

Outcome	Cumulative Use ^a N (%)	Antibiotic Initiation		Days of Antibiotic Use	
		# of Events	Incidence Rate ^{b,c} (95% CI)	# of Days	Incidence Rate ^{b,d} (95% CI)
Any Antibiotic Initiation	31 (60)	99	UB: 202.6 (164.7, 246.7) LB: NA	UB: 775 LB: 728	UB: 1586.0 (1476.3, 1701.7) LB: 1489.8 (1383.5, 1602.1)
Reason for Antibiotic Initiation					
STI Treatment	21 (40)	56	UB: 114.6 (86.6, 148.8) LB: NA	UB: 128 LB: NA	UB: 261.9 (218.5, 311.5) LB: NA
Epidemiologic Treatment for STI Contact	9 (17)	17	UB: 34.8 (20.3, 55.7) LB: NA	UB: 68 LB: NA	UB: 139.2 (108.1, 176.4) LB: NA
Other Health Condition Treatment	13 (25)	26	UB: 53.2 (34.8, 78.0) LB: NA	UB: 579 LB: 532	UB: 1184.9 (1090.3, 1285.4) LB: 1088.7 (998.1, 1185.3)
Antibiotic-specific Initiation					
Doxycycline	12 (23)	19	UB: 40.2 (24.2, 62.8) LB: 40.2 (24.2, 62.8)	UB: 509 LB: 500	UB: 1077.3 (985.7, 1175.0) LB: 1057.7 (967.0, 1154.6)
Azithromycin	23 (44)	35	UB: 72.6 (50.6, 101.0) LB: 72.6 (50.6, 101.0)	UB: 51 LB: 47	UB: 105.8 (78.8, 139.2) LB: 97.5 (71.7, 129.7)
Ceftriaxone	18 (35)	23	UB: 47.3 (30.0, 70.9) LB: NA	UB: 23 LB: NA	UB: 47.3 (30.0, 70.9) LB: NA
Benzathine-penicillin	4 (8)	4	UB: 8.2 (2.2, 21.0) LB: NA	UB: 4 LB: NA	UB: 8.2 (2.2, 21.0) LB: NA

^a Cumulative number of study participants reporting antibiotic use during follow-up, among 52 total participants

^b Incidence per 100 person-years at risk

^c Upper- and lower-bound estimates for incidence of antibiotic initiation incorporate removal of person-time at risk based on duration ranges for antibiotic regimens outlined in Supplemental Table A.1.

^d Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1. For estimates without a range of possible regimen durations, the lower bound estimate is listed as NA.

Abbreviations: CI, confidence interval; STI, sexually transmitted infection; UB, upper bound; LB, lower bound; NA, not applicable

Supplemental Table A.3. Days of Antibiotic Use for the Treatment of Other Health Conditions Among Study Participants in the ExGen Study, 2016-2018

Health Condition	# of Study Participants ^a	# of Days (% of Total Days for Other Health Conditions) ^b	
	N (%)	Lower Bound	Upper Bound
Acne and Chronic Skin Infections ^c	2 (1.4%)	511 (60.3%)	511 (54.0%)
Acute Skin and Soft Tissue Infections	8 (5.7%)	73 (8.6%)	126 (13.3%)
Dental Infections	2 (1.4%)	14 (1.7%)	28 (3.0%)
Gastrointestinal Infections	4 (2.9%)	16 (1.9%)	20 (2.1%)
Genitourinary Infections	2 (1.4%)	23 (2.7%)	27 (2.9%)
Respiratory and ENT (Ear, Nose, Throat) Infections	11 (7.9%)	184 (21.7%)	202 (21.3%)
Not Reported	7 (5.0%)	27 (3.2%)	33 (3.5%)
Total	26 (18.6%)	848 (100%)	947 (100%)

^a Cumulative number of study participants reporting antibiotic use by condition, among 140 total participants. As participants could take antibiotics for multiple conditions, the estimate for 'Total' will not equal the sum of all conditions.

^b Upper- and lower-bound estimates for days of antibiotic use are based on ranges for antibiotic regimens outlined in Supplemental Table A.1.

^c No range for acne and chronic skin infection regimens, as duration was the time reporting use only.

Supplemental Table A.4. Factors Associated with Antibiotic Initiation for STI Treatment in the ExGen Study, 2016-2018

Predictors	Univariate Analysis ^a		Multivariate Analysis ^a	
	IRR (95% CI)	p-value	IRR (95% CI)	p-value
HIV/PrEP Status				
PNWH, not on PrEP	1.00	--	--	--
PNWH, on PrEP	1.28 (0.63, 2.61)	0.49	--	--
PWH	1.23 (0.65, 2.31)	0.53	--	--
Age Group				
40+ years	1.00	--	1.00	--
25 – 39 years	1.63 (0.98, 2.70)	0.06	1.58 (0.93, 2.69)	0.09
18 – 24 years	1.06 (0.48, 2.34)	0.88	1.22 (0.47, 3.17)	0.68
History of chronic medical conditions ^b	1.02 (0.65, 1.60)	0.93	--	--
Reported methamphetamine use ^c	0.85 (0.53, 1.37)	0.51	--	--
Race/ethnicity				
Non-Hispanic White/Caucasian	1.00	--	1.00	--
Hispanic/Latinx	1.07 (0.59, 1.92)	0.83	0.99 (0.52, 1.87)	0.97
Non-Hispanic Black/African American	0.84 (0.43, 1.66)	0.62	1.00 (0.47, 2.13)	0.99
Another Race/Ethnicity	0.61 (0.30, 1.23)	0.17	0.71 (0.35, 1.41)	0.32
History of bacterial STI diagnosis, <12 months prior to enrollment ^d	2.24 (1.18, 4.25)	0.01	2.18 (1.16, 4.11)	0.02

^a Implemented negative binomial regression with generalized estimating equations

^b Compared to no history of chronic medical conditions

^c Compared to no reported methamphetamine use

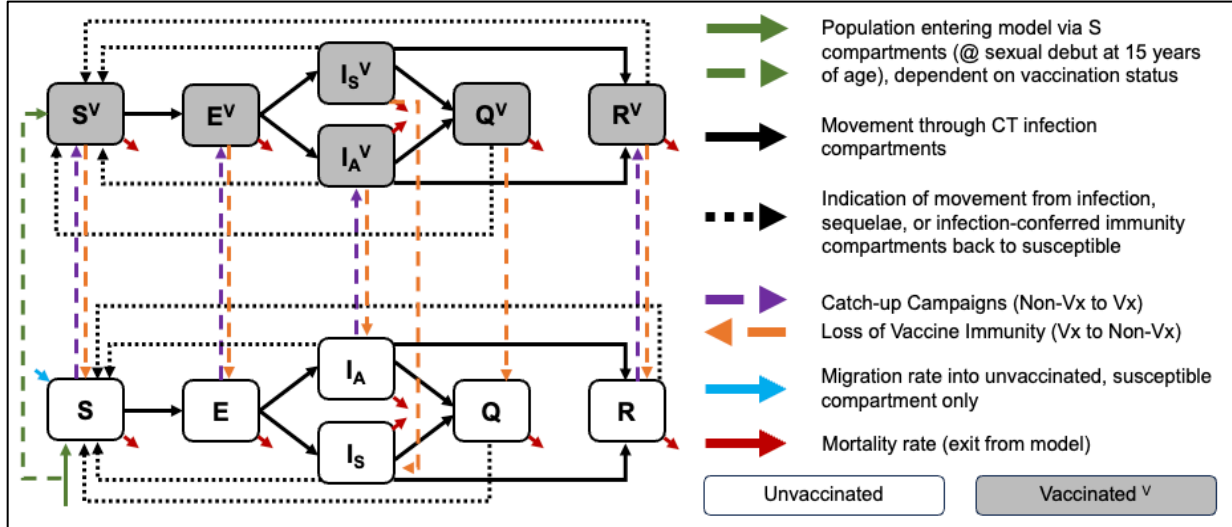
^d Compared to no history of bacterial STI diagnosis, <12 months prior to enrollment

Abbreviations: IRR, incidence rate ratio; CI, confidence interval; PWH, people living with HIV; PNWH, people not living with HIV; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection

Appendix B

Supplementary Materials for Chapter 3

B.1 MODEL STRUCTURE



The model comprises 72 ordinary differential equations, structured across 12 disease stage compartments, 2 biological sex groups, and 3 age groups, with indexing as follows:

- Biological sex at birth $j \in \{1 = \text{male}; 2 = \text{female}\}$
- Age group $k \in \{1 = 15\text{-}24 \text{ years}; 2 = 25\text{-}39 \text{ years}; 3 = 40\text{-}64 \text{ years}\}$

Compartments among the simulated, unvaccinated population include:

- $S_{j,k}$: Susceptible population of sex j and age group k
- $E_{j,k}$: Infected, non-infectious population of sex j and age group k
- $I_{S,j,k}$: Symptomatically infected, infectious population of sex j and age group k
- $I_{A,j,k}$: Asymptomatically infected, infectious population of sex j and age group k
- $Q_{j,k}$: Sequelae-experiencing population of sex j and age group k , where $j = 1$ for epididymitis; $j = 2$ for pelvic inflammatory disease (PID)
- $R_{j,k}$: Infection-conferred immune population (natural recovery) of sex j and age group k

Compartments among the simulated, vaccinated population include:

- $S^v_{j,k}$: Susceptible population of sex j and age group k

- $E_{j,k}^V$: Infected, non-infectious population of sex j and age group k
- $Is_{j,k}^V$: Symptomatically infected, infectious population of sex j and age group k
- $Ia_{j,k}^V$: Asymptomatically infected, infectious population of sex j and age group k
- $Q_{j,k}^V$: Sequelae-experiencing population of sex j and age group k , where $j = 1$ for epididymitis; $j = 2$ for pelvic inflammatory disease (PID)
- $R_{j,k}^V$: Infection-conferred immune population (natural recovery) of sex j and age group k

Model parameters include:

- η : Relative size of the population entering the model at age 15 (“birth” rate), dependent on time t
- N : Total size of the simulated population, dependent on time t
- ξ : Migration rate into susceptible, unvaccinated compartment ($S_{j,k}$), dependent on time t
- μ : Background mortality rate among simulated population, dependent on time t
- $\chi_{j,k}$: Rate of aging transition, among individuals from age group k to age group $k+1$, with aging into the youngest age group ($k = 1$) defined by separate ‘birth rate’ parameters
- Vx_j : Proportion of individuals of sex j vaccinated upon entering the population at age 15 years
- $\beta_{j,k}$: Rate of vaccination coverage via catch-up campaigns, among individuals of sex j and age group k
- θ_k : Rate of waning vaccination immunity
- VE_s : Vaccine efficacy, defined as the proportional reduction in susceptibility to infection, comparing vaccinated to unvaccinated individuals
- $\lambda_{j,k}$: Force of infection on susceptible individuals of sex j and age group k
- φ : Rate of transition of infected individuals from exposed, non-infectious to infectious (1/incubation period)
- ζ_j : Proportion of infections that present symptomatically, among individuals of sex j

- $\tau_{j,k}$: Recovery rate of symptomatically infected individuals due to treatment, among individuals of sex j and age group k , calculated as the product of:
 - dur_tx_j : Duration of treated infection, among individuals of sex j
 - ε : Sensitivity of diagnostic testing for CT detection
 - p_txt : Probability of treatment for symptomatic infection
 - tx_eff : Efficacy of antibiotic treatment among individuals receiving treatment
- $\gamma_{j,k}$: Recovery rate of asymptomatically infected individuals due to screen-and-treat, among individuals of sex j and age group k , calculated as the product of:
 - $r_{j,k}$: Annual screening rate for CT, among individuals of sex j and age group k
 - ε : Sensitivity of diagnostic testing for CT detection
 - ν : Probability of post-screening treatment among individuals following a positive nucleic acid amplification test (NAAT) result
 - tx_eff : Efficacy of antibiotic treatment among individuals receiving treatment
- ι : Rate of natural resolution among untreated symptomatic or asymptomatic infection
- κ_j : Proportion of resolved symptomatic or asymptomatic infections that develop into sequelae, among individuals of sex j
- ϖ_j : Rate of sequelae resolution, among individuals of sex j
- ψ : Rate of waning infection-conferred immunity

The force of infection $\lambda_{j,k}$ on susceptible individuals of sex j and age group k was estimated as:

$$\lambda_{j,k} = c_{j,k} * \sum_{j'} \left[(1 - \delta_{jj'}) \sum_{k'} t_{j,k,j',k'} * m_{j,k,j',k'} \frac{I_{j',k'}^{Inf}}{N_{j',k'}} \right], \text{ where:}$$

- $c_{j,k}$: Sexual partner change (number of sexual partners in the past 12 months), among susceptible individuals of sex j and age group k
- $\delta_{jj'}$: Kronecker delta function, where $\delta_{jj'} = 1$ if individuals of $j = j'$, ensuring heterosexual mixing only

- $t_{j,k,j',k'}$: Transmission probability per sexual partnership from an infected individual of sex j' and age group k' to a susceptible individual of sex j and age group k
- $m_{j,k,j',k'}$: Number of partners that susceptible individual of sex j and age group k has from sex j' and age group k' . It is based on the sexual mixing equation, representing partial assortative mixing between age groups k and k' , estimated as:

$$m_{j,k,j',k'} = (1 - \delta_{jj'}) \left[\rho \delta_{kk'} + (1 - \rho) \left(\frac{c_{j',k'} * N_{j',k'}}{\sum_{k'} c_{j',k'} * N_{j',k'}} \right) \right], \text{ where:}$$

- ρ : Assortative coefficient, where $\rho = 0$ if fully proportionate mixing and $\rho = 1$ if fully assortative mixing
- $c_{j',k'}$: Sexual partner change (number of sexual partners in the past 12 months), among sexual contacts of sex j' and age group k'
- $N_{j',k'}$: Total population size among sexual contacts of sex j' and age group k'
- $I_{j',k'}^{Inf}$: Infectious individuals among sex j' and age group k' , dependent on time t estimated as:

$$I_{j',k'}^{Inf} = I_{S_{j',k'}} + I_{a_{j',k'}} + I_{S_{j',k'}^V} + I_{a_{j',k'}^V}$$

The model is defined by the following sets of differential equations:

- Unvaccinated Individuals

$$\begin{aligned} \frac{d}{dt} S_{j,k} = & -\lambda_{j,k} S_{j,k} - \beta_{j,k} S_{j,k} - \chi_{j,k} S_{j,k} - \mu S_{j,k} + \varpi_j Q_{j,k} + \psi R_{j,k} + \tau_{j,k} I_{S_{j,k}} + \gamma_{j,k} I_{a_{j,k}} \\ & + (1 - Vx_j) \eta N_j + \theta_k S_{j,k}^V + \xi N_{j,k} + \chi_{j,k-1} S_{j,k-1} \end{aligned}$$

$$\frac{d}{dt} E_{j,k} = -\beta_{j,k} E_{j,k} - \varphi E_{j,k} - \chi_{j,k} E_{j,k} - \mu E_{j,k} + \lambda_{j,k} S_{j,k} + \theta_k E_{j,k}^V + \chi_{j,k-1} E_{j,k-1}$$

$$\begin{aligned} \frac{d}{dt} I_{S_{j,k}} = & -\tau_{j,k} I_{S_{j,k}} - \kappa_j I_{S_{j,k}} - (1 - \kappa_j) I_{S_{j,k}} - \chi_{j,k} I_{S_{j,k}} - \mu I_{S_{j,k}} + \zeta_j \varphi E_{j,k} + \theta_k I_{S_{j,k}}^V \\ & + \chi_{j,k-1} I_{S_{j,k-1}} \end{aligned}$$

$$\begin{aligned}\frac{d}{dt}Ia_{j,k} = & -\beta_{j,k}Ia_{j,k} - \gamma_{j,k}Ia_{j,k} - \kappa_j\iota Ia_{j,k} - (1 - \kappa_j)\iota Ia_{j,k} - \chi_{j,k}Ia_{j,k} - \mu Ia_{j,k} + (1 - \zeta_j)\varphi E_{j,k} \\ & + \theta_k Ia_{j,k}^V + \chi_{j,k-1}Ia_{j,k-1}\end{aligned}$$

$$\frac{d}{dt}Q_{j,k} = -\varpi_j Q_{j,k} - \chi_{j,k}Q_{j,k} - \mu Q_{j,k} + \kappa_j\iota(Is_{j,k} + Ia_{j,k}) + \theta_k Q_{j,k}^V + \chi_{j,k-1}Q_{j,k-1}$$

$$\begin{aligned}\frac{d}{dt}R_{j,k} = & -\beta_{j,k}R_{j,k} - \psi R_{j,k} - \chi_{j,k}R_{j,k} - \mu R_{j,k} + (1 - \kappa_j)\iota(Is_{j,k} + Ia_{j,k}) + \theta_k R_{j,k}^V \\ & + \chi_{j,k-1}R_{j,k-1}\end{aligned}$$

▪ Vaccinated Individuals

$$\begin{aligned}\frac{d}{dt}S_{j,k}^V = & -(1 - VE_S)\lambda_{j,k}S_{j,k}^V - \theta_k S_{j,k}^V - \chi_{j,k}S_{j,k}^V - \mu S_{j,k}^V + \varpi_j Q_{j,k}^V + \psi R_{j,k}^V + \tau_{j,k}Is_{j,k}^V \\ & + \gamma_{j,k}Ia_{j,k}^V + Vx_j\eta N_j + \chi_{j,k-1}S_{j,k-1}^V + \beta_{j,k}S_{j,k}\end{aligned}$$

$$\frac{d}{dt}E_{j,k}^V = -\varphi E_{j,k}^V - \theta_k E_{j,k}^V - \chi_{j,k}E_{j,k}^V - \mu E_{j,k}^V + (1 - VE_S)\lambda_{j,k}S_{j,k}^V + \chi_{j,k-1}E_{j,k-1}^V + \beta_{j,k}E_{j,k}$$

$$\begin{aligned}\frac{d}{dt}Is_{j,k}^V = & -\tau_{j,k}Is_{j,k}^V - \kappa_j\iota Is_{j,k}^V - (1 - \kappa_j)\iota Is_{j,k}^V - \theta_k Is_{j,k}^V - \chi_{j,k}Is_{j,k}^V - \mu Is_{j,k}^V + \zeta_j\varphi E_{j,k}^V \\ & + \chi_{j,k-1}Is_{j,k-1}^V\end{aligned}$$

$$\begin{aligned}\frac{d}{dt}Ia_{j,k}^V = & -\gamma_{j,k}Ia_{j,k}^V - \kappa_j\iota Ia_{j,k}^V - (1 - \kappa_j)\iota Ia_{j,k}^V - \theta_k Ia_{j,k}^V - \chi_{j,k}Ia_{j,k}^V - \mu Ia_{j,k}^V + (1 - \zeta_j)\varphi E_{j,k}^V \\ & + \chi_{j,k-1}Ia_{j,k-1}^V + \beta_{j,k}Ia_{j,k}\end{aligned}$$

$$\frac{d}{dt}Q_{j,k}^V = -\varpi_j Q_{j,k}^V - \theta_k Q_{j,k}^V - \chi_{j,k}Q_{j,k}^V - \mu Q_{j,k}^V + \kappa_j\iota(Is_{j,k}^V + Ia_{j,k}^V) + \chi_{j,k-1}Q_{j,k-1}^V$$

$$\begin{aligned}\frac{d}{dt}R_{j,k}^V = & -\psi R_{j,k}^V - \theta_k R_{j,k}^V - \chi_{j,k}R_{j,k}^V - \mu R_{j,k}^V + (1 - \kappa_j)\iota(Is_{j,k}^V + Ia_{j,k}^V) + \chi_{j,k-1}R_{j,k-1}^V \\ & + \beta_{j,k}R_{j,k}\end{aligned}$$

B.2 PARAMETER VALUES

Supplemental Table B.1. Fixed model parameters

Parameter Description	Group	Value	Source
Initial population size	Females, 15-24 years	19,026,294	1
	Females, 25-39 years	30,676,316	
	Females, 40-64 years	42,859,021	
	Males, 15-24 years	20,572,554	
	Males, 25-39 years	32,388,974	
	Males, 40-64 years	41,988,110	
"Birth" rate (η)	Females/Males	Year-dependent	1
Aging rate ($\chi_{j,k}$)	By age group	Year-dependent	1
Migration rate (ξ)	All groups	Year-dependent	1
Background mortality rate	All groups	Year-dependent	1
Incubation period (φ)	All groups	14 days	2,3
Average duration of infection-conferred immunity (ψ)	All groups	1 year	2,4
Probability of treatment, symptomatic (p_{txt})	All groups	0.89	2,5
Treatment efficacy (tx_{eff})	All groups	0.95	2,6
Sensitivity of CT diagnostic test (ε)	All groups	0.96	7-9
Post-screening treatment probability (ν)	All groups	0.80	2,10
Average duration of sequelae (epididymitis for males; PID and complications for females; ϖ_j)	Females	60 days	2,11,12
	Males	21 days	

Supplemental Table B.2. Calibration parameters

Parameter Description	Group	Range	Source
Probability of symptomatic infection (ζ_j)	Females	0.1 – 0.3	2,13-16
	Males	0.4 – 0.6	2,13-16
Probability of sequelae, given untreated infection (κ_j)	Females	0.10 – 0.14	2,17,18
	Males	0.01 – 0.03	2,19,20
Duration of treated symptomatic infection (dur_{tx_j})	Females	35 – 49 days	3,14,15
	Males	28 – 42 days	3,14,15
Duration of untreated infection (to natural resolution; ι)	All groups	1.25 – 2.0 years	2,3,21,22
Probability of annual screening for CT ($r_{j,k}$)	Females, 15-24 years	0.35 – 0.48	2,23-27
	Females, 25-39 years	0.35 – 0.41	
	Females, 40-64 years	0.18 – 0.25	
	Males, 15-24 years	0.01 – 0.02	2,28-30
	Males, 25-39 years	0.04 – 0.06	
	Males, 40-64 years	0.03 – 0.05	
Sexual partner change (number of sexual partners in the past 12 months; $c_{j,k}$)	Females, 15-24 years	2.4 – 2.9	2,20,31,32,Model assumption
	Females, 25-39 years	1.2 – 1.6	
	Females, 40-64 years	0.6 – 1.1	
	Males, 15-24 years	0.8 – 1.1	
	Males, 25-39 years	0.8 – 1.2	
	Males, 40-64 years	0.5 – 0.8	
Per partner transmission probability ()	Female-to-Male	0.8 – 0.99	2,33,Model assumption
	Male-to-Female	0.8 – 0.99	
Assortative mixing by age group (ρ)	All groups	0.85 – 0.95	2,14,34,Model assumption

Supplemental Table B.3. Vaccination parameters

Parameter Description	Group	Range
Vaccination coverage in 2035 (increasing linearly beginning in 2025), among individuals entering model @ 15 years (Vx_j)	Females	30%, 50%, 70%
	Males	0%, 30%, 50%, 70%
Vaccination coverage via catch-up campaigns in 2035, among 15-24-year-olds only ($\beta_{j,k}$)	Females	5%, 10%, 15%
Duration of vaccine-conferred immunity (θ_k)	All groups	0.5, 1, 5, 10, 20 years
Vaccine efficacy, defined as the proportional reduction in susceptibility to infection, comparing vaccinated to unvaccinated individuals (VE_s)	All groups	10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%

B.3 ANNUAL CT CASE DATA FOR MODEL CALIBRATION

NCHHSTP AtlasPlus data for model calibration was estimated using a similar analytical approach by Learner et al. (2020) and described briefly in Chapter 2 Methods.²³ Below, details on the analytic approach, parameter selection, results, and methodological limitations are provided.

