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Epidemiology of Any and Vaccine-Type Anogenital Human Papillomavirus among 13–26 Year-Old Young Men after HPV Vaccine Introduction

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Abstract

Purpose—The aims of this study were to determine prevalence of and factors associated with any human papillomavirus (HPV) and vaccine-type HPV among young men after vaccine introduction, stratified by vaccination status.

Methods—Young men were recruited from clinical sites from 2013–2015, completed a survey, and were tested for 36 anogenital HPV types. We determined factors associated with > 1 HPV type among all participants, and vaccine-type HPV (HPV6, 11, 16, and/or 18) among all, vaccinated and unvaccinated participants, using multivariable regression.

Results—Mean age was 21.5 years and 26% had received at least one HPV vaccine dose. HPV prevalence was lower in vaccinated vs. unvaccinated young men (50.5% vs. 62.6%, $p=.03$). HPV

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positivity was discordant by site. At both sites, 59.4% were positive for 1 HPV type and 26.0% for 1 4-valent vaccine type. In multivariable logistic regression, factors associated with 1 HPV type among all participants were frequency of oral sex (OR=1.80, 95% CI=1.00–3.24), recent smoking (OR=1.84, CI=1.17–2.90), and sexually transmitted infection history (OR=1.56, CI=1.02–2.38). Factors associated with vaccine-type HPV among all participants were White vs. Black race (OR=1.91, CI=1.10–3.34) and gonorrhea history (OR=2.52, CI=1.45–4.38); among vaccinated participants were private vs. Medicaid insurance (OR=5.6, CI=1.46–20.4) and private vs. no insurance (OR=15.9, CI=3.06–83.3); and among unvaccinated participants was gonorrhea history (OR=1.83, CI=1.03–3.24).

Conclusions—Anogenital HPV prevalence was high and vaccination rates low among young men two to four years after vaccine introduction, underscoring the urgency of increasing vaccination rates and vaccinating according to national guidelines.

Keywords

Human Papillomavirus; vaccines; young men; sexually transmitted infections

Introduction

Human papillomavirus (HPV) infects nearly 14 million people each year in the United States; almost half of infections occur in 15–24 year olds.(1) Infection may cause anogenital warts, anogenital cancers such as cervical cancer, and oropharyngeal cancers. The Centers for Disease Control and Prevention estimates that approximately 30,700 new cancers each year are attributable to HPV, including 11,600 cancers in men.(2)

Male HPV vaccination is effective, and could greatly decrease the burden of anogenital warts and cancers caused by HPV in men as well as decrease the disease burden in young women through herd immunity.(3, 4) In 2011, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of young men 11–21 years old and vaccination of young men 22–26 years old at high risk for HPV.(3) However, HPV vaccine coverage in young men is low. In 2015, only 49.8% of 13–17 year old men in the U.S. had received at least one dose of the vaccine and 28.1% had completed the series.(5)

Previous studies have demonstrated that the prevalence of any HPV among men ranges widely (1.3% to 72.9%) but is typically greater than 20%.(6) Surveillance studies have demonstrated a decrease in HPV in women and adult men after vaccine introduction.(7, 8) However, there are limited data available regarding the prevalence of HPV in adolescent men after vaccine introduction. Most studies have been conducted in adult men (i.e. men at least 18 years of age) or in young men who have sex with men (MSM).(9, 10) Furthermore, there are limited data regarding which factors are associated with HPV infection, and previous studies were conducted primarily in adults. These have demonstrated that factors associated with HPV infection include lifetime and recent number of sexual partners,(9–15) lack of circumcision,(11–14) inconsistent condom use,(12, 13, 15–17) smoking,(12, 15) and younger age.(11) Finally, little is known about concordance between anogenital sites in young men.(18)

Information regarding the epidemiology and risk factors for HPV infection in adolescent and young adult men after vaccine licensing is essential for policy decisions, public health messaging, and prevention efforts. For example, HPV epidemiology is likely to change after HPV vaccine introduction, and current data regarding HPV prevalence in vaccinated and unvaccinated young men are important for guiding policies regarding immunization, decisions about vaccine financing, and the design of public health messages for clinicians and parents. In addition, risk factors for HPV may differ after vaccine introduction because vaccinated and unvaccinated men may differ in terms of demographic characteristics, behaviors, or other factors that are associated with their risk for HPV. Information about changing risk factors is important for public health messaging and designing interventions to prevent HPV post-vaccination. Therefore, the aims of this study were to: (1) determine the prevalence of anogenital HPV, and concordance between genital sites, in a diverse sample of 13–26 year old sexually active adolescent and young adult men and (2) determine factors associated with a) any anogenital HPV (1 type) among all young men, and b) vaccine-type HPV among all, vaccinated, and unvaccinated young men. We hypothesized that prevalence of HPV would be high in this study sample, that having received at least one HPV vaccine dose would be associated with lower prevalence of vaccine-type HPV, and that factors associated with vaccine-type HPV would differ among vaccinated and unvaccinated men.

