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# Modeling HPV vaccination scale-up among urban young men who have sex with men in the context of HIV

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ABSTRACT

*Introduction:* Young men who have sex with men (YMSM) are at high risk to contract human papillomavirus (HPV). While an effective vaccination exists, its use among YMSM is markedly lower compared to non-MSM and women. This study compares scaling up HPV vaccination in conjunction with other prevention strategies.

*Methods:* An agent-based model of urban YMSM (≤26 years of age) reflective of the demography of Philadelphia, PA, simulated for up to ten years of follow-up to examine anal and oral transmission of the HPV genotypes covered in the nonavalent (9v) vaccine: 6, 11, 16, 18, 31, 33, 45, 52, 58. Starting HPV prevalences ranged from a high of 18% (type 6) to a low of 6% (type 31); overall 65% of individuals carried any HPV genotype. Simulated levels of vaccination were ranged from 0% to 13% (present-day level), 25%, 50%, 80% (Healthy People 2020 target), and 100% in conjunction with condom use and HIV seroadaptive practices. The primary outcome was the relative reduction in HPV infection.

*Results:* Compared to present-day vaccination levels (13%), scaling-up vaccination led to expected declines in 10-year post-simulation HPV prevalence. Anal HPV (any 9v types) declined by 9%, 27%, 46%, and 58% at vaccination levels of 25%, 50%, 80%, and 100%, respectively. Similarly, oral HPV (any 9v types) declined by 11%, 33%, 57%, and 71% across the same levels of vaccine uptake. Comparing the prevention strategies, condoms blocked the greatest number of anal transmissions when vaccination was at or below present-day levels. For oral transmission, vaccination was superior to condom use at all levels of coverage.

*Conclusions:* Public health HPV preventions strategies should continue to emphasize the complementary roles of condoms and vaccination, especially for preventing oral infection. Improving vaccination coverage will ultimately have the greatest impact on reducing HPV infection among YMSM.



## 1. Introduction

Compared with the general population, young men who have sex with men (YMSM) have a higher prevalence of sexually transmitted infections, including human papillomavirus (HPV) [1]. High rates are likely due to increased exposure to pathogens through their social-sexual networks (greater number of sex partners or a higher prevalence of HPV in the network) and risk taking behavior (condomless anal intercourse). This HPV disparity is even more alarming when considering HIV coinfection: 93% of MSM who were HIV positive had been infected with HPV in the anal canal compared to 64% of HIV negative MSM [2]. Infection with HPV includes oncogenic genotypes causally linked to a number of cancers of the head, neck, and anogenital regions, and non-oncogenic types causally linked to genital warts [3]. Thus, preventing infection with HPV and its sequalae are primary public health concerns.

Risk for HPV infection can be greatly reduced among YMSM who complete the immunization series prior to exposure to the viruses. A nonavalent vaccine is currently licensed in the U.S. for males aged 9–26 years and protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58; hereafter referred to as "9v." (Recently, the FDA approved an increase in the maximum age for HPV 9v vaccination among males to 45 years of age [4], but this has not been reflected in the ACIP recommendations as of this writing.) And

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while HPV immunization has been recommended for males in the U.S. since 2009, many do not receive the vaccine [5]. Population-based surveys suggest vaccination uptake among eligible MSM in the U.S. of about 15% [6,7], well short of the Healthy People 2020 goal of 80% coverage [8]. Depending on age at initiation two or three doses are recommended; individuals with HIV infection require three doses [9]. Furthermore, of those who initiate HPV vaccination, about 20% fail to complete the series [5]. Given the suboptimal vaccination rates, it is critically important to understand (1) how HPV transmission occurs in a contemporary group of at-risk young men (who are eligible for vaccination) with and without HIV infection, (2) how infection rates may be impacted as vaccination uptake increases, and (3) how this can inform allocation of scare public health prevention resources.

Simulation studies offer some of the best tools available to public health researchers in predicting or describing disease epidemics [10], and have been used for more than a decade to predict HPV vaccination's benefits at a population level, well before empiric data became available [11–14]. Despite calls for study among an MSM population [15], the overwhelming majority of existing simulations have focused on heterosexual exposure to HPV. Our literature review revealed a small number of simulation studies that have focused on MSM [16–18]. These studies examined the health economics of scaling up vaccination over many decades (up to 100 years) and found that targeted MSM vaccination might be cost-effective under certain conditions: lower vaccine price, in YMSM, and those who are HIV positive. While long term benefits are an important consideration, equally relevant are short term benefits comparing present day strategies of viral transmission and prevention, the focus of our work.

