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HPV infections among young MSM visiting sexual health centers in the Netherlands: Opportunities for targeted HPV vaccination

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ABSTRACT

Introduction: In 2009, girls-only HPV16/18 vaccination was introduced in the Netherlands which has achieved 46–61% uptake. Heterosexual men have benefitted from herd protection, but it is unknown whether men who have sex with men (MSM) also benefit from herd effects of the girls-only HPV16/18 vaccination program. Because MSM bear a high HPV-related disease burden, countries might consider targeted vaccination for MSM. To study possible herd effects and prior HPV exposure at a potential moment of vaccination, we assessed trends in the HPV prevalence and proportions (sero)negative for the various vaccine types among young MSM visiting sexual health centers (SHCs).

Methods: We used data from MSM included in PASSYON study years 2009–2017. In this biennial cross-sectional study among visitors of SHCs aged 16–24 years, MSM provided a penile and anal swab for HPV DNA testing (including vaccine types HPV6/11/16/18/31/33/45/52/58) and blood for HPV antibody testing (HPV16/18/31/33/45/52/58).

Results: In total 575 MSM were included, with a median of 22 years of age and 15 lifetime sex partners and 3.5% HIV positive. Trends in penile or anal HPV prevalence during 2009–2017 were statistically non-significant for all vaccine types. Of the 455 MSM with a penile and anal swab, 360 (79%), 283 (62%) and 242 (53%) were HPV DNA negative at both anatomical sites for HPV16/18, HPV6/11/16/18 and HPV6/11/16/18/31/33/45/52/58 respectively. Among MSM who were HPV16/18 and HPV16/18/31/33/45/52/58 DNA negative and were tested for serology (n = 335 and 279 respectively), 82% and 71% were also seronegative for the respective types.

Discussion: There were no significant declines in the HPV prevalence among MSM up to eight years after introduction of girls-only HPV16/18 vaccination, indicating that MSM are unlikely to benefit largely from herd effects from girls-only vaccination. Most MSM were vaccine-type DNA negative and seronegative, suggesting that vaccination of young MSM visiting SHCs could still be beneficial.

1. Introduction

Sexually transmitted human papillomavirus (HPV) can cause anogenital warts (AGW) and various cancers in both men and women: cervical, vaginal, vulvar, anal, and oropharyngeal cancer in women; and penile, anal, and oropharyngeal cancer in men [1]. Many different HPV types have been identified, which are classified into high-risk HPV (hrHPV) or low-risk HPV (lrHPV) based on their oncogenic potential. Currently, three prophylactic vaccines against HPV are on the European market and all are licensed for

Abbreviations: AGW, Anogenital warts; HPV, Human papillomavirus; hrHPV, high-risk HPV; lrHPV, low-risk HPV; LU, Luminex Units; MSM, Men who have sex with men; NIP, National immunization program; RCT, Randomized controlled trial; SHC, Sexual health center; STI, Sexually transmitted infection; VLP, Virus-like particle; 2vHPV, Bivalent HPV; 4vHPV, Quadrivalent HPV; 9vHPV, Nonavalent HPV; 95% CI, 95% confidence interval.

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both males and females [2–4]; a bivalent HPV (2vHPV), quadrivalent HPV (4vHPV) and nonavalent HPV (9vHPV) vaccine. All vaccines target hrHPV types 16/18. The 4vHPV and 9vHPV vaccines also target lrHPV types 6/11, the most important types causing AGW [5]. The 9vHPV vaccine targets five additional hrHPV types: HPV31/33/45/52/58. As of May 2018, nearly half of the countries worldwide have implemented HPV vaccination in their national immunization program (NIP) [6]. Studies of high-income countries have shown declines in the HPV infection prevalence and the burden of AGW and pre-malignant disease within a decade after HPV vaccination implementation [7].

Although sex-neutral HPV vaccination has been implemented in a diverse array of countries (e.g. Argentina, Australia, Austria, Brazil, Canada, Croatia, Israel, Panama) to prevent HPV-related cancers in both men and women, many countries still offer vaccination to girls only [8]. Also in the Netherlands, HPV vaccination is still a girls-only program as of 2020. 2vHPV vaccination was introduced in 2009 with the main aim to prevent cervical cancer. It started with a catch-up campaign for 13- to 16-year-old girls and in 2010 HPV vaccination was implemented in the Dutch NIP for girls in the calendar year they turn 13 years old. The vaccination uptake has ranged between 46 and 61% in vaccine-eligible cohorts [9].

Among heterosexual men, declines in the HPV vaccine type prevalence have been observed after introduction of girls-only HPV vaccination, indicating that heterosexual men benefit from herd protection [10,11]. It is unknown whether men who have sex with men (MSM) also experience decreases in the HPV16/18 prevalence as observed among heterosexual men. In Australia, AGW (mostly caused by HPV6/11) nearly disappeared in young Australian heterosexual men within 7 years of girls-only 4vHPV vaccination, whereas only a small decline in AGW was observed among MSM [12]. Accordingly, herd protection for hrHPV types among MSM is expected to be less than for heterosexual men, even though MSM are at much higher risk of HPV-related diseases than heterosexual men, especially for anal cancer. In meta-analyses published in 2012, the anal cancer incidence was estimated at 5.1 per 100,000 among HIV negative MSM and at 45.9 per 100,000 among HIV positive MSM [13]. This is about 17–30 times more frequent compared to heterosexual men [14,15], highlighting the importance of extending the protection afforded by prophylactic HPV vaccination to MSM.

