HPV Vaccine Effectiveness by Age and Timing of Vaccination Relative to Age at First Sex among Men who Have Sex with Men – Seattle, Washington, 2018-2020

Stephanie Ann Buchbinder

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Rachel Winer

Jim Hughes

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Department of Epidemiology

University of Washington

Abstract

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Stephanie Ann Buchbinder

Chair of the Supervisory Committee:

Rachel Winer

Department of Epidemiology

Men who have sex with men (MSM) are at high risk for anal human papillomavirus (HPV) infection, the primary cause of anal cancer. HPV vaccines are approved for individuals aged 9-45 years. We evaluated the effectiveness of the vaccine at preventing vaccine-type anal HPV infection among 18–45-year-old MSM using surveillance data from a sexual health clinic in Seattle, Washington from 2018-2020. Residual specimens from rectal swabs that were self-collected for routine chlamydia and gonorrhea testing were sent to the Centers for Disease Control and Prevention (CDC) laboratory for polymerase chain reaction-based HPV testing. Specimens were genotyped for 19 high-risk HPV types and 9 low-risk HPV types. For each specimen, demographic, clinical, sexual behavioral, and HPV vaccination data were extracted from routine clinical questionnaires and electronic medical records. We used log-binomial regression to calculate adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for associations between ever having received ≥1 dose of HPV vaccine and quadrivalent HPV vaccine-type (4vHPV-type) anal HPV detection, by age group (18-26, 27-35, and 36-45 years). We also evaluated age at vaccination and age at vaccination relative to age at first sex as exposures in separate models among those aged 18-26, and age at vaccination among those aged 27-35. All analyses were adjusted for race and ethnicity, history of pre-exposure prophylaxis (PrEP) use for HIV prevention, and lifetime number of sex partners of any sex. Among 1092 individuals included, documented vaccination history was observed in 290 of the 486 individuals aged 18-26 (59.7%), 130 of the 328 individuals aged 27-35 (39.6%), and 53 of the 278 individuals aged 36-45 (19.1%). Among those aged 18-26, 4vHPV-type HPV prevalence was higher in vaccinated versus unvaccinated individuals (aPR 1.49 [95% CI: 1.06-2.09). However, when considering age at vaccination, we observed a lower prevalence of 4vHPV-type HPV among those who received their first dose at or before age 18 (5.7%) compared with those who were unvaccinated (21.9%), indicating a significant protective association (aPR 0.26 [95% CI: 0.08-0.80]). Similarly, when stratified by timing of vaccination relative to age at first sex, we observed a lower prevalence of 4vHPV-type HPV among those vaccinated prior to first sex (2.9%) compared to those who were unvaccinated (21.9%), indicating a significant protective association (aPR 0.15 [95% CI: 0.02-1.07]). Among those aged 27-35, a history of HPV vaccination was not associated with 4vHPV-type HPV prevalence (aPR 0.75 [95% CI: 0.55, 1.03]). However, when considering age at vaccination, we found that the prevalence was lower among those vaccinated between the ages of 18 and 26 (23.7%) compared to those who were unvaccinated (41.9%), indicating a significant protective association (aPR 0.56 [95% CI: 0.36-0.87]). We did not observe a significant association between vaccination status and 4vHPV-type HPV infection among those aged 36-45 (aPR 1.07 [95% CI: 0.77, 1.50]). Results suggest the vaccine is effective when administered at younger ages and/or before first sex. Results do not suggest significant effectiveness among those vaccinated after age 27.

INTRODUCTION

High-risk strains of HPV are responsible for nearly 35,000 cancer cases in the U.S. each year [1]. In 2006, HPV vaccines were first introduced and recommended by the U.S. Advisory Committee on Immunization Practices (ACIP) for females as a method to reduce the burden of HPV infection and HPV-related cancer in the population [2]. Since 2011, the vaccine has also been routinely recommended for males, ideally to be administered at age 11-12 but approved for individuals age 9-26 and recently expanded in 2019 to include individuals through age 45, based on shared clinical-decision making [2]. There are two HPV vaccines licensed for use in males in the U.S.: nonavalent (9vHPV, Gardasil 9, Merck) which protects against HPV-6, HPV-11, HPV-16, and HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, HPV-58 and quadrivalent (4vHPV, Gardasil, Merck) which protects against HPV-6, HPV-11, HPV-16, HPV-18. Only 9vHPV is distributed in the U.S. as of late 2016 [2].

Men who have sex with men (MSM) are at high risk for both HPV infection and HPV-related cancer [4,5]. Anal HPV infection, the primary cause of anal cancer, is particularly common among MSM [6]. It is estimated that anal cancer incidence among MSM is 44 times higher than among the general population [7]. The quadrivalent HPV vaccine (4vHPV) is a highly efficacious, evidence-based method to prevent HPV acquisition among MSM, as demonstrated in clinical trials. In a subset of over 600 MSM participating in a clinical trial of the 4vHPV vaccine, the efficacy of the vaccine against vaccine-type HPV detection was 84% among men not infected at the time of vaccination [8]. Despite demonstrated efficacy of the HPV vaccine, uptake among MSM has been slow [9]. Thus, it has only recently become feasible to evaluate real-world vaccine effectiveness through observational studies. The vaccine impact in men (VIM) study, a cross-sectional study, sought to evaluate vaccine effectiveness among participants aged 18-26 years using self-reported vaccine history. The results found that the prevalence of anal or oral vaccine-type HPV was lower among vaccinated participants (22.9%) than unvaccinated participants (31.6%), indicating vaccine effectiveness of 29%, although vaccine effectiveness was higher among those who reported initiating vaccination before age 18 [3].

Due to the novelty of updated ACIP HPV vaccine guidelines to include a larger age-range and slow uptake of the HPV vaccine among MSM [10], this study is among the first of its kind to evaluate real-world vaccine effectiveness among adult MSM up to age 45. Our goal was to examine the effectiveness of the HPV vaccine at preventing 4vHPV-type infection among MSM in three distinct age groups (18-26, 27-35, 36-45), and whether effectiveness within each age group is modified by age at vaccine administration or timing of vaccination relative to age at first sex.

METHODS

Study Design

We conducted a cross-sectional analysis of the effectiveness of the HPV vaccine at preventing 4vHPV-type infection among MSM. We used surveillance data from Public Health Seattle King County (PHSKC) Sexual Health Clinic patients.

Study Setting and Subjects

This was a surveillance study of MSM who underwent testing for anal sexually transmitted infections (STIs) at the PHSKC Sexual Health Clinic in Seattle, Washington from December 2018-June 2020 and met the following inclusion criteria: age 18-45 years, male (assigned at birth, regardless of current gender identity or expression), and have sex with men (identify as gay or bisexual or have had any type of sexual contact with a male partner). The University of Washington Human Subjects Division determined that this public health surveillance project was not research and therefore exempt from Institutional Review Board review.