Accordingly, the primary objective of this study was to quantify the reduction in incident HPV infections among a population of YMSM through immunization with the nonavalent vaccine. We focused on 1-year, 5-year, and 10-year infection endpoints (as opposed to longer term clinical endpoints of cell dysplasia and neoplasia) because short term intervention impacts are of great importance to public health planners and elected policymakers. Secondarily, we sought to compare the impact of other non-vaccine sexually transmitted infection (STI) prevention strategies among MSM, namely condom use and HIV seroadaptive behaviors, specifically serosorting, or having sex only with individuals of the same HIV status, and seropositioning, or being insertive if the partner is HIV positive or of unknown status. HIV is crucial to consider when modeling an MSM population as it impacts partner selection, sexual behavior, and, with the introduction of pre-exposure prophylaxis, potential for risk compensation [19,20]. We specifically chose Philadelphia, PA, USA as a prototypical location to ground this work based on availability of data for model calibration and potential for generalizability to other urban areas.

## 2. Material and methods

### 2.1. Overview of simulation approach

This work expanded upon a previously described simulation model [21]. We adapted an agent-based network modeling approach with individuals moving between two infectious disease states: susceptible and infected. To reflect the estimated demography of YMSM in Philadelphia, a dynamic population of 5329 agents 18–26 years of age (34% white, 66% non-white) were initiated with various attributes, as described below. Individuals were followed for a period of ten years and engaged in zero or more sexual relationships (main partnerships, casual partnerships, one night stands). At three study endpoints – 1 year, 5 years, and 10 years – we tabulated relative measures of incidence, prevalence, and proportion of infections prevented as a result of specific prevention methods employed. These three end points emphasize the proximal benefit of various STI prevention strategies on HPV transmission rather than progression to neoplasia, which may take decades to occur and may involve other component causes than the initial HPV infection for progression. Assumptions, parameters, and starting values of ensuing model specifications are summarized in Table 1 [22–48].

### 2.2. Transmission dynamics and assumptions

Individuals entered the starting population as either susceptible or, amongst those infected, with one or more of the nine genotypes of HPV covered in the 9v vaccine. Assignment of genotypes reflected published prevalence rates among MSM [33–35]. HPV infection was modeled at two anatomic sites: oropharyngeal and anogenital. For anogenital HPV, we assume concordance between penile and anal infection for modeling simplicity. Anatomic sites and HPV genotypes were modeled independently. Individuals were additionally considered susceptible or infected with HIV, as this impacted sexual partner selection and behavior through seroadaptive practices. Starting prevalence proportions were 65% anal HPV infection (any 9v types) and 1% oral HPV infection (any 9v types) [33–35]. Baseline HIV infection was set to 16% prevalence (unpublished data, Philadelphia Department of Public Health). HPV starting prevalence differed with respect to HIV status, and HIV was 1.9 times more common among non-white agents (unpublished data, Philadelphia Department of Public Health). For those individuals who had one or more HPV infections, 19% of anal and 16% of oral infections were immediately set as "incident" [36,37], allowing for the opportunity for spontaneous clearance of the virus. In our model and as suggested in the literature, 66% of HIV negative men and 59% of HIV positive men will spontaneously clear an HPV infection by a median of 8 months [45,46]. Men were considered vulnerable to reinfection with the same HPV genotype following clearance based on inconclusive evidence surrounding natural immunity [49]. Those individuals who did not spontaneously clear were considered chronically infected for the remainder of the simulation.

Each time-step of the simulation (i.e., day) allowed for a sexual dyad to form assortatively matched by race [26] and partner availability. Age was not considered as an assortative factor for partner selection in this younger age group [50]. For those in a relationship on a given day, individuals may have engaged in anal sex, oral sex, both, or neither (e.g, avoided sex through HIV seroadaption). Likewise, individuals may have been insertive, in that they inserted their penis into their partner's mouth or anus; receptive, in that the partner's penis was inserted into their mouth or anus; or were both insertive and receptive for that encounter [27–29]. An agent's sexual preferences persisted for the duration of the simulation. For HPV infection, we evaluated per sex-act probabilities for viral transmission for all types of sexual acts described [41–44], whereas for HIV infection only anal sex placed an individual at risk for infection [47]. A gamma distribution of total number of expected sexual partnerships that may have formed in each simulation year was assumed for our models [23,24], while a Poisson distribution of total number of sex acts in each simulation year was employed [25].