Additional to preadolescent sex-neutral vaccination, countries might consider targeted vaccination for MSM. When combined with sex-neutral vaccination in preadolescence, additional vaccination of MSM, even when previously exposed to HPV, is predicted to accelerate penile and anal cancer prevention, compensate for low-uptake among preadolescents and protect previously unvaccinated MSM [16,17]. A randomized controlled trial (RCT) carried out in MSM aged up to 26 years with 1–5 lifetime sex partners, showed that vaccination is effective in preventing genital and anal lesions, especially in those DNA negative and seronegative for the HPV vaccine type under study and at the anatomical location under study [18,19]. Because it is difficult to target MSM from the general population and before sexual debut, an option would be to offer vaccination to MSM visiting sexual health centers (SHCs), comparable to targeted hepatitis B vaccination [20]. This is already being implemented in for example the United Kingdom after a successful pilot program with nearly 50% uptake [21]. However, the effectiveness of HPV vaccination targeting sexually active MSM visiting SHCs might be hampered by prior exposure to HPV vaccine types.

Here, we assessed the scope of targeted HPV vaccination for MSM attending SHCs. First, we assessed trends in the penile and anal HPV prevalence among MSM visiting SHCs in the Netherlands from pre-vaccination up to eight years post-vaccination, to study possible herd effects from girls-only vaccination. Second, we assessed the proportions HPV DNA negative at the penile and anal site and seronegative for the various vaccine-targeted types, to study prior exposure and the occurrence of prevalent infections at a potential moment of targeted vaccination, i.e. directed at MSM upon SHC visits.

2. Methods

2.1. Study design and population

We used data from the PASSYON (PApillomavirus Surveillance among STI clinic YOungsters in the Netherlands) study, a biennial cross-sectional survey among 16- to 24-year-old visitors to SHCs in the Netherlands that started in 2009 when girls-only 2vHPV vaccination was implemented [22]. In the current analysis we used data from MSM included in the PASSYON study. MSM were classified as men who indicated to be homosexual or bisexual in the questionnaire. In addition to routine sexually transmitted infection (STI) testing, MSM were asked to provide a self-collected penile and anal swab for HPV testing. For the penile swab, men were instructed to firmly move the swab up and down the entire penile shaft, the glans/coronal sulcus, and under the foreskin. For the anal swab, men were instructed to insert the swab about 3 cm into the anus and circle it around. From participants who provided blood for routine syphilis and HIV testing, serum was collected to assess their HPV serology-status. Because MSM are at higher risk for syphilis and HIV, testing is usually indicated. The PASSYON study was repeated in 2011, 2013, 2015, and 2017 using the same study protocol during which the proportion of women who had been offered HPV vaccination increased to almost 90% (of whom almost 60% reported to be HPV vaccinated with at least one dose). Participants could be included in multiple study rounds, but the probability of repeat consultations is low as we sampled for only two months in the same period (i.e. February-March) every other year. The Medical Ethical Committee of the University of Utrecht, the Netherlands, approved this study (protocol number 08/397). Data was obtained using a unique code per person and all participants gave informed consent.

2.2. Laboratory methods

Swabs were tested using the SPF10, DEIA-LiPA25 assay (DDL Diagnostics Laboratory, the Netherlands) as published in detail previously [22]. This sensitive broad-spectrum PCR is able to detect DNA of 25 HPV types, including the vaccine-targeted HPV types 6/11/16/18/31/33/45/52/58 and the non-vaccine hrHPV types 35/39/51/56/59.

HPV serum IgG antibodies were assessed using a virus-like particle (VLP) based multiplex immunoassay against the vaccine-targeted hrHPV types 16/18/31/33/45/52/58 as published in detail previously [23,24]. GSK (GlaxoSmithKline, Rixensart, Belgium) and MSD (Merck&Co, Kenilworth, NJ, USA) produced the VLPs that were used in the study. Serum samples were considered antibody seropositive at the following previously determined cut-offs: 9, 13, 27, 11, 19, 14, and 31 Luminex Units (LU)/mL for HPV types 16, 18, 31, 33, 45, 52, and 58, respectively [24].

2.3. Statistical analyses

We explored the association between characteristics of the MSM and hrHPV DNA positivity (being positive for hrHPV 16/18/31/33/35/39/45/51/52/56/58/59) using Chi-square tests, for penile and anal HPV separately. To study trends in the vaccine types over time, we calculated the penile and anal HPV DNA prevalence for each PASSYON study year and performed crude Cochran-

Armitage Trend Tests. Changes in the characteristics of the study population by study year were explored using Chi-square tests.