Data Collection

We identified residual swab specimens from patients who met the inclusion criteria. Patients self-collected rectal swabs using the Aptima Multitest Swab Specimen Collection Kit (2.9 mL Aptima swab transport media), and specimens were tested for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) via the Hologic Aptima COMBO2 assay on the Hologic Panther System. Following CT/NG testing, residual rectal swabs were stored vertically at room temperature (-20° C) and sent to the Centers for Disease Control and Prevention (CDC) laboratory for HPV testing conducted using the SeeGene Novaplex™ II HPV28 Detection system which tests for 19 high-risk HPV types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82) and 9 low-risk HPV types (6, 11, 40, 42, 43, 44, 54, 61, 70) [11]. For each specimen, the following demographic and clinical data were collected as part of routine clinical practice: age, sex, gender, race and ethnicity, documented HPV vaccination history (including number of doses received and dates of vaccination), lifetime number of sex partners, age at first sex, history of ever using pre-exposure prophylaxis (PrEP) for HIV prevention, result of most recent HIV test, history of genital warts, and concurrent CT/NG test results. Age, race and ethnicity, documented HPV vaccination history, documented HIV status, history of genital warts, and concurrent CT/NG test results were abstracted from electronic medical records (EMR). Sex, gender, lifetime number of sex partners, age at first sex, and history of PrEP use for HIV prevention were self-reported and collected via computer assisted self-interview (CASI) facilitated by a clinician.

Exposures and Outcomes

The primary exposure of interest for this study was HPV vaccination history documented in the EMR. EMR data were pulled from multiple sources, including all UW Medicine clinics and other clinics on the Care Everywhere Epic network. We defined an unvaccinated individual as someone who had no doses of HPV vaccine documented >30 days prior to specimen collection, and a vaccinated individual as someone who had ≥1 dose of any HPV vaccine documented ≥30 days prior to specimen collection. Additional exposures of interest were age at vaccination and timing of vaccination relative to age at first sex. Age at vaccination was defined as the recorded age at first dose of the HPV vaccine (<18, 18-26, >26). Timing of vaccination relative to age at first sex was calculated using recorded age at vaccination and self-reported age at first sex and categorized as: prior to first sex, at or after first sex, and unknown (if missing data for age at first sex). The primary outcome of interest for this study was any 4vHPV-type infection (HPV 6, 11, 16, and/or 18). While we collected data on both 4vHPV and 9vHPV, we selected 4vHPV as the main outcome because both vaccines contain the 4vHPV types and many individuals were vaccinated before 2019 while 4vHPV was still routinely administered. The secondary outcome of interest for this study was non4vHPV-type infection (any of the 28 HPV types captured by the assay except types 6, 11, 16, or 18). Confounders were determined *a priori* and included race and ethnicity, history of PrEP use for HIV prevention, and lifetime number of sex partners of any sex.

Data Analysis

All analyses were stratified by age group (18-26, 27-35, 36-45). We used χ^2, Wilcoxon rank-sum, or Fisher exact tests to compare the demographic, health, and sexual behavior characteristics of unvaccinated to vaccinated participants. We also used χ^2, Wilcoxon rank-sum, or Fisher exact tests to identify characteristics associated with anal HPV detection (≥1 of any HPV type, ≥1 4vHPV type, ≥1 non4vHPV type). We calculated anal HPV prevalence (≥1 of any HPV type, ≥1 4vHPV type, ≥1 9vHPV type, ≥1 additional 9vHPV type not targeted by 4vHPV, ≥1 non4vHPV type, ≥1 non9vHPV type, and individual HPV vaccine types) and 95% confidence intervals (CI) by vaccination history. We used log-binomial regression to calculate crude and adjusted prevalence ratios (aPRs) and 95% CIs for associations between documented HPV vaccination history and anal HPV detection (≥1 4vHPV or ≥1 non4vHPV type). In addition to dichotomous documented HPV vaccination history, we also evaluated age at vaccination and age at vaccination relative to age at first sex in separate models among those aged 18-26, and age at vaccination among those aged 27-35. We used generalized estimating equations log-binomial regression to assess for the significance of effect modification by HPV type group (4vHPV, non4vHPV) on associations between vaccination history, age at vaccination, and timing of first sex in relation to age

at vaccination and HPV detection. All analyses were adjusted for race/ethnicity, history of PrEP use for HIV prevention, and lifetime number of sex partners of any sex. All analyses were conducted using R version 4.0.2 software.

Results

A total of 1092 individuals who met the eligibility criteria were included in the analyses, after excluding 8 individuals whose specimens returned indeterminate HPV test results (0.7% of tested specimens). Four hundred and eighty-six participants (45%) were aged 18-26 years, 328 (30%) were aged 27-35 years, and 278 (25%) were aged 36-45 years (Table 1). In all 3 age groups, most individuals identified as non-Hispanic white (46.3%-52.2%) and male (89.9%-90.5%). Median lifetime number of sex partners of any sex increased with age, with the lowest among men aged 18-26 (30; interquartile range (IQR), 15.5, 60.5) and highest among men aged 36-45 (74; IQR, 30, 152). Most individuals in all 3 age groups reported having more than 20 sex partners in their lifetime (53.7%-69.2%). Most individuals reported history of PrEP use for HIV prevention (59.1%-61.9%) and very few were HIV-positive (0.7%-1.5%). Most individuals tested negative for both chlamydia (86.6%-91.4%) and gonorrhea (89.9%-90.5%).

More than half (59.7%) of the individuals aged 18-26 years, 39.6% of those aged 27-35 years, and 19.1% of those aged 36-45 years were vaccinated (Table 1). History of PrEP use for HIV prevention was significantly higher among vaccinated individuals in all 3 age groups (75.2%-81.1%) than among unvaccinated individuals (35.2%-50.6%). A significant difference in gender identity by vaccination status was also noted among those aged 18-26 years, as vaccinated individuals were more likely to identify as male (93.4%) than unvaccinated individuals (86.2%). A significant difference in race and ethnicity by vaccination status was noted among those aged 36-45 years, as unvaccinated individuals were more likely to self-identify as non-Hispanic white (56.0%) than vaccinated individuals (35.8%). In all 3 age groups, most vaccinated participants received 9vHPV only (53.8%- 92.5%).

In all 3 age groups, most participants had HPV detected (81.7%-87.8%), and 27.4%-43.9% had 4vHPV types detected (Table 2). Differences in type-specific prevalence between vaccinated and unvaccinated individuals varied by HPV type and age group (Figure 1).

Comparing participants by the detection of any HPV and non4vHPV-type HPV, significantly more individuals aged 18-26 years with any HPV and/or non4vHPV-type HPV had a lifetime number of sex partners greater than 20 and reported history of PrEP use for HIV prevention (Table 2). No significant differences were noted when comparing participants by detection of 4vHPV-type HPV for any age group. Observed differences in prevalence for other characteristics (race/ethnicity, gender identity, HIV status, history of genital warts, chlamydia/gonorrhea test results) were not statistically significant.

