# Applications of Mathematical Modeling to Evaluate Cervical Cancer Prevention in an HIV-Endemic Setting

Dissertation Advisor: Jane Kim Jamie Alexandra Cohen

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Dissertation Abstract

Mathematical models that simulate the burden of disease and project health and economic outcomes under various scenarios can help policymakers decide how to optimally allocate resources. This dissertation uses simulation modeling to evaluate cervical cancer prevention policy and describe its effects in South Africa, an HIV-endemic setting where the risk of cervical cancer is heterogeneous.

In the first chapter, I evaluated the cost-effectiveness of cervical cancer screening in unvaccinated women. I built a microsimulation model of HIV infection, HPV infection and cervical disease, which captured the impact of HIV infection on HPV and cervical natural history. Disease dynamics were represented by transitions between mutually exclusive health states, including oncogenic and non-oncogenic HPV infection, grade of pre-cancer, and stage of cancer. I calibrated the model to South African epidemiologic data and compared current screening guidelines to 55 alternative strategies that varied the age to start screening and screen frequency for women based on their HIV status and history of HIV testing. Costs included cancer and HIV screening, diagnosis and treatment. Health outcomes included cancer cases and disability-adjusted life years (DALYs) averted. I conducted a cost-effectiveness analysis to determine the optimal screening strategy at different willingness to pay (WTP) values.

I found it was always optimal to screen HIV-uninfected and women of unknown HIV status starting at a younger age and more frequently than current guidelines

recommend. For women with a diagnosed HIV infection, optimal screen frequency depended upon WTP; at a WTP of $1,300, it was optimal to reduce screen frequency compared to current guidelines and at a WTP of $5,200 it was optimal to increase screen frequency relative to current guidelines. These findings were robust to variations in cost and improvements in screen coverage and efficacy.

In the second chapter, I quantified the impact of HPV vaccination on the cost-effectiveness of cervical cancer screening and determined whether the impact was moderated by differential vaccine protection in women living with HIV. Human papillomavirus (HPV) vaccination may offer an opportunity to reduce the frequency of cervical cancer screening.

I refined a microsimulation model of HIV infection, HPV infection and cervical carcinogenesis. I assumed all women in the model received a completed course of the HPV vaccine at age 9. I modeled infection with HPV genotypes 16, 18, 31, 33, 45, 52, 58, other oncogenic genotypes, and all non-oncogenic genotypes. I calibrated the model to South African epidemiologic data and compared current screening guidelines (which are agnostic to vaccination status) to 15 alternative strategies that varied screen start age and screen frequency for “low-risk” women and screen frequency for “high-risk” women, and considered various rates of vaccine waning in immunocompromised women. Costs included cancer screening, diagnosis and treatment. Health outcomes included cancer cases and disability-adjusted life years (DALYs) averted. I conducted a cost-effectiveness analysis to determine the optimal screening strategy at different willingness to pay (WTP) values and rates of vaccine waning.

I found that at a willingness to pay of $5,200 per DALY averted, the upper end of an empirical WTP range for South Africa, it would always be cost-effective to increase screening relative to current guidelines for bivalent vaccinated women. The optimal strategy at this WTP was consistent with the optimal strategy in Chapter 1 in unvaccinated women, suggesting that screening guidelines need not be differentiated by vaccination status. At the lower end of the WTP range ($1,300 per DALY averted), it would be cost-effective to increase the screen start age to 40 years old for low-risk women. These results were robust to changes in rate of vaccinate decline in immunocompromised women, vaccine efficacy in women living with HIV, and screen coverage and compliance. When we considered the nonavalent vaccine and when CIN and HPV treatment was perfectly effective, the optimal screening strategy was less frequent across the WTP range.

This analysis suggested that it could be cost-effective to relax screening frequency in vaccinated women, depending upon WTP and vaccine type used. They also provided confidence that any differences in vaccine efficacy in women living with HIV will not drive major differences in screening.

In the third chapter, I explored the impact of model structural uncertainty on our epidemiologic inference and policy results. Decisions about model structure will undoubtedly have consequences for epidemiologic outcomes, estimates of cost-effectiveness, and policy conclusions. Yet structural uncertainty is frequently ignored, even though it may have a much greater impact on model results and conclusions than parameter uncertainty. While it is common to acknowledge potential limitations of model structure and identify assumptions that have been made, there is no clear guidance on

methods to explicitly evaluate structural uncertainties. And while modelers are guided by the principle of making a model only as complex as necessary, there is little consensus on what qualifies as necessary.

In this chapter, I compared several alternative model structures that capture the process of natural immunity and meaning of HPV re-detection and quantified the impact associated with these structural decisions both in terms of our prediction accuracy and policy implications. I found that all five model structures fit the calibration targets well, with only small variations in performance. The fitted models resulted in significant variation in key model parameters, such as the level and duration of natural immunity, and rates of progression between HPV infection, lesion and invasive cervical cancer. Allowing for infections to become latent and re-activate impacted the age distribution of causal HPV infections and the subsequent health impact and cost-effectiveness of vaccination strategies that vary the end age of vaccination. Model structures that do not allow for latency predicted a four-year older average age of causal HPV infection compared to models that accounted for latency. Structural decisions regarding who acquires natural immunity did not produce much difference in other model natural history outcomes nor cost-effectiveness of vaccination policy.

These results imply that the specific structural uncertainties I explored are meaningful for the way we have, and potentially should, model HPV. Specifically, models that ignore the possibility of HPV latency and re-activation may over-estimate the benefit of vaccinating up to older ages. They also demonstrate that decisions regarding who acquires natural immunity and at what level are less influential, so long as natural

immunity exists in the model. While this analysis was specific to HPV modeling decisions, it serves as an example of how structural decisions matter for modeling in general.

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## ii. Acknowledgments

Firstly, I would like to thank my incredible dissertation committee – Jane Kim, Nick Menzies, Rochelle Walensky and David Cutler – for providing constant support and critical feedback throughout my doctoral studies. Your insights have been invaluable. Jane – my committee chair, longtime mentor and friend – you have been a role model for integrity, character and grit and have influenced my career more than you will ever know.

I would like to thank the funding body which allowed me to devote my time to this work: The National Institutes of Health T32 training program, under the leadership of Ken Freedberg and Ingrid Bassett. I would like to thank the Health Policy program office – Debbie Whitney and Colleen Yout – as well as the CHDS community – Christine Bell – for always being helpful and supportive.

They say it takes a village and boy do I have an amazing one. I would like to thank my PhD cohort and DS family who provided excellent companionship and friendship every day of the last five years. To my amazing friends, thank you for always supporting and encouraging me; letting me vent on long morning runs; listening to all of my updates, big or small. I would like to thank my parents, Lauren and Gary Cohen, for their lifetime of support for me and my dreams. I would not be here without you.

To my husband Ken, thank you for always listening and being interested in my work, lifting my spirits on the hardest days, and celebrating all of the many small steps on this journey. You make me smile and laugh every single day. Your belief in me and my success propelled me to this moment.

I would like to thank the amazing women in science who I have grown with and around – Jane, Rochelle, Nicole, Emily, Allison, Stef, on and on the list goes – for showing me what is possible, leading by example, and encouraging me to dream big and set high expectations for myself.

Finally, I would like to dedicate this dissertation to the little girl who will be joining our family this August. I hope you see no limits to your dreams. Your dad and I love you so much already.

# Chapter 1.

# Cervical Cancer Screening In An HIV Endemic Population: A Model-Based Cost-Effectiveness Analysis

ABSTRACT

**Background**
South Africa provides less comprehensive cervical cancer screening than international guidelines recommend, despite having one of the highest rates of cervical cancer in the world. Using simulation modeling, we evaluated alternative screening strategies that vary the age to start screening and screen frequency based on a woman's HIV status and history of HIV testing to determine whether there is an opportunity to improve targeted cervical cancer screening.

**Methods**
We developed a microsimulation model of HIV infection, HPV infection, and cervical carcinogenesis. Disease dynamics were represented by transitions between health states (i.e., oncogenic and non-oncogenic HPV infection, grade of pre-cancer, stage of cancer, HIV infection, CD4 count). We grouped HPV genotypes into two categories: 1) oncogenic and 2) non-oncogenic. We calibrated the model to South African epidemiologic data and compared 55 strategies that varied screen start age and screen frequency for women considered "low-risk" (women without HIV and women who do not know their HIV status) and "high-risk" (women with diagnosed HIV). We included costs of screening, diagnosis and treatment, for both cervical disease and HIV. Health outcomes included cancer cases and disability-adjusted life years (DALYs) averted. We conducted a cost-effectiveness analysis to determine the optimal screening strategy for willingness to pay (WTP) values between $1,300 and $5,200 per DALY averted.

**Findings**
We found that within the reported WTP range, "low-risk" women are under-screened according to current guidelines. At a WTP less than $3,300, "high-risk" women are over-screened and above $4,290 they are under-screened. The number of cervical cancer cases would be reduced by between 75 and 83 percent compared to no screening, within the reported WTP range. Modeling results were robust to assumptions regarding screen coverage and adherence, discount rate, and costs of screening, diagnostics and treatment, and sensitive to CIN treatment efficacy and classification of women into risk groups. We found that it would no longer be cost-effective to increase screening for "high-risk" women, if all women who do not know their HIV status were classified as "high-risk" (per the WHO guidelines), or if CIN treatment was 100 percent effective.

**Conclusion**
Revising South Africa's cervical cancer screening guidelines could improve efficiency and overall health benefits. The optimal screen start age and frequency depended on a woman's risk group and specific WTP.

## 1.1. Background

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection globally. While HPV infections usually clear spontaneously within one to two years, persistent infection with an oncogenic HPV infection can cause precancerous lesions called cervical intraepithelial neoplasia (CIN) that, if untreated, may eventually progress to invasive cervical cancer.

Women living with human immunodeficiency virus (HIV) have higher HPV incidence, reduced HPV clearance, and a two- to ten-fold higher incidence of cervical cancer compared to women without HIV.[1–7] Women with HIV also face an almost 2-fold higher risk of cervical cancer mortality compared to HIV-uninfected women with cervical cancer.[2,8] Antiretroviral therapy (ART) reduces the impact of HIV on CIN2 and CIN3 regression and HPV progression.[9,10]

Despite having one of the highest rates of cervical cancer and the largest burden of HIV in the world, South Africa recommends less frequent screening than international guidelines for low- and middle-income countries[11] (see Table 1.1 for a comparison of guidelines). In South Africa, "low-risk" women are defined as women without HIV as well as women who do not know their HIV status and are recommended to receive three lifetime screens between ages 30 and 50; "high-risk" women are defined as women known diagnosis of HIV and are offered screening every three years, starting at age of HIV diagnosis over their lifetime.

**TABLE 1.1. National and International Guidelines for Cervical Cancer Screening**

| | "Low-Risk" Women | | "High-Risk" Women | |
|---|---|---|---|---|
| | Definition | Recommendation | Definition | Recommendation |
| South Africa 2017 National Policy | Women without HIV; Women with | Every 10 years from age 30-50. | Women with diagnosed HIV. | Every 3 years from age of HIV diagnosis, in perpetuity. |

| | | | | |
|---|---|---|---|---|
| | unknown HIV status. | | | |
| World Health Organization (WHO) 2013 Guidelines | Women with a negative HIV test in the last year. | A minimum interval of 5 years with HPV testing and 3-5 years with cytology among women ages 30-49. | Women with diagnosed HIV; Women with known HIV status. | Starting at age of HIV diagnosis or age of sexual debut; rescreen within 3 years, in perpetuity. |

To inform policy recommendations in South Africa, we classified women into risk groups based on the South African guidelines (Table 1.1) and evaluated the clinical impact and cost-effectiveness of current and alternative screening strategies, varying screen start ages and frequencies based on HIV status and history of HIV testing.

## 1.2. Methods

### 1.2.1. Overview

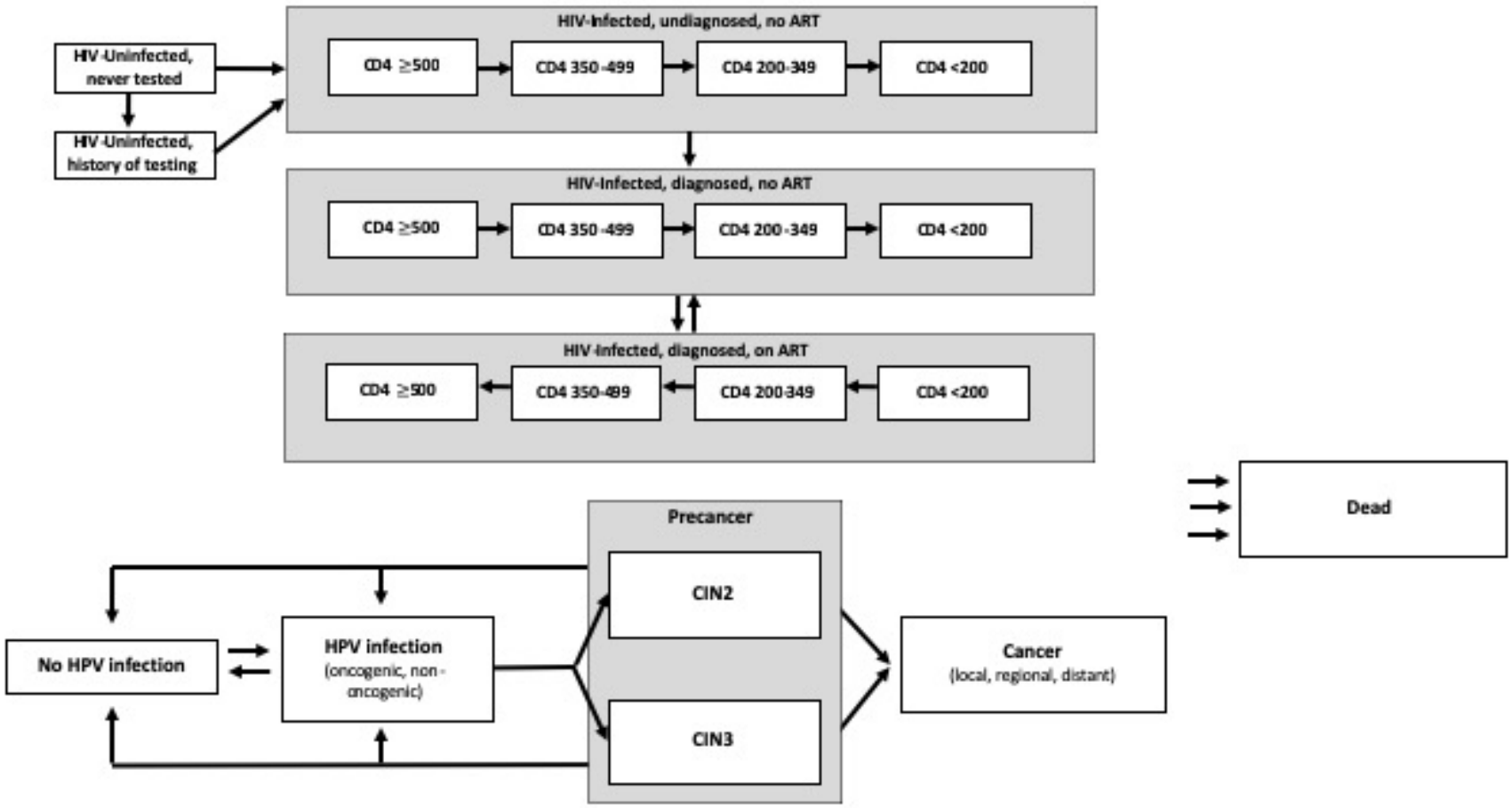
We developed a microsimulation model of HIV infection, HPV infection and cervical cancer, reflecting key features of HPV and cervical cancer natural history, HIV natural history, interactions between HIV and HPV, and patterns in testing, care and treatment for both HIV and cervical disease. We fit the model to epidemiologic data[13] from South Africa and quantified the health and economic consequences of alternative cervical cancer screening strategies. Compared to no screening, we estimated changes in cervical cancer incidence and mortality; health care costs; and the incremental cost-effectiveness of 55 screening strategies that varied screen start age and frequency to identify the optimal screening algorithms for women based on their HIV status and history of HIV testing.

### 1.2.2. Modeling Approach

We developed an individual-based microsimulation model of cervical carcinogenesis and HIV, which was represented by a sequence of annual transitions

between health states, including HPV infection (i.e., oncogenic; non-oncogenic), grade of pre-cancer (i.e., cervical intraepithelial neoplasia, CIN2 and CIN3), stage of invasive cancer (i.e., local, regional, and distant), and HIV infection (see Figure 1.1). Transitions were governed by the calendar year of the simulation, age and health history, including duration of HPV infection, prior oncogenic or non-oncogenic HPV infection, HIV status, CD4 cell count, and years on ART.

**FIGURE 1.1 Model Schematic**



### 1.2.3. HPV Natural History

#### ***1.2.3.1.*** *HPV Incidence*

Women faced an annual, age-specific probability of infection with oncogenic and non-oncogenic HPV. In the absence of robust HPV incidence data in South Africa we calibrated HPV incidence based upon published cross-sectional data of cohorts at three clinical sites in Khayelitsha township in Cape Town, South Africa. Three studies recruited women without cervical cancer from this community, for a total of 1,371 HIV+ women and 8,050 HIV-uninfected women aged 17 to 65 years[12]. We pooled all HPV types to generate age-specific HPV prevalence rates, which we used baseline values for HPV incidence.

#### *1.2.3.2. HPV Clearance and Progression*

Women could subsequently clear the infection, it could persist, or it could progress to CIN2 or CIN3. These probabilities were based on duration of infection and HPV group (oncogenic vs non-oncogenic). In the absence of data from South Africa on HPV clearance and progression, we calibrated these values and generated prior distributions based on a published model of HPV and cervical cancer that used an analysis of primary data from the control arm of the Costa Rica Vaccine Trial (2004–2010), which included 3,736 women aged 18–25 years at enrollment[13,14]. We assumed HPV clearance probabilities were constant for oncogenic and non-oncogenic HPV, and assumed oncogenic HPV infections progressed faster to CIN2 and CIN3 than non-oncogenic infections.

We assumed women who cleared their infection developed lifelong naturally-acquired immunity that reduced the probability of re-infection with the same group of HPV.

*CIN Regression and Progression*

High-grade lesions (i.e. CIN2 or CIN3) could naturally regress, persist, or progress to invasive cervical cancer, depending upon duration and grade of lesion and HPV group. In the absence of data from South Africa on CIN regression and progression, we calibrated these values. We centered the prior mean of these regression probabilities on estimates from the placebo arm of a randomized controlled trial of oral β-carotene supplementation for women with CIN2 or CIN3[15]. We calibrated and applied a risk ratio associated with a reduced risk of regression for women with oncogenic genotypes compared to non-oncogenic genotypes. We also centered the prior mean for pre-cancerous progression to invasive cervical cancer based on data derived from a natural history study of women with carcinoma in situ from whom treatment was withheld in New Zealand from 1965 to 1974[13,16].

We also assumed that among those women whose pre-cancerous lesions spontaneously regressed, some also cleared their associated HPV infection. We calibrated the share of regressed lesions that also cleared HPV infection using an uninformed prior.

*1.2.3.3. Cancer Progression, Detection and Mortality*

We modeled progression between cancer stages sequentially. Cancer detection occurred through presentation at a health clinic following the development of symptoms, or by screening. Undetected cervical cancer could progress to later stages and could be detected through symptoms or by screening and cancer progression ended upon cancer detection. Women faced cervical cancer survival based on the stage of disease at diagnosis and HIV status.[8]

Women with HIV faced an elevated risk of HPV infection, decreased probability of HPV clearance and increased risk of progression to CIN and cervical cancer. To model the heterogeneity in risk associated with HIV infection, we derived risk rates to be applied to our HPV transition probabilities for women living with HIV based on a systematic review and meta-analysis[17]. Where possible, HIV-associated risk rates were stratified by CD4 count and ART status[17]. We assumed HPV does not modify the risk of HIV infection or HIV natural history, but allow cervical cancer screening to provide an additional opportunity for HIV testing.

*1.2.4. HIV Natural History*

Women faced annual age- and year-specific risks of HIV infection, based on historical and projected HIV incidence estimates[18]. We categorized CD4 cell count to model HIV progression as follows: <200/mm$^3$, 200/mm$^3$-350/mm$^3$, 350/mm$^3$-500/mm$^3$ and >500 /mm$^3$. Upon HIV acquisition, women were assigned a CD4 count of >500/mm$^3$. A woman's CD4 count declined over time in the absence of ART and rebounded in the presence of ART, based on time on ART and CD4 cell count at ART initiation. We did not model ART failure.

Women had an probability of testing for HIV, which depended on age, HIV status, and history of prior testing[19] (see table S2 below). Women faced the same probability of testing for HIV at each cervical screen. a chance to start ART based on eligibility guidelines and individual behavior[20]. ART became publicly available in April 2004, following inception of the national public-sector ART program. Initially, treatment eligibility was limited to individuals with CD4 <200/mm$^3$. In 2011, ART was expanded to individuals

with CD4 <350/mm$^3$, and was expanded even further in 2015 to include individuals with CD4 <500/mm$^3$. In 2016, all individuals living with HIV were eligible for treatment, regardless of CD4 count. We modeled these changes in ART eligibility and initiation over time. We also allowed women to disengage from care (see table S3 below) and independently re-engage[19]. We assumed a woman's probability of being lost to ART care was uncorrelated with her probability of being screened or treated for cervical cancer. Women with HIV faced elevated risks of HPV infection, progression to CIN and invasive cervical cancer and cervical cancer-related mortality.

Each year, death could occur from cervical cancer, HIV-related causes, or non-HIV background mortality. For women not on ART, HIV-related mortality was based on the current CD4 count; in contrast, for women on ART, HIV-related mortality was based on the CD4 count at which treatment was initiated and the length of time on ART. We adjusted background mortality to account for the fraction of deaths due to HIV-related causes based on the Global Burden of Disease estimates[21]. In order to keep the population size fixed over time, for every death in the model, a woman was born into our population.

1.2.5. Model Calibration

We calibrated the model to identify parameter sets that achieved good fit to South African epidemiologic data, including HPV and CIN prevalence by age and HIV status and cervical cancer incidence by age. We calibrated 35 uncertain model parameters, selected based on in-country data availability.

We used simulated annealing to search the parameter space. For all uncertain parameters, we developed prior probability distributions expressing the uncertainty in model parameters and defined lower and upper bounds for each parameter to restrict the parameters to plausible regions (see tables below)[13]. We sampled each parameter from its prior distribution and ran the natural history model with 1,000,000 women, for 120 years. A vector of output statistics was compared to corresponding calibration data and a goodness of fit (GOF) score was calculated as the sum of the squared distance between the observed and target data weighted inversely proportional to the width of the target confidence interval (see equation 1).

Equation 1: $$GOF_j = \sum_{i=1}^{n\_targs} \left( \frac{output_{i,j} - target_i}{SD_i * 2} \right)^2,$$

where j is parameter set and i is calibration target ∈ [1,61]

In each subsequent iteration, we randomly sampled a new "neighboring" parameter set from a truncated normal distribution centered on the previously saved parameter set. We then re-ran the model, calculated the GOF of the parameter set and corresponding acceptance probability, and decided whether or not to keep the new parameter set by comparing the probability of acceptance to a randomly generated number (see equation 2). The probability of acceptance decreased over time as the temperature cooled (see equation 3).

Equation 2: $$P(accept) = \begin{cases} 1, & if\ GOF_{new} \leq GOF_{old} \\ \exp\left( \frac{GOF_{old} - GOF_{new}}{T} \right), & if\ GOF_{new} > GOF_{old} \end{cases}$$

Equation 3: $T = 1.001^i$, where i is current iteration number ∈ $[1, 1{,}000]$

We repeated this procedure 1,000 times and ran 1,000 independent searches to improve chances of finding an optimal parameter set.[22] We present the 50 best-fitting parameter sets from the compendium of calibration runs compared to target data (see Appendix).

1.2.6. Validation Procedure

As a predictive check of our calibrated model, we conducted a model validation to check how well the model fit selected epidemiologic data that were not used in the calibration process. We compared model outputs to age-standardized cancer incidence at five historical time points (2005, 2006, 2007, 2008 and 2009) and used visual inspection to determine how well we fit the data. Our validation results (see Supplemental Appendix) indicate a good model fit.

We also tested how well our calibrated model fit the current and expectations for the future HIV epidemic in South Africa. In our model simulations, HIV prevalence among 15 to 49 year old women ranged from 25 percent in year 2019 to 18 percent in year 2108 (due to declining HIV incidence over this 90-year period). According to our model simulations, an average of 92 percent of women with HIV were tested and diagnosed approximately two years after HIV infection. Additionally, ART coverage increased from 52 percent in year 2019 to 90 percent in year 2108 in our model simulations and ART initiation occurred on average four years after diagnosis. These projections remained stable over time.

We initiated the model with a population of 4 million women, chosen to minimize both Monte Carlo stochastic error and computational burden (see Supplemental Appendix). We used cervical cancer incidence to assess stochastic error because it is the most rare outcome. We distributed the population across one-year age buckets according to the South African population pyramid and ran the simulation in the absence of screening for 90 years to populate all health states and reach a steady state equilibrium (we call this the "burn-in period"). At the end of the burn-in period, we ran the simulation for 90 years for each screening strategy.

### 1.2.7. Screening Tests and Strategies

We modeled the use of conventional cytology, liquid-based cytology and HPV DNA testing, per the South African cervical cancer screening policy. These screening tests differ in their test performance, costs, and logistical requirements for successful implementation (Table 1.2).

We anchored the distribution of screen tests to the South African guidelines, which aim to gradually phase in and replace cytology with HPV-based screening. To reflect this, women in the model were assigned a screen test modality at the start of the simulation, and each year, a small share of women gained access to HPV DNA testing based on a gradual rollout (Table 1.2).