Because RCTs showed that vaccine efficacy among women was substantial even if a woman was seropositive when vaccinated (>66% against persistent infection with the vaccine types) [25,26], we first calculated the proportion DNA negative for the vaccine-targeted HPV types in the penile and anal swab, irrespective of serostatus. We did this among MSM with both swabs available, for the vaccine-targeted HPV types separately as well as combined for the types included in the currently licensed vaccines (HPV16/18, HPV6/11/16/18, HPV6/11/16/18/31/33/45/52/58).

Next, we calculated the proportion DNA negative (both swabs) and seronegative. This was done for the vaccine-targeted hrHPV types only, because serum antibodies against HPV6/11 were not determined, again for each type separately as well as combined (HPV16/18 and HPV16/18/31/33/45/52/58). MSM were considered negative if they were DNA negative for all types in both swabs and seronegative for all types.

Last, to investigate the value of seropositivity as a marker of prior exposure to HPV, we studied the HPV antibody concentration by age and number of lifetime sex partners (categorized into five categories based on percentiles). The associations between log transformed antibody concentration and age/lifetime sex partners were studied using linear regression. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) with a significance level of $p < 0.05$.

3. Results

3.1. Study population

There were 587 MSM in the PASSYON study of which 575 (98%) provided a penile and/or anal swab and were included in the current analyses; 71 in round 2009, 110 in round 2011, 136 in round 2013, 130 in round 2015, and 128 in round 2017. In total, 455 (78%) provided a penile and anal swab, 112 provided only a penile swab, and 8 provided only an anal swab. We had serum available of 531 MSM (92%) and 421 (73%) men provided both swabs and serum.

Characteristics of the study population and the association with hrHPV DNA positivity are presented in Table 1. The median age of the MSM was 22 years (range 16–24) and the median reported number of lifetime sex partners was 15 (interquartile range: 6–30). Of all MSM, 3.5% were HIV positive. Overall, 20.3% and 36.7% of the MSM were positive for hrHPV at the penile and anal site respectively. In general, higher sexual risk behavior (defined as a higher number of lifetime sex partners and a history of STIs) was associated with hrHPV positivity. Receptive anal intercourse in the past 6 months was associated with anal hrHPV and insertive anal intercourse in the past 6 months with penile hrHPV.

3.2. Prevalence of vaccine-targeted HPV types over time

No statistically significant declining trends were observed in the penile (Fig. 1A) or anal (Fig. 1B) HPV DNA prevalence among MSM for any of the vaccine-targeted types up to eight years after the introduction of girls-only 2vHPV vaccination. Also for the pooled outcome HPV16/18, no statistically significant declining trend was observed (p_{trend} = 0.75 for penile and p_{trend} = 0.50 for anal HPV). The prevalence of AGW decreased from 7.1% in 2009 to 0.8% in 2017 (p_{trend} = 0.03). Changes over time in the characteristics of the MSM included in the PASSYON study are presented in the Supplementary Table. Only sexual preference and a history of STIs were associated with PASSYON study year ($p < 0.05$). The proportion reporting no history of STIs was 57% in 2009 and 41% in 2017.

3.3. Proportion negative for the vaccine-targeted HPV types

The percentage of MSM negative for HPV DNA at the penile and anal site was the smallest for HPV6 (83%) and the largest for HPV58 (99%) (Fig. 2A). For HPV16, 88% was negative, 8.6% was positive only at the anal site, 2.2% was positive only at the penile site, and 1.5% was positive at both sites. For HPV18, 89% was negative, 6.8% was positive only at the anal site, 2.0% was positive only at the penile site, and 1.8% was positive at both sites. In total, 79%, 62%, and 53% were HPV DNA negative at both anatomic sites for HPV16/18, HPV6/11/16/18, and HPV6/11/16/18/31/33/45/52/58, respectively (Fig. 2B). Of the MSM infected with at least one of the nine vaccine-targeted types at either anatomical site (n = 213), the majority was infected with one type (n = 136, 64%). No one was positive for all vaccine-targeted types; the maximum number of types present at either anatomic site was six (n = 1). No one was positive for both HPV16 and HPV18 at both anatomic sites.

Also including serology, 76% of the MSM were HPV16 negative (DNA negative in both swabs and seronegative) and 79% were HPV18 negative (Fig. 2C). For the other vaccine-targeted hrHPV, the percentage HPV DNA negative and seronegative was even higher and up to 94% for HPV58. Among MSM HPV16/18 and HPV16/18/31/33/45/52/58 DNA negative, 82% and 71% were also seronegative for the respective vaccine types. In total, 65% and 47% were HPV DNA negative and seronegative for HPV16/18 and HPV16/18/31/33/45/52/58 respectively (Fig. 2D).

3.4. HPV antibody concentration

The HPV16 and HPV18 log antibody concentration increased both with age and number of lifetime sex partners ($p < 0.05$). However, even in the highest categories of 23-to 24–year-olds and 40 or more lifetime sex partners, the majority of the MSM was not seropositive (Fig. 3). These patterns were comparable to the other hrHPV types (data not shown).