Methods

Young men 13–26 years old (N=400) were recruited between 2013 and 2015 from a hospital-based teen health center (THC) and a health department sexually transmitted disease (STD) clinic in Cincinnati, Ohio, U.S. Both sites serve a racially diverse, urban, and predominantly low income population. Men who had sexual contact (genital-oral or genital-genital with male or female partners) were eligible to participate. All vaccinated men had received the 4-valent vaccine. Men were recruited using a sequential sampling strategy (all eligible men were invited to participate): 91% of those approached agreed to participate. The study was approved by the Institutional Review Boards of the hospital and the health department, and written informed consent was obtained from participants. Participants completed a survey instrument in English or Spanish assessing sociodemographic characteristics, HPV and HPV vaccine knowledge, vaccination history, substance use history, and sexual behaviors. The survey was developed and validated in similar populations: details are described in previous manuscripts.(19–21)

Three separate genital swabs (penile, including coronal sulcus, glans penis, and shaft of the penis, as well as scrotal) and one perianal/anal swab were collected from each male participant for HPV DNA testing using previously-described procedures.(22) Swabs were pre-moistened with sterile saline, placed immediately into tubes containing 1 mL of Digene Specimen Transport Medium (STM, Qiagen, Germantown, MD), and stored at –80°C. The three penile/scrotal samples were combined to produce one genital DNA extract per participant, and the perianal/anal sample was analyzed separately. This method has been shown to optimize HPV detection among men and to result in reproducible detection of genital HPV in men, while achieving cost savings.(22, 23) Samples were analyzed for HPV genotypes using the Roche Linear Array Assay, a polymerase chain reaction amplification technique that uses an L1 consensus primer system and reverse-line blot detection strip to

identify 36 different HPV genotypes (Roche Molecular Systems, Alameda, CA).(24) The Roche Linear Array tests for 37 high-risk and low-risk genotypes (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39, and CP6108): IS39 has been reclassified as a subtype of HPV82, so the test detects 36 distinct genotypes. The HPV test results from genital (penile and scrotal) and perianal/anal sites were analyzed separately for descriptive analyses, but were combined for univariable and multivariable analyses due to insufficient power to analyze type-specific HPV prevalence by site in the multivariable analyses.

The primary outcome variables for this study were any HPV (≥ 1 type) and 4-valent vaccine-type HPV (HPV6, 11, 16, and/or 18). Independent variables included vaccination status, number of vaccine doses, demographic factors (age, race, ethnicity, insurance status, type of insurance), recruitment site (THC vs. STD clinic), sexual behaviors (lifetime number of female and male partners; recent number of female and male partners; recent number of new female and male partners; age of first sexual intercourse with male and female partners; recent condom use with men and women; condom use at last sexual intercourse; recent history of giving or receiving oral sex), sexual orientation, substance use (recent and lifetime cigarette smoking, recent and lifetime marijuana smoking), and history of other sexually transmitted infections. These independent variables were chosen based on biological plausibility and/or because they have been associated with HPV and other STIs in previous studies.(10, 11, 13–17, 25, 26)

Any HPV, type-specific HPV (types included in the 4-valent and 9-valent vaccines, non-vaccine-type, high-risk, HPV16/18, and HPV6, 11, 16 and 18), and vaccination rates were determined using descriptive statistics. HPV results were then stratified by site (penile/scrotal vs. perianal/anal), age (13–21 vs. 22–26 years), and vaccination status. We also examined the association between number of vaccine doses and vaccine-type HPV using logistic regression.

Associations between independent and outcome variables were determined using chi-square, Fisher's exact and Wilcoxon rank-sum tests. Independent variables associated at $p < 0.10$ with outcome variables in univariable analyses were checked for multicollinearity and eliminated from multivariable analysis when appropriate. Variables associated with four outcomes (≥ 1 HPV type among all participants, and vaccine-type HPV among all, vaccinated, and unvaccinated participants) at $p < 0.10$ in univariable analysis were included in four multivariable logistic regression models. Stepwise variable selection was used and variables associated with the outcomes at $p < 0.05$ were retained in the final models.

Results

Participant characteristics, vaccination rates, and HPV prevalence

Participants' mean age was 21.5 years (20.8% 14–18 years, 28% 19–21 years, 51.3% 22–26 years), 69% were Black, 2.5% were Hispanic, 10% were MSM, 50% reported an STI history, and 4% reported being HIV positive. Most participants (66.5%) were recruited from the STD clinic, 24.3% had private insurance, and 27.5% had Medicaid (public) insurance. Overall, 26.0% had received at least one HPV vaccine dose, and 12.3% had received all 3

