MAJOR ARTICLE







Vaccine Effectiveness Against Prevalent Anal and Oral Human Papillomavirus Infection Among Men Who Have Sex With Men—United States, 2016–2018

Elissa Meites,^{1,0} Rachel L. Winer,² Michael E. Newcomb,³ Pamina M. Gorbach,⁴ Troy D. Querec,⁵ Jessica Rudd,⁶ Tom Collins,⁷ John Lin,² Janell Moore,⁴ Thomas Remble,³ Fred Swanson,⁸ Justin Franz,³ Robert K. Bolan,⁹ Matthew R. Golden,¹⁰ Brian Mustanski,³ Richard A. Crosby,⁷ Elizabeth R. Unger,⁵ and Lauri E. Markowitz¹

¹Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, ²Department of Epidemiology, University of Washington, Seattle, Washington, USA, ³Institute for Sexual and Gender Minority Health and Wellbeing and Department of Medical Social Sciences, Northwestern University and Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA, ⁴Department of Epidemiology, Fielding School of Public Health, University of California at Los Angeles, Los Angeles, California, USA, ⁵Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, ⁶Maximus Services LLC, CDC Contractor, Atlanta, Georgia, USA, ⁷College of Public Health, University of Kentucky, Lexington, Kentucky, USA, ⁸Gay City Health Project, Seattle, Washington, USA, ⁹Los Angeles LGBT Center, Los Angeles, California, USA, ¹⁰Center for AIDS & STD, University of Washington, Seattle, Washington, USA

Background. In the United States, human papillomavirus (HPV) vaccination has been recommended for young adult men who have sex with men (MSM) since 2011.

Methods. The Vaccine Impact in Men study surveyed MSM and transgender women aged 18–26 years in 3 US cities during 2016–2018. Self-collected anal swab and oral rinse specimens were assessed for 37 types of HPV. We compared HPV prevalence among vaccinated and unvaccinated participants and determined adjusted prevalence ratios (aPR) and 95% confidence intervals (CI).

Results. Among 1767 participants, 704 (39.8%) self-reported receiving HPV vaccine. Median age at vaccination (18.7 years) was older than age at first sex (15.7 years). Quadrivalent vaccine-type HPV was detected in anal or oral specimens from 475 (26.9%) participants. Vaccine-type HPV prevalence was lower among vaccinated (22.9%) compared with unvaccinated (31.6%) participants; aPR for those who initiated vaccination at age \leq 18 years was 0.41 (CI, 0.24–0.57) and at age \geq 18 years was 0.82 (CI, 0.67–0.98). Vaccine effectiveness of at least 1 HPV vaccine dose at age \leq 18 years or \geq 18 years was 59% and 18%, respectively.

Conclusions. Findings suggest real-world effectiveness of HPV vaccination among young adult MSM. This effect was stronger with younger age at vaccination.

Keywords. papillomavirus infections; papillomavirus vaccines; sexual and gender minorities; vaccination.

Men who have sex with men (MSM) are at high risk for human papillomavirus (HPV) infection and HPV-related diseases, including anal cancer. Previous studies have found anal HPV prevalence among MSM to be twice as high as among men who have sex exclusively with women, and especially high among those with human immunodeficiency virus (HIV) [1, 2]. A meta-analysis noted that the pooled prevalence of anal HPV type 16 was 12.5% among HIV-negative MSM (95% confidence interval [CI], 9.8–15.5) and 35.4% among HIV-positive MSM (95% CI, 32.0–37.9); annual incidence of anal cancer was

estimated to be 46 per $100\ 000$ in HIV-positive MSM and 5 per $100\ 000$ in HIV-negative MSM [3].

In clinical trials of quadrivalent HPV vaccine (4vHPV), efficacy against vaccine-type HPV infection (HPV types 6, 11, 16, or 18), anogenital warts, and cervical precancers was first demonstrated among women [4, 5]. Later, a trial among men aged 16 through 26 years was conducted, and this trial showed efficacy against infection and anogenital warts [6]. In a subset of 602 MSM participating in this trial, 4vHPV efficacy against detection of HPV types 6, 11, 16, or 18 was 84.0% (95% CI, 68.6–92.7) in the per-protocol efficacy population (ie, men not infected at the time of vaccination) and 48.5% (95% CI, 32.3–61.1) in the intention-to-treat population [7]. The trial was limited to men with 5 or fewer sex partners in their lifetime [6, 7].