HIV infection required some additional considerations with respect to propensity for viral transmission. These details are more thoroughly provided in Table 1 and LeVasseur et al. [21], and are only briefly presented here. Per sex-act probability of HIV transmission was a function of sexual position and viral load. Individuals may have been in acute viremia, chronically infected, or virally suppressed through antiretroviral therapy. To be on antiretroviral therapy, individuals must have been aware of their HIV serostatus,

**Table 1**
Assumptions and input parameters for an urban young men who have sex with men HPV simulation model.

| Parameter | Description | Values | Source |
|---|---|---|---|
| ***Population*** | | | |
| Geography | Hypothetical location of simulation | Philadelphia, PA | Assumption |
| Age | Age of YMSM population, in years | 18–26 | Assumption |
| Size | Size of YMSM population (number of agents in model) | 5329 | ACS & literature [22] |
| Race | Racial breakdown of YMSM population | White: 34%<br>Non-white: 66% | ACS & literature [22] |
| Migration | Entry and exit rate from the study population per year | 12.8% | ACS |
| ***Sexual behavior*** | | | |
| Partners[a] | Expected number of sexual partners per year | Gamma(0.5,10) | Literature [23,24] |
| Sexual acts | Expected number of sexual acts per year | Poisson(80.6) | Literature [25] |
| Assortative mixing | Probability of same-race partner selection | White: 50%<br>Non-white: 7% | Literature [26] |
| Act | Sexual act(s) performed for a given encounter | Anal only: 22%<br>Oral only: 44%<br>Both: 34% | Literature [27,28] |
| Anal positioning[b] | Anal sexual positioning for a given encounter | Insertive only: 24%<br>Receptive only: 32%<br>Both: 44% | Literature [29] |
| Oral positioning[b] | Oral sexual positioning for a given encounter | Insertive only: 16%<br>Receptive only: 14%<br>Both: 70% | Literature [27,28] |
| Condom, anal, white | Distribution of condom use for anal intercourse, white | 100% of time: 23%<br>75% of time: 20%<br>50% of time: 15%<br>25% of time: 14%<br>Never: 28% | Literature [30] |
| Condom, anal, non-white | Distribution of condom use for anal intercourse, non-white | 100% of time: 27%<br>75% of time: 22%<br>50% of time: 17%<br>25% of time: 14%<br>Never: 20% | Literature [30] |
| Condom, oral | Condom use for oral intercourse | 4% | Literature [31] |
| Condom effectiveness | Condom effectiveness, per sex-act | Anal: 70.5%<br>Oral: 70.5% | Literature (anal) [32] & assumption (oral) |
| ***Baseline infection*** | | | |
| HIV | Prevalence of being HIV seropositive, 18–26 years of age | White: 10%<br>Non-white: 19% | NHBS |
| HPV-6 | Prevalence of HPV genotype 6 from sampled site | Anal, HIV-: 15.4%<br>Oral, HIV-: 0.8%<br>Anal, HIV+: 32.9%<br>Oral, HIV+: 3.4% | Literature [33] |
| HPV-11 | Prevalence of HPV genotype 11 from sampled site | Anal, HIV-: 7.4%<br>Oral, HIV-: 0%<br>Anal, HIV+: 18.2%<br>Oral, HIV+: 1.1% | Literature [33] |
| HPV-16 | Prevalence of HPV genotype 16 from sampled site | Anal, HIV-: 12.5%<br>Oral, HIV-: 1.1%<br>Anal, HIV+: 36.4%<br>Oral, HIV+: 2.3% | Literature [26] |
| HPV-18 | Prevalence of HPV genotype 18 from sampled site | Anal, HIV-: 7.3%<br>Oral, HIV-: 0.5%<br>Anal, HIV+: 32.9%<br>Oral, HIV+: 3.4% | Literature [33] |
| HPV-31 | Prevalence of HPV genotype 31 from sampled site | Anal, HIV-: 3.6%<br>Oral, HIV-: 0.2%<br>Anal, HIV+: 14.1%<br>Oral, HIV+: 2.5% | Literature [34,35] |
| HPV-33 | Prevalence of HPV genotype 33 from sampled site | Anal, HIV-: 6.4%<br>Oral, HIV-: 1.0%<br>Anal, HIV+: 6.9%<br>Oral, HIV+: 5.1% | Literature [34,35] |
| HPV-45 | Prevalence of HPV genotype 45 from sampled site | Anal, HIV-: 12.1%<br>Oral, HIV-: 0.2%<br>Anal, HIV+: 15.2%<br>Oral, HIV+: 1.8% | Literature [34,35] |
| HPV-52 | Prevalence of HPV genotype 52 from sampled site | Anal, HIV-: 9.0%<br>Oral, HIV-: 1.0%<br>Anal, HIV+: 24.2%<br>Oral, HIV+: 1.8% | Literature [34,35] |
| HPV-58 | Prevalence of HPV genotype 58 from sampled site | Anal, HIV-: 9.8%<br>Oral, HIV-: 0%<br>Anal, HIV+: 21.1%<br>Oral, HIV+: 0.7% | Literature [34,35] |

(*continued on next page*)

