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Decline in vaccine-type human papillomavirus prevalence in young men from a Midwest metropolitan area of the United States over the six years after vaccine introduction

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Abstract

Purpose: The aim of this study was to determine changes in human papillomavirus (HPV) prevalence among young men from a Midwest metropolitan area over the six years after vaccine introduction, including HPV prevalence in men overall, in vaccinated men to examine vaccine

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Kahn: Dr. Kahn served as Co-chair of a study of HPV vaccines in HIV-infected men; the study was funded by NIH but Merck provided vaccine and serology testing.
Dr. Franco: Dr. Franco has occasionally served as consultant to companies involved with HPV diagnostics (Roche, BD, Abbott) and HPV vaccines (Merck and GSK).
Dr. Brown: Dr. Brown has received an investigator initiated studies program award from Merck entitled "Cervical cancer prevention in Kenya".
Dr. Ermel: Dr. Ermel serves as a co-investigator on Dr. Brown's investigator initiated studies program award from Merck entitled "Cervical cancer prevention in Kenya". The remaining authors (Widdice, Bernstein, Ding, Higgins) report no potential conflicts of interest.
All authors attest they meet the ICMJE criteria for authorship.

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impact and in unvaccinated men to examine herd protection. An exploratory aim was to examine associations between number of vaccine doses and HPV prevalence.

Methods: Men aged 14–26 years reporting male-female and/or male-male sexual contact were recruited from a primary care clinic, sexually transmitted disease clinic, and community setting during two waves of data collection: 2013–2014 (N = 400) and 2016–2017 (N = 347). Participants completed a questionnaire and were tested for penile, scrotal and anal HPV. Changes in prevalence of any (≥1 type) and vaccine-type HPV (HPV6, 11, 16, and/or 18) were examined using propensity score weighted logistic regression. Associations between number of doses and HPV infection were determined using chi-square tests and logistic regression.

Results: The proportion of men with a history of ≥1 HPV vaccine doses increased from 23% to 44% ($p < 0.001$) from waves 1 to 2. After propensity score weighting, infection with ≥1 vaccine-type HPV significantly decreased among all men (29% to 20%; 31% decrease; odds ratio [OR] = 0.62, 95% confidence interval [CI] = 0.44–0.88) and unvaccinated men (32% to 21%; 36% decrease; OR = 0.56, 95%CI = 0.34–0.86); there was a non-significant decrease (21%) among vaccinated men. Associations between number of doses and HPV prevalence were not statistically significant.

Conclusions: Prevalence of vaccine-type HPV decreased among all, vaccinated, and unvaccinated men six years after HPV vaccine recommendation, supporting vaccine impact and herd protection. Decreases in vaccine-type HPV in all men appear to be due to decreases in unvaccinated men, suggesting that the full impact of vaccination has yet to be realized. Continued monitoring and efforts to vaccinate men prior to sexual initiation are warranted.

Keywords

Human papillomavirus; Male; Prevalence; Vaccine; Herd protection; Effectiveness

1. Introduction

Human papillomavirus (HPV) vaccination for men was recommended by the U.S. Centers for Disease Control and Prevention in 2011. Clinical trials have demonstrated that HPV vaccines have high efficacy in men [1]. However, the impact of the HPV vaccine among men after the introduction of HPV vaccines into the community is not well characterized. Evidence from the first nationally representative study of HPV prevalence in men in the United States in 2013–2014 show lower rates of vaccine-type HPV among younger men, compared to older men, suggesting that vaccination has reduced HPV prevalence [2]. The impact may be due to direct protection of vaccinated men or herd protection of unvaccinated men due to HPV vaccination efforts that began for women in 2006. Herd protection after HPV vaccine introduction for women has been described in unvaccinated women [3-6] and early evidence suggests herd protection among unvaccinated men [7,8].

During the study period, routine vaccination was recommended for men 11–12 years of age, catch-up vaccination was recommended for unvaccinated men 13–21 years of age, and permissive use was recommended for men aged 22–26 who had sex with men or were immunocompromised. Routine HPV vaccination was recommended for women 11–12 years of age, and catch-up vaccination was recommended for women 13–26 years of age. In 2016,

the HPV vaccine dosing schedule was changed from three doses for 9 to 26 year olds to two doses for those initiating vaccination between ages 9 to 14 years and three doses for those initiating vaccination at 15 years of age or older. This change was supported by immunogenicity data demonstrating that 9–14 year-olds had higher antibody titers after vaccination than 16–26 year-olds, the age group included in the majority of clinical efficacy trials [9]. Little evidence for real-world vaccine effectiveness of the 2-dose schedule is available.

To better understand HPV vaccine impact and herd protection in a community setting, we conducted two surveillance studies in a Midwest metropolitan area of the United States in 2013–2014 and 2016–2017 involving recruitment of unique cohorts of sexually active, vaccinated and unvaccinated, young men (aged 13–26 years) at two time points after HPV vaccine introduction from the same urban community to assess HPV prevalence. The primary aim of this study was to examine changes in the prevalence of 4-valent vaccine-type HPV (HPV6, 11, 16 and/or 18) infection in young men recruited from clinical and community settings from 2013–14 (wave 1) to 2016–17 (wave 2). We examined changes in HPV prevalence overall and stratified by vaccination status (vaccinated and unvaccinated). We examined changes in HPV prevalence in vaccinated men to determine vaccine impact and in unvaccinated men to determine herd protection. Additionally, we conducted stratified analyses to examine vaccine impact by men who initiated sex after vaccination, men who initiated sex before vaccination, recruitment site, and age at study enrollment. An exploratory aim was to examine, among men from waves 1 and 2 combined, the association between number of doses and HPV prevalence among all men, among men who received their first HPV vaccine dose at 15 years of age or older, and among men who initiated sex after vaccination and men who initiated sex before vaccination.

