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Anal Human Papillomavirus Prevalence Among Vaccinated and Unvaccinated Gay, Bisexual, and Other Men Who Have Sex With Men in Canada

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Background: Starting in 2015, human papillomavirus (HPV) vaccine has been publicly funded for gay, bisexual, and other men who have sex with men (GBM) 26 years or younger in Canada.

Methods: Self-identified GBM who reported having sex with another man within the past 6 months were enrolled using respondent-driven sampling (RDS) between February 2017 and August 2019 in Montreal, Toronto, and Vancouver, Canada. Men aged 16 to 30 years self-collected anal specimens for HPV-DNA testing. Prevalence was estimated using RDS-II weights. We compared the prevalence of quadrivalent (HPV-6/11/16/18) and 9-valent (HPV-6/11/16/18/31/33/45/52/58) vaccine types between GBM who self-reported HPV vaccination (≥1 dose) and those reporting no vaccination using a modified Poisson regression for binary outcomes.

Results: Among 645 GBM who provided a valid anal specimen (median age, 26 years; 5.9% HIV positive), 40.3% reported receiving ≥1 dose of HPV vaccine, of whom 61.8% received 3 doses. One-quarter were infected with ≥1 quadrivalent type (crude, 25.7%; RDS weighted, 24.4%). After adjustment for potential confounders, vaccinated GBM had a 27% lower anal prevalence of quadrivalent types compared with unvaccinated GBM (adjusted prevalence ratio [aPR], 0.73; 95% confidence interval [CI], 0.54–1.00). Lower prevalence ratios were found among vaccinated participants who were vaccinated >2 years before enrollment (aPR, 0.47; 95% CI, 0.25–0.86) or received their first vaccine dose at age ≤23 years (aPR, 0.64; 95% CI, 0.42–0.99). Point estimates were similar for ≥2 or 3 doses and 9-valent types.

Conclusions: Human papillomavirus vaccination was associated with a lower anal prevalence of vaccine-preventable HPV types among young, sexually active GBM. Findings will help inform shared decision making around HPV vaccination for GBM and their healthcare providers.

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Human papillomavirus (HPV) vaccination is recommended for gay, bisexual, and other men who have sex with men (GBM) because of their high burden of HPV-associated disease, such as anal cancer.[1] Starting in 2015, GBM 26 years or younger who disclose same-sex activity to a healthcare provider have been eligible for publicly funded HPV vaccine under most provincial and territorial programs in Canada. Despite these targeted programs, vaccine uptake remains low: less than half of self-identified GBM 26 years or younger in major Canadian cities have received ≥1 dose.[2]

Human papillomavirus is the most common sexually transmitted infection (STI). Before the introduction of male HPV vaccination, the prevalence of anal infection with at least one HPV type was 50% to 70% among HIV-negative GBM and even higher at 80% to 90% among GBM living with HIV.[3,4] These estimates are 2 to 4 times higher than men who have sex with women.[3] Infection with vaccine-preventable HPV types, most notably oncogenic types 16 and 18, follow similar demographic patterns.[3,5,6] The majority of HPV prevalence studies published to date were conducted among unvaccinated men; few studies have measured HPV infection among young GBM who are eligible for publicly funded HPV vaccination.[7]

Human papillomavirus vaccine is highly efficacious in males, preventing up to 85% of incident anal infections with vaccine-preventable types in young GBM 26 years or younger who were HPV-naive at baseline and had ≤5 lifetime sexual partners.[8] Current vaccination guidelines are predicated on receipt of HPV vaccine before sexual exposure to confer maximum benefit. However, less information is known about how well this vaccine works in real-world settings among sexually active GBM who may have had multiple exposures to HPV before vaccination.[9–11] Our objective was to estimate the prevalence of anal HPV infection among young, sexually active GBM soon after implementation of targeted HPV vaccination programs in Canada and to compare the anal prevalence of vaccine-preventable types between vaccinated and unvaccinated men.

MATERIALS AND METHODS

Setting

Since 2012, national immunization guidelines have recommended HPV vaccine for all males aged 9 to 26 years and GBM 9 years or older without upper age restriction.[1] Under Canada's publicly funded healthcare system, self-identified GBM aged 9 to 26 years have been eligible for free HPV vaccine as of September 2015 in British Columbia (BC),[12] January 2016 in Quebec,[13] and September 2016 in Ontario.[14] Gay, bisexual, and other men who have sex with men 27 years and older who are ineligible for the publicly funded programs can purchase the vaccine or may have coverage through private insurance. Nine-valent (9vHPV) replaced quadrivalent (4vHPV) vaccine for the targeted programs starting in May 2017 (BC and Quebec) and September 2017 (Ontario).[15] Three doses are recommended for immunocompetent males who initiate their vaccine series at age 15 years or older,[15] which would apply to all participants in the current study based on their age at vaccination; in Quebec, 3 doses are recommended for males 18 years and older.[13] Although all 3 provinces expanded their school-based HPV vaccination programs to be gender neutral as of September 2016 (Quebec and Ontario) and August 2017 (BC), participants in the current study were outside the eligible birth cohorts for these programs.

Study Participants and Recruitment

The Engage sexual health study is a prospective cohort of GBM, including cisgender and transgender men, in Montreal, Toronto, and Vancouver—3 cities with the largest GBM populations in Canada.[16] At enrollment, men 16 years or older were eligible if they self-identified as a man, reported having sex with another man within the past 6 months, read English or French, and provided written informed consent. Participants were recruited between February 2017 and August 2019 using respondent-driven sampling (RDS), a form of chain-referral sampling that aims to generate more representative samples for hard-to-reach populations.[17,18] Briefly, initial participants (or seeds) were purposively selected to represent subgroups of the GBM community based on age group, gender, ethnocultural background, and HIV status. Seeds were provided with up to 6 coupons each, which were used to recruit members of their social networks. Recruitment continued through waves until the target sample size was reached in each city (Supplemental Table S1, http://links.lww.com/OLQ/A755). For the present study, participants received $60 CAD plus $15 CAD for each additional eligible participant recruited. Protocols were approved by research ethics boards at participating institutions.