4. Discussion

We assessed the scope for targeted HPV vaccination for sexually active MSM, by studying trends in the HPV prevalence over time and by studying the proportions (sero)negative for the various vaccine-targeted HPV types among young sexually active MSM who visited SHCs in the Netherlands. We did not discern trends for any of the vaccine types up to eight years after the introduction of girls-only vaccination, and the majority of the MSM in our study population were HPV DNA negative and seronegative for the various vaccine types. Our study provides important baseline measurements in case male HPV vaccination will be implemented in the Netherlands. Moreover, because young MSM visiting SHCs are a natural target population for a selective vaccination program, our study may provide relevant input for countries considering targeted HPV vaccination for MSM.

We do acknowledge some limitations. First, MSM definition was based on self-identification of sexual preference instead of behavior, because information on the sex of the sex partners was unavailable. Second, relatively small numbers of MSM were included per PASSYON study round, resulting in limited power to detect possible trends. Last, we only had data from young MSM up to 24 years of age with 3.5% being HIV positive. We cannot extrapolate the results to older MSM visiting SHCs or MSM populations with a higher HIV prevalence. Whether prophylactic HPV

Table 1
Characteristics of the MSM over all PASSYON study years and the relation with high-risk HPV DNA positivity.

	Total study population (N = 575)	Penile high-risk HPV[a] (N = 567)		Anal high-risk HPV[a] (N = 463)	
	N (%)	% positive (95% CI)	p value	% positive (95% CI)	p value
Overall		20.3 (17.2–23.8)		36.7 (32.5–41.2)	
Age			0.09		0.11
16- to 18-years	51 (8.9)	8.0 (3.2–18.8)		30.2 (18.6–45.1)	
19- to 20-years	143 (24.9)	18.0 (12.5–25.2)		28.9 (21.4–37.9)	
21- to 22-years	177 (30.8)	22.2 (16.7–28.9)		42.3 (34.4–50.7)	
23- to 24-years	204 (35.5)	23.3 (18.0–29.6)		39.1 (32.0–46.6)	
Self-defined ethnicity			0.53		<0.01
Dutch	476 (82.9)	19.8 (16.5–23.7)		33.1 (28.6–37.9)	
Not Dutch	98 (17.1)	22.7 (15.5–32.0)		55.1 (44.1–65.7)	
Education level[b]			0.83		<0.01
Low	190 (33.1)	19.8 (14.7–26.1)		45.7 (38.0–53.6)	
High	384 (66.9)	20.6 (16.8–24.9)		32.5 (27.5–37.9)	
Self-reported sexual preference			0.70		0.56
Homosexual	483 (84.0)	20.0 (16.6–23.8)		37.2 (32.6–42.0)	
Bisexual	92 (16.0)	21.7 (14.5–31.2)		33.3 (22.7–45.9)	
Age sexual debut			0.76		0.02
≤14 years[c]	85 (14.9)	21.4 (14.0–31.3)		31.9 (22.1–43.6)	
15- to 16-years	202 (35.4)	22.1 (16.9–28.4)		40.6 (33.4–48.2)	
17- to 18 years	184 (32.2)	19.3 (14.2–25.7)		41.7 (33.9–49.8)	
19- to 24-years	100 (17.5)	17.2 (11.0–25.8)		23.2 (15.4–33.4)	
Sex partners, past 6 months			0.08		0.07
0–1 partners	106 (18.5)	15.5 (9.8–23.8)		28.6 (20.0–39.0)	
2–3 partners	191 (33.3)	18.1 (13.2–24.2)		35.4 (28.1–43.5)	
4–6 partners	148 (25.8)	19.9 (14.2–27.1)		35.4 (27.7–44.1)	
≥7 partners[c]	129 (22.5)	27.9 (20.9–36.2)		46.7 (37.6–56.1)	
Lifetime sex partners			<0.01		<0.01
≤5 partners	111 (19.8)	10.2 (5.8–17.3)		16.3 (10.0–25.5)	
6–9 partners	85 (15.1)	11.8 (6.5–20.3)		33.3 (23.2–45.3)	
10–19 partners	128 (22.8)	23.0 (16.5–31.1)		42.9 (33.5–52.7)	
20–39 partners	124 (22.1)	22.0 (15.5–30.1)		38.1 (29.4–47.6)	
≥40 partners[c]	114 (20.3)	29.2 (21.6–38.2)		49.0 (39.3–58.7)	
Insertive anal sex, past 6 months			0.02		0.05
No	154 (26.9)	14.0 (9.3–20.5)		29.3 (22.0–37.8)	
Yes	419 (73.1)	22.7 (18.9–26.9)		39.3 (34.3–44.6)	
Receptive anal sex, past 6 months			0.79		<0.01
No	143 (25.0)	19.6 (13.9–26.8)		24.7 (16.9–34.6)	
Yes	430 (75.0)	20.6 (17.0–24.7)		39.5 (34.7–44.6)	
Notified[d]			0.75		0.22
No	479 (83.6)	20.6 (17.2–24.5)		35.5 (30.9–40.5)	
Yes	94 (16.4)	19.1 (12.5–28.3)		42.7 (32.5–53.5)	
STI-related symptoms[d]			0.92		0.03
No	451 (78.7)	20.3 (16.8–24.3)		34.3 (29.6–39.3)	
Yes	122 (21.3)	20.7 (14.4–28.7)		46.0 (36.6–55.7)	
Previous STI			<0.01		<0.01
No	269 (46.9)	15.8 (11.9–20.7)		27.2 (21.6–33.6)	
Yes	229 (39.9)	28.2 (22.7–34.4)		48.4 (41.5–55.5)	
Never tested	76 (13.2)	12.2 (6.5–21.5)		31.3 (21.2–43.4)	
Current STI[d,e]			0.72		<0.01
No	478 (83.4)	20.1 (16.7–23.9)		33.2 (28.7–38.1)	
Yes	95 (16.6)	21.7 (14.5–31.2)		53.8 (42.9–64.3)	
HIV infection[d]			0.23		<0.01
No	502 (96.5)	19.8 (16.5–23.5)		34.0 (29.5–38.8	
Yes	18 (3.5)	33.3 (16.3–56.3)		83.3 (60.8–94.2)	
Condom use with casual partners, past 6 months[f]			0.66		0.28
Inconsistent	124 (21.6)	17.4 (11.6–25.1)		35.1 (26.3–45.0)	
Consistent	382 (66.4)	21.2 (17.3–25.6)		38.9 (33.6–44.5)	
No casual partners	69 (12.0)	20.6 (12.7–31.6)		28.3 (18.5–40.8)	