2. Methods

Participants were 13–26 year old men with a history of sexual contact (genital-oral, genital-genital) with one or more male or female partners, recruited in 2013–2014 (wave 1) and 2016–2017 (wave 2). We recruited men using a sequential sampling strategy. Men were recruited from a hospital-based adolescent primary care clinic (Teen Health Center, THC), health department sexually transmitted disease (STD) clinics and the community. Recruitment from the community included advertising in print and digital media (both in the community – e.g. university and larger community), mailing lists maintained by the Division of Infectious Diseases and the Office of Clinical and Translational Research, and advertisements to hospital employees. Participants provided written informed consent. Parental consent for minors was waived because an inclusion criterion was sexual contact, and disclosure of this criterion could breach patient confidentiality. During recruitment for wave 2, potentially eligible participants were excluded if they had participated in wave 1. The study was reviewed and approved by the institutional review boards of the hospital and the health department where recruitment occurred.

Participants completed a validated paper/pencil survey, available in English and Spanish [10]. The survey assessed participant's sociodemographic characteristics, HPV vaccination history, substance use history, and sexual behaviors. HPV vaccination history, including date

of vaccinations and vaccine type received, was verified by electronic medical record (EMR) and/or the Ohio Impact Statewide Immunization System. Documentation in at least one of these systems was available for 85% of the participants who reported having received the vaccine. All vaccinations have been entered into the EMR system in these settings since the HPV vaccine was approved for men [11].

Sample collection and testing has been described previously [12]. In short, a trained study team member used separate, moistened swabs to collect samples of the glans penis, including coronal sulcus; penile shaft; scrotum; and the perianal/anal area. Prior to DNA extraction, samples from the genital areas (glans, shaft, and scrotum) were combined; genital and perianal/anal samples were analyzed separately [13]. Roche Linear Array (Roche Molecular Systems, Alameda, CA) was used to detect individual high-risk and low-risk genotypes.

2.1. Outcome and independent variables

The primary outcome variable was at least one 4-valent vaccine-type HPV (HPV6, 11, 16 and/or 18). Secondary outcomes were high-risk vaccine-type HPV (HPV16 and/or 18), low-risk 4-valent vaccine-type HPV (HPV6 and/or 11), and ≥1 HPV type. An individual was considered infected with an HPV type if that type was detected from the genital and/or perianal/anal sample.

Independent variables included sociodemographic characteristics; HPV vaccination history; reproductive health history, including history of sexually transmitted infections, age of first sex, and number of lifetime sexual partners; and sexual behaviors, including condom use, number and gender of recent sexual partners and sexual practices. Men with verified and self-report of vaccination were included in analyses. Age of first HPV vaccine dose was calculated from date of vaccination and date of birth. A variable was calculated to describe the timing of initiation of vaginal intercourse (subsequently referred to as sexual initiation) related to vaccination among men who reported sexual intercourse with women. This variable was calculated using self-reported age of first vaginal intercourse and age of first HPV vaccine dose.

2.2. Statistical analyses

Descriptive statistics were used to summarize independent variables overall and stratified by vaccination status (vaccinated and unvaccinated) in wave 1 and wave 2. We first compared participants in wave 1 and wave 2 to determine if there were differences in demographic characteristics, health history and behaviors, and sexual history and behaviors that have been associated with HPV infection in previous studies (Table 1). Comparisons were tested for significance ($p < 0.05$) using Chi square, Fisher's exact test, two-sample *t*-test or Wilcoxon rank-sum test, as appropriate. Between-waves comparisons were completed for all men, vaccinated men, unvaccinated men, and stratified analyses of vaccinated and unvaccinated men. Additional stratified analyses were conducted among vaccinated men by sexual initiation after vaccination, sexual initiation before vaccination, recruitment site (THC and STD clinic only, as the number of participants from the community in wave 1 was low), and age (14–18 years and 1926 years). Additional stratified analyses were conducted among

unvaccinated men by recruitment site (THC, STD clinic, and community) and age (14–21 years and 22–26 years). Age categories were different for vaccinated and unvaccinated men in the stratified analyses due to differences in distribution of age in vaccinated and unvaccinated men.

As there were a number of statistically significant differences in comparison of participants in waves 1 and 2, propensity score analyses based on inverse probability of treatment weighting was performed for each between-wave comparison [5,14]. Each propensity score analysis used candidate variables listed in Table 1, with the exception that stratified analyses did not include stratified variables. Logistic regression models were used in propensity score analyses. The propensity score is the probability that a participant belongs to a naturally occurring treatment group based on a set of background characteristics. The propensity score adjusts for selection bias in an observational study, allowing one to analyze an observational study so that it mimics the characteristics of a randomized controlled trial. It provides a one-dimensional summary of multidimensional covariates, X, such that when the propensity scores are balanced across the two treatment groups, the distribution of observed baseline covariates is similar between participants in the two groups [5]. After the propensity score analyses, all previously unbalanced variables were balanced.