**TABLE 1.2. Baseline and Sensitivity Analysis Values for Selected Model Variables**

| | Baseline | Sensitivity Analysis |
|---|---|---|
| Screening, triage, and diagnostic test performance (sensitivity/specificity to detect CIN2+)[a] | | |
| Cytology (HIV-uninfected) | 0.78/0.86[23,24] | 0.65/0.95 |
| Cytology (HIV-infected) | 0.97/0.61[23,24] | 0.65/0.95 |
| Colposcopy | 0.95/1.0[23,24] | -- |
| Liquid-based cytology adequacy | 0.979[23,24] | -- |
| Conventional cytology adequacy | 0.909[23,24] | -- |

| | | |
|---|---|---|
| Distribution of screen tests by 2020/2030/2050 (%) | | |
| Liquid-based cytology | 30/10/5 | -- |
| Conventional cytology | 50/30/15 | -- |
| HPV | 20/60/80 | -- |
| Coverage and adherence[b] | | |
| Access to routine screening (% of population) | 100% | 50% |
| Screen adherence (probability of returning for next recommended clinical visit) | 100% | 80% |
| Access to colposcopy (% of HPV-based facilities) | 50% | -- |
| Access to cryotherapy[c] | 10% | -- |
| HIV testing[d] | Based on age, prior history of testing, current CD4[19] | -- |
| ART initiation[d] | Based on current year, current CD4 count, and time[19] since HIV diagnosis | -- |
| ART lost to follow up rate[d] (r) | $r = \theta e^{-at}$ $\theta = 0.13$ , $a = 0.75$ and t = years on ART[19] | -- |
| Treatment eligibility and efficacy | | |
| Eligibility for cryotherapy (CIN2, CIN3, Cancer) | 85%, 75%, 10%[25] | -- |
| Effectiveness of cryotherapy to treat CIN2/3 | 83%[26] | 100% |
| Effectiveness of cryotherapy to clear HPV[e] | 84%[27,28] | 100% |
| Effectiveness of LLETZ to treat CIN2/3 | 79%[26] | 100% |
| Effectiveness of LLETZ to clear HPV[e] | 79%[27,28] | 100% |
| Direct Medical Costs (2019 US$) | | |
| Conventional cytology | $8[25] | -- |
| Liquid-based cytology | $17[25] | -- |
| HPV DNA test | $59[25] | $0 - $60 |
| Colposcopy | $73[25] | $0 - $75 |
| Cryotherapy | $4[25] | -- |
| LLETZ | $59[25] | $0 - $60 |
| Local cancer treatment | $3,200[25] | -- |
| Regional cancer treatment | $9,700[25] | -- |
| Distant cancer treatment | $9,800[25] | -- |
| HIV test (positive result) | $5[29] | -- |
| HIV test (negative result) | $3[29] | -- |
| HIV treatment and care (per year) | $260[29] | $0 - $260 |
| Direct Non-Medical Costs (2019 US$) | | |
| Patient time (hourly) | $1.42[30] | -- |
| Disability values | | |
| HIV, no ART | 0.582[31] | -- |
| HIV, ART, no cancer | 0.081[31] | -- |
| HIV, localized cancer | 0.215[31] | -- |
| Local cancer | 0.049[31] | -- |
| Regional cancer | 0.288[31] | -- |
| Distant cancer | 0.540[31] | -- |

Notes: a) The Hybrid Capture HPV test detects oncogenic HPV infection. b) Low- and high-risk women face the same probability of screen coverage. c) Women who do not have access to or are not eligible for cryotherapy receive LLETZ. d) Probability of ART initiation is agnostic to prior/disrupted ART care. See appendix for more details. e) Probability that a woman clears her HPV infection after cryotherapy or LLETZ, which is conditioned on clearing CIN2/CIN3 lesion.

Current South African guidelines recommend that “low-risk” women (i.e. women who have tested HIV-negative or have unknown HIV status) are screened every 10 years from age 30 to 50 and “high-risk” women (i.e. women with an HIV diagnosis) are screened every three years, starting at age of HIV diagnosis for their lifetime (Table 1.1).

For each alternative strategy, we varied the screen interval and ages to start and end screening (Table 1.3). For “low-risk” women, we considered starting screening at age 20, 25 or 30 and screening at 3-, 5-, 7-, or 10-year intervals. Screening always ended at age 50. For “high-risk” women, screening always started at age of HIV diagnosis and ended at age 80, and we considered screening at 1-, 2-, 3-, 4-, or 5-year intervals. Because women are able to acquire HIV over time, we consider combinations of strategies for both low- and high-risk women. We did not consider any strategies where “low-risk” women were screened more aggressively than “high-risk” women. This resulted in a total of 55 strategies, including no screening as a comparator.

We assumed that women could be offered an HIV test at their cervical screen encounter, and if a woman living with HIV was diagnosed, she would be switched to the “high-risk” screening strategy. On average, less than 10 percent of women living with HIV in the simulated population had unknown HIV status and thereby were classified as “low-risk”.

**TABLE 1.3. Cervical Cancer Screening Strategies**

| Screen Interval | Screen Start Age | Screen Stop Age |
|---|---|---|
| “Low-Risk” Women | | |
| 1. 3-year<br>2. 5-year<br>3. 7-year<br>4. 10-year | 1. 20 years<br>2. 25 years<br>3. 30 years | 50 years |
| “High-Risk” Women | | |
| 1. 1-year<br>2. 2-year<br>3. 3-year | Age of HIV diagnosis | 80 years |

4. 4-year
5. 5-year

Our follow-up and management strategies for cervical screen-positive women were based on South African guidelines. For liquid-based and conventional cytology, a result of atypical squamous cells of undetermined significance or worse (ASCUS+) was followed by a confirmatory colposcopy, which occurred at a separate clinical encounter. Women also faced a risk of having an inadequate smear, which required repeat testing (at a separate clinical encounter). In total, cytology could result in three or more clinical visits for a result of ASCUS+. For HPV-based screening, a positive HPV test was followed by confirmatory colposcopy (we assume 10 percent availability), depending on availability. In the absence of colposcopy, women were referred for immediate same-day treatment. HPV-based screening could result in between one and three clinical visits for an HPV positive result.

Women with a histologically confirmed diagnosis of CIN2 or CIN3 a received large-loop excision of the transformation zone (LLETZ) or cryotherapy, depending on availability and eligibility (see Table 1.2). We assumed that among women whose lesions were removed, some failed to clear their HPV infection, and we varied the probability of HPV clearance after cryotherapy in sensitivity analyses. Following treatment, women were re-screened the following year and if negative, returned to routine screening. Women with detected cancers underwent staging and subsequent stage-specific treatment. Surgeries were used to remove cancer in early stages, and chemotherapy and radiotherapy were used to treat regional and distance cancers. We assumed that all

women who had access to and received screening services, as well as women who are symptom-detected, had access to cancer treatment services.

In our main analysis, we assumed all women have access to screening services and adhere to management protocols. We relaxed these assumptions in sensitivity analyses (Table 1.2).

1.2.8. Estimation of cost and cost-effectiveness

Costs were estimated from in-country data sources, including direct medical and non-medical costs (Table 1.2). Direct medical costs of screening, diagnosis and treatment of CIN were estimated from a study of cervical cancer screening and treatment in women living with HIV in Johannesburg from 2009 to 2010[26,32]. Direct medical costs of HIV testing, laboratory-based CD4 count testing, and antiretroviral therapy and its associated care were derived from a review of cost data that was used to inform a recent HIV investment case prepared by the South African government.[29] Non-medical costs included women's time, which was valued using an estimate of patient-reported hourly income[30]. We assumed a single patient visit required on average a full day of lost income, which we estimated at 8 hours. Costs are reported in 2019 US dollars (US$).

Model outcomes included total and HIV-stratified cervical cancer incidence, cancer and non-cancer related mortality, disability-adjusted life years (DALYs) and total costs. Costs and DALYs were discounted at an annual rate of 3 percent. In sensitivity analyses, we considered a higher discount rate pegged to the South African Reserve Bank repurchase rate of 6.5 percent.

For each of a sample of 50 best-fitting parameter sets, we simulated 55 screening strategies over a 90-year period with a starting population of 4 million women (chosen to minimize both stochastic error and computational burden), based on the current population age profile. We used an open cohort disease model, where new individuals enter the simulation in each year, to capture multiple incoming birth cohorts[33]. We summed the costs and health benefits for all women for each strategy and averaged across the 50 parameter sets. We rounded costs to the nearest $100 and ICERs to the nearest $10.

We conducted a cost-effectiveness analysis to determine the optimal screening strategy for the mixed population of women with and without HIV. We first eliminated strategies that were dominated strongly, meaning that there is always a combination of other strategies with both lower costs and greater health benefits or weakly, meaning any intervention that has an incremental cost-effectiveness ratio (ICER) that is greater than that of a more effective intervention. We then compared ICERs of non-dominated strategies to a range of willingness to pay (WTP) values between $1,300 - $5,200 USD per DALY averted for South Africa[34]. We identified the strategy with the highest ICER less than the WTP threshold to be the optimal screening strategy.

## 1.3. Results

Cervical cancer screening significantly reduced cervical cancer incidence, with variation based on screen frequency and age. Screening annually for “high-risk” women and every three years for “low-risk” women starting at age 20 was the most aggressive and effective strategy, yielding an 84 percent reduction in cervical cancer incidence

compared to no screening. Screening “low-risk” women every 10 years starting at age 30 and “high-risk” women every five years, the least aggressive screening strategy, decreased cervical cancer incidence by 65 percent compared to no screening.

Resource use varied widely across the 55 screening strategies considered. With current screening guidelines, total costs for a cohort of 4 million women, including HIV and cancer care, exceeded $4.6 billion. The most resource intensive screening strategy considered increased the cost by 28 percent compared to current guidelines ($5.9 billion).

The total cost and total DALYs averted of screening with each strategy are displayed in Figure 1.2. The strategies on the efficiency frontier consist of cervical screening strategies that are considered cost-effective at different WTP values. Of the 55 screening strategies considered, nine strategies were on the efficiency frontier. All other screening strategies, including current guidelines, were dominated.

Working our way along the efficiency frontier, we found that 10-yearly screening for “low-risk” women starting at age 30 and 5-yearly screening for “high-risk” women reduced cervical cancer incidence by 65 percent compared to no screening at a cost of $270 per DALY averted. Lowering the screen start age for “low-risk” women to age 25 cost an additional $30 per DALY averted and yielded an additional 4 percentage point reduction in cervical cancer incidence.

In all other non-dominated strategies, screening started at age 20 for “low-risk” women, 10 years younger than current guidelines, and occurred more frequently than current guidelines. 7-yearly screening for “low-risk” women and 5-yearly screening for

"high-risk" women reduced cervical incidence by 75 percent at a cost of $1,020 per DALY averted. It cost at least $4,290 per DALY averted to also screen "high-risk" women more frequently than current guidelines. Screening "low-risk" women 3-yearly and "high-risk" women 2-yearly reduced cervical cancer by 83 percent. The most costly and effective strategy on the efficiency frontier, screening "high-risk" women annually, cost $12,430 per DALY averted.

Within a WTP range of $1,300 to $5,200, we found that "low-risk" women were under-screened according to current guidelines – it was always optimal to lower the age to start screening 20 years and increase the interval of screening to at least 7-yearly. Within this range, there was variation in the optimal strategy for "high-risk" women. At a WTP less than $3,300, "high-risk" women were over-screened according to current guidelines; above $4,290 they were under-screened.

**FIGURE 1.2. Efficiency Frontier**

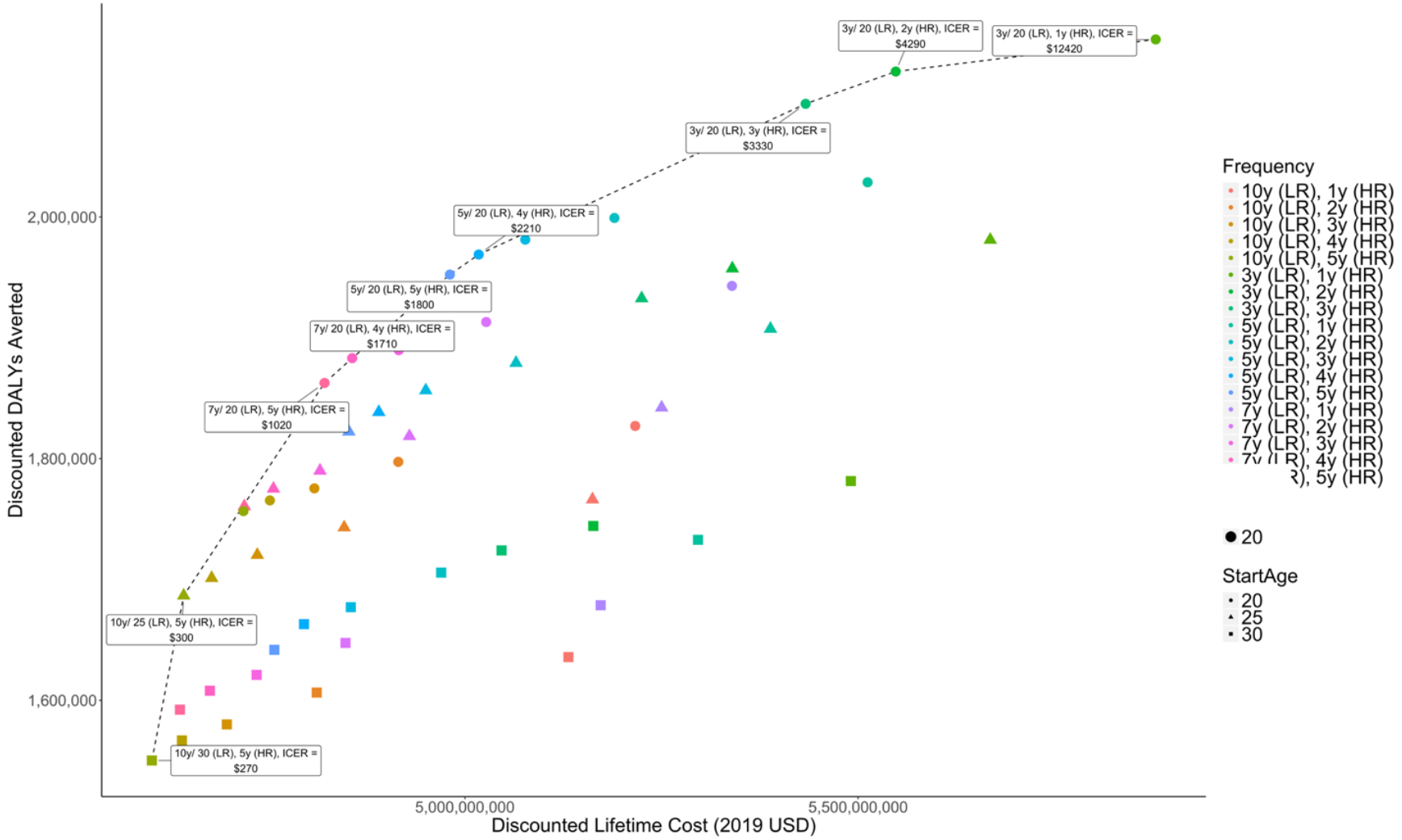


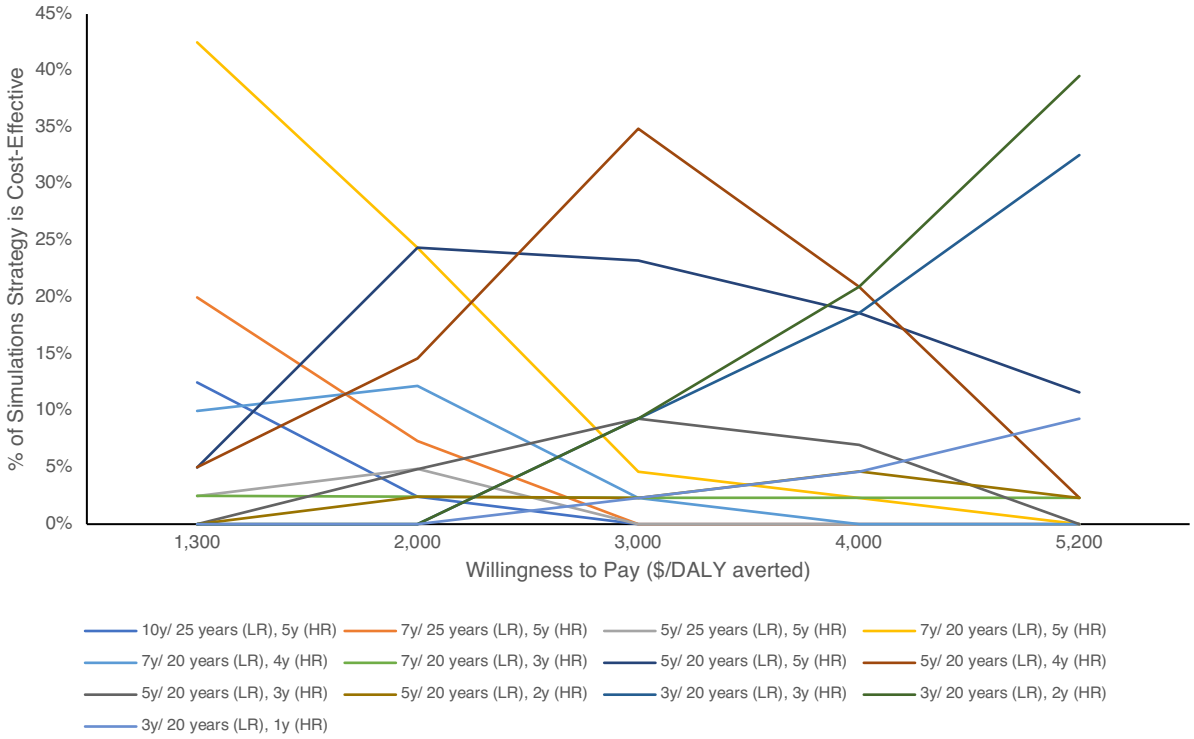
**TABLE 1.4. Health Impact, Cost, and ICERs of Efficient Screening Strategies**

| Strategy | Incidence Reduction* | Discounted Lifetime Cost** (000,000s) | Discounted DALYs** (000s) | ICER |
|---|---|---|---|---|
| No Screen | -- | $4,178 (2,896-5,956) | 39,115 (35,560-44,200) | -- |
| 10y/ 30 years (LR), 5y (HR) | 65 | $4,602 (3,295-6,373) | 37,565 (34,150-41,928) | $270 |
| 10y/ 25 years (LR), 5y (HR) | 69 | $4,642 (3,330-6,418) | 37,428 (34,009-41,873) | $300 |
| 7y/ 20 years (LR), 5y (HR) | 75 | $4,821 (3,490-6,596) | 37,252 (33,927-41,634) | $1,020 |
| 7y/ 20 years (LR), 4y (HR) | 76 | $4,857 (3,503-6,661) | 37,232 (33,918-41,630) | $1,710 |
| 5y/ 20 years (LR), 5y (HR) | 78 | $4,981 (3,631-6,754) | 37,162 (33,809-41,601) | $1,800 |
| 5y/ 20 years (LR), 4y (HR) | 78 | $5,018 (3,649-6,819) | 37,146 (33,785-41,587) | $2,210 |
| 3y/ 20 years (LR), 3y (HR) | 82 | $5,433 (4,031-7,254) | 37,021 (33,724-41,425) | $3,330 |
| 3y/ 20 years (LR), 2y (HR) | 83 | $5,548 (4,097-7,441) | 36,994 (33,693-41,417) | $4,290 |
| 3y/ 20 years (LR), 1y (HR) | 84 | $5,878 (4,281-7,941) | 36,968 (33,616-41,383) | $12,420 |

*Percent reduction compared to no screening.
**Values represent the average model output across the 50 best-fitting input parameter sets from the calibrated model; values in parentheses indicate the minimum and maximum values across the 50 parameter sets.

There was variation in the optimal strategy across the simulations. At a WTP of $5,200, screening “low-risk” women every three years starting at age 20 and “high-risk” women every two years was cost-effective in 40 percent of simulations (Figure 1.3). At this WTP, it was always cost-effective to increase the screen frequency for “low-risk” women to at least every five years, starting at age 20.

**FIGURE 1.3. Variation Across Simulations**




We tested assumptions regarding screen coverage and adherence, treatment efficacy, discount rate, classification of high- and low-risk based on HIV status, and costs of screening, diagnostics and treatment, to determine the robustness of our results. We found that at a WTP of $5,200, our results were robust to all assumptions tested except CIN treatment efficacy and definition of risk. When treatment for CIN was assumed to be 100% effective or when we classified women with unknown HIV status as “high-risk”, (according to the WHO definition), increasing the screening frequency for “high-risk” women was no longer cost-effective within the WTP range (Figure 1.4, Table 1.5).

**FIGURE 1.4. Cost-Effectiveness Plane, Sensitivity Analysis**

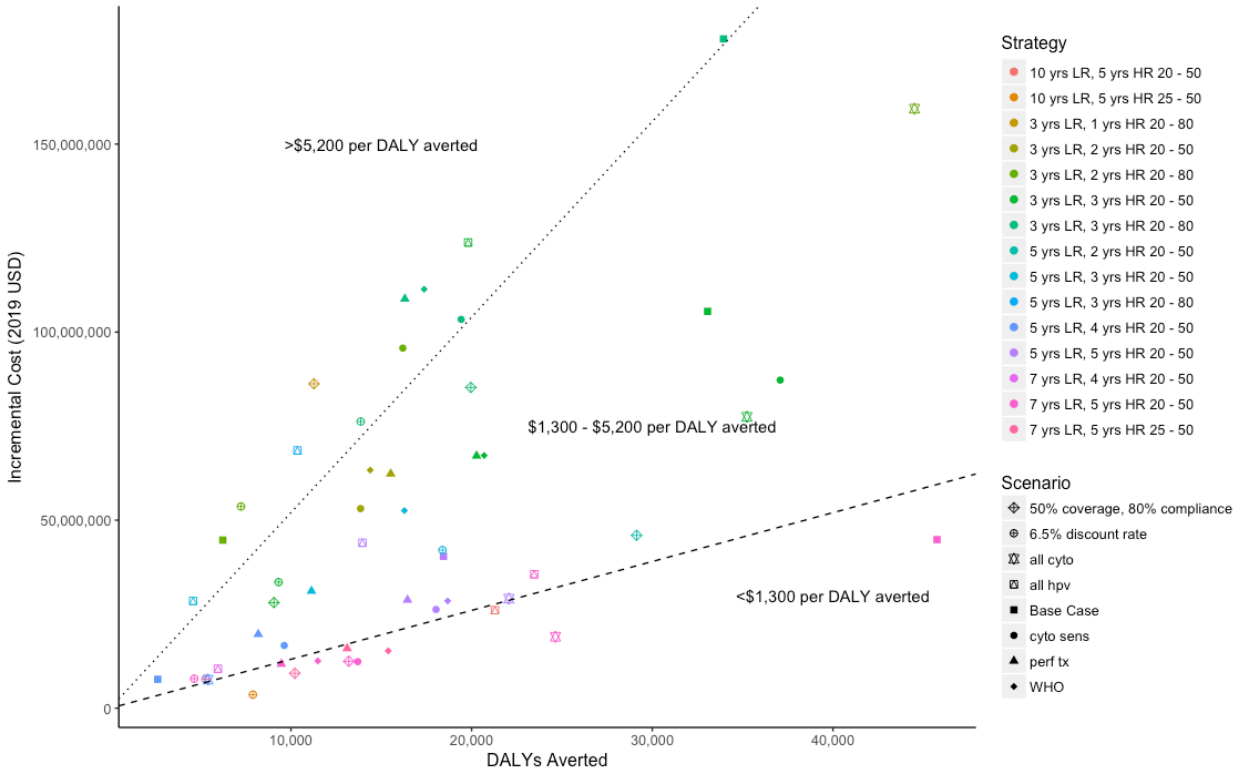



**TABLE 1.5. Impact of Cost on Optimal Screening Strategies, Under Different Willingness to Pay Values***

| Scenario | $1,300 | $2,000 | $3,000 | $4,000 | $5,200 |
|---|---|---|---|---|---|
| Cost of ART (base case $260): $0 - $120 | 5y/ 20 years (LR), 5y (HR) | 5y/ 20 years (LR), 4y (HR) | 3y/ 20 years (LR), 3y (HR) | 3y/ 20 years (LR), 2y (HR) | |
| Cost of ART (base case $260): $120 - $260 | 7y/ 20 years (LR), 5y (HR) | | | | |
| Cost of Colposcopy (base case $73): $0 | 5y/ 20 years (LR), 4y (HR) | 3y/ 20 years (LR), 3y (HR) | | | |
| Cost of Colposcopy (base case $73): $20 - $70 | 5y/ 20 years (LR), 5y (HR) | 5y/ 20 years (LR), 4y (HR) | | | |
| Cost of HPV (base case $59): $0 - $30 | 5y/ 20 years (LR), 4y (HR) | 3y/ 20 years (LR), 3y (HR) | 3y/ 20 years (LR), 2y (HR) | | |
| Cost of HPV (base case $59): $30 - $60 | 5y/ 20 years (LR), 5y (HR) | 5y/ 20 years (LR), 4y (HR) | 3y/ 20 years (LR), 3y (HR) | | |
| Cost of HPV (base case $59): $60+ | 7y/ 20 years (LR), 5y (HR) | | | | |

*The table indicates the optimal screening strategy under a range of willingness to pay values as benchmarks of good value for money. The optimal strategy was the most effective strategy with an ICER less than the indicated threshold. Color coding indicates unique screening strategies ordered from most aggressive (light green) to least aggressive (dark green).

## 1.4. Discussion

In this analysis, we found that cervical cancer screening has a large impact on cervical cancer incidence, mortality and DALYs, and that depending on WTP, South African guidelines could be changed to improve efficiency and health outcomes. Our results indicate that, while accounting for the dynamic nature of HIV, and within the reported WTP range, it is always cost-effective to increase the frequency of screening for "low-risk" women and may be cost-effective to either decrease or increase the frequency for "high-risk" women, depending on WTP.