Totals vary because of missing values.
Abbreviations: HPV: human papillomavirus; MSM: men who have sex with men; STI: sexually transmitted infection; 95% CI: 95% confidence interval.
[a] Being DNA positive for HPV16/18/31/33/35/39/45/51/52/56/58/59.
[b] High educational level included school of higher general secondary education, pre-university education, university of applied sciences, and university. Low/middle educational level included all other levels of education.
[c] The minimum reported age at sexual debut was 8. The maximum number of reported sex partners in the past six months was 100 and lifetime 900.
[d] Based on the visits at the sexual health center.
[e] Including chlamydia, gonorrhea, and syphilis.
[f] Inconsistent included reporting never, rarely and "sometimes I do, sometimes I do not" condom use. Consistent included reporting often or always condom use.

vaccination of HIV positive MSM would be effective is still unclear; an RCT to study the vaccine efficacy among HIV infected adults aged 27 years or older was ended prematurely due to lack of effectiveness [27].

No significant declining trends were observed in the HPV16/18 prevalence among MSM in the aftermath of girls-only HPV16/18 vaccination. Given that a declining trend in the HPV16/18 prevalence was observed among heterosexual men in the PASSYON

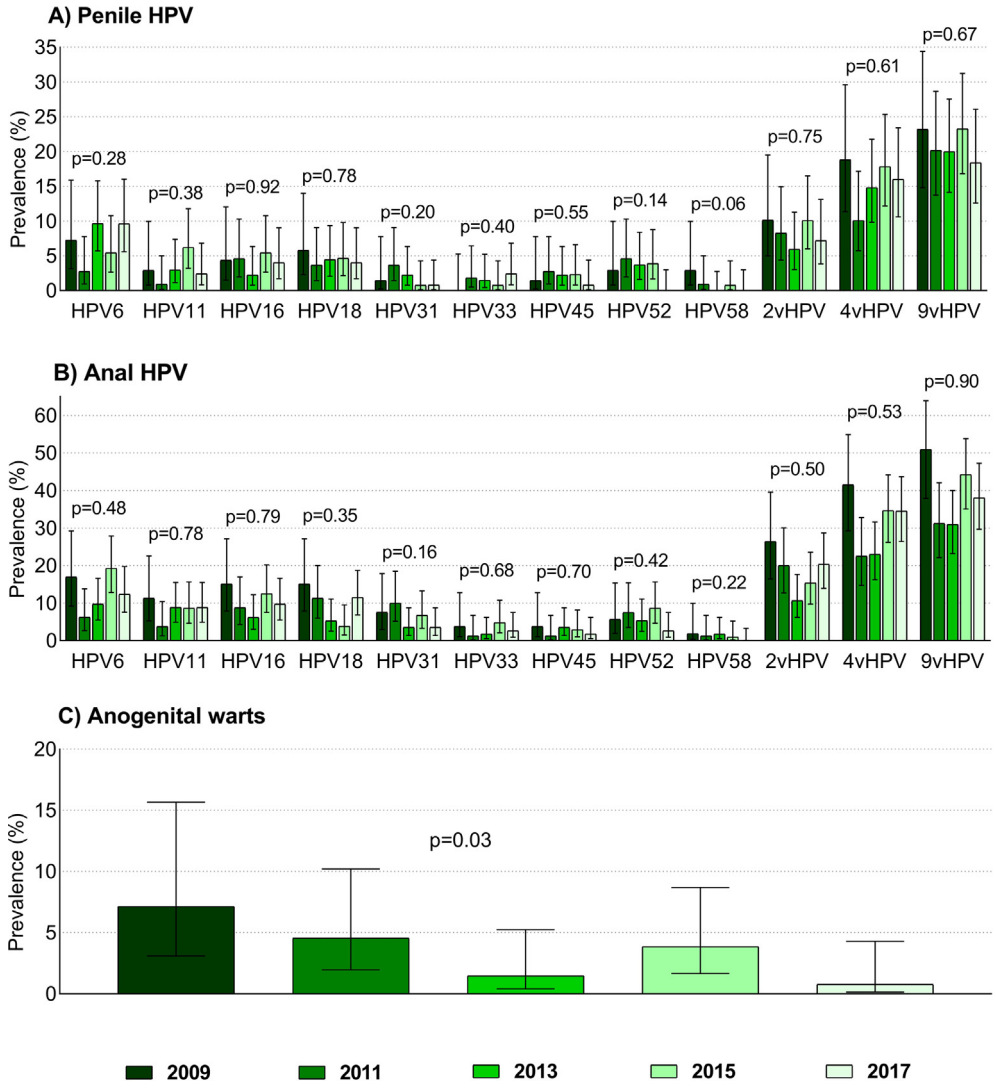

Fig. 1. Prevalence of penile and anal HPV DNA and anogenital warts among MSM over time and the crude trend.
Notes: the p value presents the Cochran-Armitage Trend Test. The y-axis differs for the different outcomes. For (A) penile HPV, in total 567 MSM were included; 69 in 2009, 109 in 2011, 135 in 2013, 129 in 2015, and 125 in 2017. For (B) anal HPV, in total 463 MSM were included; 53 in 2009, 80 in 2011, 113 in 2013, 104 in 2015, and 113 in 2017. For (C) anogenital warts, in total 575 MSM were included; 71 in 2009, 110 in 2011, 136 in 2013, 130 in 2015, and 128 in 2017. Abbreviations: 2vHPV: bivalent HPV vaccine types (HPV16/18); 4vHPV: quadrivalent HPV vaccine types (HPV6/11/16/18); 9vHPV: nonavalent HPV vaccine types (HPV6/11/16/18/31/33/45/52/58); HPV: human papillomavirus; MSM: men who have sex with men.

