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Short communication

Anal human papillomavirus infections in young unvaccinated men who have sex with men attending a sexual health clinic for HPV vaccination in Melbourne, Australia

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ABSTRACT

The Victorian Government introduced a time-limited quadrivalent human papillomavirus (HPV) vaccination catch-up program targeting gay and bisexual men who have sex with men (MSM) aged up to 26 years in 2017. As of 2017, men aged ≥20 years were not eligible for the school-based HPV vaccination program. This study examined the prevalence of anal HPV among 496 MSM aged 20–26 years before they received the first dose of the HPV vaccine at the Melbourne Sexual Health Centre, Australia. More than half (56.5%) had any high-risk HPV genotypes detected in the anus. Almost half (43.1%) had at least one quadrivalent HPV vaccine-preventable genotype (6, 11, 16 or 18) and one-fifth (21.0%) had HPV 16 detected in the anus. These findings suggest that a targeted catch-up HPV vaccination program for MSM is still beneficial to protect against high-risk HPV genotypes associated with anal cancer, as well as low-risk HPV genotypes.

1. Introduction

Australia introduced a quadrivalent human papillomavirus (4vHPV) vaccination program for females in April 2007 and extended it to include school-aged boys in February 2013 [1]. In 2018, the nonavalent HPV (9vHPV) vaccine replaced the 4vHPV in the national school-based HPV vaccination program for girls and boys aged 12–13 years. The HPV vaccination program has achieved a high coverage (i.e. 78% of females aged ≤15 years received all three doses of 4vHPV in 2016) [2], and has been associated with a large reduction in genital warts and 4vHPV vaccine-preventable genotypes in young Australian females [3,4], and unvaccinated heterosexual males from herd protection [4–6].

Gay, bisexual and other men who have sex with men (MSM) have a high prevalence of anal HPV infection in particular, and are also at higher risk of anal cancer [7–9]. Unlike heterosexual males, MSM are not likely to receive herd protection from the female-only HPV vaccination program. While the HPV program for boys will provide greater protection with time, large numbers of young MSM currently remain unprotected against HPV infection, particularly at an age when the incidence of anal HPV infection is high [9]. To address this issue, the State of Victoria introduced a time-limited targeted catch-up HPV vaccination program for MSM in April 2017 [10]. The 4vHPV vaccine is licensed for use in males aged from 9 to 26 years in Australia. All MSM aged 26 or under who live in Victoria were eligible to receive three doses of the 4vHPV vaccine from this catch-up program free of charge at

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sexual health clinics, general practices and other immunisation providers. As of 2017, most men aged 19 years or below were offered the HPV vaccine from the school-based program. The aim of this study was to estimate the prevalence of anal HPV infection among unvaccinated MSM aged 20–26 years before they received the first dose of HPV vaccine from this time-limited targeted catch-up program in Melbourne, Australia.

2. Method

2.1. Study population and data collection

This was a cross-sectional study conducted at the Melbourne Sexual Health Centre (MSHC) in Australia between May and December 2017. During this period, the 4vHPV vaccines were provided for MSM aged up to 26 years, free of charge at MSHC. We defined MSM as men who have had any sexual contacts with another man in the last 12 months. Ethical approval was obtained from the Alfred Hospital Ethics Committee in Melbourne, Australia (approval number: 384/17).

Demographic characteristics (i.e. age, country of birth), sexual practices (i.e. gender of sexual partners, number of male partners and condomless anal sex in the last 12 months) were collected via computer-assisted self-interviewing as part of routine clinical care and management at MSHC.

2.2. Laboratory testing

Before receiving the first dose of the 4vHPV vaccine, an anal swab was taken as part of routine STI screening by nucleic acid amplification test (NAAT). Anal swabs were collected using the Aptima™ Multitest Swab Specimen Collection Kit (Hologic Inc, San Diego, USA), and subsequently screened for *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* infection using the Aptima Combo 2 Assay (Hologic Inc, San Diego, USA). Following testing, the residual specimen transport medium from anal swab samples was stored at −80° C for HPV testing.