We found that the optimal strategy is sensitive to the WTP, meaning that the value South Africa places on averting an additional DALY will make a difference in determining its optimal screening strategy. We presented results for a WTP range of $1,300 to $5,200[34]. Within this range, it was always cost-effective to increase the frequency of screening for "low-risk" women and to start screening at a younger age. For "high-risk" women, there was more variation – at the lower end of the WTP range, it was cost-effective to decrease the frequency of screening to every five years, whereas at the top end of the range it was cost-effective to increase screening frequency to every two years.

This analysis supports a review of cervical cancer screening guidelines in South Africa, where cervical cancer is the leading causing of female cancer mortality and approximately 3.5 million women are living with HIV and face an elevated risk of HPV and cervical cancer compared to HIV-uninfected women. This work builds upon the existing

literature on the impact of HIV on cervical cancer, including a model-based analysis of screening in HIV-infected women in South Africa which concluded that HPV screen-and-treat every 2 years was optimal for women living with HIV[25]. We add to this literature by simulating multiple cohorts of women that are representative of the general female population in South Africa, accounting for lifetime HIV risk, natural history and historical and projected HIV testing and treatment patterns. Furthermore, we evaluated cervical screening in this population by HIV status and history of testing, per the current guidelines. Our conclusions were consistent with prior results.

If South Africa classified women who have not been tested for HIV in the last year as "high-risk" (per the WHO guidelines), it would no longer be cost-effective to increase screening for "high-risk" women, suggesting that our results were sensitive to the classification of women who do not know their HIV status. These results are driven by the large share of HIV-uninfected women who do not know their HIV status, who would be driving up the cost of screening while not be benefitting from additional screening.

Our analysis has important limitations. In the absence of robust registry and population-level data, we relied upon primary data collected in small studies across South Africa, which impacts the generalizability of our results. In order to address this, we tested assumptions in sensitivity analyses, such as cost of services and test performance, and calibrated uncertain parameters to capture the range of uncertainty.

We made structural choices to reduce the uncertainty and dimensionality of the model, such as pooling HPV genotypes into oncogenic and non-oncogenic groups. We felt comfortable with this simplifying structural assumption since the screening strategies

considered in this analysis did not detect differentially detect by individual HPV genotypes. However, this is a limitation in the model's ability to evaluate new technologies that rely on genotyping, which are increasingly being used in South Africa.

We did not account for HPV vaccination, which was introduced in South Africa in 2014, targeting age 9-10 year old girls. As a result, we may have overestimated the effect of screening on cancer prevention, especially as vaccination coverage increases over time, since cervical cancer burden is expected to decrease with benefits accruing to both vaccinated and unvaccinated women. Therefore, any conclusions from this analysis are relevant to unvaccinated women and women who are not gaining herd immunity benefits from vaccination.

The HIV component of the model was simplified based on our best understanding of the natural history and the availability of data. While we captured our understanding of the impact of HIV on HPV, we were not able to capture all aspects of HIV natural history, including HIV treatment failure, drug resistance and the potential impact of HPV natural history on HIV acquisition. Women infected with genital HPV appear to have an elevated risk of acquiring HIV compared to women without HPV, perhaps due to an increase in HIV-susceptible cells in the genital tract following the immune response to an HPV infection[35,36]. We do not expect it to systematically bias our results as we are not considering any variation in HIV natural history within cervical cancer screening strategies. We also faced limitations in understanding HPV natural history and cancer incidence in women living with HIV and relied on calibration to observed data to inform

model parameters. Additionally, behavioral processes such as ART disengagement and re-engagement in care are uncertain were not included in the model.

## 1.5. Conclusion

Our analysis found that screening “low-risk” women starting at age 20 and every 3 to 7 years and “high-risk” women every 2 to 5 years was good value for money given a WTP range of $1,300 to $5,200 per DALY averted. These findings suggest that current South African guidelines may be under-screening both “low-risk” and “high-risk” women. However, cost-effectiveness is but one consideration in designing health policy. Policymakers must also be concerned with the distribution of health benefits and costs, feasibility, and budget impact.

# Chapter 2.

# The Impact of HPV Vaccination on Optimal Cervical Cancer Screening in an HIV Endemic Population

Abstract

**Background**
Widespread human papillomavirus (HPV) vaccination is expected to significantly decrease cervical cancer incidence and may allow a reduction in the intensity of screening. The protective benefit of vaccination may be lower or wane more rapidly in women living with HIV whose immune systems becomes compromised, but despite this uncertainty, no modeling analyses account for a reduction in vaccine efficacy in the presence of untreated HIV. As a result, prior analyses may be overly optimistic about the impact of vaccination in HIV-endemic settings. In this analysis, I explore the conditions under which cervical cancer screening intensity could be decreased in HPV-vaccinated women in South Africa and separate cervical cancer screening guidelines established for vaccinated women.

**Methods**
I developed a microsimulation model of HIV infection, type-specific HPV infection, cervical carcinogenesis and patterns of HIV and cancer testing and treatment. Disease dynamics were governed by individual-level attributes such as age, prior health history, and current health status. I calibrated the model to South African epidemiologic data and compared current screening guidelines to 15 alternative strategies, varying the duration of vaccine waning in women whose CD4 count fell below 350 cells/mm$^3$. I calculated the expected discounted lifetime costs and DALYs for each strategy, the incremental cost-effectiveness ratios (ICERs) for non-dominated strategies and compared these to willingness to pay (WTP) values ranging from $1,300 and $5,200 per DALY averted, based on empirical cost-effectiveness estimates.

**Results**
HPV vaccination had a large impact on cervical cancer incidence in this population. In the absence of screening, vaccination reduced incidence of cervical cancer by 42 to 79 percent, depending on vaccine type and duration of vaccine waning in women whose CD4 falls below 350 cells/mm$^3$. I found that at a WTP of $5,200 per DALY averted, it would be optimal to screen vaccinated women *equally or more aggressively* than current guidelines recommend for all vaccine waning duration scenarios. When I considered a lower WTP of $1,300 per DALY averted, I found it would be optimal to screen vaccinated women *less aggressively* than current guidelines recommended. Compared to my analysis of unvaccinated women, it would always be optimal to screen vaccinated women equally or less aggressively than unvaccinated women.

**Conclusions**
These results demonstrate that there may be opportunities to differentiate screening guidelines according to HPV vaccination status, even in an HIV-endemic setting where vaccine efficacy may be diminished. However, the optimal strategy depends on willingness to pay.

## 2.1. Background

Human papillomavirus (HPV) vaccination provides promising primary prevention against cervical cancer[40–44]. Bivalent, quadrivalent and nonavalent vaccines protect against HPV types 16/18, 6/11/16/18, and 6/11/16/18/31/33/45/52/58, respectively, and are highly efficacious against infection with vaccine-targeted HPV and associated precancers[45,46].

The best evidence to date on the population health impact of HPV vaccination comes from Australia, where the vaccine was first introduced to girls in 2007 and extended to include boys in 2014. Australian researchers were among the first to report reductions in the prevalence of vaccine-type HPV infections, by 86 percent in 18- to 24-year-olds who had received three vaccine doses and 76 percent for those who had received one or two doses[47–49]. Reductions in grade 2 and 3 cervical intraepithelial neoplasia (CIN) have also been seen in Australia, where women under the age of 20 had a prevalence decline from 10.9 to 5.0 per 1,000 screened women over a period of 10 years, and prevalence in 20- to 24-year-olds decreased from 21.5 to 13.5 per 1,000 screened women in a similar time period[47,50].

While it is too early to observe changes in the incidence of cervical cancer as a result of HPV vaccination, it has been estimated that with 50 percent coverage of the bivalent vaccine, there could be a worldwide reduction of cervical cancer incidence of 246,086 cases annually[51]. If coverage reached 90 percent, the number of averted cases would increase to a total of 442,955 per year and up to 93 percent of cervical cancers could be prevented with widespread coverage of the nonavalent vaccine[51].

Vaccination against HPV is expected to have the greatest impact in low- and lower-middle-income countries (LLMICs), where the highest burden of cervical cancer exists and access to screening and treatment is limited. At a cost of $4.50 per dose (the bivalent vaccine price negotiated for Gavi-eligible countries), HPV vaccination is considered highly cost-effective in LLMICs[52,53]. In the last ten years, 43 LLMICs have delivered the HPV vaccine to young adolescent girls through pilot programs, demonstration programs, and national introductions, thanks largely to the inclusion of HPV vaccines in the Gavi portfolio[54]. As of June 2018, there were eight countries in sub-Saharan Africa with a national HPV immunization program, and nearly twice as many with pilot programs[55,56].

Widespread HPV vaccination may offer a unique opportunity to reduce cervical cancer screening intensity over time, as the risk of HPV infection, pre-cancerous lesions and related cancers decreases. However, it will likely not obviate the need for screening entirely, as the vaccine does not protect against all oncogenic HPV types. Modeling analyses of cervical screening in the United States and the United Kingdom has found that screening in HPV-vaccinated women can be modified to start at later ages and occur at decreased frequency[57,58]. However, no separate screening algorithm for HPV-vaccinated women has been agreed upon, and the WHO cervical cancer prevention guidelines provide no differential guidance for screening in HPV-vaccinated women. Changes in optimal screening approaches among HPV-vaccinated women may depend on a variety of factors, including age of vaccination, vaccine completion rates, type-specific vaccine efficacy, duration of protection, and setting-specific elements, such as

HPV genotype distribution in cancer, the burden of human immunodeficiency virus (HIV), and availability of HIV screening and treatment services.

The benefit of HPV vaccination may be attenuated by immune compromise from untreated HIV infection – acquired before or after vaccination. CD4 T-cells are important for initial control of HPV at the vaginal and uterine epithelium, are key to recruit memory B-cells to the female genital tract, and provide growth factors for B cells and plasma cells[59]. Depletion of CD4 T-cells caused by untreated HIV infection may impact production of HPV antibodies and the subsequent efficacy and duration of the vaccine, an effect which has been seen in other vaccines[60,61]. In a review of the literature on routine vaccines, the duration of seroprotection was shorter in individuals with HIV, and a substantial proportion of patients with HIV lost protective antibodies before guideline-recommended timing for a booster[60]. This effect was evident in vaccination against hepatitis B, measles, varicella[60], where HIV reduced long-term immunity against these pathogens.

HPV vaccine safety and immunogenicity studies show that the bivalent and quadrivalent vaccines have acceptable safety and reactogenicity in women with HIV[62–65]. However, they also show evidence of lower HPV seroconversion among women with low CD4 counts[62,65], as well as among women not on antiretroviral therapy (ART)[64]. The clinical significance of these findings is unclear, as the protective titers of HPV antibodies have not been defined and to date, there have been no studies with vaccine efficacy as endpoints in women with HIV and no studies in women who acquired HIV after HPV vaccination.

While the majority of data on the effect of HIV on long-term vaccine-induced immunity comes from individuals who had a compromised immune system at the time of vaccination, in this analysis I am interested in the effect of immune compromise/decline *after* vaccination (I assumed women were immune-competent at time of vaccination – either HIV-uninfected or living with treated, suppressed HIV infection). The literature establishes a mechanism for the effect of CD4 decline on antibody level and I use this to explore the impact of a range of scenarios, varying the rate of vaccine waning in immunocompromised women.

Despite uncertainty in the duration of HPV vaccine protection in immunocompromised women, disease simulation models and policy analyses of HPV vaccination and cervical cancer screening have not accounted for a possible reduction in vaccine duration and efficacy in women with untreated HIV[66,67]. As a result, these models may overestimate the magnitude of health effects and therefore be overly optimistic about the impact of HPV vaccination in HIV-endemic settings.

South Africa introduced the HPV vaccine in 2014, targeting grade 4 girls with two doses of the bivalent vaccine. In its first campaign, over 350,000 grade 4 girls were vaccinated in more than 16,000 public schools across South Africa, which translated to 94.6 percent of schools reached and 86.6 percent of age-eligible girls vaccinated.[68] South Africa is also home to the largest number of people living with HIV in the world; 24 percent of 15- to 49-year-old women are living with HIV. Thanks to a highly effective and prolific prevention of mother-to-child transmission program, perinatal HIV infection has been virtually eliminated, meaning that almost all girls who are vaccinated against

HPV are not living with HIV at the time of vaccination. Additionally, for the vanishingly small group of HIV-infected 9-year-old girls, I assume that all have suppressed infection and are on antiretroviral therapy (ART). However, young women and adolescent girls account for a disproportionate share of new HIV infections. In this analysis, I explored the impact of different levels of vaccine efficacy and duration among women living with HIV with immune decline and subsequent optimal cervical cancer screening policy.

Specifically, I compared the cost-effectiveness of various cervical cancer screening strategies in women who were vaccinated against HPV at age 9 with the bivalent vaccine; I identified the optimal mix of screening strategies for these women and considered how the optimal strategy would change based on rate of vaccine waning in immunocompromised women.

## 2.2. Methods

### 2.2.1. Overview

Using an individual-based microsimulation model, I quantified the health and economic consequences of alternative cervical cancer screening strategies in HPV-vaccinated women. I estimated cervical cancer incidence and mortality; health care costs; and the incremental cost-effectiveness of 15 screening strategies that varied the screen frequency and screen ages to identify the optimal screening strategy for HPV-vaccinated women based on their HIV status and history of HIV testing. I varied rate of vaccine waning in women living with HIV whose CD4 count is below 350 cells/$mm^3$ to determine the influence of vaccination on screening in an HIV-endemic setting.

### 2.2.2. Modeling Approach

I refined an individual-based model of HPV infection, HIV infection and cervical carcinogenesis that I developed and described in Chapter 1. Disease dynamics were

governed by individual attributes, including age, HIV status, ART status and time on ART, current and baseline CD4 count, genotype-specific HPV infection and duration of infection, grade and duration of pre-cancerous lesion (i.e., cervical intraepithelial neoplasia, CIN, grade 2 and 3), stage of cancer (i.e., local, regional and distant) and duration with cancer. Details of the model structure and assumptions are described in Chapter 1. Some changes were made for this analysis, which are described in detail here.

Women faced an age- and type-specific risk of HPV infection. Unlike the binary stratification of HPV genotype in Chapter 1 (oncogenic and non-oncogenic), I stratified HPV genotypes into nine categories to capture the impact of various vaccination strategies on future burden of cervical cancer. These included types 16, 18, 31, 33, 45, 52, 58, other high-risk (oncogenic types that are not covered by the nonavalent vaccine) and all low-risk. A woman with an HPV infection could clear the infection (and subsequently acquire type-specific natural immunity that decreased future risk of infection with the same type), persist with the infection, or develop CIN2 or CIN3. These transitions were all governed by duration and type of infection. CIN could clear, persist, or progress to invasive cervical cancer based on lesion duration and associated HPV type. I assumed that women could acquire multiple HPV infections and lesions independently, but assumed an HPV infection could cause only a single lesion. I assumed a woman with CIN could only clear the associated causal HPV infection when the CIN cleared. Once a woman developed invasive cervical cancer, I assumed she could not acquire new HPV infections or lesions.

Women faced an annual probability of HIV infection that was based on reported HIV incidence trends over time for South Africa. A detailed description of the HIV natural history assumptions can be found in Chapter 1. In summary, women were assigned a CD4 cell count of 500 cells/mm$^3$ at the time of HIV infection. In the absence of ART, CD4 count declined over time. Once a woman was tested and diagnosed, she was able to initiate ART and her CD4 count rebounded. Women could drop out from ART care and re-engage; I assumed that women who dropped out of ART care faced a reduced probability of re-initiating care by a factor of 0.5. Women faced HIV-specific mortality based on her current and nadir CD4 count. I also assumed HPV infection did not impact HIV natural history.

Unlike the multi-cohort open model used in Chapter 1, I simulated a single cohort of 10 million girls from age of vaccination until death. I chose 10 million in order to minimize Monte Carlo error around estimates of the impact of HIV natural history on HPV vaccination and screening. All women received two doses of the bivalent HPV vaccine at age 9, which reduced future risk of type-specific HPV infection. I also considered the nonavalent vaccination, which protects against an additional 5 high-risk genotypes. I assumed the vaccine was 100 percent effective against the genotypes it targeted and this protection lasted lifelong for all immunocompetent women in the model (women without HIV and women with a CD4 count above 350 cells/mm$^3$) (Table 2.1). In sensitivity analysis, I considered baseline vaccine efficacy of 80 percent in all HIV-infected women, rather than 100 percent, to test the robustness of this assumption. If a women's CD4 count fell below 350 cells/mm$^3$, I assumed her vaccine efficacy began to

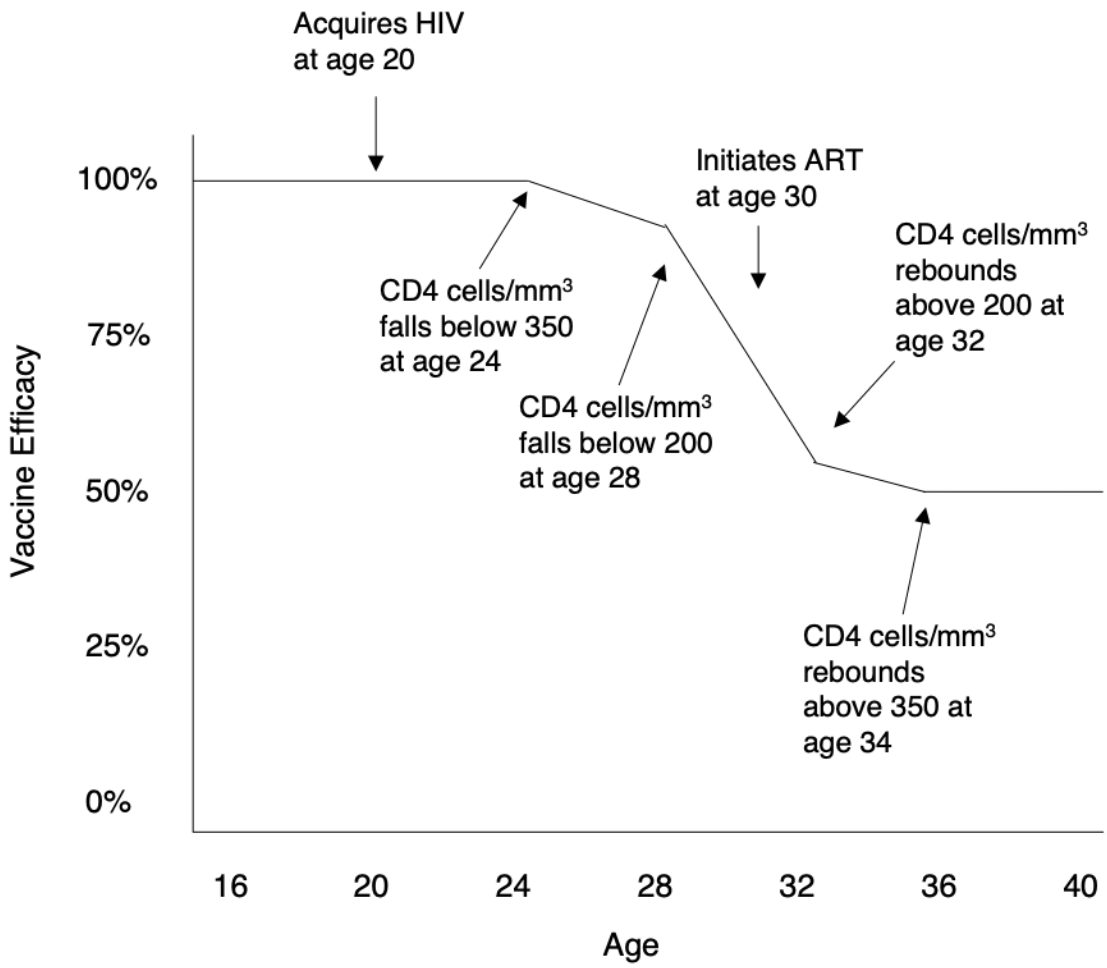
wane, and varied the rate of waning from 2.5 to 50 percentage point decline per year (meaning that it takes between 2 and 40 years for a woman to lose any vaccine protection). If her CD4 count fell below 200 cells/mm$^3$, I assumed her vaccine efficacy waned twice as quickly compared to below 350 cells/mm$^3$. If she re-initiated ART and her CD4 count rebounded above 200 cells/mm$^3$, her vaccine efficacy waning slowed and once it rebounded above 350 cells/mm$^3$ it stopped waning entirely, but never returned to its initial level (see Figure 2.1 for an example of vaccine efficacy decline following CD4 decline and Equation 1 below for full specification).

*Equation 1*

$$VE = SE - \delta * Dur_{CD4\ 200-350} - 2\delta * Dur_{CD4<200}$$

where, SE is the starting efficacy and $\delta$ is the rate of vaccine decline.

**Figure 2.1. Example of HPV Vaccine Efficacy Decline in Immunocompromised Women**




2.2.3. Calibration

I calibrated the model to identify parameter sets that would achieve a good fit to South African epidemiologic data. I calibrated 49 model parameters and fit to 100 calibration targets. I developed prior probability distributions to express uncertainty in model parameters. I used simulated annealing to search the parameter space and weighted least-squares, weighted by the relative strength of each calibration target, to score the model output. Details of the calibration approach I used for this analysis were previously provided in Chapter 1.

Calibrated model parameters included infection duration-specific HPV clearance and progression, lesion duration-specific CIN2+ clearance, and CIN2+ progression to

cancer, and genotype-specific hazard rates for HPV and CIN clearance and progression that were applied for each duration. For these parameters, I defined prior means and standard deviations using empirical data[13,15,37,69] and applied HIV-related hazard rates on transition probabilities from a meta-analysis of the impact of HIV on HPV natural history[17]. Calibration targets included high-risk HPV prevalence by age and HIV status, CIN2+ prevalence by age and HIV status, HPV type distribution by HIV status in CIN2, CIN3 and cancer, and age-specific cancer incidence[7,12,70].

I ran the natural history model (with no screening or vaccination) with 10 million women starting at age 9 until death. Results for a sample of the 50 best-fitting parameter sets are presented in the appendix. I simulated each scenario using these 50 best-fitting sets and calculated a point estimate for each outcome of interest by calculating the mean across the simulation results.

### 2.2.4. Screening Strategies

I modeled the use of conventional cytology, liquid-based cytology and HPV DNA testing, per South African cervical cancer screening policy. As a baseline, I simulated the current distribution of screen tests in South Africa, per current guidelines and in sensitivity analysis explored HPV testing and cytology testing alone in sensitivity analysis (Table 2.1).

**TABLE 2.1. Baseline and Sensitivity Analysis Values for Selected Model Variables**

| | Baseline | Sensitivity Analysis |
|---|---|---|
| Vaccine characteristics | | |
| Vaccine Type | Bivalent | Nonavalent |
| Efficacy (genotype-specific) | 100% protective against 16, 18 | 100% protective against 16, 18, 31, 33, 45, 52, 58 |
| Efficacy reduction in women living with HIV | 0% | 20% |
| Annual rate of vaccine decline in women with CD4 200 - 350 cells/mm$^3$ ($\delta$) | 10%, 25%, 50% | -- |

| | | |
|---|---|---|
| Annual rate of vaccine decline in women with CD4 < 200 cells/mm$^3$ | $2\delta$ | -- |
| Screening, triage, and diagnostic test performance (sensitivity/specificity to detect CIN2+)[a] | | |
| Cytology (HIV-uninfected) | 0.78/0.86[23,24] | -- |
| Cytology (HIV-infected) | 0.97/0.61[23,24] | -- |
| Colposcopy | 0.95/1.0[23,24] | -- |
| Fraction of liquid-based cytology requiring re-testing | 0.979[23,24] | -- |
| Fraction of conventional cytology requiring re-testing | 0.909[23,24] | -- |
| Distribution of screen tests (%) | | |
| Liquid-based cytology | 30% | 0%, 50% |
| Conventional cytology | 50% | 0%, 50% |
| HPV | 20% | 100%, 0% |
| Coverage and adherence[b] | | |
| Access to routine screening (% of population) | 100% | 50% |
| Screen adherence (probability of returning for next recommended clinical visit) | 100% | 80% |
| Access to colposcopy (% of HPV-based facilities) | 50% | -- |
| Access to cryotherapy[c] | 10% | -- |
| HIV testing[d] | Based on age, prior history of testing, current health[19] | -- |
| ART initiation[d] | Based on time since HIV diagnosis[19] | -- |
| ART lost to follow up rate[d] (r) | $r = \theta e^{-at}$ $\theta = 0.43$ , $a = 0.75$ and t = years on ART[19] | -- |
| Treatment eligibility and efficacy | | |
| Eligibility for cryotherapy (CIN2, CIN3, Cancer) | 85%, 75%, 10%[25] | -- |
| Effectiveness of cryotherapy to treat CIN2/3 | 83%[26] | 100% |
| Effectiveness of cryotherapy to clear HPV[e] | 84%[27,28] | 100% |
| Effectiveness of LLETZ to treat CIN2/3 | 79%[26] | 100% |
| Effectiveness of LLETZ to clear HPV[e] | 79%[27,28] | 100% |
| Direct Medical Costs (2019 US$) | | |
| Conventional cytology | $8[25] | -- |
| Liquid-based cytology | $17[25] | -- |
| HPV DNA test | $59[25] | -- |
| Colposcopy | $73[25] | -- |
| Cryotherapy | $4[25] | -- |
| LLETZ | $59[25] | -- |
| Local cancer treatment | $3,200[25] | -- |
| Regional cancer treatment | $9,700[25] | -- |
| Distant cancer treatment | $9,800[25] | -- |
| HIV test (positive result) | $5[29] | -- |
| HIV test (negative result) | $3[29] | -- |
| HIV treatment and care (per year) | $260[29] | -- |
| Direct Non-Medical Costs (2019 US$) | | |
| Patient time (hourly) | $1.42[30] | -- |

| | | |
|---|---|---|
| Disability values | | |
| HIV, asymptomatic (CD4 > 500 cells/mm$^3$) | 0[31] | -- |
| HIV, symptomatic no AIDS (CD4 > 200 cells/mm$^3$ and < 500 cells/mm$^3$) | 0.274[31] | -- |
| HIV, AIDS (CD4 < 200 cells/mm$^3$) | 0.582[31] | -- |
| Local cancer | 0.049[31] | -- |
| Regional cancer | 0.288[31] | -- |
| Distant cancer | 0.540[31] | -- |

Notes: a) The Hybrid Capture HPV test detects oncogenic HPV infection. b) Low- and high-risk women faced the same probability of screen coverage. c) Women who did not have access to or were not eligible for cryotherapy received LLETZ. d) Women with prior/disrupted ART care had a 0.5 reduction in probability of re-initiating ART. See appendix for more details. e) Probability that a woman cleared her HPV infection after cryotherapy or LLETZ, which was conditional on clearing CIN2/CIN3 lesion.