**Table 1** (*continued*)

| Parameter | Description | Values | Source |
|---|---|---|---|
| Incidence, HPV | Annual incidence of HPV | Anal: 19%<br>Oral: 16% | Literature [36,37] |
| ***HIV*** | | | |
| Status | Knowledge of HIV status | HIV-: 36.9%<br>HIV+: 44.0% | Literature [38] |
| Testing | Last tested for HIV | <6mos: 19%<br>6–12mos: 11%<br>>12mos: 36%<br>Never: 30% | Literature [30] |
| Treatment as prevention | HIV+, on antiretroviral therapy, and virally suppressed | 42% | Literature [39] |
| Seroadaption, HIV- | Serosorting or seropositioning | Insertive: 9.5%<br>Serosort: 30.7%<br>Neither: 59.8% | Literature [40] |
| Seroadaption, HIV+ | Serosorting or seropositioning | Receptive: 13.3%<br>Serosort: 21.4%<br>Neither: 65.3% | Literature [40] |
| Seroadaption, HIV? | Serosorting or seropositioning | Insertive: 5.3%<br>Serosort: 32.1%<br>Neither: 62.6% | Literature [40] |
| PrEP | HIV- and on pre-exposure prophylaxis | 12.2% | NHBS |
| ***Transmission*** | | | |
| Anal, HPV[c] | Per sex-act probability of anal transmission | Receptive: 54.6%<br>Insertive: 7.1% | Literature [41,42] |
| Oral, HPV[c] | Per sex-act probability of oral transmission | Receptive: 3.2%<br>Insertive: 1.4% | Literature [41-44] |
| HPV clearance, rate | Proportion of men who spontaneously clear an HPV infection by median time | HIV-: 66%<br>HIV+: 59% | Literature [45] |
| HPV clearance, time | Median time in months (days) for clearance of a given HPV infection | 7.5 (2 2 8) | Literature [46] |
| HIV, primary | Per sex-act probability of anal transmission | Receptive: 12.8%<br>Insertive: 5.7% | Literature [47] |
| HIV, chronic | Per sex-act probability of anal transmission | Receptive: 1.3%<br>Insertive: 0.6% | Literature [47] |
| ***Vaccination*** | | | |
| Doses | Distribution of doses among eligible YMSM | 0: 87%<br>1: 4%<br>2: 2%<br>3: 7% | Literature [6] |
| Efficacy | Vaccine efficacy, one or more doses | 59.4% | Literature [48] |

*ACS*, American Community Survey 2016 5-year estimates; *HPV*, human papillomavirus; *HIV*, human immunodeficiency virus; *NHBS*, National HIV Behavioral Surveillance Philadelphia 2014 and 2017; *YMSM*, young men who have sex with men; *PrEP*, pre-exposure prophylaxis.

[a] Gamma distribution represents a right-skewed distribution of number of partnerships.

[b] Sexual positioning was regarded as a preference. When two agents had the same preference (i.e. insertive/insertive or receptive/receptive) we applied a "scale of dominance" approach whereby the agent regarded as more dominant had their preference honored.

[c] Per sex-act partner probability calculated from closed cohort data following a group of adolescent men who have sex with men, and is equal to the (number of incident site-specific infections)/(number of position-specific partners) * (prevalence of site-specific HPV infection).

with a test and treat strategy employed in the HIV module of the simulation. Further, individuals known to be HIV negative may have taken pre-exposure prophylaxis, negating subsequent risk for HIV infection. Finally, based on their HIV status (known positive, known negative, or unknown) individuals may have adhered to seroadaptive practices.

### 2.3. STI prevention strategies

We compared the effects of condom use and vaccination as primary prevention strategies (as these are specific interventions against HPV), and seroadaptive practices as a secondary strategy (as it impacts sexual behavior practices for HIV prevention). The probability of condom use for anal sex was governed by the following distribution: 25% of MSM used condoms all of the time, 21% used condoms 75% of the time, 16% used condoms 50% of the time, 14% used condoms 25% of time, and 24% never used a condom [30]. This distribution was modified by race so that white agents were less likely to use a condom consistently and non-white agents were more likely to use a condom consistently based on self-reported behavior [30]. Condom use during oral sex is infrequent and limited data suggested a 4% probability [31]. The efficacy of condoms for HPV prevention among MSM was unclear, therefore we inferred a 30% per sex-act failure rate based on heterosexual data [32].

Best estimates for HPV vaccination coverage suggested that 87% of eligible gay and bisexual men aged 18–26 years have *not* received any vaccination irrespective of race [6,51]. A breakdown of doses among the 13% vaccinated indicated 31% received one dose, 15% received two doses, and 54% completed the series. While both a quadrivalent and nonavalent vaccine are licensed for use among males in the U.S., our simulation employed only the nonavalent vaccine due to a shift in availability of this vaccine. Results from a randomized clinical trial of the quadrivalent HPV vaccine against persistent anal infection among MSM demonstrated 59% efficacy in the intention-to-treat analysis for those who received one or more doses. For our model, we assumed equivalent protection for the nonavelent vaccine; that is, the vaccine was immunogenic in 59% of individuals and provided 100% protection for the duration of the simulation [48].