study (35% decline in a six year period) [11], the lack of a noticeable trend among MSM in an eight year period indicates that MSM are unlikely to benefit to a large extent from herd protection from girls-only vaccination. We did observe a declining trend in the AGW prevalence, presumably as a result of changes in the policy of the SHCs; persons with AGW were more often referred to the general practitioner in recent years [28]. The declining trend is likely not a result of herd protection as the current vaccination program for girls does not include vaccination against HPV6/11, the main causes of AGW [5].

In contrast to what is often assumed, our study shows that many young MSM visiting SHCs are HPV DNA negative and seronegative for the vaccine-targeted types, at least until the age of 24 years. For two-thirds of the MSM there was no evidence of current or past infection with both HPV16 and HPV18 at the penile as well as the anal site, suggesting that vaccination could still be beneficial. Note that this definition of negativity based on DNA and serostatus (negative for all measures for both HPV vaccine types) is more stringent than used in the RCT's per-protocol definition where negativity was defined as being DNA negative at the anatomic location and HPV type under study and seronegative for the HPV type under study [18,19]. Therefore, the proportion of MSM to experience vaccine-induced protection similar to the per-protocol efficacy demonstrated in RCTs will likely exceed two-thirds of 16- to 24-year-old MSM. If one is positive at one anatomical site, vaccination could possibly still prevent infections at the other site and if one is positive for only one type included in the vaccine, vaccination could still be effective in preventing infections with the other type(s) [29]. All MSM were negative for at least one of the 2vHPV types at one or more anatomical sites, indicating that all MSM could derive at least partial benefit from vaccination. Focusing on HPV16, by far the most oncogenic type in men, 98% of the MSM were DNA negative at one or more anatomical sites. Moreover, although vaccination does not have a therapeutic effect on infections prevalent at the time of vaccination, it might still prevent future infections [30]. In contrast to women, where the peak of infection is before the mid-twenties, many MSM will keep being exposed and infected during many