Among individuals aged 18-26, the prevalence of 4vHPV-type HPV was higher among those who were vaccinated (31.0%) compared with those who were unvaccinated (21.9%) (aPR 1.49 [95% CI: 1.06-2.09) (Table 3). When stratified by age at vaccination, however, we observed a lower prevalence of 4vHPV-type HPV among those who received their first dose at or before age 18 (5.7%) compared with those who were unvaccinated (21.9%), indicating a significant protective association (aPR 0.26 [95% CI: 0.08-0.80]), and corresponding to a vaccine effectiveness of 74%. Similarly, when stratified by timing of vaccination relative to age at first sex, we observed a lower prevalence of 4vHPV-type HPV among those vaccinated prior to first sex (2.9%) compared to those who were unvaccinated (21.9%), indicating a significant protective association (aPR 0.15 [95% CI: 0.02-1.07]), and corresponding to a vaccine effectiveness of 85%. We observed a significant difference between timing of vaccination relative to first sex and HPV status by HPV type (p=0.057).

Among individuals aged 27-35, we found that the prevalence of 4vHPV-type HPV was lower among those who were vaccinated (31.5%) compared to those who were unvaccinated (41.9%), although the association was not significant (aPR 0.75 [95% CI: 0.55, 1.03]). The relationship between vaccination history and HPV status did not differ significantly by HPV type (p=0.996). However, when stratifying by age at vaccination, we found that the prevalence was lower among those vaccinated between the ages of

18 and 26 (23.7%) compared to those who were unvaccinated (41.9%), indicating a significant protective association (aPR 0.56 [95% CI: 0.36-0.87]), and corresponding to a vaccine effectiveness of 44%.

We did not observe a significant association between vaccination status and 4vHPV-type HPV infection among those aged 36-45 (aPR 1.07 [95% CI: 0.77, 1.50]).

We did not observe any significant associations between vaccination status and non4vHPV-type HPV in any of the age groups. No significant interactions between vaccination history, age at vaccination, or timing of vaccination relative to first sex by HPV type group were observed.

Discussion

This study was one of the few to evaluate real-world HPV vaccine effectiveness among men who have sex with men (MSM). We found that among those aged 18-26 years, the vaccine showed a protective effect against 4vHPV-type anal HPV infection among those who were vaccinated at or before age 18 or before first sex. We also found that among those aged 27-35 years, the vaccine showed a protective effect among those who were vaccinated between the ages of 18-26 years, which was the earliest time at which this age group was eligible to receive the vaccine given that guidelines did not recommend vaccination for males until 2011. We did not observe a protective effect among those aged 36-45 years.

The protective effect we observed among those aged 18-26 years who were vaccinated at or before age 18 or before first sex aligns with findings from other research studies that found that vaccination at or before age 18 or before first sex maximized vaccine effectiveness against HPV infection and disease, including cervical lesions in women [12,13] and anogenital warts in both men and women [14,15]. A prior study of MSM recruited from the same sexual health clinic in Seattle and from similar clinics in Chicago and Los Angeles also found that there was a stronger protective effect against anal and oral 4vHPV-type HPV among those vaccinated before or at age 18 than among those vaccinated after age 18 [3]. Using a subset of participants from Seattle, the same study evaluated 4vHPV protection against penile vaccine-type HPV and found a significant protective effect only in those vaccinated before or at age 18, and no infections in those vaccinated before first sex [16].

Among those aged 18-26 years, we observed a significantly higher prevalence of 4vHPV-type HPV infection among those who were vaccinated after age 18 or after first sex compared with unvaccinated individuals, an unexpected finding. Data regarding vaccination status was extracted from EMR data only. While EMR data were pulled from multiple sources, including all UW Medicine clinics and other clinics that use Care Everywhere, it is possible that some individuals could have been vaccinated by their primary care (or other) provider outside of this EMR system, and subsequently misclassified as unvaccinated due to the absence of documentation within this reporting system. If misclassification was more likely among those vaccinated in early adolescence (when vaccination is most effective), this could partially explain the lower prevalence of 4vHPV-type HPV observed among "unvaccinated" individuals. Another possibility is that the development of STI symptoms, such as genital warts, may increase the likelihood that an individual will seek testing and/or treatment, providing an opportunity for catch-up vaccination that may not exist among those who do not have symptoms or seek services. Thus, it is plausible that the individuals in this age group who were vaccinated after age 18 may be engaging in riskier sexual behavior and more frequent clinic visits than unvaccinated individuals, potentially explaining the higher prevalence among vaccinated individuals despite vaccination history. We also observed that vaccinated participants in this age group were more likely to report a history of genital warts than unvaccinated participants (though the difference was not statistically significant), and a higher prevalence of genital wart-related types HPV-6 and HPV-11 (but not HPV-16 or HPV-18). Although we attempted to address this by adjusting for some risk behaviors (lifetime number of sex partners, PrEP use), it is also plausible that this association is a result of residual or unmeasured confounding by other relevant risk behaviors we were unable to measure.

In contrast to our findings in the 18-26-year-old age group, we found a protective effect of HPV vaccination against anal 4vHPV infection among those aged 27-35 who were vaccinated between the ages of 18-26. Observational data in this age group are limited. A randomized trial in women aged 24-45 found

that while the 4vHPV vaccine was most efficacious among those with no evidence of prior or current infection, it still showed a protective effect among those with evidence of previous exposure to 4vHPV-type HPV infection (seropositive and DNA negative) [17]. The difference in effect we observed between age groups may suggest differences in HPV status at the time of vaccination. Thus, despite higher number of lifetime sex partners and subsequent higher exposure to HPV in the 27-35 age group, it is plausible that if few individuals in this age group had active infection at the time of vaccination, regardless of previous infection, the vaccine would be more effective. A report released by the National Center for Health Statistics in 2020 on HPV vaccination coverage in the United States found that despite increasing rates of vaccination overall, only 27% of men aged 18-26 had received the HPV vaccine as of 2018 [18]. Our finding suggests that vaccination between the ages of 18-26, despite being outside of the ideal timeframe for vaccination in adolescence, can offer significant protection against 4vHPV in MSM over the next decade of life.

We did not observe any significant protective effect among those aged 36-45, likely due either to significant exposure to HPV prior to vaccination or active infection at the time of vaccination. All individuals in this age group were vaccinated after age 26, consistent with the timing of the 2019 change in vaccination guidelines to include adults through aged 27-45 years [2]. Among individuals in this age group, the median lifetime number of sex partners was 75. As lifetime number of sex partners is a strong risk factor for HPV infection [10, 11], vaccinated individuals in this age group likely had more frequent exposure to HPV than their unvaccinated counterparts, thus decreasing vaccine effectiveness. It is also possible that individuals in this age group had active infection at the time of vaccination, thus diminishing any protective effect the vaccine may have offered. It is likely that the absence of a protective effect in our study population was attributable to a combination of the effects of high-risk sexual behavior and high levels of exposure to HPV over several decades. Prior to changing guidelines to include adults through age 45, ACIP considered data from 11 clinical trials of 9vHPV, 4vHPV, and/or 2vHPV in adults aged 27-45 [2]. They concluded that vaccine effectiveness will be lower in older age groups because of prior infections and some previously exposed adults will have already developed natural immunity, so population benefit would be minimal but recommended shared clinical decision making for individuals who may benefit from the vaccine. Our findings highlight the importance of shared clinical decision making to determine the benefit of vaccination among older adults.