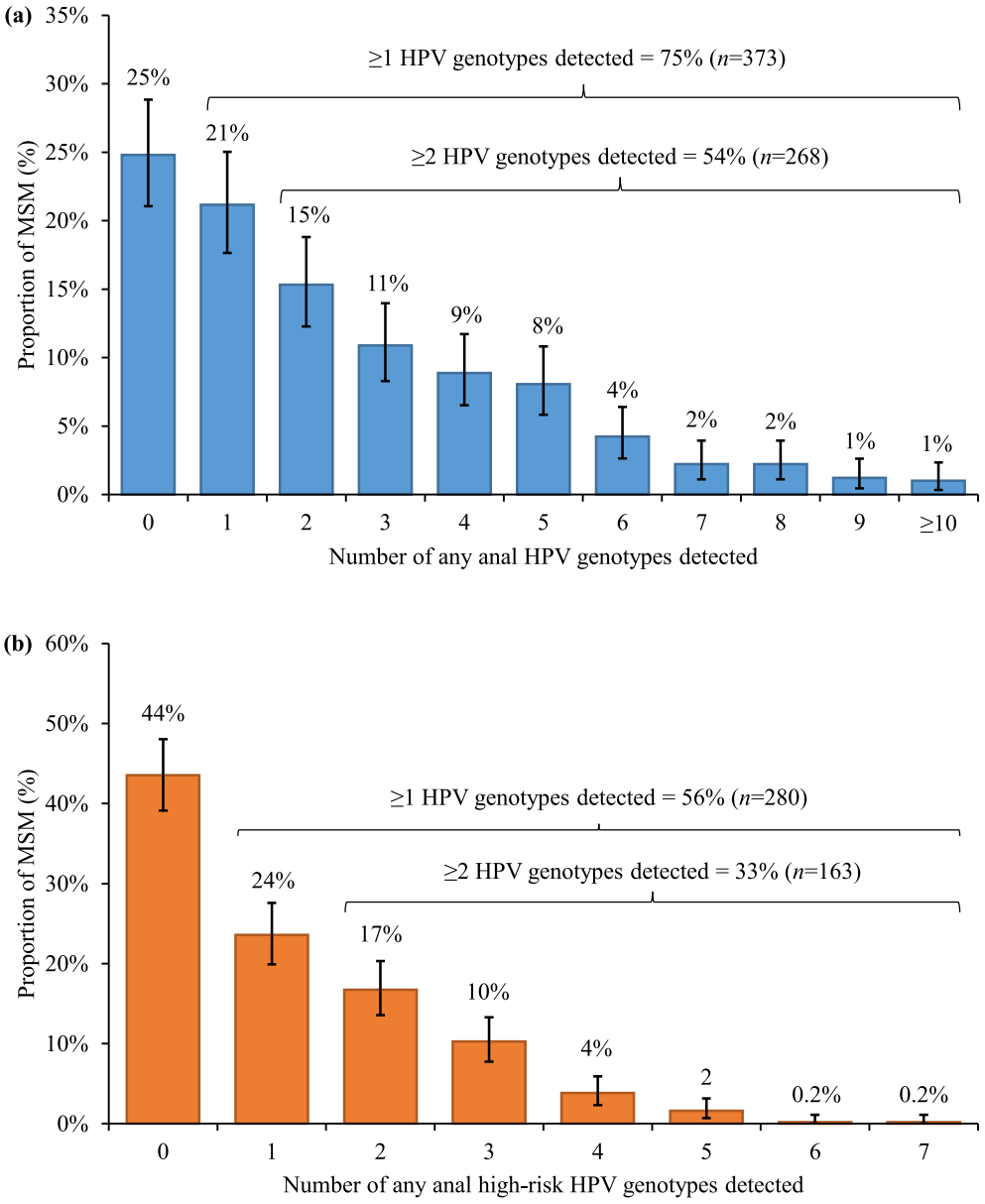

Fig. 1. The number of prevalence of (a) any of the 28 HPV genotypes; and (b) any of the 13 high-risk HPV genotypes detected in the anus among 496 unvaccinated men who have sex with men.

DNA was extracted from stored samples (1 mL) using the MagNA Pure 96 system (DNA and Viral NA Large Volume kit; Roche Diagnostics, Mannheim, Germany) according to the manufacturer's protocol, and eluted in 100 μL. Sample adequacy was assessed as described previously [3].