Data Collection

Participants self-completed a questionnaire by computer-assisted self-interview including items on demographics and socioeconomic status; gender and sexual orientation; medical history, including history of STI and blood-borne infection testing; HIV status; lifetime and recent (past 6 months) sexual behaviors; and substance use. Questionnaire items were informed by the Sexual Health Framework and the Global AIDS Monitoring Indicators.[19,20] Human papillomavirus vaccine-specific questionnaire items included the following: awareness of HPV vaccine and willingness to be vaccinated, HPV vaccination history, lifetime number of doses, health service location of most recent dose of HPV vaccine, and age at first dose.

At enrollment, young GBM aged 16 to 30 years were invited to provide an anal specimen for HPV genotyping. The HPV substudy was an optional add-on component to the larger Engage Cohort Study. Anal specimens were self-collected at study sites using moistened Dacron swabs inserted 3 to 5 cm into the anal canal using illustrated instructions.[21] Samples were kept at +4°C and transported to the laboratory under wet ice conditions.

HPV DNA Genotyping

All specimens were screened for HPV DNA using an in-house generic probe assay.[22] Human papillomavirus DNA–positive specimens were genotyped using the polymerase chain reaction–based Linear Array (Roche Molecular Systems) for the L1 HPV gene that detects 36 mucosal HPV genotypes, including all 9 vaccine-preventable types and 2 variants of HPV-82.[23] This assay has been shown to have good agreement with conventional research-based assays (mean, 96.4% ± 2.4%; range, 86%–100% by HPV type) and greater sensitivity.[23] Coamplification of a β-globin human DNA sequence was performed to assess specimen adequacy. Analyses were restricted to valid anal specimens, defined as those with detection of either β-globin or HPV DNA.

HPV Vaccination Status

Vaccination status was defined as self-reported receipt of ≥1 lifetime HPV vaccine dose before study enrollment. Participants were asked if they had ever heard of the HPV vaccine and, if yes, to report if they had ever received 1 or more doses. Those who were unaware of the HPV vaccine were assumed to be unvaccinated, whereas those who reported an unknown HPV vaccination history were excluded. Alternative definitions of vaccination completion (≥2 doses or all 3 doses) were explored in sensitivity analyses. Time since vaccination was derived as the difference

(in years) between self-reported age at first dose and age at enrollment; biological male participants reporting vaccination before the Canadian approval of the 4vHPV vaccine for males in February 2010 were excluded from analyses of vaccination timing.[24] Data on the type of vaccine or timing of doses were not collected; we assumed that most vaccinated GBM received 4vHPV based on the earliest availability of 9vHPV in each province relative to self-reported age at vaccination.

Analyses

Type-specific HPV prevalence at enrollment was estimated for each genotype, along with composite outcomes for ≥1 4vHPV-preventable type (HPV-6/11/16/18) or 9vHPV-preventable type (HPV-6/11/16/18/31/33/45/52/58). We derived weighted HPV prevalence estimates and 95% confidence intervals (CIs) pooled across the 3 cities and accounting for strata by city. Because RDS relies on chain-referral sampling, individuals who have smaller social networks will be underrepresented in the RDS sample, whereas those who have larger social networks will be overrepresented. For this reason, prevalence estimates were weighted using RDS-II weights (Volz-Heckathorn estimator), which are inversely proportional to a participant's self-reported social network size within each city, to adjust for selection biases inherent to chain-referral sampling.[25] Self-reported network size was truncated at a minimum of 1, based on study eligibility criteria, and a maximum of 150, based on the maximum number of possible current relationships.[26] All other results are RDS unweighted, unless otherwise specified.

Prevalence ratios (PRs) and 95% CI comparing anal HPV prevalence between vaccinated and unvaccinated GBM were estimated using a modified Poisson regression with robust standard errors for binary outcomes including RDS seeds.[27,28] For the focal comparison of HPV prevalence by vaccination status, we calculated PRs without RDS-II weights.[29] However, because there is no agreed-upon method for multivariable regression using RDS data,[30,31s] we report RDS-weighted PRs in Supplemental Digital Content, http://links.lww.com/OLQ/A755.[29] Because HPV genotyping results were only available for a subset of participants within each city, we did not account for potential clustering within RDS recruitment chains.[31s]

Potential confounders for multivariable regression models were identified based on prior literature and informed by directed acyclic graphs.[32s,33s] All potential confounders independently associated with both HPV infection and HPV vaccine uptake at a P value of <0.25 were considered. A backward elimination procedure was used to reduce the number of covariates included in the final multivariable models.[34s,35s] Age group and city were included in all models regardless of statistical significance. Final models were adjusted for age group (based on eligibility for publicly funded vaccine at enrollment), city, education (indicator for socioeconomic status), smoking history, self-reported STI diagnosis in lifetime (excluding HIV and anogenital warts), and number of condomless receptive anal sex encounters in the past 6 months (based on quintiles). Sensitivity analyses explored vaccination status based on self-reported number of doses, time since vaccination (restricted vaccinated participants to those who were vaccinated >1 or >2 years before enrollment), and age at first dose. We also conducted a sensitivity analysis restricted to participants who had ≥1 prevalent HPV infection (i.e., excluding participants who were HPV DNA negative) and compared the prevalence of vaccine-preventable types with nonvaccine types to control for HPV exposure risk. All analyses were conducted in SAS (Cary, NC). A P value of $\alpha < 0.05$ was considered statistically significant.