Analytic Approach

Analytic Approach - Females

Adjusted annual CT cases among females aged 15-24, 25-39, and 40-64 years were estimated as the sum of infections due to either treatment-seeking behaviors (symptomatic infections, exposure, etc.) or annual screen-and-treat services (asymptomatic infections) in a given year. Case counts from treatment-seeking behaviors in a given year (A_T) were calculated by adjusting the reported cases from AtlasPlus (C_R) due to treatment-seeking behaviors ($1 - p_{scr}$) and imperfect reporting to the CDC (R), where p_{scr} represents the proportion of all diagnosed CT cases due to screening:

$$A_T = \frac{C_R * (1 - p_{scr})}{R}$$

This assumes all diagnosed cases from treatment-seeking behaviors were reported to the CDC. Adjusted CT case counts from annual asymptomatic screening (A_S) were estimated through a multi-step process accounting for under-reporting, diagnostic test performance, and screening coverage. Sensitivity (Se) and specificity (Sp) of CT diagnostic testing were calculated as weighted averages dependent on the sensitivity and specificity of NAAT (Se_{NAAT} ; Sp_{NAAT}) and non-NAAT ($Se_{NonNAAT}$; $Sp_{NonNAAT}$) diagnostic tests and the proportion of NAAT tests among all diagnostic tests performed in a given year (Pr_{NAAT}):

$$Se = (Pr_{NAAT} * Se_{NAAT}) + (1 - Pr_{NAAT})(Se_{NonNAAT})$$

$$Sp = (Pr_{NAAT} * Sp_{NAAT}) + (1 - Pr_{NAAT})(Sp_{NonNAAT})$$

The prevalence of true asymptomatic CT in the screened population (P) was estimated using reported cases due to screening ($C_R \times p_{scr}$), reporting fraction (R), the total at-risk population (N_F), age- and year-specific screening coverage among the at-risk population (Sc), and weighted-average diagnostic test performance (Se ; Sp). The total at-risk population (N_F) was estimated as the product of the total population size and the proportion of women eligible for screening, by age and year.

$$P = \frac{\frac{C_R * p_{scr}}{R} - Sc * N_F(1 - Sp)}{Sc * N_F(Se + Sp - 1)}$$

False positive diagnoses among females screened (FrT) were estimated using the weighted-average specificity (Sp), prevalence of true asymptomatic CT in the screened population (P), the screening coverage (Sc), and the total at-risk population (N_F):

$$FrT = (1 - Sp)(1 - P) * Sc * N_F$$

The number of true CT cases among females screened in a given year (A) was estimated as:

$$A = \frac{\frac{C_R * p_{scr}}{R} - FrT}{Se}$$

Finally, the total number of infections that would be expected as a result of asymptomatic screening (A_s), assuming perfect reporting, diagnostic testing, and screening coverage, were estimated as the quotient of the number of true CT cases among females screened in a given year (A) and the screening coverage (Sc):

$$A_s = \frac{A}{Sc}$$

The total adjusted, annual CT cases ($Total\ Cases_{Female}$) were the sum of infections due to treatment-seeking behaviors (A_T) and annual screening (A_s):

$$Total\ Cases_{Female} = A_T + A_s$$

Analytic Approach - Males

Adjusted annual CT cases among males aged 15-24, 25-39, and 40-64 years were estimated as the sum of infections due to either treatment-seeking behaviors (symptomatic infections, exposure, etc.), annual screen-and-treat services (asymptomatic among men who have sex with men, high-risk men who have sex with women, etc.), or asymptomatic infections unaccounted for by treatment-seeking behaviors or screen-and-treat services (low-risk men who have sex with women) in a given year. Low-risk men who have sex with women are unlikely to receive any screening services; therefore, diagnosis of cases in this population rely on treatment seeking behaviors that would not capture all asymptomatic infections and need to be further accounted for in case adjustments.³⁵

Case counts from treatment-seeking behaviors in a given year (A_T) were calculated by adjusting the reported cases from AtlasPlus (C_R) due to treatment-seeking behaviors ($1 - p_{scr}$) and imperfect reporting to the CDC (R), where p_{scr} represents the proportion of all diagnosed CT cases due to screening:

$$A_T = \frac{C_R * (1 - p_{scr})}{R}$$

This assumes all diagnosed cases from treatment-seeking behaviors were reported to the CDC. Adjusted CT case counts from annual asymptomatic screening (A_S) were estimated through a multi-step process accounting for under-reporting, diagnostic test performance, and screening coverage. Sensitivity (Se) and specificity of CT diagnostic testing were calculated in the same manner as above:

$$Se = (PrNAAT * SeNAAT) + (1 - PrNAAT)(SeNonNAAT)$$

$$Sp = (PrNAAT * SpNAAT) + (1 - PrNAAT)(SpNonNAAT)$$

The prevalence of true asymptomatic CT in the screened population (P) was estimated using reported cases due to screening ($C_R \times p_{scr}$), reporting fraction (R), the total at-risk population (N_M), age- and year-specific screening coverage among the at-risk population (Sc_M), and weighted-average diagnostic test performance (Se ; Sp). The total at-risk population (N_M) was

estimated as the product of the total population size and the proportion of all males eligible for screening (men who have sex with men, high-risk men who have sex with women, etc.), by age and year.

$$P = \frac{\frac{C_R * p_{scr}}{R} - Sc_M * N_M(1 - Sp)}{Sc_M * N_M(Se + Sp - 1)}$$

False positive diagnoses among males screened (FrT) were estimated using the weighted-average specificity (Sp), prevalence of true asymptomatic CT in the screened population (P), the screening coverage (Sc), and the total at-risk population (N_M):

$$FrT = (1 - Sp)(1 - P) * Sc_M * N_M$$

The number of true CT cases among males screened in a given year (A) was estimated as:

$$A = \frac{\frac{C_R * p_{scr}}{R} - FrT}{Se}$$

Finally, the total number of infections that would be expected as a result of asymptomatic screening (A_s), assuming perfect reporting, diagnostic testing, and screening coverage, were estimated as the quotient of the number of true CT cases among males screened in a given year (A) and the screening coverage (Sc_M):

$$A_s = \frac{A}{Sc_M}$$

Adjustment for asymptomatic infections not captured among males via treatment-seeking behaviors (A_T) or screening (A_s) in a given year (A_A) were estimated as the quotient of adjusted treatment-seeking cases (A_T) by the proportion of all infections that present asymptotically among males ($PrAsymp$) over one minus the proportion of asymptotically presenting infections:

$$A_A = \frac{A_T * PrAsymp}{1 - PrAsymp}$$

Adjusted, annual CT cases were estimated as the sum of infections due to treatment-seeking behaviors (A_T), annual screen-and-treat services (A_S), and uncaptured asymptomatic infections (A_A):

$$Total\ Cases_{Male} = A_T + A_S + A_A$$

Parameter Selection

Annual CT Cases:

Annual CT cases from 2000 to 2022 by sex and age group were pulled directly from AtlasPlus (see **Figure B.1** below).³⁶

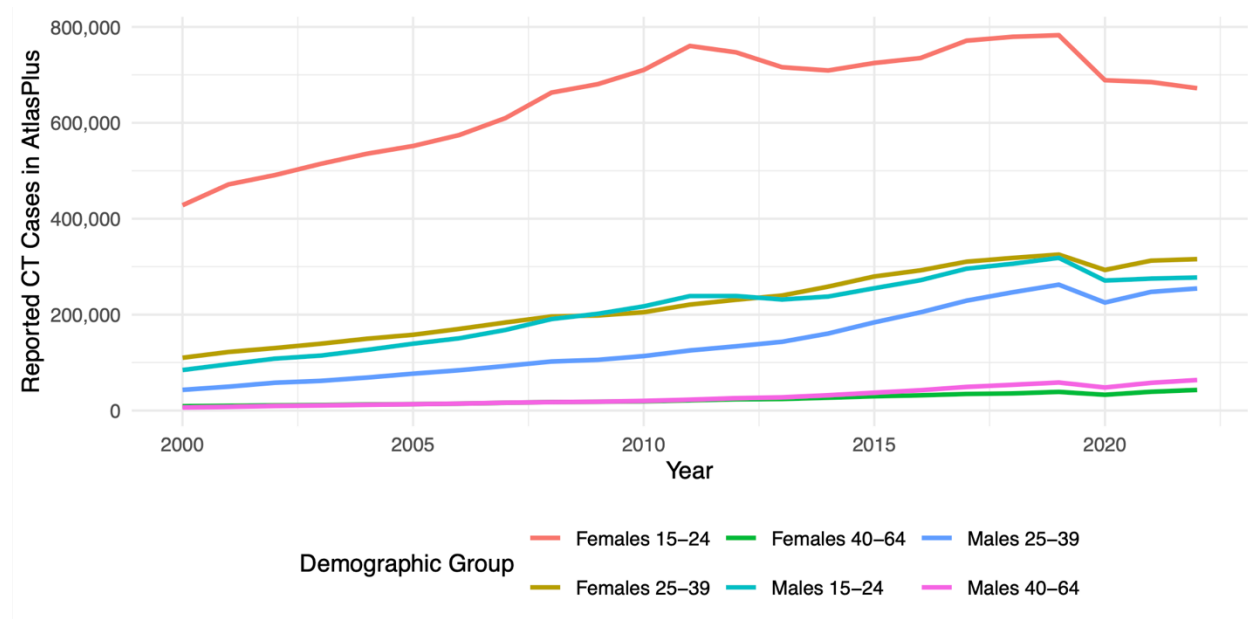


Figure B.1: Annual AtlasPlus CT cases reported, by demographic group

Reported Cases by Reason for Testing:

Limited data are available quantifying the proportion of reported CT cases due to either treatment-seeking behaviors or annual screen-and-treat services. We developed sex- and age-specific triangular distributions for reported cases due to annual screening using data from Tao et al. 2024, with further refinement using data from additional sources.³⁷⁻³⁹ The modes for each distribution (males 15-24: 58.9%, males 25-39: 58.8%, males 40-64: 55.0%, females 15-24:

62.8%, females 25-39: 60.0%, females 40-64: 58.5%) remained fixed over time but were accompanied by +/- 5% lower and upper bounds.

Reporting Fraction:

Year-specific triangular distributions for reporting fraction (proportion of diagnosed cases successfully reported to CDC) were created using the same approach as Learner et al (2020).²³ We assumed the mode of annual reporting fractions rose from 70% in 2000 to 95% in 2022, as to account for incomplete data entry, transmission errors, and the improvement of reporting systems over time. We also assumed an asymptotically decreasing range to the triangular distribution to account for improved reporting certainty over time (**Figure B.2**).

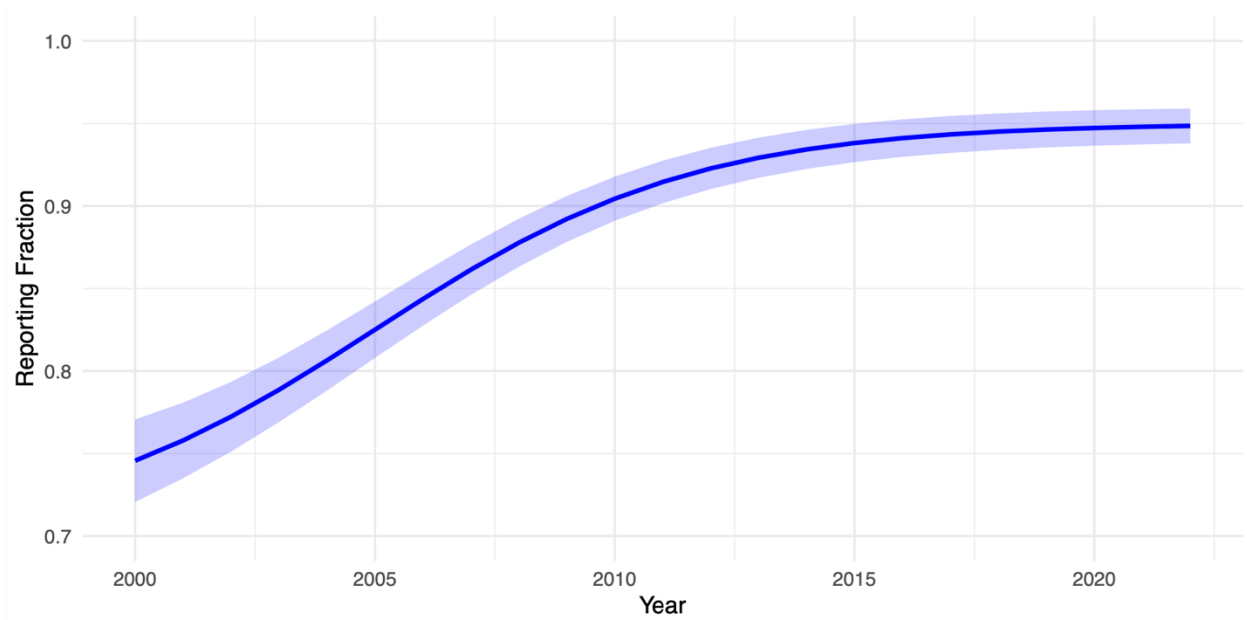


Figure B.2: Estimated reporting fraction by year in the United States

Weighted Diagnostic Test Performance:

Year-specific triangular distributions for diagnostic test performance were created to account for the transition from non-NAAT to NAAT.²³ Similar to Learner et al. (2020), we made the following assumptions:

- Non-NAAT Sensitivity: 75% (LB: 65%, UB: 85%)
- Non-NAAT Specificity: 99.5% (LB: 99%, UB: 100%)

- NAAT Sensitivity: 96% (LB: 93%, UB: 99%)
- NAAT Specificity: 99.5% (LB: 99%, UB: 100%)

A triangular distribution for the proportion of NAAT tests among all diagnostic tests performed in a given year was also estimated as to account for the increased use of NAAT testing over time (Figure B.3).

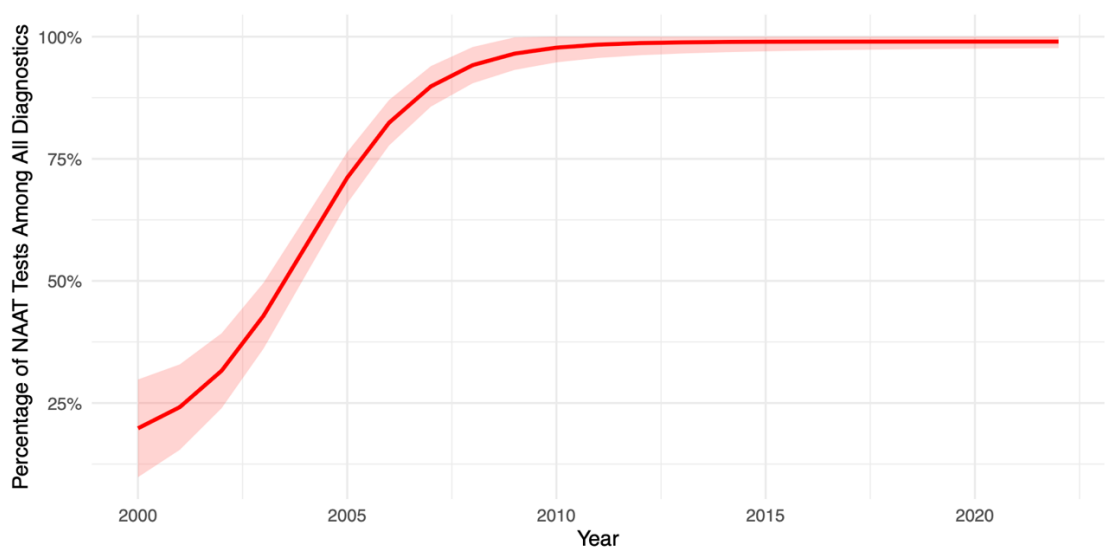


Figure B.3: Proportion of NAAT tests used by year

Using the above distributions for NAAT performance, non-NAAT performance, and the proportion of NAAT tests over time, we estimated weighted sensitivity and specificity values by year (Figure B.4).

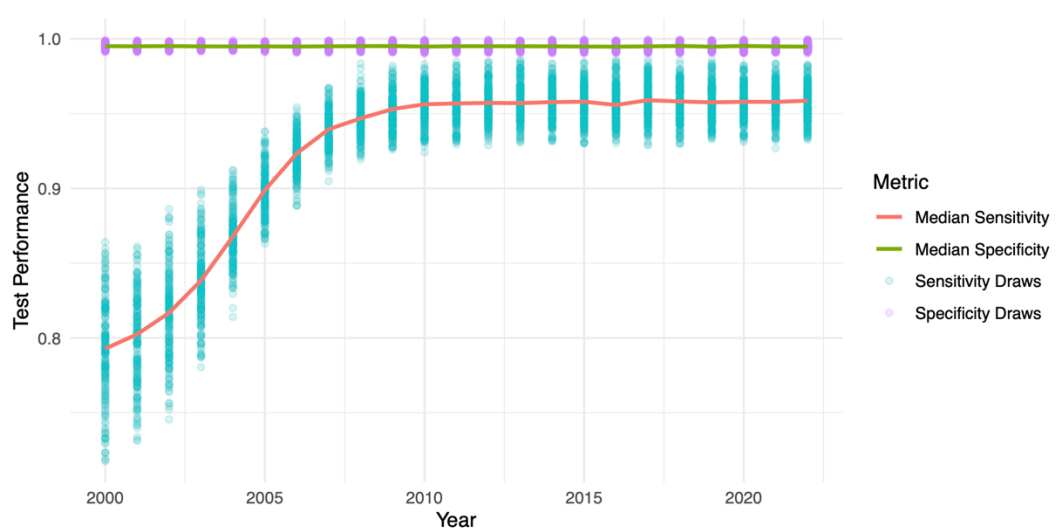


Figure B.4: Weighted sensitivity and specificity of diagnostic tests by year

Total At-risk Population (N_F & N_M):

Estimates of the total at-risk population for annual screening were calculated using United Nations (U.N.) Population Projections data by demographic group.¹ U.N. data by demographic group from 2000 to 2022 is presented in **Figure B.5**.

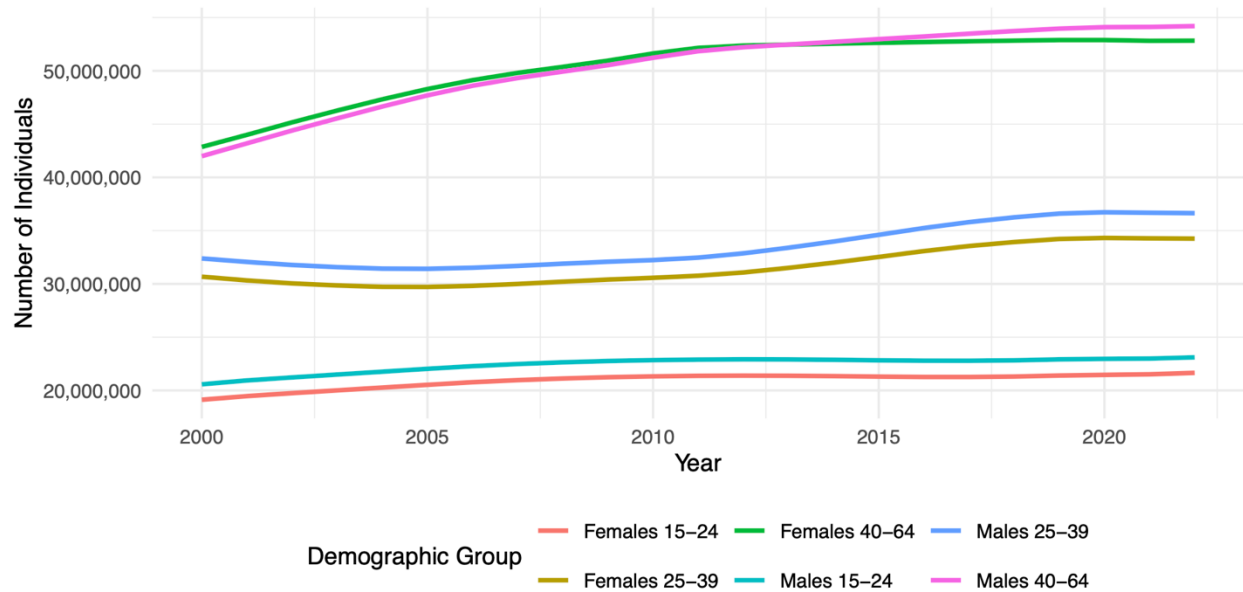


Figure B.5: Annual U.S. population data from the U.N., by demographic group and year

To estimate the proportion of the population eligible for screening services (N_F and N_M), we assumed all females aged 15-39 years could be screened annually, reflecting CDC recommendations for women 15-24 years and observed screening uptake in women aged 25-39 years, despite the lack of formal screening recommendations for this group.^{24,35} For females aged 40-64 years, where data is limited, we used a triangular distribution (mode: 15%, LB: 10%, UB: 20%) to account for lower screening uptake and greater uncertainty. Thus, we assume 15% of the total female population aged 40-64 years, based on U.N. population projections, were “at risk” for screening annually.

For males, we assumed that only those at greatest risk for CT acquisition would be eligible for screening. To estimate the proportion of males eligible for screening, we used

published literature to develop age- and year-specific triangular distributions (**Figure B.6**).⁴⁰⁻⁴²

These values were then applied to UN data to identify the population of males by age group that were “at risk” for screening annually.

