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Effectiveness of bivalent and quadrivalent human papillomavirus vaccination in Luxembourg

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ABSTRACT

Background: In Luxembourg, the human papillomavirus (HPV) vaccination program introduced in 2008, provided either bivalent (BV) or quadrivalent (QV) vaccines to girls aged 12–17 years. Here, we estimate the effectiveness of BV and QV vaccines combined and separately in reducing type-specific HPV prevalence eight years after the introduction of the vaccination program.

Methods: A cross-sectional prevalence study was conducted among women aged 18–29 years in 2015-2017. Seven hundred sixteen participants were recruited at family planning centres or private gynaecology practices in Luxembourg. Vaccination records were verified in the social security database. Cervical samples were tested using the Anyplex II HPV28 assay. Vaccine effectiveness was estimated using logistic regression.

Results: In total, 363/716 (50.7%) participants were HPV positive with any HPV and 209/716 (29.2%) with carcinogenic HPV genotypes. HPV vaccination offered high protection against HPV16/18 (adjusted odds ratio (AOR) = 0.13; 95% CI 0.03-0.63), HPV6/11 (AOR = 0.16; 95% CI 0.05-0.48) and cross-protection against HPV31/33/45 (AOR = 0.41; 95% CI 0.18-0.94). The AORs were generally enhanced when only considering vaccination before sexual debut corresponding to AORs: 0.05 (95% CI 0.00-0.88), 0.08 (95% CI 0.02-0.36) and 0.20 (0.06-0.65) against HPV16/18, HPV6/11 and HPV31/33/45, respectively. We observed significant protection against carcinogenic genotypes included in nonavalent vaccine for BV (AOR = 0.29; 95% CI 0.13-0.67), but not for QV (AOR = 0.81; 95% CI 0.47–1.40) (heterogeneity Chi^2 P = 0.04).

Conclusions: Our study suggests high effectiveness of HPV vaccination against HPV6/11, HPV16/18 and a cross-protection against HPV31/33/45. Vaccination effectiveness was slightly higher for women vaccinated before sexual debut.

1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted pathogen worldwide and the principal cause of cervical cancer [1]. HPV genotypes have been classified into three groups according to their oncogenic potential; carcinogenic group 1 (16/18/31/33/35/39/45/51/52/56/58/59), probable/possible carcinogenic group 2 (26/30/34/53/66/67/68/69/70/73/82/85/97) and group 3 (6/11 and others not classifiable as carcinogenic to humans) [2]. Genotypes 16/18 are responsible for 72% and genotypes 31/33/45/52/58 for an additional 18% of HPV-related cancers [3]. Genotypes 6/11 account for 90% of genital wart cases [4].

Three prophylactic HPV vaccines are currently available: bivalent vaccine (BV) protecting against genotypes 16/18, quadrivalent vaccine (QV) protecting against genotypes 6/11/16/18, and nonavalent vaccine protecting against genotypes 6/11/16/18/31/33/45/52/58. By

Abbreviations: AGC-NOS, atypical glandular cells not otherwise specified; AOR, adjusted odds ratios; ASC-H, atypical squamous cells of undetermined significance in which a high-grade squamous intraepithelial lesion cannot be excluded; ASC-US, atypical squamous cells of undetermined significance; BV, bivalent vaccine; HPV, Human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions; NILM, negative for intraepithelial lesions and malignancies; QV, quadrivalent vaccine; VE, vaccine effectiveness

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February 2019, 92 countries or territories had introduced HPV vaccination programmes distributing over 270 million vaccine doses during the last decade [5,6]. A significant reduction in the prevalence of vaccine-related and non-vaccine genotypes has been reported in vaccine trials and observational studies [7–12]. HPV vaccines have been proven to be effective against cervical lesions and genital warts and have thus the potential to prevent cervical and anogenital HPV-related cancers [12–16].

In Luxembourg, the national HPV vaccination programme was introduced in 2008, offering the choice of either BV or QV vaccine to 12–17 year old girls free of charge. The vaccines were delivered by private physicians with the three-dose schedule over a 6-month interval. In 2015, the vaccination schedule changed offering only two doses of BV vaccine separated by 6 months [17]. In previous work we showed that overall vaccination coverage with at least one dose was moderately high in Luxembourg, reaching 62% of women born between 1991 and 2003 [17].