HPV detection and genotyping were performed using the Anyplex™ II HPV28 Detection assay (Seegene, Seoul, Korea) on a CFX96™ real-time PCR system (Bio-Rad) according to the Seegene HP7S00X HPV 28 detection manual, and edition 1.6 of the Bio-Rad CFX Manager software with version 2.0 of Seegene viewer. This is a multiplex real-time PCR system which detects a total of 28 HPV genotypes (6/11/16/18/26/31/33/35/39/40/42/43/44/45/51/52/53/54/56/58/59/61/66/68/69/70/73/82), in addition to an internal control to monitor low nucleic acid concentration and possible PCR inhibition. Samples for which the internal control is not detected were un-assessable, and not included in the analysis.

2.3. Statistical analysis

We calculated the frequency and prevalence of each of the 28 HPV genotypes and the following groups: any HPV genotype, any high-risk genotype (16/18/31/33/35/39/45/51/52/56/58/59/68), 4vHPV vaccine-preventable (6/11/16/18), 9vHPV vaccine-preventable (6/11/16/18/31/33/45/52/58), low-risk vaccine-preventable (6/11), and high-risk 4vHPV vaccine-preventable (16/18). The 95% confidence intervals (CI) of the HPV prevalence were calculated using the exact binomial distribution. Two univariable logistic regression analyses were performed to examine the factors associated with the prevalence of anal 4vHPV and 9vHPV vaccine-preventable genotypes, respectively. All analyses were performed in Stata (version 14, Stata, College Station, Texas, USA).

3. Results

Of the 505 anal swabs collected and tested for HPV, 496 had assessable results for the Anyplex™ II HPV28 assay. The age of MSM ranged from 20 to 26 years with a median of 24 (IQR 23–25) years. Twelve MSM (2.4%) were HIV-positive. The majority (53.4%; $n = 265$) of MSM were born in Australia. The median number of male partners in the last 12 months was 5 (IQR 1–10). A proportion of MSM had anorectal gonorrhoea (6.5%; 32/489) and anorectal chlamydia (8.1%; 40/491) on the same anal specimen. The proportion of gonorrhoea or chlamydia detected in the anal specimens did not differ significantly between non-assessable samples and assessable samples for HPV (22.2% [2/9] *versus* 67/496 [13.5%]; $p = 0.354$).

Fig. 1 shows that 75.2% of MSM had at least one HPV genotype detected and 54.0% had two or more HPV genotypes detected in the anus, and more than half of MSM (56.5%) had at least one high-risk anal HPV genotype detected. The most common genotype was HPV 6 (22.6%) followed by HPV 16 (21.0%). There were 265 (53.4%) and 214 (43.1%) MSM who had at least one anal 9vHPV or 4vHPV vaccine-preventable genotype detected, respectively (Table 1). There were 131 (26.4%) MSM who had HPV 16 and/or 18 detected and 144 (29.0%) MSM who had HPV 6 and/or 11 detected. One man (0.2%) had all four 4vHPV vaccine-preventable genotypes (6, 11, 16 and 18).

Univariable logistic regressions showed that the prevalence of 4vHPV and 9vHPV vaccine-preventable genotypes was not associated with individuals' demographic characteristics and sexual behaviours (Table 2) except men who declined to report condom use with their male partners had higher odds of testing positive for 4vHPV and 9vHPV in the anus compared to men who always

Table 1
Prevalence of anal human papillomavirus among 496 unvaccinated young men who have sex with men attending the Melbourne Sexual Health Centre, 2017.