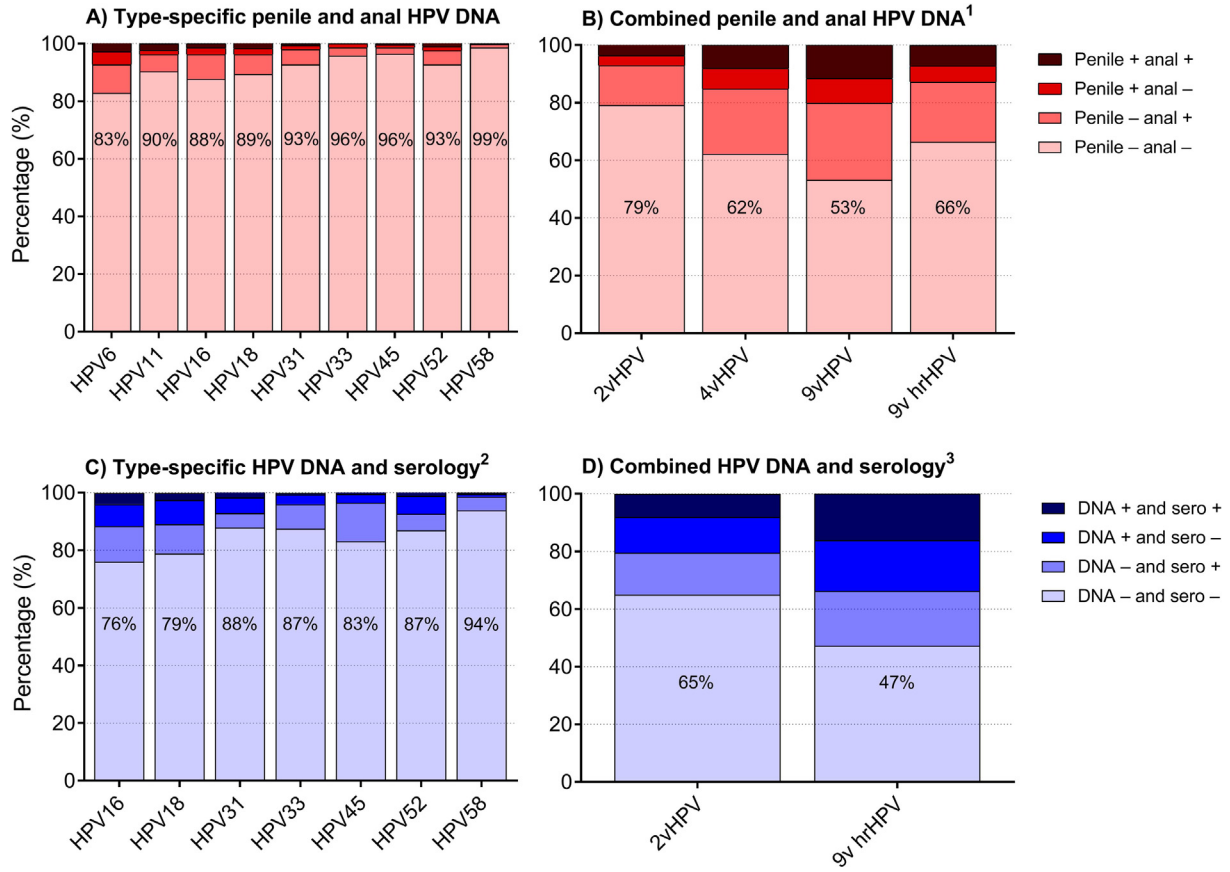

Fig. 2. Percentage of MSM who were DNA negative (panel A en B) and seronegative (panel C and D) for the vaccine-targeted HPV types.
Notes: For panel A and B, all MSM with both swabs available were included (n = 455). For panel C and D, all MSM with both swabs and serum available were included (n = 421). Abbreviations: 2vHPV: bivalent HPV vaccine types (HPV16/18); 4vHPV: quadrivalent HPV vaccine types (HPV6/11/16/18); 9vHPV: nonavalent HPV vaccine types (HPV6/11/16/18/31/33/45/52/58); 9v hrHPV: high-risk nonavalent HPV vaccine types (HPV16/18/31/33/45/52/58); HPV: human papillomavirus; MSM: men who have sex with men. 1 Negative was definied as being negative for all the types. Positivity was definied as being positive for ≥1 type. 2 DNA negative was defined as being negative in the penile as well as the anal swab, DNA positive was defined as being positive in ≥1 swab. Seropositivity was based on the predefined type-specific cut-off levels. 3 DNA negative was defined as being negative for all the types in the penile as well as the anal swab, DNA positive was defined as being positive for ≥1 type in ≥1 swab. Seronegative was defined as being seronegative for all types, seropositivity was definied as being seropositive for ≥1 type based on the predefnied type-specific cut-off levels.

years of their lifetime [31]. Thus, as the risk of HPV acquisition does not diminish with age, vaccinating MSM at older age is still likely to be beneficial.

One of the inclusion criteria of the RCT where efficacy of HPV vaccination among MSM has been demonstrated, was having 1–5 lifetime sex partners [18,19]. Of the MSM in our study, 80% had six or more partners and 20% even 40 or more. Despite these high numbers of partners, we observed a low type-specific (sero)prevalence for the various vaccine types. It could be that MSM without evidence of HPV exposure were previously infected but cleared the infection without seroconversion [32] or had a latent infection [33]. Prophylactic vaccination probably has no effect on latent infections and one could argue that MSM who previously cleared an infection are able to also clear a future infection, diminishing an additional benefit of vaccination. However, chance could play an important role in clearance [34] and build-up of (long lasting) natural immunity in men is not apparent from epidemiological data [35,36]. Moreover, viral persistence and oncogenic potential might differ between different variants of the same HPV type [37]. Therefore, even if an MSM already cleared an infection, there is still a risk of acquiring a persistent infection in the future. Future research should focus on the role of latency and of clearance in relation to prior exposure, and how these factors could affect vaccine effectiveness when offering HPV vaccination to MSM with high numbers of lifetime sex partners.

The antibody concentration among MSM increased only slightly with age and number of lifetime partners; even among those with over 40 partners, the majority was not yet seropositive. The median HPV16- and HPV18-specific antibody concentrations among MSM with over 40 partners were also considerably lower than among vaccinated women in the PASSYON study (0.62 and 1.41, compared to 7.61 and 6.94 Ln LU/mL, respectively) [38]. In another study among MSM with a median age of 40 years, HPV16/18 antibody concentrations of over 6.2 Ln LU/mL (i.e. > 500 LU/mL) were not associated with a lower acquisition of anal or penile HPV infections over a 12-month period [35]. Vaccination could increase the antibody concentration of MSM, even among those previously exposed, up to levels affording protection against subsequent infections.