The primary aim of this study was to estimate the effectiveness of the HPV vaccination programme in Luxembourg 8 years after implementation based on HPV prevalence in vaccinated and unvaccinated women. The secondary aim was to estimate the effectiveness of bivalent and quadrivalent vaccines separately. To our knowledge, this is one of the first studies assessing the effectiveness of BV and QV vaccines in the same population setting.

2. Methods

2.1. Study design and epidemiological data collection

A cross-sectional prevalence study was conducted from November 2015 until December 2017 in Luxembourg. Women, attending regular cervical cancer screening or seeking sexual health service at family planning centres (http://www.planningfamilial.lu/) or private gynaecology practices were recruited if they were sexually active and belonged to the age group 18–29 years. Participants signed an informed consent form and completed a questionnaire on vaccination status and sexual behaviour (Supplement 1). To ascertain vaccination status, vaccination records consisting of vaccination dates and type of vaccine (BV or QV) were obtained from the social security database and linked with the self-reported questionnaire, HPV test and cytology results using unique national personal identifiers. Vaccination status was defined in four categories as follows: unvaccinated (no evidence of vaccination according to questionnaire and social security records), vaccinated with at least two BV doses verified by social security records, vaccinated with at least two QV doses verified by social security records and other vaccinated (i.e. self-report only, one verified dose only or different vaccine types according to social security records). The vaccinated category included participants who received at least two doses of BV or QV vaccines regardless of the interval between the doses and vaccination age. Only 10% of the participants were vaccinated with 2 doses above the recommended vaccination age (range 15–18 years) or having a between dose interval lower than 6 months.

2.2. Cytology

Cervical samples were collected by gynaecologists with a cervical broom and placed in a vial containing PreservCyt medium for liquid-based cytology according to European Guidelines [18]. Samples were examined according to the ThinPrep Pap Test and Imaging System (Hologic, Bedford, MA, USA) and interpreted according to the Bethesda 2001 nomenclature: negative for intraepithelial lesions and malignancies (NILM), atypical squamous cells of undetermined significance (ASC-US), atypical glandular cells not otherwise specified (AGC-NOS), low-grade squamous intraepithelial lesions (LSIL), atypical squamous cells of undetermined significance, in which a high-grade squamous intraepithelial lesion cannot be excluded (ASC-H), and high-grade squamous intraepithelial lesions (HSIL) [19].

2.3. HPV genotyping

DNA extraction from ThinPrep samples was performed using the QIAamp DNA mini kit according to the manufacturer's instructions (Qiagen, Hilden, Germany) [20]. HPV detection and genotyping were performed with the Anyplex II HPV28 assay (Seegene, Seoul, South Korea) based on a pilot study, which is based on multiplex real-time PCR targeting L1 gene [21]. The Anyplex II HPV28 assay simultaneously detects and identifies 28 HPV genotypes including all of the carcinogenic and probable/possibly carcinogenic genotypes [2]. Amplification was performed in two multiplex reactions on a CFX96 real-time thermocycler (Bio-Rad, Hercules, CA; 5 µL input volume for both multiplex reaction). Data recording and interpretation (automated with the Seegene viewer software) were performed according to the manufacturer instructions [21].

2.4. Statistical analysis

Statistical analysis was performed using STATA 14 (College Station, Texas, USA). Differences between proportions were assessed by Pearson's Chi^2 test. We used stepwise logistic regression analysis to evaluate the association between potential risk/protective factors and HPV infection. As HPV infection with any type was significantly associated with the number of lifetime sexual partners and last partnership duration ($p < 0.05$), these variables were controlled for in the multivariable logistic regression model to study the effect of vaccination status on HPV prevalence. Although age was not significantly associated with HPV in the stepwise logistic regression, we included the variable in the main analysis, since it is a strong epidemiological predictor of HPV infection [22]. We studied the effect of each vaccine separately and of HPV vaccination jointly. Adjusted odds ratios (AOR) estimated from the logistic regression model were used to calculate vaccine effectiveness (VE) as follows: VE = (1-AOR) * 100 [8,23,24]. Missing values were included in the model as a separate category.