Our simulated population of Philadelphia-based YMSM reflected an open cohort of young adults, 18–26 years of age, aligning with the upper age limit on the current Advisory Committee on

Immunization Practices vaccination schedule [9]. While we did not enforce any specific criteria that would affect vaccination eligibility (e.g., being immunocompromised), we made several simplifying assumptions. First, we assumed that all individuals who received vaccination did so prior to study start. Second, if vaccination was given subsequent to an earlier in life infection, it was still immunogenic against all of the exposed HPV types where chronic infection did not occur. Third, immunity lasted for the duration of the simulation.

To simulate the scale-up of HPV vaccination and its theorized benefits we undertook several complementary and counterfactual analyses replicating the models at six levels of vaccination: 0% (used for comparison), 13% (current best estimates for coverage level in our population), 25%, 50%, 80% (Healthy People 2020 goal), and 100% (theoretical maximum). Within each level of vaccination, we allowed the number of doses to vary as defined previously. These models were counterfactual in nature as the same population was used at the start of each simulation run with only the STI prevention strategies employed changing.

### 2.4. Model calibration and validation

To ensure internal and external validity of our simulation, we performed a best-fit validation [52]. *Ex ante* input validation ensured that the most appropriate input parameters were specified for the model (Table 1). A descriptive output validation matched the predicted versus actual incidence data specific to HIV. HIV was the focus of output validation as these models were originally constructed to reflect the dynamics of HIV transmission in a non-specific urban-based population of MSM. To tune this model to represent the Philadelphia population of YMSM, we compared 5-year HIV incidence data from the Philadelphia Department of Public Health to model estimates, discarding a 5-year burn-in period, and calibrating sexual network parameters including number of partners, number of sexual contacts, and type of sex until targets were achieved. Models were successfully tuned to reflect the most recent 5-year Philadelphia HIV surveillance data (Fig. 1).

### 2.5. Statistical analysis

Sexual networks were estimated using EpiModel [53] v1.5.0 and disease transmission models were implemented using the R Platform for Statistical Computing (Vienna, Austria) v3.2.1. Annotated source code and simulated datasets can be downloaded from https://doi.org/10.5281/zenodo.2652534. Statistics presented in the results include mean estimates of point prevalence, cumulative incidence, and proportion of infections averted at 1-year, 5-year, and 10-year end points. Precision estimates were obtained by running 50 iterations of the simulated models. Results are presented both overall for any HPV infection (labeled as "any 9v types") and specific to each of the nine independently modeled HPV genotypes.

We include the results of two main sensitivity analyses. In the first, the efficacy of the HPV vaccine was raised from 59% to 95% reflecting the results of per-protocol analysis assessing the quadrivalent HPV vaccine against persistent anal infection among MSM. This sensitivity analysis can be thought of as vaccination prior to sexual debut. In the second, the per sex-act failure rate of condoms was raised from 30% to 50% acknowledging the unclear evidence on the exact efficacy of condoms against HPV transmission.

## 3. Results

All simulations commenced with 5,329 agents. Baseline prevalence of anal HPV (any 9v types) was 63% and oral HPV (any 9v types) was 8%. HIV positivity at baseline was 15%. At the end of 10 years and allowing for in- and out-migration, a mean of 12,125 agents (standard deviation: 144) were tracked for incident HPV infections. Agents had a median of 7 sexual partners (interquartile range: 2, 14) and engaged in a median of 164 distinct sex acts (oral, anal, or both; interquartile range: 51, 363).

Compared to present-day estimated vaccination levels (13%) scaling-up vaccination led to expected declines in 10-year post-simulation prevalence. Anal HPV (any 9v types) declined by 9%, 27%, 46%, and 58% at vaccination levels of 25%, 50%, 80%, and 100%, respectively. Oral HPV (any 9v types) declined by 11%, 33%, 57%, and 71% at the same vaccination comparison levels. Setting vaccination coverage at 80% (Healthy People 2020 goal) and compared with present-day vaccination levels (13%), reduction in anal HPV infections ranged from 39% (type 6) to 54% (type 31) and reduction in oral HPV infection ranged from 54% (type 6) to 60% (type 31).