For cervical cancer screening, I classified women into cervical cancer risk groups based on the South African guidelines, and varied screen ages and frequencies for women based on their risk classification. Women were “low-risk” (LR) if they did not have HIV or if they had not been diagnosed with HIV and were “high-risk” (HR) if they had a diagnosed HIV infection. The model reclassified HIV-infected women as HR when her HIV was diagnosed. Each screening strategy varied the screen interval for HR and LR women and age to start screening for LR women. I kept the screen end age for LR women (50 years old) and the screen start and end ages for HR women (age of HIV diagnosis, in perpetuity) constant. I anchored the most aggressive strategy to the optimal strategy at a willingness to pay (WTP) of $5,200 per DALY averted in my analysis of screening among unvaccinated women in South Africa (2y HR, 3y LR starting at age 20) and the least aggressive to the optimal strategy in an analysis of screening after HPV vaccination in the United Kingdom (5y HR, 10y LR starting at age 40)[57]. I considered 15 screening strategies (Table 2.2) and five vaccine waning scenarios for immunocompromised women (Table 2.1).

**TABLE 2.2. Screening Strategies**

| Screen Start Age (LR) | Screen Frequency (LR) | Screen Frequency (HR) |
|---|---|---|
| 20 years | 3-year | 2-year |

| | | |
|---|---|---|
| 20 years | 3-year | 3-year |
| 20 years | 5-year | 4-year |
| 20 years | 5-year | 5-year |
| 20 years | 7-year | 4-year |
| 20 years | 7-year | 5-year |
| 30 years | 10-year | 3-year |
| 30 years | 10-year | 4-year |
| 30 years | 10-year | 5-year |
| 35 years | 10-year | 3-year |
| 35 years | 10-year | 4-year |
| 35 years | 10-year | 5-year |
| 40 years | 10-year | 3-year |
| 40 years | 10-year | 4-year |
| 40 years | 10-year | 5-year |

Notes: Routine screening starts at age of HIV diagnosis and continues in perpetuity for HR women. Routine screening ends at age 50 for LR women.

Follow-up and management strategies for cervical screen-positive women were based on South African guidelines. For liquid-based and conventional cytology, a result of atypical squamous cells of undetermined significance or worse (ASCUS+) was followed by a confirmatory colposcopy, which occurred at a separate clinical encounter. Women also faced a risk of having an inadequate smear (cytologist was unable to read the pap smear), which required repeat testing (at a separate clinical encounter). In total, cytology could result in three or more clinical visits for a result of ASCUS+. For HPV-based screening, a positive HPV test was followed by confirmatory colposcopy, depending on availability (Table 2.1). In the absence of colposcopy, women were referred for immediate same-day treatment. HPV-based screening could result in between one and three clinical visits for a positive HPV result. I assumed that, unless a woman was lost to follow-up (LTFU), all of her clinical encounters resulting from a positive screening test occurred within one year. I assumed that LTFU from HIV care was uncorrelated with cervical cancer screening adherence and compliance.

Women with a histologically confirmed diagnosis of CIN2 or CIN3 received large-loop excision of the transformation zone (LLETZ) or cryotherapy, depending on availability and eligibility (see Table 2.1). I assumed that among women whose lesions were removed, some HPV infection failed to resolve, and varied the probability of CIN/HPV treatment efficacy in sensitivity analyses (see Table 2.1). Following treatment, women were re-screened with the same screening test the following year and if negative, returned to routine screening. Women with detected cancers underwent staging and subsequent stage-specific treatment. Surgeries were used to remove cancer in early stages, and chemotherapy and radiotherapy were used to treat regional and distance cancers. I assumed that all women who had access to and received screening services, as well as women who are symptom-detected, had access to cancer treatment services. I assumed all women have access to screening services and adhere to management protocols.

For each parameter set, I simulated each screening strategy in a cohort of 10 million girls who had been vaccinated with the bivalent vaccine, starting at age 9 over their lifetime. At the end of the simulation, I summed the lifetime costs and health benefits for the entire cohort of girls, for each intervention and averaged across the 50 parameter sets.

### 2.2.5. Estimation of cost and cost-effectiveness

Costs were estimated from in-country data sources, including direct medical and non-medical costs (Table 2.1). Direct medical costs of screening, diagnosis and treatment of precancerous lesions were estimated from a study of cervical cancer

screening in women living with HIV in Johannesburg in 2014.[32] I did not include vaccine costs because I assumed these did not differ between strategies (all simulated women were assumed to be previously vaccinated) and did not compete bivalent and nonavalent vaccine scenarios against each other. Non-medical costs included women's time, which was valued using an estimate of patients' reported income[30]. Model outcomes included absolute lifetime cervical cancer incidence and mortality, disability-adjusted life years (DALYs) and lifetime costs. For the cost-effectiveness analysis, costs and DALYs were discounted at an annual rate of 3 percent.

I conducted a cost-effectiveness analysis to determine the optimal screening strategy. I first eliminated dominated strategies (strategies that were more costly and less effective than a linear combination of other strategies). I considered the strategy with the highest ICER less than the willingness to pay (WTP) threshold to be the most cost-effective screening strategy. For the main analysis, I assumed South Africa was willing to pay $5,200 to an avert an additional DALY. This WTP value is equal to the 2016 GDP per capita of South Africa and the upper end of a reported WTP range[34]. I explored the impact of lower WTP values in sensitivity analyses.

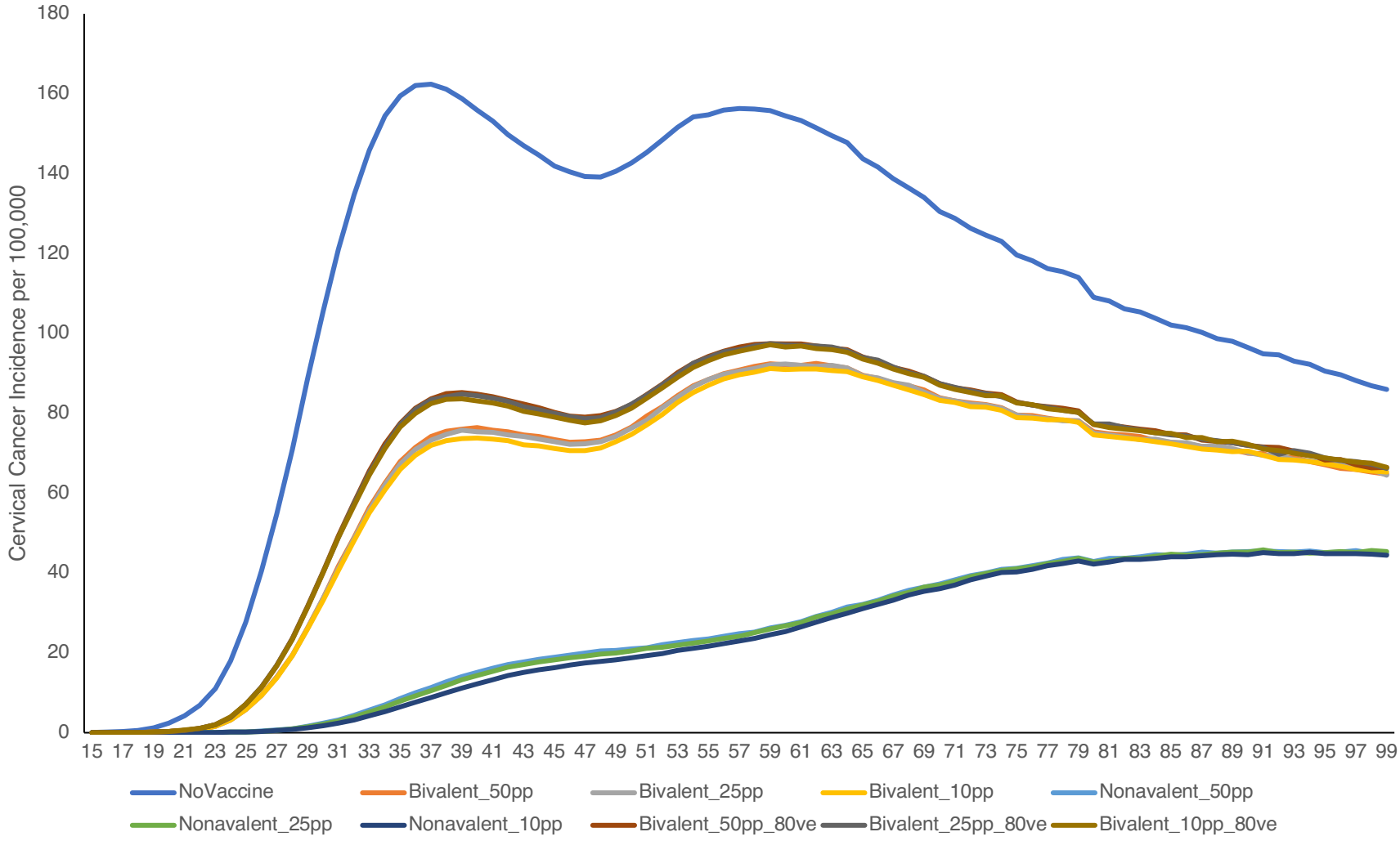
## 2.3. Results

### 2.3.1. Health Impact

Before considering screening, I explored the impact of HPV vaccination on health metrics that may influence optimal screen age and interval, including cervical cancer incidence, age of causal infection and average time between causal HPV infection, CIN lesion and invasive cervical cancer. I found that the bivalent vaccine reduced cervical

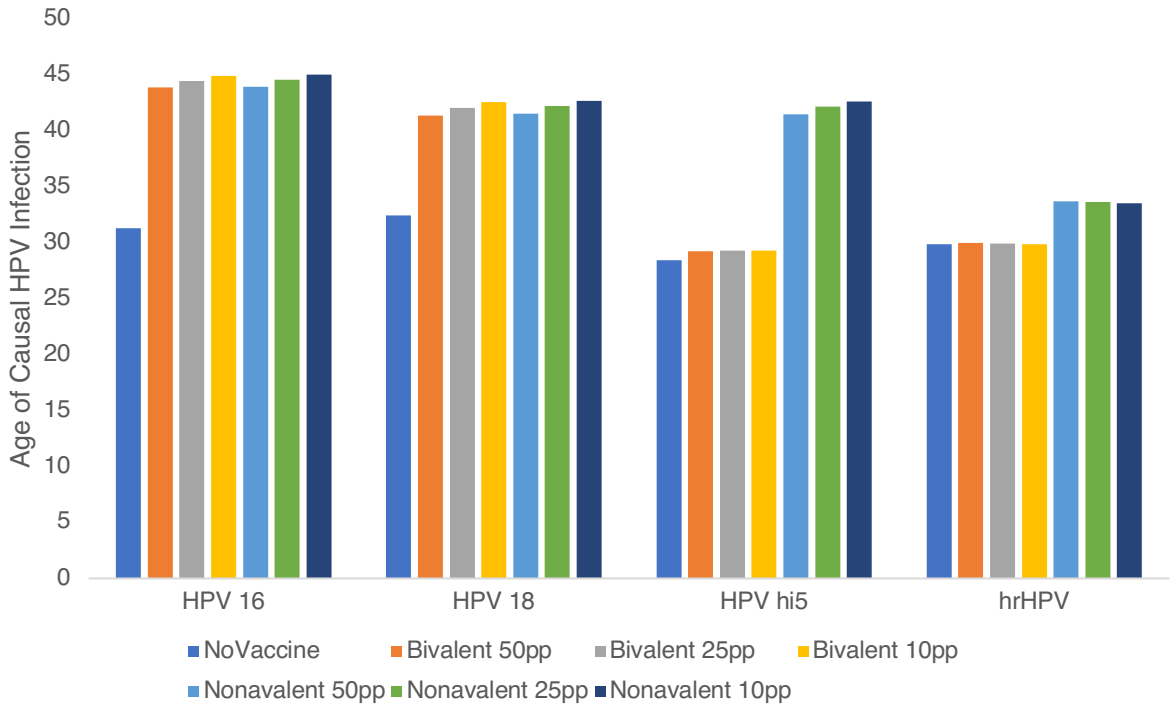
cancer incidence by 42 – 43 percent and the nonavalent vaccine yielded a 77 – 78 percent reduction, depending on rate of vaccine waning in immunocompromised women. If the vaccine was only 80 percent effective in women living with HIV, the vaccine impact on cervical cancer decreased by approximately four percentage points (Figure 2.2). On average, rate of vaccine waning in immunocompromised women did not drive large variation in vaccine impact on the population level, likely because there were very few women with a CD4 below 350 cells/$mm^3$ in the model who lived long enough to acquire cervical cancer.

**FIGURE 2.2. Cervical cancer incidence by vaccination scenario**



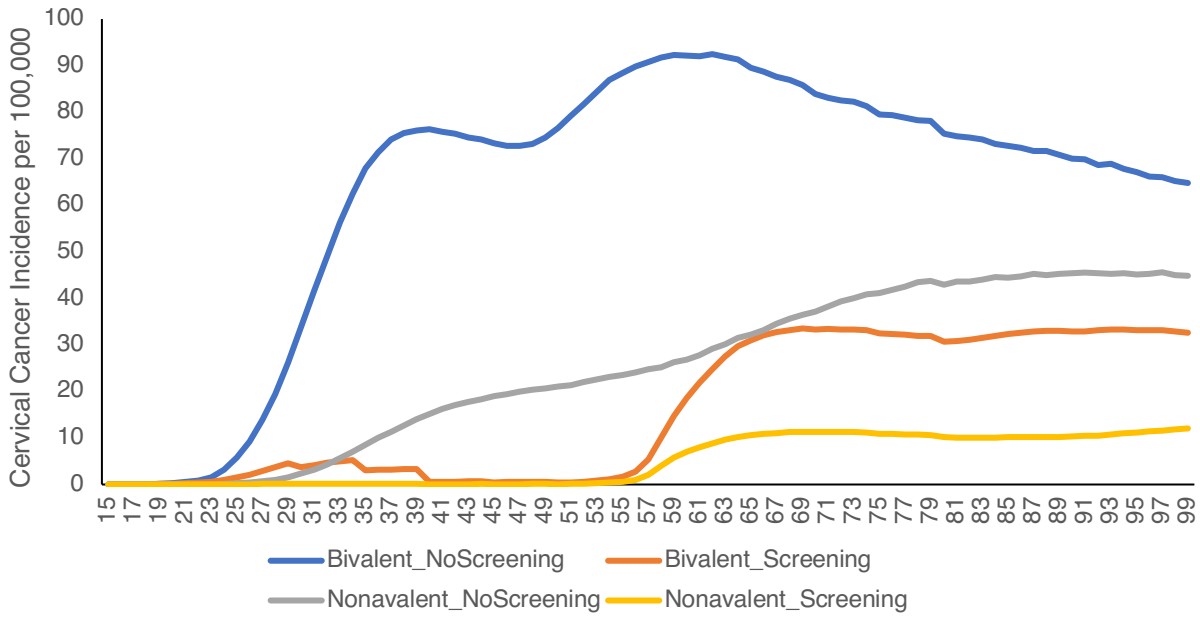
In the absence of vaccination or screening, I found the average age of causal HPV 16, 18, high-5 (31, 33, 45, 52, 58), and all high-risk infections to be 31, 32, 28 and 30 years old, respectively. Vaccination delayed the average age of causal HPV infection by 9 to 17 years, depending on the HPV genotype and rate of vaccine decline (Figure 2.3).

**FIGURE 2.3. Age of causal HPV infection by rate of vaccine waning**



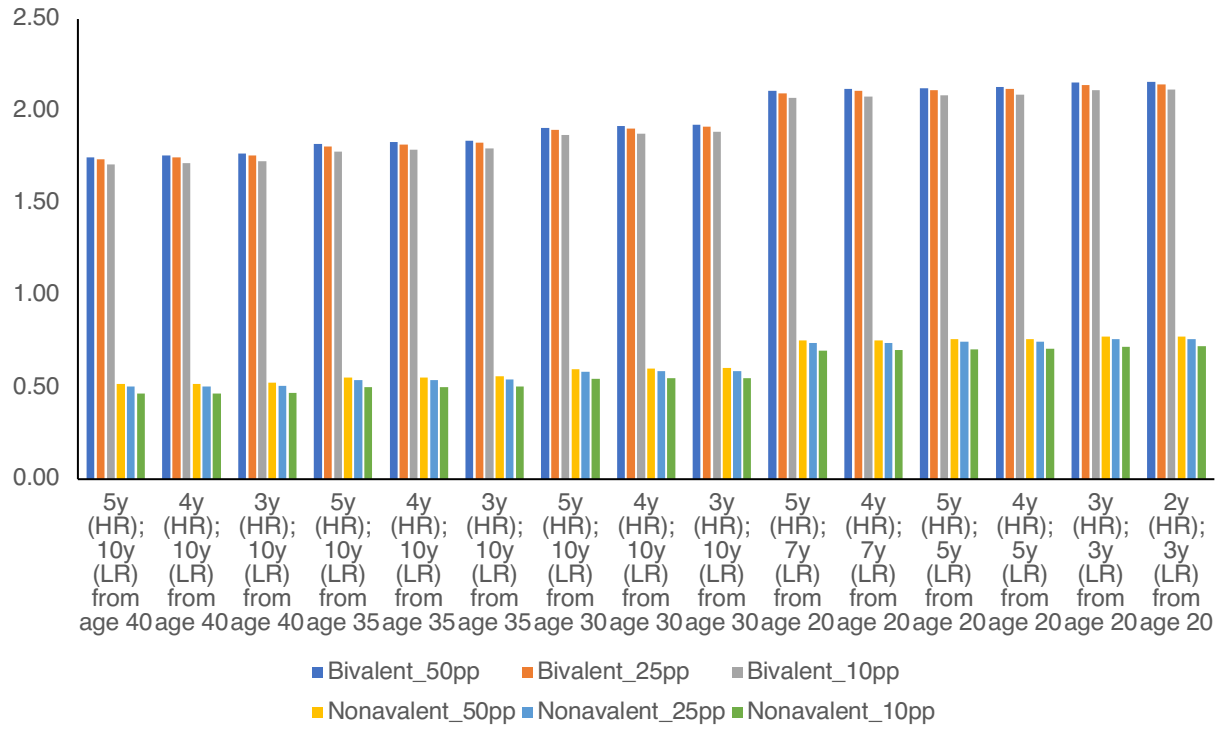

I evaluated the health impact of various cervical cancer screening strategies in vaccinated women. Cervical cancer screening yielded a 72 to 81 percent reduction in cervical cancer incidence, depending on the frequency and age of screening and vaccine type (Figure 2.4).

**FIGURE 2.4. Cervical cancer incidence by vaccine and screening**




Screening averted between 0.46 and 2.16 disability-adjusted life years (DALYs) per girl compared to no screening, depending upon rate of vaccine waning in immunocompromised women and screening age and frequency (Figure 2.5). The faster the rate of vaccine waning in immunocompromised women, the more beneficial screening was in terms of DALYs averted. Though these differences were very small and so may not drive differences in cost-effectiveness.

**FIGURE 2.5. Total DALYs averted by screening strategy in vaccinated women**




### 2.3.2. Cost-effectiveness analysis

At a WTP of $5,200 per DALY averted, it was always optimal to screen bivalent-vaccinated women *more aggressively* than current guidelines recommend, independent of rate of vaccine waning in women with CD4 < 350 cells/mm$^3$ (Table 2.3). I found that it was optimal to screen HR women every two years (instead of currently recommended 3 years) and LR women every 3 years (instead of currently recommended 10 years) starting at age 20. This strategy cost $3,100 - $4,100 per DALY averted compared to the next best alternative strategy, depending on rate of vaccine efficacy decline. These screening strategies reduced cervical cancer incidence and mortality by 77 to 78 percent relative to no screening.

**TABLE 2.3. ICERs of cervical cancer screening strategies after bivalent vaccination**

| | Rate of annual vaccine efficacy decline after CD4 falls below 350 cells/mm$^3$ | | |
|---|---|---|---|
| | 50% | 25% | 10% |
| 5y (HR); 10y (LR) from age 40 | $600 | $600 | $600 |

| | | | |
|---|---|---|---|
| 4y (HR); 10y (LR) from age 40 | $700 | $700 | $800 |
| 3y (HR); 10y (LR) from age 40 | **$1,000** | **$900** | **$1,000** |
| 3y (HR); 10y (LR) from age 30 | $2,100 | $2,100 | $2,100 |
| 4y (HR); 7y (LR) from age 20 | $2,100 | $2,100 | $2,100 |
| 4y (HR); 5y (LR) from age 20 | $2,900 | $2,800 | $2,800 |
| 3y (HR); 3y (LR) from age 20 | D | $3,100 | $3,000 |
| 2y (HR); 3y (LR) from age 20 | **$3,100** | **$4,100** | **$3,500** |

Notes: **Grey shading** indicates strategy that is optimal at a WTP of $5,200/DALY averted. **Blue shading** indicates strategy that is optimal at a WTP of $1,300/DALY averted.
Abbreviations: LR, low-risk; HR, high-risk; D, dominated.

At a WTP of $1,300 per DALY averted, it was always optimal to *reduce* screen intensity for bivalent-vaccinated women relative to current guidelines. For bivalent-vaccinated women, it was optimal to increase the age to start screening to age 40 for LR women every 10 years (resulting in 1-2 lifetime screens) and to screen HR women every 3 years, independent of rate of vaccine waning in immunocompromised women (Table 2.3). This strategy would reduce cervical cancer incidence by 73 to 74 percent relative to current guidelines and would cost between $900 and $1,000 per DALY averted relative to the next best alternative, depending on rate of vaccine waning in immunocompromised women.

### 2.3.3. Sensitivity Analysis

I explored the impact of the nonavalent vaccine, varying CIN treatment efficacy, screen modality (HPV testing alone vs. cytology alone), and vaccine efficacy in women living with HIV on policy conclusions.

The nonavalent vaccine protects against an additional 5 oncogenic genotypes, that combined with types 16 and 18 cause 75 to 80 percent of cancers. At a WTP of $5,200, It was also always optimal to screen LR nonavalent-vaccinated women more aggressively than current guidelines recommend and optimal to screen HR women equally or less frequently than current guidelines recommend, depending on rate of

vaccine waning after immune decline (Table 2.5). Irrespective of WTP and rate of vaccine decline after immune compromise, it was always optimal to screen nonavalent-vaccinated women less frequently than bivalent-vaccinated women. At a WTP of $1,300 per DALY averted, no screening algorithm considered was cost-effective.

I found that when CIN and HPV treatment was 100% effective at clearing lesions and infections, screening could be reduced even further at both ends of the WTP range (Table 2.4). For all other parameters, my results were consistent with the main analysis.

**TABLE 2.4. Optimal screening strategy based on key sensitive parameters**

| | WTP = $1,300 | | | WTP = $5,200 | | |
|---|---|---|---|---|---|---|
| | 50% | 25% | 10% | 50% | 25% | 10% |
| Baseline | 3y (HR); 10y (LR) from age 40 | | | 2y (HR); 3y (LR) from age 20 | | |
| Nonavalent | No Screening | | | 3y (HR); 3y (LR) from age 20 | | 4y (HR); 5y (LR) from age 20 |
| All Cytology Screening | | | | | | |
| All HPV Screening | | | | | | |
| 80% VE in HIV+ | 3y (HR); 10y (LR) from age 40 | | | 2y (HR); 3y (LR) from age 20 | | |
| 50% screen coverage, 80% screen compliance | | | | | | |
| Perfect CIN/HPV Treatment | 5y (HR); 10y (LR) from age 40 | | | 5y (HR); 5y (LR) from age 20 | | |

## 2.4. Discussion

In this analysis, I found that HPV vaccination had a large impact on cervical cancer incidence. In the absence of screening, vaccination reduced incidence of cervical cancer by 42 to 79 percent, depending on vaccine type and duration of vaccine waning in women whose CD4 falls below 350 cells/mm$^3$. These findings suggested that the health impact (and cost-effectiveness) of screening may vary based on vaccine type, but that rate of waning in women whose CD4 falls below 350 cells/mm$^3$ may not drive variation in cost-effectiveness. They also revealed that screening would still be important in the era of vaccination, especially for bivalent vaccinated women. A bivalent vaccine that wanes at a rate of 50 percentage points per year in immunocompromised women would only reduce cervical cancer incidence by 44 percent.

I found that at a WTP of $5,200/DALY, it would be optimal to screen vaccinated women *equally or more aggressively* than current guidelines recommend for all vaccine waning scenarios. I found it was optimal to screen bivalent-vaccinated women every 2 years if HR and every 3 years if LR, starting at age 30. This is the same algorithm that was optimal in my analysis of unvaccinated women in Chapter 1, suggesting that we should not differentiate cervical cancer screening by vaccination status.

These results were sensitive to WTP. At a WTP of $1,300, it was optimal to *reduce* screen intensity for nonavalent- and bivalent-vaccinated women relative to both current guidelines and my results for screening in unvaccinated women in Chapter 1. These results suggest that at a low WTP, it may be optimal to differentiate screening guidelines by vaccine status.