Proportions of HPV-infected men were calculated for each outcome variable, overall and stratified by vaccination status (vaccinated and unvaccinated), in each of the two waves both before and after propensity score adjustment. Logistic regression analysis with HPV infection as the outcome and wave as the independent variable were used to estimate odds of HPV prevalence across the study waves, unadjusted and adjusted for the propensity score [5,15-18]. Because all variables were balanced after propensity score analysis, no baseline variables were included as covariates in logistic regression models adjusted for the propensity score.

Analyses of vaccine-type HPV infection among vaccinated men were then stratified by sexual initiation after vaccination, sexual initiation before vaccination, recruitment site (THC and STD clinic only, as the number of participants from the community in wave 1 was low), and age (14–18 years and 19–26 years). Analyses of unvaccinated men were stratified by recruitment site (THC, STD clinic, and community) and age (14–21 years and 22–26 years; categories were different for vaccinated and unvaccinated men due to distribution of age). Logistic regression analysis with vaccine-type HPV infection as the outcome and wave as the independent variable were used to estimate odds of vaccine-type HPV prevalence across the study waves, unadjusted and adjusted for the propensity score. Because all baseline variables were balanced after propensity score analysis, no baseline variables were included as covariates in logistic regression models adjusted for the propensity score.

To examine associations between number of vaccine doses and HPV prevalence, we categorized number of doses received before study enrollment (0, 1, 2, and ≥3). We examined the associations between number of doses and HPV infection (4-valent vaccine-type HPV and ≥1 HPV type) using a Chi-square test and Cochran-Armitage Trend test. We then conducted logistic regression analyses with infection (4-valent vaccine-type and ≥1 HPV type) as the outcome variable and number of doses as the predictor variable. We then

repeated these analyses among the subset of men who received their first dose at 15 years of age or older, men who initiated sex after vaccination, and men who initiated sex before vaccination. Data analyses were conducted using SAS version 9.4 (SAS Institute, Cary NC).

Two post hoc analyses were conducted. The first, using prevalence of HPV in the study population, examined the power to detect a significant ($p < 0.05$) difference in vaccine-type HPV prevalence among vaccinated men between waves. With a sample size of 242 vaccinated men and 471 unvaccinated men and a vaccine-type HPV prevalence of 25.5% in unvaccinated men, this study had 80% power to detect a decrease of 36% (from 25.5% to 16.4%) for vaccinated men. The second, compared vaccine-type HPV prevalence among vaccinated men who initiated sex with women after and before vaccination (waves 1 and 2 combined). Men who reported sexual initiation at the same age as HPV vaccination were excluded from this analysis.

3. Results

A total of 875 men were approached and 747 (85.4%) enrolled: 400 in wave 1 and 347 in wave 2. Comparison of those screened but not enrolled and those enrolled demonstrated that enrollment was higher among men who reported Black vs. White or other race, men with private vs. public or no insurance, and men who were older vs. younger.

The proportion of vaccinated men increased from 22.5% (n = 90) in wave 1 to 43.5% (n = 163) in wave 2 ($p < 0.001$). The mean age of vaccination decreased from 16.2 years (SD 2.3) in wave 1 to 15.1 years (SD 2.3) in wave 2 ($p < 0.01$). All men in wave 1 received only 4-valent HPV vaccine (Merck & Co., Inc.). Of the 160 men in wave 2 for whom the specific HPV vaccine (4-valent or 9-valent) they received was recorded in their medical record, 125 (78.1%) received only 4-valent HPV vaccine, 12 (7.5%) received only 9-valent HPV vaccine (Merck & Co., Inc.); the remaining 23 (14.4%) received a combination of 4-valent and 9-valent HPV vaccine doses.

Characteristics of participants are shown in Table 1. A majority (>65%) self-identified as Black. The average age of men was 21.5 (standard deviation [SD] 3.1) years and 21.0 (SD 3.0) years in waves 1 and 2, respectively ($p = 0.04$). The highest proportion of men were recruited from the STD clinic, followed by the THC and community. About one-third of participants initiated vaginal intercourse at 14 years or younger: 34.5% in wave 1 and 30.5% in wave 2. The proportion of vaccinated participants who reported vaginal intercourse before vaccination was 47.8% in wave 1 and 39.3% in wave 2 ($p = 0.02$).

3.1. Proportions of men with HPV in wave 1 and wave 2

Table 2 shows the proportions with ≥1 HPV type, 4-valent vaccine-type HPV, HPV16 and/or 18, and HPV6 and/or 11 by wave among all men, vaccinated men, and unvaccinated men. The proportion of men infected with ≥1 HPV type increased, although not significantly, from wave 1 to wave 2 among all men (62.8–69.0%, adjusted; 10% increase), vaccinated (57.0–63.5%, adjusted; 11% increase), and unvaccinated men (67.1–69.8%, adjusted; 4% increase).

The proportion of men infected with 4-valent vaccine-type HPV decreased significantly from wave 1 to wave 2 among all men (28.8–20.0%, adjusted; 31% decrease, odds ratio [OR] 0.62, 95% confidence interval [Cl] 0.44–0.88]) and unvaccinated men (32.2–20.5%, adjusted; 36% decrease, OR 0.56 [95% CI 0.34–0.86]). The decrease in vaccinated men (25.7–20.0%, adjusted; 21% decrease) was not statistically significant.

Similarly, the proportion of men infected with HPV16 and/or 18 decreased significantly from wave 1 to wave 2 among all men (26.1–16.5%, adjusted; 37% decrease, OR 0.56 [95%CI 0.39–0.81]) and unvaccinated men (29.2–15.7%, adjusted; 44% decrease, OR 0.47 [95%CI 0.29–0.77]). The decrease in vaccinated men (24.4–19.9%, adjusted; 19% decrease) was not statistically significant.