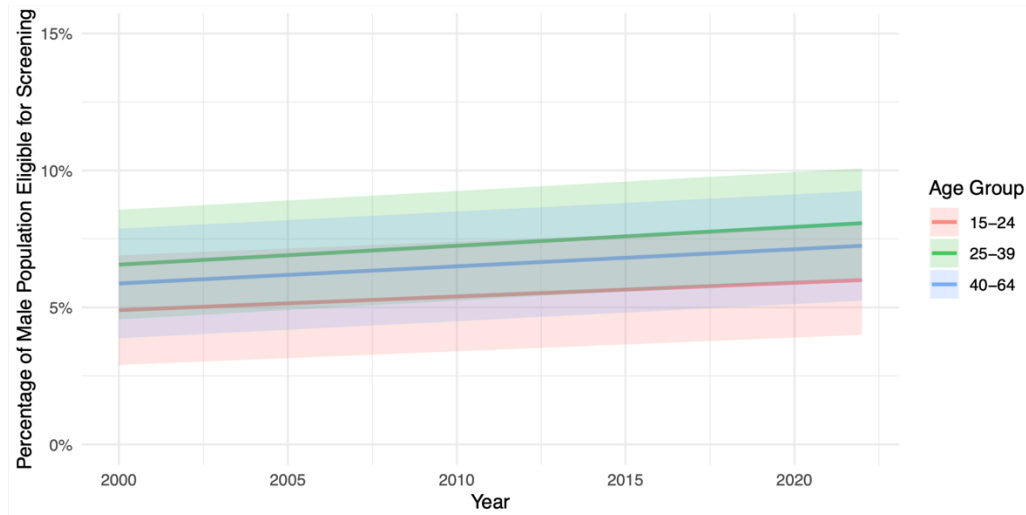


Figure B.6: Proportion of male population eligible for screening, by age group and year

Screening Coverage in At-risk Population:

We used a similar approach as Learner et al. (2020) to develop year- and age-specific triangular distributions for screening coverage estimates among females, further informed by published literature (**Figure B.7**).^{23-25,27}

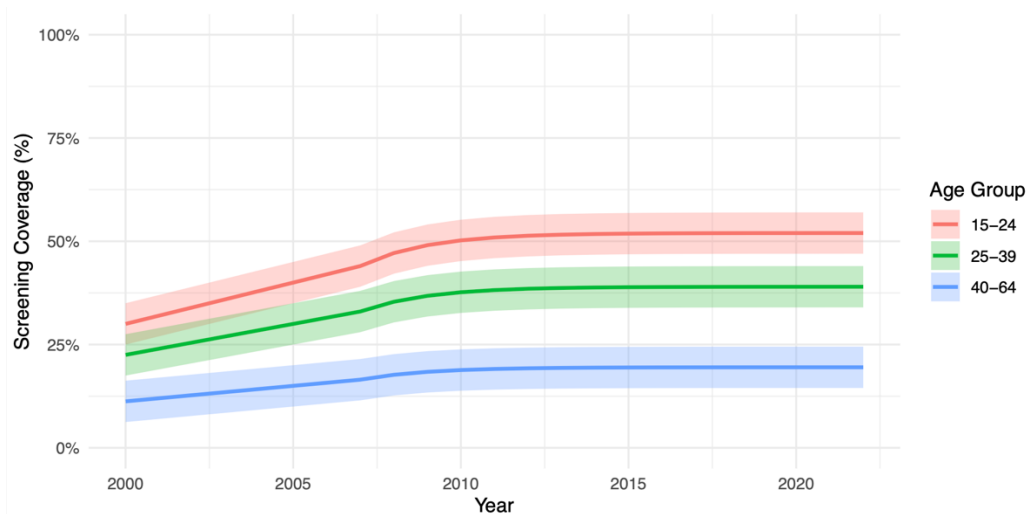


Figure B.7: Screening coverage among eligible females, by age group and year

Data on screening coverage among eligible males by age and year is limited. To estimate coverage, we used American Men's Internet Survey (AMIS) data (2013-2019) to approximate CT screening rates among eligible males.³⁰ We assumed age-dependent screening coverage increased linearly from 2013-2022. For 2000-2012, we applied a similar linear increase but at half the annual rate to account for the influence of HIV PrEP uptake on screening practices in the later time period.^{28,29,43,44} To reflect uncertainty, we incorporated a $\pm 5\%$ lower and upper bound in all triangular distributions. Age- and year-specific distributions for males are shown in **Figure B.8**. Importantly, these estimates represent screening coverage only among males eligible for screening, not the entire male population, which explains the relatively high coverage values.

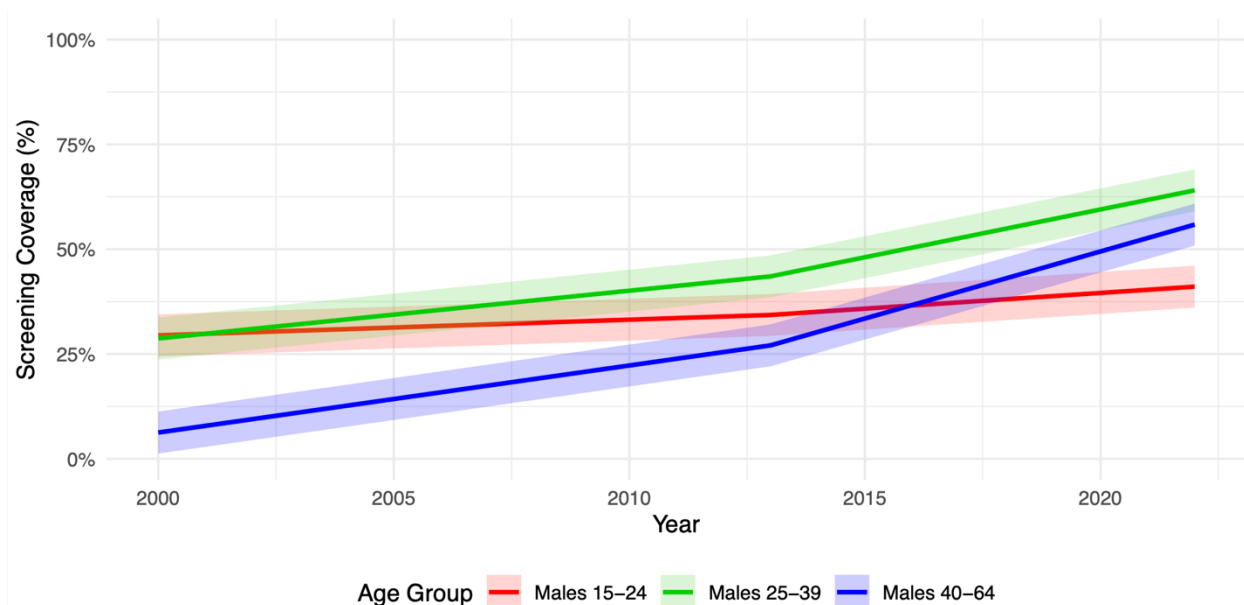


Figure B.8: Screening coverage among eligible males, by age group and year

Proportion of Symptomatic Cases Among Males:

A triangular distribution for the proportion of all CT cases presenting symptomatically was developed using published literature (mode: 50% (LB: 20%, UB: 80%)).^{2,14,45} We assumed that year and age did not impact this distribution.

Results

Adjusted annual CT cases are provided for females (**Figure B.9**), males (**Figure B.10**), and total population (**Figure B.11**) for all years between 2000 and 2022, below. Values by year and demographic group are further presented in **Supplemental Table B.4**, below. Model calibration uses a subset of the data, by demographic group, from 2013 to 2019 (see **Figure 3.4** in main text).

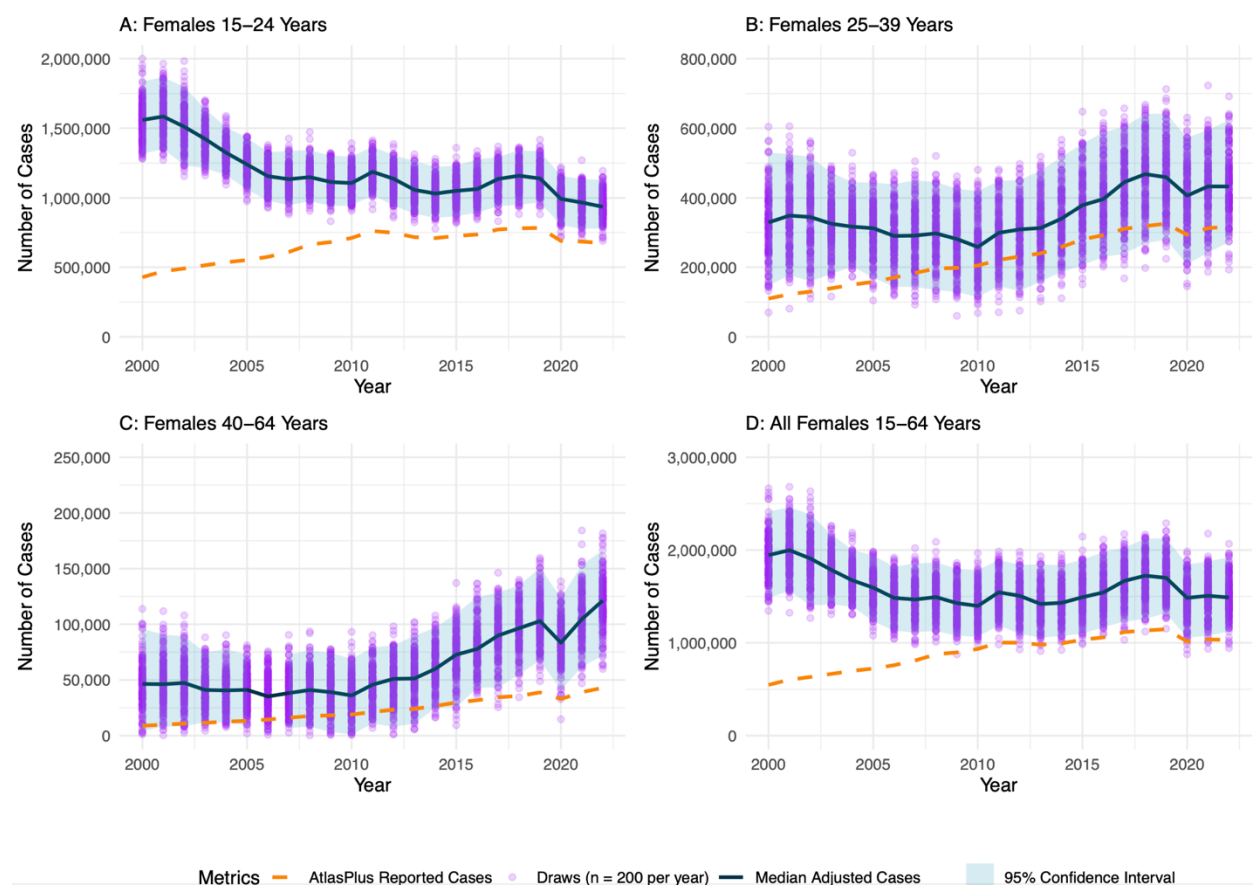


Figure B.9: Adjusted versus reported AtlasPlus case by year in the United States, among females

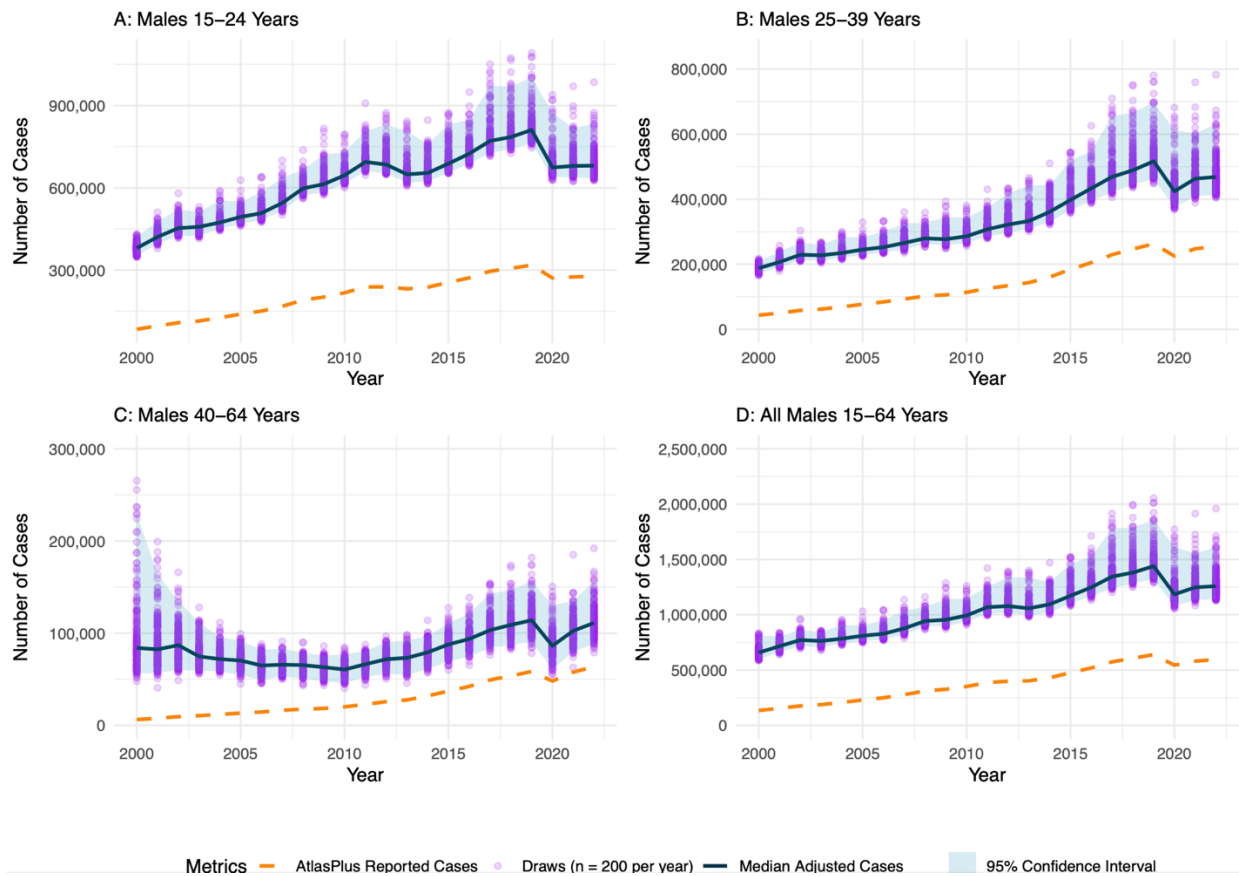


Figure B.10: Adjusted versus reported AtlasPlus case by year in the United States, among males

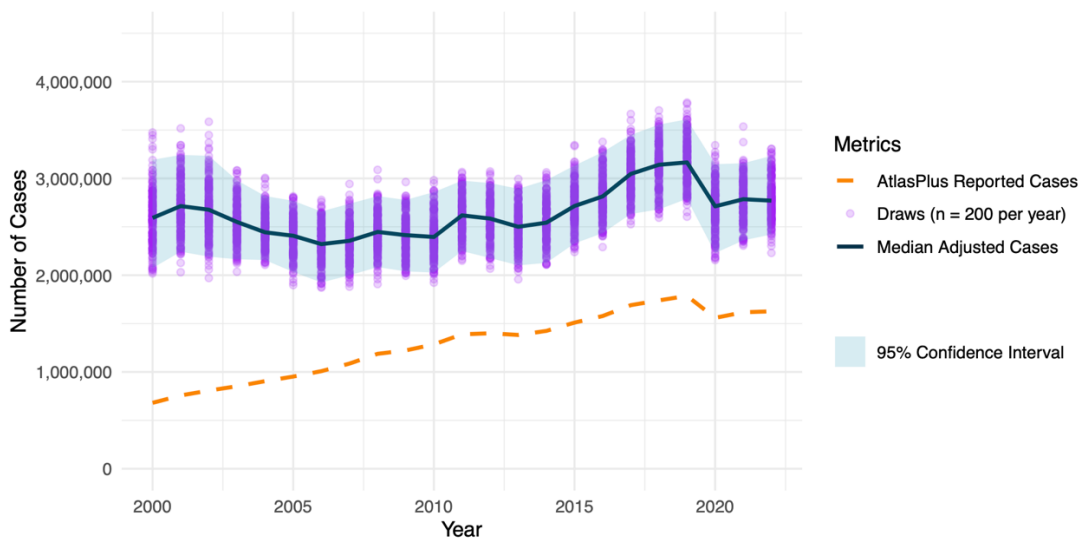


Figure B.11: Adjusted versus reported AtlasPlus cases by year in the United States, among all males and females aged 15-64 years

Supplemental Table B.4. Median adjusted annual CT cases in the United States between 2000 and 2022, by demographic groups of interest

Year	Males 15-24 Years	Males 25-39 Years	Males 40-64 Years	Females 15-24 Years	Females 25-39 Years	Females 40-64 Years
2000	380,151	187,744	83,980	1,559,586	328,589	46,440
2001	420,885	206,661	82,434	1,584,445	348,353	46,196
2002	452,935	228,998	86,934	1,510,896	344,204	47,342
2003	457,597	227,305	74,742	1,423,079	324,969	41,034
2004	473,374	234,451	71,845	1,324,952	316,437	40,647
2005	493,698	245,082	70,279	1,239,879	312,141	41,142
2006	507,419	252,190	64,910	1,155,545	289,895	35,198
2007	544,926	265,378	65,805	1,134,009	290,872	38,219
2008	598,268	279,480	65,324	1,148,995	297,165	41,008
2009	613,650	276,795	63,052	1,113,903	281,009	39,086
2010	645,876	285,707	60,516	1,106,199	258,167	36,062
2011	694,581	307,293	66,250	1,187,120	298,810	45,766
2012	685,068	321,862	71,721	1,137,449	308,665	51,000
2013	649,444	332,785	73,143	1,057,203	312,692	51,313
2014	654,333	360,813	79,194	1,030,709	339,562	59,990
2015	688,573	397,907	87,811	1,050,578	378,997	72,755
2016	724,930	433,514	93,709	1,062,759	396,700	77,840
2017	771,028	468,768	103,243	1,135,891	445,125	89,935
2018	785,042	489,070	108,966	1,158,949	468,244	96,455
2019	811,102	516,815	113,980	1,139,219	459,155	102,937
2020	674,298	424,585	86,236	992,607	406,504	83,436
2021	680,036	463,212	102,504	966,769	432,912	104,610
2022	680,924	468,673	111,117	935,835	432,687	121,352

Abbreviations: CT, *Chlamydia trachomatis*

Limitations

There are important limitations to our analysis. First, several parameters were developed using limited data from published sources. As such, we included plausible distributions around parameter modes and took random draws from those distributions to account for uncertainty. Future research is necessary to refine adjusted case analyses, given these known data gaps. Second, we could not explicitly account for extragenital CT cases, and little is known about screening coverage and diagnostic test performance by age and sex over time for extragenital testing. Third, adjusted CT cases among males were estimated as the sum of infections due to treatment-seeking behaviors, annual screen-and-treat services, and uncaptured asymptomatic infections. Due to data limitations, uncaptured asymptomatic infections were estimated using the reported symptomatic cases and the proportion of all infections presenting asymptotically in males. As we were not able to explicitly differentiate symptomatic infections by sub-populations (MSM vs MSW), our estimates of uncaptured asymptomatic infections may repeat infections covered by screening among MSM. Fourth, we could not account for false positives among treatment-seeking cases due to high uncertainty in identifying individuals classified as “at risk” for seeking treatment for symptomatic infections. However, it is unlikely that adjustment for false positives among treatment-seeking cases would impact our adjusted estimates substantially.

Despite uncertainty in the adjusted estimates, they provide a more accurate representation of true CT infections in the United States and are essential for model calibration. Relying on unadjusted AtlasPlus data would underestimate the impact of CT vaccination for both disease burden and costs.

B.4 ADDITIONAL RESULTS

Supplemental Table B.5. Absolute and relative (%) reduction in CT infections between 2025-2075, comparing Scenario A¹ to No Vaccination by vaccine coverage, efficacy, and duration of protection.

Duration of Protection	VE	30% Coverage		50% Coverage		70% Coverage	
		Absolute Reduction ²	Relative Reduction ³	Absolute Reduction	Relative Reduction	Absolute Reduction	Relative Reduction
0.5 Years	10%	971,733	0.3	1,618,900	0.6	2,263,009	0.8
	20%	2,138,003	0.8	3,557,957	1.3	4,971,480	1.8
	30%	3,305,872	1.2	5,497,563	2.0	7,677,590	2.8
	40%	4,479,832	1.6	7,444,171	2.7	10,388,818	3.7
	50%	5,659,396	2.0	9,396,576	3.4	13,103,960	4.7
	60%	6,843,523	2.5	11,353,840	4.1	15,820,635	5.7
	70%	8,032,443	2.9	13,315,772	4.8	18,540,964	6.7
	80%	9,225,987	3.3	15,281,749	5.5	21,262,681	7.6
	90%	10,424,471	3.7	17,252,717	6.2	23,976,204	8.6
1 Year	10%	1,805,529	0.6	3,005,324	1.1	4,197,158	1.5
	20%	3,985,157	1.4	6,622,505	2.4	9,242,282	3.3
	30%	6,176,991	2.2	10,249,769	3.7	14,282,902	5.1
	40%	8,379,850	3.0	13,886,583	5.0	19,324,025	6.9
	50%	10,596,058	3.8	17,531,973	6.3	24,363,009	8.7
	60%	12,821,979	4.6	21,185,863	7.6	29,376,915	10.6
	70%	15,062,835	5.4	24,839,163	8.9	34,364,535	12.3
	80%	17,313,389	6.2	28,483,631	10.2	39,339,163	14.1
	90%	19,572,325	7.0	32,131,588	11.5	44,281,527	15.9
5 Years	10%	6,308,878	2.3	10,452,201	3.8	14,537,831	5.2
	20%	13,658,059	4.9	22,513,663	8.1	31,153,821	11.2
	30%	21,011,347	7.5	34,439,190	12.4	47,305,999	17.0
	40%	28,372,156	10.2	46,148,580	16.6	62,749,927	22.5
	50%	35,695,348	12.8	57,507,191	20.7	77,281,207	27.8
	60%	42,965,976	15.4	68,497,806	24.6	90,550,674	32.5
	70%	50,143,618	18.0	78,843,032	28.3	102,591,441	36.9
	80%	57,226,022	20.5	88,597,608	31.8	113,186,108	40.7
	90%	64,110,079	23.0	97,686,136	35.1	122,399,714	44.0
10 Years	10%	9,231,207	3.3	15,252,598	5.5	21,168,745	7.6
	20%	19,690,317	7.1	32,255,098	11.6	44,306,628	15.9
	30%	30,067,676	10.8	48,684,532	17.5	65,876,794	23.7
	40%	40,292,302	14.5	64,322,993	23.1	85,405,873	30.7
	50%	50,352,929	18.1	78,933,473	28.3	102,284,372	36.8
	60%	60,100,963	21.6	92,216,103	33.1	116,387,709	41.9
	70%	69,515,281	25.0	104,104,432	37.4	127,740,899	46.0
	80%	78,457,331	28.2	114,437,796	41.2	136,976,713	49.3
	90%	86,949,690	31.2	123,295,768	44.4	144,299,940	51.9
20 Years	10%	11,948,562	4.3	19,684,815	7.1	27,222,529	9.8
	20%	25,150,618	9.0	40,893,190	14.7	55,621,532	20.0
	30%	38,108,044	13.7	60,831,627	21.9	80,841,382	29.1
	40%	50,671,977	18.2	79,037,535	28.4	102,131,847	36.7
	50%	62,724,183	22.5	95,288,463	34.2	118,855,840	42.7
	60%	74,126,442	26.7	109,058,318	39.2	131,583,541	47.3
	70%	84,871,956	30.5	120,536,021	43.4	141,313,388	50.8
	80%	94,713,900	34.0	129,919,938	46.8	148,638,860	53.5
	90%	103,687,242	37.3	137,703,227	49.5	154,292,082	55.5

¹ Scenario A: Vaccinating only 15-year-old girls entering the model between 2025-2075.