I also found that rate of vaccine waning in immunocompromised women does not drive variation in the cost-effectiveness of cervical cancer screening algorithms. The main reason is that I assumed the vaccine began to wane when a woman's CD4 fell below 350 cells/mm$^3$ and waned at a faster rate when CD4 fell further below 200 cells/mm$^3$. However, when women acquire HIV, they are assigned an initial CD4 count of 500 cells/mm$^3$, that declines in the absence of ART. However, it takes many years to fall below 350 cells/mm$^3$, and once a woman starts ART, her CD4 count rebounds. Most HIV-infected women in the model did not persist with a CD4 count below 350 and 200 cells/mm$^3$ for very long. Additionally, a woman with a CD4 count this low faced a competing risk of AIDS-related mortality, which likely occurred long before development of invasive cervical cancer. On average in South Africa[71], women take 4-5 years to be linked to care following HIV infection, and initiate care at a CD4 count of 350 cells/mm$^3$. Therefore, on average, women with HIV will never lose HPV vaccine protection, and among those who do, they will either initiate ART, rebound and their efficacy will cease to wane, or they will die before the effects of diminished immunity are realized. I may have detected a larger effect of HIV on vaccine impact in a setting with less robust HIV screening and treatment than South Africa. However, in the era of universal ART following diagnosis, this analysis suggests that women living with HIV will benefit from HPV vaccination and their HIV will not drive a need for differential screening.

South Africa introduced the bivalent vaccine to 9-year-old girls nationally in 2014, but included no special provision for cervical cancer screening in vaccinated women in its 2017 Cervical Cancer Prevention Policy Strategic Plan [cite]. Our analysis evaluated

in what circumstances it would be cost-effective to develop separate guidelines for vaccinated women, accounting for the uncertain effect of HIV on vaccine efficacy. I found that only at a WTP of $1,300 would it always be optimal to reduce screening for vaccinated women relative to unvaccinated women. At a WTP of $5,200, it depended on the vaccine type used as well as parameters such as CIN treatment efficacy.

This analysis builds upon literature on the impact of HPV vaccination on cervical cancer incidence and cervical cancer screening by explicitly accounting for the heterogeneous and highly uncertain impact of HIV and immune decline on duration of vaccine protection. To my knowledge, no other analyses of HPV vaccination consider a differential vaccine impact by HIV status, despite considerable evidence that HIV may impair vaccine durability. This analysis also motivates further exploration of the relative value of cytology versus HPV-based screening tools in an era of HPV vaccination, and the possibility of dual or co-testing.

This analysis faced some limitations resulting from choices made around model structure and data availability. I assumed HPV infection status had no impact on HIV infection or natural history, despite limited evidence that HPV may increase risk of HIV acquisition. Therefore, I did not allow HPV vaccination to impact HIV incidence. As a result, I may be underestimating the impact of vaccination. I also assumed that the vaccine efficacy waned linearly, and the slope of decline was twice as steep when a woman's CD4 count fell below 200 cells/$mm^3$ compared to below 350 cells/$mm^3$. These assumptions were not data driven, but rather explorations in the absence of clinical trial data to determine what level of efficacy is required to impact screening. With respect to

HIV and cervical cancer screening and treatment behavior, I did not account for any correlation in cervical cancer screen compliance and ART compliance – I assumed these were independent. I suspect that outcomes may have been better if I accounted for any correlation, as all of the mortality risk would be concentrated in those lost to follow up from both cervical cancer and HIV screening and care.

Due to model structure (static vs. dynamic), we did not account for herd immunity. To overcome this limitation, we restricted our analysis to vaccinated women, assuming 100 percent vaccine coverage. However, women who lose protection against the vaccine gain no secondary benefits from other vaccinated women. Therefore, I consider these results to be a conservative estimate of vaccine impact.

I also did not explicitly compare screen modalities. Future analyses should consider the impact of HPV vaccination on the relative value of HPV-based screening and value of co-testing[72].

## 2.5. Conclusion

This analysis found that depending on vaccine type and WTP, it may be optimal to reduce cervical cancer screening in vaccinated women and to differentiate screening based on vaccination status. These results were not driven by nor dependent upon differential vaccine waning in HIV-infected women. While these results describe the conditions when differential screening guidelines may be optimal based on a cost-effectiveness analysis, I do not consider the feasibility of separating guidelines for vaccinated and unvaccinated women, including accurately identifying an individual's vaccination history, which must also be factored into health policy decision-making.

# Chapter 3.

# The Impact of Structural Uncertainty in HPV Modeling: A Case Study

Abstract

**Background**
Decisions about model structure may have consequences for epidemiologic outcomes, estimates of cost-effectiveness, and policy conclusions. Yet structural uncertainty is frequently ignored. In this chapter, I explored a highly uncertain process of HPV natural history – naturally-acquired immunity and the meaning of an HPV re-detection – to determine in what circumstances the way these mechanisms are modeled influenced the ability to fit the model to target data, the assumptions made about disease natural history, and the health impact and cost-effectiveness of HPV vaccination policies.

**Methods**
I used a microsimulation model of type-specific HPV infection and cervical carcinogenesis to compare five alternative model structures that capture decisions around who acquires natural immunity and the meaning of HPV re-detection. I calibrated all five model structures to South African epidemiologic data. I compared (i) calibration fit, (ii) other model natural history outcomes such as age of causal HPV infection that were not included in calibration, and (iii) the health impact and cost-effectiveness of HPV vaccination. I compared five vaccine strategies that varied the upper age limit of vaccination, using both the bivalent and nonavalent vaccine.

**Results**
I found that all five model structures fit the calibration targets well, with only small variations in performance. The fitted models resulted in significant variation in key model parameters, such as the level and duration of natural immunity, and rates of progression between HPV infection, lesion and invasive cervical cancer. Allowing for infections to become latent and re-activate impacted the age distribution of causal HPV infections and the subsequent health impact and cost-effectiveness of vaccination strategies that vary the end age of vaccination. Model structures that do not allow for latency predicted a five-year older average age of causal HPV infection compared to models that accounted for latency. Structural decisions regarding who acquires natural immunity did not produce much difference in other model natural history outcomes nor cost-effectiveness of vaccination policy.

**Conclusion**
These results imply that the specific structural uncertainties I explored are meaningful for the way we have, and potentially should, model HPV. Specifically, models that ignore the possibility of HPV latency and re-activation may over-estimate the benefit of vaccinating up to older ages. They also demonstrate that decisions regarding who acquires natural immunity and at what level are less influential, so long as natural immunity exists in the model. While this analysis was specific to HPV modeling decisions, it serves as an example of how structural decisions matter for modeling in general.

## 3.1. Background

Decision analytic models are increasingly used to inform health care resource allocation and decision-making. The growing profile of decision analysis in policymaking begets a need for robust methods for appropriately characterizing uncertainty. There are a number of sources of uncertainty, which have been generally classified and described as parameter, methodological, and structural[73]. Parameter uncertainty reflects uncertainty in the true value of a given parameter. Methodological uncertainty can be defined uncertainty that leads to differences in the choice of analytic methods, such as the perspective of the evaluation.

This analysis focuses on structural uncertainty, which includes uncertainties that lead to differences in the types of simplifications and scientific judgments that must be made when developing and interpreting a model. In the context of disease modeling, this includes uncertainty in our scientific understanding of a disease process, as it may be unobserved or unobservable. Even for the most well-understood disease mechanisms, there are alternative and plausible ways to describe those mechanisms. There are also trade-offs between capturing process complexity and managing computational burden; additional complexity is costly, and decision analysts and modelers must decide how much complexity is required and what can be simplified. Additionally, models are only as good as the data that we input, and we may make structural choices based on data availability, as the absence of data adds parameter uncertainty to the model, which we wish to minimize. In fact, structural sensitivity and uncertainty analyses can be used to quantify the value of generating new data.

The 2012 ISPOR (a professional society for health economics and outcomes research) report on good modeling practice makes specific recommendations about how to characterize and report parameter uncertainty, including use of probabilistic sensitivity analysis, a technique used to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs[74]. Little attention, however, has been paid to structural uncertainty, as it is more difficult to sample from the space of plausible model structures than to sample from the parameter space. Despite this, structural uncertainty may have greater impact on model results and conclusions than parameter uncertainty[73,75].

Decisions about model structure will likely have consequences for estimates of epidemiologic outcomes, estimates of cost-effectiveness, and policy conclusions. While it is common to acknowledge potential limitations of model structure and identify assumptions that have been made, there is no clear guidance on methods to explicitly incorporate structural uncertainties into policy analyses. Some approaches that have been considered include model averaging, where a set of plausible models are weighted by some measure of model adequacy; as well as creating a global model that includes as many relevant features as is computationally feasible and expresses structural uncertainties as parameters[76]. Both of these approaches are difficult and imply that we have built a set of models or features and are able to weight or parameterize each accordingly. Modelers are often guided by the principle of making a model only as complex as necessary, based on the premise that adding detail may propagate uncertainty and lead to overfitting, where model results cannot be

generalized outside of the exact model setting. However, there is little consensus on what qualifies as necessary and what a modeler should do in a specific modeling situation.

There has been a growing trend of case studies exploring the impact of structural assumptions on model prediction and policy choices[77,78]. One analysis used the concepts of inference robustness assessment[79] to isolate the effects of structural choices in a model of HIV vaccination[80]. Another compared twelve mathematical models of HIV to isolate the effects of model structure, parameters and assumptions about the underlying epidemic on estimates of intervention impact[81]. A recent analysis explored the impact of structural assumptions about viral latency and reactivation on human papillomavirus (HPV) vaccine impact in South Africa[82]. Consortia of modeling groups like CISNET (the Cancer Intervention and Surveillance Modeling Network) have conducted comparative modeling, using common inputs and common outputs[83,84]. While these analyses are informative, efforts to expand the volume of work is hampered by the high costs and low incentives for undertaking such model comparisons.

This analysis contributes towards an understanding of the impact of structural uncertainty in HPV modeling. I explored a highly uncertain process of HPV natural history – naturally-acquired immunity and the meaning of an HPV re-detection – to determine in what circumstances the way these mechanisms are modeled influenced the ability to fit the model to target data, the assumptions made about disease natural history, and the health impact and cost-effectiveness of HPV vaccination policies.

### 3.1.1. HPV Natural History

HPV is a sexually transmitted infection that can cause high-grade pre-cancerous cervical lesions (called cervical intraepithelial neoplasia, CIN, grade 2 or grade 3) that can progress to invasive cervical cancer. A large share of HPV infections, especially at a young age, are transient. However, while much is known about the natural history of HPV, there is a high degree of uncertainty around the biological process that occurs after HPV is no longer detectable by available tests, and if this has implications for risk of future infection.

Neutralizing antibodies generated during and after HPV infection are thought to be a critical mechanism for preventing, controlling, and eliminating HPV infection[85]. Serological assays, which measure antibodies against HPV, are able to identify individuals who mounted an immune response to a previous genotype-specific HPV infection and may therefore be protected against subsequent HPV infection. Studies have shown that women with the highest seropositive tertile of HPV type-specific antibodies have a significantly reduced risk of subsequent infection with the same genotype[86]. These studies suggest that some women may not mount an immune response that is sufficient to generate protection against future infection. Some mount no immune response at all – only approximately half of women in whom HPV DNA is detected generate antibodies[86]. Additionally, natural immunity may wane over time, leading a woman's risk of re-infection to increase.

There is also uncertainty around the meaning of a re-detected HPV infection of the same type. As assumed in many existing models, it could mean a newly-acquired

HPV infection, caused by a new sexual exposure. In contrast, a re-detected HPV infection could also mean re-activation of a latent infection that was acquired previously. Empirical data suggests that among older women with a newly re-detected HPV infection, some had no recent sexual contact that would have led to a new HPV infection, providing evidence for some reactivation of a latent infection[87,88].

Despite these uncertain aspects of HPV natural history, analyses typically do not account for and quantify the impact of these structural assumptions. Based on a systematic review of modeling approaches to evaluate the cost-effectiveness of HPV vaccination, out of thirty-four models selected, none assumed that re-detection of a prior HPV infection could have been the result of reactivated latent infection.[89] Models varied in the their assumptions regarding the acquisition and duration of natural immunity.

## **3.2.** Methods

In this analysis, I examined structural assumptions around the development of natural immunity and plausible interpretation of re-detection of an HPV infection.

### 3.3.1. Who gets immunity?

The first source of structural uncertainty is around who develops natural immunity, which I modeled in three ways. In the first model structure, I assumed that no one develops natural immunity, meaning that all women are fully susceptible to future infection following HPV clearance. In all other model structures, I assumed women develop some form of immunity following clearance of an HPV infection. In the second model structure, all women who clear an HPV infection were assumed to acquire the same level of natural immunity, meaning that they all face the same future risk reduction

of type-specific HPV infection. This structure assumes women are homogenous in their immune response following HPV clearance. In the third model structure, I assumed that a fraction of women acquire full natural immunity against future type-specific infection. Women who do not acquire full immunity have no immunity. This model structure allows for heterogeneity among women in their response to HPV.

### 3.3.2. Meaning of a re-detected HPV infection

The second source of uncertainty is around the meaning of a re-detected HPV infection of the same type as a prior infection, which I modeled in two possible ways. In the first, when an infection becomes no longer detectable, the woman is assumed to have cleared the infection from her system. Therefore, a new infection with the same type could only have occurred through a new sexual exposure. In the second model structure, when an infection becomes no longer detectable, it is assumed to be latent in a woman's system but below the limits of detection by conventional testing. In this case, a re-detected infection of the same type as a prior infection implies re-activation of a latent infection.

This assumption impacts the duration of HPV infection (referred to as the HPV timer), which drives the probability of progression to a high-grade cervical lesion. In the first model structure, the infection timer starts when the new infection occurs, meaning that it is agnostic to any prior infections. In the second model structure, the duration of prior infection is counted in the HPV timer. To illustrate the difference, imagine a woman acquired an HPV 16 infection at age 15. It cleared spontaneously in a year, as most infections do at that age. Then she acquired another HPV 16 infection at age 26. In the

first model structure, her risk of clearance, persistence and progression would be based on a duration with HPV 16 of less than one year (i.e. she faced the same risk at 26 she faced at 15). In the second model structure, I assumed that her re-activated infection at age 26 was dormant in her tissue for 10 years. When the infection re-activated, I counted the duration of the prior active infection (but not the dormancy period), such that a woman would face a higher probability of infection persistence and progression with a re-activated infection.

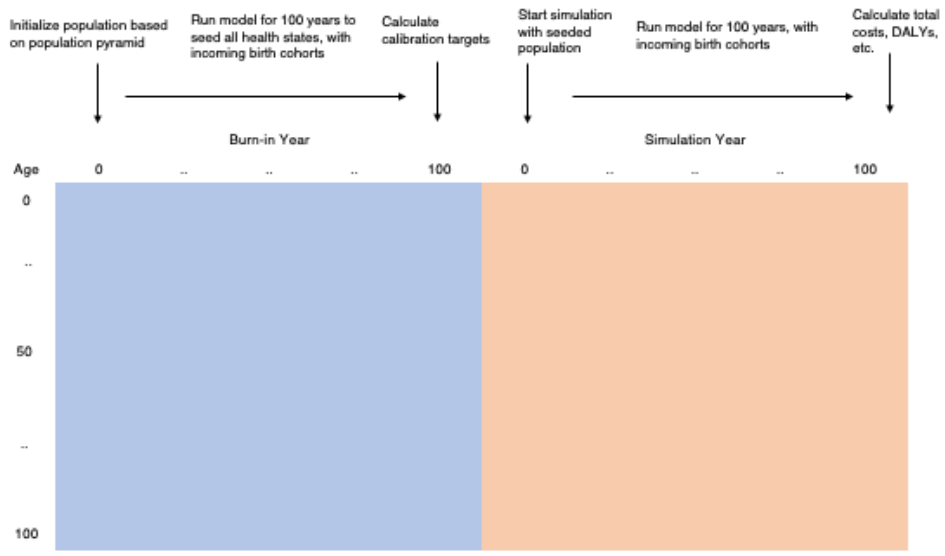
### 3.3.3. Generic Model Overview

I adapted the microsimulation model of type-specific HPV infection and cervical cancer I developed and described in Chapter 2. In summary, women face a risk of HPV infection with types 16, 18, 31, 33, 45, 52, 58, other high-risk and low-risk. HPV infection can clear, persist, or progress to high-grade cervical lesion, dependent upon HPV genotype and duration of infection. High-grade lesions can also clear, persist, or progress to invasive cervical cancer, dependent upon the associated HPV genotype and lesion duration. I assumed women could have multiple HPV infections and CINs simultaneously, and that an HPV infection could only cause a single lesion. Once a lesion progressed to invasive cervical cancer, I stopped HPV and lesion natural history. A detailed description of the model can be found in chapters 1 and 2.

I simulated a total of 5 million women who are distributed across all ages according to the population pyramid, starting in the first year of vaccination for 100 years, with incoming birth cohorts. In order to generate a representative population in year 2014, I ran an open population model for 100 years in the absence of screening or

vaccination. At the end of the 100-year burn-in period, I calculated calibration targets. For the policy analyses, I took the simulated population in year 100 as the starting population and simulated these women for an additional 100 years, with annual incoming birth cohorts. See Figure 3.1 for a schematic of the simulation process.

**Figure 3.1. Schematic of simulation process**




In contrast to the model in chapters 1 and 2, I did not model HIV natural history. I took this element out of the modeling framework to minimize structural and parameter uncertainty and to better isolate the structural uncertainty I wanted to interrogate.

I specified five unique model structures, calibrated the same parameters in each model to the same data using the same procedure (Table 3.1). I compared the ability of each model structure to fit the target data. Then, I quantified differences in underlying disease natural history across the five unique model structures. I compared age of causal HPV infection, dwell-time between causal HPV infection and progression to CIN and to cancer. I evaluated the health impact and cost-effectiveness of HPV vaccination

policy that extends the age of vaccination to women of older ages using all five models to assess whether model structure impacted policy conclusions.

**TABLE 3.1. Summary of model structures**

| Model | Who gets immunity? | Duration of HPV infection |
|---|---|---|
| Model 1 | No women get immunity | Infection timer starts at re-infection |
| Model 2 | All women get the same degree of immunity | Infection timer starts at re-infection |
| Model 3 | All women get the same degree of immunity | Infection timer counts duration of prior infection |
| Model 4 | The fraction of women who get complete immunity, all else get none | Infection timer starts at re-infection |
| Model 5 | The fraction of women who get complete immunity, all else get none | Infection timer counts duration of prior infection |

### 3.3.4. Calibration

For all five model structures, I calibrated the same set of uncertain parameters, using the same calibration procedure, to the same calibration target data, with the exception of the no immunity model, for which I fixed immune degree to zero. See Chapter 1 for technical details of calibration procedure. In summary, I used simulated annealing to iteratively search the parameter space and weighted-least squares to score the model output.

Calibration parameters included immune degree for HPV 16 and for all other HPV types (assumed it was the same from all other genotypes), as well as duration- or age- and genotype-specific relative risks of HPV incidence, clearance and progression and CIN progression and regression. The relative risks were applied to baseline incidence, clearance, progression and regression probabilities[69]. Calibration targets included age-specific HPV prevalence[12], type- specific HPV prevalence[90], HPV type distribution in CIN2 and CIN3[12] and cancer[91], and age-specific cancer incidence[92].

### 3.3.5. Vaccination Strategies

I compared the health impact and cost-effectiveness of vaccine strategies that varied the age of vaccination by model structure. I considered bivalent and nonavalent vaccination, with 100 percent coverage, and compared no vaccination to five strategies that varied the upper age limit of vaccination from 12 to 45 years old (Table 3.3).

**TABLE 3.3. Vaccination Strategies**

| Parameter | Value |
|---|---|
| Vaccine Start Age | 9 |
| Vaccine End Age | -12, -26, -35, -45 |
| Vaccine Type | Bivalent[a], Nonvalent[b] |
| Vaccine Efficacy (% reduction in risk of future infection) | |
| Women with no prior infection | 100% |
| Women with latent infection | 0% |
| Vaccine Duration | Lifelong |

[a] Bivalent vaccine protected against types 16/18.
[b] Nonavalent vaccine protected against types 16/18/31/33/45/52/58.

I assumed the vaccine was 100 percent protective against targeted genotypes, with no cross-protection against untargeted genotypes. I assumed that the vaccine offered no therapeutic benefit for active infection and no efficacy against re-infection for women with a latent infection, suggesting vaccination may not protect against re-activated HPV.

## 3.3. Results

### *3.3.1. Calibration Results*

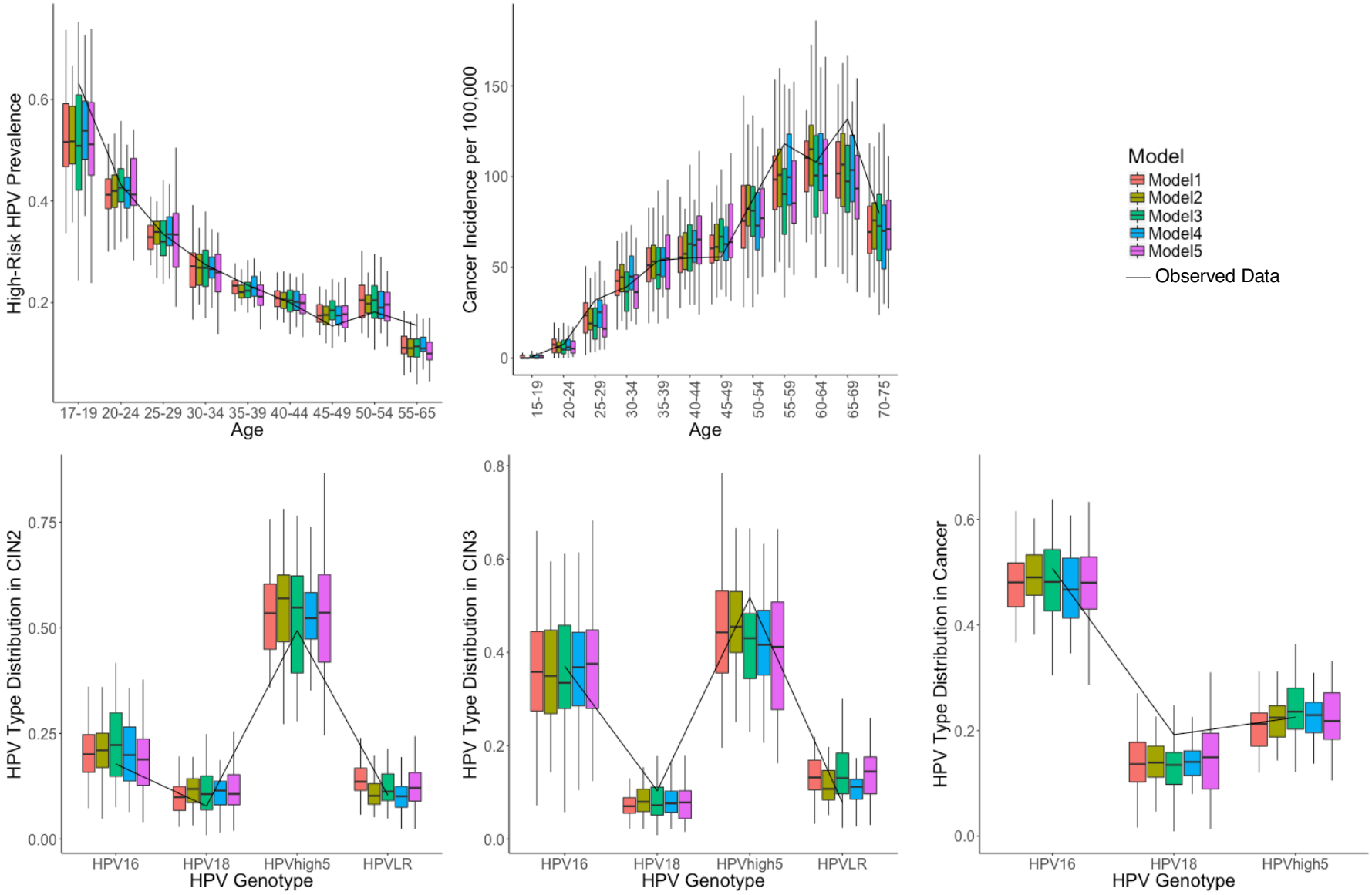
All five model structures were able to fit the target calibration data, meaning that I was able to find parameter sets that generated model output that closely resembled observed data. I found that Model 2 was able to achieve the “best fit” and Models 3 and 5 did not perform as well, as measured by both minimum goodness of fit and difference between the minimum and maximum goodness of fit across the top 50 best-fitting parameter sets (Table 3.2).

**TABLE 3.2. Summary of Calibration Performance by Model Structure**

| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|---|---|---|---|---|---|
| Minimum GOF | 55.3744 | 48.1943 | 85.3272 | 52.5975 | 88.5265 |
| Max - Min | 34.6058 | 33.572 | 44.6738 | 27.2384 | 42.0415 |

Plotted below are boxplots generated from the top 50-best fitting parameter sets of model output for each calibration target and model structure alongside the observed data (Figure 3.2). I found that for age-specific cervical cancer incidence calibration targets, models 3 and 5 overestimated incidence in 40 to 50-year-old women, and underestimated incidence in 50 to 70-year-old women (Figure 3.2). For all other targets, the models generated a similar fit to the observed data.