RESULTS

Participant Characteristics

Of the 1003 eligible GBM aged 16 to 30 years at enrollment, 847 (84.4%) provided an anal specimen for HPV genotyping. Participants who provided anal specimens did not significantly differ from those who did not on any covariate, except for city (data not shown). Participants with anal specimens were more likely to be from Montreal (90.1%) or Toronto (86.3%) compared with Vancouver (75.2%) because of delays in introducing the optional collection of specimens for HPV testing at some sites. Of the 847 anal specimens available for genotyping, 645 (76.2%) were considered valid, including 402 (47.5%) that were β-globin positive. Human papillomavirus vaccine uptake did not significantly differ between participants who did and did not provide valid specimens (40.3% vs. 37.0%, $P = 0.428$).

Of the 645 participants included in the analysis, the median age was 26 years (interquartile range [IQR], 24–28 years; Table 1). Most participants were from Montreal (n = 270; 41.9%), with fewer from Toronto (n = 171; 26.5%) or Vancouver (n = 204; 31.6%). Most participants (80.5%) self-identified as gay; 10 (1.6%) identified as transgender. Few (n = 38; 5.9%) had a laboratory-confirmed HIV infection. Almost all participants (98.3%) reported having anal sex with a man in their lifetime. The median age at first anal sex with a man was 18 years (IQR, 16–20 years). Almost two-thirds (62.8%) reported engaging in condomless receptive anal sex in the past 6 months; the median number of times was 5 (IQR, 2–15 times) among participants who reported ≥1 episode. Almost one-fifth (18.5%) had a self-reported history of anogenital warts.

HPV Vaccine Uptake

Of the 608 of 645 participants (94.3%) with known vaccination history, 245 (40.3%) self-reported receiving ≥1 dose of HPV vaccine; the corresponding RDS-weighted proportion was 30.6%. Among vaccinated participants, 34 (15.5%) received 1 dose, 50 (22.7%) received 2 doses, and 136 (61.8%) received all 3 recommended doses; 25 (10.2%) vaccinated participants had an unknown number of doses. The median age at first dose was 23 years (IQR, 21–25 years); 12 (4.9%) vaccinated participants had missing or invalid data for age at first dose. The majority (88.8%) of vaccinated participants, including 69.4% of participants who were aged 27 to 30 years at enrollment, were vaccinated before age 27 years as part of publicly funded programs. The median time from HPV vaccination to study enrollment was 2 years (IQR, 1–3 years). Only 9 (3.9%) participants reported receiving their first dose of HPV vaccine before their first anal sexual episode; the median time from first anal sex to HPV vaccination was 5 years (IQR, 2–8 years).

Anal HPV Prevalence

Overall RDS-weighted anal HPV prevalence was 66.7% (95% CI, 59.7%–73.6%) for ≥1 tested HPV type, 35.1% (95% CI, 28.7%–41.5%) for ≥1 9vHPV-preventable type, and 25.4% (95% CI, 19.5%–31.3%) for ≥1 4vHPV-preventable type (Table 2). Among unvaccinated participants (n = 363), the corresponding prevalence estimates were 63.2% (95% CI, 53.7%–72.8%), 35.9% (95% CI, 27.6%–44.1%), and 26.4% (95% CI, 18.9%–34.0%), respectively. Vaccine-preventable types HPV-16 (RDS-weighted, 12.0%) and HPV-6 (9.1%) were among the most commonly detected, along with HPV-51 (10.9%) and HPV-39 (8.0%) in unvaccinated participants; lower prevalence was seen for 4vHPV types HPV-11 (6.3%) and HPV-18 (2.9%; Fig. 1). Vaccine-preventable types were less common overall among vaccinated participants

TABLE 1. Baseline Characteristics of Gay, Bisexual, and Other Men Who Have Sex With Men Aged 16 to 30 Years by Self-Reported HPV Vaccination Status, Engage Cohort Study, 2017 to 2019

Characteristic	Overall* (n = 645)	Unvaccinated (n = 363)	Vaccinated† (n = 245)	P‡
Age group at enrollment, n (%)				<0.001
16–26 y	354 (54.9)	175 (48.2)	156 (63.7)	
27–30 y	291 (45.1)	188 (51.8)	89 (36.3)	
City, n (%)				0.048
Montreal	270 (41.9)	163 (44.9)	87 (35.5)	
Toronto	171 (26.5)	95 (26.2)	68 (27.8)	
Vancouver	204 (31.6)	105 (28.9)	90 (36.7)	
Education, n (%)				0.144
High school or less§	122 (18.9)	74 (20.4)	40 (16.3)	
Postsecondary	412 (63.9)	219 (60.3)	167 (68.2)	
Graduate or professional degree	111 (17.2)	70 (19.3)	38 (15.5)	
Ethnicity, n (%)				0.170
English or French Canadian	295 (45.7)	150 (41.3)	123 (50.2)	
Other European	122 (18.9)	69 (19.0)	50 (20.4)	
Asian	73 (11.3)	46 (12.7)	23 (9.4)	
Black, African, Caribbean	18 (2.8)	11 (3.0)	7 (2.9)	
Indigenous	9 (1.4)	7 (1.9)	2 (0.8)	
Other or mixed	128 (19.8)	80 (22.0)	40 (16.3)	
Sexual orientation, n (%)				0.024
Gay	519 (80.5)	293 (80.7)	198 (80.8)	
Queer	69 (10.7)	35 (9.6)	32 (13.1)	
Bisexual	30 (4.7)	21 (5.8)	8 (3.3)	
Other¶	27 (4.2)	14 (3.9)	7 (2.9)	
Has a regular current partner, n (%)	301 (46.7)	171 (47.1)	112 (45.7)	0.736
Laboratory-confirmed HIV infection, n (%)	38 (5.9)	18 (5.0)	15 (6.2)	0.529
Self-reported STI diagnosis, lifetime, n (%)‖	353 (55.9)	166 (47.2)	170 (70.0)	<0.001
Smoking history, lifetime, n (%)				0.030
Never smoker	199 (31.1)	100 (27.8)	87 (36.0)	
Current smoker	299 (46.8)	184 (51.1)	98 (40.5)	
Former smoker	141 (22.1)	76 (21.1)	57 (23.6)	
Alcohol risk, past 6 mo, n (%)**				0.082
Lower risk	392 (63.3)	225 (64.7)	146 (62.1)	
Moderate risk	190 (30.7)	97 (27.9)	80 (34.0)	
High risk	37 (6.0)	26 (7.5)	9 (3.8)	
Any illicit drug use, lifetime, n (%)	512 (80.5)	276 (77.3)	205 (84.7)	0.026
Poppers use, lifetime, n (%)	372 (58.4)	189 (52.8)	162 (66.7)	0.001
Male anal sex partners, past 6 mo, n (%)				<0.001
0–1 partners	147 (22.8)	97 (26.7)	40 (16.3)	
2–5 partners	248 (38.4)	147 (40.5)	85 (34.7)	
6–10 partners	121 (18.8)	65 (17.9)	54 (22.0)	
>10 partners	129 (20.0)	54 (14.9)	66 (26.9)	
Condomless receptive anal sex, past 6 mo, n (%)				0.003
0 times	240 (37.2)	153 (42.1)	73 (29.8)	
1–2 times	123 (19.1)	77 (21.2)	42 (17.1)	
3–5 times	100 (15.5)	48 (13.2)	45 (18.4)	
6–15 times	88 (13.6)	41 (11.3)	42 (17.1)	
>15 times	94 (14.6)	44 (12.1)	43 (17.6)	
Rimming (received), past 6 mo, n (%)	519 (80.5)	287 (79.1)	205 (83.7)	0.156
Fisting (received), past 6 mo, n (%)	28 (4.3)	14 (3.9)	12 (4.9)	0.534
RDS network size, median (IQR)††	30 (15–55)	25 (10–50)	35 (20–78)	<0.001
RDS-II weights, median (IQR)‡‡	0.53 (0.28–1.06)	0.63 (0.31–1.39)	0.45 (0.18–0.79)	<0.001