² Refers to difference in total CT infections comparing Scenario A to the referent scenario (no vaccination) from 2025-2075.

³ Refers to percent reduction in total CT infections comparing Scenario A to the referent scenario (no vaccination) from 2025-2075.

Abbreviations: CT, Chlamydia trachomatis; VE, vaccine efficacy.

Supplemental Table B.6. Absolute and relative reduction in CT infections between 2025-2075, comparing Scenario B¹ to No Vaccination by vaccine coverage, efficacy, and duration of protection.

Duration of Protection	VE	30% Coverage		50% Coverage		70% Coverage	
		Absolute Reduction ²	Relative Reduction ³	Absolute Reduction	Relative Reduction	Absolute Reduction	Relative Reduction
0.5 Years	10%	1,947,395	0.7	3,242,243	1.2	4,529,475	1.6
	20%	4,224,743	1.5	7,019,001	2.5	9,793,234	3.5
	30%	6,500,300	2.3	10,781,429	3.9	15,013,875	5.4
	40%	8,775,877	3.1	14,527,360	5.2	20,191,510	7.2
	50%	11,050,682	4.0	18,255,590	6.6	25,325,789	9.1
	60%	13,322,646	4.8	21,967,352	7.9	30,409,607	10.9
	70%	15,591,952	5.6	25,659,655	9.2	35,440,381	12.7
	80%	17,858,333	6.4	29,326,727	10.5	40,423,790	14.5
	90%	20,125,677	7.2	32,970,627	11.8	45,300,306	16.3
1 Year	10%	3,620,123	1.3	6,017,375	2.2	8,395,106	3.0
	20%	7,880,784	2.8	13,057,758	4.7	18,156,412	6.5
	30%	12,136,292	4.4	20,025,457	7.2	27,736,121	10.0
	40%	16,372,735	5.9	26,910,566	9.7	37,123,897	13.3
	50%	20,595,563	7.4	33,708,676	12.1	46,294,282	16.6
	60%	24,799,097	8.9	40,422,588	14.5	55,206,595	19.8
	70%	28,974,220	10.4	46,996,610	16.9	63,842,560	22.9
	80%	33,139,659	11.9	53,465,701	19.2	72,096,564	25.9
	90%	37,264,705	13.4	59,793,299	21.4	79,942,212	28.7
5 Years	10%	12,560,323	4.5	20,687,703	7.4	28,599,107	10.3
	20%	26,714,866	9.6	43,375,544	15.6	58,856,764	21.1
	30%	40,470,845	14.5	64,356,053	23.1	85,227,316	30.6
	40%	53,666,062	19.3	83,292,385	29.9	106,749,230	38.4
	50%	66,227,376	23.8	99,699,777	35.8	123,488,397	44.4
	60%	77,980,043	28.0	113,565,158	40.8	136,137,167	49.0
	70%	88,787,585	31.9	124,930,685	44.9	145,550,591	52.4
	80%	98,727,601	35.5	134,258,437	48.3	152,649,002	54.9
	90%	107,699,645	38.7	141,769,166	51.0	158,106,721	56.9
10 Years	10%	18,278,014	6.6	29,924,555	10.7	41,011,396	14.7
	20%	38,064,137	13.7	60,580,168	21.8	80,286,972	28.9
	30%	56,670,200	20.4	86,925,767	31.3	110,167,154	39.6
	40%	73,749,547	26.5	108,205,467	38.9	130,472,434	47.0
	50%	89,064,430	32.0	124,291,034	44.7	144,176,307	51.8
	60%	102,457,719	36.8	136,394,100	49.1	153,346,587	55.2
	70%	113,920,458	41.0	145,407,355	52.3	159,787,984	57.5
	80%	123,489,031	44.4	152,168,291	54.7	164,538,431	59.2
	90%	131,520,263	47.3	157,383,524	56.6	168,211,152	60.6
20 Years	10%	23,528,367	8.4	38,162,802	13.7	51,807,501	18.6
	20%	47,982,765	17.2	74,630,038	26.8	96,403,946	34.6
	30%	70,023,429	25.2	103,269,392	37.1	125,420,551	45.1
	40%	89,280,634	32.1	123,716,601	44.5	142,860,512	51.4
	50%	105,466,508	37.9	137,820,818	49.6	153,604,518	55.2
	60%	118,510,909	42.6	147,686,470	53.1	160,633,793	57.8
	70%	128,876,958	46.4	154,666,652	55.6	165,645,391	59.6
	80%	137,264,608	49.4	159,831,312	57.5	169,429,158	61.0
	90%	143,958,455	51.8	163,834,883	59.0	172,409,745	62.1

¹ Scenario B: Vaccinating 15-year-old girls and boys entering the model between 2025-2075.

² Refers to difference in total CT infections comparing Scenario B to the referent scenario (no vaccination) from 2025-2075.

³ Refers to percent reduction in total CT infections comparing Scenario B to the referent scenario (no vaccination) from 2025-2075.

Abbreviations: CT, Chlamydia trachomatis; VE, vaccine efficacy.

Supplemental Table B.7. Absolute and relative reduction in CT infections between 2025-2075, comparing Scenario C¹ at 50% coverage to No Vaccination by catch-up coverage, efficacy, and duration of protection.

Duration of Protection	VE	5% Catch-up Coverage		10% Catch-up Coverage		15% Catch-up Coverage	
		Absolute Reduction ²	Relative Reduction ³	Absolute Reduction	Relative Reduction	Absolute Reduction	Relative Reduction
0.5 Years	10%	1,668,248	0.6	1,715,621	0.6	1,761,486	0.6
	20%	3,656,528	1.3	3,752,270	1.3	3,845,131	1.4
	30%	5,644,965	2.0	5,790,027	2.1	5,931,697	2.1
	40%	7,641,905	2.7	7,833,866	2.8	8,022,650	2.9
	50%	9,645,759	3.5	9,887,379	3.5	10,122,036	3.6
	60%	11,653,841	4.2	11,945,728	4.3	12,230,057	4.4
	70%	13,666,455	4.9	14,007,670	5.0	14,340,640	5.1
	80%	15,682,634	5.6	16,073,981	5.8	16,455,666	5.9
	90%	17,703,512	6.4	18,143,971	6.5	18,574,550	6.7
1 Year	10%	3,096,973	1.1	3,185,093	1.1	3,270,276	1.2
	20%	6,807,030	2.4	6,985,603	2.5	7,157,272	2.6
	30%	10,528,518	3.8	10,798,584	3.9	11,058,064	4.0
	40%	14,259,960	5.1	14,621,337	5.2	14,969,286	5.4
	50%	17,998,348	6.5	18,450,817	6.6	18,889,929	6.8
	60%	21,748,071	7.8	22,293,120	8.0	22,822,425	8.2
	70%	25,501,937	9.2	26,143,096	9.4	26,759,293	9.6
	80%	29,242,609	10.5	29,977,813	10.8	30,690,116	11.0
	90%	32,977,968	11.8	33,804,006	12.1	34,607,031	12.4
5 Years	10%	10,762,285	3.9	11,059,851	4.0	11,344,444	4.1
	20%	23,133,037	8.3	23,725,921	8.5	24,294,005	8.7
	30%	35,370,729	12.7	36,261,281	13.0	37,112,019	13.3
	40%	47,379,547	17.0	48,556,540	17.4	49,679,759	17.9
	50%	59,024,084	21.2	60,474,255	21.7	61,860,942	22.2
	60%	70,288,310	25.2	71,997,887	25.8	73,630,318	26.4
	70%	80,869,251	29.1	82,800,397	29.7	84,640,781	30.4
	80%	90,821,768	32.6	92,937,586	33.4	94,950,126	34.1
	90%	100,072,340	36.0	102,347,168	36.8	104,507,402	37.6
10 Years	10%	15,695,733	5.6	16,118,918	5.8	16,523,069	5.9
	20%	33,131,312	11.9	33,968,006	12.2	34,767,007	12.5
	30%	49,980,931	18.0	51,218,106	18.4	52,398,979	18.8
	40%	66,005,708	23.7	67,608,737	24.3	69,135,819	24.8
	50%	80,939,554	29.1	82,845,065	29.7	84,655,424	30.4
	60%	94,488,865	33.9	96,639,426	34.7	98,668,848	35.4
	70%	106,543,186	38.3	108,837,005	39.1	110,994,293	39.9
	80%	116,970,848	42.1	119,331,079	42.9	121,535,059	43.7
	90%	125,844,834	45.3	128,215,507	46.1	130,422,757	46.9
20 Years	10%	20,249,613	7.3	20,790,316	7.5	21,306,073	7.6
	20%	42,004,201	15.1	43,063,132	15.5	44,072,489	15.8
	30%	62,430,046	22.4	63,950,062	23.0	65,395,583	23.5
	40%	81,039,627	29.2	82,937,049	29.8	84,735,608	30.5
	50%	97,578,494	35.1	99,735,848	35.8	101,768,353	36.6
	60%	111,499,819	40.1	113,783,115	40.9	115,917,859	41.7
	70%	123,017,009	44.3	125,321,340	45.1	127,457,649	45.9
	80%	132,389,826	47.6	134,659,264	48.5	136,745,183	49.2
	90%	140,072,026	50.4	142,226,134	51.1	144,184,292	51.9

¹ Scenario C: Scenario A at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035

² Refers to difference in total CT infections comparing Scenario C to the referent scenario (no vaccination) from 2025-2075.

³ Refers to percent reduction in total CT infections comparing Scenario C to the referent scenario (no vaccination) from 2025-2075.

Abbreviations: CT, Chlamydia trachomatis; VE, vaccine efficacy.

Supplemental Table B.8. Absolute and relative reduction in CT infections between 2025-2075, comparing Scenario D¹ at 50% coverage to No Vaccination by catch-up coverage, efficacy, and duration of protection.

Duration of Protection	VE	5% Catch-up Coverage		10% Catch-up Coverage		15% Catch-up Coverage	
		Absolute Reduction ²	Relative Reduction ³	Absolute Reduction	Relative Reduction	Absolute Reduction	Relative Reduction
0.5 Years	10%	3,290,959	1.2	3,338,288	1.2	3,384,281	1.2
	20%	7,116,963	2.6	7,212,561	2.6	7,305,841	2.6
	30%	10,928,765	3.9	11,072,224	4.0	11,211,862	4.0
	40%	14,725,062	5.3	14,917,519	5.4	15,104,957	5.4
	50%	18,502,814	6.6	18,743,647	6.7	18,978,274	6.8
	60%	22,261,910	8.0	22,549,307	8.1	22,831,127	8.2
	70%	26,002,407	9.3	26,338,182	9.5	26,667,682	9.6
	80%	29,719,856	10.7	30,103,816	10.8	30,480,024	10.9
	90%	33,411,496	12.0	33,842,758	12.1	34,263,699	12.3
1 Year	10%	6,108,618	2.2	6,197,139	2.2	6,282,925	2.3
	20%	13,240,908	4.8	13,417,659	4.8	13,588,220	4.9
	30%	20,302,563	7.3	20,570,683	7.4	20,829,559	7.5
	40%	27,279,767	9.8	27,635,466	9.9	27,979,351	10.1
	50%	34,165,445	12.3	34,608,965	12.4	35,039,602	12.6
	60%	40,968,899	14.7	41,497,500	14.9	42,009,003	15.1
	70%	47,627,520	17.1	48,238,234	17.3	48,829,426	17.5
	80%	54,181,482	19.4	54,873,150	19.7	55,543,147	19.9
	90%	60,591,699	21.7	61,363,872	22.0	62,111,711	22.3
5 Years	10%	20,993,837	7.5	21,286,539	7.6	21,566,260	7.7
	20%	43,976,438	15.8	44,549,552	16.0	45,096,780	16.2
	30%	65,211,381	23.4	66,030,741	23.7	66,815,532	24.0
	40%	84,367,092	30.3	85,392,574	30.7	86,371,240	31.0
	50%	100,922,868	36.3	102,085,063	36.7	103,191,195	37.1
	60%	114,870,495	41.3	116,108,123	41.7	117,281,740	42.1
	70%	126,255,594	45.4	127,506,288	45.9	128,692,362	46.3
	80%	135,568,585	48.8	136,799,617	49.2	137,956,774	49.6
	90%	143,031,245	51.5	144,211,352	51.9	145,315,399	52.3
10 Years	10%	30,357,511	10.9	30,769,178	11.0	31,162,233	11.2
	20%	61,396,734	22.1	62,175,516	22.4	62,918,449	22.6
	30%	88,022,053	31.6	89,064,818	32.0	90,056,859	32.4
	40%	109,454,698	39.3	110,637,325	39.8	111,757,243	40.2
	50%	125,566,658	45.2	126,766,725	45.6	127,899,329	46.0
	60%	137,641,383	49.5	138,808,388	49.9	139,900,887	50.3
	70%	146,564,401	52.7	147,639,675	53.1	148,639,794	53.5
	80%	153,228,906	55.1	154,208,949	55.5	155,115,525	55.8
	90%	158,340,455	57.0	159,219,740	57.3	160,028,794	57.6
20 Years	10%	38,709,811	13.9	39,230,441	14.1	39,726,718	14.3
	20%	75,603,461	27.2	76,529,605	27.5	77,410,821	27.8
	30%	104,473,641	37.5	105,613,311	37.9	106,696,575	38.3
	40%	124,959,816	45.0	126,127,419	45.4	127,224,527	45.8
	50%	139,004,987	50.0	140,109,650	50.4	141,140,876	50.8
	60%	148,754,512	53.5	149,743,701	53.8	150,659,511	54.2
	70%	155,611,426	56.0	156,480,648	56.3	157,281,487	56.6
	80%	160,669,384	57.8	161,436,606	58.1	162,140,193	58.3
	90%	164,578,875	59.2	165,257,229	59.5	165,877,002	59.7

¹ Scenario D: Scenario B @ 50% cov. + catch-up campaign among unvaccinated 15-24-year-old women in 2035 at 5/10/15% cov.

² Refers to difference in total CT infections comparing Scenario D to the referent scenario (no vaccination) from 2025-2075.

³ Refers to percent reduction in total CT infections comparing Scenario D to the referent scenario (no vaccination) from 2025-2075.

Abbreviations: CT, Chlamydia trachomatis; VE, vaccine efficacy.

Supplemental Table B.9. CT incidence rates among all individuals aged 15-64 years between 2025-2075 for Scenario A ^{1,2,3,4}

Duration of Protection	VE	30% Coverage			50% Coverage			70% Coverage		
		2025	2050	2075	2025	2050	2075	2025	2050	2075
0.5 Years	10%	16.9	18.4	18.5	16.9	18.3	18.4	16.9	18.2	18.3
	20%	16.9	18.3	18.4	16.9	18.1	18.2	16.9	18.0	18.0
	30%	16.9	18.1	18.2	16.9	17.9	18.0	16.9	17.7	17.7
	40%	16.9	18.0	18.1	16.9	17.7	17.7	16.8	17.5	17.3
	50%	16.9	17.9	17.9	16.8	17.6	17.5	16.8	17.2	17.0
	60%	16.9	17.8	17.8	16.8	17.4	17.2	16.8	16.9	16.6
	70%	16.9	17.7	17.7	16.8	17.2	17.0	16.8	16.7	16.3
	80%	16.8	17.6	17.5	16.8	17.0	16.7	16.8	16.4	15.9
	90%	16.8	17.4	17.3	16.8	16.8	16.5	16.8	16.1	15.6
1 Year	10%	16.9	18.3	18.4	16.9	18.2	18.2	16.9	18.1	18.1
	20%	16.9	18.1	18.1	16.9	17.8	17.8	16.9	17.6	17.4
	30%	16.9	17.9	17.9	16.9	17.5	17.3	16.8	17.1	16.8
	40%	16.9	17.7	17.6	16.8	17.1	16.9	16.8	16.6	16.1
	50%	16.9	17.4	17.3	16.8	16.8	16.4	16.8	16.1	15.5
	60%	16.8	17.2	17.0	16.8	16.4	15.9	16.8	15.6	14.8
	70%	16.8	17.0	16.7	16.8	16.0	15.4	16.8	15.1	14.2
	80%	16.8	16.8	16.4	16.8	15.7	15.0	16.8	14.6	13.5
	90%	16.8	16.6	16.2	16.8	15.3	14.5	16.8	14.2	12.9
5 Years	10%	16.9	17.9	17.7	16.9	17.5	17.1	16.9	17.1	16.5
	20%	16.9	17.2	16.8	16.9	16.3	15.5	16.9	15.5	14.2
	30%	16.9	16.4	15.8	16.8	15.1	13.8	16.8	13.9	12.0
	40%	16.9	15.7	14.7	16.8	14.0	12.2	16.8	12.5	9.8
	50%	16.8	15.0	13.7	16.8	12.9	10.7	16.8	11.1	7.8
	60%	16.8	14.3	12.8	16.8	11.9	9.1	16.8	9.8	6.1
	70%	16.8	13.6	11.8	16.8	10.9	7.7	16.8	8.6	4.6
	80%	16.8	13.0	10.8	16.8	9.9	6.4	16.8	7.5	3.3
	90%	16.8	12.3	9.9	16.8	9.0	5.3	16.8	6.5	2.4
10 Year	10%	16.9	17.6	17.3	16.9	17.0	16.3	16.9	16.5	15.4
	20%	16.9	16.6	15.8	16.9	15.4	13.9	16.9	14.3	12.1
	30%	16.9	15.6	14.3	16.8	13.8	11.6	16.8	12.2	9.0
	40%	16.9	14.6	12.9	16.8	12.4	9.3	16.8	10.3	6.3
	50%	16.8	13.7	11.5	16.8	10.9	7.3	16.8	8.6	4.1
	60%	16.8	12.7	10.1	16.8	9.6	5.5	16.8	7.2	2.6
	70%	16.8	11.8	8.7	16.8	8.4	4.0	16.8	5.9	1.5
	80%	16.8	11.0	7.5	16.8	7.4	2.9	16.8	4.8	0.8
	90%	16.8	10.1	6.3	16.8	6.4	2.0	16.8	3.9	0.5
20 Years	10%	16.9	17.4	16.8	16.9	16.6	15.5	16.9	16.0	14.3
	20%	16.9	16.1	14.9	16.9	14.6	12.4	16.9	13.3	10.1
	30%	16.9	14.9	13.0	16.8	12.8	9.5	16.8	10.9	6.5
	40%	16.9	13.7	11.1	16.8	11.0	6.9	16.8	8.7	3.8
	50%	16.8	12.6	9.3	16.8	9.4	4.7	16.8	6.9	2.0
	60%	16.8	11.5	7.7	16.8	8.0	3.1	16.8	5.4	1.0
	70%	16.8	10.4	6.2	16.8	6.7	1.9	16.8	4.2	0.4
	80%	16.8	9.4	4.9	16.8	5.6	1.1	16.8	3.2	0.2
	90%	16.8	8.5	3.8	16.8	4.6	0.6	16.8	2.4	0.1

¹ IR estimated as # of incident infections per 1,000 person-years (PY)

² IR estimates are for the total population (males and females)

³ Under no vaccination, IRs in 2025, 2050, and 2075 were 16.9, 18.5, and 18.7/1000 PY, respectively

⁴ Scenario A: Vaccinating only 15-year-old girls entering the model between 2025-2075.