Outside of clinical trials, demonstrations of HPV vaccine effectiveness among MSM have been lacking. In an earlier study we conducted in 2012–2014 among 1033 MSM with a mean age of 23 years, at least 1 of 37 HPV types was detectable in 73.9% and 4vHPV-type HPV was detectable in 35.1%. This earlier study demonstrated no significant difference in HPV

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Correspondence: Elissa Meites, MD, MPH, HPV Team, Division of Viral Diseases, NCIRD, Centers for Disease Control and Prevention, 1600 Clifton Road NE, H24-5, Atlanta, GA 30329 (emeites@cdc.gov).

prevalence by vaccination history, likely due to HPV exposures before vaccination given a mean age at first sex of 16 years and mean age at vaccination of 21 years [8, 9].

In the United States, HPV vaccination has been routinely recommended since 2006 for girls and 2011 for boys [10]. Since 2011, catch-up HPV vaccination has been recommended for MSM and transgender people through age 26 years, if they were not adequately vaccinated previously [10, 11]. Among males aged 13–17 years, coverage with at least 1 dose of any HPV vaccine has risen from 8.3% in 2011 to 66.3% in 2018, according to data from the National Immunization Survey-Teen [12, 13]. Vaccination coverage among young adult MSM ages 18–26 years remains low, but it has increased from 4.9% in 2011 to 17.2% in 2014 and to 32.8% in 2017, according to data from National HIV Behavioral Surveillance [14, 15] (National HIV Behavioral Surveillance, unpublished data).

To date, no studies have reported effectiveness of HPV vaccination among MSM outside of a clinical trial setting. We evaluated anal and oral prevalence of vaccine-type HPV among young adult MSM and transgender women and analyzed data by vaccination history to understand real-world vaccine effectiveness in this population.

METHODS

The cross-sectional Vaccine Impact in Men (VIM) study enrolled a convenience sample of gay, bisexual, and other MSM, and transgender women, aged 18–26 years, in 3 US cities during February 2, 2016 through September 29, 2018. Enrollment occurred at community centers or clinics serving lesbian, gay, bisexual, and transgender (LGBT) clients and included a sexually transmitted diseases (STD) clinic and a community HIV/STD testing site in Seattle, WA, a community center in Chicago, IL, and an LGBT clinic in Los Angeles, CA.

Participants were eligible if they provided written informed consent and met all of the following criteria at enrollment: (1) assigned male sex at birth, regardless of current gender identity or expression; (2) ever had anal or oral sex with a male partner, or identified as gay/homosexual or bisexual, or intended to have sex with a male partner in the future; and (3) aged 18–26 years, within the recommended target age range for catch-up HPV vaccination for MSM.

Participants self-reported demographic characteristics, sexual behaviors, and health information including HIV status and HPV vaccination history. Responses to a set of core questions were captured at all enrollment sites. Behavioral information was collected by survey either on paper or electronically via Qualtrics (Provo, UT); in Seattle, additional data were from clinic records. Participants were considered vaccinated if they self-reported ever receiving any number of doses of any HPV vaccine, unvaccinated if they self-reported having never received any HPV vaccine doses, or unknown if they were unsure

of their HPV vaccination history or did not respond. Age at first sex was with any partner.

Each participant received compensation of nominal value. Most were enrolled and completed all study elements on the same day during a visit for another purpose, such as a clinic visit or participation in an ongoing cohort study [16]. Human papillomavirus vaccination was not provided as part of the study. Each participant was assigned a unique study identification code; no personally identifiable information was collected for these study activities. Study procedures were reviewed and approved by institutional review boards at the participating institutions.

Each participant submitted 3 biologic specimens: a self-collected anal swab, a self-collected oral rinse specimen, and a blood specimen collected by a phlebotomist (for serum, data not presented). Detailed methods for specimen self-collection have been reported previously [9]. Specimens were stored and shipped frozen on dry ice to the HPV laboratory at the Centers for Disease Control and Prevention in Atlanta, GA, for batch processing. Long-term storage was at -80° C.

Testing of deoxyribonucleic acid (DNA) extracts was done using Roche Linear Array HPV genotyping assay (Roche Diagnostics, Indianapolis, IN), a commercial research use only L1-consensus polymerase chain reaction assay that detects type-specific DNA of 37 HPV types (types 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, 89, and IS39), as reported previously [9]. Specimen adequacy was assessed in every test by coamplification and detection of the human β -globin gene; any specimen negative for all 37 types of HPV and negative for the β -globin gene was considered inadequate. In total, 95.3% of anal specimens and 99.6% of oral specimens were adequate for analysis. Quadrivalent HPV vaccine types were HPV 6, 11, 16, and 18. Nonavalent (9vHPV) types were HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

