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Exploration of the effect of human papillomavirus (HPV) vaccination in a cohort of pregnant women in Montreal, 2010–2016

El Hadji Malick Sarr [a], Marie-Hélène Mayrand [b,c], François Coutlée [d], Joseph Niyibizi [a], Louise Laporte [e], Patricia Monnier [f], Ana Maria Carceller [g], Jacques Lacroix [h], François Audibert [i], Marie-Josée Bédard [j], Isabelle Girard [k], Paul Brassard [l], William D. Fraser [m], Helen Trottier [a,*], and the HERITAGE study group [1]

[a] *Department of Social and Preventive Medicine, Université de Montréal, Sainte-Justine University Hospital Centre, Montreal, Canada*
[b] *Department of Obstetrics and Gynecology, Université de Montréal and Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Montreal, Canada*
[c] *Department of Social and Preventive Medicine, Université de Montréal and Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Montreal, Canada*
[d] *Department of Microbiology, Université de Montréal and CRCHUM, Montreal, Canada*
[e] *Sainte-Justine University Hospital Centre, Montreal, Canada*
[f] *Department of Obstetrics and Gynecology and the Research Institute of the McGill University Health Centre [RI-MUHC), McGill University, Royal Victoria Hospital, Montreal, Canada*
[g] *Department of Pediatrics, Université de Montréal, Sainte-Justine University Hospital Centre, Montreal, Canada*
[h] *Department of Pediatrics, Division of Pediatric, Intensive Care Medicine, Sainte-Justine University Hospital Centre, Université de Montréal, Canada*
[i] *Department of Obstetrics and Gynecology, Sainte-Justine University Hospital Centre, Montreal, Canada*
[j] *Department of Obstetrics and Gynecology, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Canada*
[k] *Department of Obstetrics and Gynecology, St-Mary's Hospital Center, Montreal, Canada*
[l] *Division of Clinical Epidemiology, McGill University Health Center, Montreal, Canada*
[m] *Department of Obstetrics and Gynecology, Université de Sherbrooke, Centre de recherche du CHUS*

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ABSTRACT

HPV vaccination efficacy has been shown in clinical trials but it is important to verify population level vaccine effectiveness (VE). We aimed to explore VE and herd effect using HPV infection data from a cohort study of Canadian pregnant women. We analyzed the baseline data of the HERITAGE study, which includes pregnant women recruited in Montreal between 2010-2012 and 2015–2016. Cervicovaginal samples self-collected in the first trimester were tested for 36 HPV types. Vaccination status was self-reported. VE and 95% confidence intervals (CI) were estimated by comparing the prevalence of HPV between vaccinated and unvaccinated women. Herd effect was explored by comparing HPV prevalence in unvaccinated women between the 2 recruitment periods. Adjusted ORs (95%CI) were estimated using exact logistic regression. The proportion of vaccinated women with at least one dose of 4vHPV was 7.5%. Although most of them were vaccinated after the onset of sexual activity, a high VE was found for HPV-16/18 (86.1% (95%CI: 15.0–99.7)). For HPV-6/11/16/18 and for HPV-31/33/45, VE was 61.9% (-23.5–92.6) and 57.0% (-47.7–92.0%), respectively. We also observed a non-statistically significant reduction in the prevalence of HPV-6/11/16/18 and HPV-31/33/45 among unvaccinated women recruited during the second recruitment period (adjusted OR: 0.8 (0.4–1.8) and 0.8 (0.3–1.7), respectively).

* Corresponding author.
E-mail address: helen.trottier@umontreal.ca (H. Trottier).

[1] The HERITAGE study group: Marie-Hélène Mayrand, François Coutlée, Patricia Monnier, Louise Laporte, Joseph Niyibizi, Monica Zahreddine, Ana Maria Carceller, William D. Fraser, Paul Brassard, Jacques Lacroix, Diane Francoeur, Marie-Josée Bédard, Isabelle Girard, François Audibert, Helen Trottier (Principal investigator).