3. Results

3.1. Characteristics of study participants

Overall 716 female study participants with a mean age of 22.3 years were recruited, of which 654 (91.3%) at family planning and 62 (8.7%) at private gynaecology practices. Four hundred seven (56.8%) were Luxembourgish, 188 (26.3%) had Portuguese nationality and 121 (16.9%) had other nationalities reflecting the population composition of this age group in Luxembourg [25]. The mean age at sexual debut was 16.7 years, and 531 (76.5%) of 694 participants reported more than one lifetime sexual partner. The characteristics of the study population by vaccination status are presented in Table 1.

3.2. Vaccination status

Overall, 401 (56.0%) participants reported having been vaccinated, 248 (34.6%) reported to be unvaccinated and 67 (9.4%) did not know their vaccination status. Vaccination with at least two doses of the same vaccine was verified in the social security database for 347 (48.5%) participants corresponding to 86.4% of women who reported to be vaccinated. Among the 347 vaccinated women with two verified doses of the same vaccine, 131 (37.8%) were vaccinated with BV and 216 (62.2%) were vaccinated with QV. An additional 137 (19.1%) of participants had some evidence of vaccination (self-report or vaccine dose recorded), but two doses of the same vaccine could not be verified in the social security database, including 32 (4.5%) participants with a single dose or two doses with different vaccines (Table 2).

The proportion of participants who received three doses did not differ significantly ($p = 0.879$) between BV (115/131, 87.8%) and QV recipients (185/216, 85.6%). Similarly, the proportion of participants

Table 1
Characteristics of study population by vaccination status.