Abbreviations: CT, *Chlamydia trachomatis*, IR, incidence rate; PY, person-years

Supplemental Table B.10. CT incidence rates among all individuals aged 15-64 years between 2025-2075 for Scenario B ^{1,2,3,4}

Duration of Protection	VE	30% Coverage			50% Coverage			70% Coverage		
		2025	2050	2075	2025	2050	2075	2025	2050	2075
0.5 Years	10%	16.9	18.3	18.4	16.9	18.2	18.2	16.9	18.0	18.0
	20%	16.9	18.1	18.1	16.9	17.8	17.7	16.9	17.5	17.4
	30%	16.9	17.8	17.8	16.8	17.4	17.3	16.8	17.0	16.7
	40%	16.9	17.6	17.5	16.8	17.1	16.8	16.8	16.5	16.0
	50%	16.8	17.4	17.3	16.8	16.7	16.3	16.8	16.0	15.4
	60%	16.8	17.2	17.0	16.8	16.3	15.8	16.8	15.5	14.7
	70%	16.8	16.9	16.7	16.8	16.0	15.4	16.8	15.0	14.0
	80%	16.8	16.7	16.4	16.8	15.6	14.9	16.8	14.6	13.4
	90%	16.8	16.5	16.1	16.8	15.3	14.4	16.8	14.1	12.8
1 Year	10%	16.9	18.1	18.2	16.9	17.9	17.8	16.9	17.7	17.5
	20%	16.9	17.7	17.6	16.8	17.2	16.9	16.8	16.7	16.2
	30%	16.9	17.3	17.1	16.8	16.5	16.0	16.8	15.8	15.0
	40%	16.8	16.9	16.5	16.8	15.9	15.1	16.8	14.9	13.7
	50%	16.8	16.5	16.0	16.8	15.2	14.2	16.8	14.0	12.5
	60%	16.8	16.1	15.4	16.8	14.6	13.3	16.8	13.2	11.3
	70%	16.8	15.7	14.9	16.8	13.9	12.5	16.8	12.4	10.2
	80%	16.8	15.2	14.3	16.8	13.3	11.6	16.8	11.6	9.1
	90%	16.8	14.8	13.8	16.8	12.7	10.8	16.8	10.8	8.1
5 Years	10%	16.9	17.3	16.8	16.9	16.5	15.6	16.9	15.8	14.4
	20%	16.9	15.9	14.9	16.8	14.3	12.5	16.8	12.9	10.2
	30%	16.8	14.6	13.0	16.8	12.3	9.6	16.8	10.3	6.6
	40%	16.8	13.3	11.2	16.8	10.5	7.0	16.8	8.2	3.9
	50%	16.8	12.1	9.4	16.8	8.9	4.9	16.8	6.4	2.2
	60%	16.8	11.0	7.8	16.8	7.5	3.3	16.8	5.0	1.1
	70%	16.8	9.9	6.4	16.8	6.3	2.1	16.8	3.9	0.6
	80%	16.8	9.0	5.1	16.8	5.2	1.3	16.8	3.0	0.3
	90%	16.8	8.0	4.0	16.8	4.3	0.8	16.8	2.3	0.1
10 Year	10%	16.9	16.8	15.9	16.9	15.7	14.1	16.9	14.6	12.3
	20%	16.9	14.9	13.1	16.8	12.7	9.7	16.8	10.9	6.8
	30%	16.8	13.1	10.4	16.8	10.2	6.1	16.8	7.9	3.1
	40%	16.8	11.5	8.0	16.8	8.1	3.4	16.8	5.6	1.2
	50%	16.8	10.0	5.9	16.8	6.3	1.8	16.8	3.9	0.4
	60%	16.8	8.6	4.2	16.8	4.9	0.9	16.8	2.7	0.2
	70%	16.8	7.4	2.9	16.8	3.7	0.4	16.8	1.9	0.1
	80%	16.8	6.4	2.0	16.8	2.9	0.2	16.8	1.4	0.0
	90%	16.8	5.4	1.3	16.8	2.2	0.1	16.8	1.0	0.0
20 Years	10%	16.9	16.3	15.0	16.9	15.0	12.6	16.9	13.7	10.4
	20%	16.9	14.0	11.4	16.8	11.5	7.3	16.8	9.4	4.3
	30%	16.8	11.9	8.2	16.8	8.6	3.6	16.8	6.2	1.3
	40%	16.8	10.0	5.5	16.8	6.4	1.6	16.8	3.9	0.4
	50%	16.8	8.4	3.5	16.8	4.6	0.6	16.8	2.5	0.1
	60%	16.8	7.0	2.1	16.8	3.3	0.2	16.8	1.6	0.0
	70%	16.8	5.7	1.2	16.8	2.4	0.1	16.8	1.1	0.0
	80%	16.8	4.7	0.7	16.8	1.8	0.0	16.8	0.7	0.0
	90%	16.8	3.9	0.4	16.8	1.3	0.0	16.8	0.5	0.0

¹ IR estimated as # of incident infections per 1,000 person-years (PY)

² IR estimates are for the total population (males and females)

³ Under no vaccination, IRs in 2025, 2050, and 2075 were 16.9, 18.5, and 18.7/1,000 PY, respectively

⁴ Scenario B: Vaccinating 15-year-old girls and boys entering the model between 2025-2075.

Abbreviations: CT, *Chlamydia trachomatis*, IR, incidence rate; PY, person-years

Supplemental Table B.11. CT incidence rates among all individuals aged 15-64 years between 2025-2075 for Scenario C ^{1,2,3,4}

Duration of Protection	VE	5% Coverage			10% Coverage			15% Coverage		
		2025	2050	2075	2025	2050	2075	2025	2050	2075
0.5 Years	10%	16.9	18.3	18.4	16.9	18.3	18.4	16.9	18.3	18.4
	20%	16.9	18.1	18.2	16.9	18.1	18.2	16.9	18.1	18.2
	30%	16.9	17.9	18.0	16.9	17.9	18.0	16.9	17.9	17.9
	40%	16.9	17.7	17.7	16.9	17.7	17.7	16.9	17.7	17.7
	50%	16.8	17.5	17.5	16.8	17.5	17.5	16.8	17.5	17.5
	60%	16.8	17.3	17.2	16.8	17.3	17.2	16.8	17.3	17.2
	70%	16.8	17.1	17.0	16.8	17.1	17.0	16.8	17.1	17.0
	80%	16.8	16.9	16.7	16.8	16.9	16.7	16.8	16.8	16.7
	90%	16.8	16.7	16.5	16.8	16.7	16.5	16.8	16.6	16.4
1 Year	10%	16.9	18.2	18.2	16.9	18.2	18.2	16.9	18.1	18.2
	20%	16.9	17.8	17.8	16.9	17.8	17.8	16.9	17.8	17.8
	30%	16.9	17.4	17.3	16.9	17.4	17.3	16.9	17.4	17.3
	40%	16.8	17.1	16.9	16.8	17.0	16.8	16.8	17.0	16.8
	50%	16.8	16.7	16.4	16.8	16.7	16.4	16.8	16.6	16.4
	60%	16.8	16.3	15.9	16.8	16.3	15.9	16.8	16.2	15.9
	70%	16.8	16.0	15.4	16.8	15.9	15.4	16.8	15.8	15.4
	80%	16.8	15.6	14.9	16.8	15.5	14.9	16.8	15.4	14.9
	90%	16.8	15.2	14.5	16.8	15.1	14.4	16.8	15.0	14.4
5 Years	10%	16.9	17.4	17.1	16.9	17.4	17.1	16.9	17.3	17.1
	20%	16.9	16.2	15.5	16.9	16.1	15.4	16.9	16.1	15.4
	30%	16.8	15.0	13.8	16.8	14.9	13.8	16.8	14.8	13.8
	40%	16.8	13.9	12.2	16.8	13.7	12.2	16.8	13.5	12.1
	50%	16.8	12.7	10.6	16.8	12.5	10.5	16.8	12.4	10.5
	60%	16.8	11.7	9.1	16.8	11.4	9.0	16.8	11.2	8.9
	70%	16.8	10.6	7.6	16.8	10.4	7.6	16.8	10.1	7.5
	80%	16.8	9.6	6.3	16.8	9.4	6.2	16.8	9.1	6.1
	90%	16.8	8.7	5.2	16.8	8.4	5.1	16.8	8.2	5.0
10 Year	10%	16.9	17.0	16.3	16.9	16.9	16.3	16.9	16.8	16.3
	20%	16.9	15.3	13.9	16.9	15.1	13.9	16.9	15.0	13.8
	30%	16.8	13.6	11.5	16.8	13.5	11.5	16.8	13.3	11.4
	40%	16.8	12.1	9.3	16.8	11.9	9.2	16.8	11.7	9.1
	50%	16.8	10.7	7.2	16.8	10.4	7.1	16.8	10.2	7.0
	60%	16.8	9.3	5.4	16.8	9.0	5.3	16.8	8.8	5.2
	70%	16.8	8.1	3.9	16.8	7.8	3.8	16.8	7.5	3.7
	80%	16.8	7.0	2.8	16.8	6.7	2.7	16.8	6.4	2.6
	90%	16.8	6.0	1.9	16.8	5.7	1.8	16.8	5.4	1.7
20 Years	10%	16.9	16.6	15.5	16.9	16.5	15.5	16.9	16.4	15.5
	20%	16.9	14.5	12.4	16.9	14.3	12.3	16.9	14.2	12.3
	30%	16.8	12.5	9.4	16.8	12.3	9.3	16.8	12.1	9.3
	40%	16.8	10.7	6.8	16.8	10.5	6.7	16.8	10.2	6.6
	50%	16.8	9.1	4.6	16.8	8.8	4.5	16.8	8.5	4.4
	60%	16.8	7.6	3.0	16.8	7.3	2.9	16.8	7.0	2.8
	70%	16.8	6.4	1.8	16.8	6.0	1.7	16.8	5.7	1.7
	80%	16.8	5.2	1.1	16.8	4.9	1.0	16.8	4.6	0.9
	90%	16.8	4.3	0.6	16.8	4.0	0.6	16.8	3.7	0.5

¹ IR estimated as # of incident infections per 1,000 person-years (PY)

² IR estimates are for the total population (males and females)

³ Under no vaccination, IRs in 2025, 2050, and 2075 were 16.9, 18.5, and 18.7/1,000 PY, respectively

⁴ Scenario C: Scenario A at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035
Abbreviations: CT, *Chlamydia trachomatis*, IR, incidence rate; PY, person-years

Supplemental Table B.12: CT incidence rates among all individuals aged 15-64 years between 2025-2075 for Scenario D ^{1,2,3,4}

Duration of Protection	VE	5% Catch-up Coverage			10% Catch-up Coverage			15% Catch-up Coverage		
		2025	2050	2075	2025	2050	2075	2025	2050	2075
0.5 Years	10%	16.9	18.2	18.2	16.9	18.1	18.2	16.9	18.1	18.2
	20%	16.9	17.8	17.7	16.9	17.8	17.7	16.9	17.8	17.7
	30%	16.8	17.4	17.3	16.8	17.4	17.3	16.8	17.4	17.3
	40%	16.8	17.0	16.8	16.8	17.0	16.8	16.8	17.0	16.8
	50%	16.8	16.7	16.3	16.8	16.6	16.3	16.8	16.6	16.3
	60%	16.8	16.3	15.8	16.8	16.3	15.8	16.8	16.2	15.8
	70%	16.8	15.9	15.3	16.8	15.9	15.3	16.8	15.9	15.3
	80%	16.8	15.6	14.9	16.8	15.5	14.9	16.8	15.5	14.8
	90%	16.8	15.2	14.4	16.8	15.2	14.4	16.8	15.1	14.4
1 Year	10%	16.9	17.9	17.8	16.9	17.9	17.8	16.9	17.9	17.8
	20%	16.8	17.2	16.9	16.8	17.2	16.9	16.8	17.1	16.9
	30%	16.8	16.5	16.0	16.8	16.5	16.0	16.8	16.4	16.0
	40%	16.8	15.8	15.1	16.8	15.8	15.1	16.8	15.7	15.1
	50%	16.8	15.1	14.2	16.8	15.1	14.2	16.8	15.0	14.2
	60%	16.8	14.5	13.3	16.8	14.4	13.3	16.8	14.4	13.3
	70%	16.8	13.9	12.4	16.8	13.8	12.4	16.8	13.7	12.4
	80%	16.8	13.2	11.6	16.8	13.2	11.6	16.8	13.1	11.6
	90%	16.8	12.6	10.8	16.8	12.5	10.7	16.8	12.5	10.7
5 Years	10%	16.9	16.5	15.6	16.9	16.4	15.6	16.9	16.4	15.5
	20%	16.8	14.2	12.5	16.8	14.2	12.4	16.8	14.1	12.4
	30%	16.8	12.2	9.5	16.8	12.1	9.5	16.8	12.0	9.5
	40%	16.8	10.4	6.9	16.8	10.2	6.9	16.8	10.1	6.8
	50%	16.8	8.7	4.8	16.8	8.6	4.8	16.8	8.4	4.7
	60%	16.8	7.3	3.2	16.8	7.1	3.2	16.8	7.0	3.1
	70%	16.8	6.1	2.0	16.8	5.9	2.0	16.8	5.8	2.0
	80%	16.8	5.0	1.3	16.8	4.9	1.2	16.8	4.7	1.2
	90%	16.8	4.2	0.8	16.8	4.0	0.7	16.8	3.9	0.7
10 Year	10%	16.9	15.6	14.0	16.9	15.5	14.0	16.9	15.5	14.0
	20%	16.8	12.6	9.7	16.8	12.5	9.6	16.8	12.4	9.6
	30%	16.8	10.1	6.0	16.8	9.9	6.0	16.8	9.8	5.9
	40%	16.8	7.9	3.4	16.8	7.7	3.3	16.8	7.6	3.3
	50%	16.8	6.1	1.8	16.8	5.9	1.7	16.8	5.8	1.7
	60%	16.8	4.7	0.9	16.8	4.5	0.8	16.8	4.4	0.8
	70%	16.8	3.6	0.4	16.8	3.4	0.4	16.8	3.3	0.4
	80%	16.8	2.7	0.2	16.8	2.6	0.2	16.8	2.5	0.2
	90%	16.8	2.1	0.1	16.8	2.0	0.1	16.8	1.9	0.1
20 Years	10%	16.9	14.9	12.6	16.9	14.8	12.6	16.9	14.7	12.6
	20%	16.8	11.3	7.3	16.8	11.2	7.2	16.8	11.1	7.2
	30%	16.8	8.5	3.6	16.8	8.3	3.5	16.8	8.1	3.5
	40%	16.8	6.2	1.5	16.8	6.0	1.5	16.8	5.9	1.4
	50%	16.8	4.4	0.6	16.8	4.3	0.6	16.8	4.1	0.5
	60%	16.8	3.2	0.2	16.8	3.0	0.2	16.8	2.9	0.2
	70%	16.8	2.3	0.1	16.8	2.2	0.1	16.8	2.1	0.1
	80%	16.8	1.7	0.0	16.8	1.6	0.0	16.8	1.5	0.0
	90%	16.8	1.2	0.0	16.8	1.1	0.0	16.8	1.1	0.0

¹ IR estimated as # of incident infections per 1,000 person-years (PY)

² IR estimates are for the total population (males and females)

³ Under no vaccination, IRs in 2025, 2050, and 2075 were 16.9, 18.5, and 18.7/1,000 PY, respectively

⁴ Scenario D: Scenario B @ 50% cov. + catch-up campaign among unvaccinated 15-24-year-old women in 2035 at 5/10/15% cov.
Abbreviations: CT, *Chlamydia trachomatis*, IR, incidence rate; PY, person-years

Supplemental Table B.13. Infections prevented per 1,000 doses of vaccine given, by vaccine efficacy, duration of protection, and coverage for Scenario Group A ¹

Duration of Protection	VE	30% Coverage	50% Coverage	70% Coverage
		Median (IQR) ²	Median (IQR)	Median (IQR)
0.5 Years	10%	37.6 (37.2, 37.9)	37.6 (37.2, 37.9)	37.5 (37.1, 37.8)
	20%	82.7 (81.7, 83.2)	82.6 (81.7, 83.2)	82.5 (81.5, 83)
	30%	127.9 (126.5, 128.9)	127.7 (126.2, 128.7)	127.4 (125.9, 128.4)
	40%	173.4 (171.5, 174.7)	172.9 (171, 174.3)	172.3 (170.5, 173.8)
	50%	219 (216.7, 220.8)	218.2 (216, 220.1)	217.4 (215.1, 219.3)
	60%	264.8 (262, 267.1)	263.7 (260.9, 266)	262.5 (259.7, 264.8)
	70%	310.9 (307.5, 313.5)	309.3 (306, 312)	307.6 (304.3, 310.4)
	80%	357 (353.2, 360.2)	354.9 (351.1, 358.1)	352.7 (348.8, 356.2)
	90%	403.4 (399.1, 407)	400.7 (396.3, 404.5)	397.8 (393.4, 401.9)
1 Year	10%	69.9 (69.1, 70.4)	69.8 (69, 70.3)	69.6 (68.9, 70.1)
	20%	154.2 (152.5, 155.3)	153.8 (152.1, 154.9)	153.3 (151.6, 154.4)
	30%	239 (236.3, 240.8)	238 (235.3, 239.9)	236.9 (234.3, 238.8)
	40%	324.3 (320.6, 326.9)	322.4 (319, 325.3)	320.5 (317.3, 323.4)
	50%	410 (405.7, 413.5)	407.1 (402.9, 410.8)	404.1 (399.8, 408)
	60%	496.1 (490.9, 500.6)	491.9 (486.7, 496.7)	487.2 (482.1, 492.5)
	70%	582.9 (576.5, 588.2)	576.8 (570.7, 582.8)	569.9 (563.9, 576.8)
	80%	669.9 (662.8, 676.3)	661.4 (654.3, 669)	652.4 (645.5, 660.7)
	90%	757.3 (749, 765)	746.1 (738.1, 755.2)	734.4 (726.5, 744)
5 Years	10%	244 (241.1, 246.4)	242.5 (239.7, 245.1)	240.9 (238.2, 243.6)
	20%	528.3 (522.6, 533.7)	522.4 (517.3, 528.2)	516.2 (511, 522.3)
	30%	812.7 (804.6, 821.5)	799.1 (790.5, 809.2)	783.8 (775.7, 795.2)
	40%	1097.4 (1085.9, 1110.7)	1070.8 (1059.2, 1086.6)	1039.7 (1027.2, 1054.8)
	50%	1380.6 (1366.3, 1399.7)	1334.4 (1319.5, 1353.7)	1280.4 (1264.5, 1300.6)
	60%	1661.9 (1644.2, 1686.3)	1589.4 (1568.9, 1612.5)	1500.3 (1481.5, 1528.8)
	70%	1939.5 (1918.5, 1967.1)	1829.5 (1807.1, 1860.3)	1699.8 (1677.3, 1735.5)
	80%	2213.4 (2186.8, 2244.4)	2055.8 (2030.4, 2094.8)	1875.3 (1850.4, 1919)
	90%	2479.7 (2450.9, 2517)	2266.7 (2237.5, 2313.6)	2028 (1999.4, 2078.9)
10 Years	10%	357 (353.2, 361.1)	353.8 (350.2, 358.1)	350.6 (347, 355)
	20%	761.5 (753.7, 771.6)	748.3 (740.9, 758.8)	733.9 (726.5, 744.4)
	30%	1162.8 (1151.7, 1179.7)	1129.4 (1118.1, 1146.6)	1091.1 (1078.7, 1108.6)
	40%	1558.2 (1543.9, 1582.6)	1492.2 (1474.7, 1515.9)	1414.6 (1395.7, 1441.2)
	50%	1947.3 (1924.7, 1976.7)	1831.1 (1806.7, 1862.8)	1694.1 (1671.2, 1731.7)
	60%	2324.3 (2296.1, 2360.5)	2139.2 (2109.8, 2183.2)	1927.7 (1900.3, 1976.1)
	70%	2688.4 (2654.6, 2732.3)	2415 (2380.5, 2468.6)	2115.8 (2083.3, 2175.5)
	80%	3034.2 (2995.9, 3091)	2654.7 (2617.1, 2720.6)	2268.8 (2229.8, 2337.8)
	90%	3362.6 (3318, 3432.1)	2860.2 (2817.5, 2938.1)	2390.1 (2347, 2466.5)
20 Years	10%	462 (457.1, 467.8)	456.6 (451.6, 463.1)	450.8 (446, 457.5)
	20%	972.6 (963.3, 987.4)	948.5 (939, 963.2)	921.1 (911.3, 936.3)
	30%	1473.6 (1458.3, 1496.3)	1411 (1394.7, 1434.3)	1338.7 (1320.8, 1366.4)
	40%	1959.5 (1937.1, 1990.6)	1833.2 (1809, 1870.6)	1691.3 (1666.6, 1730.3)
	50%	2425.5 (2397, 2467)	2210.2 (2177.2, 2258.6)	1968.2 (1937.5, 2020.6)
	60%	2866.4 (2829.3, 2923.4)	2529.6 (2491.9, 2592.6)	2179 (2142.9, 2244)
	70%	3281.9 (3237.3, 3351.1)	2795.8 (2751.8, 2872.7)	2340.1 (2295.7, 2413.9)
	80%	3662.5 (3610.9, 3745.1)	3013.4 (2964.5, 3103.1)	2461.4 (2411, 2542.9)
	90%	4009.5 (3950.3, 4106.1)	3194 (3135.4, 3293.3)	2555 (2499.9, 2642.5)

¹ Scenario A: Vaccinating only 15-year-old girls entering the model between 2025-2075.

² Refers to median (IQR) CT infections prevented per 1,000 doses of vaccine given comparing Scenario A to the referent scenario (no vaccination) from 2025-2075.