The proportion of men infected with HPV6 and/or 11 did not change significantly for all, vaccinated, or unvaccinated men. The adjusted proportion of vaccinated men infected with HPV6 and/or 11 decreased 40% from 1.5% to 0.9%, but the decrease was not significant.

Fig. 1 demonstrates that among vaccinated men, there were no statistically significant differences in vaccine-type HPV infection between waves 1 and 2 by sexual initiation after or before vaccination, recruitment site, or age. Among unvaccinated men enrolled in the community, the proportion of those with vaccine-type HPV decreased significantly from wave 1 to wave 2 (31.4% vs. 9.7%, $p = 0.02$). Among 14–21 year old unvaccinated men, the proportion of those with 4-valent vaccine-type HPV decreased from wave 1 to wave 2 (35.0% vs. 13.0%, $p<0.01$, 62.9% decrease). Among 22–26 year old unvaccinated men, the proportion of those with 4-valent vaccine-type HPV decreased, but not significantly, from wave 1 to wave 2 (35.0% vs. 13.0%, $p > 0.05$, 29.8% decrease). In post hoc analyses, a significantly higher proportion of men who reported sexual initiation before vaccination (33 of 128 men [25.8%]) had 4-valent vaccine-type HPV infection compared to men who reported sexual initiation after HPV vaccination (14 of 95 men, [14.7%]) ($p = 0.05$ Chi square test).

3.2. HPV prevalence and number of vaccine doses

Among the 746 men from waves 1 and 2, 471 were unvaccinated (63.1%), 58 (7.8%) had received 1 dose, 37 (5.0%) received 2 doses, and 143 (19.1%) received 3 or more doses; 38 (5.1%) had missing data on number of doses. There were no statistically significant differences in the proportions of men infected with ≥1 4-valent vaccine-type HPV who received no HPV vaccine doses (25%, n = 120 positive), 1 dose (19%, n = 11 positive), 2 doses (27%, n = 10 positive), and 3 or more doses (22%, n = 31 positive). The number of doses was not associated with ≥1 HPV type or HPV16 and/or 18. There were no statistically significant differences in proportion of men infected with ≥1 4-valent vaccine-type HPV by number of doses among men who were vaccinated at ≥15 years of age, had sexual initiation after vaccination, and had sexual initiation before vaccination. The number of doses was not associated with >1 HPV type among men vaccinated at >15 years (data not shown).

4. Discussion

In this study of young men recruited from clinical and community settings after HPV vaccine introduction, we demonstrated that between 2013–2014 and 2016–2017, the proportion of men infected with 4-valent vaccine-type HPV and with HPV16 and/or 18 decreased from wave 1 to wave 2 among all men, vaccinated men, and unvaccinated men: decreases were statistically significant only among all and unvaccinated men. Among the relatively small number of vaccinated men, we found no associations between number of doses and HPV prevalence.

The decrease in any type HPV prevalence in men from wave 1 to wave 2 may be due to herd immunity induced by vaccination of women since 2006. The decrease in 4-valent vaccine-type HPV and HPV16/18 in all men appears to be primarily due to decreases in unvaccinated men. It is likely that unvaccinated men are incurring protection from herd immunity. Prevalence decreased in vaccinated men, although the change was not statistically significant. The lower magnitude of decline in vaccinated men than in unvaccinated men may be due to demographic or behavioral differences between vaccinated and unvaccinated men. Unmeasured characteristics of participants may also account for this difference, but this conclusion is unlikely. Additionally, it is unlikely that, over time, herd protection will offer greater protection than direct protection from the vaccine. These findings are not unexpected and are supported by modeling data examining the impact on HPV prevalence among men; if a male vaccination program is added to an existing female vaccination program, decreases in HPV prevalence are gradual and continue for many years after the implementation of the male vaccination program [19]. Continued surveillance is necessary to fully describe the impact of the HPV vaccination program in men.

The significant decrease in 4-valent vaccine-type HPV infection in unvaccinated men suggests that men are benefitting from vaccination efforts in women that have led to lower HPV prevalence among women, i.e., men are benefitting from herd protection from vaccine-type HPV infection. In studies of women recruited from the same geographic area from 2006 to 2017, high vaccine effectiveness among women was suggested by a decrease of 80.9% in the prevalence of 4-valent vaccine-type HPV among vaccinated women [17]. Additionally, a decrease of 40% in the prevalence of 4-valent vaccine-type HPV was noted among unvaccinated women [18]. Thus men recruited into this study between 2013 and 2017 may have benefited from decreasing HPV prevalence among women with whom they have sexual contact. Herd protection of men from vaccination of women is further supported by our findings of significant decreased 4-valent vaccine-type HPV among 14–21 year-olds but not 22–26 year-olds. Younger men in wave 2 appear to have benefited from HPV vaccination efforts among women.

Our data are consistent with a retrospective observational study based in Australia which tested for HPV in archived urine and urethral swabs from a Chlamydia trachomatis screening program that demonstrated a decrease in 4-valent vaccine-type HPV among men during the period of widespread vaccination of women [8]. As increases in HPV vaccination rates in women occurred in 2013–14 and 2016–17, prevalence of HPV in males decreased. The occurrence of herd protection was supported by greater decreases of HPV infection in

Australian men versus immigrants from countries with low vaccination rates. Our findings are also consistent with findings from an Australian-based HPV prevalence study of unvaccinated men during a time when younger women had a high vaccination coverage compared to older women. The authors found that younger men, who were likely to have had sexual contact with similarly aged women, had lower rates of HPV than older men, who were likely to have had more sexual contact with older, unvaccinated women [7].