This analysis includes all VIM study participants who responded to the survey and whose specimens were adequate for analysis. We conducted statistical analysis using χ^2 tests to compare (1) characteristics of participants who reported being unvaccinated (no HPV vaccine doses) and those who reported being vaccinated with at least 1 dose of HPV vaccine and (2) characteristics associated with anal and/or oral prevalence of at least 1 of any HPV type or 4vHPV-type DNA. We also determined prevalence ratios (PRs) and 95% CIs for HPV detection and adjusted for variables significantly associated with vaccination on bivariate analysis (ie, age, race/ethnicity, city, number of sex partners, and HIV status) to determine adjusted PRs (aPRs). Vaccine effectiveness against combined anal and/or oral HPV was calculated as $(1-aPR) \times 100$. Variables with P < .05were considered significant. Type-specific PRs and aPRs were stratified by age at vaccination and by self-reported HIV status.

All calculations were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

A total of 1881 people were enrolled in the study, and 1767 completed all study elements (ie, responded to the survey and provided 3 biologic specimens with an adequate laboratory test result). A higher percentage of the study population was enrolled from Seattle (39.8%) than from Chicago (34.9%) or Los Angeles (25.2%) (Table 1). Approximately two thirds (64.5%) were aged 22–26 years; all others were younger. All had been assigned male sex at birth, and most reported their current gender identity as

male, although approximately 5% reported being transgender, queer, or other. Approximately three quarters (73.3%) identified as gay or homosexual; others were bisexual or had had sex with a male partner. A variety of race/ethnicities were reported: 545 (30.8%) non-Hispanic white, 261 (14.8%) non-Hispanic black, 136 (7.7%) Asian/Pacific Islander, 557 (31.5%) Hispanic, and 268 (15.2%) other or unknown race/ethnicity. Among 1767 participants, 139 (7.9%) disclosed being HIV-positive. Mean/median lifetime number of sex partners of any sex were 41.2/21 (IQR, 10–50); in total, 82.9% reported having more than 5 sex partners in their lifetime, and 45.3% reported having more than 20 sex partners in their lifetime. By self-report, 704 (39.8%) had received at least 1 HPV vaccine dose, 687 (38.9%) reported no

Table 1. Characteristics of Participating Transgender Women and Gay, Bisexual, and Other Men Who Have Sex With Men, by HPV Vaccination History

	Total	Unvaccinated	Vaccinated	
Characteristic	N (%)	n (%)	n (%)	Р
Total	1767* (100)	687 (100)	704** (100)	
City				
Chicago	617 (34.9)	271 (39.4)	228 (32.4)	<.001
Los Angeles	446 (25.2)	240 (34.9)	123 (17.5)	
Seattle	704 (39.8)	176 (25.6)	353 (50.1)	
Age, years				
18–21	628 (35.5)	211 (30.7)	273 (38.8)	.003
22–26	1139 (64.5)	476 (69.3)	431 (61.2)	
Gender identity				
Male	1671 (94.6)	651 (94.8)	667 (94.7)	.064
Female/transgender female	53 (3.0)	26 (3.8)	14 (2.0)	
Other/unknown	43 (2.4)	10 (1.5)	23 (3.3)	
Race/ethnicity				
Non-Hispanic white	545 (30.8)	166 (24.2)	264 (37.5)	<.001
Non-Hispanic black	261 (14.8)	141 (20.5)	77 (10.9)	
Asian/Pacific Islander	136 (7.7)	40 (5.8)	67 (9.5)	
Hispanic	557 (31.5)	219 (31.9)	200 (28.4)	
Other/unknown	268 (15.2)	121 (17.6)	96 (13.6)	
Sexual orientation				
Gay/homosexual	1295 (73.3)	500 (72.8)	513 (72.9)	.53
Straight/heterosexual	29 (1.6)	15 (2.2)	8 (1.1)	
Other/unknown	443 (25.1)	172 (25.0)	183 (26.0)	
Lifetime number of sex partners of any sex				
≤5	247 (14.0)	105 (15.3)	87 (12.4)	<.001
6–10	276 (15.6)	124 (18.0)	89 (12.6)	
11–20	388 (22.0)	159 (23.1)	141 (20.0)	
>20	801 (45.3)	283 (41.2)	369 (52.4)	
Other/unknown	55 (3.1)	16 (2.3)	18 (2.6)	
Lifetime number of sex partners of any sex (mean/median, IQR)	41.2/21 (10–50)	35.7/20 (10–40)	48.9/25 (11–51)	<.001
Most recent HIV test result				
Positive	139 (7.9)	52 (7.6)	62 (8.8)	.42
Negative or unknown	1628 (92.1)	635 (92.4)	642 (91.2)	
Age at first HPV vaccination (mean/median, IQR)			18.7/19 (16–22)	-
Age at first sex with any partner (mean/median, IQR)	15.8/16 (14–18)	15.9/16 (14-18)	15.7/16 (15–18)	.17

Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; IQR, interquartile range

NOTE: Bold font indicates significance of χ^2 analysis at P < .05.