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1. Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide, with a global prevalence estimated at almost 12% and HPV 16 being the most prevalent HPV type with a world prevalence of 3.2% [1]. In the province of Quebec, the overall prevalence of HPV varies between 21.8% and 64%, depending on the type of test used, and the age and sexual behaviour profile of the studied population [2, 3, 4, 5]. A higher number of sexual partners, a younger age at first sexual intercourse and an increased frequency of sexual intercourse have all been associated with a higher prevalence of HPV all around the world [2, 6, 7, 8, 9, 10, 11, 12]. Other risk factors associated with HPV infections in women include: young age with those under the age of 25 having the highest prevalence [2], smoking [9, 13], immunosuppression [14, 15], long-term use of oral contraceptives [16, 17, 18].

Certain low-risk HPVs, namely HPV-6 and 11, cause benign lesions such as anogenital condylomas and respiratory papillomatosis [19, 20]. HR-HPV infection is recognized unequivocally as a necessary cause for cervical cancer and has been found to be involved in many other anogenital neoplasms (anal, vaginal, vulvar and penile cancers), head and neck cancers, non-melanoma skin cancers and conjunctiva cancers [18, 21, 22]. In Quebec, between 2004 and 2007, approximately 710 new cases and 194 deaths caused by cervical, vaginal, vulvar, penile, anal and oropharyngeal cancers were recorded annually [22]. The cost of cervical cancer screening and follow-up of abnormal cases in Quebec is estimated at over 40 million dollars per year for a population of approximately 8.3 millions [22]. Globally HPV infections in pregnant women have also been associated with other, non-cancerous adverse outcomes, such as preterm birth, preeclampsia and premature rupture of membranes [23, 24].

Three vaccines against HPV are approved in Canada. The AS04 adjuvanted bivalent HPV-16 and 18 vaccine (Cervarix®, 2vHPV) (GlaxoSmithKline Biologicals, Rixensart, Belgium), approved by Health Canada in 2010, protects against HPV 16 and 18, the most oncogenic of the HR-HPV types [25]. The quadrivalent HPV-6, 11, 16 and 18 aluminum-adjuvanted (Gardasil®, 4vHPV) (Merck and Co., West Point, PA, USA), approved in 2006, protects, in addition to HPV 16 and 18, against types 6 and 11 which are associated with genital warts and respiratory papillomatosis annually [26]. The nonavalent HPV vaccine (Gardasil-9®, 9vHPV) (Merck and Co., West Point, PA, USA), approved in 2015, in addition to protecting against HPV-6, 11, 16 and 18, also protects against HR-HPV 31, 33, 45, 52 and 58 [27]. In September 2008, the province of Quebec implemented a school-based immunization program against HPV, targeting initially 9–10 years old girls and 14–15 year old female adolescents with the 4vHPV Gardasil® vaccine. Vaccination was free outside of the school program for female adolescents up to 18 years of age [28, 29]. Province wide vaccination coverage of the school-program targeted cohorts has varied between 81% and 76% since its implementation annually [22]. A cross-sectional study conducted in Quebec in 2013–2014 indicated that vaccination coverage was closely associated with age: 83.5%, 65.7% and 19.1% for women aged 17–19 years, 20–22 years and 23–29 years, respectively [30]. In 2016, the Quebec HPV vaccination program added boys in Grade 4 and switched to Gardasil 9® (9vHPV). In 2018, a mixed schedule was adopted, with one dose of 9vHPV followed 6 months later with a dose of 2vHPV [31].

Randomized clinical trials have shown a very high vaccine efficacy against persistent HPV infections (~100%) [32, 33, 34]. "Real world" effectiveness appears also to be very high [35, 36]. Vaccine effectiveness (VE) refers to the proportion of infection or disease prevented among vaccinated individuals, and is estimated by comparing the proportion of infection among vaccinated versus unvaccinated individuals within a similar population. The primary objective of this study is to explore the vaccine effectiveness against HPV 6, 11, 16 and 18 in a cohort of pregnant women who were recruited in 2010–2012 and 2015–2016 in Montreal. A second objective explores herd effect (reduction of infections in the unvaccinated population as a result of vaccinating a proportion of the population) by comparing the prevalence of HPV in unvaccinated women between the 2 recruitment periods (approximately two years after the implementation of the vaccination program for the first period versus 7 years post-program implementation for the second period).