The decreases in 4-valent vaccine HPV types and HPV16/18 among vaccinated men between waves 1 and 2 were not statistically significant. This may be due to the fact that a high proportion of men in both waves were vaccinated after sexual initiation. However, a 21% decrease in the proportions of vaccinated men with vaccine-type HPV infection between wave 1 and wave 2 is clinically significant, although ad hoc power analysis indicated that the study sample size did not have adequate power to detect the effect size we observed in this study. The decreases in proportion of vaccinated men with HPV 16/18 and HPV 6/11 is also reassuring when considering the impact of vaccination. Although the proportion of vaccinated men with HPV6/11 decreased by 40%, the change was not significant, likely because there were so few men who were infected with HPV 6 or 11, thereby limiting power to detect a significant decrease in prevalence. Therefore, continued surveillance will be needed to show changes in vaccine-type HPV and HPV 6/11 after vaccine introduction. We expect the prevalence in vaccine-type HPV among vaccinated men will continue to decrease with continued vaccination efforts; however, continued surveillance will be necessary to confirm this.

When analyses were stratified by age, sexual initiation after vaccination, sexual initiation before vaccination, and recruitment site, there were no statistically significant changes in HPV prevalence among vaccinated men from wave 1 to wave 2. Increases in vaccine-type prevalence in the stratified analysis of vaccinated men are most likely due to uncertainty of the measurement due to the low number of vaccinated men infected with HPV. Differences in unmeasured participant characteristics may explain the nonsignificant changes between waves 1 and 2, although this is unlikely. The sample sizes of vaccinated men in the different categories may have been too small to detect significant differences. When analysis included vaccinated men from both waves, prevalence was significantly lower among men who initiated sex after vaccination compared to before vaccination. This is expected and supports the 11–12 year old target age for vaccination in men.

The prevalence of any HPV increased, although not statistically significantly, from wave 1 to 2 among all, vaccinated and unvaccinated men. Continued surveillance of HPV prevalence among men is important to determine if this trend towards increasing overall HPV prevalence persists. Our previous work in women suggests that some observed changes in non-vaccine HPV types in men may be explained by different sociodemographic and behavioral characteristics in vaccinated vs. unvaccinated men that correlate with HPV prevalence [16]. Analysis of changes in non-vaccine HPV types in men is important to assess if cross-protection and type-replacement are occurring, however these analyses are beyond the scope of this paper examining vaccine impact and herd protection. Among women, evidence from clinical trials and real-world based studies have demonstrated cross-protection [15,20-22]. Evidence of type-replacement is less conclusive, some studies suggest

type-replacement may be occurring [22-24] while others demonstrate no type replacement [25-27].

Prompted by changes in vaccination recommendations for men 14 years and younger to receive two HPV vaccine doses, rather than the previously recommended three doses [9], we examined the association of 4-valent vaccine-type HPV infection with number of doses among men from both waves 1 and 2. In this study, 4-valent vaccine-type HPV infection was not associated with number of doses. Although we anticipated a higher proportion of unvaccinated men to be infected compared to men who had received 1, 2, or 3 vaccine doses, both participant characteristics and the low number of vaccinated men with HPV infection may explain our findings. Because of the high prevalence of HPV in this community, it is likely we detected HPV in vaccinated men that was acquired before vaccination. The lack of association between prevalence of HPV and number of vaccine doses among men who initiated vaginal intercourse after vaccination is likely due to men acquiring HPV prior to vaccination from sexual behaviors other than vaginal intercourse. Previous studies in women [28-30] and men [31] have shown that HPV may be acquired prior to initiation of vaginal intercourse, and we did not control for other types of sexual contact. It is also possible that differences in demographic and sexual behaviors between vaccinated and unvaccinated men that were not included in the analysis may be associated with HPV prevalence. However, differences in the number of infected men in each dose category may have been too small to detect with the current sample size. It will be important to examine the association of HPV infection with number of vaccine doses in men ≥15 years old to provide information necessary to evaluate the need for two vs. three vaccine doses.

There are a number of reasons that men who were vaccinated prior to sexual initiation might have had vaccine-type HPV detected: this finding does not indicate vaccine failure. First, participants were not asked directly about the timing of vaccination in relation to sexual initiation; therefore some participants may have been miscategorized as having had been vaccinated after sexual initiation. In addition, the participants may have acquired HPV through behaviors other than vaginal intercourse: the calculated variable did not include age of first oral sex or anal sex. The finding of a lower prevalence of vaccine-type HPV among men who were vaccinated prior to (vs. after) initiating vaginal intercourse is expected, and supports the 11–12 year old target age for vaccination in men so that they are vaccinated prior to sexual initiation.

In conclusion, findings from this study suggest herd protection is occurring among unvaccinated men in the first six years after HPV vaccination was initiated in men, and 11 years after HPV vaccination was initiated among women in the United States. Continued surveillance of HPV infection among men will be critical to fully assess vaccine impact as vaccination efforts continue. Despite evidence of herd protection, men remain at high risk for HPV infection. Continued vaccination efforts among men and women are critical for men to realize the benefits offered by HPV vaccination. Clinical and public health efforts to vaccinate men prior to sexual initiation are important for realization of the full benefits offered by HPV vaccination.