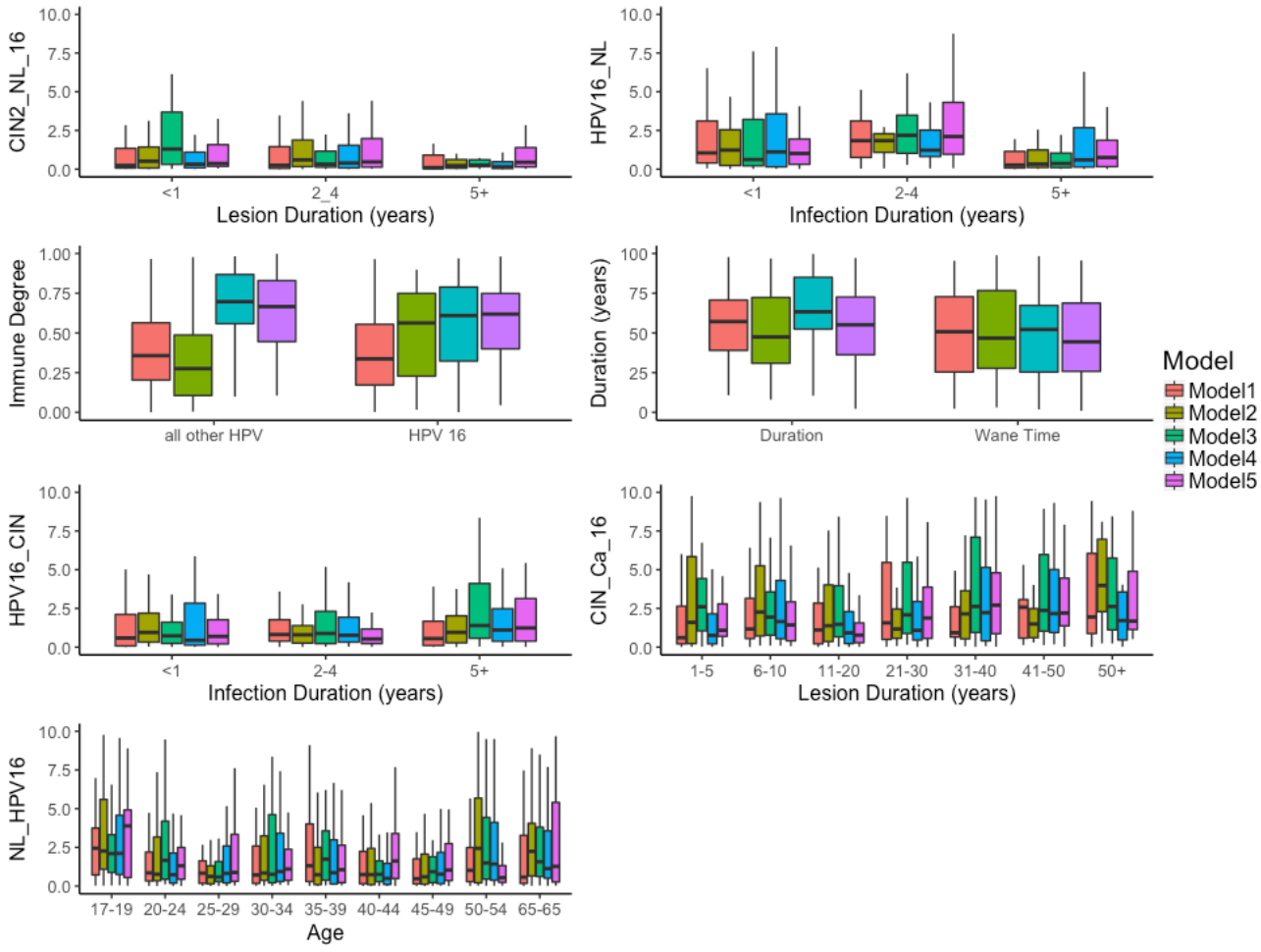
**FIGURE 3.2. Comparison of Calibration Fit Across Model Structures**



### 3.3.2. Calibration Parameters

Given the relatively good fit of the calibration targets for all five model structures, I hypothesized that either the calibration targets were statistically independent of the structural decisions (for fixed values of the model parameters), or there were compensatory changes in other parameters to allow the model to fit. To explore this, I compared the calibrated parameter values across model structures. Through visual inspection, I could see some differences between model structures in certain model parameters, including notably degree/fraction of immunity (Figure 3.3).

**FIGURE 3.3. Selected Calibration Parameter Values by Model Structure**



### 3.3.3. Other Model Natural History Outcomes

I first evaluated the impact of model structure on the underlying disease natural history in the absence of screening or vaccination. I quantified and compared the implied distribution of age of HPV causal infection for HPV types 16, 18 and 31/33/45/52/58.

For all HPV genotypes, model structure impacted the age of causal HPV infection; the effect was most pronounced for HPV 16 and 18 infections, which are targeted by the bivalent vaccine currently being used in South Africa (Figures 3.4 and 3.5). Additionally, most of the variation was driven by the meaning of a re-infection, rather than by who gets natural immunity. For HPV 31/33/45/52/58, which represent the additional five oncogenic genotypes targeted by the nonavalent vaccine, there was almost no difference in the age of causal HPV infection between the model structures (Figure 3.6).

For HPV 16, the genotype attributed to the largest share of cervical cancers, there was a six year age difference across the five model structures in the age by which 50 percent of causal infections occurred and that age difference doubled by the age at which 75 percent of causal infections occurred (Figure 3.4). Both model structures that assume that re-infections are latent yielded the youngest age by which 50 percent of causal infections occurred. The model structure that assumed no women acquired immunity after clearing an infection yielded the oldest age of causal HPV 16 infection.

**FIGURE 3.4. Distribution of Age of Causal HPV 16 Infection**

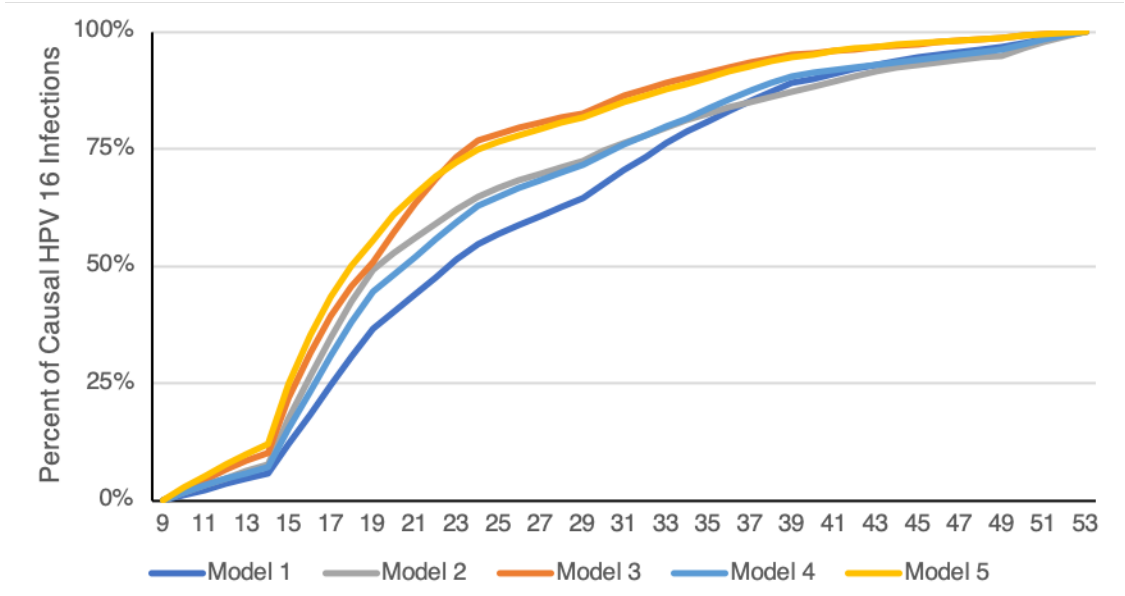



**FIGURE 3.5. Distribution of Age of Causal HPV 18 Infection**

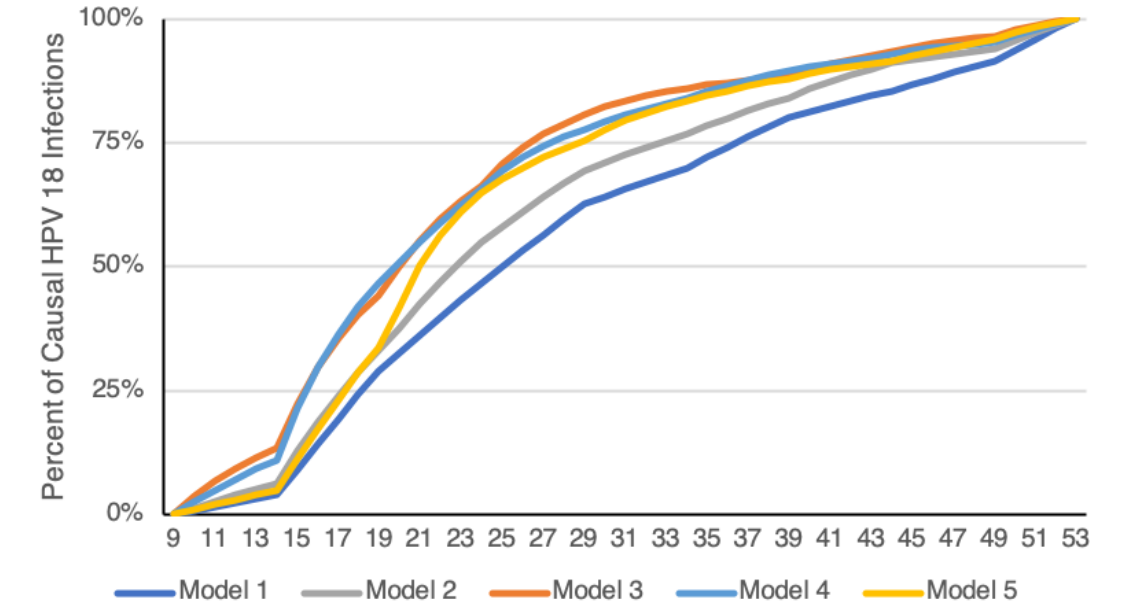
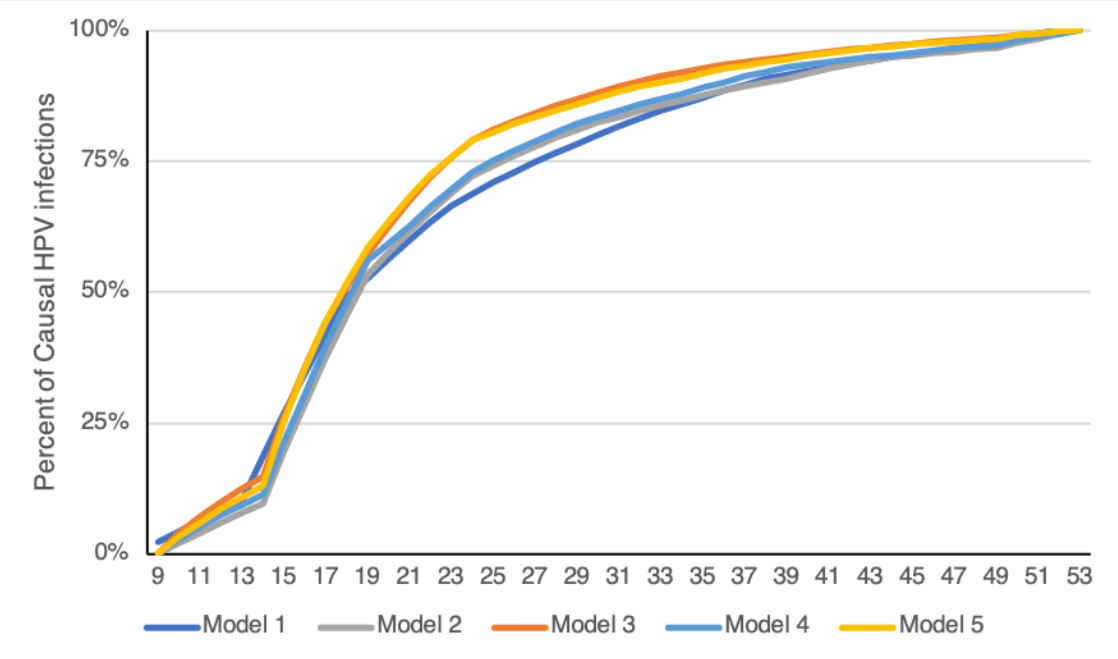



**FIGURE 3.6. Distribution of Age of Causal HPV 31/33/45/52/58 Infections**

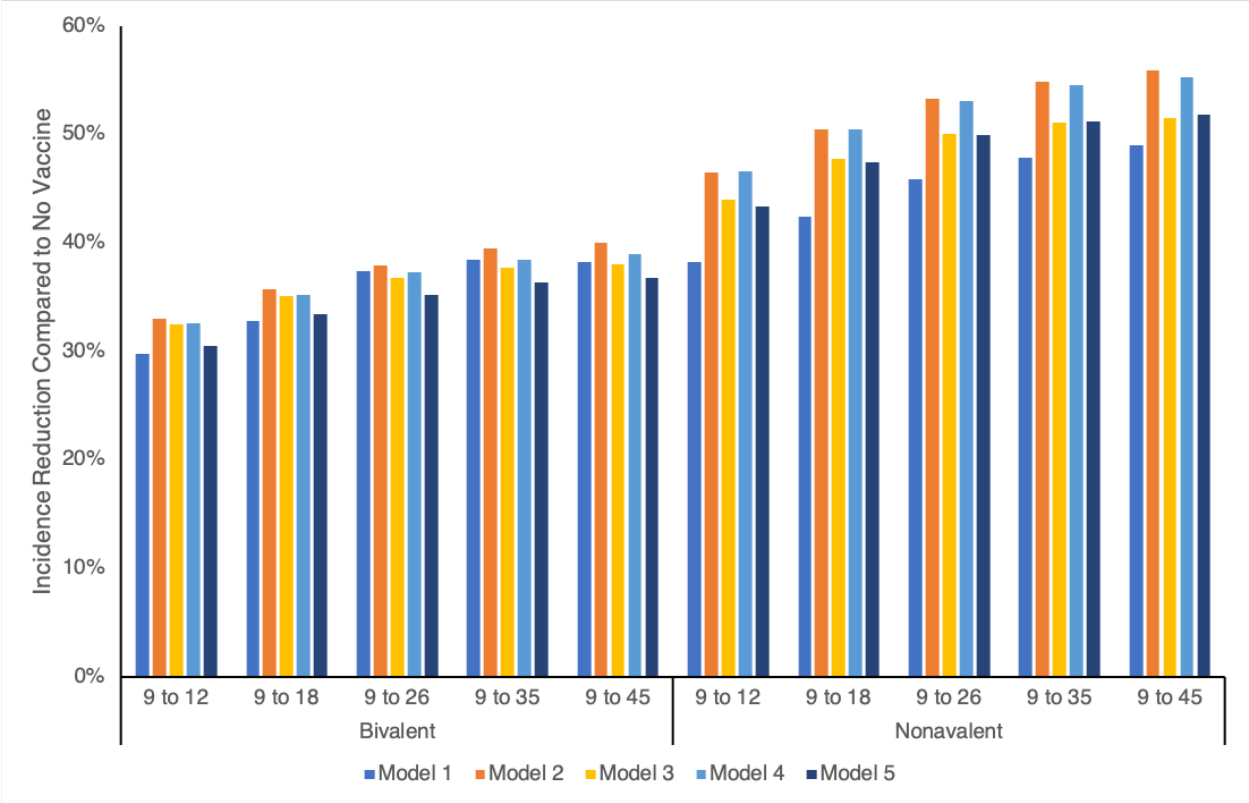



### 3.3.4. Policy Outcomes

I found significant differences by model structure in the health impact of vaccine strategies that varied the end age of vaccination, driven by differences in the distribution of age of causal HPV infection. For the bivalent vaccine, which protects against HPV genotypes 16 and 18, Models 1 had the smallest reductions in cervical cancer incidence at vaccine end ages below 26 and Model 2 had the largest cervical cancer incidence reductions at all vaccine end ages (Figure 3.7).

For models 3 and 5, the slope of incidence reduction relative to vaccine end age was flatter than for the other models, indicating that latency models may predict diminishing marginal gains to vaccinating at older ages.

**FIGURE 3.7. Cervical cancer incidence reduction by model structure and age of vaccination**




I found that bivalent vaccination up to age 45 was always cost-effective, even at the lower-bound empirical estimate of WTP in South Africa ($1,300 per DALY averted)[34] (Table 3.3). Model structure had a small impact on estimates of cost-effectiveness (ICERs ranged from $108 - $328), but not enough to impact policy conclusions.

**Table 3.3. ICERs for Bivalent Vaccine Strategies**

| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|---|---|---|---|---|---|
| 9 to 12 | Dominated | Dominated | Dominated | Dominated | Dominated |
| 9 to 18 | $19 | $16 | $14 | $15 | $19 |
| 9 to 26 | $22 | $28 | $27 | $24 | $36 |
| 9 to 35 | $47 | $43 | $80 | $47 | $85 |
| 9 to 45 | **$106** | **$130** | **$328** | **$152** | **$222** |

Notes: **Grey shading** indicates strategy that is optimal at a WTP of $5,200/DALY averted. **Blue shading** indicates strategy that is optimal at a WTP of $1,300/DALY averted.

For the nonavalent vaccine, at the lower-bound empirical estimate of WTP in South Africa ($1,300 per DALY averted)[34], vaccinating up to age 45 was cost-effective

only for models 1 and 4. For all other models, it was cost-effective to vaccinate women up to age 35. At the upper-bound empirical estimate of WTP in South Africa ($5,200 per DALY averted)[34], vaccinating up to age 45 was cost-effective for all model structures (Table 3.4).

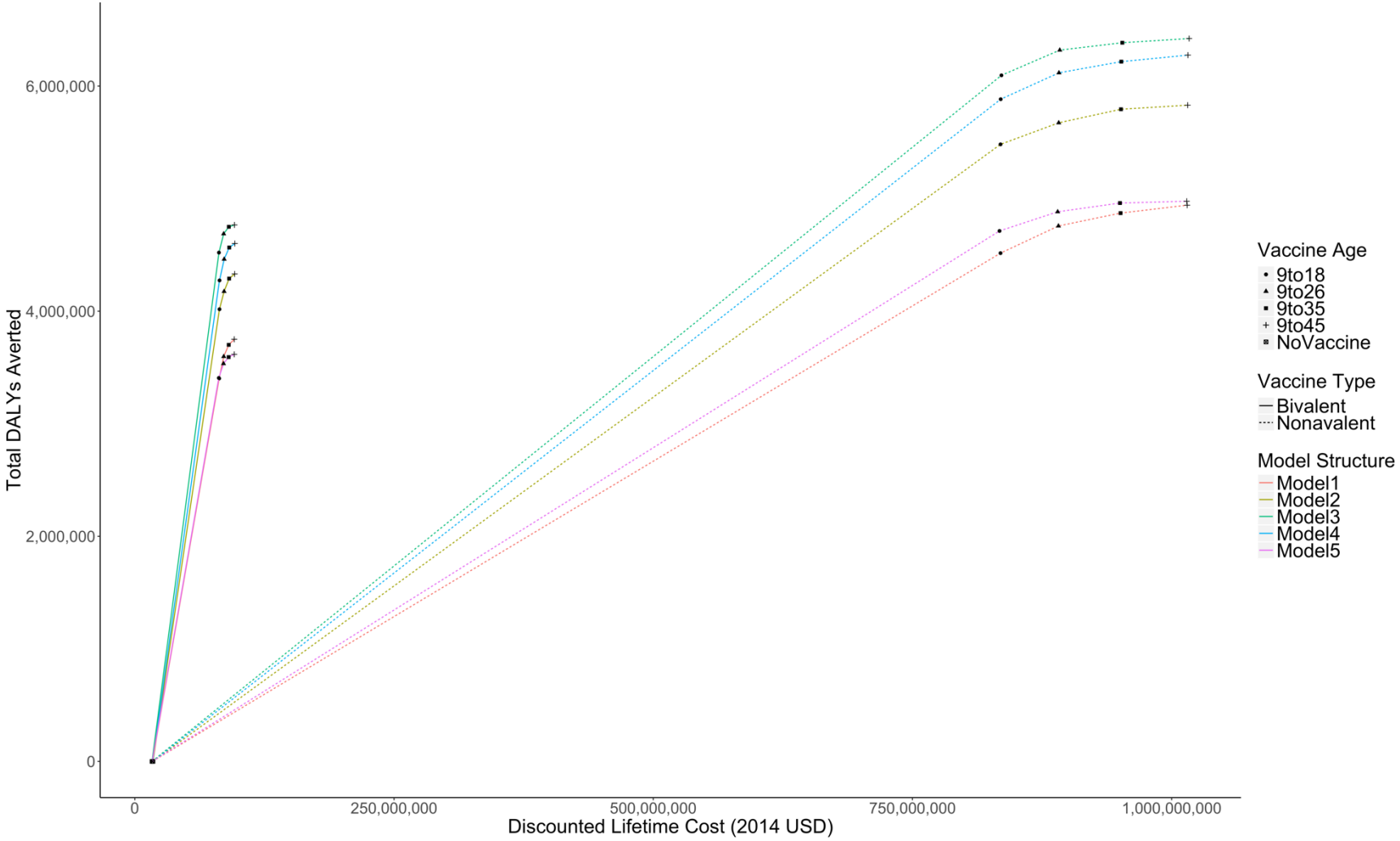
**Table 3.4. ICERs for Nonavalent Vaccine Strategies**

| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|---|---|---|---|---|---|
| 9 to 12 | Dominated | Dominated | Dominated | Dominated | Dominated |
| 9 to 18 | $181 | $149 | $134 | $139 | $173 |
| 9 to 26 | $232 | $293 | $251 | $240 | $329 |
| 9 to 35 | $524 | **$498** | **$918** | $606 | **$774** |
| 9 to 45 | **$911** | **$1,771** | **$1,728** | **$1,107** | **$3,994** |

Notes: **Grey shading** indicates strategy that is optimal at a WTP of $5,200/DALY averted. **Blue shading** indicates strategy that is optimal at a WTP of $1,300/DALY averted.

Consistent with expectations, vaccinating past age 26 was more expensive per DALY averted for Models 3 and 5, relative to other model structures, for both the bivalent and nonavalent vaccination. I found that vaccination women from 9 to 12 years old was dominated by vaccinating up to age 18 for all model structures and for both the nonavalent and bivalent vaccine. I also found that vaccinating resulted in the most DALYs averted for Model 3 at every age and for both vaccine types relative to all other model structures (Figure 3.8).

**FIGURE 3.8. Efficiency Frontier for Vaccine Strategy by Model Structure**



## 3.4. Discussion

Appropriately characterizing uncertainty is critical in cost-effectiveness analysis. While much attention has been paid to parameter uncertainty, other and potentially equally or more important sources of uncertainty include the decisions we make when constructing a model. In this analysis, I explored the impact of structural uncertainties on calibration performance, non-calibrated model natural history parameters, and policy conclusions, within the context of HPV and cervical cancer modeling. I looked at decisions regarding the acquisition of natural immunity and the meaning of a re-detected HPV infection. I specified five distinct models that varied along these dimensions.

I found that all five model structures were able to fit the data used for model calibration, with minimal differences in performance. I determined that there was significant parameter variation in order to fit to the observed data, which yielded differences in non-calibrated model natural history outcomes, such as age of causal HPV 16 and 18 infection. I explored whether strategies that varied the upper age limit of vaccination were impacted by model structure, and found that vaccinating past age 26 was more expensive per DALY averted for the model structures that interpreted a re-detected HPV infection as a re-activated latent infection.

These results imply that the specific structural uncertainties I explored are meaningful for the way we have, and potentially should, model HPV. Specifically, models that ignore the possibility of HPV latency and re-activation may over-estimate the benefit of vaccinating up to older ages. They also demonstrate that decisions

regarding who acquires natural immunity and at what level are less influential, so long as natural immunity exists in the model.

This analysis faced several limitations. First, in order to minimize the number of model structures, we assumed that the dimensions of uncertainty were mutually exclusive, meaning that either a re-detected infection resulted from a latent infection or a new infection, but not both (and similarly for who acquires natural immunity). We expect reality to fall somewhere in between – some women clear infection, and some women have latent infections. Moreover, women may sometimes clear infection and other times have latent infections – meaning that there may be variation both within and between individuals. While we did not explore this possibility, in a future analysis we could parameterize the model structures themselves to allow for and explore the impact of combinations of model structures.

Additionally, the model is static, meaning that agents in the model do not interact with each other. Therefore, the effects vaccination and natural immunity are only realized at the individual level and herd immunity cannot be captured. This also means we cannot distinguish between a new infection that resulted from a sexual contact and one that resulted from a re-activated latent infection.

We also were not able to conduct out of sample model prediction or validation, as we used all observed data we had access to for calibration. Out of sample prediction would have been a secondary measure of model fit, by comparing model output to observed data that were not used in the fitting process.

## 3.5. Conclusion

In this analysis, I used HPV as a case study to explore the impact of structural uncertainty on model fit, natural history outcomes, and cost-effectiveness results. This analysis suggested that the specific structural uncertainties I explored are meaningful for the way we have, and potentially should, model HPV. While this analysis was specific to HPV modeling decisions, it serves as an example of how structural decisions matter for modeling in general.

# Supplemental Material

## Chapter 1 Appendix

### Calibration Parameter Priors

HPV Incidence Risk Ratio in HIV-Uninfected Women[a]

| HPV Type | Prior Mean | Lower Bound | Upper Bound | Source |
|---|---|---|---|---|
| **Non-Oncogenic** | 0.272 | 0 | 1 | Based on distribution of HPV types in prevalent infection[12] |
| **Oncogenic** | 0.728 | 0 | 1 | |

Abbreviations: HPV, human papillomavirus
[a]Annual probability of new type-specific HPV infection applied to HPV prevalence inputs.

HPV Clearance[a] in HIV-Uninfected Women

| Infection Duration (years) | Prior Mean | Lower Bound | Upper Bound | Source |
|---|---|---|---|---|
| <1 | 0.55 | 0 | 1 | Pooled genotypes-specific monthly- risk of clearance and converted to annual probabilities[13,37]. |
| 1-2 | 0.44 | 0 | 1 | |
| 2-5 | 0.35 | 0 | 1 | |
| 5+ | 0.216 | 0 | 1 | |

Abbreviations: HPV, human papillomavirus
[a]Annual probability of HPV clearance.