Table 2 depicts the expected reduction in incident HPV infections at 1 year, 5 year, and 10 year study end points. Larger reduc-

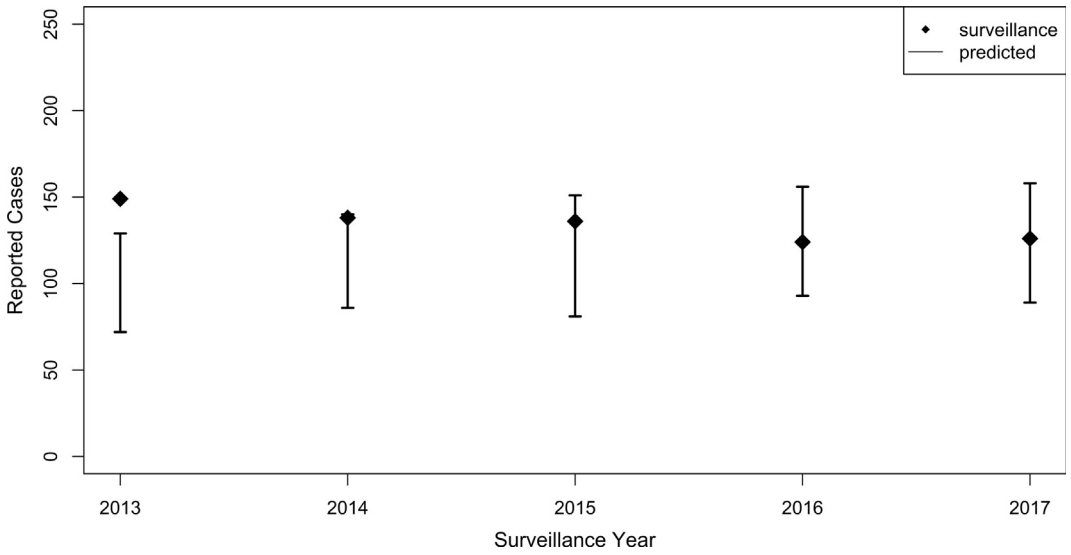


**Fig. 1.** Model validation predicting 5-year HIV incidence among YMSM compared to Philadelphia surveillance. Error bars indicate variability across 50 simulated runs. A 5-year burn-in period was discarded. *YMSM*, young men who have sex with men; *HIV*, human immunodeficiency virus.

**Table 2**
Percent reduction in new HPV infections among YMSM at 1 year, 5 year, and 10 year time points for each vaccination level compared to present day vaccination levels (13%). Statistics summarized across 50 simulated runs of the model.

| Anatomic site | Immunization level[a] | Percent reduction in new infections at time point mean (range) | | |
|---|---|---|---|---|
| | | 1 year | 5 year | 10 year |
| Anal transmission | 25% | 15% (13%, 18%)[b] | 13% (12%, 14%)[b] | 12% (11%, 12%)[b] |
| | 50% | 40% (36%, 45%) | 37% (35%, 40%) | 35% (34%, 37%) |
| | 80% | 64% (60%, 69%) | 62% (59%, 66%) | 60% (57%, 63%) |
| | 100% | 76% (73%, 81%) | 76% (72%, 80%) | 74% (71%, 77%) |
| Oral transmission | 25% | 15% (13%, 18%) | 13% (12%, 14%) | 12% (12%, 13%) |
| | 50% | 41% (38%, 46%) | 38% (36%, 41%) | 36% (35%, 38%) |
| | 80% | 65% (62%, 70%) | 64% (61%, 67%) | 61% (59%, 64%) |
| | 100% | 78% (74%, 81%) | 77% (74%, 81%) | 75% (73%, 78%) |

*YMSM*, young men who have sex with men; *HPV*, human papillomavirus.
[a] Within each group of those vaccinated, 31% received one dose, 15% received two doses, and 54% completed the series.
[b] For example, compared to present day 13% vaccination coverage among YMSM, increasing coverage to 25% would result in an expected 15% additional reduction in new cases of anal HPV at one year, 13% additional reduction in new cases at five years, and 12% additional reduction in new cases at ten years.

tions were observed at proximal time points, indicating vaccination effects are the greatest when a large proportion of the population are susceptible. As the simulation progressed, the number of new infections declined suggesting a shrinking of the pool of susceptible individuals (who may have become infected or were immune). In both the post-simulation prevalence and the reduction in incidence, vaccinations effects were similar in reducing oral HPV infection versus anal HPV infection.

Considering non-vaccination strategies, condoms proved the most effective method to reduce anal transmission of HPV when vaccination coverage was at or below present day levels (~13%), and when coverage exceeded this threshold, vaccination blocked the majority of anal transmissions. Scaled up to Healthy People 2020 goals of 80% vaccinated, condoms blocked 36% of anal transmissions, whereas vaccination blocked 64% of potential infections. Although HIV seroadaptive practices indirectly block anal HPV transmission (for example, through abstinence or risk-modifying behavior) overall it was negligible at a population level, ranging between 0.1% and 0.2% of all infections blocked. Meanwhile, for oral transmission of HPV, vaccination was superior to condom use at all levels of coverage. See Table 3 for a comparison of strategies.