*Overall column includes 37 participants with missing data for HPV vaccination status.

†Self-reported receipt of ≥1 dose of HPV vaccine.

‡*P* value comparing participant characteristics between unvaccinated and vaccinated participants from χ^2 test.

§Includes participants with trade, vocational, or technical institute training.

¶Other sexual orientations include straight, pansexual, or other.

‖Excludes HIV and anogenital warts.

**Alcohol risk classified according to the World Health Organization's Alcohol, Smoking and Substance Involvement Screening Test as lower (scores 0–10), moderate (scores 11–26), or high (scores ≥27) risk.

††Based on response to "How many men who have sex with men aged 16 years or older, including trans men, do you know who live or work in the [city] metropolitan area (whether they identify as gay or otherwise)? This includes gay/bi guys you see or speak to regularly, e.g. close friends, boyfriends, spouses, regular sex partners, roommates, relatives, people you regularly hang out with, etc." Values truncated at a minimum of 1 and a maximum of 150.

‡‡RDS-II weights are inversely proportional to self-reported RDS network size within each city; RDS-II weights sum to total number of participants in each city with a mean of 1.00.

HPV indicates human papillomavirus; IQR, interquartile range; RDS, respondent-driven sampling; STI, sexually transmitted infection.

TABLE 2. Anal HPV Prevalence by Self-Reported Vaccination Status Among Gay, Bisexual, and Other Men Who Have Sex With Men Aged 16 to 30 Years, Engage Cohort Study, 2017 to 2019

	Overall* (n = 645)			Unvaccinated (n = 363)			Vaccinated† (n = 245)		
HPV Type	n	Sample %	Weighted%‡ (95% CI)	n	Sample %	Weighted %‡ (95% CI)	n	Sample %	Weighted %‡ (95% CI)
≥1 HPV type	471	73.0	66.7 (59.7–73.6)	259	71.3	63.2 (53.7–72.8)	184	75.1	74.0 (65.6–82.5)
≥1 4vHPV type	167	25.9	25.4 (19.5–31.3)	102	28.1	26.4 (18.9–34.0)	54	22.0	19.8 (10.6–29.0)
HPV-6	65	10.1	8.2 (5.0–11.5)	38	10.5	9.1 (4.3–13.8)	21	8.6	5.9 (2.6–9.2)
HPV-11	37	5.7	8.4 (4.3–12.4)	27	7.4	6.3 (2.9–9.7)	7	2.9	8.7 (0.0–17.6)
HPV-16	70	10.9	11.0 (6.4–15.6)	42	11.6	12.0 (6.2–17.8)	25	10.2	8.2 (0.1–16.2)
HPV-18	29	4.5	4.5 (1.7–7.4)	14	3.9	2.9 (0.9–5.0)	13	5.3	7.9 (0.0–16.2)
≥1 additional 9vHPV type	104	16.1	14.0 (9.7–18.3)	58	16.0	13.4 (8.6–18.3)	38	15.5	12.7 (5.0–20.4)
HPV-31	21	3.3	3.3 (1.2–5.5)	13	3.6	4.1 (0.9–7.4)	6	2.4	1.5 (0.0–3.2)
HPV-33	13	2.0	2.3 (0–4.6)	6	1.7	1.2 (0.0–2.4)	5	2.0	1.3 (0.0–3.0)
HPV-45	29	4.5	4.3 (1.4–7.2)	16	4.4	2.5 (0.8–4.3)	9	3.7	4.1 (0.0–9.5)
HPV-52	33	5.1	4.4 (1.7–7.2)	20	5.5	3.9 (1.4–6.4)	12	4.9	2.9 (0.6–5.2)
HPV-58	28	4.3	4.7 (1.7–7.8)	12	3.3	3.7 (1.0–6.3)	14	5.7	4.7 (0.0–10.1)
≥1 9vHPV type	236	36.6	35.1 (28.7–41.5)	139	38.3	35.9 (27.6–44.1)	79	32.2	30.4 (19.9–41.0)
≥1 non-9vHPV type	394	61.1	52.3 (45.4–59.2)	212	58.4	49.0 (40.0–58.0)	160	65.3	62.0 (51.9–72.2)

4vHPV types include HPV-6/11/16/18; 9vHPV types include HPV-6/11/16/18/31/33/45/52/58.