Abbreviations: CT, Chlamydia trachomatis; VE, vaccine efficacy; IQR, interquartile range

Supplemental Table B.14. Infections prevented per 1,000 doses of vaccine given, by vaccine efficacy, duration of protection, and coverage for Scenario Group B ¹

Duration of Protection	VE	30% Coverage	50% Coverage	70% Coverage
		Median (IQR) ²	Median (IQR)	Median (IQR)
0.5 Years	10%	37 (36.6, 37.3)	37 (36.6, 37.3)	36.9 (36.5, 37.2)
	20%	80.3 (79.4, 80.9)	80.1 (79.2, 80.6)	79.8 (79, 80.4)
	30%	123.6 (122.3, 124.5)	123 (121.7, 124)	122.4 (121, 123.4)
	40%	166.9 (165, 168.2)	165.8 (164, 167.2)	164.6 (162.9, 166.1)
	50%	210.1 (207.8, 211.9)	208.3 (206.2, 210.2)	206.4 (204.5, 208.3)
	60%	253.3 (250.7, 255.5)	250.7 (248.2, 253)	247.9 (245.5, 250.3)
	70%	296.5 (293.5, 299.1)	292.8 (289.9, 295.5)	288.9 (286, 291.9)
	80%	339.6 (336.2, 342.6)	334.7 (331.3, 337.9)	329.5 (325.8, 333.1)
	90%	382.7 (378.8, 386.1)	376.3 (372.4, 380.1)	369.3 (365.1, 373.7)
1 Year	10%	68.8 (68.1, 69.3)	68.7 (67.9, 69.2)	68.4 (67.7, 68.9)
	20%	149.8 (148.2, 150.9)	149 (147.4, 150.1)	148 (146.4, 149.2)
	30%	230.8 (228.1, 232.5)	228.5 (226, 230.4)	226 (223.8, 228.2)
	40%	311.3 (307.9, 313.9)	307 (304.1, 310)	302.5 (299.7, 305.9)
	50%	391.6 (387.5, 395.1)	384.6 (380.9, 388.8)	377.3 (373.3, 381.9)
	60%	471.5 (466.8, 476)	461.2 (456.4, 466.5)	449.9 (444.6, 455.8)
	70%	550.9 (545.4, 556.6)	536.2 (530.4, 543)	520.3 (514, 527.2)
	80%	630.1 (623.6, 636.9)	610 (602.9, 618)	587.5 (580.3, 596)
	90%	708.6 (700.9, 716.8)	682.2 (673.9, 691.2)	651.5 (643.3, 661.7)
5 Years	10%	238.7 (236.1, 241.3)	235.9 (233.5, 238.6)	232.8 (230.7, 235.7)
	20%	507.7 (502.7, 513.6)	494.6 (489.6, 501.1)	479.2 (473.8, 486.4)
	30%	769.2 (761.3, 779.2)	733.8 (725.1, 744.9)	693.9 (684.8, 705.1)
	40%	1020 (1008.6, 1035.3)	949.7 (937.3, 965)	869.1 (857.6, 887.7)
	50%	1258.7 (1242.1, 1277)	1136.8 (1122.1, 1159.3)	1005.4 (991.5, 1030.7)
	60%	1482.1 (1462.9, 1505.3)	1294.9 (1277, 1324.5)	1108.4 (1090.3, 1140)
	70%	1687.5 (1666.1, 1718.3)	1424.5 (1404.5, 1460.5)	1185 (1164.1, 1221.7)
	80%	1876.4 (1852.5, 1913.9)	1530.8 (1506.5, 1573.4)	1242.8 (1220.3, 1283.3)
	90%	2046.9 (2018.6, 2091.4)	1616.4 (1588.4, 1665)	1287.2 (1262.2, 1330.7)
10 Years	10%	347.3 (343.9, 352)	341.1 (337.7, 345.5)	333.8 (330.5, 338.6)
	20%	723.3 (716.6, 733.6)	690.6 (682.2, 701.6)	653.4 (644.6, 665.5)
	30%	1076.9 (1063.6, 1093.5)	990.9 (977.6, 1009.8)	896.6 (883.5, 917.9)
	40%	1401.5 (1383.3, 1424.4)	1233.5 (1215.6, 1261.8)	1061.9 (1045.3, 1092.2)
	50%	1692.5 (1670.5, 1726.4)	1416.8 (1395.8, 1455.3)	1173.4 (1151.4, 1210.2)
	60%	1947 (1920.4, 1989.9)	1554.8 (1528.7, 1601.8)	1248.1 (1222.5, 1289.4)
	70%	2164.9 (2133.4, 2217.8)	1657.5 (1626.7, 1710.1)	1300.5 (1272.5, 1345.6)
	80%	2346.7 (2312, 2409.9)	1734.6 (1700.1, 1791.7)	1339.1 (1310.1, 1386.9)
	90%	2499.3 (2459.7, 2571.8)	1794 (1756.1, 1855.3)	1369 (1339.2, 1419.4)
20 Years	10%	447.1 (442.3, 453.4)	435 (430.2, 441.7)	421.6 (416.6, 428.6)
	20%	911.7 (901.4, 925.5)	850.6 (839.1, 867)	784.4 (773.3, 802.3)
	30%	1330.5 (1313.1, 1354.6)	1177 (1159.6, 1203.9)	1020.6 (1003.7, 1048.9)
	40%	1696.5 (1672.9, 1732.7)	1410 (1387.2, 1448.8)	1162.5 (1140, 1199.2)
	50%	2004 (1974.1, 2051.5)	1570.8 (1542.7, 1619.7)	1249.9 (1222.8, 1292)
	60%	2251.9 (2217, 2311.1)	1683.2 (1649.1, 1737.5)	1307.1 (1278.3, 1353.3)
	70%	2448.8 (2409.6, 2519.7)	1762.8 (1724.6, 1822.7)	1347.9 (1318.2, 1396.7)
	80%	2608.2 (2561.9, 2689.3)	1821.7 (1781.6, 1885.8)	1378.7 (1348.4, 1429.9)
	90%	2735.4 (2682.5, 2822.3)	1867.3 (1826.3, 1934.5)	1402.9 (1372.3, 1455.6)

¹ Scenario B: Vaccinating 15-year-old girls and boys entering the model between 2025-2075.

² Refers to median (IQR) CT infections prevented per 1,000 doses of vaccine given comparing Scenario B to the referent scenario (no vaccination) from 2025-2075.

Abbreviations: CT, Chlamydia trachomatis; VE, vaccine efficacy; IQR, interquartile range

Supplemental Table B.15. Infections prevented per 1,000 doses of vaccine given, by vaccine efficacy, duration of protection, and coverage for Scenario Group C ¹

Duration of Protection	VE	5% Catch-up Coverage	10% Catch-up Coverage	15% Catch-up Coverage
		Median (IQR) ²	Median (IQR)	Median (IQR)
0.5 Years	10%	37.9 (37.5, 38.2)	38.2 (37.8, 38.5)	38.5 (38.1, 38.8)
	20%	83.1 (82.1, 83.7)	83.6 (82.6, 84.1)	84.1 (83, 84.6)
	30%	128.4 (126.9, 129.3)	129 (127.6, 130)	129.7 (128.2, 130.6)
	40%	173.8 (171.8, 175.2)	174.6 (172.6, 176)	175.4 (173.4, 176.8)
	50%	219.3 (217, 221.1)	220.4 (217.9, 222.1)	221.3 (218.8, 223.1)
	60%	265 (262.2, 267.2)	266.2 (263.4, 268.4)	267.4 (264.5, 269.5)
	70%	310.8 (307.4, 313.5)	312.2 (308.8, 314.9)	313.5 (310.1, 316.1)
	80%	356.6 (352.9, 359.8)	358.2 (354.4, 361.4)	359.8 (355.9, 362.9)
	90%	402.6 (398.2, 406.3)	404.4 (400.1, 408)	406.1 (401.8, 409.8)
1 Year	10%	70.4 (69.6, 71)	71 (70.2, 71.6)	71.6 (70.8, 72.1)
	20%	154.8 (153.1, 155.9)	155.8 (154.1, 156.9)	156.7 (154.9, 157.8)
	30%	239.5 (236.8, 241.3)	240.8 (238.1, 242.6)	242.1 (239.4, 243.8)
	40%	324.3 (320.8, 327)	326.1 (322.5, 328.7)	327.7 (324.1, 330.4)
	50%	409.3 (405.1, 413)	411.5 (407.2, 415.1)	413.5 (409.2, 417.1)
	60%	494.6 (489.3, 499.3)	497.2 (491.8, 501.7)	499.6 (494.2, 504)
	70%	580 (573.9, 585.9)	583 (576.7, 588.8)	585.8 (579.4, 591.5)
	80%	665.1 (658, 672.5)	668.6 (661.4, 675.9)	671.8 (664.7, 679)
	90%	750 (742.1, 759.1)	753.9 (745.7, 762.9)	757.6 (749.5, 766.5)
5 Years	10%	245 (242.1, 247.5)	247.3 (244.3, 249.7)	249.4 (246.4, 251.7)
	20%	526.6 (521.4, 532.4)	530.5 (525.3, 536.4)	534.1 (528.8, 540.1)
	30%	805.2 (796.4, 815.2)	810.7 (802, 820.8)	815.8 (807.1, 825.9)
	40%	1078.5 (1067, 1094.4)	1085.6 (1074.2, 1101.6)	1092.1 (1080.7, 1108.3)
	50%	1343.6 (1328.7, 1363.2)	1352 (1337.1, 1371.9)	1359.9 (1344.9, 1379.9)
	60%	1600 (1579.3, 1623.1)	1609.7 (1588.8, 1633)	1618.6 (1597.5, 1642)
	70%	1840.8 (1818.3, 1871.9)	1851.2 (1828.4, 1882.5)	1860.7 (1837.7, 1892.2)
	80%	2067.4 (2041.9, 2107)	2077.8 (2052.2, 2118.1)	2087.3 (2061.4, 2128)
	90%	2278 (2248.5, 2325.6)	2288.2 (2258.3, 2336.2)	2297.3 (2267, 2345.6)
10 Years	10%	357.5 (353.8, 361.7)	360.8 (357.1, 365.1)	363.9 (360.1, 368.2)
	20%	754.6 (747.3, 765.3)	760.4 (753.1, 771.3)	765.7 (758.4, 776.8)
	30%	1138.3 (1127.1, 1155.8)	1146.5 (1135.4, 1164.2)	1154 (1143, 1171.9)
	40%	1503.2 (1485.6, 1527.3)	1513.4 (1495.6, 1537.7)	1522.7 (1504.7, 1547.2)
	50%	1843.4 (1818.8, 1875.8)	1854.4 (1829.7, 1887.5)	1864.5 (1839.5, 1898.2)
	60%	2151.9 (2122.1, 2196.4)	2163.2 (2133.1, 2208.1)	2173.1 (2142.8, 2218.6)
	70%	2426.5 (2391.6, 2480.9)	2436.2 (2401, 2491.6)	2444.5 (2409, 2500.8)
	80%	2663.9 (2625.7, 2731)	2671.1 (2632.4, 2739.4)	2676.6 (2637.5, 2746.2)
	90%	2866 (2822.8, 2945.4)	2870 (2826.3, 2950.6)	2872.4 (2828.2, 2954)
20 Years	10%	461.3 (456.4, 468)	465.8 (460.8, 472.5)	469.9 (464.9, 476.6)
	20%	957 (947.3, 971.9)	964.8 (955, 979.9)	972 (962, 987.2)
	30%	1422.4 (1405.9, 1446)	1432.7 (1416.2, 1456.8)	1442.3 (1425.6, 1466.6)
	40%	1846.3 (1821.8, 1884.5)	1858.1 (1833.3, 1897)	1868.7 (1843.7, 1908.1)
	50%	2223.1 (2190, 2272.2)	2234.5 (2201.3, 2284.2)	2244.4 (2211.1, 2294.8)
	60%	2540.3 (2502.4, 2604.5)	2549.2 (2511.4, 2614.4)	2556.5 (2518.8, 2622.4)
	70%	2802.7 (2758.4, 2881.1)	2807.7 (2763.1, 2887.2)	2810.9 (2766, 2891.2)
	80%	3016.2 (2966.4, 3106.9)	3016.9 (2966.2, 3108.8)	3015.8 (2963.9, 3108.7)
	90%	3191.3 (3131.9, 3291.2)	3186.4 (3126.4, 3286.9)	3179.8 (3119.3, 3281.1)

¹ Scenario C: Scenario A at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035

² Refers to median (IQR) CT infections prevented per 1,000 doses of vaccine given comparing Scenario C to the referent scenario (no vaccination) from 2025-2075.

Abbreviations: CT, Chlamydia trachomatis; VE, vaccine efficacy; IQR, interquartile range

Supplemental Table B.16. Infections prevented per 1,000 doses of vaccine given, by vaccine efficacy, duration of protection, and coverage for Scenario Group D ¹

Duration of Protection	VE	5% Catch-up Coverage	10% Catch-up Coverage	15% Catch-up Coverage
		Median (IQR) ²	Median (IQR)	Median (IQR)
0.5 Years	10%	37.2 (36.8, 37.4)	37.3 (36.9, 37.6)	37.5 (37.1, 37.7)
	20%	80.4 (79.5, 80.9)	80.6 (79.7, 81.2)	80.9 (80, 81.4)
	30%	123.4 (122.1, 124.4)	123.8 (122.4, 124.7)	124.2 (122.8, 125.1)
	40%	166.3 (164.5, 167.7)	166.8 (164.9, 168.2)	167.3 (165.4, 168.7)
	50%	209 (206.8, 210.8)	209.6 (207.3, 211.4)	210.1 (207.9, 211.9)
	60%	251.4 (248.9, 253.7)	252.1 (249.6, 254.4)	252.8 (250.3, 255.1)
	70%	293.7 (290.8, 296.4)	294.5 (291.6, 297.2)	295.3 (292.4, 298)
	80%	335.6 (332.2, 338.9)	336.6 (333.1, 339.8)	337.5 (334, 340.7)
	90%	377.3 (373.5, 381.2)	378.4 (374.5, 382.3)	379.4 (375.5, 383.3)
1 Year	10%	69 (68.3, 69.5)	69.3 (68.6, 69.8)	69.6 (68.9, 70.1)
	20%	149.5 (147.9, 150.7)	150.1 (148.4, 151.2)	150.6 (148.9, 151.7)
	30%	229.3 (226.8, 231.2)	230.1 (227.5, 232)	230.8 (228.3, 232.7)
	40%	308.1 (305.1, 311)	309.1 (306, 312)	310 (306.9, 312.9)
	50%	385.9 (382.1, 390)	387.1 (383.3, 391.2)	388.2 (384.4, 392.3)
	60%	462.7 (457.9, 468)	464.1 (459.3, 469.4)	465.4 (460.7, 470.8)
	70%	537.9 (532.1, 544.7)	539.5 (533.8, 546.3)	541 (535.4, 547.9)
	80%	611.9 (604.8, 619.9)	613.7 (606.5, 621.8)	615.4 (608.2, 623.5)
	90%	684.3 (676, 693.3)	686.3 (678, 695.3)	688.2 (679.9, 697.3)
5 Years	10%	237.1 (234.7, 239.9)	238.3 (235.9, 241.1)	239.4 (236.9, 242.2)
	20%	496.7 (491.7, 503.2)	498.7 (493.6, 505.2)	500.5 (495.4, 507.1)
	30%	736.5 (727.9, 747.7)	739.1 (730.5, 750.4)	741.6 (733, 752.8)
	40%	952.9 (940.4, 968.3)	955.9 (943.3, 971.4)	958.6 (946, 974.3)
	50%	1139.9 (1125.2, 1162.6)	1142.7 (1128, 1165.6)	1145.3 (1130.5, 1168.4)
	60%	1297.4 (1279.5, 1327.3)	1299.7 (1281.8, 1329.9)	1301.7 (1283.9, 1332.1)
	70%	1426 (1405.9, 1462.3)	1427.3 (1407, 1463.9)	1428.4 (1407.9, 1465.2)
	80%	1531.2 (1506.6, 1574.3)	1531.3 (1506.5, 1574.8)	1531.2 (1506.2, 1575.1)
	90%	1615.5 (1587.1, 1664.3)	1614.3 (1585.7, 1663.4)	1612.8 (1584.3, 1662.3)
10 Years	10%	342.9 (339.4, 347.4)	344.6 (341.1, 349.2)	346.2 (342.6, 350.8)
	20%	693.5 (685.1, 704.6)	696.3 (687.9, 707.4)	698.9 (690.4, 710)
	30%	994.3 (981, 1013.5)	997.4 (984.1, 1016.9)	1000.4 (987, 1020)
	40%	1236.4 (1218.5, 1265)	1239 (1221, 1267.9)	1241.4 (1223.3, 1270.6)
	50%	1418.4 (1397.2, 1457.2)	1419.7 (1398.4, 1458.8)	1420.7 (1399.3, 1460.1)
	60%	1554.8 (1528.4, 1602.1)	1554.5 (1527.8, 1602)	1554 (1527, 1601.6)
	70%	1655.6 (1624.8, 1708.3)	1653.4 (1622.7, 1706.3)	1651.1 (1620.3, 1704.1)
	80%	1730.8 (1696.1, 1788.2)	1727 (1691.9, 1784.5)	1723 (1687.6, 1780.7)
	90%	1788.6 (1750.6, 1850)	1783.1 (1745.1, 1844.6)	1777.6 (1739.6, 1839.2)
20 Years	10%	437.3 (432.5, 444)	439.5 (434.7, 446.3)	441.6 (436.8, 448.3)
	20%	854.1 (842.6, 870.6)	857.4 (845.8, 874)	860.4 (848.9, 877.1)
	30%	1180.3 (1162.8, 1207.4)	1183.2 (1165.7, 1210.7)	1185.9 (1168.3, 1213.6)
	40%	1411.7 (1388.8, 1450.7)	1413 (1390, 1452.4)	1414.1 (1391, 1453.7)
	50%	1570.4 (1541.9, 1619.3)	1569.7 (1540.8, 1618.7)	1568.8 (1539.6, 1617.9)
	60%	1680.5 (1646.1, 1735)	1677.6 (1642.9, 1732.3)	1674.6 (1639.7, 1729.5)
	70%	1758 (1719.7, 1818.1)	1753.1 (1714.7, 1813.4)	1748.2 (1709.8, 1808.6)
	80%	1815.1 (1775.1, 1879.3)	1808.6 (1768.8, 1872.8)	1802.2 (1762.5, 1866.3)
	90%	1859.3 (1818.4, 1926.4)	1851.4 (1810.8, 1918.4)	1843.7 (1803.3, 1910.6)

¹ Scenario D: Scenario B at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035

² Refers to median (IQR) CT infections prevented per 1,000 doses of vaccine given comparing Scenario D to the referent scenario (no vaccination) from 2025-2075. Abbreviations: CT, Chlamydia trachomatis; VE, vaccine efficacy; IQR, interquartile range.

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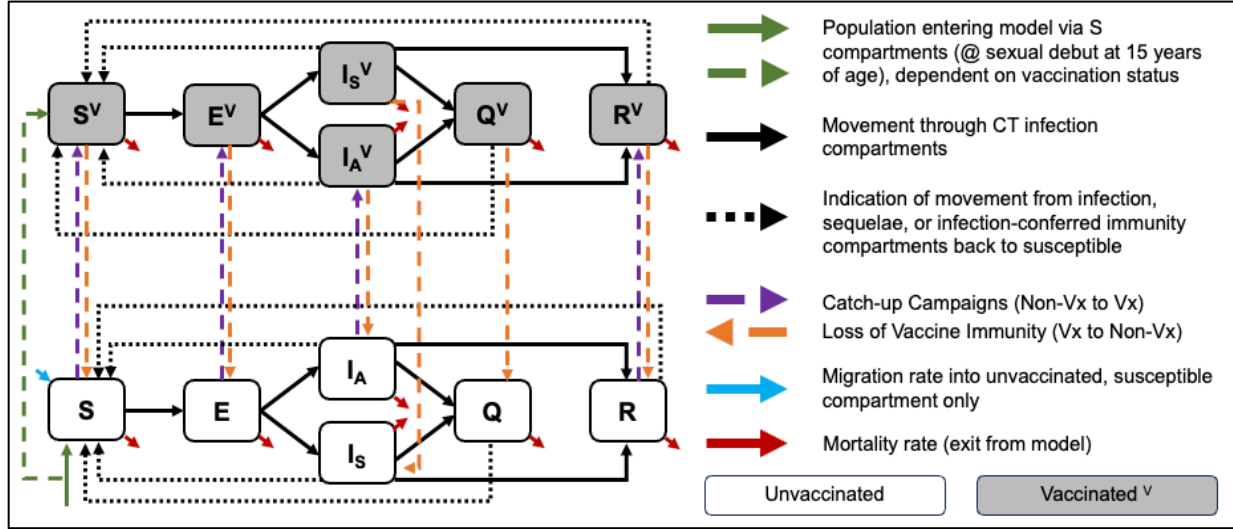
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Appendix C

Supplementary Materials for Chapter 4

C.1 MODEL STRUCTURE



The model comprises 72 ordinary differential equations, structured across 12 disease stage compartments, 2 biological sex groups, and 3 age groups, with indexing as follows:

- Biological sex at birth $j \in \{1 = \text{male}; 2 = \text{female}\}$
- Age group $k \in \{1 = 15\text{-}24 \text{ years}; 2 = 25\text{-}39 \text{ years}; 3 = 40\text{-}64 \text{ years}\}$

Compartments among the simulated, unvaccinated population include:

- $S_{j,k}$: Susceptible population of sex j and age group k
- $E_{j,k}$: Infected, non-infectious population of sex j and age group k
- $I_{s,j,k}$: Symptomatically infected, infectious population of sex j and age group k
- $I_{a,j,k}$: Asymptomatically infected, infectious population of sex j and age group k
- $Q_{j,k}$: Sequelae-experiencing population of sex j and age group k , where $j = 1$ for epididymitis; $j = 2$ for pelvic inflammatory disease (PID)
- $R_{j,k}$: Infection-conferred immune population (natural recovery) of sex j and age group k

Compartments among the simulated, vaccinated population include:

- $S^v_{j,k}$: Susceptible population of sex j and age group k

- $E_{j,k}^V$: Infected, non-infectious population of sex j and age group k
- $Is_{j,k}^V$: Symptomatically infected, infectious population of sex j and age group k
- $Ia_{j,k}^V$: Asymptomatically infected, infectious population of sex j and age group k
- $Q_{j,k}^V$: Sequelae-experiencing population of sex j and age group k , where $j = 1$ for epididymitis; $j = 2$ for pelvic inflammatory disease (PID)
- $R_{j,k}^V$: Infection-conferred immune population (natural recovery) of sex j and age group k

Additional details on model parameters, force of infection, and ODEs relevant to disease burden can be found in **Appendix B.1 Model Structure**.