2. Methods

We conducted a cross-sectional analysis using baseline data collected for the ongoing "HERITAGE" cohort study. Study design and methods have previously been described [37]. Briefly, HERITAGE is a prospective cohort study of more than 1000 pregnant women recruited during their first trimester (6–14 weeks), in three Montreal hospitals (Centre hospitalier de l'Université de Montréal (CHUM), St-Mary's Hospital, and Sainte-Justine University Hospital Center and affiliated clinics) in two phases, 2010–2012 and 2015–2016. Pregnant women over 18 years of age who planned to give birth in these hospitals were eligible to participate. Exclusion criteria included: inability to provide informed consent, inability to read English or French, and HIV infection. For the current analysis, we used data and specimens collected at the time of recruitment (visit 1) for the 167 women recruited in 2010–2012 and from the 884 women recruited in 2015–2016 time period. The Ethics committee and Institutional Review Board at each Institution approved the protocol and participants were asked to sign a consent form.

At baseline, participants provided a self-collected cervicovaginal specimen, using a dry Polyester swab (Copan Italia S.p.A). Swabs were rinsed individually in 1.5 ml of PreservCyt (Cytyc Corporation, Boxborough, MA) in a plastic vial. DNA was purified with the Master pure procedure [38, 39] and stored at -70° until testing. A questionnaire also documented socio-demographic data and baseline characteristics including age, ethnicity, marital status, education, annual household income, gestational age at recruitment, medical history including HPV vaccination status, sexual activity (lifetime number of sexual partners, age at the time of first intercourse, number of sexual partners during the last year, number of new sexual partners during the last year), smoking, and alcohol and drug consumption.

2.1. HPV DNA testing

The Linear Array HPV genotyping assay (LA-HP; Roche Molecular Systems) was used to detect 36 mucosal HPV types, including types 6, 11, 16, 18, 26, 31, 33, 34 (formerly known as type 64), 35, 39, 40, 42, 44 (formerly the name type 55), 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, and 89. β-globin DNA was co-amplified in order to evaluate DNA integrity and to screen for the presence of inhibitors [38, 40, 41, 42]. Negative, weak positive and strong positive controls were included in each amplification run. Extensive safeguards to avoid contamination were used. Samples that were both β-globin and HPV-negative were considered inadequate. HPV-52 was detected in the LA with a probe that also cross-reacts with types 33, 35 and 58. Samples reactive in the LA with the cross-reactive probe for HPV-52 were further tested with a validated HPV-52-specific real-time PCR [RT-PCR) assay [43].

2.2. Statistical analysis

We estimated VE by comparing the prevalence of HPV between vaccinated and unvaccinated women using exact logistic regression adjusted for age and number of new sexual partners in the last 12 months. VE and 95% confidence intervals (CI) were estimated using the formula: VE = 1-Odd Ratio (OR). We estimated VE for combined vaccine types (16, 18; and 16, 18, 6 and 11) as well as for HPV- 31, 33 and 45 (types with possible cross-protection) and all HR-HPV defined as types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

We also explored herd effect by comparing the prevalence of HPV for types 6, 11, 16, and 18, as well as for types 31, 33 and 45 and HR-HPV among unvaccinated women recruited during the 2010–2012 period, to those recruited during the 2015–2016 period. ORs and 95% CI were

estimated using exact logistic regression and adjusted for age (continuous) and number of new sexual partners in the last 12 months (no new partner versus one new partner or more). Women were considered as vaccinated if they reported having received at least one dose of HPV vaccine. Herd immunity was explored for combined vaccine types (16, 18; and 16, 18, 6 and 11), for HPV- 31, 33 and 45 and for all HR-HPV. We also analyzed other HR-HPV infections except the targeted types: 6/11/16/18, and 31/33/45 in order to explore if, as expected, prevalence had remained stable over time for those types. All analyses were performed with Stata 14.2 (StataCorp, College Station, TX).