	Total N (col %)	Unvaccinated N (col %)	Other vaccinated N (col %)	P-value[a]	BV N (col %)	P-value	QV N (col %)	P-value
Total	716	232 (32.4)	137 (19.1)		131 (18.3)		216 (30.2)	
Vaccinated before sexual debut					97 (74.0)		162 (75.0)	
Age				< 0.001		< 0.001		< 0.001
18-20	244 (34.1)	34 (14.7)	50 (36.5)		71 (54.2)		89 (41.2)	
21-23	234 (32.7)	65 (28.0)	39 (28.5)		43 (32.8)		87 (40.3)	
24+	238 (33.2)	133 (57.3)	48 (35.0)		17 (13.0)		40 (18.5)	
Mean age (range)	22.3 (18-29)	24.2 (18-29)	22.2 (18-29)	< 0.001	20.6 (18-26)	< 0.001	21.3 (18-26)	< 0.001
Nationality				0.120		0.244		< 0.001
Luxembourgish	407 (56.8)	129 (55.6)	61 (44.5)		75 (57.3)		142 (65.7)	
Portuguese	188 (26.3)	54 (23.3)	40 (29.2)		37 (28.2)		57 (26.4)	
Other	121 (16.9)	49 (21.1)	36 (26.3)		19 (14.5)		17 (7.9)	
Language				0.191		0.298		0.068
French	503 (70.3)	151 (65.1)	99 (72.3)		93 (71.0)		160 (74.1)	
German	152 (21.2)	57 (24.6)	23 (16.8)		28 (21.4)		44 (20.4)	
Others	61 (8.5)	24 (10.3)	15 (10.9)		10 (7.6)		12 (5.5)	
Age of sexual debut								
< 16	178 (24.9)	61 (26.3)	28 (20.4)	0.136	31 (23.7)	0.008	58 (26.9)	0.144
16-17	329 (46.0)	89 (38.4)	67 (48.9)		72 (55.0)		101 (46.8)	
≥18	197 (27.5)	76 (32.8)	39 (28.5)		27 (20.6)		55 (25.5)	
Mean age (range)	16.7 (12-29)	16.9 (12-26)	16.8 (13-29)	0.728	16.4 (13-21)	0.036	16.5(12-24)	0.037
Lifetime sexual partners				0.011		< 0.001		< 0.001
0-2	307 (42.9)	72 (31.0)	58 (42.3)		68 (51.9)		109 (50.5)	
3-4	213 (29.8)	69 (29.7)	45 (32.9)		40 (30.5)		59 (27.3)	
≥5	174 (24.3)	84 (36.2)	30 (21.9)		20 (15.3)		40 (18.5)	
Duration with last partner in years				0.465		0.065		0.712
0-1	267 (37.3)	82 (35.3)	51 (37.2)		56 (42.8)		78 (36.1)	
2-3	186 (26.0)	54 (23.3)	40 (29.2)		34 (26.0)		58 (26.9)	
≥4	186 (26.0)	68 (29.3)	35 (25.6)		24 (18.3)		59 (27.3)	
Mean duration in years (range)	2.7 (0-13)	3.0 (0-13)	2.8 (0-11)	0.524	2.3 (0-10)	0.036	2.6 (0-9)	0.165
Last partner age				0.001		< 0.001		< 0.001
< 21	183 (25.6)	35 (15.1)	38 (27.7)		52 (39.7)		58 (26.9)	
22-25	273 (38.1)	74 (31.9)	51 (37.2)		52 (39.7)		96 (44.4)	
≥26	236 (33.0)	115 (49.6)	45 (32.9)		20 (15.3)		56 (25.9)	
Mean age (range)	24.3 (16-45)	26.0 (16-45)	24.1 (16-41)	< 0.001	22.4 (17-36)	< 0.001	23.7 (16-37)	< 0.001
Absolute age difference with last partner in years				0.240		0.259		0.998
0-1	290 (40.5)	89 (38.4)	63 (46.0)		55 (42.0)		83 (38.4)	
2-3	197 (27.5)	62 (26.7)	38 (27.7)		39 (29.8)		58 (26.9)	
≥4	205 (28.6)	73 (31.5)	33 (24.1)		30 (22.9)		69 (31.9)	
Mean absolute difference (range)	2.8 (0-18)	3.0 (0-18)	2.6 (0-17)	0.274	2.4 (0-13)	0.039	2.9 (0-14)	0.755
Condom use				0.825		0.874		0.367
Never	184 (25.8)	57 (24.7)	38 (27.9)		32 (24.4)		57 (26.4)	
Sometimes	277 (38.8)	96 (41.6)	58 (42.7)		50 (38.2)		73 (33.8)	
Often	138 (19.3)	44 (19.0)	22 (16.2)		26 (19.9)		46 (21.3)	
Always	115 (16.1)	34 (14.7)	18 (13.2)		23 (17.6)		40 (18.5)	
Smoking status				0.327		0.904		0.089
Never	448 (62.6)	141 (60.8)	77 (56.2)		82 (62.6)		148(68.5)	
Sometimes	69 (9.6)	23 (9.9)	16 (11.7)		10 (7.6)		20 (9.3)	
Often	41 (5.7)	18 (7.8)	6 (4.4)		11 (8.4)		6 (2.8)	
Daily	158 (22.1)	50 (21.5)	38 (27.7)		28 (21.4)		42 (19.4)	

Abbreviations: BV, bivalent vaccine; QV, quadrivalent vaccine;
P-values are reported comparing each category (BV, QV and other vaccinated) to unvaccinated category using Chi^2 test. Mean values were compared using t-test. Missing values were excluded from the analysis. Data are no. (%) of participants, unless otherwise indicated.

Table 2
Comparison of self-reported and verified vaccination status from the social security database among study participants.

Self-reported vaccination status			Vaccination status from social security database Verified vaccinated		
	Unvaccinated N (%)	Other vaccinated N (%)	BV N (%)	QV N (%)	Total
Unvaccinated	232 (100)	6 (4.4)	4 (3.1)	6 (2.8)	248 (34.6)
Unknown vaccination status	0 (0)	48 (35.0)	10 (7.6)	9 (4.2)	67 (9.4)
vaccinated with QV	0 (0)	24 (17.5)	2 (1.5)	93 (43.0)	119 (16.6)
vaccinated with BV	0 (0)	13 (9.5)	60 (45.8)	3 (1.4)	76 (10.6)
Vaccinated, unknown type	0 (0)	46 (33.6)	55 (42.0)	105 (48.6)	206 (28.8)
Total	232 (100)	137 (100)	131 (100)	216 (100)	716 (100)

Abbreviations: BV, bivalent vaccine; QV, quadrivalent vaccine;

who started vaccination before sexual debut did not differ significantly (p = 0.940) between BV (97/131, 74%) and QV recipients (162/216, 75%).