In addition to our primary analyses evaluating vaccine effectiveness against 4vHPV-type HPV, we conducted additional analyses to evaluate vaccine effectiveness against non4vHPV-type HPV with the goal of elucidating potential unmeasured confounding that might indicate differences between unvaccinated and vaccinated individuals regarding sexual behavior. Given that we did not observe any protective effect, it is likely that unvaccinated and vaccinated individuals had similar levels of exposure to HPV, perhaps due to similar sexual behavior, as evidenced by similar age at first sex and lifetime number of sex partners between unvaccinated and vaccinated individuals within the same age groups.

Our analysis has two main strengths. First, our use of documented vaccination history, rather than self-report, reduced misclassification bias by eliminating any inconsistencies that may arise from individual recall of details surrounding the administration and timing of vaccinations, especially among those with longer time since their first dose [19]. Second, our use of surveillance data eliminated participation bias. Our analysis is subject to three main limitations. First, our data is subject to social desirability and/or recall bias, specifically for variables regarding sexual behavior including age at first sex and lifetime number of sex partners. Second, while documented vaccination history is more accurate than self-report, it is probable that some individuals were misclassified as unvaccinated as we did not have access to data on vaccinations received outside of the Care Everywhere EMR system. Third, the cross-sectional nature of our study did not allow for evaluation of HPV vaccination effectiveness against anal HPV acquisition.

Conclusions

This study reports HPV vaccine effectiveness against vaccine-type HPV infection among MSM in 3 distinct age groups (18-26, 27-35, 36-45) in a real-world setting. Among those aged 18-26 years,

HPV vaccination was shown to be effective against anal 4vHPV-type HPV infection when administered at or before age 18 or before initiation of sexual activity. Among those aged 27-35, HPV vaccination was effective against anal 4vHPV-type HPV infection when administered between the ages of 18-26 years. No protective effect was observed with HPV vaccination among those aged 36-45 likely attributable to late vaccination after age 26 (due to the timing of vaccination guidelines for different age groups) and HPV exposure before vaccination. Results highlight the importance of routine HPV vaccination as early as possible and support efforts to increase uptake of the vaccine among MSM. As time evolves and more observational data become available, additional analyses will be possible in different age groups. Future research should consider additional factors that may modify HPV vaccine effectiveness.

Table 1. Characteristics of Participating Men Who Have Sex with Men, by documented HPV vaccination status- Seattle, Washington, 2018-2020, N=1092

Characteristic	Total N (%)	Unvaccinated[1] n (%)	Vaccinated[2] n (%)	p[3]
Age 18-26	486	196 (40.3)	290 (59.7)	
Race/ethnicity				
Non-Hispanic white	225 (46.3)	99 (50.5)	126 (43.4)	0.45[4]
Non-Hispanic black	32 (6.6)	11 (5.6)	21 (7.2)	
Asian/Pacific Islander	78 (16.0)	26 (13.3)	52 (17.9)	
Hispanic	117 (24.1)	45 (23.0)	72 (24.8)	
Other or unknown	34 (7.0)	15 (7.7)	29 (6.6)	
Gender Identity				
Male	440 (90.5)	169 (86.2)	271 (93.4)	**0.02[5]**
Female/Transgender Female	8 (1.6)	4 (2.0)	4 (1.4)	
Other/Unknown/Missing	38 (7.8)	23 (11.7)	15 (5.2)	
Lifetime number of partners of any sex				
≤5	28 (5.8)	14 (7.1)	14 (4.8)	0.07[4]
6-10	50 (10.3)	24 (12.2)	26 (9.0)	
11-20	84 (17.3)	32 (16.3)	52 (17.9)	
>20	261 (53.7)	93 (47.4)	168 (57.9)	
Unknown	63 (13.0)	33 (16.8)	30 (10.3)	
Lifetime number of sex partners of any sex (median, IQR)	30 (15.5, 60)	27 (12, 60.5)	30 (20, 60)	0.07[6]
Age at first sex (median, IQR)	17 (15, 18)	17 (15, 18)	17 (15, 18)	0.35[6]
History of ever taking PrEP for HIV prevention				
No or unknown	199 (40.9)	127 (64.8)	72 (24.8)	**<0.001**[4]
Yes	287 (59.1)	69 (35.2)	218 (75.2)	
Most Recent HIV Test Result				
Negative or unknown	479 (98.6)	193 (98.5)	286 (98.6)	1.0[5]
Positive	7 (1.4)	3 (1.5)	4 (1.4)	
History of Genital Warts				
No/Unknown	463 (95.3)	190 (96.9)	273 (94.1)	0.23[4]
Yes	23 (4.7)	6 (3.1)	17 (5.9)	
Chlamydia test result				
Negative or other[7]	421 (86.6)	166 (84.7)	255 (87.9)	0.37[4]
Positive	65 (13.4)	30 (15.3)	35 (12.1)	
Gonorrhea test result				
Negative or other[7]	440 (90.5)	177 (90.3)	263 (90.7)	1.0[4]
Positive	46 (9.5)	19 (9.7)	27 (9.3)	
Age at first HPV vaccination				
<18			53 (18.3)	-
18-26			237 (81.7)	
Age at first HPV vaccination (median, IQR)			22 (18, 24)	-
HPV vaccine type				
4-valent			48 (16.6)	-
9-valent			194 (66.9)	
Combination of 4-valent and 9-valent			42 (14.5)	
Unknown			6 (2.1)	
Timing of HPV vaccination relative to first sex				