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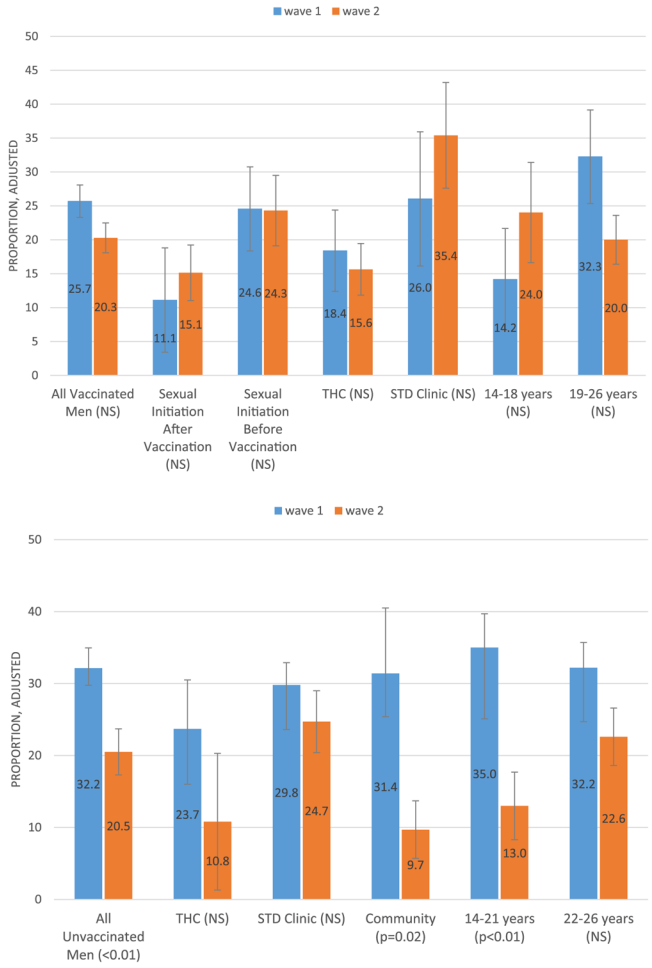

Fig. 1.

(top) Proportion (adjusted) and standard error of the mean of vaccinated men infected with ≥1 4-valent vaccine-type HPV stratified by sexual initiation after vaccination, sexual initiation before vaccination, recruitment from the Teen Health Center (THC), recruitment from the STD clinic, 14–18 years of age at time of enrollment, and 19–26 years of age at time of enrollment. Too few participants recruited from the community were vaccinated in wave 1 to conduct stratified analyses. Differences between wave 1 and 2 were tested for significance using logistic regression. Results represented in this Figure cannot be used to infer differences in characteristics or HPV prevalence between vaccinated and unvaccinated men. (bottom) Proportion (adjusted) and standard error of the mean of unvaccinated men infected with ≥1 4-valent vaccine-type HPV stratified by recruitment from the Teen Health Center (THC), recruitment from the STD clinic, recruitment from the community, 14–21 years of age at time of enrollment, and 22–26 years of age at time of enrollment. Differences between wave 1 and 2 were tested for significance using logistic regression. Results represented in this Figure cannot be used to infer differences in characteristics or HPV prevalence between vaccinated and unvaccinated men.

Table 1

Comparison of all participants' demographic characteristics, health history and behaviors, and sexual history and behaviors in Waves 1 and 2 (2013–2014 and 2016–2017).

	Wave 1 (N = 400)		Wave 2 (N = 347)		p-value, unadusted[1,2]
	n (%)	Mean (SD)	n (%)	Mean (SD)	
Sociodemographic characteristics					
Enrollment site					<0.001
THC	97 (24.3)		112 (29.8)		
STD	266 (66.5)		160 (46.1)		
Community	37 (9.3)		75 (21.6)		
Age at enrollment		21.5 (3.1)		21.0 (3.0)	0.04
Black race	278 (69.5)		227 (65.4)		0.29
Appalachian decent	7 (1.7)		11 (3.2)		0.21
Hispanic ethnicity	10 (2.5)		16 (4.6)		0.12
Insured	234 (58.5)		272 (78.4)		<0.001
Marital status, never married	384 (96)		337 (97.1)		0.41
Sexual preference, self-identified as straight	359 (90.2)		288 (83.5)		0.006
Health history and behaviors					
Any sexually transmitted infection, excluding warts	211 (52.8)		143 (41.2)		0.002
Last time washed genital area					0.64
Today	282 (70.5)		250 (72.1)		
Yesterday or before	118 (29.5)		97 (28.0)		
Smoked at least 100 cigarettes in lifetime, yes	128 (32.0)		90 (25.9)		0.07
Smoked cigarettes in past 30 days, yes	143 (35.8)		109 (31.4)		0.21
Ever smoked marijuana, yes	309 (77.3)		276 (79.6)		0.45
Number of days smoked marijuana in past 30 days					0.36
0 days	107 (26.8)		80 (23.1)		
1–30 days	208 (52.0)		198 (57.1)		
Never	85 (21.7)		69 (19.9)		
Timing of first vaginal intercourse in relation to vaccination[3]					0.02
First vaginal intercourse after vaccination	31 (34.0)		84 (51.5)		