3.3. HPV prevalence

In total, 363 (50.7%) participants were positive for at least one of the 28 HPV genotypes tested and 199 (27.8%) were infected with more than one genotype. HPV prevalence was similar (p = 0.334) in verified 2-dose vaccinated women (161/347, 46.4%) as in unvaccinated women (124/232, 53.5%). HPV prevalence was similar (p = 0.434) between verified 2-dose recipients of BV (55/131, 42%) and QV (106/216, 49.1%) (Supplementary Table 1). The average number of HPV genotypes per participant was significantly lower in verified 2-dose recipients of BV (0.78) than in recipients of QV (1.11, p = 0.035) or than in unvaccinated participants (1.15, p = 0.016). In total, 773 genotypes were detected with 1.08 average number of genotypes per participants.

Prevalence of 12 carcinogenic (group 1) genotypes was 209 (29.2%). We did not observe a significant difference (p = 0.347) in the prevalence of carcinogenic genotypes in verified 2-dose vaccinated women (91/347, 26.2%) and unvaccinated women (72/232, 31%). The prevalence of carcinogenic types also did not differ (p = 0.229) between BV (29/131, 22.1%) and QV recipients (62/216, 28.7%). The average number of carcinogenic HPV genotypes per participant was significantly lower in verified 2-dose recipients of BV (0.28) than in unvaccinated participants (0.45, p = 0.030), but not compared to verified 2-dose recipients of QV (0.39, p = 0.070).

The three most frequently observed carcinogenic genotypes in vaccinated women were 51 (6.3%), 59 (6.3%) and 58 (5.5%) compared to 16 (6.9%), 51 (6.9%), 31 (6.5%) in unvaccinated women (Fig. 1, Supplementary Tables 1 and 2). Crude type-specific prevalences of genotypes 16, 31 and 33 (p < 0.05) were significantly lower in vaccinated compared to unvaccinated participants (Supplementary Tables 1 and 2).

3.4. Cytological results

Two samples could not be analysed due to unsatisfactory specimen quality. Prevalence of cytological abnormalities was as follows; 23/714 (3.2%) ASC-US, 41/714 (5.7%) LSIL, 1/714 (0.1) ASC-H, 1/714 (0.1%) HSIL, and 648/714 (90.8%) were negative for abnormal lesions. No significant difference of abnormal lesions (ASCUS+) was observed between vaccinated and unvaccinated populations (p = 0.293) (Supplementary Table 3).

3.5. Effectiveness of HPV vaccination and sexual debut

After controlling for sexual activity and age the protection induced by two doses of the same vaccine against infection with genotypes 16/18 and 6/11 was 0.13 (95% CI 0.03-0.63) and 0.16 (95% CI 0.05-0.48), respectively (Table 3). We observed significant cross-protection against genotypes 31/33/45 (AOR = 0.41; 95% CI 0.18-0.94) in verified 2-dose recipients. The AOR associated with carcinogenic genotypes not included in the nonavalent vaccine (35/39/51/56/59) was marginally non-significant (AOR = 1.65; 95% CI 0.97–2.81). The corresponding AORs were generally enhanced when only considering vaccination before sexual debut: 0.05 (95% CI 0.00-0.88), 0.08 (95% CI 0.02-0.36), 0.20 (95% CI 0.06-0.65) against genotypes 16/18, 6/11 and 31/33/45, respectively.

There was no evidence of vaccination impact on other carcinogenic genotypes (35/39/51/52/56/58/59) not covered by vaccines and not cross-protection types (AOR = 1.35; 95% CI 0.85–2.14) (Table 3). Other type-specific AORs are presented in Supplementary Table 2.

3.6. BV and QV vaccine effectiveness

Protection against genotypes 16/18 was 0.19 (95% CI 0.02–1.62) and 0.10 (95% CI 0.01-0.82) for BV and QV vaccine recipients, respectively (Table 4). Significant protection against nonavalent vaccine types was 0.29 (95% CI 0.13-0.67) for BV recipients compared to 0.81 (95% CI 0.47–1.40) for QV (heterogeneity Chi^2 p = 0.031). There was no evidence of protection with ether vaccine against genotypes not covered by vaccines and not cross-protection types (35/39/51/52/56/58/59): BV (AOR = 1.04; 95% CI 0.58–1.87) and QV (AOR = 1.53; 95% CI 0.94–2.50) (Table 4). Type-specific AORs are presented in Supplementary Table 4.