Prior to first sex			35 (12.1)	-
At or after first sex			226 (77.9)	
Unknown			29 (10.0)	
Age 27-35	328	198 (60.4)	130 (39.6)	
Race/ethnicity				
Non-Hispanic white	154 (47.0)	97 (49.0)	57 (43.8)	0.27[4]
Non-Hispanic black	28 (8.5)	21 (10.6)	7 (5.4)	
Asian/Pacific Islander	37 (11.3)	20 (10.1)	17 (13.1)	
Hispanic	84 (25.6)	45 (22.7)	39 (30.0)	
Other/unknown	25 (7.6)	15 (7.6)	10 (7.7)	
Gender Identity				
Male	296 (90.2)	178 (89.9)	118 (90.8)	0.58[5]
Female/Transgender Female	3 (0.9)	1 (0.5)	2 (1.5)	
Other/Unknown/Missing	29 (8.8)	19 (9.6)	10 (7.7)	
Lifetime number of partners of any sex				
≤5	6 (1.8)	4 (2.0)	2 (1.5)	0.64[5]
6-10	21 (6.4)	15 (7.6)	6 (4.6)	
11-20	31 (9.5)	18 (9.1)	13 (10.0)	
>20	227 (69.2)	132 (66.7)	95 (73.1)	
Unknown	43 (13.1)	29 (14.6)	14 (10.8)	
Lifetime number of sex partners of any sex (median, IQR)	50 (25, 100)	50 (24, 100)	50 (26.8, 100)	0.26[6]
Age at first sex (median, IQR)	17 (15, 19)	17 (16, 19)	17 (15, 20)	0.50[6]
History of ever taking PrEP for HIV prevention				
No or unknown	125 (38.1)	98 (49.5)	27 (20.8)	**<0.001**[4]
Yes	203 (61.9)	100 (50.5)	103 (79.2)	
Most Recent HIV Test Result				
Negative or unknown	323 (98.5)	195 (98.5)	128 (98.5)	1.0[5]
Positive	5 (1.5)	3 (1.5)	2 (1.5)	
History of Genital Warts				
No/unknown	306 (93.3)	183 (92.4)	123 (94.6)	0.58[4]
Yes	22 (6.7)	15 (7.6)	7 (5.4)	
Chlamydia test result				
Negative	284 (86.6)	166 (83.8)	118 (90.8)	0.10[4]
Positive	44 (13.4)	32 (16.2)	12 (9.2)	
Gonorrhea test result				
Negative or other[1]	295 (89.9)	178 (89.9)	117 (90.0)	1.0[4]
Positive	33 (10.1)	20 (10.1)	13 (10.0)	
Age at first HPV vaccination				
<18			0 (0.0)	-
18-26			76 (58.5)	
>26			54 (41.5)	
Age at first HPV vaccination (median, IQR)			26 (25, 29.75)	-
HPV vaccine type				
4-valent			47 (36.2)	-
9-valent			70 (53.8)	
Combination of 4-valent and 9-valent			13 (10.0)	
Timing of HPV vaccination relative to first sex				
Prior to first sex			0 (0.0)	-
At or after first sex			117 (90.0)	
Unknown			13 (10.0)	

Age 36-45	278	225 (80.9)	53 (19.1)	
Race/ethnicity				
Non-Hispanic white	145 (52.2)	126 (56.0)	19 (35.8)	**0.01**[5]
Non-Hispanic black	16 (5.8)	15 (6.7)	1 (1.9)	
Asian/Pacific Islander	25 (9.0)	15 (6.7)	10 (18.9)	
Hispanic	72 (25.9)	55 (24.4)	17 (32.1)	
Other/unknown	20 (7.2)	14 (6.2)	6 (11.3)	
Gender Identity				
Male	250 (89.9)	202 (89.8)	48 (90.6)	0.21[5]
Female/Transgender Female	1 (0.4)	0 (0.0)	1 (1.9)	
Other/Unknown/Missing	27 (9.7)	23 (10.2)	4 (7.5)	
Lifetime number of partners of any sex				
≤5	8 (2.9)	5 (2.2)	3 (7.3)	0.43[5]
6-10	12 (4.3)	10 (4.4)	2 (4.9)	
11-20	23 (8.3)	20 (8.9)	3 (7.3)	
>20	187 (67.3)	154 (68.4)	33 (80.5)	
Unknown	48 (17.3)	36 (16.0)	12 (22.6)	
Lifetime number of partners of any sex (median, IQR)	74 (30, 152)	75 (30, 152)	50 (25, 151)	0.36[6]
Age at first sex (median, IQR)	18 (16, 21)	18 (15.2, 21)	18 (16, 22)	0.20[6]
History of ever taking PrEP for HIV prevention				
No or unknown	110 (39.6)	100 (44.4)	10 (18.9)	**0.001**[4]
Yes	168 (60.4)	125 (55.6)	43 (81.1)	
Most Recent HIV Test Result				
Negative or unknown	276 (99.3)	223 (99.1)	53 (100.0)	1.00[5]
Positive	2 (0.7)	2 (0.9)	0 (0.0)	
History of Genital Warts				
No/unknown	243 (87.4)	195 (86.7)	48 (90.6)	0.59[4]
Yes	35 (12.6)	30 (13.3)	5 (9.4)	
Chlamydia test result				
Negative or other[1]	256 (91.4)	209 (92.9)	45 (84.9)	0.11[4]
Positive	24 (8.6)	16 (7.1)	8 (15.1)	
Gonorrhea test result				
Negative	250 (89.9)	200 (88.9)	50 (94.3)	0.31[5]
Positive	28 (10.1)	25 (11.1)	3 (5.7)	
Age at first HPV vaccination				
<18			0 (0.0)	-
18-26			0 (0.0)	
>26			53 (100.0)	
Age at first HPV vaccination (median, IQR)			38 (36, 40)	-
HPV vaccine type				
4-valent			3 (5.7)	-
9-valent			49 (92.5)	
Combination of 4-valent and 9-valent			1 (1.9)	
Timing of HPV vaccination relative to first sex				
Prior to first sex			0 (0.0)	-
At or after first sex			43 (81.1)	
Unknown			10 (18.9)	

[1] No documented HPV vaccine doses >30 days prior to specimen collection.
[2] ≥1 dose of any HPV vaccine ≥30 days prior to specimen collection.
[3] Bold font indicates significance of statistical test at p <.05.
[4] Based on χ^2 test.
[5] Based on Fisher's exact test.
[6] Based on Wilcoxon rank-sum test.
[7] "Other" indicates test result that was invalid, equivocal, or returned an error.
Abbreviations: HPV, human papillomavirus; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; HIV, human immunodeficiency virus; IQR, interquartile range.

Table 2: Prevalence of Any Human Papillomavirus (HPV), Quadrivalent HPV Vaccine (4vHPV)–Type HPV or Non–4vHPV-Type HPV, by Characteristics of Participating Men Who Have Sex with Men—Seattle, Washington, 2018-2020