HPV vaccine doses. Data addressing the first aim of the study are shown in Table 1. Among all participants, 59.4% were positive for 1 HPV type, 26% for 1 4-valent vaccine type, 18.9% for HPV16, and 4.5% for HPV18 (Table 1). HPV prevalence in vaccinated vs. unvaccinated young men was: any HPV (50.5% vs. 62.6%, $p=.03$), 4-valent vaccine-type HPV (20.4% vs. 27.9%, $p=.13$), 9-valent vaccine-type HPV (25.2% vs. 34.4%, $p=.09$), non-vaccine-type HPV (37.9% vs. 54.4%, $p=.004$), high-risk HPV (44.7% vs. 49.3%, $p=.42$), high-risk non-vaccine-type HPV (31.1% vs. 37.4%, $p=.25$), HPV16/18 (18.5% vs. 24.8%, $p=.18$), HPV6 (1.9% vs. 4.4%, $p=.26$), HPV11 (0% vs. 1.7%, $p=.18$), HPV16 (14.6% vs. 20.4%, $p=.19$), and HPV18 (4.9% vs. 4.4%, $p=.86$). The association between number of vaccine doses and vaccine-type HPV among vaccinated men was not significant: 1 vs. 3 doses (odds ratio [OR] 0.99, 95% confidence interval [CI] 0.33–2.96) and 2 vs. 3 doses (OR 0.60, 95% CI 0.17–2.12). Among participants positive for anogenital HPV, results were generally discordant when stratified by site (penile/scrotal vs. perianal/anal). For example, among the 75 men positive for HPV16, 39 (52%) were positive at the genital site only, 27 (36%) at the anal site only, and 9 (12%) at both sites. (Table 1). There were no statistically significant differences in HPV by age.

Factors associated with 1 HPV type among all young men

In univariable analyses the following factors were significantly associated with positivity for 1 HPV type (Table 2): vaccination status, recruitment from STD clinic vs. THC, higher lifetime number of female partners, higher number of new male partners in the past 3 months, inconsistent condom use, higher frequency of oral sex in the past 3 months, history of STI, lifetime smoking, recent smoking, and recent marijuana use. In multivariable logistic regression the variables independently associated with HPV positivity were higher frequency of oral sex in the past 3 months, recent smoking, and history of STI (Table 3).

Factors associated with vaccine-type HPV among all, vaccinated, and unvaccinated young men

In univariable analysis, the factors significantly associated with vaccine-type HPV among all young men included: ever had sexual intercourse with a male partner, homosexual or bisexual preference, higher number of male partners (any and new) in the past 3 or 12 months, and history of gonorrhea (Table 4). Although unvaccinated men were more likely than vaccinated men to be positive for vaccine type HPV, the difference was not statistically significant. In multivariable logistic regression, factors independently associated with vaccine-type HPV among all participants were White vs. Black race and a history of gonorrhea (Table 5). In univariable analyses, factors significantly associated with vaccine-type HPV among vaccinated young men included: private (vs. Medicaid or no) insurance, having had sexual intercourse with a male partner, higher number of male partners in the past 12 months, having a male main sexual partner, and identification as bisexual or homosexual vs. heterosexual (Table 4). In multivariable logistic regression, factors independently associated with vaccine-type HPV among vaccinated young men were private vs. Medicaid insurance and private vs. no insurance (Table 5). In univariable analyses, factors significantly associated with vaccine-type HPV in unvaccinated young men included: history of gonorrhea, history of herpes, and higher number of new male partners in the past 3 months (Table 4). In multivariable logistic regression analyses one factor was independently

associated with vaccine-type HPV among unvaccinated participants: history of gonorrhea (Table 5).

Discussion

In this study, we examined the prevalence of and factors associated with any HPV infection and vaccine-type HPV infection, as well as HPV type concordance between anogenital sites, in a diverse sample of adolescent and young adult men. The study provides novel data about HPV epidemiology in young men, two to four years after HPV vaccination was recommended for young men in the U.S.

As hypothesized, the prevalence of HPV was high in this study sample: 59% were positive for at least one HPV type, 26% for at least one 4-valent vaccine-type HPV, 23.2% for HPV16/18, and 18.9% for HPV16. Prevalence did not differ by age. In a study of HIV-seronegative adult MSM, Goldstone et al. reported a prevalence of 48.1% for any HPV, 19% for HPV 16/18, and 13.7% for HPV 16.(10) In a study of 18–44 year-old men, Giuliano et al. demonstrated a prevalence of 52.8 % for 1 HPV, 10.0% for HPV 16/18, and 8.6% for HPV 16.(27) Furthermore, Burchell et al. found a prevalence of 55.9% for any HPV, 20.2% for HPV 16/18, and 16.4% for HPV 16 in a study of HPV transmission and prevalence among new heterosexual couples.(28) The prevalence of any HPV in our study was similar to what was reported in these studies, and the prevalence of HPV16 and/or HPV18 was even higher, despite the fact that a small proportion of the men in our study were MSM and they were recruited after vaccine introduction.

Although limited data have been published regarding HPV prevalence among men younger than 18 years, two studies have examined HPV incidence in this age group. In a study of 16–20 year-old men who have sex with men, the incidence rate for any anal HPV infection was 57 and for vaccine-type anal HPV was 33 cases per 100 person-years, and in an study of 16–24 year-old men, the incidence rate of vaccine-type HPV was 9 cases per 100 person-years. (29, 30) Together with our findings of high HPV prevalence in young men, these data suggest that higher vaccination rates are needed to achieve the benefits of vaccination.