4. Discussion

To our knowledge, our study is the first to provide type-specific HPV prevalence in Luxembourg and to estimate the effectiveness of BV and QV vaccines combined and separately in the same population. Our findings suggest that the vaccination programme already had a substantial impact on HPV genotype distribution in vaccinated young women 8 years after its introduction.

First, the prevalence of HPV types included in the vaccine and some other non-vaccine genotypes is lower in vaccinated young women independent of vaccine type. Our results suggest that VE against certain HPV genotypes not included in the vaccines (i.e. cross-protection) is higher in BV compared to QV recipients. In addition, the prevalence of nonavalent vaccine genotypes was significantly lower in BV compared to QV recipients (Supplementary Table 1). A Cochrane review also showed similar protection of BV and QV against cervical pre-cancers related to types 16/18, but BV offered better protection against cervical precancers overall [26]. Interestingly, immunogenicity studies reported significantly higher antibody levels against vaccine and non-vaccine types among BV recipients compared to QV [27–29].

Second, concerns have been raised that carcinogenic genotypes not

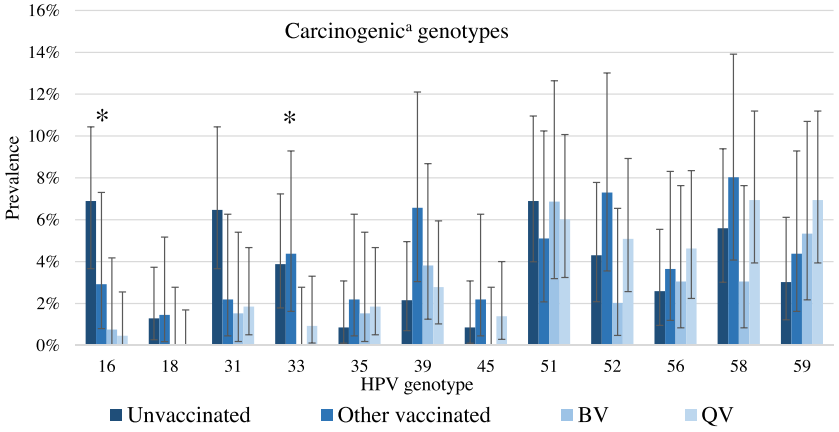

Fig. 1. Carcinogenic human papillomavirus prevalence (95%CI) by vaccination status.
Abbreviations: BV, bivalent vaccine; CI, confidence interval; QV, quadrivalent vaccine;
[a]12 HPV genotypes classified by International Agency for Research on Cancer as carcinogenic to humans.
*Individual HPV types significantly associated with vaccination status in logistic regression model.
(Supplementary Table 3).

Table 3
Association between human papillomavirus infection and verified 2-dose vaccination status, considering all vaccinations and vaccinations before sexual debut.

HPV types	HPV Prevalence N (%)			Adjusted[a] OR vaccinated vs unvaccinated		Adjusted OR vaccinated before sexual debut vs unvaccinated	
	Unvaccinated (N = 232)	Vaccinated all (N = 347)	Vaccinated before sexual debut (N = 259)	AOR (95%CI)	P-value	AOR (95%CI)	P-value
16/18	19 (8.2)	2 (0.6)	0 (0.0)	0.13 (0.03-0.63)	0.012	0.05 (0.00-0.88)	0.038
6/11	13 (5.6)	5 (1.4)	2 (0.8)	0.16 (0.05-0.48)	0.001	0.08 (0.02-0.36)	0.001
31/33/45[b]	25 (10.8)	11 (3.2)	4 (1.5)	0.41 (0.18-0.94)	0.034	0.20 (0.06-0.65)	0.007
nonavalent[c]	54 (23.3)	40 (11.5)	25 (9.7)	0.60 (0.34-1.02)	0.060	0.52 (0.29-0.94)	0.031
35/39/51/52/56/58/59[d]	49 (21.1)	86 (24.8)	63 (24.3)	1.35 (0.85-2.14)	0.204	1.33 (0.81-2.20)	0.263
35/39/51/56/59[e]	32 (13.8)	65 (18.7)	48 (18.5)	1.65 (0.97-2.81)	0.065	1.68 (0.94-2.98)	0.078