Characteristic	Total N	Any HPV n (%)	p[1]	4vHPV-type HPV n (%)	p[1]	Non-4vHPV-type HPV n (%)	p[1]
Age 18-26	486	397 (81.7)		133 (27.4)		386 (79.4)	
Race/ethnicity							
Non-Hispanic white	225	176 (78.2)	0.086[2]	66 (29.3)	0.575[2]	174 (77.3)	0.076[2]
Non-Hispanic black	32	29 (90.6)		7 (21.9)		29 (90.6)	
Asian/Pacific Islander	78	60 (76.9)		18 (23.1)		56 (71.8)	
Hispanic	117	103 (88.0)		30 (25.6)		100 (85.5)	
Other/unknown	34	29 (85.3)		12 (35.3)		27 (79.4)	
Gender Identity							
Male	440	361 (82.0)	0.367[2]	124 (28.2)	0.487[3]	350 (79.5)	0.469[2]
Female/Transgender Female	8	5 (62.5)		1 (12.5)		5 (62.5)	
Other/Unknown/Missing	38	31 (81.6)		8 (21.1)		31 (81.6)	
Lifetime number of sex partners of any sex							
≤5	28	17 (60.7)	**0.002**[2]	4 (14.3)	0.328[3]	17 (60.7)	**0.001**[2]
6-10	50	36 (72.0)		14 (28.0)		32 (64.0)	
11-20	84	71 (84.5)		25 (29.8)		69 (82.1)	
>20	261	225 (86.2)		77 (29.5)		220 (84.3)	
Unknown	63	48 (76.2)		13 (20.6)		48 (76.2)	
History of ever taking PrEP for HIV prevention							
No or unknown	199	151 (75.9)	**0.008**[2]	54 (27.1)	1.0[2]	143 (71.9)	**<0.001**[2]
Yes	287	246 (85.7)		79 (27.5)		243 (84.7)	
Documented HIV status							
Negative/Unknown	479	391 (81.6)	1.0[2]	130 (27.1)	0.398[3]	380 (79.3)	1.00[2]
Positive	7	6 (85.7)		3 (42.9)		6 (85.7)	
History of Genital Warts							
No/Unknown	463	276 (59.6)	0.344[2]	124 (26.8)	0.291[2]	366 (79.0)	0.515[2]
Yes	23	21 (91.3)		9 (39.1)		20 (87.0)	
Chlamydia test result							
Negative/other[4]	421	340 (80.8)	0.241[2]	118 (28.0)	0.494[2]	330 (78.4)	0.202[2]
Positive	65	57 (87.7)		15 (23.1)		56 (86.2)	
Gonorrhea test result							
Negative/other[4]	440	356 (80.9)	0.241 [2]	119 (27.0)	0.751[2]	345 (78.4)	0.129[2]
Positive	46	41 (89.1)		14 (30.4)		41 (89.1)	
Age 27-35	328	288 (87.8)		124 (37.8)		280 (85.4)	
Race/ethnicity							
Non-Hispanic white	154	141 (91.6)	0.211[2]	59 (38.3)	0.801[2]	138 (89.6)	0.103[2]
Non-Hispanic black	28	23 (82.1)		11 (39.3)		23 (82.1)	

Asian/Pacific Islander	37	32 (86.5)		13 (35.1)		31 (83.8)	
Hispanic	84	69 (82.1)		29 (34.5)		65 (77.4)	
Other/unknown	25	23 (92.0)		12 (48.0)		23 (92.0)	
Gender Identity							
Male	296	259 (87.5)	1.00[3]	108 (36.5)	0.240[3]	251 (84.8)	0.748[3]
Female/Transgender Female	3	3 (100.0)		2 (66.7)		3 (100.0)	
Other/Unknown/Missing	29	26 (89.7)		14 (48.3)		26 (89.7)	
Lifetime number of sex partners of any sex							
≤5	6	5 (83.3)	0.521[2]	2 (33.3)	0.358[3]	4 (66.7)	0.323[3]
6-10	21	16 (76.2)		5 (23.8)		16 (76.2)	
11-20	31	27 (87.1)		13 (41.9)		27 (87.1)	
>20	227	201 (88.5)		83 (36.6)		194 (85.5)	
Unknown	43	39 (90.7)		21 (48.8)		39 (90.7)	
History of ever taking PrEP for HIV prevention							
No or unknown	125	108 (86.4)	0.663[2]	50 (40.0)	0.277[2]	108 (86.4)	0.799[2]
Yes	203	180 (88.7)		74 (36.5)		172 (84.7)	
Documented HIV status							
Negative/Unknown	323	283 (87.6)	0.880[2]	121 (37.5)	0.370[3]	275 (85.1)	0.768[2]
Positive	5	5 (100.0)		3 (60.0)		5 (87.0)	
Presence of Genital Warts							
No/Unknown	306	269 (87.9)	1.00[2]	116 (37.9)	1.00[2]	262 (85.6)	0.861[2]
Yes	22	19 (86.4)		8 (36.4)		18 (81.8)	
Chlamydia test result							
Negative	284	247 (87.0)	0.356[2]	106 (37.3)	0.772[2]	239 (84.2)	0.178[2]
Positive	44	41 (93.2)		18 (40.9)		41 (93.2)	
Gonorrhea test result							
Negative or other[4]	295	256 (86.8)	0.157[2]	113 (38.3)	0.712[2]	248 (84.1)	0.084[2]
Positive	33	32 (97.0)		11 (33.3)		32 (97.0)	
Age 36-45	278	239 (86.0)		122 (43.9)		227 (81.7)	
Race/ethnicity							
Non-Hispanic white	145	123 (84.8)	0.436[2]	72 (49.7)	**0.002**[3]	119 (82.1)	0.860[2]
Non-Hispanic black	16	12 (75.0)		3 (18.8)		12 (75.0)	
Asian/Pacific Islander	25	21 (84.0)		13 (52.0)		19 (76.0)	
Hispanic	72	66 (91.7)		32 (44.4)		60 (83.3)	
Other/unknown	20	17 (85.0)		2 (10.0)		17 (85.0)	
Gender Identity							
Male	250	214 (85.6)	0.809[3]	112 (44.8)	0.222[3]	202 (80.8)	0.538[3]
Female/Transgender Female	1	1 (100.0)		1 (100.0)		1 (100.0)	
Other/Unknown/Missing	27	24 (88.9)		9 (33.3)		24 (88.9)	
Lifetime number of sex partners of any sex							
≤5	8	7 (87.5)	0.638[2]	6 (75.0)	0.429[2]	6 (75.0)	0.471[2]
6-10	12	10 (83.3)		6 (50.0)		9 (75.0)	
11-20	23	18 (78.3)		11 (47.8)		17 (73.9)	

>20	187	160 (85.6)		78 (41.7)		152 (81.3)	
Unknown	48	44 (91.7)		21 (43.8)		43 (89.6)	
History of ever taking PrEP for HIV prevention							
No or unknown	110	93 (84.5)	0.706[2]	51 (46.4)	0.582[2]	90 (81.8)	1.00[2]
Yes	168	146 (86.9)		71 (42.3)		137 (81.5)	
Documented HIV status							
Negative or unknown	276	237 (86.9)	1.00[3]	121 (43.8)	1.00[3]	225 (81.5)	0.469[3]
Positive	2	2 (100.0)		1 (50.0)		2 (100.0)	
Presence of Genital Warts							
No/Unknown	243	208 (85.6)	0.831[2]	104 (42.8)	0.436[2]	199 (81.9)	0.971[2]
Yes	35	31 (88.6)		18 (51.4)		28 (80.0)	
Chlamydia test result							
Negative or other[4]	256	218 (85.2)	1.00[2]	111 (43.4)	1.00[2]	207 (80.9)	1.00[2]
Positive	24	21 (87.5)		11 (45.8)		20 (83.3)	
Gonorrhea test result							
Negative	250	213 (85.2)	0.413[2]	110 (44.0)	1.00[2]	201 (80.4)	0.175[2]
Positive	28	26 (92.9)		12 (42.9)		26 (92.9)	

[1] Bold font indicates significance of statistical test at $p<.05$.