We recruited a sample of young women during the same time period, with similar demographic characteristics and from comparable clinical sites. In young women, the prevalence of 1 HPV type was higher (67.4%), but the prevalence of 4-valent vaccine-type HPV much lower (8.7%) as was the prevalence of HPV 16/18 (7.3%).(7) The higher vaccine-type HPV prevalence in young men vs. women is likely due to the five-year lag between vaccine recommendations in women and men, and the resulting higher rates of vaccination in women (71.3% in women vs. 26% in men).

We found fairly low concordance in type-specific HPV by site: most HPV-infected young men were positive only at the genital or anal sites, but not at both sites. Although few studies are available for comparison, in a study of HIV-infected MSM, Welling et al. demonstrated that anal HPV was significantly associated with a type-concordant penile infection and penile infection was associated with a type-concordant anal infection.(31) Kofoed et al. found a 78.1% concordance between anal and genital wart HPV types among men and

women with genital warts.(32) Blas et al. noted a higher rate of anal HPV compared to HPV at other genital sites among adult MSM.(33) The relatively high discordance found in our study could be due to sexual behaviors: most study participants practiced only vaginal sex with women, and had never had anal sex with a women or man. Other factors that may influence concordance rates include HPV sampling and detection methods and study population characteristics.

Recent studies have demonstrated that introduction of HPV vaccines greatly decreases HPV prevalence.(34) Young men participating in this study who were vaccinated, compared to those who were unvaccinated, had a significantly lower prevalence of any HPV infection (50.5% vs. 62.6%). Although those who were vaccinated compared to those who were unvaccinated also had a lower prevalence of vaccine-type HPV, the differences were not statistically significant. This finding may be explained by the fact that many of these young men had not been fully vaccinated and may have acquired vaccine-type HPV prior to vaccination: prophylactic HPV vaccines are most effective if given prior to sexual initiation. It is also possible that we had insufficient power to detect differences in vaccine-type HPV by vaccination status due to the relatively small number of vaccinated men who were infected with vaccine-type HPV (N=21). We are conducting surveillance studies in this population, and expect that we will observe a protective effect in young men with a larger number of participants and when vaccination rates are higher. Vaccination rates in this sample were described in more detail in a previous publication,(35) and differed substantially by age: 69.9% of 13–18 year-olds and 4.9% of 22–26 year-olds received at least one dose.(35) These findings are comparable to those of national studies, which demonstrated that 49.8% of 13–17 year olds and 8.2% of 19–26 year-olds had received at least one dose.(5, 36) The results support the importance of effective, comprehensive interventions to improve vaccination rates among young men. The evidence base for such interventions is growing, and includes addressing healthcare systems issues (reducing cost, improving reimbursement, enhancing vaccination infrastructure, optimizing delivery systems), promoting national recommendations, reducing missed opportunities to administer vaccines, strengthening clinician recommendations for the vaccine, increasing parental and adolescent acceptance of vaccination, and offering vaccination in alternative settings as noted in a recent President’s Cancer Panel Report (<http://deainfo.nci.nih.gov/advisory/pcp/annualReports/HPV/#sthash.6fNIYd6p.dpbs>).

Factors associated with HPV infection in these young men included higher frequency of recent oral sexual encounters, recent smoking, and history of an STI. The association between oral sex and anogenital HPV may be due to direct oral-genital transmission or be a marker of higher exposure to sexual behaviors that would put young men at risk for HPV transmission. In a recent systematic review and meta-analysis of oral HPV infection in men who have sex with men, the authors found that while a proportion of men were concordant for oral and anogenital HPV, type-specific concordance between oral and anogenital sites was rare.(37) Given that HPV-associated oropharyngeal cancer incidence rates are rising, especially in men, a better understanding of oral-genital transmission patterns in young men, the natural history of oral HPV in men, and the pathogenesis of HPV-associated oropharyngeal cancer will be important to design interventions that will reverse this trend. (38) Several recent studies have confirmed an association between smoking and HPV

infection in men.(12, 15) Furthermore, Schabath et al demonstrated that current smoking was associated with higher incidence of genital HPV infection.(39) In MSM, smoking is associated with a higher viral load of high-risk HPV types, abnormal anal cytology, and an increased risk for anal cancer.(40) Given the strong association between number of sexual partners and HPV infection,(11–15) it is not surprising that history of an STI is associated with HPV infection.

Finally, we identified factors associated with prevalent vaccine-type HPV by vaccination status, and as hypothesized, factors differed among vaccinated and unvaccinated men. Moreira et al. examined risk factors for incident vaccine-type HPV among heterosexual adolescent and young adult men, and found that that higher number of sexual partners, less frequent condom use, and living in Africa were associated with incident HPV.(30) In our study, sexual behaviors (including male sexual partners and number of male partners) were associated with prevalent vaccine-type HPV in univariable, but not multivariable analyses. Among all participants, White race and history of gonorrhea were associated with vaccine-type HPV; among vaccinated participants, private insurance was associated with vaccine-type HPV; and among unvaccinated participants, history of gonorrhea was associated with vaccine-type HPV. Those participants recruited from the STD clinic, compared to those recruited from the THC, were older, more likely to be White, more likely to have private insurance, and less likely to have been vaccinated. They were also more likely to be positive for HPV. These factors may explain why White race and private insurance were associated with HPV infection. A history of gonorrhea may be a marker for riskier sexual behaviors that could increase HPV acquisition. The fact that we could not identify a set of modifiable risk factors for HPV or vaccine-type HPV suggests that it is challenging to determine who is at risk for HPV, underscoring the importance of primary prevention through vaccination and counseling about limiting sexual partners and consistent condom use.