Taken together, even though the vaccine effectiveness among MSM with a high number of sex partners is not clear-cut, it is likely that many young MSM visiting SHCs in the Netherlands could still benefit from HPV vaccination given the high proportions of HPV (sero)negativity for the relevant vaccine types and the likely limited build-up of natural immunity. This was also suggested in previous research [39–42]. Various modeling studies have indicated that targeted prophylactic vaccination for sexually active MSM could also be a (cost) effective strategy on a population-level [17,43], including a recent study using the context of the Netherlands [16]. The HPV16 prevalence in our study was in line with

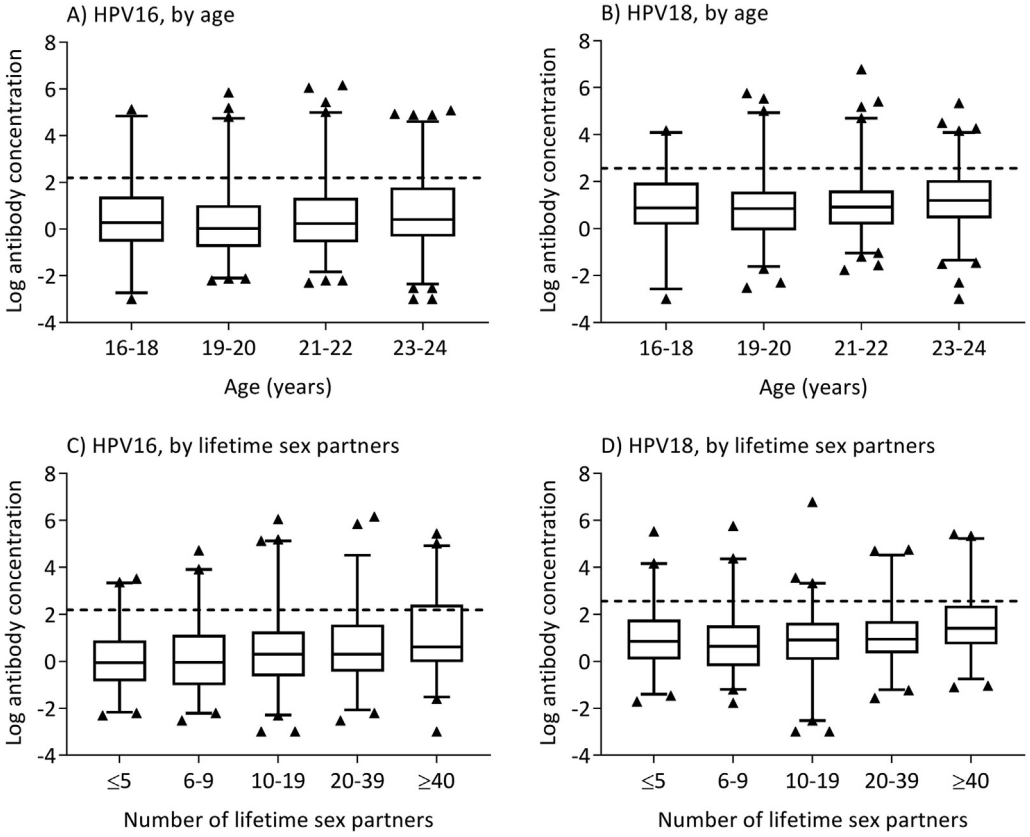

Fig. 3. Log antibody concentration for HPV16 and HPV18 by age and number of lifetime sex partners.
Notes: Abbreviations: HPV: human papillomavirus. The dashed line represents the type-specific pre-defined cut-off level for seropositivity. The maximum number of reported lifetime sex partners was 900. The error bars represent the 2.5th and 97.5th percentiles.

the predicted penile and anal HPV16 prevalence among MSM in that modeling study. However, projected reductions in HPV16 prevalence were strongly reduced if no effectiveness was assumed in MSM with prevalent infection at the time of vaccination. Because vaccination is most effective before HPV exposure and HPV positivity increases with lifetime number of partners, it is desirable to vaccinate MSM as early as possible. While our data suggest that vaccination might be effective for the population of 16- to 24-year-old MSM who visit a SHC, vaccination is preferably offered at the initial SHC visit. In our study, 13% reported never being tested for STIs indicating this was their first visit; the other MSM (87%) had possibly visited the SHC in the past. HPV vaccination may also be beneficial for MSM not visiting SHCs; those are more difficult to target, but might be reached via the GP or snowball sampling through MSM who do visit SHCs.

5. Conclusions

This study did not find evidence for declines in the prevalence of HPV vaccine types among MSM, indicating that they are unlikely to benefit to a large extent from herd effects from girls-only vaccination. Moreover this study shows that many young MSM visiting SHCs are HPV DNA negative and seronegative for the relevant vaccine types, indicating they could still benefit from HPV vaccination. Targeted MSM vaccination might be considered and SHCs could play an important role in promoting HPV vaccination to young MSM.

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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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.03.002.

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