Results from the sensitivity analyses confirmed that vaccination prior to sexual debut, where the vaccine efficacy is improved, further decreased new infections. Comparing 80% targeted vaccination coverage to present day levels, a 95% efficacious vaccine reduced 10-year anal infections by 87% and oral infections by 88% contrasted to a 59% efficacious vaccine that reduced 10-year anal infections by 60% and oral infections by 61% (Supplemental Table 1). With vaccine efficacy markedly strengthened, the majority of HPV infections blocked at all vaccination levels were due to immunity rather than condom use (Supplemental Table 3). Varying condom effectiveness did not appreciably change incident infections although more infections were blocked as a result of vaccination (Supplemental Tables 2 and 4).

## 4. Discussion

Prevention of the HPV-associated cancers starts at prevention of exposure to the viruses. Exposure to HPV among MSM occurs through oral-genital, anal-genital, and oral-anal contacts. Current prevention methods include HPV immunization, barrier protection through use of condoms, and risk adaptive behaviors, such as serosorting by HIV status. These strategies have been used with varying degrees of success. For example, the vaccines against HPV have been demonstrated to be immunogenic, safe, and efficacious [48]. Yet remarkably, compared to other vaccines during childhood, HPV vaccination lags well behind, and may be related to regional, racial and ethnic, socioeconomic, and sexual minority disparities [54]. Additionally, as only sexually active individuals are at-risk of being exposed, many parents may be hesitant, misinformed, or unaware to immunize their children prior to first engaging in sex, despite this being the opportune time to vaccinate [3].

**Table 3**
Proportion of anal and oral HPV infections prevented among YMSM based on three STI prevention strategies: HPV vaccination, condom use, and HIV seroadaptive behaviors (anal sex only). Statistics summarized across 50 simulated runs of the model.

| Anatomic site | Immunization level[a] | Vaccination | Condoms | HIV seroadaption |
|---|---|---|---|---|
| Anal transmission | 0% | 0% | 100% | <1% |
| | 13% | 50%[b] | 50%[b] | <1%[b] |
| | 25% | 57% | 43% | <1% |
| | 50% | 61% | 39% | <1% |
| | 80% | 64% | 36% | <1% |
| | 100% | 64% | 36% | <1% |
| Oral transmission | 0% | 0% | 100% | – |
| | 13% | 87% | 13% | – |
| | 25% | 92% | 8% | – |
| | 50% | 95% | 5% | – |
| | 80% | 96% | 4% | – |
| | 100% | 96% | 4% | – |

*YMSM*, young men who have sex with men; *HPV*, human papillomavirus; *HIV*, human immunodeficiency virus; *STI*, sexually transmitted infection.
[a] Within each group of those vaccinated, 31% received one dose, 15% received two doses, and 54% completed the series.
[b] For example, when examining the proportion of new anal infections averted at 13% vaccination coverage among YMSM, 50% can be attributed to immunization and 50% can be attributed to condoms. HIV seroadaptive practices blocked a negligible proportion.

Our study observed that to have the greatest reduction in viral transmissions among YMSM required multiple concomitant prevention strategies. A meta-analysis conducted in 2008 compared efficacy of condom use versus vaccination against HPV and noted the vaccine was the better performing STI prevention method, although MSM were not the focus of this review [55]. The author then went on to note that "despite the strong efficacy of the HPV vaccine, it does not protect against all types of HPV; therefore, condom use may still play a role in reducing infection transmission for both men and women." At the time, a nonavalent vaccine was not available, although condoms should protect against all types of HPV, including oncogenic types not covered in the nonavalent vaccine, as well as other sexually transmitted infections [32,56]. Our study observed an inflection point at around the estimated present day levels of immunization coverage among MSM (13%) [6] whereby vaccination effectively blocked more HPV transmissions only when coverage exceeded present day levels. Based on these observations, additional HPV preventive strategies are always warranted.

Coupled with the increase in HIV pre-exposure prophylaxis (PrEP) use, the landscape for STI prevention among MSM is changing. PrEP has lowered fear surrounding condomless anal intercourse and has been associated with improved detection of STIs [20,57]. With fear of HIV reduced, sexual behavior may be changing, although the evidence is mixed. Some studies have suggested that MSM may have more sexual partners and decreased condom use, while other studies have found no change in behavior [20]. If this phenomenon is real and MSM are having greater amounts of condomless sex, this places an even greater emphasis on vaccination as a tool for preventing HPV acquisition. As an aside, the evidence surrounding male circumcision to prevent HPV is inconclusive in U.S.-based populations [58].

The impact of HPV vaccination on oral transmission is not as well studied as anogenital transmission. Recent evidence confirmed that HPV vaccination successfully protects against oral HPV [59]. Overall prevalence of HPV in the oropharynx is lower compared to anogenital areas; reasons posited for this divergence include greater persistence of the virus at the anal site and technical difficulties in oral testing [60]. Nevertheless, given the hypothesized low rate of condom use during oral sex, we contend that scaling up HPV vaccination will have a substantial public health impact for lowering head and neck HPV-associated cancers among YMSM.