There are several limitations to this study. The design is cross-sectional; therefore, we cannot draw conclusions from the results about causality. Behaviors were self-reported which may limit validity. Participants were recruited from clinical sites, which diminishes the generalizability of the findings; it is possible that HPV prevalence is higher in those not accessing clinical care. The sample size was relatively small, limiting our ability to detect significant associations between independent variables and HPV infection. Although we used established methods for anogenital sampling and reliable HPV DNA testing methods, as noted in the Methods section, there are limitations to all HPV testing methods and it is possible that there were false positives or false negatives. Furthermore, we only tested HPV at one point in time. Finally, we tested a limited number of HPV DNA genotypes, so it should be noted that throughout the manuscript when we refer to “any HPV,” this actually signifies any HPV among the types detected by the Roche Linear Array test.

Conclusion

Any and vaccine-type HPV prevalence were high and vaccination coverage was low among young men in this study sample, two to four years after the vaccine was introduced. Furthermore, our analyses did not identify a set of risk factors associated with vaccine-type HPV that could be targeted in interventions. Our findings emphasize the importance of

primary prevention of HPV through increasing vaccination rates in young men and vaccinating before sexual initiation. The findings also suggest that interventions to promote STI prevention such as limiting sexual partners and using condoms consistently will be important, though challenging.

Acknowledgments

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Abbreviations

HPV	human papillomavirus
STI	sexually transmitted infection
CI	confidence interval
ACIP	Advisory Committee on Immunization Practices
MSM	men who have sex with men
THC	Teen Health Center
STD	sexually transmitted disease

References

1. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2014; 63:1–30.
2. Viens LJ, Henley SJ, Watson M, et al. Human Papillomavirus-Associated Cancers - United States, 2008-2012. *MMWR Morb Mortal Wkly Rep.* 2016; 65:661–666. [PubMed: 27387669]
3. Recommendations on the use of quadrivalent human papillomavirus vaccine in males— Advisory Committee on Immunization Practices (ACIP) 2011. *MMWR Morb Mortal Wkly Rep.* 2011; 60:1705–1708. [PubMed: 22189893]
4. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N Engl J Med.* 2011; 364:401–411. [PubMed: 21288094]
5. Reagan-Steiner S, Yankey D, Jeyarajah J, et al. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13-17 Years - United States, 2015. *MMWR Morb Mortal Wkly Rep.* 2016; 65:850–858. [PubMed: 27561081]
6. Dunne EF, Nielson CM, Stone KM, et al. Prevalence of HPV infection among men: A systematic review of the literature. *J Infect Dis.* 2006; 194:1044–1057. [PubMed: 16991079]