3. Results

A total of 1051 pregnant women were considered for analysis (167 and 884 in the first and second phase, respectively). Overall, 79 (7.5%) reported being vaccinated with at least one dose of 4vHPV and 956 (91.0%) reported not being vaccinated. In order to be able to analyze VE for HPV-6 and 11, we excluded 2 (0.2%) women who were vaccinated with the 2vHPV, 11 (1.0%) who did not report the type of vaccine and 3 (0.3%) who did not report their HPV vaccination status. Thus, our sample size for analysis was of 1035. Table 1 shows the characteristics of the women included in our study according to vaccination status. The mean age of women included in the analysis was 31.6 years old (SD+/- 4.5) for unvaccinated women and 27.7 years old (SD +/- 5.3) for those who were vaccinated. For those vaccinated with the 4vHPV, 66 participants (83.5%) reported having been vaccinated post sexual debut, 10 (12.7%) prior to sexual debut, and 3 (3.8%) women reported the same calendar year for vaccination and sexual debut. Three women failed to report their age at vaccination. The mean age at vaccination was 23.4 years (standard deviation (SD) = +/-6.2).

Table 2 summarizes the characteristics of the unvaccinated women stratified according to the period of recruitment (2010–2012 versus 2015–2016). In the first period, 156 (93.4%) women reported no vaccination compared to 800 (83.7%) in the second period. The mean age of the women recruited in the first and second phase was 26.6 years old (SD +/- 2.1) and 32.6 years old (SD +/- 4.1), respectively.

The VE estimates are presented in Table 3. We found a statistically significant VE for HPV-16/18 (adjusted VE = 86.1% (95% CI: 15.0–99.7). When HPV-6/11/16 and 18 were all combined, results were not statistically significant with a VE estimated at 61.9% (95% CI: -23.5–92.6%). Similarly, the adjusted VE for HPV-31, 33 and 45 was 57.0% (95% CI: -47.7–92.0%).

Table 4 presents the results comparing HPV prevalence among unvaccinated women between both periods of recruitment. A statistically significant reduction of HPV-31 was observed between the periods (adjusted OR = 0.3 (95% CI: 0.1–0.9)). There was a non-statistically significant reduction of the prevalence of HPV-6/11/16/18 in unvaccinated women recruited during the 2015–2016 time period compared to those recruited in 2010–2012 time period (adjusted OR = 0.8 (95% CI: 0.4–1.8)). We also did find a non-statistically significant reduction of prevalence in HPV-31, 33 and 45 in unvaccinated women tested in 2015–2016 compared to those tested in 2010–2012 (adjusted OR = 0.8 (95% CI: 0.3–1.7)). For all HR-HPV except 16, 18, 31, 33, 45, no reduction was found (adjusted OR = 1.0 (95% CI: 0.6–1.8)). For both analyses (Tables 3 and 4), adjustment with the total number of sexual partners in the last 12 months instead of the number of new sexual partners in the last 12 months gave similar results (data not shown).

Table 1
Baseline characteristics of study participants according to HPV vaccination status.

	Not vaccinated (n = 956) N (%) or mean (SD)	Vaccinated (n = 79) N (%) or mean (SD)
Age (Mean (SD))	31.6 (4.5)	27.7 (5.3)
Age at vaccination (mean (SD))	NA	23.4 years (6.2)
Race		
Caucasian	673 (70.4%)	67 (84.8%)
Black	108 (11.3%)	5 (6.3%)
Asian	107 (11.2%)	2 (2.5)
Other	62 (6.5%)	4 (5.1%)
Missing	6 (0.6%)	1 (1.3%)
Level of education		
High school or less	85 (8.8%)	15 (19.0%)
College/technical degree	229 (24.0%)	23 (29.1%)
University	629 (65.8%)	40 (50.6%)
Missing	13 (1.4%)	1 (1.3%)
Number of sexual partners in the last 12 months		
One partner	910 (95.2%)	69 (87.3%)
Two partners or more	36 (3.8%)	10 (12.7%)
Missing	10 (1.0%)	0
Number of new sexual partners in the last 12 months		
No new partner	882 (92.3%)	70 (88.6%)
One new partner or more	66 (6.9%)	9 (11.4%)
Missing	8 (0.8%)	0
Has smoked over 100 cigarettes (ever)		
Yes	285 (29.8%)	18 (22.8%)
No	669 (70.0%)	61 (77.2%)
Missing	2 (0.2%)	0

SD: standard deviation; N: Number; NA: not applicable.

Table 2
Characteristics of unvaccinated participants stratified according to the recruitment periods.