HPV Progression[a] to CIN2 in HIV-Uninfected Women

| Infection Duration (years) | Prior Mean | Lower Bound | Upper Bound | Source |
|---|---|---|---|---|
| **Oncogenic** | | | | |
| <1 | 0.006 | 0 | 0.1 | Pooled genotypes-specific monthly- risk of progression and converted to annual probabilities[13,37]. |
| 1-2 | 0.015 | 0 | 0.2 | |
| 2-5 | 0.05 | 0 | 0.3 | |
| 5+ | 0.08 | 0 | 0.4 | |
| **Risk Ratio for non-oncogenic types** | 0.1 | 0 | 1 | Author assumption |

Abbreviations: HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia

[a]Annual probability of progression from HPV to CIN2. Assume HPV progresses to CIN3 at a 20% higher rate compared to CIN2.

CIN2 Clearance[a] in HIV-Uninfected Women

| Lesion Duration (years) | Prior Mean | Lower Bound | Upper Bound | Source |
|---|---|---|---|---|
| 1-5 | 0.459 | 0 | 0.8 | Pooled genotype-specific monthly-risk of clearance and converted to annual probabilities[13,37]. |
| 6-10 | 0.387 | 0 | 0.7 | |
| 11-20 | 0.306 | 0 | 0.6 | |
| 21-29 | 0.024 | 0 | 0.5 | |
| 30-39 | 0.012 | 0 | 0.3 | |
| 40-49 | 0.006 | 0 | 0.2 | |
| 50+ | 0.006 | 0 | 0.1 | |
| **Risk Ratio for non-oncogenic** | 1.1 | 1 | 2 | Author assumption |
| **Regress to NL**[b] | 0.5 | 0 | 1 | |

Abbreviations: HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; NL, no lesion

[a]Annual probability of CIN2 clearance. Assume constant by age and duration with infection. Assume CIN3s regress at 50% of CIN2 regression probabilities. [b]Share of regressed CIN2+ lesions that clear HPV as well (all others persist with HPV).

**CIN3 Progression[a] to Invasive Cervical Cancer in HIV-Uninfected Women**

| Lesion Duration (years) | Prior Mean | Lower Bound | Upper Bound | Source |
|---|---|---|---|---|
| **1-5** | 0 | 0 | 0.1 | Pooled genotype-specific monthly- risk of clearance and converted to annual probabilities[13,37] |
| **6-10** | 0.0016 | 0 | 0.2 | |
| **11-20** | 0.0018 | 0 | 0.3 | |
| **21-29** | 0.042 | 0 | 0.4 | |
| **30-39** | 0.118 | 0 | 0.5 | |
| **40-49** | 0.44 | 0 | 0.8 | |
| **50+** | 0.53 | 0 | 0.8 | |

[a]Annual probability of CIN3 progression to invasive cervical cancer. We assume CIN2s are less cancerous and therefore progress to cancer at 20% of the calibrated CIN3 progression rates.

Relative Risks in HIV-Infected Women[a]

| | Prior Mean | Lower Bound | Upper Bound | Source |
|---|---|---|---|---|
| NL to HPV | 2.6 | 1 | 4 | |
| HPV to NL | 0.68 | 0 | 1 | |

| | | | | |
|---|---|---|---|---|
| HPV to CIN2 | 2 | 1 | 5 | Meta-analysis on impact of HIV on HPV natural history[17] |
| CIN2 to NL | 0.67 | 0 | 1 | |
| CIN3 to CA | 2 | 1 | 5 | |

Abbreviations: HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; NL, no lesion

[a]Relative to HIV-uninfected women

Calibration Targets

| **Prevalence of Oncogenic HPV Infection[a] (by age and HIV status)[4]** | **Observed Value (95% CI)** |
|---|---|
| **HIV-Infected** | |
| 17-24 | 0.75 (0.7108,0.7892) |
| 25-29 | 0.6 (0.5608,0.6392) |
| 30-34 | 0.59 (0.5508,0.6292) |
| 35-39 | 0.55 (0.5108,0.5892) |
| 40-44 | 0.46 (0.4208,0.4992) |
| 45-49 | 0.42 (0.3808,0.4592) |
| 50-54 | 0.43 (0.3908,0.4692) |
| 55-59 | 0.54 (0.5008,0.5792) |
| 60-65 | 0.34 (0.3008,0.3792) |
| **HIV-Uninfected** | |
| 17-24 | 0.6 (0.5608,0.6392) |
| 25-29 | 0.38 (0.3408,0.4192) |
| 30-34 | 0.25 (0.2108,0.2892) |
| 35-39 | 0.2 (0.1608,0.2392) |
| 40-44 | 0.19 (0.1508,0.2292) |
| 45-49 | 0.18 (0.1408,0.2192) |
| 50-54 | 0.13 (0.0908,0.1692) |
| 55-59 | 0.17 (0.1308,0.2092) |
| 60-65 | 0.14 (0.1008,0.1792) |

Abbreviations: HPV, human papillomavirus

[a] Among all women

| **Prevalence of CIN2+, Oncogenic HPV (by age and HIV status)[4]** | **Observed Value (95% CI)** |
|---|---|
| **HIV-Infected** | |
| 17-24 | 0.13 (0.0908,0.1692) |
| 25-29 | 0.055 (0.0158,0.0942) |
| 30-34 | 0.13 (0.0908,0.1692) |
| 35-39 | 0.155 (0.1158,0.1942) |
| 40-44 | 0.08 (0.0408,0.1192) |
| 45-49 | 0.055 (0.0158,0.0942) |
| 50-54 | 0.08 (0.0408,0.1192) |

| | |
|---|---|
| 55-59 | 0.075 (0.0358,0.1142) |
| 60-65 | 0.08 (0.0408,0.1192) |
| **HIV-Uninfected** | |
| 17-24 | 0.02 (0.0004,0.0396) |
| 25-29 | 0.03 (0.0104,0.0496) |
| 30-34 | 0.025 (0.0054,0.0446) |
| 35-39 | 0.04 (0.0008,0.0792) |
| 40-44 | 0.035 (0.0154,0.0546) |
| 45-49 | 0.035 (0.0154,0.0546) |
| 50-54 | 0.035 (0.0154,0.0546) |
| 55-59 | 0.03 (0.0104,0.0496) |
| 60-65 | 0.02 (0.0004,0.0396) |

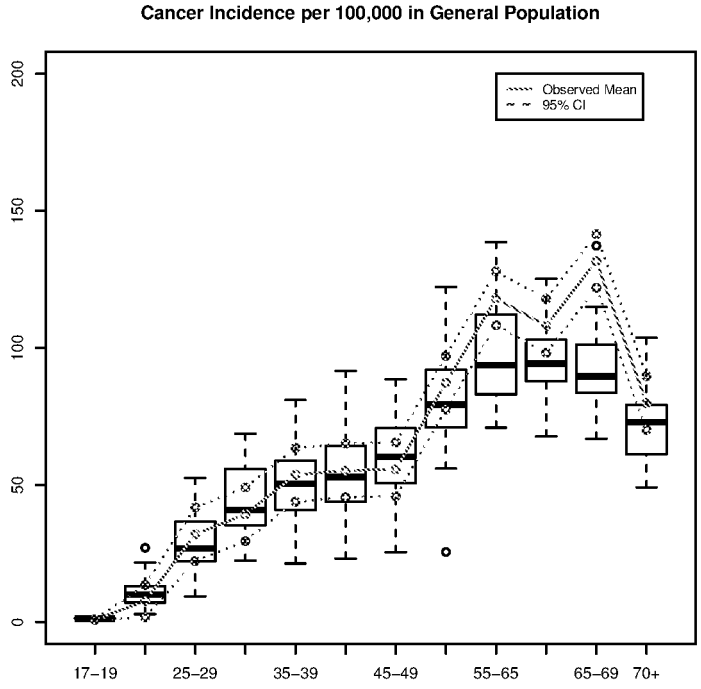
Abbreviations: CIN, cervical intra-epithelial neoplasia

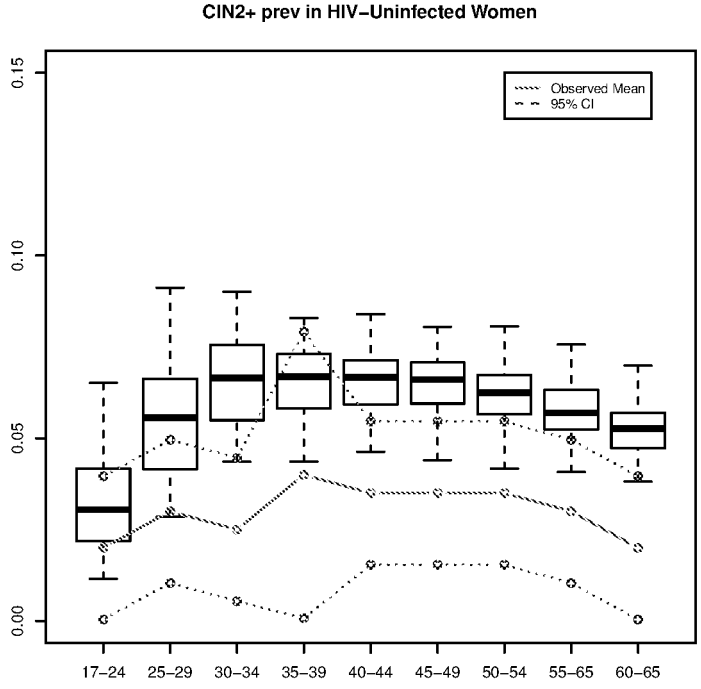
| **Cancer Incidence per 100,000 (by age)**[38] | **Observed Value (95% CI)** |
|---|---|
| 15-19 | 0.9 (0.802,0.998) |
| 20-24 | 7.6 (1.72,13.48) |
| 25-29 | 32 (22.2,41.8) |
| 30-34 | 39.3 (29.5,49.1) |
| 35-39 | 53.7 (43.9,63.5) |
| 40-44 | 55.3 (45.5,65.1) |
| 45-49 | 55.7 (45.9,65.5) |
| 50-54 | 87.3 (77.5,97.1) |
| 55-59 | 118.1 (108.3,127.9) |
| 60-64 | 108 (98.2,117.8) |
| 65-69 | 131.7 (121.9,141.5) |
| 70+ | 79.9 (70.1,89.7) |

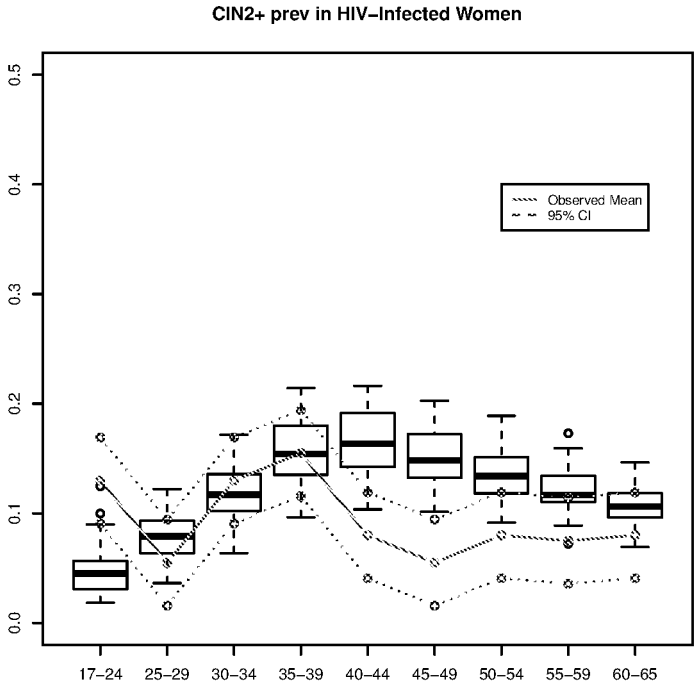
| **HPV Type Distribution in CIN**[4] | **Observed Value (95% CI)** |
|---|---|
| **CIN2, HIV-Infected** | |
| Oncogenic | 0.222 (0.183,0.261) |
| Non-oncogenic | 0.1 (0.061,0.139) |
| **CIN2, HIV-Uninfected** | |
| Oncogenic | 0.226 (0.187,0.265) |
| Non-oncogenic | 0.097 (0.058,0.136) |
| **CIN3, HIV-Infected** | |
| Oncogenic | 0.519 (0.450,0.558) |
| Non-oncogenic | 0.148 (0.109,0.187) |
| **CIN3, HIV-Uninfected** | |
| Oncogenic | 0.403 (0.364,0.442) |
| Non-oncogenic | 0.111 (0.072,0.150) |

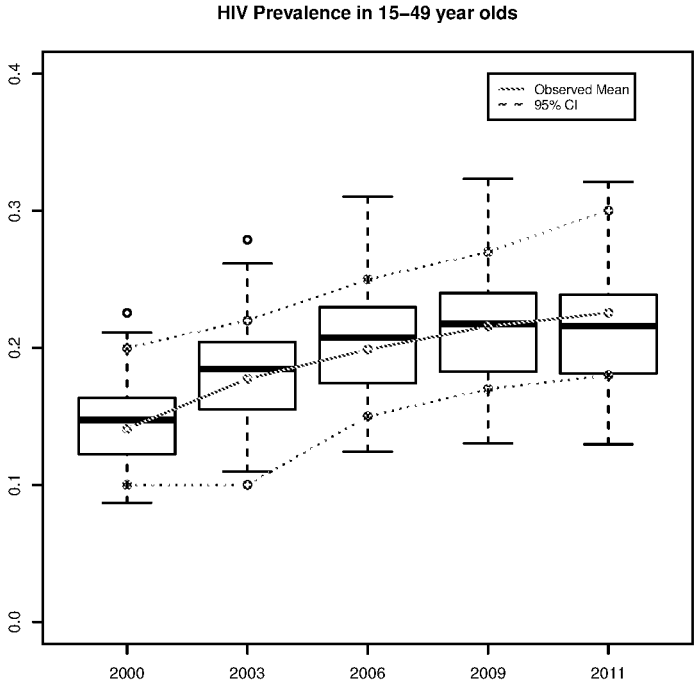
Calibration Fit Results

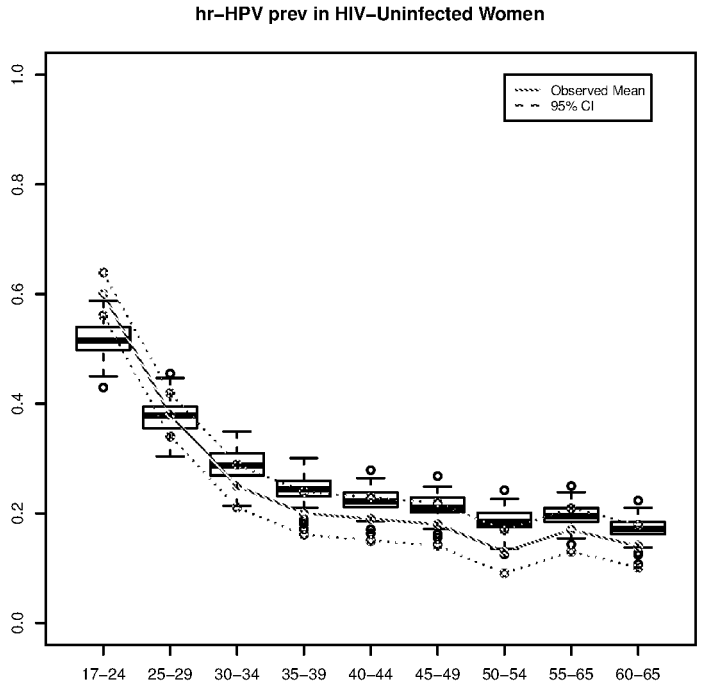
Boxplots represent the distribution of model results and the dashed lines represent the mean and 95% confidence interval of the calibration targets.

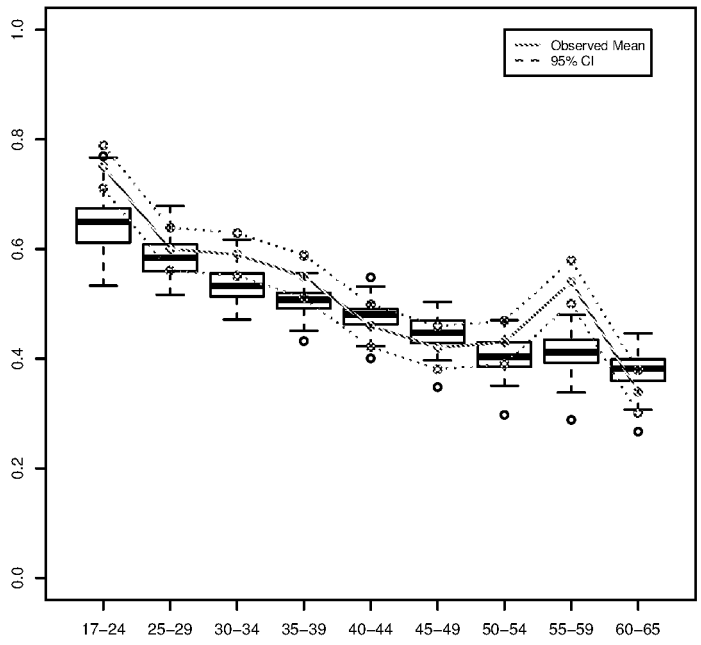


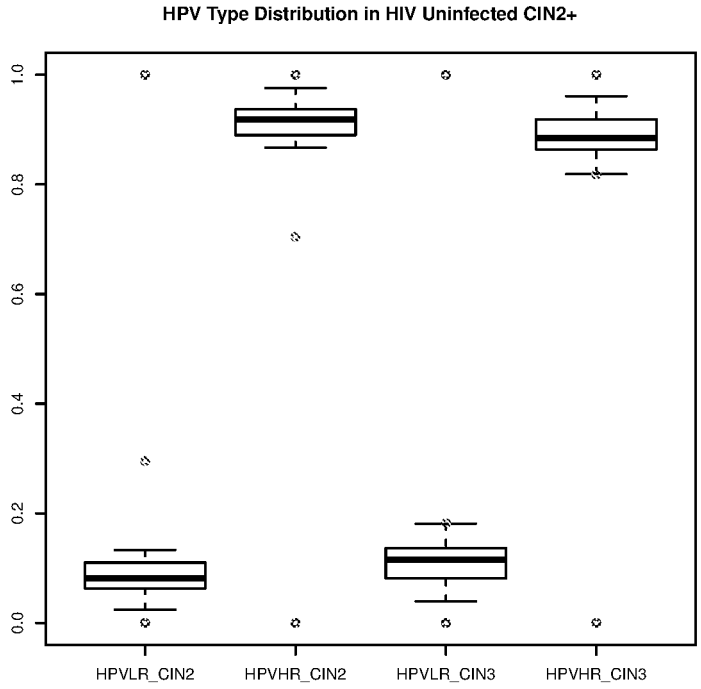



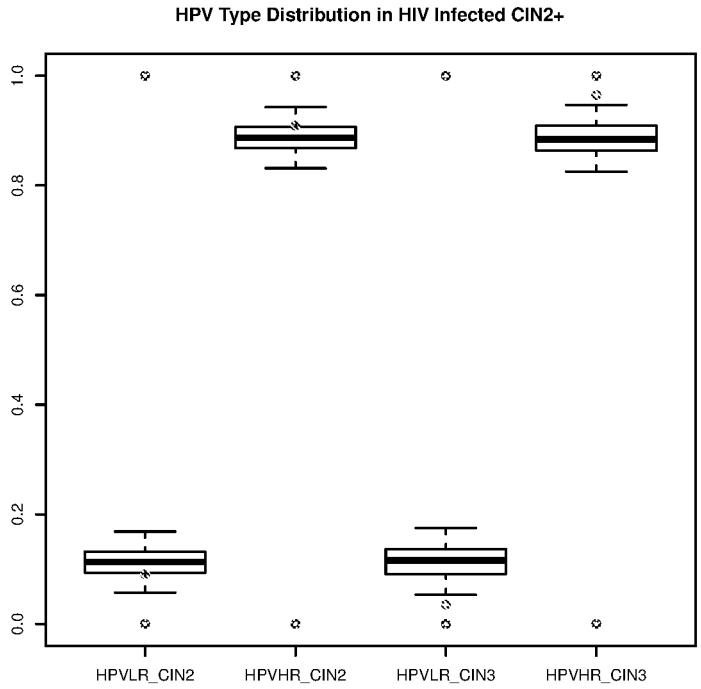

CIN2+ prev in HIV−Infected Women
Observed Mean
95% CI
0.0
0.1
0.2
0.3
0.4
0.5
17−24
25−29
30−34
35−39
40−44
45−49
50−54
55−59
60−65


HIV Prevalence in 15−49 year olds
Observed Mean
95% CI
0.0
0.1
0.2
0.3
0.4
2000
2003
2006
2009
2011


hr−HPV prev in HIV−Uninfected Women
Observed Mean
95% CI
0.0
0.2
0.4
0.6
0.8
1.0
17−24
25−29
30−34
35−39
40−44
45−49
50−54
55−65
60−65


hr−HPV prev in HIV−Infected Women
Observed Mean
95% CI
0.0
0.2
0.4
0.6
0.8
1.0
17−24
25−29
30−34
35−39
40−44
45−49
50−54
55−59
60−65



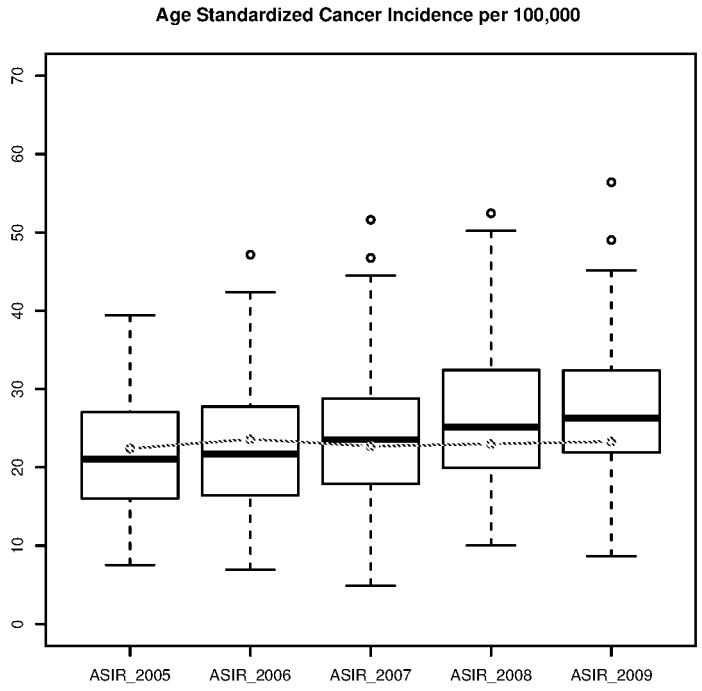



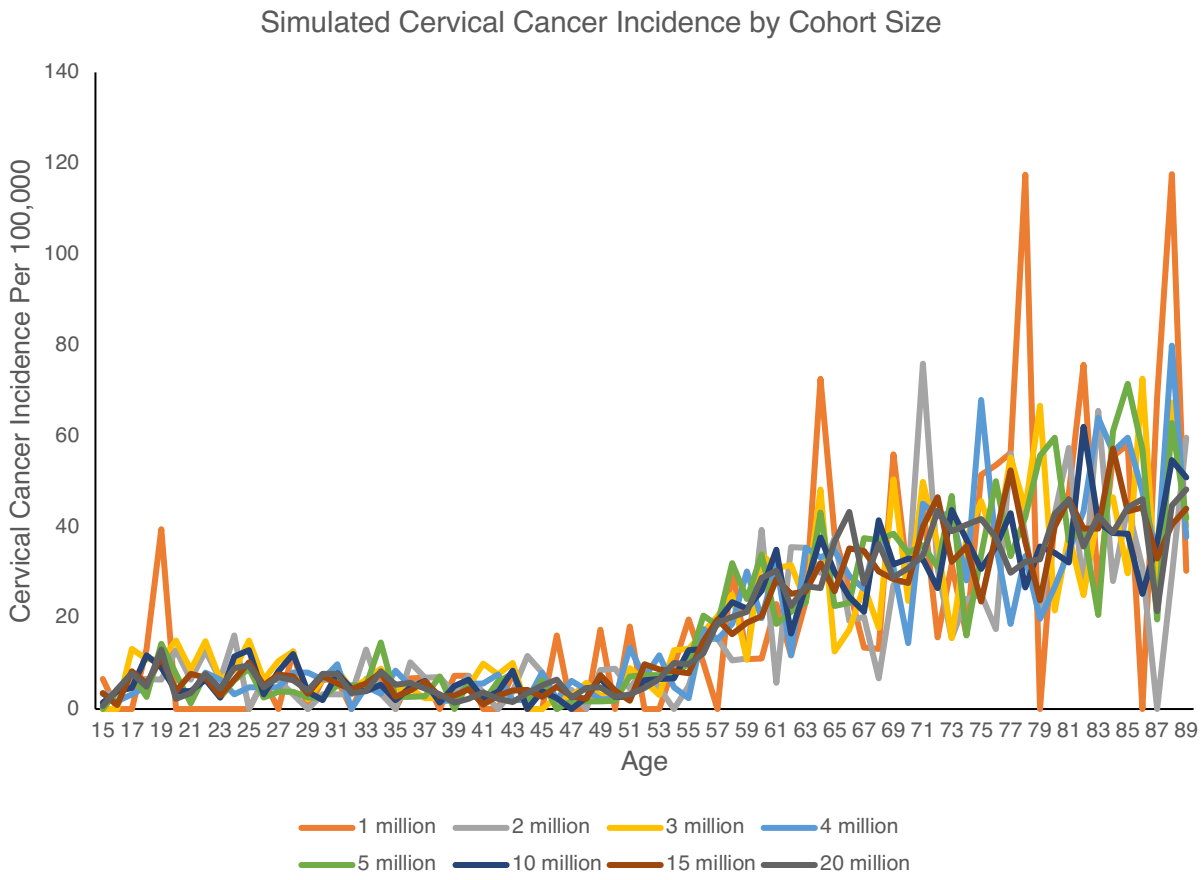

Validation Targets

| **Age-Standardized Cancer Incidence per 100,000 (by year)**[39] | **Observed Value (95% CI)** |
|---|---|

| | |
|---|---|
| 2005 | 22.4 (12.6,32.2) |
| 2006 | 23.6 (13.8,33.4) |
| 2007 | 22.7 (12.9,32.5) |
| 2008 | 23 (13.2,32.8) |
| 2009 | 23.3 (13.5,33.1) |
| 2013 | 22.06 (12.26,31.86) |