7. Kahn JA, Widdice LE, Ding L, et al. Substantial Decline in Vaccine-Type Human Papillomavirus (HPV) Among Vaccinated Young Women During the First 8 Years After HPV vaccine Introduction in a Community. *Clin Infect Dis*. 2016; 63:1281–1287. [PubMed: 27655996]
8. Chow EPF, Machalek DA, Tabrizi SN, et al. Quadrivalent vaccine-targeted human papillomavirus genotypes in heterosexual men after the Australian female human papillomavirus vaccination programme: a retrospective observational study. *Lancet Infect Dis*. 2017; 17:68–77. [PubMed: 27282422]
9. Meites E, Gorbach PM, Gratz B, et al. Monitoring for Human Papillomavirus vaccine Impact Among Gay, Bisexual, and Other Men Who Have Sex With Men—United States, 2012–2014. *J Infect Dis*. 2016; 214:689–696. [PubMed: 27296847]
10. Goldstone S, Palefsky JM, Giuliano AR, et al. Prevalence of and risk factors for human papillomavirus (HPV) infection among HIV-seronegative men who have sex with men. *J Infect Dis*. 2011; 203:66–74. [PubMed: 21148498]
11. Svare EI, Kjaer SK, Worm AM, et al. Risk factors for genital HPV DNA in men resemble those found in women: a study of male attendees at a Danish STD clinic. *Sex Transm Infect*. 2002; 78:215–218. [PubMed: 12238658]
12. Vaccarella S, Lazcano-Ponce E, Castro-Garduno JA, et al. Prevalence and determinants of human papillomavirus infection in men attending vasectomy clinics in Mexico. *Int J Cancer*. 2006; 119:1934–1939. [PubMed: 16708372]
13. Baldwin SB, Wallace DR, Papenfuss MR, et al. Condom use and other factors affecting penile human papillomavirus detection in men attending a sexually transmitted disease clinic. *Sex Transm Dis*. 2004; 31:601–607. [PubMed: 15388997]
14. Giuliano AR, Lazcano E, Villa LL, et al. Circumcision and sexual behavior: factors independently associated with human papillomavirus detection among men in the HIM study. *Int J Cancer*. 2009; 124:1251–1257. [PubMed: 19089913]
15. Nielson CM, Harris RB, Dunne EF, et al. Risk factors for anogenital human papillomavirus infection in men. *J Infect Dis*. 2007; 196:1137–1145. [PubMed: 17955431]
16. Repp KK, Nielson CM, Fu R, et al. Male human papillomavirus prevalence and association with condom use in Brazil, Mexico, and the United States. *J Infect Dis*. 2012; 205:1287–1293. [PubMed: 22396601]
17. Nielson CM, Harris RB, Nyitray AG, et al. Consistent condom use is associated with lower prevalence of human papillomavirus infection in men. *J Infect Dis*. 2010; 202:445–451. [PubMed: 20569156]
18. Steinau M, Gorbach P, Gratz B, et al. Concordance Between Anal and Oral Human Papillomavirus Infections Among Young Men Who have Sex With Men. *J Infect Dis*. 2017; 215:1832–1835. [PubMed: 28505338]
19. Kahn JA, Rosenthal SL, Jin Y, et al. Rates of human papillomavirus vaccination, attitudes about vaccination, and human papillomavirus prevalence in young women. *Obstet Gynecol*. 2008; 111:1103–1110. [PubMed: 18448742]
20. Mayhew A, Mullins TL, Ding L, et al. Risk perceptions and subsequent sexual behaviors after HPV vaccination in adolescents. *Pediatrics*. 2014; 133:404–411. [PubMed: 24488747]
21. Mullins TL, Widdice LE, Rosenthal SL, et al. Risk perceptions, sexual attitudes, and sexual behavior after HPV vaccination in 11–12 year-old girls. *Vaccine*. 2015; 33:3907–3912. [PubMed: 26116249]
22. Giuliano AR, Nielson CM, Flores R, et al. The optimal anatomic sites for sampling heterosexual men for human papillomavirus (HPV) detection: the HPV detection in men study. *J Infect Dis*. 2007; 196:1146–1152. [PubMed: 17955432]
23. Flores R, Abalos AT, Nielson CM, et al. Reliability of sample collection and laboratory testing for HPV detection in men. *J Virol Methods*. 2008; 149:136–143. [PubMed: 18279976]
24. Gravitt PE, Peyton CL, Alessi TQ, et al. Improved amplification of genital human papillomaviruses. *J Clin Microbiol*. 2000; 38:357–361. [PubMed: 10618116]
25. Meites E, Gorbach PM, Gratz B, et al. Monitoring for Human Papillomavirus vaccine Impact Among Gay, Bisexual, and Other Men Who Have Sex With Men—United States, 2012– 2014. *Journal of Infectious Diseases*. 2016; 214:689–696. [PubMed: 27296847]

26. Vaccarella S, Herrero R, Dai M, et al. Reproductive factors, oral contraceptive use, and human papillomavirus infection: pooled analysis of the IARC HPV prevalence surveys. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:2148–2153. [PubMed: 17119039]
27. Giuliano AR, Lu B, Nielson CM, et al. Age-specific prevalence, incidence, and duration of human papillomavirus infections in a cohort of 290 US men. *J Infect Dis.* 2008; 198:827–835. [PubMed: 18657037]
28. Burchell AN, Tellier PP, Hanley J, et al. Influence of partner's infection status on prevalent human papillomavirus among persons with a new sex partner. *Sex Transm Dis.* 2010; 37:34–40. [PubMed: 19704391]
29. Zou H, Tabrizi SN, Grulich AE, et al. Site-specific human papillomavirus infection in adolescent men who have sex with men (HYPER): an observational cohort study. *Lancet Infect Dis.* 2015; 15:65–73. [PubMed: 25435055]
30. Moreira ED Jr, Giuliano AR, Palefsky J, et al. Incidence, clearance, and disease progression of genital human papillomavirus infection in heterosexual men. *J Infect Dis.* 2014; 210:192–199. [PubMed: 24495910]
31. Welling CA, Mooij SH, van der Sande MA, et al. Association of HIV Infection With Anal and Penile Low-Risk Human Papillomavirus Infections Among Men Who Have Sex With Men in Amsterdam: The HIV & HPV in MSM Study. *Sex Transm Dis.* 2015; 42:297–304. [PubMed: 25970305]
32. Kofoed K, Sand C, Forslund O, et al. Prevalence of human papillomavirus in anal and oral sites among patients with genital warts. *Acta Derm Venereol.* 2014; 94:207–211. [PubMed: 24096893]
33. Blas MM, Brown B, Menacho L, et al. HPV Prevalence in Multiple Anatomical Sites among Men Who Have Sex with Men in Peru. *PLoS One.* 2015; 10:e0139524. [PubMed: 26437318]
34. Drolet M, Benard E, Boily MC, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis.* 2015; 15:565–580. [PubMed: 25744474]
35. Thomas R, Higgins L, Ding L, et al. Factors Associated With HPV vaccine Initiation, Vaccine Completion, and Accuracy of Self-Reported Vaccination Status Among 13- to 26-Year-Old Men. *Am J Mens Health.* 2016
36. Williams WW, Lu PJ, O'Halloran A, et al. Surveillance of Vaccination Coverage Among Adult Populations - United States, 2014. *MMWR Surveill Summ.* 2016; 65:1–36.
37. King EM, Oomeer S, Gilson R, et al. Oral Human Papillomavirus Infection in Men Who Have Sex with Men: A Systematic Review and Meta-Analysis. *PLoS One.* 2016; 11:e0157976. [PubMed: 27384050]
38. Chaturvedi AK, Graubard BI, Broutian T, et al. NHANES 2009-2012 Findings: Association of Sexual Behaviors with Higher Prevalence of Oral Oncogenic Human Papillomavirus Infections in U.S. Men. *Cancer Res.* 2015; 75:2468–2477. [PubMed: 25873485]
39. Schabath MB, Villa LL, Lin HY, et al. A prospective analysis of smoking and human papillomavirus infection among men in the HPV in Men Study. *Int J Cancer.* 2014; 134:2448–2457. [PubMed: 24222514]
40. Wieland U, Hellmich M, Wetendorf J, et al. Smoking and anal high-risk human papillomavirus DNA loads in HIV-positive men who have sex with men. *Int J Med Microbiol.* 2015; 305:689–696. [PubMed: 26319939]