As we move beyond the first decade since HPV-vaccines have been used, real-world data allow measurement of the risk reduction attributed to vaccination, albeit in females initially. Markowitz et al. used virologic data from the National Health and Nutrition Examination Survey (obtained from cervical swabs) to show a 64% decline in prevalence of the four HPV types in the current quadrivalent vaccine among females aged 14–19 years [61]. However, given the licensure of a nonavalent vaccine that provides protection against additional oncogenic HPV genotypes and the comparatively low uptake among YMSM, the benefits need to be evaluated through simulation studies.

Short term benefits of vaccination are useful for public health officials when using incidence rates to evaluate policy and program impacts. In the study by Zhang et al., which included a twenty year simulation horizon, the authors observed a 51% to 71% reduction in HPV by deploying a "targeted" program for Australian YMSM that vaccinates 20% of unvaccinated MSM per year [18]. Both our and Zhang's results provide empirically-grounded estimates of the range of short-term benefits that could be expected from different combinations of MSM-focused STI prevention strategies. Short term estimates are also of greater interest to policymakers, especially elected officials, than long term benefits because short term benefits have immediate implications for budget impact and are can be used for political purposes to demonstrate what policymakers' have accomplished during their term in office [62]. Long term estimates often lack political relevance because benefits will be achieved well after elected officials terms in office have ended. Further, for the individual who is not immune or has a compromised immune system due to HIV infection, condom use and risk adaptive behaviors become even more important to guard against exposure to the virus. It is worth noting that comparing estimates across various HPV models may be hampered by assumptions about vaccine efficacy. Our default model condition was assuming YMSM get vaccinated post sexual debut as suggested by the literature [18,48]. We based our vaccine efficacy estimates on results from an intention-to-treat analysis, which can be thought of as its real-world effectiveness as some of the individuals in the intention-to-treat arm would have received vaccine after exposure to HPV [63]. If we examine the per-protocol analysis, the comparison groups was not potentially confounded by this factor, and therefore the treatment group was naïve to HPV as YMSM would be prior to sexual debut.

### 4.1. Limitations and strengths

There are several simplifying limitations to keep in mind when interpreting results. First, we considered an HPV infection of the genitals (penis) to also indicate an HPV infection of the anus or rectum, and did not consider other sexual acts that may have conferred risk of HPV transmission, such as rimming (oral-anal contact), nudging (non-insertive genital-anal contact), and dipping (briefly-insertive genital-anal contact). Limited evidence suggests type-specific concordance between anal and penile infections [64]. Second, given the inconclusive evidence surrounding natural immunity to HPV [49], we chose not to model this phenomenon, potentially overestimating vaccinations benefits if immunity follows clearance. HPV clearance in HIV positive individuals may also be mediated by immune reconstitution due to HIV antiretroviral therapy with viral suppression [65]. Extant studies have been conducted only in vaginal mucosa, although it may be possible for this to occur in the oral and anal mucosa of males. Third, our focus was on viral transmission, not epithelial changes leading to neoplasms. Bearing in mind the natural history of HPV-associated cancers, our estimates should not be inferred as reduction in oropharyngeal or anogenital neoplasms. Fourth, our focus on a YMSM population ignores sexual partnerships between YMSM and older men. As an older population were ineligible for vaccination, this is a potential important reservoir for HPV. Finally, STI prevention strategies were modeled independently. It is plausible to believe that condom use, vaccination, and HIV seroadaptive strategies are necessarily related to one another, yet data are lacking to indicate how these strategies are employed in conjunction. Study strengths included modeling both anal and oral transmission, HIV coinfection, a network modeling approach incorporating assortative mixing, and a well-calibrated model representing YMSM sexual partnerships in Philadelphia with potential broad generalizability to other urban areas.

## 5. Conclusions

In this simulation study of HPV among a population of men who have sex with men, we found both condom use and vaccination to be key public health tools to reduce viral transmission. HIV seroadaptive strategies should not be viewed as a primary prevention method for HPV, as they incidentally blocked only a marginal proportion of total HPV transmissions. Meanwhile, condom use should be further promoted for oral sex given its potential to block not only the HPV types not covered in the nonavalent vaccine, but

other sexually transmitted infections. Yet recognizing that MSM chose not to always use condoms, for example due to perceived loss of intimacy, scaling up vaccination pre-sexual debut should continue to be a focus of HPV prevention campaigns especially for oral transmission.

## Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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## Contributions

NDG and MTL conceptualized the study. NDG, MTL, and NKT programmed the statistical models and interpreted the results. NDG drafted the initial manuscript. All authors contributed to and approved of the final manuscript.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.05.047.

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