*Overall column includes 37 participants with missing data for HPV vaccination status.

†Self-reported receipt of ≥1 dose of HPV vaccine.

‡Prevalence estimates weighted using RDS-II weights to account for the RDS recruitment approach.

CI indicates confidence interval; HPV, human papillomavirus.

(n = 245) but remained high at 30.4% (95% CI, 19.9%–41.0%) for ≥1 9vHPV type and 19.8% (95% CI, 10.6%–29.0%) for ≥1 4vHPV type. Type-specific estimates were 8.7% for HPV-11, 8.2% for HPV-16, 7.9% for HPV-18, and 5.9% for HPV-6 in vaccinated participants.

In general, prevalence estimates did not significantly differ by city (Table 3 and Supplemental Table S2, http://links.lww.com/OLQ/A755). In unweighted analyses, anal prevalence of vaccine-preventable types was significantly higher among current or former smokers and participants who reported a higher number of anal sex partners in the past 6 months, engaged in condomless receptive anal sex in the past 6 months, and self-reported an STI diagnosis in their lifetime (Table 3). In RDS-weighted analyses, only number of anal sex partners in the past 6 months remained statistically significant. Associations were similar among unvaccinated and vaccinated participants, although some failed to reach statistical

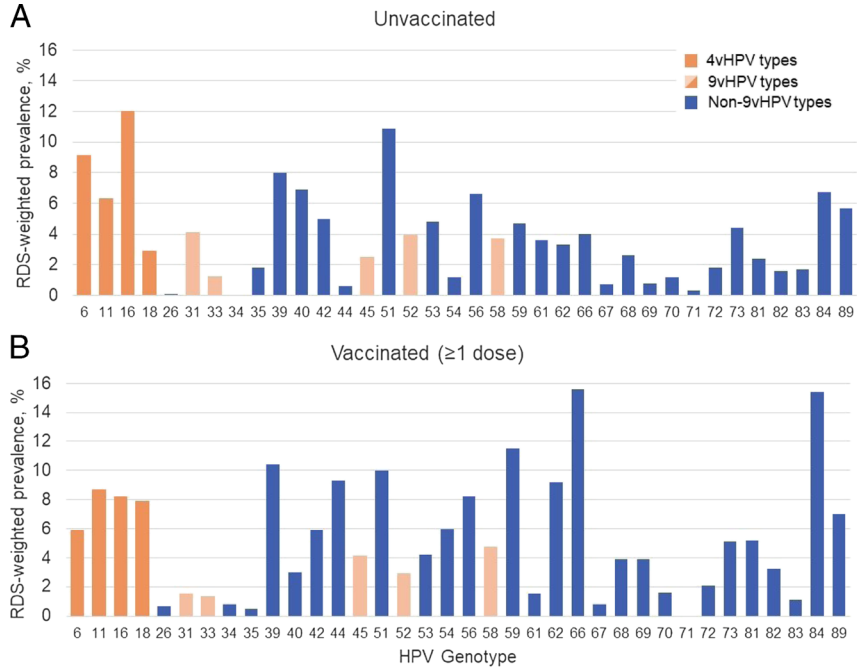

Figure 1. Type-specific anal HPV prevalence among unvaccinated (A) and vaccinated (B) gay, bisexual, and other men who have sex with men aged 16 to 30 years, Engage Cohort Study, 2017 to 2019. HPV indicates human papillomavirus.

TABLE 3. Anal HPV Prevalence by Covariates Among Gay, Bisexual, and Other Men Who Have Sex With Men Aged 16 to 30 Years, Engage Cohort Study, 2017 to 2019