Implications and Contributions

Few studies have examined the prevalence and risk factors for HPV and concordance between genital sites in adolescent males after vaccine introduction. This study demonstrates that HPV prevalence was high and vaccination rates low among young men 2–4 years after vaccine introduction, underscoring the importance of vaccination according to national guidelines.

Table 1

Type-specific HPV prevalence by anatomical site

HPV Types	HPV prevalence, any site N (%)			HPV prevalence, site-specific N (%)		
	Genital and/or anal ¹	Genital only	Anal only	Both genital and anal	Neither genital nor anal	
1	236 (59.4)	132 (35.0)	40 (10.6)	64 (17.0)	141 (37.4)	
Included in the 4-valent vaccine ²	103 (26.0)	50 (13.3)	32 (8.5)	21 (5.6)	272 (72.5)	
Included in the 9-valent vaccine ³	127 (32.0)	68 (18.1)	32 (8.5)	27 (7.2)	249 (66.2)	
Non-vaccine ⁴	199 (50.1)	126 (33.5)	27 (7.2)	46 (12.2)	177 (47.1)	
High-risk ⁵	191 (48.1)	108 (29.0)	43 (11.5)	40 (10.7)	184 (49.1)	
High-risk, non-vaccine ⁶	142 (35.8)	94 (25.1)	25 (6.7)	23 (6.1)	232 (62.0)	
High-risk, included in the vaccine ⁷	92 (23.2)	43 (11.5)	35 (9.4)	14 (3.7)	282 (75.4)	
HPV 6	15 (3.8)	9 (2.4)	2 (0.5)	4 (1.1)	359 (96.0)	
HPV 11	5 (1.3)	0 (0)	3 (0.8)	2 (0.5)	368 (98.7)	
HPV 16	75 (18.9)	39 (10.4)	27 (7.2)	9 (2.4)	299 (80.0)	
HPV 18	18 (4.5)	4 (1.1)	9 (2.4)	5 (1.3)	355 (95.2)	

¹ Genital refers to penile/scrotal samples and anal refers to perianal/anal samples

² Included in the 4-valent vaccine: HPV6, 11, 16, and/or 18

³ Included in the 9-valent vaccine: HPV6, 11, 16, 18, 31, 33, 45, 52, and/or 58

⁴ Non-vaccine: any HPV types detected except for HPV6, 11, 16, and/or 18

⁵ High-risk: HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 67, 68, 70, 73, 82, and/or 89

⁶ High-risk, non-vaccine: all high-risk types other than HPV16 and 18

⁷ High risk, included in the vaccine: HPV16, 18

Table 2

Factors significantly associated with positivity for 1 HPV type among all participants: Results of univariable analyses¹

	N (%)	P Value ²
Vaccination status		0.03
Vaccinated	52 (50.5)	
Unvaccinated	184 (62.6)	
Enrollment site		0.0001
Teen Health Center	58 (43.9)	
STD Clinic	178 (67.2)	
Lifetime number of female partners		0.01
0	16 (61.5)	
1	8 (32.0)	
2–5	40 (50.0)	
6–10	66 (67.4)	
11–20	54 (60.0)	
21	48 (64.9)	
Number of new male partners in past 3 months		0.04
0	219 (58.4)	
1	9 (64.3)	
2	8 (100)	
Condom use during anal sex with female partners, past 3 months		0.046
Mostly/Always	5 (33.3)	
Never/Occasionally	23 (63.9)	
Had oral sex in past 3 months		0.01
0 time	33 (47.1)	
1 time	13 (41.9)	
2–5 times	99 (65.1)	
5 times	90 (62.9)	
Smoked at least 100 cigarettes (5 packs) in lifetime		0.03
No	144 (55.4)	
Yes	86 (67.2)	
Number of days smoked cigarettes in the last 30 days		0.001
0 days	136 (53.5)	
1+ days	100 (69.9)	
Number of days smoked marijuana in the last 30 days		0.049
Never smoked	44 (52.4)	
0 days	57 (53.8)	
1+ days	135 (65.2)	