^{*}Three hundred seventy-six participants included in the total column were unsure of their HPV vaccination history or did not respond.

^{**}Seven hundred four participants reported receiving at least 1 dose of HPV vaccine dose, including 335 who reported receiving 3 doses of HPV vaccine.

HPV vaccine doses, and 376 (21.3%) were unsure of their vaccination history or did not respond.

Characteristics by Vaccination History

Comparing participants by vaccination history, differences were noted in city of enrollment, age group, race/ethnicity, and number of sex partners. Mean/median lifetime number of sex partners of any sex were 49/25 among 704 vaccinated participants, and 36/20 among 687 unvaccinated participants. Other characteristics were not significantly associated with HPV vaccination among these study participants. Among vaccinated participants, median age at vaccination (18.7 years) was several years older than median age at first sex (15.7 years) (Table 1).

Human Papillomavirus Prevalence

Among all 1767 participants, any type of HPV was detected in anal and/or oral specimens from 1253 (70.9%), with 1236 (69.9%) having anal HPV and 133 (7.5%) having oral HPV (Table 2). At least 1 4vHPV type was detected in 475 (26.9%); 465 (26.3%) in the anal specimen and 33 (1.9%) in the oral specimen. At least one 9vHPV type was detected in 669 (37.9%); 658 (37.2%) in the anal specimen, and 40 (2.3%) in the oral specimen. No participants had all 4vHPV or 9vHPV types.

Among the 139 participants who disclosed being HIV-positive, any type of HPV was detected in anal and/or oral specimens from 127 (91.4%). At least 1 4vHPV type was detected in 70 (50.4%), and at least 1 9vHPV type was detected in 91 (65.5%). None had all 4vHPV or 9vHPV types.

Comparing participants by detection of any HPV, differences were noted in city of enrollment, age group, number of sex partners, and HIV status. Significantly more participants had at least one 4vHPV type detected in anal and/or oral specimens who (1) were aged 22–26 years, (2) reported more sex partners in their lifetime, and (3) disclosed being HIV-positive (Table 3).

Human Papillomavirus Prevalence by Vaccination History

Prevalence of any anal or oral HPV (at least 1 of 37 HPV types) was high among all participants and did not differ significantly by vaccination history (Table 4). In contrast, prevalence of anal or oral 4vHPV-type HPV was lower (22.9%) among 704 vaccinated participants compared with prevalence (31.6%) among 687 unvaccinated participants (aPR 0.71; 95% CI, 0.59–0.83), indicating vaccine effectiveness of 29%. Compared with unvaccinated participants, aPR for 4vHPV-type HPV in either specimen was significantly lower among participants who reported initiating HPV vaccination at age \leq 18 years (aPR 0.41; 95% CI, 0.24–0.57) and at age \geq 18 years (aPR 0.82; 95% CI, 0.67–0.98). Estimated vaccine effectiveness of at least 1 dose of HPV vaccine at age \leq 18 years and \geq 18 years was 59% and 18%, respectively.

In anal specimens alone, significantly lower prevalence of vaccine-type HPV was also observed among vaccinated compared with unvaccinated participants. However, vaccine-type oral HPV prevalence was too low to identify differences by vaccination history in oral specimens alone (Supplementary Tables 1–4).

Among the 139 participants who disclosed being HIV-positive, prevalence of 4vHPV-type HPV was lower among those vaccinated (46.8%) compared with those unvaccinated (57.7%) (aPR 0.85; 95% CI, 0.29–1.42), but the difference was not statistically significant. Prevalence of any HPV type was similarly high among 62 vaccinated (93.6%) and 52 unvaccinated HIV-positive participants (90.4%) (aPR 0.88; 95% CI, 0.66–1.10). Numbers were too small to further stratify HIV-positive

Table 2. Prevalence of Type-Specific HPV in Anal and Oral Specimens From Participating Transgender Women and Gay, Bisexual, and Other Men Who Have Sex With Men