		≥1 4vHPV Type			≥1 9vHPV Type		
Characteristic	**N**	**n**	**Sample %**	**Weighted %* (95% CI)**	**n**	**Sample %**	**Weighted %* (95% CI)**
Overall	645	167	25.9	25.4 (19.5–31.3)	236	36.6	35.1 (28.7–41.5)
Age group at enrollment							
16–26 y	354	90	25.4	25.9 (18.1–33.8)	122	34.5	34.6 (26.2–43.1)
27–30 y	291	77	26.5	24.7 (15.8–33.5)	114	39.2	35.7 (26.1–45.3)
City							
Montreal	270	71	26.3	27.3 (18.3–36.3)	99	36.7	33.8 (24.5–43.0)
Toronto	171	49	28.7	27.3 (14.9–39.8)	68	39.8	43.5 (29.3–57.8)
Vancouver	204	47	23.0	21.2 (11.6–30.7)	69	33.8	29.8 (19.2–40.4)
Education							
High school or less[†]	122	27	22.1	19.0 (6.1–32.0)	37	30.3	30.7 (16.1–45.3)
Postsecondary	412	112	27.2	25.8 (18.6–33.0)	160	38.8	35.4 (27.4–43.3)
Graduate or professional degree	111	28	25.2	32.6 (17.6–47.5)	39	35.1	40.2 (25.3–55.1)
Ethnicity							
English or French Canadian	295	74	25.1	20.6 (12.9–28.3)	107	36.3	28.7 (19.9–37.5)
Other European	122	33	27.0	22.0 (11.7–32.4)	47	38.5	31.9 (19.3–44.6)
Asian	73	16	21.9	28.0 (8.7–47.3)	24	32.9	41.6 (22.7–60.4)
Black, African, Caribbean	18	5	27.8	44.5 (0.0–89.5)	5	27.8	44.5 (0.0–89.5)
Indigenous	9	3	33.3	64.6 (19.9–100.0)	3	33.3	64.6 (19.9–100.0)
Other or mixed	128	36	28.1	29.3 (16.6–42.1)	50	39.1	42.4 (28.8–55.9)
Self-identifies as gay[‡]							
No	126	26	20.6	22.4 (8.4–36.3)	39	31.0	33.5 (19.0–48.1)
Yes	519	141	27.2	26.2 (19.7–32.7)	197	38.0	35.5 (28.4–42.6)
Has a regular current partner							
No	344	95	27.6	27.7 (18.6–36.7)	129	37.5	35.3 (25.9–44.7)
Yes	301	72	23.9	22.8 (15.6–29.9)	107	35.5	34.9 (26.5–43.3)
Laboratory-confirmed HIV infection							
Negative	603	154	25.5	24.2 (18.3–30.0)	216	35.8	34.0 (27.5–40.4)
Positive	38	12	31.6	40.4 (10.8–70.0)	19	50.0	49.9 (22.3–77.6)
Self-reported STI diagnosis, lifetime[§]							
No	279	66	23.7	23.7 (16.0–31.3)	86	30.8	30.1 (21.9–38.4)
Yes	353	97	27.5	28.0 (18.6–37.3)	144	40.8	40.1 (30.2–50.0)
Smoking history, lifetime							
Never smoker	199	41	20.6	20.0 (9.9–30.2)	62	31.2	31.3 (20.0–42.6)
Current smoker	299	83	27.8	29.0 (19.7–38.2)	106	35.5	36.2 (26.6–45.9)
Former smoker	141	42	29.8	28.7 (17.2–40.2)	65	46.1	40.7 (27.8–53.7)
Alcohol risk, past 6 mo[¶]							
Lower risk	392	97	24.7	22.8 (16.0–29.7)	137	34.9	34.7 (26.9–42.5)
Moderate risk	190	53	27.9	27.2 (16.2–38.3)	77	40.5	33.9 (22.3–45.5)
High risk	37	9	24.3	60.1 (31.8–88.5)	11	29.7	65.7 (40.5–90.8)
Any illicit drug use, lifetime							
No	124	27	21.8	19.6 (8.2–30.9)	39	31.5	30.2 (17.2–43.3)
Yes	512	138	27.0	28.3 (21.5–35.0)	195	38.1	37.8 (30.7–44.9)
Poppers use, lifetime							
No	265	62	23.4	21.8 (13.8–29.8)	88	33.2	31.8 (22.8–40.9)
Yes	372	103	27.7	30.7 (22.1–39.4)	146	39.2	40.6 (31.8–49.4)
Male anal sex partners, past 6 mo							
0–1 partners	147	26	17.7	16.7 (7.5–25.9)	37	25.2	25.8 (15.0–36.6)
2–5 partners	248	67	27.0	29.2 (19.3–39.0)	95	38.3	38.9 (28.6–49.3)
6–10 partners	121	30	24.8	19.8 (9.1–30.5)	41	33.9	28.8 (15.4–42.2)
>10 partners	129	44	34.1	41.3 (24.4–58.2)	63	48.8	53.5 (37.8–69.3)
Condomless receptive anal sex, past 6 mo							
0 times	240	59	24.6	24.4 (15.2–33.5)	74	30.8	30.1 (20.5–39.7)
1–2 times	123	28	22.8	18.8 (9.3–28.4)	41	33.3	30.4 (17.7–43.1)
3–5 times	100	31	31.0	37.8 (21.2–54.3)	36	36.0	47.0 (30.9–63.0)
6–15 times	88	23	26.1	28.8 (10.6–47.1)	41	46.6	46.8 (28.6–65.0)
>15 times	94	26	27.7	23.0 (8.4–37.6)	44	46.8	40.8 (24.4–57.2)
Rimming (received), past 6 mo							
No	126	28	22.2	26.6 (12.7–40.6)	38	30.2	32.6 (18.1–47.1)
Yes	519	139	26.8	24.9 (18.8–31.1)	198	38.2	36.0 (29.2–42.9)

Continued next page

TABLE 3. *(Continued)*

Characteristic	N	≥1 4vHPV Type			≥1 9vHPV Type		
		n	Sample %	Weighted %* (95% CI)	n	Sample %	Weighted %* (95% CI)
Fisting (received), past 6 mo							
No	617	158	25.6	25.3 (19.3–31.3)	222	36.0	35.2 (28.7–41.7)
Yes	28	9	32.1	28.1 (0.0–56.8)	14	50.0	32.7 (2.7–62.8)

4vHPV types include HPV-6/11/16/18; 9vHPV types include HPV-6/11/16/18/31/33/45/52/58.

*Prevalence estimates weighted using RDS-II weights to account for the RDS recruitment approach.

†Includes participants with trade, vocational, or technical institute training.

‡Versus other sexual orientations including bisexual, queer, straight, pansexual, and other.

§Excludes HIV and anogenital warts.

¶Alcohol risk classified according to the World Health Organization's Alcohol, Smoking and Substance Involvement Screening Test as lower (scores 0–10), moderate (scores 11–26), or high (scores ≥27) risk.

CI indicates confidence interval; HPV, human papillomavirus.

significance because of the smaller sample size in stratified analyses (data not shown).

PRs by HPV Vaccination Status

In unadjusted models, anal prevalence of vaccine-preventable types did not significantly differ between vaccinated and unvaccinated participants (Table 4). After adjustment for potential confounders, RDS-unweighted PRs for receipt of ≥1 dose were 0.73 (95% CI, 0.54–1.00) for 4vHPV types and 0.72 (95% CI, 0.57–0.91) for 9vHPV types. Findings were similar when vaccination status was defined as either ≥2 or 3 doses and for RDS-weighted analyses (Supplemental Table S3, http://links.lww.com/OLQ/A755).