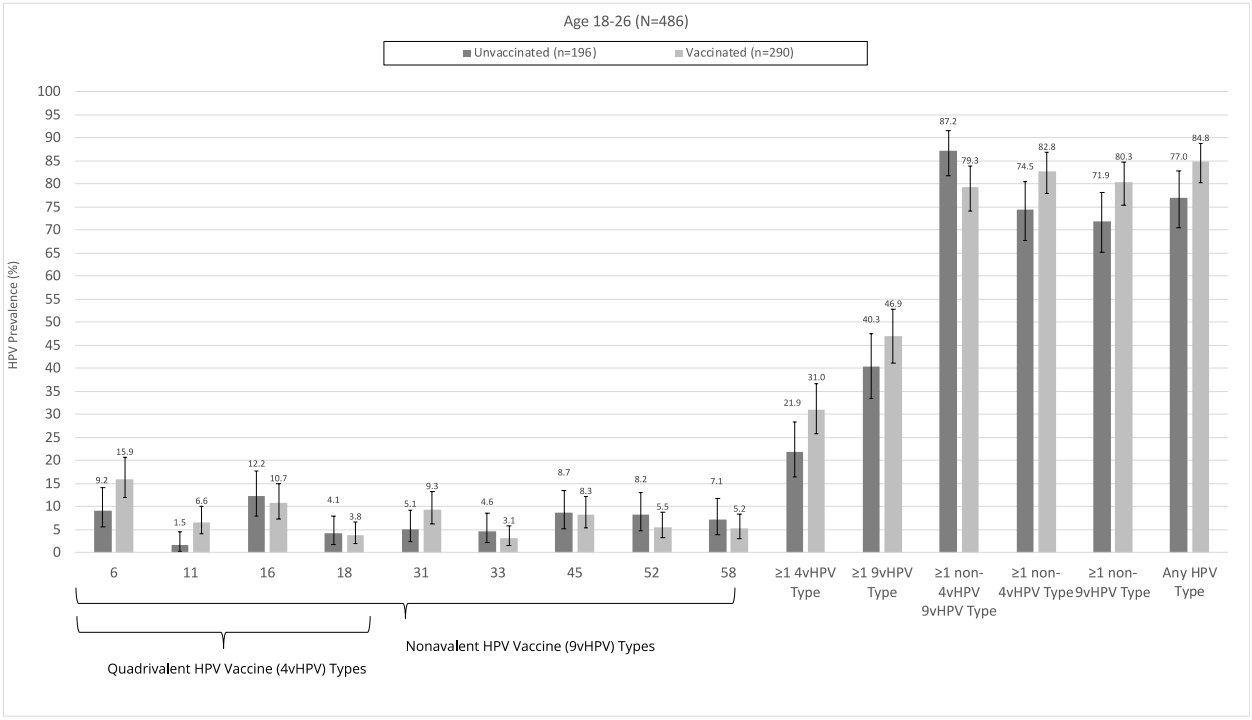
[2] Based on χ^2 test.

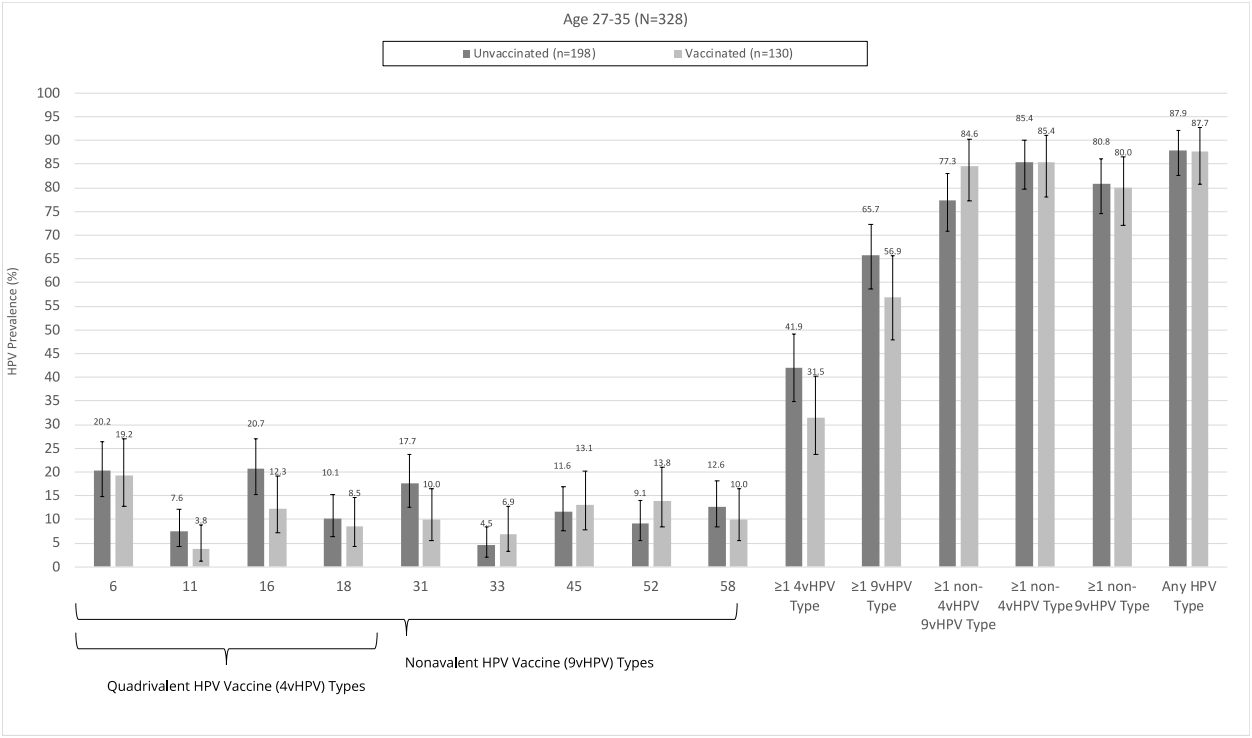
[3] Based on Fisher's exact test.

[4] "Other" indicates test result that was invalid, equivocal, or returned an error

Abbreviations: HPV, human papillomavirus; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine; HIV, human immunodeficiency virus; IQR, interquartile range.

Figure 1. Human papillomavirus (HPV) prevalence in anal swab specimens from 18–45-year- old men who have sex with men, overall and by documented HPV vaccination history (Seattle, Washington, 2018–2020). Error bars show 95% confidence intervals.