	Anal and/or Oral HPV	Anal HPV	Oral HPV n (%)	
HPV Туре	n (%)	n (%)		
Any HPV types			,	
≥1 HPV type	1253 (70.9)	1236 (69.9)	133 (7.5)	
4vHPV types				
HPV 6	252 (14.3)	244 (13.8)	16 (0.9)	
HPV 11	72 (4.1)	71 (4.0)	3 (0.2)	
HPV 16	182 (10.3)	177 (10.0)	8 (0.5)	
HPV 18	84 (4.8)	83 (4.7)	6 (0.3)	
≥1 4vHPV type	475 (26.9)	465 (26.3)	33 (1.9)	
All 4	0 (0)	0 (0)	0 (0)	
Additional 9vHPV types not targeted by 4	vHPV*			
≥1 additional 9vHPV type	346 (19.6)	342 (19.4)	10 (0.6)	
All 5	0 (0)	O (O)	0 (0)	
9vHPV types				
≥1 9vHPV type	669 (37.9)	658 (37.2)	40 (2.3)	
All 9	0 (0)	0 (0)	0 (0)	

Abbreviations: HPV, human papillomavirus; 4vHPV, quadrivalent HPV vaccine; 9vHPV, nonavalent HPV vaccine.

^{*}Additional 9vHPV types defined as HPV 31, 33, 45, 52, and/or 58.

Table 3. Prevalence of Any HPV or Quadrivalent Vaccine-Type HPV in Anal and/or Oral Specimens, by Characteristics of Participating Transgender Women and Gay, Bisexual, and Other Men Who Have Sex With Men

Characteristic	Total N	Any HPV	Any HPV Type		≥1 4vHPV Type	
		n (%)	Р	n (%)	Р	
Total	1767	1253 (100)	-	475 (100)	-	
City						
Chicago	617	405 (65.6)	<.001	149 (24.2)	.13	
Los Angeles	446	318 (71.3)		121 (27.1)		
Seattle	704	530 (75.3)		205 (29.1)		
Age, years						
18–21	628	393 (62.6)	<.001	112 (17.8)	<.001	
22–26	1139	860 (75.5)		363 (31.9)		
Gender Identity						
Male	1671	1182 (70.7)	.075	449 (26.9)	.98	
Female/transgender female	53	44 (83.0)		14 (26.4)		
Other/unknown	43	27 (62.8)		12 (27.9)		
Race/ethnicity						
Non-Hispanic white	545	364 (66.8)	.087	146 (26.8)	.69	
Non-Hispanic black	261	188 (72.0)		78 (29.9)		
Asian/Pacific Islander	136	105 (77.2)		35 (25.7)		
Hispanic	557	400 (71.8)		151 (27.1)		
Other/unknown	268	196 (73.1)		65 (24.3)		
Sexual orientation						
Gay/homosexual	1295	942 (72.7)	.014	365 (28.2)	.54	
Straight/heterosexual	29	21 (72.4)		6 (20.7)		
Other/unknown	443	290 (65.5)		113 (25.5)		
Lifetime number of sex partners of any	/ sex					
≤5	247	117 (47.4)	<.001	30 (12.1)	<.001	
6–10	276	178 (64.5)		55 (19.9)		
11–20	388	256 (66.0)		83 (21.4)		
>20	801	659 (82.3)		282 (35.2)		
Other/unknown	55	43 (78.2)		25 (45.4)		
Most recent HIV test result						
Positive	139	127 (91.4)	<.001	70 (50.4)	<.001	
Negative or unknown	1628	1126 (69.2)		405 (24.9)		
Ever received any HPV vaccine						
No, none	687	474 (69.0)	.35	217 (31.6)	.001	
Yes, any	704	510 (72.4)		161 (22.9)		
Other/unknown*	376	269 (71.5)		97 (25.8)		

Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; 4vHPV, quadrivalent HPV vaccine.

NOTE: Bold font indicates significance of χ^2 analysis at P < .05.

Table 4. Prevalence of Any HPV and Vaccine-Type HPV in Anal and/or Oral Specimens, by HPV Vaccination History among Participating Transgender Women and Gay, Bisexual, and Other Men Who Have Sex With Men

	Total		Any HPV Type		≥1 4vHPVType		
HPV Vaccination History	N	n (%)	PR (95% CI)	aPR* (95% CI)	n (%)	PR (95% CI)	aPR* (95% CI)
No HPV vaccine doses	687	474 (69.0)	Ref	Ref	217 (31.6)	Ref	Ref
≥1 HPV vaccine dose	704	510 (72.4)	1.05 (0.98-1.12)	1.01 (0.96-1.05)	161 (22.9)	0.72 (0.60-0.85)	0.71 (0.59-0.83)
First dose at age ≤18 years	289	169 (58.5)	0.85 (0.75-0.94)	0.90 (0.80-1.00)	32 (11.1)	0.35 (0.23-0.47)	0.41 (0.24-0.57)
First dose at age >18 years	366	306 (83.6)	1.21 (1.13-1.29)	1.10 (1.00-1.19)	118 (32.2)	1.02 (0.83-1.21)	0.82 (0.67-0.98)

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; HPV, human papillomavirus; PR, prevalence ratio; Ref, reference; 4vHPV, quadrivalent HPV vaccine. NOTE: Bold font indicates significance at P < .05.