Prevalence ratios were comparable when vaccinated participants were restricted to those vaccinated >1 year before enrollment (4vHPV: adjusted PR [aPR], 0.77 [95% CI, 0.52–1.13]; 9vHPV: aPR, 0.73 [95% CI, 0.54–0.99]) but departed further from the null

TABLE 4. RDS-Unweighted Prevalence Ratios for Anal HPV Infection With Vaccine-Preventable Types Comparing Vaccinated With Unvaccinated Gay, Bisexual, and Other Men Who Have Sex With Men Aged 16 to 30 Years, Engage Cohort Study, 2017 to 2019

Model*	Anal HPV Prevalence		Unadjusted PR (95% CI)	Adjusted† PR (95% CI)
	n/N	%		
4vHPV types				
Unvaccinated	98/349	28.1	Ref	Ref
Vaccinated (≥1 dose)‡	53/241	22.0	0.78 (0.59–1.05)	**0.73 (0.54–1.00)**
No. doses				
≥2 doses§	43/184	23.4	0.83 (0.61–1.14)	0.77 (0.55–1.07)
3 doses¶	31/136	22.8	0.81 (0.57–1.15)	0.75 (0.52–1.10)
Time since vaccination				
>1 y before enrollment	28/121	23.1	0.82 (0.57–1.19)	0.77 (0.52–1.13)
>2 y before enrollment	9/61	14.8	**0.53 (0.28–0.98)**	**0.47 (0.25–0.86)**
Age at first dose				
≤23 y	23/118	19.5	0.69 (0.46–1.04)	**0.64 (0.42–0.99)**
>23 y	28/112	25.0	0.89 (0.62–1.28)	0.82 (0.55–1.20)
9vHPV types				
Unvaccinated	134/349	38.4	Ref	Ref
Vaccinated (≥1 dose)‡	76/241	31.5	0.82 (0.65–1.03)	**0.72 (0.57–0.91)**
No. doses				
≥2 doses§	63/184	34.2	0.89 (0.70–1.13)	**0.76 (0.59–0.98)**
3 doses¶	44/136	32.4	0.84 (0.64–1.11)	**0.70 (0.52–0.94)**
Time since vaccination				
>1 y before enrollment	40/121	33.1	0.86 (0.65–1.15)	**0.73 (0.54–0.99)**
>2 y before enrollment	16/61	26.2	0.68 (0.44–1.06)	**0.55 (0.36–0.85)**
Age at first dose				
≤23 y	34/118	28.8	0.75 (0.55–1.03)	**0.69 (0.49–0.96)**
>23 y	40/112	35.7	0.93 (0.70–1.23)	0.76 (0.56–1.02)

4vHPV types include HPV-6/11/16/18; 9vHPV types include HPV-6/11/16/18/31/33/45/52/58.

*Analyses restricted to 590 (97.0%) participants who had complete data for all covariates.

†Analyses adjusted for age group, city, education, lifetime smoking history, lifetime history of STIs (excluding HIV and anogenital warts), and number of condomless receptive anal sex encounters in the past 6 months.

‡HPV vaccination status defined as self-reported receipt of ≥1 dose or unknown number of doses (vs. 0 doses).

§HPV vaccination status defined as self-reported receipt of ≥2 doses (vs. 0 doses); excludes participants who self-reported 1 dose or had an unknown number of doses.

¶HPV vaccination status defined as self-reported receipt of 3 doses (vs. 0 doses); excludes participants who self-reported 1 or 2 doses or had an unknown number of doses.

CI indicates confidence interval; HPV, human papillomavirus; PR, prevalence ratio; RDS, respondent-driven sampling.

Boldface text indicates statistically significant results ($P < 0.05$).

when restricted to those vaccinated >2 years ago (4vHPV: aPR, 0.47 [95% CI, 0.25–0.86]; 9vHPV: aPR, 0.55 [95% CI, 0.36–0.85]). We observed lower PRs among men who received their first vaccine dose at age ≤23 years (median age at first dose in sample) compared with those vaccinated at age >23 years, although CIs overlapped: 0.64 (95% CI, 0.42–0.99) versus 0.82 (95% CI, 0.55–1.20) for 4vHPV types and 0.69 (95% CI, 0.49–0.96) versus 0.76 (95% CI, 0.56–1.02) for 9vHPV types. Restricting the analysis to participants who had ≥1 prevalent HPV infection, the PRs were 0.77 (95% CI, 0.57–1.03) for 4vHPV types and 0.76 (95% CI, 0.61–0.94) for 9vHPV types.

DISCUSSION

In this sexually active cohort of young GBM, anal HPV infection with vaccine-preventable types was highly prevalent. After accounting for RDS recruitment, we estimated that more than one-third of unvaccinated GBM aged 16 to 30 years living in Canada's 3 largest cities were infected with 9vHPV-preventable types and more than one-quarter were infected with 4vHPV-preventable types. These estimates are comparable with prior studies conducted in the prevaccine era that measured anal HPV prevalence against vaccine-preventable types among young, HIV-negative GBM recruited in community settings,[36s–39s] but are lower than prevalence estimates from clinic-based samples.[40s–44s] Anal HPV prevalence remained high in our sample despite targeted HPV vaccination programs for GBM that were implemented 2 to 4 years before study enrollment with 40% vaccine uptake.

We did not find a statistically significant difference in HPV prevalence between vaccinated and unvaccinated GBM. Potential explanations for this nonsignificant finding include lack of vaccine effectiveness against prevalence outcomes in previously infected men, confounding between exposure groups, or differential misclassification of HPV vaccination history. Vaccinated GBM were more likely to engage in condomless receptive anal sex and self-report a prior STI diagnosis, suggesting that targeted vaccination efforts are likely reaching those most at risk for HPV exposure.[2] After adjusting for this confounding between exposure groups, we found that the prevalence of anal infection with vaccine-preventable types was about 30% lower in participants who received ≥1 dose. As expected, this vaccine effectiveness estimate is lower than the vaccine efficacy of 84% (95% CI, 69%–93%) against incident 4vHPV detection measured in clinical trials among GBM who were HPV-naive and had received a complete 3-dose series.[8] Our results are more comparable with the observed efficacy of 49% (95% CI, 32%–61%) in the intent-to-treat sample of GBM who may have been previously infected with HPV and received ≥1 dose.[8] In that analysis, more than one-quarter of participants had evidence of infection with 4vHPV types before vaccination.[8] Differences in study populations should be taken into account, including younger age, limited number of sexual partners, and absence of anogenital warts/lesions and HIV infection among clinical trial participants.