HPV genotype	Number of men with HPV detected	Prevalence	95% CI
Any HPV genotype	373	75.2%	71.2–78.9%
Any high-risk genotype	280	56.5%	52.0–60.9%
Any 4vHPV vaccine-preventable genotype (6, 11, 16 or 18)	214	43.1%	38.7–47.6%
Any 9vHPV vaccine-preventable genotype (6, 11, 16, 18, 31, 33, 45, 52, or 58)	265	53.4%	48.9–57.9%
HPV 6 and/or 11	144	29.0%	25.1–33.2%
HPV 16 and/or 18	131	26.4%	22.6–30.5%
HPV 6	112	22.6%	19.0–26.5%
HPV 11	44	8.9%	6.5–11.7%
HPV 16	104	21.0%	17.5–24.8%
HPV 18	43	8.7%	6.3–11.5%
HPV 26	6	1.2%	0.4–2.6%
HPV 31	32	6.5%	4.5–9.0%
HPV 33	17	3.4%	2.0–5.4%
HPV 35	22	4.4%	2.8–6.6%
HPV 39	47	9.5%	7.0–12.4%
HPV 40	49	9.9%	7.4–12.8%
HPV 42	71	14.3%	11.4–17.7%
HPV 43	52	10.5%	7.9–13.5%
HPV 44	25	5.0%	3.3–7.4%
HPV 45	37	7.5%	5.3–10.1%
HPV 51	74	14.9%	11.9–18.4%
HPV 52	29	5.8%	4.0–8.3%
HPV 53	60	12.1%	9.4–15.3%
HPV 54	38	7.7%	5.5–10.4%
HPV 56	43	8.7%	6.3–11.5%
HPV 58	29	5.8%	4.0–8.3%
HPV 59	41	8.3%	6.0–11.0%
HPV 61	19	3.8%	2.3–5.9%
HPV 66	48	9.7%	7.2–12.6%
HPV 68	47	9.5%	7.0–12.4%
HPV 69	14	2.8%	1.6–4.7%
HPV 70	14	2.8%	1.6–4.7%
HPV 73	37	7.5%	5.3–10.1%
HPV 82	40	8.1%	5.8–10.8%

HPV: human papillomavirus; 4vHPV: quadrivalent human papillomavirus; 9vHPV: nonavalent human papillomavirus; CI: confidence intervals.

Table 2
Characteristics associated with at least one quadrivalent and at least one nonavalent vaccine-preventable genotypes among 496 unvaccinated young men who have sex with men.

Characteristics	Number of MSM, *N*	4vHPV vaccine-preventable genotypes positivity			9vHPV vaccine-preventable genotypes positivity		
		Number tested positive, *n* (%)	Odds ratio (95% CI)	P value	Number tested positive, *n* (%)	Odds ratio (95% CI)	P value
Age (years)	496	–	0.95 (0.85–1.07)	0.429	–	0.99 (0.88–1.11)	0.836
Country of birth							
Australia	265	119 (44.9%)	1	Ref	145 (54.7%)	1	Ref
Overseas	214	85 (39.7%)	0.81 (0.56–1.17)	0.254	109 (50.9%)	0.86 (0.60–1.23)	0.410
Unknown	17	10 (58.8%)	1.75 (0.65–4.74)	0.269	11 (64.7%)	1.52 (0.55–4.22)	0.425
ATSI							
No	488	209 (42.8%)	1	Ref	259 (53.1%)	1	Ref
Yes	8	5 (62.5%)	2.22 (0.53–9.41)	0.277	6 (75.0%)	2.65 (0.53–13.27)	0.235
HIV status							
Negative	484	207 (42.8%)	1	Ref	256 (52.69%)	1	Ref
Positive	12	7 (58.3%)	1.87 (0.59–5.99)	0.290	9 (75.0%)	2.67 (0.71–9.99)	0.144
Sexual orientation[^]							
Gay	476	205 (43.1%)	1	Ref	254 (53.4%)	1	Ref
Bisexual	20	9 (45.0%)	1.08 (0.44–2.66)	0.864	11 (55.0%)	1.07 (0.43–2.63)	0.886
Number of male partners in the last 12 months[φ]							
≤5	291	121 (41.6%)	1	Ref	146 (50.2%)	1	Ref
>5	205	93 (45.4%)	1.17 (0.81–1.67)	0.402	119 (58.1%)	1.37 (0.96–1.97)	0.084
Condom use with male partners in the last 12 months[δ]							
Always/no anal sex	115	40 (34.8%)	1	Ref	52 (45.2%)	1	Ref
Not always	285	127 (44.6%)	1.51 (0.96–2.36)	0.074	156 (54.7%)	1.47 (0.95–2.26)	0.085
Declined to report	96	47 (49.0%)	1.80 (1.03–3.13)	0.038	57 (59.4%)	1.77 (1.02–3.06)	0.041

ATSI: Aboriginal and Torres Strait Islander peoples. 4vHPV: quadrivalent human papillomavirus genotypes (6, 11, 16 or 18). 9vHPV: nonavalent human papillomavirus genotypes (6, 11, 16, 18, 31, 33, 45, 52 or 58).

[^] MSM were categorised into gay or bisexual based on the sexual contact with men and women but not sexual identity. Gay men were defined as men who have sex with men only in the last 12 months. Bisexual men were defined as men who have sex with men and women in the last 12 months.