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval;
[a] OR adjusted for number of lifetime sexual partners, last partnership duration and age.
[b] Carcinogenic HPV genotypes, genetically related to HPV16/18.
[c] Carcinogenic HPV genotypes included in nonavalent vaccine.
[d] Carcinogenic HPV genotypes not included in BV/QV and not cross-protection types 31/33/45.
[e] Carcinogenic HPV genotypes not included in nonavalent vaccine.

Table 4
Association between human papillomavirus infections and verified 2-dose bivalent and quadrivalent vaccine recipients.

HPV types	HPV prevalence N (%)			Adjusted OR BV vs unvaccinated		Adjusted[a] OR QV vs unvaccinated		Heterogeneity test[f]
	Unvaccinated N = 232	BV N = 131	QV N = 216	AOR (95%CI)	P-value	AOR (95%CI)	P-Value	P-Value
16/18	19 (8.2)	1 (0.8)	1 (0.5)	0.19 (0.02-1.62)	0.130	0.10 (0.01-0.82)	0.032	0.686
6/11	13 (5.6)	2 (1.5)	3 (1.4)	0.16 (0.04-0.76)	0.022	0.15 (0.04-0.58)	0.006	0.949
31/33/45[b]	25 (10.8)	2 (0.5)	9 (4.2)	0.19 (0.04-0.88)	0.034	0.54 (0.23-1.27)	0.159	0.246
nonavalent[c]	54 (23.3)	8 (6.1)	32 (14.8)	0.29 (0.13-0.67)	0.004	0.81 (0.47-1.40)	0.443	0.041
35/39/51/52/56/58/59[d]	49 (21.1)	28 (21.4)	58 (26.9)	1.04 (0.58-1.87)	0.892	1.53 (0.94-2.50)	0.088	0.321
35/39/51/56/59[e]	32 (13.4)	23 (17.6)	42 (19.4)	1.47 (0.76-2.84)	0.250	1.75 (1.00-3.07)	0.052	0.693

[a] OR adjusted for number of lifetime sexual partners, last partnership duration and age.
[b] Carcinogenic HPV genotypes, genetically related to HPV16/18.
[c] Carcinogenic HPV genotypes included in nonavalent vaccine.
[d] Carcinogenic HPV genotypes not included in BV/QV and not cross-protection types 31/33/45.
[e] Carcinogenic HPV genotypes not included in nonavalent vaccine.
[f] Inter vaccine heterogeneity was assessed using Pearson Chi^2 test.

included in the vaccines could potentially replace the niche occupied by vaccine types [30]. In our study, we did not find a statistically significant difference in the prevalence of carcinogenic genotypes in vaccinees and non-vaccinees. Similarly, several vaccine monitoring studies and long-term follow-up of clinical trials have shown that HPV vaccines do not induce type replacement [24,31–34]. Pooled analysis of the Costa Rica and PATRICA trials evaluated 21,596 women (with 50% vaccination coverage of BV) suggested that type replacement is unlikely to occur in populations with low vaccination coverage. In addition, this study suggested protection against oncogenic HPV types 35, 52, 58, and 68/73, as well as non-oncogenic types 6 and 70 [33]. This is inconsistent with a meta-analysis by Mesher et al. reporting a significant increase of genotype 39 and 52 in the post-vaccination era [35] and a community-randomised trial by Gray et al. showing significantly increased prevalence ratio of genotypes 39 and 51 in BV recipients [32]. In both studies, results were inconsistent in different age groups and increases could have different explanations, therefore both studies reported no clear evidence of type-replacement. Another potential explanation of this phenomenon could be the so-called “unmasking” effect. It occurs when consensus primer PCR assays detect non-vaccine carcinogenic HPV genotypes (e.g. type 52) more frequently in absence of HPV16 or 18 due to primer competition [30,36]. However, Anyplex is a type-specific multiplex PCR not based on consensus primers and is therefore less prone to unmasking. During the WHO HPV LabNet Proficiency Study in 2013 and 2014, the Anyplex assay showed high performance in detecting single and multiple infections at concentrations of 5, 50 and 500 IU per 5 µl [21,37].