To our knowledge, only one other observational study has measured real-world HPV vaccine effectiveness in this population. In a convenience sample of GBM aged 18 to 26 years recruited at community centers or clinics in 3 US cities during the period 2016–2018, Meites et al.[9] found that the prevalence of ≥1 4vHPV type in anal and/or oral specimens was about 30% lower among GBM who self-reported receiving ≥1 HPV vaccine dose. Higher vaccine effectiveness (~60%) was observed in GBM who received their first dose at age ≤18 years.[9] In the HYPER2 study in Australia, Chow et al.[7] found a significantly lower anal prevalence of 4vHPV types in GBM who were eligible for universal school-based vaccination (vaccine uptake of ≥1 dose, 75%) compared with a vaccine-ineligible cohort (7% vs. 28%; aPR, 0.24; 95% CI, 0.14–0.42). In females, early evidence of HPV vaccine impact in real-world settings has been observed, with vaccine effectiveness estimates for ≥1 dose against prevalent infection with 4vHPV types ranging from 36% to 90% (compared with >90% observed in clinical trials), with greater impact in younger cohorts vaccinated before HPV exposure and with high vaccine uptake.[45s–48s]

In our cross-sectional analysis, the timing of vaccination relative to HPV acquisition was unknown. Human papillomavirus outcomes may be capturing prevalent infections present at the time of HPV vaccination rather than incident infection acquired afterward. Because most individuals will acquire an incident HPV infection shortly after sexual debut,[49s,50s] participants were likely infected with at least one vaccine-preventable HPV type before vaccination, which would make the vaccine less effective. We found a stronger association between HPV vaccination and anal prevalence among those who initiated vaccination at younger ages and likely had fewer exposures to HPV before vaccination. However, because nearly all participants reported being sexually active for multiple years before HPV vaccination, differences in PRs between participants who were vaccinated at ≤23 years old compared with >23 years old were not statistically significant. Current HPV vaccines are not approved for therapeutic indications.[1] Analyses including participants who were recently vaccinated may not fully account for the necessary time to complete the 3-dose vaccine series (6 months)[15] or time to clear prevalent anal infection at vaccination (typically 6–12 months depending on type).[51s] In sensitivity analyses restricted to participants who were vaccinated >2 years before enrollment, which more likely captures the effect of vaccination against incident infections acquired after HPV vaccination, vaccine effectiveness estimates exceeded 50%.

Differences in anal HPV prevalence between vaccinated and unvaccinated participants were driven by 4vHPV types, especially HPV-16, which was the most prevalent vaccine-preventable type in our study. Human papillomavirus type 16 is consistently associated with higher incidence and longer time to clearance, underscoring its higher oncogenic potential.[52s] Conversely, anal prevalence of HPV-18 was higher in vaccinated compared with unvaccinated participants, although differences were not statistically significant. Immunogenicity studies have found lower immune response and greater antibody waning over time for HPV-18.[53s,54s] However, there was no evidence of reduced vaccine efficacy for the HPV-18 component in the clinical trial of GBM[8] or in longer-term follow-up of vaccinated cohorts.[55s]

Strengths of this analysis include the observational study design to measure real-world vaccine effectiveness and the RDS recruitment to estimate population-based HPV prevalence, which is likely more representative than clinic-based samples.[40s–44s] It is one of the largest community-recruited studies of HPV prevalence among GBM to date, including both unvaccinated and vaccinated men. Limitations include the nonnegligible number of invalid specimens and self-reported HPV vaccination status. Although we failed to detect human β-globin in some anal specimens, our proportion of valid specimens was similar to other studies among GBM using self-collection methods.[37s] Vaccine uptake was similar between those with and without valid specimens, suggesting that our analysis restricted to valid specimens is unbiased. Although self-reported HPV vaccination status has high sensitivity (>90%) and moderate specificity (>75%) in adults,[56s] self-report may be associated with nondifferential misclassification, which would bias our estimates toward the null. We have attempted to address potential confounding associated with nonrandom allocation of HPV vaccine through multivariable regression adjustment. Although some residual confounding may remain, findings were similar in sensitivity analyses restricted to participants who had ≥1 prevalent HPV infection that controlled for differences in HPV exposure risk. The

few people living with HIV in our sample of young GBM precluded us from looking at differences in vaccine effectiveness by HIV status; HIV was not a significant confounder in our analysis because of its lack of association with HPV vaccine uptake. Men were recruited using RDS, which relies on several assumptions inherent to chain-referral sampling, including accurate reporting of network size.[18,30] Respondent-driven sampling-II weights were applied to minimize biases in HPV prevalence estimates, although this may increase variability in weighted regression estimates.[31s] Although RDS is better able to recruit members of the GBM community who would not traditionally be captured in research studies, men who are less engaged with their health, and thus have higher rates of HPV infection and/or lower vaccination, may have been missed.

Using observational data, we show that HPV vaccination was associated with a lower anal prevalence of vaccine-preventable types among young, sexually active GBM soon after implementation of publicly funded HPV vaccination. This protective association was observed despite the high incidence of HPV infection in this population. Many participants likely had sexual exposure before HPV vaccination and may not have had the opportunity to benefit from these recently launched programs. Lower point estimates suggestive of better vaccine protection were observed in those vaccinated >2 years before enrollment and in those who initiated vaccination at younger ages. Overall, our findings provide further support for current universal HPV vaccination policies targeting school-aged youth before sexual debut but also suggest some vaccine benefit in high-risk programs for young GBM. These findings will help inform shared decision making around HPV vaccination for GBM and their healthcare providers.[57s,58s] Future analyses will explore vaccine effectiveness against clinically relevant outcomes, including longitudinal end points such as HPV incidence and persistence.

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For further references, please see "Supplemental References," http://links.lww.com/OLQ/A755.