	Wave 1 (N = 400)		Wave 2 (N = 347)		p-value, unadusted[1,2]
	n (%)	Mean (SD)	n (%)	Mean (SD)	
First vaginal intercourse before vaccination	43 (47.8)		64 (39.3)		
Vaginal intercourse and vaccination at same age	16 (17.8)		15 (9.2)		
Sexual history and behaviors					
History of vaginal intercourse	371 (92.8)		309 (89.1)		0.08
Last vaginal intercourse					0.45
0–24 h ago	42 (10.5)		26 (7.5)		
>24 h ago	332 (83)		283 (81.6)		
Never	26 (6.5)		38 (11)		
Age of first vaginal intercourse, years					0.02
Never[4]	26 (6.5)		38 (11.0)		
≤14	138 (34.5)		106 (30.5)		
15–17	179 (44.8)		136 (39.2)		
>18	57 (14.3)		67 (19.3)		
Lifetime female sexual partners					0.01
0	26 (6.6)		38 (11.0)		
1	27 (6.8)		32 (9.2)		
2–10	178 (44.9)		167 (41.8)		
≥11	165 (41.7)		110 (31.7)		
Female sexual partners in past 3 months					0.006
0	48 (12)		29 (8.4)		
1	142 (35.6)		150 (43.2)		
≥2	183 (45.9)		130 (37.5)		
Never[4]	26 (6.5)		38 (11)		
New female sexual partners in past 3 months					0.07
0	176 (44)		160 (46)		
1	111 (27.8)		91 (26.2)		
≥2	87 (21.8)		58 (16.7)		
Never	26 (6.5)		38 (11)		
Female sexual partners in past 12 months					0.09
0	18 (4.5)		14 (4.0)		

	Wave 1 (N = 400)		Wave 2 (N = 347)		p-value, unadusted[1,2]
	n (%)	Mean (SD)	n (%)	Mean (SD)	
1	101 (25.3)		98 (28.2)		
≥2	254 (63.7)		197 (56.8)		
Never[4]	26 (6.5)		38 (11)		
New female sexual partners in past 12 months					0.18
0	103 (25.8)		89 (25.7)		
1	105 (26.3)		89 (25.7)		
≥2	165 (41.4)		131 (37.8)		
Never[4]	26 (6.5)		38 (11)		
Gender of main partner					<0.001
Male	29 (7.3)		22 (6.3)		
Female	306 (76.5)		193 (55.6)		
No main partner	65 (16.3)		132 (38.0)		
History of anal sex with man, yes	41 (10.3)		55 (15.9)		0.023
Last anal sex with man					0.038
0–24 h ago	7 (1.8)		5 (1.4)		
>24 h ago	34 (8.5)		50 (14.4)		
Never[4]	349 (89.8)		292 (84.2)		
Age of first anal sex with man, years					0.049
Never[4]	359 (89.8)		292 (84.2)		
≤17	24 (6.0)		27 (7.8)		
≥18	17 (4.3)		28 (8.1)		
Lifetime number of male anal sex partners					0.022
1–10	22 (5.5)		38 (11.0)		
>11	18 (4.5)		17 (4.9)		
Never[4]	359 (90.0)		292 (84.15)		
Male anal sex partners in past 3 months					0.06
0	4 (1.0)		9 (2.59)		
1	20 (5.0)		19 (5.48)		
≥2	17 (4.25)		27 (7.78)		

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	Wave 1 (N = 400)		Wave 2 (N = 347)		p-value, unadusted[1,2]
	n (%)	Mean (SD)	n (%)	Mean (SD)	
Never[4]	359 (89.8)		292 (84.2)		
New male anal sex partners in past 3 months					0.02
0	19 (4.75)		25 (7.2)		
1	14 (3.5)		10 (2.88)		
≥2	8 (2.0)		20 (5.76)		
Never[4]	359 (89.75)		292 (84.15)		
Male anal sex partners in past 12 months					0.12
0	3 (0.8)		5 (1.4)		
1	12 (3)		12 (3.5)		
≥2	26 (6.5)		38 (11)		
Never had anal sex with man	359 (89.8)		292 (84.2)		
Condom use with main partner, if partner female					0.0003
Never/every once in a while	174 (43.5)		130 (37.5)		
Most of the time/every single time	98 (24.5)		58 (16.7)		
Condom use at last vaginal intercourse with main partner, if main partner female					<0.0001
Yes	112 (28.0)		58 (16.7)		
No	185 (46.3)		58 (16.7)		
Condom use during anal sex in past 3 months with main partner, if main partner female					0.75
Never/every once in a while	36 (9)		35 (10.1)		
Most of the time/every single time	16 (4)		11 (3.2)		
Condom use at last anal sex with main female partner, if main partner female					0.63
Yes	18 (4.5)		11 (3.2)		
No	38 (9.5)		35 (10.1)		
Condom use during insertive anal sex in past 3 months with main partner, if main partner male					0.95
Never/every once in a while	14 (3.5)		12 (3.5)		
Most of the time/every single time	9 (2.3)		9 (2.6)		
Condom use during last insertive anal sex with main partner, if main partner male					0.77