[φ] The number of male sexual partners in the last 12 months was categorised into two groups at the median (i.e. 5 partners in the last 12 months).

[δ] Not always condom use: sometimes or never used condom in the last 12 months.

used condom for anal sex in the last 12 months. Multivariable analysis was not performed.

4. Discussion

This cross-sectional study assessed the proportion of anal HPV detection among 496 unvaccinated sexually active MSM aged 20–26 years attending a sexual health clinic in Melbourne for an HPV vaccine. About half of the young MSM had at least one of the genotypes from the 4vHPV or 9vHPV vaccines. The findings that only 21% of MSM in our sample had HPV 16 suggest that about 80% of young MSM would derive protection against the HPV type that causes most cases of anal cancer. The relatively high proportion of MSM in the sexual health clinic setting who are likely to benefit from this targeted catch-up HPV vaccination program for MSM support it being extended until those vaccinated in the school-boy program reach the age of 26 [10].

This study has some limitations. Firstly, this study was conducted among MSM attending a single sexual health clinic and so the proportion with HPV and proportion who may benefit from the vaccine may not be generalisable to the MSM in other settings. Secondly, we only had a small number of HIV-positive MSM in this young population ($n = 12$) and therefore we did not stratify the HPV prevalence by HIV status although previous studies reported higher HPV prevalence in HIV-positive MSM than HIV-negative MSM [7]. Thirdly, we only tested for anal HPV among unvaccinated MSM because anal HPV is much more common than penile and oral infections among young MSM; therefore, we may have overestimated the potential benefit from vaccination [11–13]. Fourthly, we only tested HPV DNA and not antibodies to different HPV genotypes. Some men may have acquired HPV previously but no longer have HPV DNA detected and they may still derive benefit from the vaccine if it prevents re-infection. Finally, sexual behaviours were self-reported and hence recall bias might have occurred.

Our observation that a substantial proportion of young MSM already had one or more of the HPV vaccine-preventable genotypes will impair the effectiveness of a catch-up program to control HPV at a population level. This is because the effectiveness of the vaccine will be lower in a population where some individuals are already infected with vaccine-preventable HPV genotypes because the vaccine essentially fails in these individuals. HPV 16 was already present in 21% of men and these men have a higher risk of developing anal cancer. In addition, some of these men with persistent HPV 16 who will continue to transmit this genotype within the MSM population despite having the vaccine. This means that to reach the critical vaccination threshold in this population and provide substantial herd protection, a higher proportion of 'all' men will need to be vaccinated to achieve this threshold than would be required in a wholly susceptible population such as children vaccinated before they become sexually active.

We found that MSM who declined to report condom use with their male partners are at higher risk of acquiring the 4vHPV or 9vHPV infection. One possible explanation for this observation is that they have engaged in condomless anal sex but were reticent about reporting this. A previous study has shown that MSM who declined to report the number of male partners were more likely to have HIV/STI [14].

A number of different strategies have been used to protect MSM against HPV related cancers through vaccination in Australia and overseas. Australia has opted for a universal school-based HPV vaccination program which is likely to provide high levels of herd protection as this cohort reaches sexual activity although this will take many decades to be realised [15]. To address this delay, some countries have added a time-limited targeted catch-up program for MSM. In Victoria, when a catch-up program includes MSM aged

up to 26 years, it has been estimated to result in a ≥90% reduction in HPV infection among MSM over the next two decades in Australia [16]. However, an even greater reduction in HPV infection is predicted in Australia if the targeted catch-up program is expanded to MSM older than 26 years and modelling studies have shown vaccinating MSM to age 40 years is cost-effective [17]. In contrast, other countries such as the UK, initially adopted a targeted HPV vaccination program for MSM in 2016 and then extended the school-based program to include boys by 2019 [18,19]. Further research over the next decade is required to evaluate the impact of the targeted catch-up HPV vaccination program in MSM by monitoring the HPV prevalence in this population.

Contributors

EPFC and CKF designed the study. EPFC performed the statistical analysis and wrote the first draft. JAD and GLM performed the laboratory testing and were involved in result interpretation. EPFC, JAD, GLM and CKF were involved in data interpretation. MYC, CSB, SMG assisted with data interpretation. GF was involved in sample collection, storage and management. All authors critically revised the manuscript for important intellectual content and approved the final version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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