^{*}Includes participants who were unsure of their HPV vaccination history or did not respond.

^{*}Adjusted for age, race/ethnicity, city, number of sex partners, and HIV status.

participants by age at vaccination; among the 62 HIV-positive participants reporting vaccination, only 20 (32.2%) reported first HPV vaccination at age \leq 18 years.

DISCUSSION

Findings from this large study suggest real-world effectiveness of HPV vaccination against vaccine-type HPV infections among young adult gay, bisexual, and other MSM and transgender women, particularly those who initiate vaccination during early adolescence. After adjusting for age, race/ethnicity, city, number of sex partners, and HIV status, vaccinated participants had a significantly lower prevalence of vaccine-type HPV in anal and oral specimens compared with unvaccinated participants, despite no significant difference in prevalence of any type of HPV. In fact, prevalence of any HPV and proportion reporting >20 sex partners in their lifetime were slightly higher among participants who were vaccinated compared with unvaccinated, suggesting that findings of vaccine effectiveness were not due to fewer HPV exposures among vaccinated MSM. Overall vaccine effectiveness in this study (29%) was lower than reported for the intention-to-treat population (48%) of the clinical trial among MSM in this age range; this likely reflects more HPV exposure before vaccination among the young adults in our study.

We found higher vaccine effectiveness among those who reported initiating HPV vaccination at a younger age (59%) versus after age 18 years (18%). Other studies evaluating vaccine effectiveness by age at vaccination have consistently found higher effectiveness with vaccine initiation at younger ages (ie, during adolescence rather than during adulthood). These include studies of vaccine effectiveness against prevalent vaccine-type HPV among women screened for cervical cancer [17-19], effectiveness against cervical precancers among women [20-23], and effectiveness against anogenital warts among adolescents [24-27] and adults [26-28]. Lower vaccine effectiveness estimates among persons vaccinated at older ages are likely because of infection or disease outcomes due to HPV infection present at the time of vaccination. Human papillomavirus vaccination is prophylactic (ie, prevents new HPV infections), and thus it is more likely to be effective when given before sexual exposure to HPV. In our study, compared with unvaccinated participants, HPV prevalence was significantly lower among participants reporting first vaccination by age 18 years. The lower prevalence of any HPV suggests lower risk behaviors, which could account for part of the vaccine effectiveness we observed. Conversely, prevalence of any HPV was significantly higher among participants reporting first HPV vaccination after age 18 years, which could bias our results away from finding vaccine effectiveness in this group. In the multivariable analysis, we did find some effectiveness, although low, in participants reporting first HPV vaccination after age 18 years. Although HPV vaccination is most effective when administered before first sexual activity, none

of our participants had all 4vHPV or 9vHPV types, suggesting that they might still benefit from vaccination.

The high prevalence of any anal HPV in our study population of sexually active MSM is similar to estimates from other studies of MSM, including our previous study conducted in 2012–2014 [3]. Although anal HPV prevalence estimates are lacking among US males in the general population, genital prevalence of any HPV (at least 1 of 37 types detected by Linear Array) and high-risk HPV (at least 1 of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68) among US males aged 14–59 years during 2013–2014 was 42.2% and 23.4%, respectively [29]. Anal HPV prevalence is generally higher than genital HPV prevalence among MSM [30, 31].

Among HIV-infected participants, any HPV infection was detected in over 90%. This study did not observe HPV vaccine effectiveness among HIV-infected participants; this may have been due to low power given the small number of HIV-infected participants, since the estimates were similar to the overall population. Nevertheless, absolute difference in vaccine-type HPV prevalence between vaccinated and unvaccinated participants was greater among HIV-infected participants (11%) than among other participants (9%). Although HPV vaccines have been shown to be safe and immunogenic among persons with HIV, vaccine effectiveness has not been demonstrated in this population [32-34]. One randomized, placebo-controlled trial evaluating 4vHPV efficacy among HIV-positive adults older than age 27 years did not show efficacy for prevention of new anal HPV infections, but it suggested efficacy for prevention of oral infection [35].