	Wave 1 (N = 400)		Wave 2 (N = 347)		p-value, unadusted[1,2]
	n (%)	Mean (SD)	n (%)	Mean (SD)	
Yes	10 (2.5)		9 (2.6)		
No	18 (4.5)		12 (3.5)		
No main partner or main partner is not male	372 (93)		326 (94.0)		
Condom use during receptive anal sex in past 3 months with main partner, if main partner male					0.5
Never/every once in a while	11 (2.8)		14 (4)		
Most of the time/every single time	7 (1.8)		8 (2.3)		
Did not have receptive anal sex	382 (95.6)		325 (93.7)		
Condom use at last anal receptive sex with main male partner, if main partner male					0.84
Yes	7 (1.8)		8 (2.3)		
No	15 (3.8)		14 (4)		
Condom use at last insertive anal sex with male partner other than main partner					<0.0001
Yes	22 (5.5)		25 (7.2)		
No	13 (3.3)		21 (6.1)		
No main partner	61 (15.5)		112 (32.3)		
Main partner not male	304 (76)		189 (54.5)		
Condom use at last receptive anal sex with male partner other than male partner					<0.0001
Yes	19 (4.8)		20 (5.8)		
No	11 (2.8)		9 (5.5)		
No main partner	65 (16.3)		116 (33.4)		
Main partner not male	305 (76.3)		192 (55.3)		
Condom use at last insertive anal sex with a female partner other than main partner					0.91
Yes	39 (9.8)		33 (9.5)		
No	52 (13)		50 (14.4)		
No main partner	281 (70.3)		242 (70.0)		
Main partner not female	28 (7)		21 (6.1)		
Gave oral sex in past 3 months to any partner, yes	240 (60)		236 (68)		0.02
Received oral sex in past three months from any partner, yes	319 (79.8)		295 (85)		0.06

	Wave 1 (N = 400)		Wave 2 (N = 347)		p-value, unadusted[1,2]
	n (%)	Mean (SD)	n (%)	Mean (SD)	
Number of times had oral sex in past 3 months with any partner					0.0006
0	71 (77.8)		40 (11.5)		
1	31 (7.8)		36 (10.4)		
2–5	153 (38.3)		102 (29.4)		
>5	145 (36.3)		169 (48.7)		
Concurrency, lifetime[5]					0.90
Yes	190 (47.5)		159 (45.8)		
No	194 (48.5)		174 (50.1)		
Don’t remember	16 (4)		14 (4.0)		

Notes:

[1] Differences between wave 1 and wave 2 were tested for significance using Chi square, Fisher’s exact test, two-sample t-test or Wilcoxon rank-sum test, as appropriate.

[2] After the propensity scoring procedure, differences between waves were balanced for each variable (p values for each comparison were > 0.05).

[3] Calculated using self-reported age of first vaginal intercourse and age of vaccination (calculated from date of birth and date of vaccination). Only vaccinated men were included. Only men who reported vaginal intercourse were included.

[4] Some participants had a history of oral and/or anal intercourse but no history of vaginal intercourse.

[5] Concurrency is defined as overlapping sexual relationships (being in more than one sexual relationship at the same time).

Table 2

Comparison of proportion of participants in Wave 1 (2013–2014) and Wave 2 (2016–2017) surveillance studies with vaccine-type and any HPV infection: total, vaccinated, and unvaccinated.

HPV Types	2013–2014 Surveillance Study (N = 400)		2016–2017 Surveillance Study (N = 347)		Change in adjusted proportions, wave 1 to wave 2	% Difference in adjusted proportions, wave 1 to wave 2	Odds Ratio (95%CI)[1]
	n and proportion, unadjusted n (%)	Proportion, adjusted for propensity score %	n and proportion, unadjusted n (%)	Proportion, adjusted for propensity score %			
≥1 HPV type							
All	236 (62.6)	62.8	221 (65.0)	69.0	6.2	10	1.32 (0.97–1.80)
Vaccinated	47 (57.3)	57.0	100 (62.1)	63.5	6.5	11	1.31 (0.76–2.26)
Unvaccinated	189 (64.1)	67.1	121 (67.6)	69.8	2.7	4	1.14 (0.75–1.72)
≥1 4-valent vaccine-type HPV							
All	103 (27.5)	28.8	70 (20.7)	20.0	**−8.8**	**−31**	**0.62 (0.44–0.88)**
Vaccinated	19 (23.2)	25.7	34 (21.3)	20.3	−5.4	−21	0.74 (0.39–1.38)
Unvaccinated	84 (28.7)	32.2	36 (20.2)	20.5	**−11.7**	**−36**	**0.56 (0.34–0.86)**
HPV 16 and/or 18							
All	92 (24.6)	26.1	60 (17.8)	16.5	**−9.6**	**−37**	**0.56 (0.39–0.81)**
Vaccinated	17 (21.0)	24.4	32 (20.0)	19.9	−4.6	−19	0.77 (0.4–1.46)
Unvaccinated	75 (25.6)	29.2	28 (15.7)	16.3	**−12.9**	**−44**	**0.47 (0.29–0.77)**
HPV6 and/or 11							
All	18 (4.8)	5.1	15 (4.4)	5.2	0.1	1	1.01 (0.52–1.98)
Vaccinated	2 (2.4)	1.5	3 (1.9)	0.9	−0.6	−40	0.60 (0.05–6.67)
Unvaccinated	16 (5.5)	5.7	12 (6.7)	6.8	1.0	18	1.19 (0.54–2.63)

Note: n values represent the number of participants with detection of ≥1 HPV type, ≥1 4-valent vaccine-type HPV, HPV16 and/or 18, and HPV6 and/or 11. CI, confidence interval.

Bolded numbers represent statistically significant differences between wave 1 and wave 2.

[1]Odds ratios and confidence intervals were derived from logistic regression analyses with HPV prevalence as the outcome and wave as the independent variable, adjusted for the propensity score.