Third, our study also highlights that ascertainment of whether vaccination occurred before sexual debut is relevant and should be considered in future prevalence studies. Genotypes 16 and 18 were not detected in women receiving two doses before sexual debut equivalent to 100% effectiveness. Similarly, cross-protection against genotypes 31/33/45 was slightly higher for women vaccinated before sexual debut compared to all vaccinated women. Our estimates of VE of 87% against HPV16/18 (Table 3 and Supplementary Table 5) are in agreement with a similar Belgian surveillance study where good protection was observed among women aged 18–19 years, with decreasing effectiveness in older women [7]. Even though a minority (24%) of women were vaccinated after sexual debut, our results suggest a higher VE in women vaccinated before sexual debut, in agreement with studies in the Netherlands and Italy [23,24].

Interestingly, the prevalence of HPV18 was not significantly different across the groups; while the low case numbers may explain the lack of significance, it could also be that the prevalence of HPV18 in all groups was higher prior to vaccination program and may have dropped due to herd protection. We have not observed such an effect for HPV16 given its higher prevalence and persistence. According to modelling studies, herd protection effect might be stronger for HPV6, 11, 18 compared to HPV16 [38]. Studies from other countries with good vaccine coverage have demonstrated declines in vaccine-type HPV

prevalence even in unvaccinated women and men due to herd protection [12,39–43]. A study from Norway reported a 54% reduction of vaccine genotypes in unvaccinated women due to herd protection [43]. Low prevalence of HPV18 in our study could be also explained by the lower sensitivity of the assay for this particular genotype. However, during the LabNet 2013/2014 study, all 14 laboratories using the Anyplex correctly identified HPV genotypes 6, 11, 16 and 18 at concentrations of 5, 50 and 500 IU per 5 µl [37], and thus assay sensitivity does not appear to be problematic for genotype 18 in particular.

One of the limitations of our study was the rather small sample size. The study size was determined by budgetary and logistic constraints. Nevertheless, power calculations a posteriori, showed that our surveillance was sufficiently large to address protection of HPV vaccination against HPV16/18 infection and against cross-reacting types HPV31/33/45 (Supplementary Table 7). Another limitation, which could have an impact on representativeness, was the context of recruitment mainly taking place in family planning centres where young women seek sexual health services. Thus, by definition, sexual activity levels in our study group are likely to be higher than in the general population. Apart from different sexual behaviour, women attending family planning might also have another socio-economic status, compared to the general population, but we did not collect this information. While we attempted to implicate private gynaecologists with study recruitment, obtaining informed consent with questionnaires is very challenging in this setting.

One of the strengths of our study was that self-reported vaccination status could be verified using records from the social security database. This allowed us to stratify vaccinated women in different categories according to the strength of vaccination evidence. We created an extra vaccination category which included women vaccinated with only one dose or with self-reported vaccination status to keep information for these participants. Even though the group classified as "others" is also a limitation and represents 19% of the study population, this categorisation provided us with a more reliable ascertainment of actual vaccination status.

4.1. Conclusions

Our findings suggest high VE against vaccine genotypes 16/18 and cross protection against genotypes 31/33/45 for 2-dose vaccine recipients irrespective of vaccine type. VE was higher for women vaccinated before sexual debut, showing the importance of vaccination before exposure to HPV infection.

Authors contribution

JM designed and conducted the study. AL and JM analysed the data and wrote the paper. JT performed HPV genotyping. MF's lab performed cytological testing. PP lead recruitment at the Planning Familial, MA and SW advised and reviewed the manuscript. All authors listed approve the submission and confirm that neither this manuscript nor any part of it has been published or is under consideration for publication elsewhere.

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Ethical approval

The study was approved by the Comité National d'Ethique de Recherche (CNER # 201501/02) and authorized by the Commission Nationale pour la Protection des Données (CNPD 288/2016).

Declaration of Competing Interest

All authors report no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101593.

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