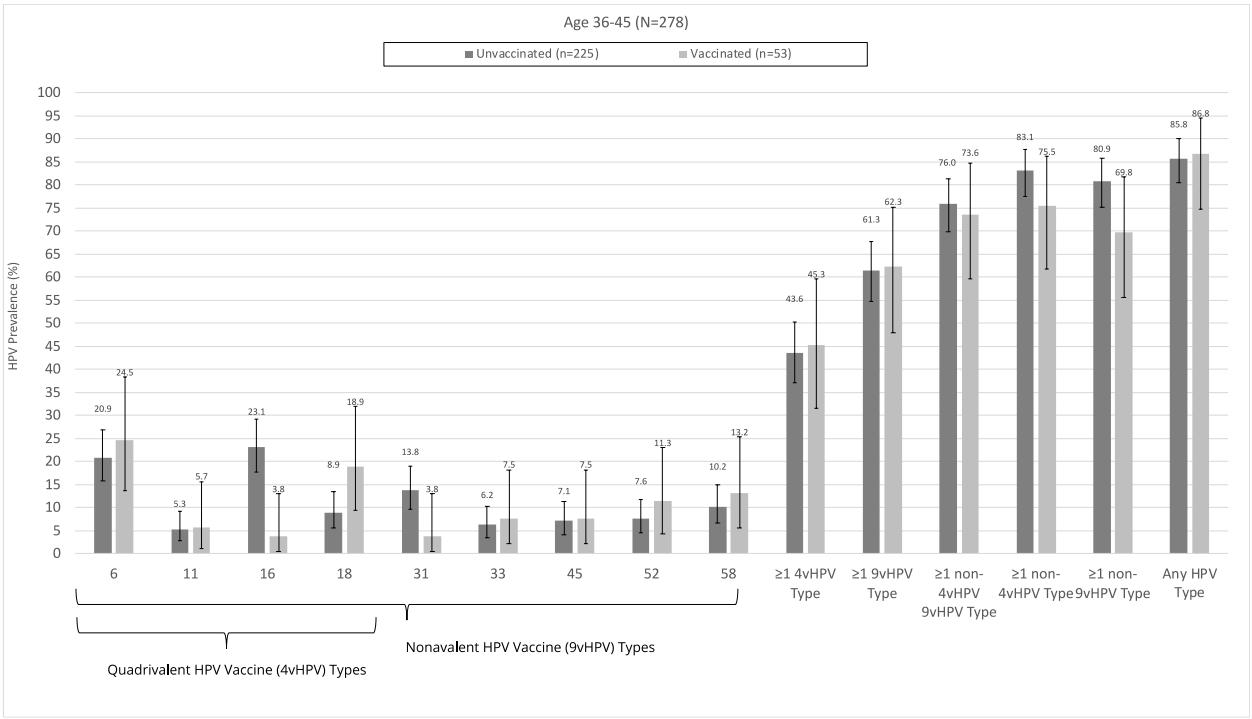

Age 36-45 (N=278)
Unvaccinated (n=225)
Vaccinated (n=53)
HPV Prevalence (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
20.9
24.5
5.3
5.7
23.1
3.8
8.9
18.9
13.8
3.8
6.2
7.5
7.1
7.5
7.6
11.3
10.2
13.2
43.6
45.3
61.3
62.3
76.0
73.6
83.1
75.5
80.9
69.8
85.8
86.8
6
11
16
18
31
33
45
52
58
≥1 4vHPV Type
≥1 9vHPV Type
≥1 non-4vHPV 9vHPV Type
≥1 non-4vHPV Type
≥1 non-9vHPV Type
Any HPV Type
Quadrivalent HPV Vaccine (4vHPV) Types
Nonavalent HPV Vaccine (9vHPV) Types

Table 3. Association between HPV vaccination history and HPV infection among MSM in three distinct age groups, overall and by age at vaccination and timing of vaccination relative to first sex

		4vHPV-type HPV infection			Non-4vHPV-type HPV infection		
	N	n (%)	PR (95% CI)	aPR[1] (95% CI)	n (%)	PR (95% CI)	aPR[1] (95% CI)
Age 18-26 (N=486)							
HPV vaccination status							
Unvaccinated[2]	196	43 (21.9)	*Ref.*	*Ref.*	146 (74.5)	*Ref.*	*Ref.*
Vaccinated[3]	290	90 (31.0)	**1.41 (1.03, 1.94)**	**1.49 (1.06, 2.09)**	240 (82.8)	**1.11 (1.01, 1.22)**	1.01 (0.93, 1.10)
Age at vaccination							
Unvaccinated[2]	196	43 (21.9)	*Ref.*	*Ref.*	146 (74.5)	*Ref.*	*Ref.*
First dose ≤18	53	3 (5.7)	**0.26 (0.08, 0.80)**	**0.28 (0.09, 0.86)**	41 (77.4)	1.04 (0.88, 1.23)	0.96 (0.83, 1.12)
First dose 18-26	237	87 (36.7)	**1.67 (1.22, 2.29)**	**1.73 (1.24, 2.41)**	199 (84.0)	**1.13 (1.02, 1.24)**	1.02 (0.94, 1.12)
Timing of vaccination relative to age at first sex							
Unvaccinated[2]	196	43 (21.9)	*Ref.*	*Ref.*	146 (74.5)	*Ref.*	*Ref.*
Prior to first sex	35	1 (2.9)	**0.13 (0.02, 0.91)**	**0.15 (0.02, 1.07)**	26 (74.3)	1.00 (0.81, 1.23)	0.95 (0.78, 1.16)
At or after first sex	226	85 (37.6)	**1.71 (1.25, 2.34)**	**1.87 (1.31, 2.68)**	193 (72.6)	**1.15 (1.04, 1.26)**	1.03 (0.94, 1.13)
Unknown	29	4 (13.8)	0.63 (0.24, 1.62)	0.55 (0.19, 1.61)	21 (72.4)	0.97 (0.77, 1.23)	0.95 (0.71, 1.26)
Age 27-35 (N=328)							
HPV Vaccination Status							
Unvaccinated[2]	198	83 (41.9)	*Ref.*	*Ref.*	169 (85.4)	*Ref.*	*Ref.*
Vaccinated[3]	130	41 (31.5)	0.75 (0.56, 1.02)	0.75 (0.55, 1.03)	111 (85.4)	1.00 (0.91, 1.10)	1.00 (0.91, 1.09)
Age at vaccination							
Unvaccinated[2]	198	83 (41.9)	*Ref.*	*Ref.*	169 (85.4)	*Ref.*	*Ref.*
First dose 18-26	76	18 (23.7)	**0.56 (0.37, 0.87)**	**0.56 (0.36, 0.87)**	66 (86.8)	1.02 (0.92, 1.13)	0.99 (0.90, 1.11)
First dose >26	54	23 (42.6)	1.02 (0.72, 1.44)	1.06 (0.74, 1.52)	45 (59.2)	0.98 (0.86, 1.11)	1.00 (0.87, 1.13)
Age 36-45 (N=278)							
HPV vaccination status							
Unvaccinated[2]	225	98 (43.6)	*Ref.*	*Ref.*	187 (83.1)	*Ref.*	*Ref.*
Vaccinated	53	24 (45.3)	1.04 (0.75, 1.45)	1.07 (0.77, 1.50)	40 (75.5)	0.91 (0.77, 1.07)	0.88 (0.76, 1.02)

[1]Adjusted for race/ethnicity, history of PrEP use for HIV prevention, and lifetime number of sex partners of any sex.
[2] No documented HPV vaccine doses >30 days prior to specimen collection.
[3] ≥1 dose of any HPV vaccine ≥30 days prior to specimen collection.
Abbreviations: PR, prevalence ratio; aPR, adjusted prevalence ratio; CI, confidence interval; HPV, human papillomavirus; Ref., reference; 4vHPV, quadrivalent HPV vaccine.
Note: Bold font indicates statistical significance.

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