Validation Fit Results






**Computational Cost of Simulation per Cohort Size**

| Cohort Size | Computational Time (minutes) | Memory (GB) |
|---|---|---|
| 1 million | 5.85 | 0.37 |
| 2 million | 11.7 | 0.74 |
| 3 million | 17.55 | 1.11 |
| 4 million | 24.5 | 1.52 |
| 5 million | 29.25 | 1.85 |
| 10 million | 58.5 | 3.7 |
| 15 million | 87.75 | 5.55 |
| 20 million | 117 | 7.4 |

# Chapter 2 Appendix

## Calibration Parameter Priors

| HPV Prevalence by Age and HIV status | Observed Value |
|---|---|
| Living with HIV | |
| 17-24 | 0.75 |
| 25-29 | 0.6 |
| 30-34 | 0.59 |
| 35-39 | 0.55 |
| 40-44 | 0.46 |
| 45-49 | 0.42 |
| 50-54 | 0.43 |
| 55-59 | 0.54 |
| 60-64 | 0.34 |
| Living without HIV | |
| 17-24 | 0.6 |
| 25-29 | 0.38 |
| 30-34 | 0.25 |
| 35-39 | 0.2 |
| 40-44 | 0.19 |
| 45-49 | 0.18 |
| 50-54 | 0.13 |
| 55-59 | 0.17 |
| 60-64 | 0.14 |

| HPV Genotype Distribution in CIN2 by HIV status | Observed Value |
|---|---|
| Living with HIV | |
| HPV 16 | 0.2020202 |
| HPV 18 | 0.09090909 |
| HPV 31 | 0.14141414 |
| HPV 33 | 0.1010101 |
| HPV 45 | 0.07070707 |
| HPV 52 | 0.09090909 |
| HPV 58 | 0.22222222 |
| HPV other high-risk | 0.5959596 |
| Living without HIV | |
| HPV 16 | 0.15909091 |
| HPV 18 | 0.06818182 |
| HPV 31 | 0.06060606 |
| HPV 33 | 0.09090909 |

| | |
|---|---|
| HPV 45 | 0.0530303 |
| HPV 52 | 0.09090909 |
| HPV 58 | 0.09848485 |
| HPV other high-risk | 0.33333333 |

| **HPV Genotype Distribution in CIN3 by HIV status** | **Observed Value** |
|---|---|
| Living with HIV | |
| HPV 16 | 0.5 |
| HPV 18 | 0.14285714 |
| HPV 31 | 0.07142857 |
| HPV 33 | 0.25 |
| HPV 45 | 0.07142857 |
| HPV 52 | 0.07142857 |
| HPV 58 | 0.17857143 |
| HPV other high-risk | 0.64285714 |
| Living without HIV | |
| HPV 16 | 0.32954545 |
| HPV 18 | 0.09090909 |
| HPV 31 | 0.10227273 |
| HPV 33 | 0.10227273 |
| HPV 45 | 0.13636364 |
| HPV 52 | 0.03409091 |
| HPV 58 | 0.10227273 |
| HPV other high-risk | 0.22727273 |

| **HPV Genotype Distribution in Cancer by HIV status** | **Observed Value** |
|---|---|
| Living with HIV | |
| HPV 16 | 0.406 |
| HPV 18 | 0.189 |
| HPV 31 | 0.019 |
| HPV 33 | 0.002 |
| HPV 45 | 0.094 |
| HPV 52 | 0.007 |
| HPV 58 | 0.007 |
| HPV other high-risk | 0.276 |
| Living without HIV | |
| HPV 16 | 0.489 |
| HPV 18 | 0.15 |
| HPV 31 | 0.011 |
| HPV 33 | 0.04 |

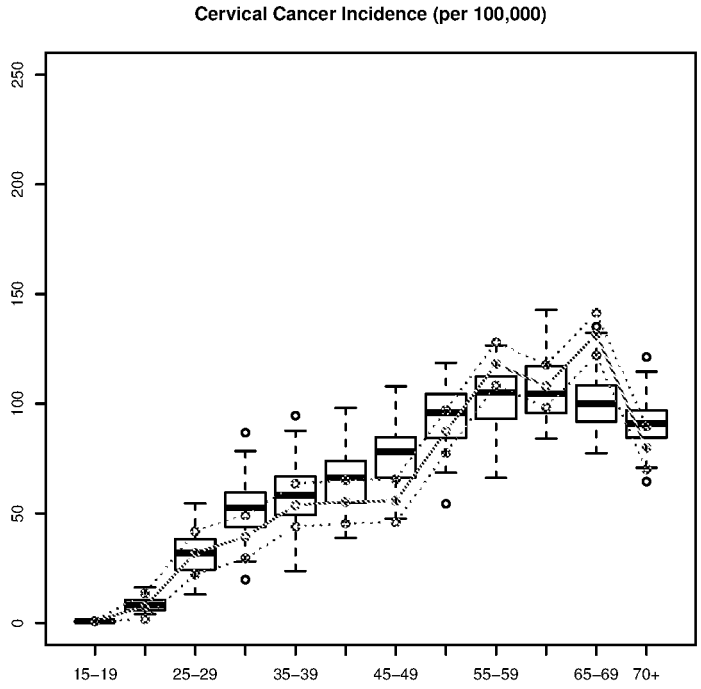
| | |
|---|---|
| HPV 45 | 0.08 |
| HPV 52 | 0.018 |
| HPV 58 | 0.008 |
| HPV other high-risk | 0.204 |

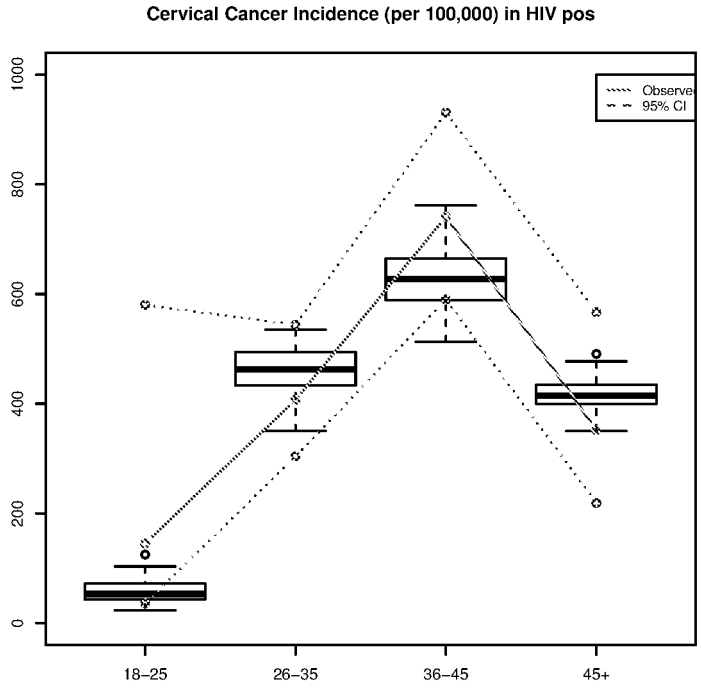
| **Cancer incidence by age** | **Observed Value** |
|---|---|
| 15-19 | 0.9 |
| 20-24 | 7.6 |
| 25-29 | 32 |
| 30-34 | 39.3 |
| 35-39 | 53.7 |
| 40-44 | 55.3 |
| 45-49 | 55.7 |
| 50-54 | 87.3 |
| 55-59 | 118.1 |
| 60-64 | 108 |
| 65-69 | 131.7 |
| 70+ | 79.9 |

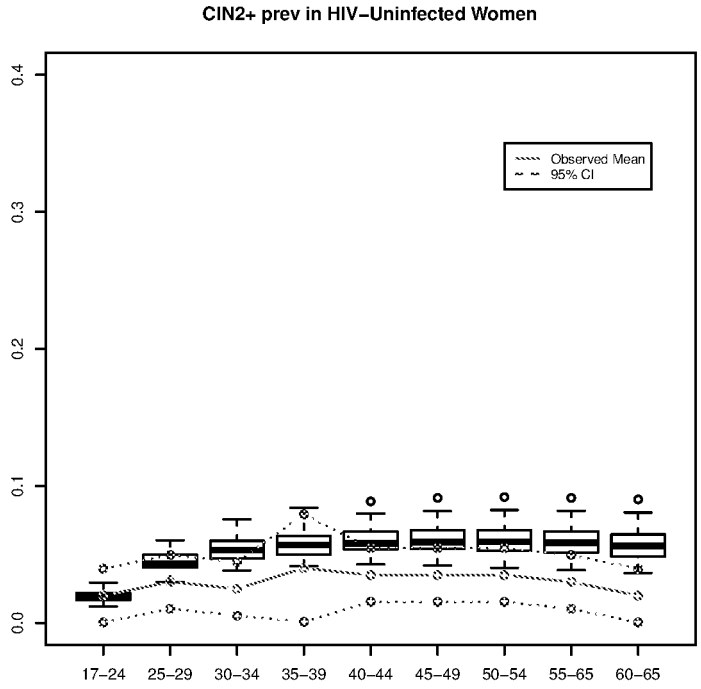
| **Cancer incidence by age in women living with HIV** | **Observed Value** |
|---|---|
| 18-25 | 145 |
| 26-35 | 407 |
| 36-45 | 741 |
| 46+ | 352 |

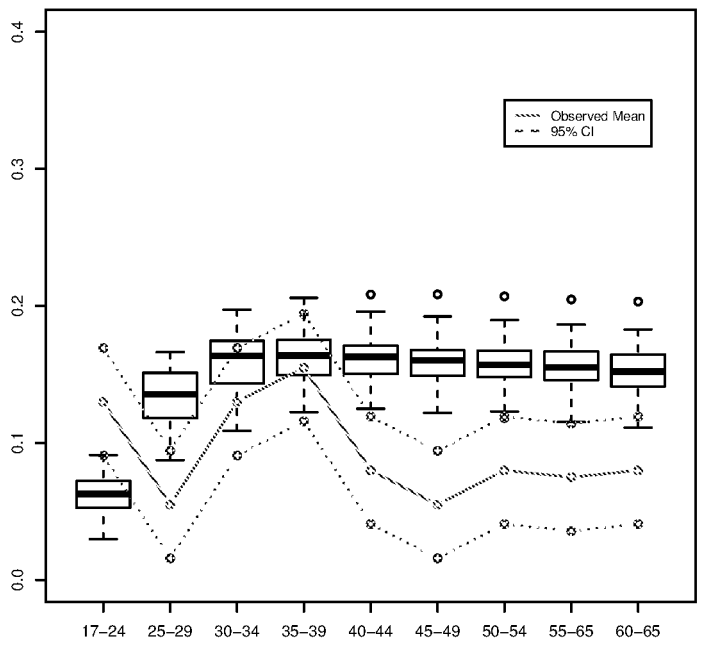
Calibration Fit Results

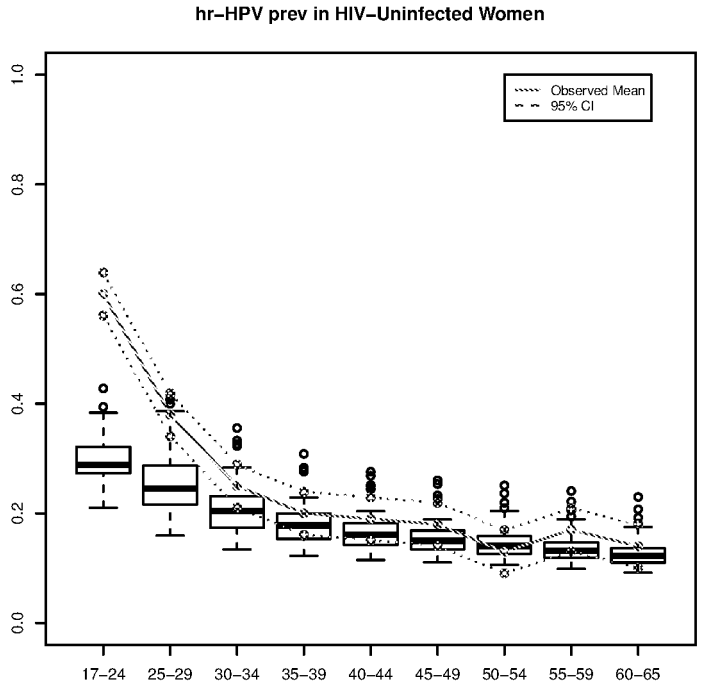
Boxplots represent the distribution of model results and the dashed lines represent the mean and 95% confidence interval of the calibration targets.

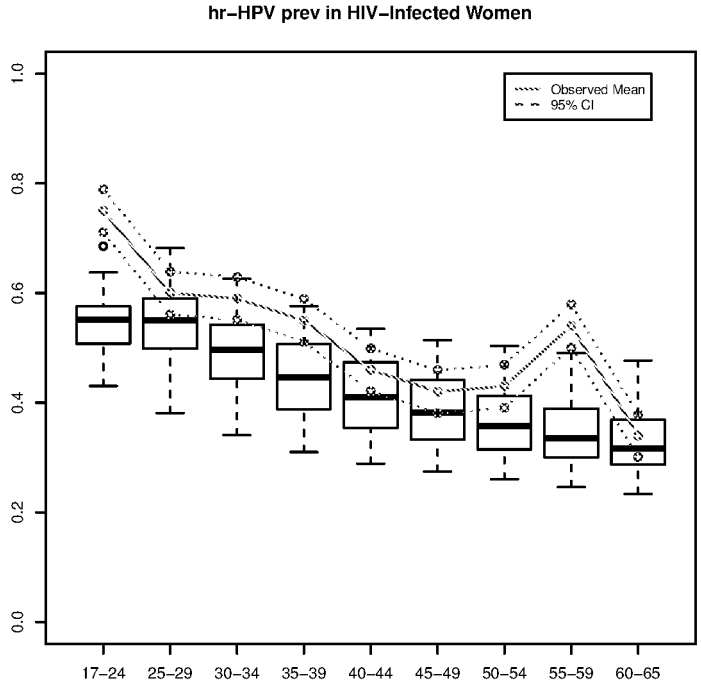

Cervical Cancer Incidence (per 100,000)
0
50
100
150
200
250
15–19
25–29
35–39
45–49
55–59
65–69
70+

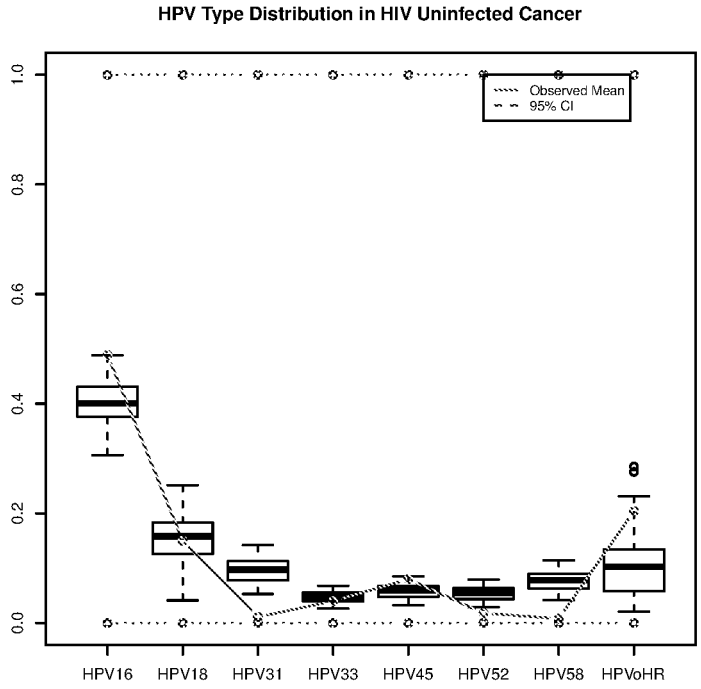

Cervical Cancer Incidence (per 100,000) in HIV pos
Observe
95% CI
0
200
400
600
800
1000
18–25
26–35
36–45
45+

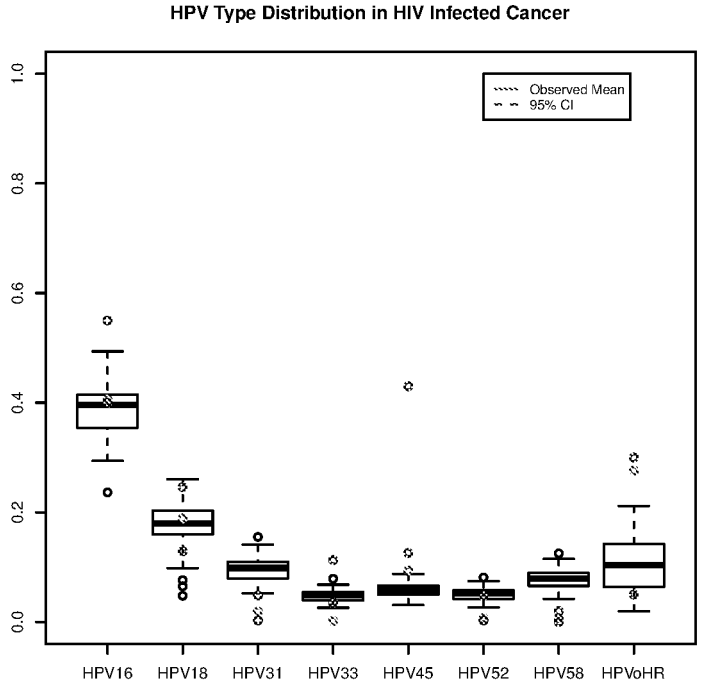

CIN2+ prev in HIV−Uninfected Women
Observed Mean
95% CI
0.0
0.1
0.2
0.3
0.4
17−24
25−29
30−34
35−39
40−44
45−49
50−54
55−65
60−65


CIN2+ prev in HIV−Infected Women
Observed Mean
95% CI
0.0
0.1
0.2
0.3
0.4
17−24
25−29
30−34
35−39
40−44
45−49
50−54
55−65
60−65

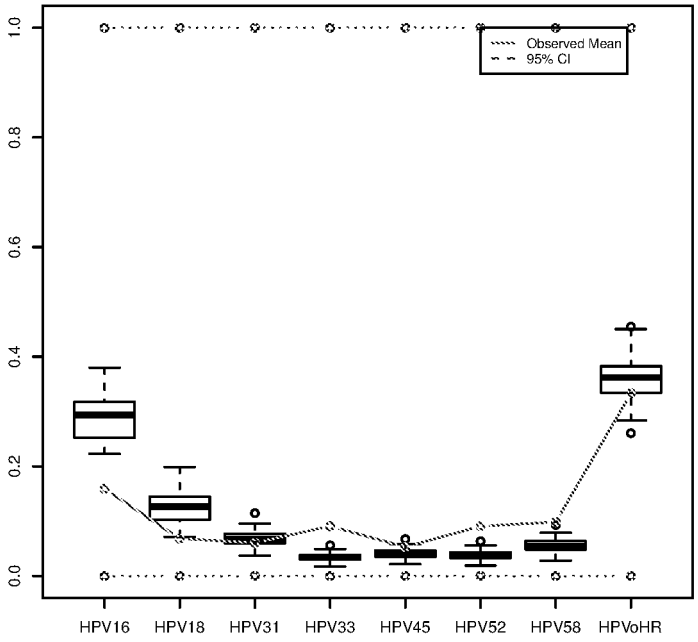

hr−HPV prev in HIV−Uninfected Women
Observed Mean
95% CI
0.0
0.2
0.4
0.6
0.8
1.0
17−24
25−29
30−34
35−39
40−44
45−49
50−54
55−59
60−65


hr−HPV prev in HIV−Infected Women
Observed Mean
95% CI
0.0
0.2
0.4
0.6
0.8
1.0
17−24
25−29
30−34
35−39
40−44
45−49
50−54
55−59
60−65

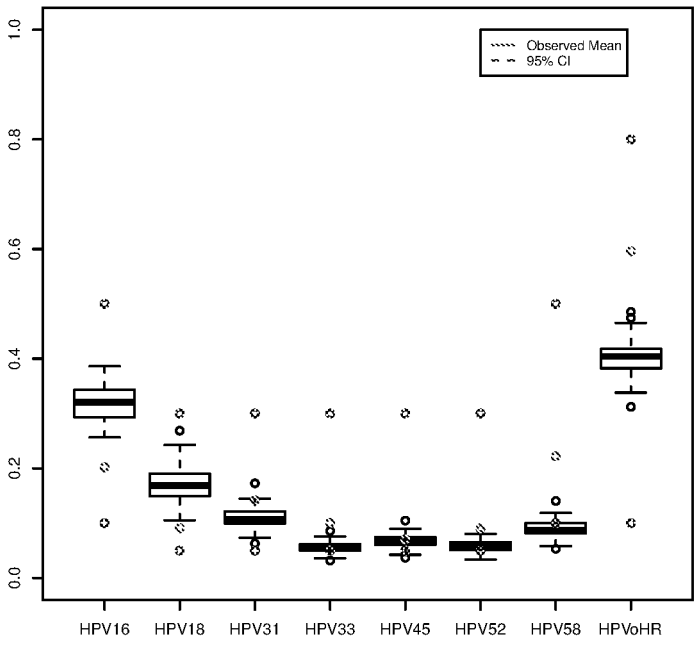

HPV Type Distribution in HIV Uninfected Cancer
Observed Mean
95% CI
1.0
0.8
0.6
0.4
0.2
0.0
HPV16
HPV18
HPV31
HPV33
HPV45
HPV52
HPV58
HPVoHR

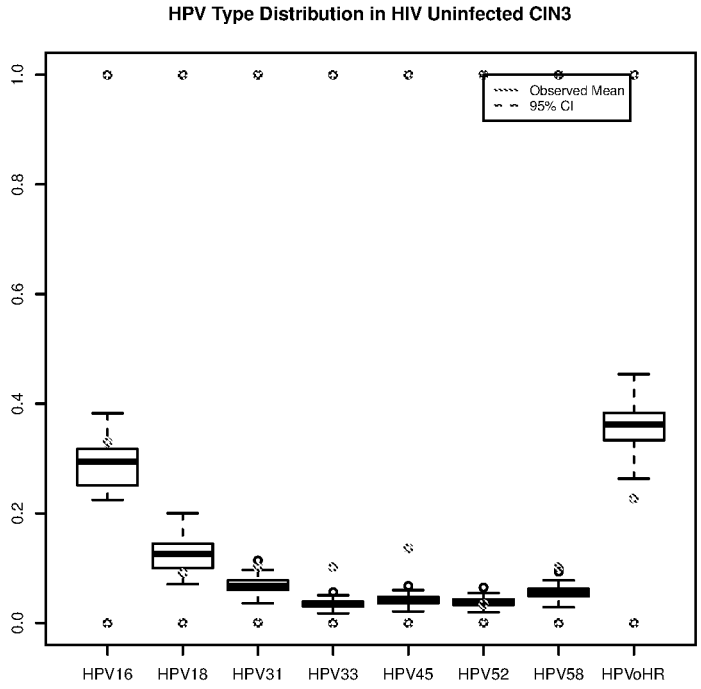

HPV Type Distribution in HIV Infected Cancer
Observed Mean
95% CI
1.0
0.8
0.6
0.4
0.2
0.0
HPV16
HPV18
HPV31
HPV33
HPV45
HPV52
HPV58
HPVoHR

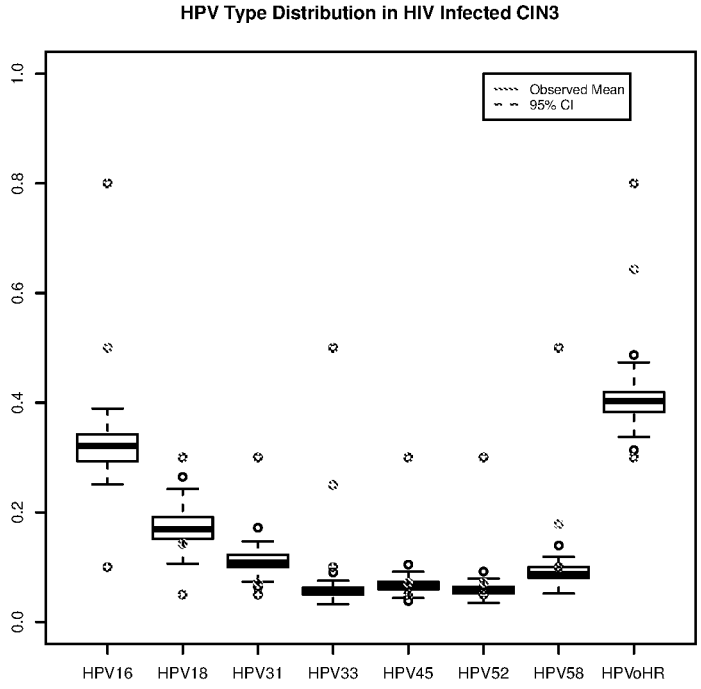
**HPV Type Distribution in HIV Uninfected CIN2**




**HPV Type Distribution in HIV Infected CIN2**




HPV Type Distribution in HIV Uninfected CIN3
Observed Mean
95% CI
1.0
0.8
0.6
0.4
0.2
0.0
HPV16
HPV18
HPV31
HPV33
HPV45
HPV52
HPV58
HPVoHR


HPV Type Distribution in HIV Infected CIN3
Observed Mean
95% CI
1.0
0.8
0.6
0.4
0.2
0.0
HPV16
HPV18
HPV31
HPV33
HPV45
HPV52
HPV58
HPVoHR

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