	N (%)	P Value ²
History of a sexually transmitted infection		0.004
No	103 (52.3)	
Yes	133 (66.5)	

¹Only those independent variables significantly associated with HPV are shown in the table. The complete list of independent variables is as follows: age, race, ethnicity, recruitment site, insurance status, type of insurance, lifetime number of female and male partners, recent number of female and male partners, recent number of new female and male partners, age of first sexual intercourse with male and female partners, recent condom use (with men and women; if men, with receptive or insertive anal sex), condom use at last sexual intercourse, recent history of giving or receiving oral sex, sexual orientation, last time genitals were washed, lifetime and recent cigarette smoking, lifetime and recent marijuana smoking, STI history.

²P value derived from a chi-square test

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Table 3

Factors significantly associated with positivity for 1 HPV type among all participants: Results of multivariable analysis¹

Variable	Categories	AOR ²	95% CI ³
Had oral sex in the past 3 months	2–5 vs. 0 days (ref.)	1.80	1.00–3.24
Smoked cigarettes in the past 30 days	1 vs. 0 days (ref.)	1.84	1.17–2.90
History of a sexually transmitted infection	Yes vs. no (ref.)	1.56	1.02–2.38

¹ Additional variables included in the model were number of lifetime female partners, number of new male partners in the past 3 months, history of anal sex with a female partner, condom use during anal sex with a female partner in the past 3 months, and recent marijuana use

² AOR= Adjusted Odds Ratio

³ CI= confidence interval

Table 4

Factors significantly associated with 4-valent vaccine-type HPV in all, vaccinated, and unvaccinated young men: Results of univariable analyses

	Vaccine Type HPV N (%)	P-Value ^I
All Young Men		
Vaccination Status		0.13
Vaccinated	21 (20.4)	
Unvaccinated	82 (27.9)	
Ever had sex with a male partner		0.02
No	86 (24.2)	
Yes	17 (41.5)	
Sexual orientation		0.009
Heterosexual	86 (24.2)	
Homosexual	10 (32.3)	
Bisexual	5 (71.4)	
Number of male partners, past 3 months		0.01
0	86 (23.9)	
1	9 (45.0)	
2	8 (47.1)	
Number of new male partners, past 3 months		0.009
0	93 (24.8)	
1	4 (28.6)	
2	6 (75)	
Number of male partners, past 12 months		0.01
0	86 (24.0)	
1	4 (33.3)	
2	13 (50.0)	
Number of new male partners, past 12 months		0.02
0	88 (24.1)	
1	5 (41.7)	
2	10 (50.0)	
Ever had gonorrhea		0.006
No	72 (22.9)	
Yes	31 (37.8)	
Vaccinated Young Men		
Health insurance plan		0.0009
None/Not sure	3 (8.1)	
Medicaid	11 (20.4)	
Private	7 (58.3)	
Ever had sex with a male partner		0.01

	Vaccine Type HPV N (%)	P-Value ^I
No	15 (16.7)	
Yes	6 (46.2)	
Number of male partners, past 12 months		0.02
0	15 (16.7)	
1	1 (20.0)	
2	5 (62.5)	
Number of new male partners, past 12 months		0.04
0	16 (17.4)	
1	2 (33.3)	
2	3 (60.0)	
Gender of main sexual partner		0.01
Female	11 (15.5)	
Male	6 (54.6)	
No main partner	4 (19.1)	
Sexual orientation		0.02
Heterosexual	15 (16.9)	
Homosexual	3 (30.0)	
Bisexual	3 (75.0)	
Unvaccinated Young Men		
History of gonorrhea		0.04
No	56 (24.9)	
Yes	26 (37.7)	
History of genital herpes		0.03
No	79 (27.2)	
Yes	3 (75.0)	
Number of new male partners, past 3 months		0.04
0	75 (26.9)	
1	2 (22.2)	
2	5 (71.4)	

^I P value derived from a chi-square test or Fisher's exact test

Table 5

Factors significantly associated with vaccine-type HPV in all, vaccinated, and unvaccinated participants: results of multivariable analyses¹

Variable	Categories Contrasted	AOR ²	95% CI ³
Model 1: All Participants			
Race	White vs. Black (ref.)	1.91	1.10–3.34
History of gonorrhea	Yes vs no (ref.)	2.52	1.45–4.38
Model 2: Vaccinated Participants			
Insurance Plan	Private vs. Medicaid (ref.)	5.46	1.46–20.4
	Private vs. no health insurance (ref.)	15.9	3.06–83.3
Model 3: Unvaccinated Participants			
History of gonorrhea	Yes vs. no (ref.)	1.83	1.03–3.24

¹ Additional variables included in model 1: insurance plan, number of new male partners in the past 3 months, and sexual preference; model 2: insurance status, ever had sex with male, last sex with a female, history of gonorrhea, number of new male partners in 3 months, number of male partners in 12 months; model 3: number of new male partners in 3 months, history of herpes

² AOR= adjusted odds ratio

³ CI= confidence interval