Although postlicensure vaccine effectiveness studies have been conducted among women, data are limited among men; 1 study reported that among 400 young men aged 13-26 years recruited from clinical sites in 2013-2015, prevalence of 4vHPV-type HPV was not significantly different among vaccinated versus unvaccinated young men (20.4% vs 27.9%, P=.13) [36]. This cross-sectional study was limited by its relatively small sample size, and, like ours, reliant on self-reported vaccination history. Although several studies have assessed HPV prevalence among MSM [2], no previously published studies have reported HPV vaccine effectiveness in this population. Vaccine effectiveness estimates may be refined as vaccinated persons age and vaccination coverage among adolescents increases over time.

Although race/ethnicity was not significantly associated with prevalent HPV infections in our study population, self-reported HPV vaccination history did vary significantly by race/ethnicity, which may also reflect racial/ethnic makeup of our participating cities.

This analysis focused on vaccine effectiveness among MSM, and it did not evaluate the overall impact of the US HPV vaccination program on prevalent HPV infection among MSM or potential herd effects. Data from other countries suggest that herd effects from a female vaccination program have been limited

among MSM [37]. Our analysis is subject to at least 4 other limitations. First, clinical information such as HPV vaccination history and HIV status were self-reported, allowing the possibility of reporting or recall biases; over one fifth of participants were unsure of their vaccination history and could not be further analyzed. Underreporting or overreporting HPV vaccination history or HIV status could have impacted our vaccine effectiveness estimates. Second, low prevalence of oral HPV precluded a separate evaluation of vaccine effectiveness against oral HPV. Third, we conducted HPV testing at only 1 point in time for each participant, and we could not assess duration of infection before or after their participation. Finally, our participants were enrolled from urban sites serving LGBT clients and may not be representative of MSM and transgender women in general.

CONCLUSIONS

This study reports HPV vaccine effectiveness against vaccinetype HPV among MSM and transgender women in a real-world setting. Findings support catch-up HPV vaccination for young adult MSM and transgender women who were not vaccinated as adolescents [11]. Vaccine effectiveness was higher among people who initiated vaccination by age 18 years, supporting routine recommendations to administer HPV vaccination early in adolescence.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Supplementary Table 1. Prevalence of any HPV or quadrivalent vaccine-type HPV in anal specimens, by characteristics of participating transgender women and gay, bisexual, and other men who have sex with men.

Supplementary Table 2. Prevalence of any HPV and vaccine-type HPV in anal specimens, by HPV vaccination history among participating transgender women and gay, bisexual, and other men who have sex with men.

Supplementary Table 3. Prevalence of any HPV or quadrivalent vaccine-type HPV in oral specimens, by characteristics of participating transgender women and gay, bisexual, and other men who have sex with men.

Supplementary Table 4. Prevalence of any HPV and vaccine-type HPV in oral specimens, by HPV vaccination history among participating transgender women and gay, bisexual, and other men who have sex with men.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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References

- Nyitray AG, Carvalho da Silva RJ, Baggio ML, et al. Agespecific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study. J Infect Dis 2011; 203:49–57.
- Marra E, Lin C, Clifford GM. Type-specific anal human papillomavirus prevalence among men, according to sexual preference and HIV status: a systematic literature review and meta-analysis. J Infect Dis 2019; 219:590–8.
- 3. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol **2012**; 13:487–500.
- Garland SM, Hernandez-Avila M, Wheeler CM, et al.; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007; 356:1928–43.
- Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007; 356:1915–27.
- 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; 364:401–11.
- Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med 2011; 365:1576–85.
- Meites E, Steinau M, Panicker G, et al. Monitoring for HPV vaccine impact among men who have sex with men — United States, 2012–2014. 30th International Papillomavirus Conference (Lisbon, Portugal) September 17–21, 2015. 2015.
- 9. Meites E, Gorbach PM, Gratzer 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**; 214:689–96.
- Markowitz LE, Dunne EF, Saraiya M, et al.; Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2014; 63:1–30.
- Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory

- Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep **2019**; 68:698–702.
- Walker TY, Elam-Evans LD, Yankey D, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years United States, 2018. MMWR Morb Mortal Wkly Rep 2019; 68:718–23.
- Centers for Disease Control and Prevention (CDC).
 National and state vaccination coverage among adolescents aged 13–17 years United States, 2011. MMWR Morb Mortal Wkly Rep 2012; 61:671–7.
- 14. Oliver SE, Hoots BE, Paz-Bailey G, Markowitz LE, Meites E; NHBS Study Group. Increasing human papillomavirus vaccine coverage among men who have sex with men National HIV Behavioral Surveillance, United States, 2014. J Acquir Immune Defic Syndr 2017; 75 (Suppl 3):S370–4.
- Meites E, Markowitz LE, Paz-Bailey G, Oster AM, NHBS Study Group. HPV vaccine coverage among men who have sex with men — National HIV Behavioral Surveillance, United States, 2011. Vaccine 2014; 32:6356–9.
- 16. Mustanski B, Morgan E, D'Aquila R, Birkett M, Janulis P, Newcomb ME. Individual and network factors associated with racial disparities in HIV among young men who have sex with men: results from the RADAR cohort study. J Acquir Immune Defic Syndr 2019; 80:24–30.
- 17. Dunne EF, Naleway A, Smith N, et al. Reduction in human papillomavirus vaccine type prevalence among young women screened for cervical cancer in an integrated US healthcare delivery system in 2007 and 2012–2013. J Infect Dis 2015; 212:1970–5.
- 18. Kavanagh K, Pollock KG, Cuschieri K, et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. Lancet Infect Dis **2017**; 17:1293–302.
- Markowitz LE, Naleway AL, Klein NP, et al. Human papillomavirus vaccine effectiveness against HPV infection: evaluation of one, two, and three doses. J Infect Dis 2020; 221:910–8.
- 20. Silverberg MJ, Leyden WA, Lam JO, et al. Effectiveness of catch-up human papillomavirus vaccination on incident cervical neoplasia in a US health-care setting: a populationbased case-control study. Lancet Child Adolesc Health 2018; 2:707–14.
- 21. Crowe E, Pandeya N, Brotherton JM, et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ 2014; 348:g1458.
- 22. Brotherton JM, Saville AM, May CL, Chappell G, Gertig DM. Human papillomavirus vaccination is changing the epidemiology of high-grade cervical lesions in Australia. Cancer Causes Control **2015**; 26:953–4.

- 23. Herweijer E, Sundström K, Ploner A, Uhnoo I, Sparén P, Arnheim-Dahlström L. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: a population-based study. Int J Cancer 2016; 138:2867–74.
- 24. Zeybek B, Lin YL, Kuo YF, Rodriguez AM. The impact of varying numbers of quadrivalent human papillomavirus vaccine doses on anogenital warts in the United States: a database study. J Low Genit Tract Dis **2018**; 22:189–94.
- 25. Willows K, Bozat-Emre S, Righolt CH, Kliewer EV, Mahmud SM. Early evidence of the effectiveness of the human papillomavirus vaccination program against anogenital warts in Manitoba, Canada: a registry cohort study. Sex Transm Dis 2018; 45:254–9.
- Leval A, Herweijer E, Ploner A, et al. Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. J Natl Cancer Inst 2013; 105:469–74.
- Herweijer E, Leval A, Ploner A, et al. Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma. JAMA 2014; 311:597–603.
- Dominiak-Felden G, Gobbo C, Simondon F. Evaluating the early benefit of quadrivalent HPV vaccine on genital warts in Belgium: a cohort study. PLoS One 2015; 10:e0132404.
- 29. Gargano JW, Unger ER, Liu G, et al. Prevalence of genital human papillomavirus in males, United States, 2013–2014. J Infect Dis **2017**; 215:1070–9.
- 30. van Rijn VM, Mooij SH, Mollers M, et al. Anal, penile, and oral high-risk HPV infections and HPV seropositivity in HIV-positive and HIV-negative men who have sex with men. PLoS One **2014**: 9:e92208.
- 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.
- 32. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. J Infect Dis **2010**; 202: 1246–53.
- 33. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis **2014**; 59:127–35.
- 34. Levin MJ, Huang S, Moscicki AB, et al.; IMPAACT P1085 Protocol Team. Four-year persistence of type-specific immunity after quadrivalent human papillomavirus vaccination in HIV-infected children: effect of a fourth dose of vaccine. Vaccine 2017; 35:1712–20.
- 35. Wilkin TJ, Chen H, Cespedes MS, et al. A randomized, placebo-controlled trial of the quadrivalent human

- papillomavirus vaccine in human immunodeficiency virus-infected adults aged 27 years or older: AIDS clinical trials group protocol A5298. Clin Infect Dis **2018**; 67:1339–46.
- 36. Chandler E, Ding L, Gorbach P, et al. Epidemiology of any and vaccine-type anogenital human papillomavirus among
- 13–26 year-old young men after HPV vaccine introduction. J Adolesc Health **2018**; 63:43–9.
- 37. Chow EP, Read TR, Wigan R, et al. Ongoing decline in genital warts among young heterosexuals 7 years after the Australian human papillomavirus (HPV) vaccination programme. Sex Transm Infect **2015**; 91:214–9.