C.2 HEALTH OUTCOMES & COST EQUATIONS

Parameters associated with total QALYs include:

- $QALY_{Symp}$: QALY decrement associated with symptomatic CT infection
- $QALY_{Epid}$: QALY decrement associated with a single case of epididymitis among males experiencing sequelae
- $QALY_{PID}$: QALY decrement associated with a single case of PID among females experiencing sequelae, accounting for the likelihood of additional complications including chronic pelvic pain, tubal factor infertility, ectopic pregnancy, or no complications.
- d : Discount rate per year
- y : Year, between 2025 - 2050
- ζ_j : Proportion of infections that present symptomatically, among individuals of sex j
- ϕ : Rate of transition among infected individuals from exposed, non-infectious to infectious
- ι : Rate of natural resolution among untreated symptomatic or asymptomatic infection
- κ_j : Proportion of resolved symptomatic or asymptomatic infections that develop into sequelae, among individuals of sex j

Total QALYs were discounted at 3% over the 25-year time horizon using the following equation:

$$\begin{aligned} \text{Total QALYs} = & \int_{y=1}^{25} e^{-d*y} ((\text{QALY}_{\text{symp}} * \zeta_j \varphi * (E_{j,k} + E_{j,k}^V)) + (\text{QALY}_{\text{Epid}} * \kappa_{j=1} (I_{S_{j=1,k}} + I_{a_{j=1,k}} \\ & + I_{S_{j=1,k}}^V + I_{a_{j=1,k}}^V)) + \text{QALY}_{\text{PID}} * \kappa_{j=2} (I_{S_{j=2,k}} + I_{a_{j=2,k}} + I_{S_{j=2,k}}^V + I_{a_{j=2,k}}^V))) \end{aligned}$$

Parameters associated with total costs include:

- **Cost_{Screen}** : Costs associated with 1.) screening among “true negative” individuals, 2.) combined screening/treatment among “false positive” individuals in the susceptible, exposed, and recovered compartments who receive unnecessary treatment, and 3.) screening among “false positive” individuals in the susceptible, exposed, and recovered compartments who do not receive unnecessary treatment. Importantly, these costs reflect screening in individuals who are truly negative only, calculated as:

$$\begin{aligned} \text{Cost}_{\text{Screen}} = & (r_{j,k} * \text{spec} * \text{screen_cost} * (S_{j,k} + E_{j,k} + R_{j,k} + S_{j,k}^V + E_{j,k}^V + R_{j,k}^V)) + (r_{j,k} * \\ & (1 - \text{spec}) * v * \text{treat_cost} * (S_{j,k} + E_{j,k} + R_{j,k} + S_{j,k}^V + E_{j,k}^V + R_{j,k}^V)) + (r_{j,k} * (1 - \text{spec}) * \\ & (1 - v) * \text{screen_cost} * (S_{j,k} + E_{j,k} + R_{j,k} + S_{j,k}^V + E_{j,k}^V + R_{j,k}^V)), \text{ where:} \end{aligned}$$

- **r_{j,k}** : Screening rate for CT, among individuals of sex *j* and age group *k*
- **spec** : Specificity of diagnostic testing for CT detection via NAAT
- **screen_cost** : Total direct and indirect costs associated with CT screening alone
- **v** : Probability of post-screening treatment among individuals following a positive NAAT result
- **treat_cost** : Total direct and indirect costs associated with CT testing and treatment
- **S_{j,k} + E_{j,k} + R_{j,k} + S_{j,k}^V + E_{j,k}^V + R_{j,k}^V** : Uninfected population eligible for annual CT screening
- **Cost_{Asymp}** : Costs associated with 1.) screening among asymptotically infected “false negative” individuals, 2.) combined screening/treatment among asymptotically

infected “true positive” individuals, and 3.) screening among asymptotically infected “true positive” individuals who do not receive treatment, calculated as:

$$\mathbf{Cost}_{Asymp} = (r_{j,k} * (1 - \varepsilon) * screen_cost * (Ia_{j,k} + Ia_{j,k}^V)) + (r_{j,k} * \varepsilon * v * treat_cost * (Ia_{j,k} + Ia_{j,k}^V)) + (r_{j,k} * \varepsilon * (1 - v) * screen_cost * (Ia_{j,k} + Ia_{j,k}^V)), \text{ where:}$$

- $r_{j,k}$: Screening rate for CT, among individuals of sex j and age group k
 - ε : Sensitivity of diagnostic testing for CT detection via NAAT
 - $screen_cost$: Total direct and indirect costs associated with CT screening alone
 - v : Probability of post-screening treatment among individuals following a positive NAAT result
 - $treat_cost$: Total direct and indirect costs associated with CT testing and treatment
 - $Ia_{j,k} + Ia_{j,k}^V$: Asymptotically infected population eligible for annual CT screening
- $\mathbf{Cost}_{Symp}$: Costs associated with 1.) testing among symptomatically infected “false negative” individuals, 2.) combined testing/treatment among symptomatically infected “true positive” individuals, and 3.) testing among symptomatically infected “true positive” individuals who do not receive treatment, calculated as:

$$\mathbf{Cost}_{Symp} = \left(dur_{txj} * (1 - \varepsilon) * screen_cost * (Is_{j,k} + Is_{j,k}^V) \right) + \left(dur_{txj} * \varepsilon * p_{txt} * treat_cost * (Is_{j,k} + Is_{j,k}^V) \right) + \left(dur_{txj} * \varepsilon * (1 - p_{txt}) * screen_cost * (Is_{j,k} + Is_{j,k}^V) \right), \text{ where:}$$

- dur_{txj} : Duration of treated infection, among individuals of sex j
- ε : Sensitivity of diagnostic testing for CT detection via NAAT
- p_{txt} : Probability of treatment for symptomatic infection, given positive diagnosis

- ***treat_cost*** : Total direct and indirect costs associated with CT testing and treatment
- ***screen_cost*** : Total direct and indirect costs associated with CT screening alone
- ***Is_{j,k} + Is_{j,k}^V*** : Total symptomatically infected population
- ***Cost_{Epid}*** : Costs associated with treatment of Epididymitis in males with untreated CT infection, calculated as:

Cost_{Epid} = *epid_costs* * $\varpi_{j=1}(Q_{j=1,k} + Q_{j=1,k}^V)$, where:

- ***epid_costs*** : Total direct and indirect costs associated with treatment of epididymitis in males with untreated CT infection
- ***ϖ_{j=1}*** : Rate of sequelae resolution, among males
- ***Is_{j=1,k} + Ia_{j=1,k} + Is_{j=1,k}^V + Ia_{j=1,k}^V*** : Total infected population, inclusive of symptomatic and asymptomatic infections among males
- ***Q_{j=1,k} + Q_{j=1,k}^V*** : Total population experiencing epididymitis
- ***Cost_{PID}*** : Costs associated with treatment of PID and subsequent complications (chronic pelvic pain, ectopic pregnancy, tubal factor infertility, or no complications) among females with untreated CT infection, calculated as:

Cost_{PID} = *pid_costs* * $\varpi_{j=2}(Q_{j=2,k} + Q_{j=2,k}^V)$, where:

- ***pid_costs*** : Total direct and indirect costs associated with treatment of PID (and subsequent complications) in females with untreated CT infection
- ***ϖ_{j=2}*** : Rate of sequelae resolution, among females
- ***Q_{j=2,k} + Q_{j=2,k}^V*** : Total population experiencing PID and associated complications
- ***Cost_{Vx_Dose}*** : Costs of CT vaccination (only price per dose), calculated as:

Cost_{Vx_Dose} = (*dose_cost* * $Vx_j\eta N_j$) + (*dose_cost* * $\beta_{j,k}(S_{j,k} + E_{j,k} + Ia_{j,k} + R_{j,k})$), where:

- ***dose_cost*** : Total cost of CT vaccination doses

- Vx_j : Proportion of individuals of sex j vaccinated upon entering the population at age 15 years
- η : Relative size of the population entering the model at age 15, dependent on time t
- N_j : Total size of the simulated population, among individuals of sex j dependent on time t
- $\beta_{j,k}$: Rate of vaccination coverage via catch-up campaigns, among individuals of sex j and age group k
- $S_{j,k} + E_{j,k} + Ia_{j,k} + R_{j,k}$: Total population eligible for vaccination via catch-up campaigns
- $Cost_{vx_Imp}$: Costs of CT vaccination implementation (excluding price per dose), calculated as:

$$Cost_{vx_Imp} = (vximp_costs * Vx_j \eta N_j) + (vximp_costs * \beta_{j,k} (S_{j,k} + E_{j,k} + Ia_{j,k} + R_{j,k})),$$

where:

- $vximp_costs$: Total direct and indirect costs associated with CT vaccination implementation
- Vx_j : Proportion of individuals of sex j vaccinated upon entering the population at age 15 years
- η : Relative size of the population entering the model at age 15, dependent on time t
- N_j : Total size of the simulated population, among individuals of sex j dependent on time t
- $\beta_{j,k}$: Rate of vaccination coverage via catch-up campaigns, among individuals of sex j and age group k

- $S_{j,k} + E_{j,k} + Ia_{j,k} + R_{j,k}$: Total population eligible for vaccination via catch-up campaigns

Total costs were discounted at 3% over the 25-year time horizon using the following equation:

$$\text{Total Costs} = \int_{y=1}^{25} e^{-d*y} (\text{Cost}_{\text{Screen}} + \text{Cost}_{\text{Asymp}} + \text{Cost}_{\text{Symp}} + \text{Cost}_{\text{Epid}} + \text{Cost}_{\text{PID}} + \text{Cost}_{\text{Vx_Dose}} + \text{Cost}_{\text{Vx_Imp}})$$

C.3 ICER ESTIMATION & SCENARIOS

An outline of ICER estimation and all scenarios included in scenario analysis are presented below.

Supplemental Table C.1. Outline of Incremental Cost-Effectiveness Ratios (ICERs)

ICER	Comparison Groups	ICER Equation
1	Scenario A vs Referent Scenario ^A	$ICER = \frac{Cost_{\text{Scenario A}} - Cost_{\text{Referent}}}{QALY_{\text{Scenario A}} - QALY_{\text{Referent}}}$
2	Scenario B vs Scenario A	$ICER = \frac{Cost_{\text{Scenario B}} - Cost_{\text{Scenario A}}}{QALY_{\text{Scenario B}} - QALY_{\text{Scenario A}}}$
3	Scenario C vs Scenario A	$ICER = \frac{Cost_{\text{Scenario C}} - Cost_{\text{Scenario A}}}{QALY_{\text{Scenario C}} - QALY_{\text{Scenario A}}}$
4	Scenario D vs Scenario B	$ICER = \frac{Cost_{\text{Scenario D}} - Cost_{\text{Scenario B}}}{QALY_{\text{Scenario D}} - QALY_{\text{Scenario B}}}$

^A Referent Scenario: standard of care in the United States (screen-and-treat for asymptomatic infections and test-and-treat for symptomatic infections) without vaccination.

Supplemental Table C.2. Outline of Scenario Analysis

Scenario #	Scenario Group	Coverage by 2035 ^A	Duration of Protection	VE	Catch-up Coverage ^B	Difference to Base-case
1	A	50%	10 Years	70%	--	-- *
2	A	50%	10 Years	30%	--	VE
3	A	50%	10 Years	50%	--	VE
4	A	50%	10 Years	90%	--	VE
5	A	50%	5 Years	70%	--	Duration of Protection
6	A	50%	20 Years	70%	--	Duration of Protection
7	A	30%	10 Years	70%	--	Coverage
8	A	70%	10 Years	70%	--	Coverage
9	B	50%	10 Years	70%	--	-- *
10	B	50%	10 Years	30%	--	VE
11	B	50%	10 Years	50%	--	VE
12	B	50%	10 Years	90%	--	VE
13	B	50%	5 Years	70%	--	Duration of Protection
14	B	50%	20 Years	70%	--	Duration of Protection
15	B	30%	10 Years	70%	--	Coverage
16	B	70%	10 Years	70%	--	Coverage
17	C	50%	10 Years	70%	10%	-- *
18	C	50%	10 Years	30%	10%	VE
19	C	50%	10 Years	50%	10%	VE
20	C	50%	10 Years	90%	10%	VE
21	C	50%	5 Years	70%	10%	Duration of Protection
22	C	50%	20 Years	70%	10%	Duration of Protection
23	C	50%	10 Years	70%	5%	Coverage (Catch-up)
24	C	50%	10 Years	70%	15%	Coverage (Catch-up)
25	D	50%	10 Years	70%	10%	-- *
26	D	50%	10 Years	30%	10%	VE
27	D	50%	10 Years	50%	10%	VE
28	D	50%	10 Years	90%	10%	VE
29	D	50%	5 Years	70%	10%	Duration of Protection
30	D	50%	20 Years	70%	10%	Duration of Protection
31	D	50%	10 Years	70%	5%	Coverage (Catch-up)
32	D	50%	10 Years	70%	15%	Coverage (Catch-up)

^A Vaccination coverage among 15-year-olds (girls and/or boys, dependent on Scenario Group) entering the simulated population, beginning in 2025. Value represents coverage reached linearly by 2035.

^B Vaccination coverage among unvaccinated 15-24-year-old females for catch-up campaign occurring in 2035, only.

* Represents base-case scenario within Scenario Group

Abbreviation: VE, vaccine efficacy

C.4 SCENARIO ANALYSIS RESULTS

Results from scenario analysis are presented below.

Supplemental Table C.3. Sequential cost-effectiveness analysis for female-only, sex-neutral, and catch-up vaccination strategies, under base-case assumptions ¹ with 30%, 50%, or 90% VE (2025 - 2050)

30% VE							
A. Female-only Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	148,468.41	1,149,221	546.47	107,888	5,065.15
3	Scenario C	Scenario A	148,453.03	1,136,710	-15.38	12,511	Cost Saving
B. Sex-neutral Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	148,468.41	1,149,221	546.47	107,888	5,065.15
3	Scenario B	Scenario A	149,165.68	1,061,454	697.27	87,767	7,944.56
4	Scenario D	Scenario B	149,182.04	1,050,750	16.36	10,704	1,528.56
50% VE							
A. Female-only Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	147,159.66	1,072,825	-762.28	184,284	Cost Saving
3	Scenario C	Scenario A	147,032.98	1,053,829	-126.69	18,996	Cost Saving
B. Sex-neutral Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--

2	Scenario A	No Vaccination	147,159.66	1,072,825	-762.28	184,284	Cost Saving
3	Scenario B	Scenario A	147,176.56	947,167	16.89	125,658	134.45
4	Scenario D	Scenario B	147,136.15	933,146	-40.41	14,021	Cost Saving

90% VE

A. Female-only Vaccination

Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	144,846.78	938,160	-3,075.16	318,949	Cost Saving
3	Scenario C	Scenario A	144,584.79	911,378	-261.99	26,782	Cost Saving

B. Sex-neutral Vaccination

Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	144,846.78	938,160	-3,075.16	318,949	Cost Saving
3	Scenario B	Scenario A	144,355.73	785,219	-491.05	152,941	Cost Saving
4	Scenario D	Scenario B	144,311.30	770,897	-44.43	14,322	Cost Saving

¹ Base-case assumptions include Scenarios A-D: 50% coverage by 2035, 10-year duration of protection, and 70% VE; Scenarios C/D: 10% catch-up campaign coverage in 2035.

² Costs and QALYs are discounted at 3% annually.

³ Costs are in 2025 USD

Abbreviations: USD, United States Dollar, QALY, quality-adjusted life years; VE, vaccine efficacy

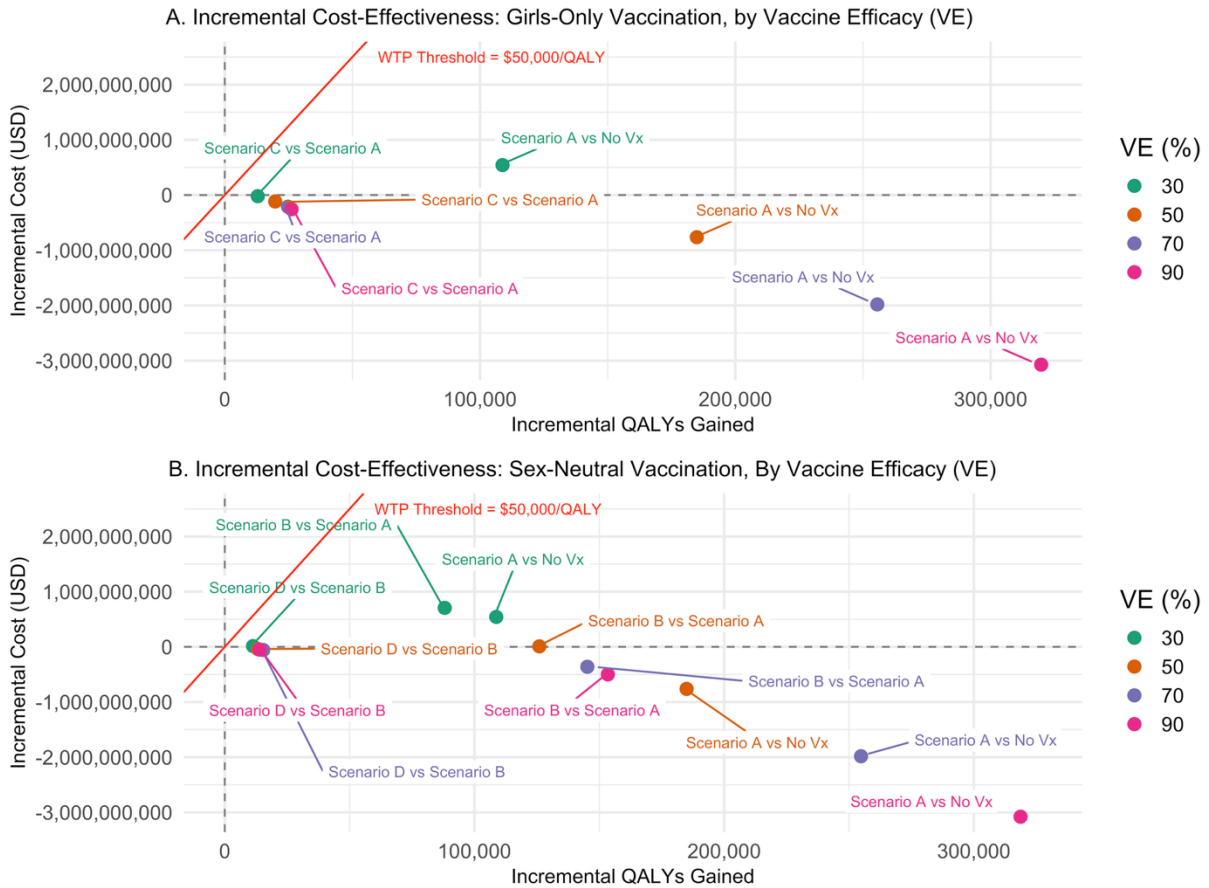


Figure C.1: Cost-effectiveness planes for female-only, sex-neutral, and catch-up CT vaccination strategies under base-case assumptions, varied by vaccine efficacy (2025 - 2050)

Supplemental Table C.4. Sequential cost-effectiveness analysis for female-only, sex-neutral, and catch-up vaccination strategies, under base-case assumptions ¹ with 5- or 20-year duration of protection (2025 - 2050)

5 Years							
A. Female-only Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	146,883.14	1,058,827	-1,038.80	198,282	Cost Saving
3	Scenario C	Scenario A	146,731.75	1,037,991	-151.39	20,836	Cost Saving
B. Sex-neutral Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	146,883.14	1,058,827	-1,038.80	198,282	Cost Saving
3	Scenario B	Scenario A	146,796.49	927,028	-86.65	131,799	Cost Saving
4	Scenario D	Scenario B	146,743.37	911,761	-53.12	15,267	Cost Saving
20 Years							
A. Female-only Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	145,298.09	962,984	-2,623.85	294,125	Cost Saving
3	Scenario C	Scenario A	145,066.22	938,269	-231.87	24,715	Cost Saving
B. Sex-neutral Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	145,298.09	962,984	-2,623.85	294,125	Cost Saving
3	Scenario B	Scenario A	144,873.26	813,863	-424.83	149,121	Cost Saving

4	Scenario D	Scenario B	144,832.87	800,151	-40.38	13,712	Cost Saving
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¹ Base-case assumptions include Scenarios A-D: 50% coverage by 2035, 10-year duration of protection, and 70% VE; Scenarios C/D: 10% catch-up campaign coverage in 2035.

² Costs and QALYs are discounted at 3% annually.

³ Costs are in 2025 USD

Abbreviations: USD, United States Dollar, QALY, quality-adjusted life years; VE, vaccine efficacy

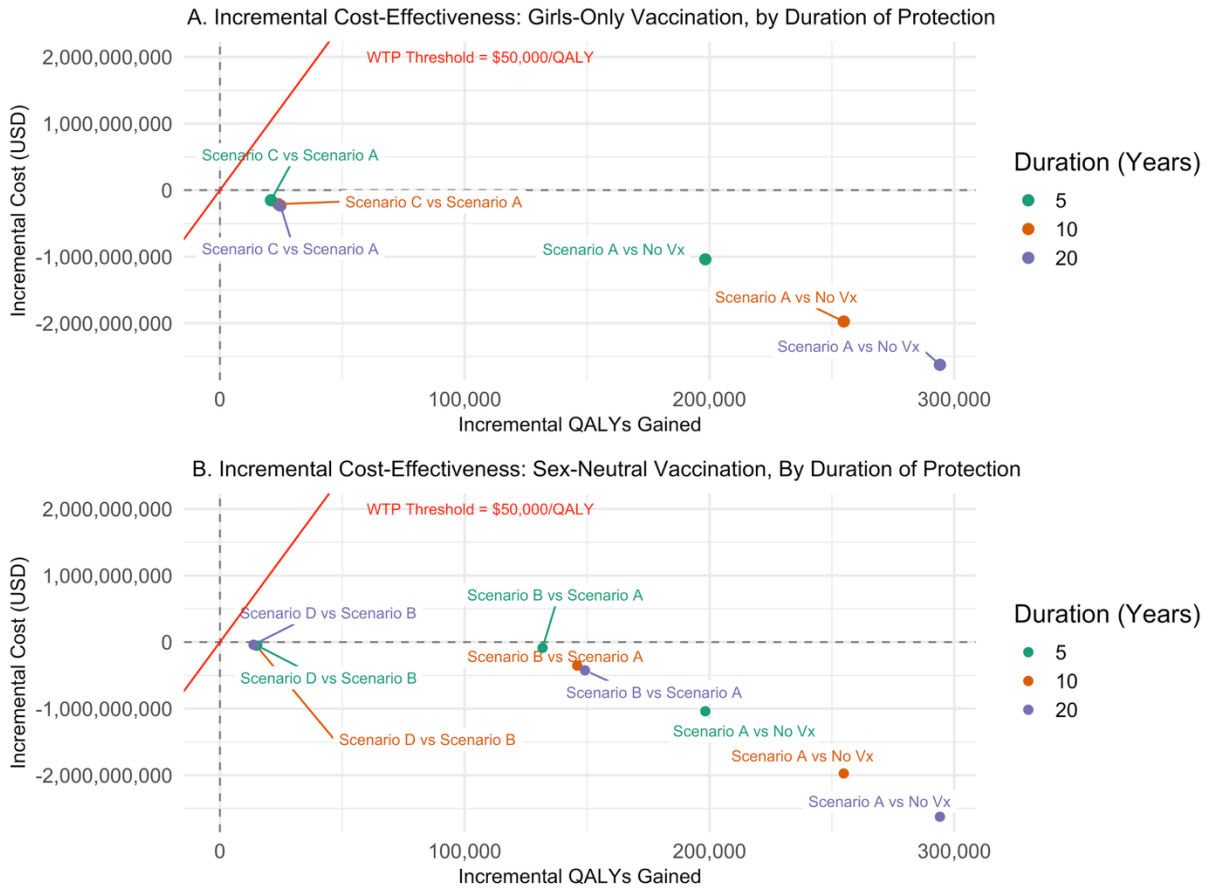


Figure C.2: Cost-effectiveness planes for female-only, sex-neutral, and catch-up CT vaccination strategies under base-case assumptions, varied by duration of protection (2025 - 2050)

Supplemental Table C.5. Sequential cost-effectiveness analysis for female-only, sex-neutral, and catch-up vaccination strategies, under base-case assumptions ¹ with 30% or 70% vaccine coverage by 2035 (2025 - 2050)

30% Coverage by 2035							
A. Female-only Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	146,545.46	1,092,704	-1,376.48	164,405	Cost Saving
B. Sex-neutral Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	146,545.46	1,092,704	-1,376.48	164,405	Cost Saving
3	Scenario B	Scenario A	145,864.42	978,480	-681.04	114,224	Cost Saving
70% Coverage by 2035							
A. Female-only Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	145,584.33	925,448	-2,337.61	331,661	Cost Saving
B. Sex-neutral Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	No Vaccination	--	147,921.94	1,257,109	--	--	--
2	Scenario A	No Vaccination	145,584.33	925,448	-2,337.61	331,661	Cost Saving
3	Scenario B	Scenario A	145,944.09	769,895	359.75	155,553	Cost Saving

¹ Base-case assumptions include Scenarios A-D: 50% coverage by 2035, 10-year duration of protection, and 70% VE; Scenarios C/D: 10% catch-up campaign coverage in 2035.

² Costs and QALYs are discounted at 3% annually.

³ Costs are in 2025 USD

Abbreviations: USD, United States Dollar, QALY, quality-adjusted life years; VE, vaccine efficacy

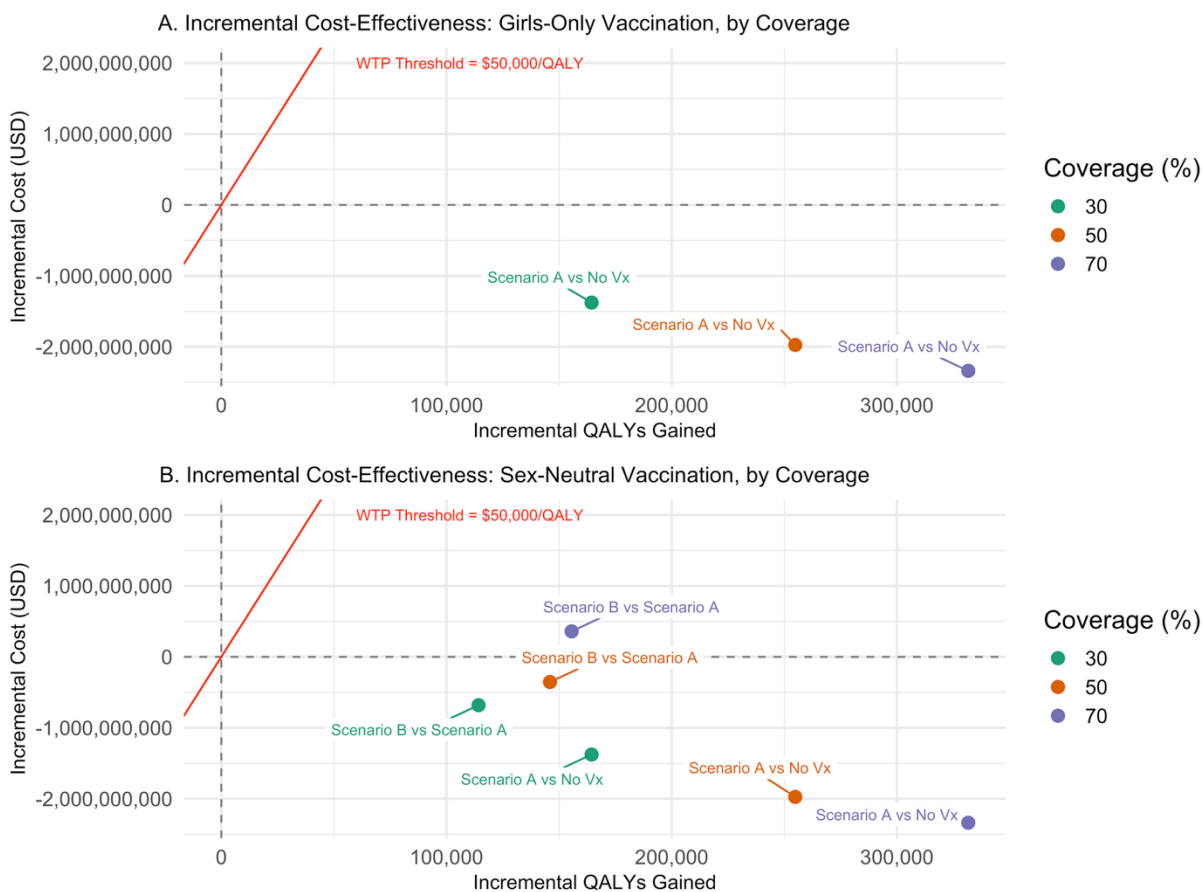


Figure C.3: Cost-effectiveness planes for female-only, sex-neutral, and catch-up CT vaccination strategies under base-case assumptions, varied by vaccine coverage reached by 2035 (2025 - 2050)

Supplemental Table C.6. Sequential cost-effectiveness analysis for catch-up vaccination, under base-case assumptions ¹ with 5% or 15% catch-up campaign coverage by 2035 (2025 - 2050)

5% Catch-up Campaign Coverage							
A. Female-only Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	Scenario A	--	145,948.52	1,002,268	--	--	--
2	Scenario C	Scenario A	145,838.65	989,942	-109.87	12,326	Cost Saving
B. Sex-neutral Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	Scenario B	--	145,594.28	856,325	--	--	--
2	Scenario D	Scenario B	145,564.83	848,614	-29.45	7,711	Cost Saving
15% Catch-up Campaign Coverage							
A. Female-only Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	Scenario A	--	145,948.52	1,002,268	--	--	--
2	Scenario C	Scenario A	145,646.22	967,693	-302.30	34,575	Cost Saving
B. Sex-neutral Vaccination							
Step	Intervention	Comparator	Total Cost (Million USD) ^{2,3}	Total QALY Decrements ²	Δ Cost (Million USD)	Δ QALYs Gained	ICER (\$/QALY)
1	Scenario B	--	145,594.28	856,325	--	--	--
2	Scenario D	Scenario B	145,518.48	834,752	-75.81	21,573	Cost Saving

¹ Base-case assumptions include Scenarios A-D: 50% coverage by 2035, 10-year duration of protection, and 70% VE; Scenarios C/D: 10% catch-up campaign coverage in 2035.

² Costs and QALYs are discounted at 3% annually.

³ Costs are in 2025 USD

Abbreviations: USD, United States Dollar, QALY, quality-adjusted life years; VE, vaccine efficacy

C.5 Additional Results - Sensitivity Analysis

Tornado plots of one-way sensitivity analyses under base case-assumptions are presented below.

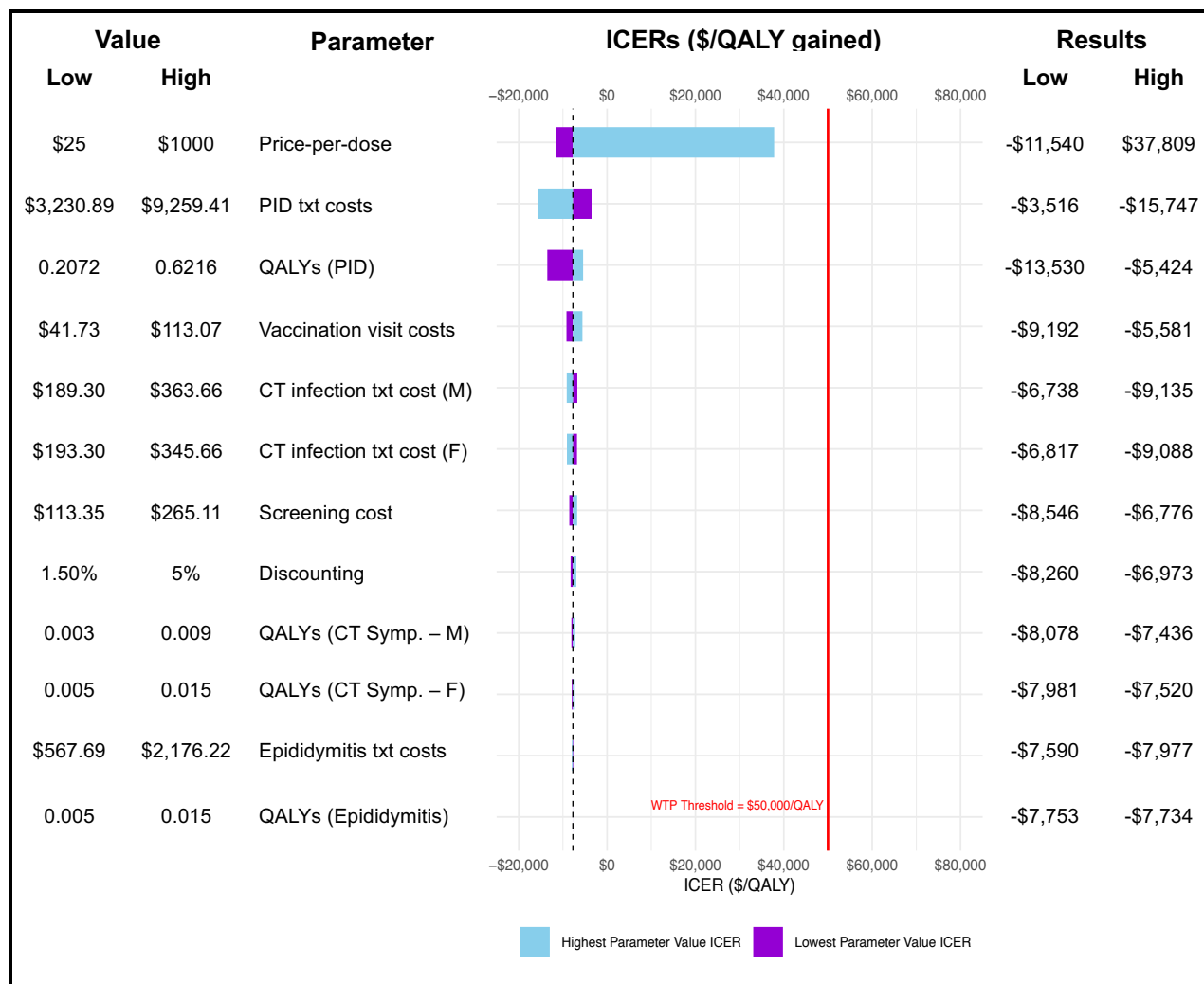


Figure C.4: Tornado plot of one-way sensitivity analyses examining the impact of parameter uncertainty on incremental cost-effectiveness ratios comparing Scenario A vs. No Vaccination, assuming base-case assumptions. Scenario A: Vaccinating 15-year-old girls entering the model between 2025-2075.

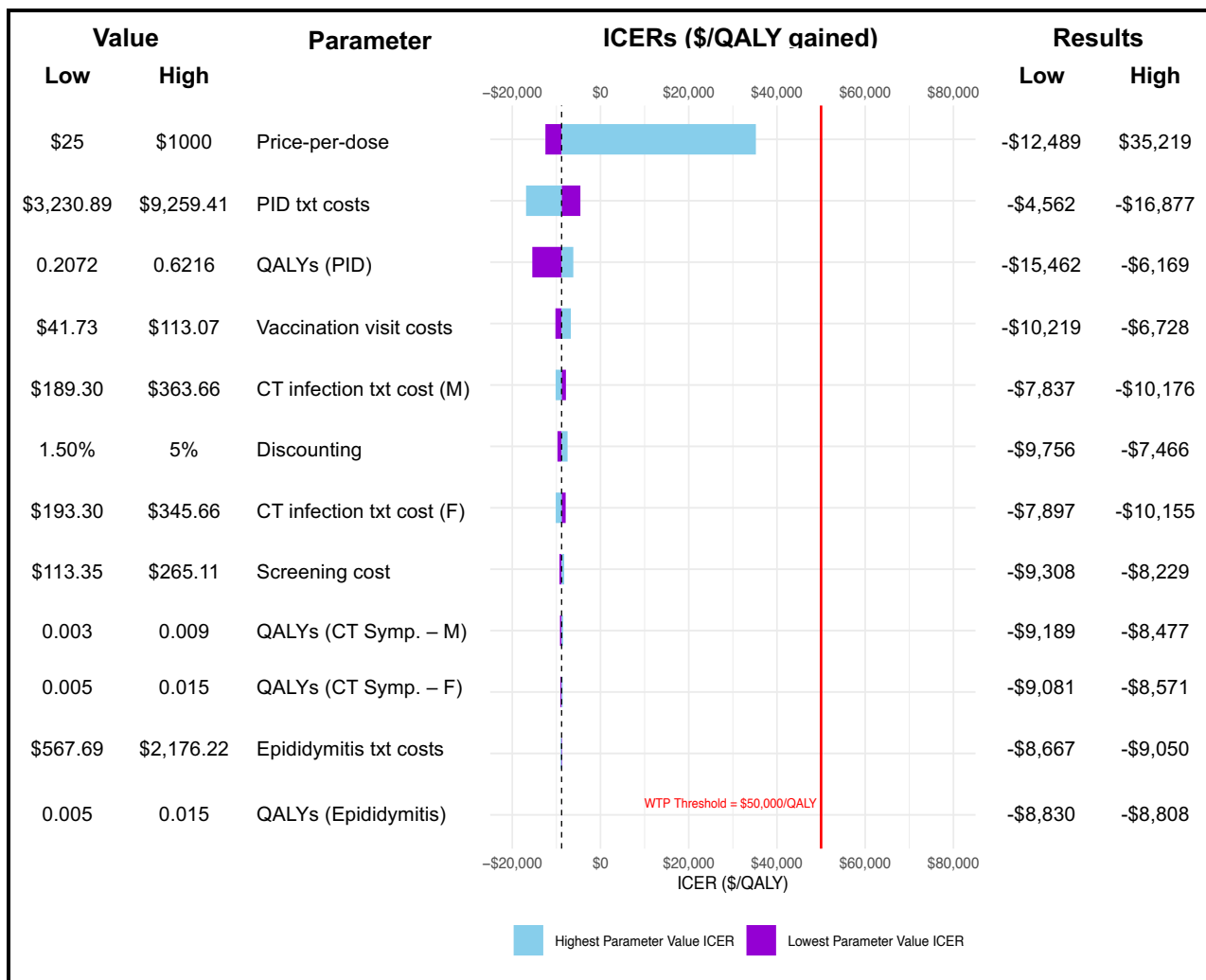


Figure C.5: Tornado plot of one-way sensitivity analyses examining the impact of parameter uncertainty on incremental cost-effectiveness ratios comparing Scenario C vs. Scenario A, assuming base-case assumptions. Scenario C: Scenario A at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035.

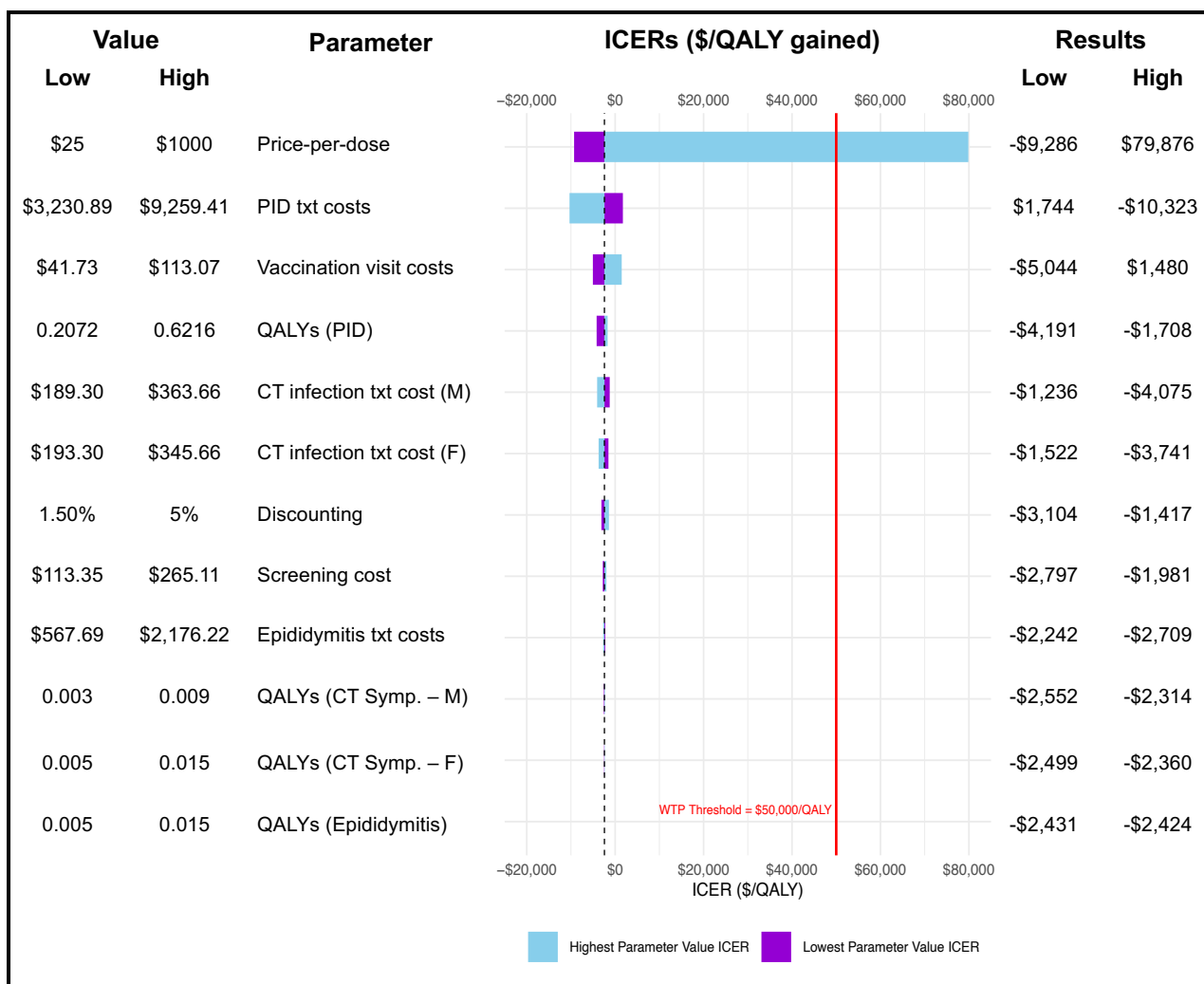


Figure C.6: Tornado plot of one-way sensitivity analyses examining the impact of parameter uncertainty on incremental cost-effectiveness ratios comparing Scenario B vs. Scenario A, assuming base-case assumptions, Scenario B: Vaccinating 15-year-old girls and boys entering the model between 2025-2075.

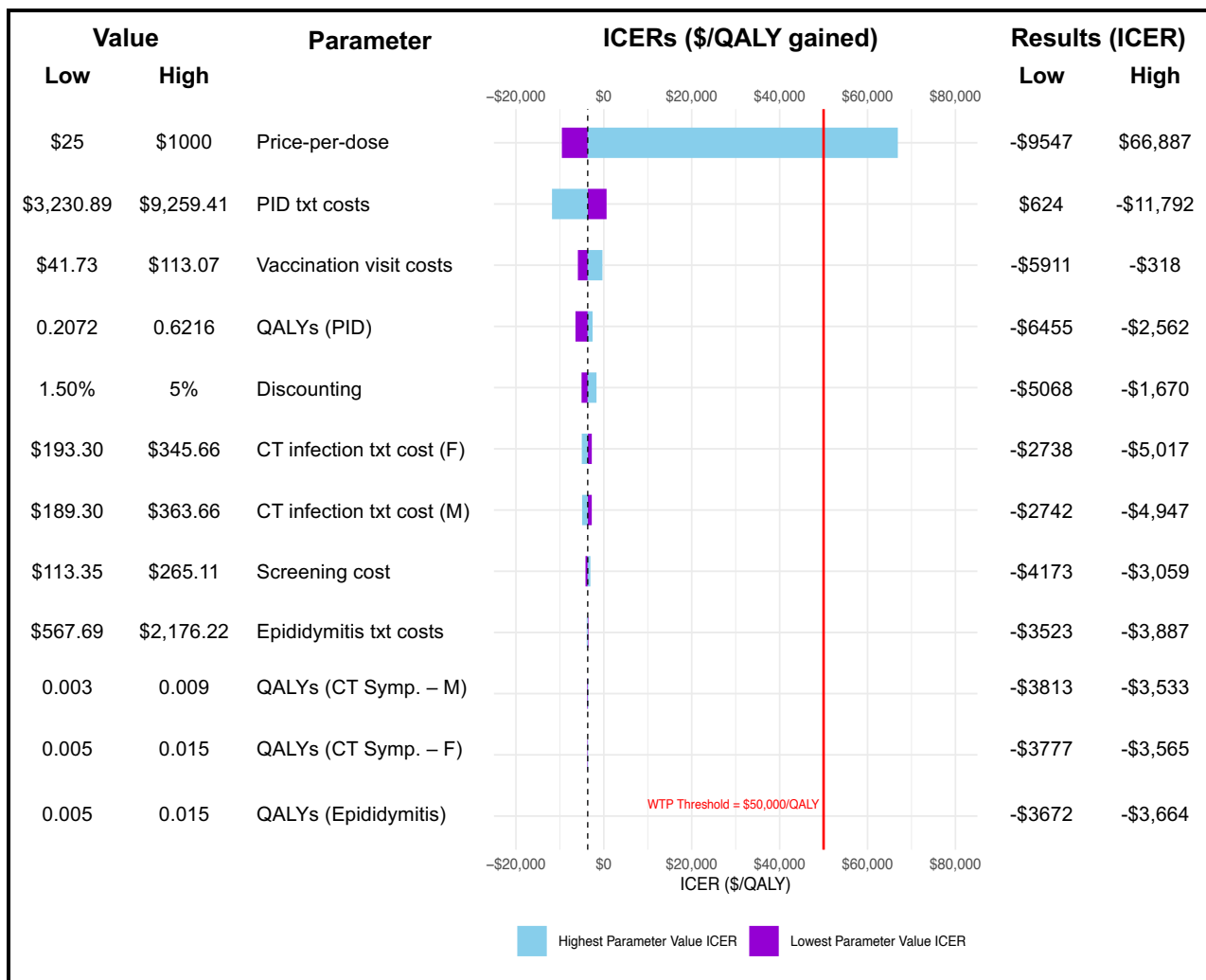


Figure C.7: Tornado plot of one-way sensitivity analyses examining the impact of parameter uncertainty on incremental cost-effectiveness ratios comparing Scenario D vs. Scenario B, assuming base-case assumptions. Scenario D: Scenario B at 50% coverage + catch-up campaign among unvaccinated 15-24-year-old women in 2035.