	First period (2010–2012) (N total = 156) N (%) or mean (SD)	Second period (2015–2016) (N total = 800) N (%) or mean (SD)
Age (Mean (SD))	26.6 (2.1)	32.6 (4.1)
Race		
Caucasian	121 (77.6%)	552 (69.0%)
Black	10 (6.4%)	98 (12.3%)
Asian	7 (4.5%)	100 (12.5%)
Other	18 (11.5%)	44 (5.5%)
Missing	0	6 (0.7%)
Level of education		
High school or less	31 (19.9%)	54 (6.7%)
College/technical degree	42 (26.9%)	187 (23.4%)
University	83 (53.2%)	546 (68.3%)
Missing	0	13 (1.6%)
Number of sexual partners in the last 12 months		
One partner	146 (93.6%)	764 (95.5%)
Two partners or more	10 (6.4%)	26 (3.3%)
Missing	0	10 (1.2%)
Number of new sexual partners in the last 12 months		
No new partner	141 (90.4%)	741 (92.6%)
One new partner or more	15 (9.6%)	51 (6.4%)
Missing	0	8 (1.0%)
Has smoked over 100 cigarettes (ever)		
Yes	56 (35.9%)	229 (28.6%)
No	100 (64.1%)	569 (71.1%)
Missing	0	2 (0.3%)

SD standard deviation; N: Number.

4. Discussion

We found in our study a relatively strong and statistically significant adjusted VE for the 4vHPV vaccine against HPV-16/18 (adjusted VE = 86.1% (95% CI: 15.0–99.7)). When combined with other 4vHPV vaccine types, the VE for HPV-6, 11, 16 and 18 was 61.9% (95% CI: -23.5–92.6%). In the HERITAGE study only 15 cases of HPV6 and 11 were documented globally (13 cases among unvaccinated and 2 cases among vaccinated) and may explain why the results were not statistically significant once combined. A study conducted among individuals aged 14–24 years in the United States found a VE for 4vHPV against HPV-6, 11, 16 and 18 of 89% (95% CI: 76–95%) [44]. In a study conducted in women aged 18–24 years, six years after the implementation of the Australian vaccination program against HPV with 4vHPV in 2007, the adjusted VE reported for the HPV-6, 11, 16 and 18 was similar with a

Table 3
Vaccine effectiveness (VE) estimates.

Types	Unvaccinated (956 women) n (%)	Vaccinated (79 women) n (%)	Vaccine effectiveness (%)	Adjusted* vaccine effectiveness (%) (95% CI)
HPV16/18	69 (7.2%)	1 (1.3%)	**83.5 (2.1–99.4)**	**86.1 (15.0–99.7)**
HPV6/11/16/18	82 (8.6%)	3 (3.8%)	57.9 (-32.5–91.7)	61.9 (-23.5–92.6)
HPV31	24 (2.5%)	1 (1.3%)	50.2 (-214.0–98.8)	74.1 (-81.5–99.4)
HPV31/33/45	52 (5.4%)	3 (3.8%)	31.4 (-120.1–86.6)	57.0 (-47.7–92.0)
HR-HPV	242 (25.3%)	25 (31.6%)	-36.5 (-128.9–20.5)	-1.8 (-76.5–42.8)

n: number; CI: confidence intervals.
HR-HPV (high-risk HPV) includes types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.
Statistically significant values are marked in bold.
* Adjusted for age and number of new sexual partners in the last 12 months.

Table 4
Associations between HPV prevalence and recruitment period.

Types	First period 2010–2012 (156 women) n (%)	Second period 2015–2016 (800 women) n (%)	OR (95% CI)	Adjusted OR** (95% CI)
HPV16/18	16 (10.3%)	53 (6.6%)	0.6 (0.3–1.2)	0.7 (0.3–1.5)
HPV6/11/16/18	16 (10.3%)	66 (8.2%)	0.8 (0.4–1.5)	0.8 (0.4–1.8)
HPV31	11 (7.1%)	13 (1.6%)	**0.2 (0.1–0.5)**	**0.3 (0.1–0.9)**
HPV31/33/45	15 (9.6%)	37 (4.6%)	**0.5 (0.2–0.9)**	0.8 (0.3–1.7)
HR-HPV	50 (32.1%)	192 (24%)	**0.7 (0.4–0.9)**	0.9 (0.6–1.5)
HR-HPV except 16/18/31/33/45	29 (18.6%)	120 (15%)	0.8 (0.5–1.2)	1.0 (0.6-1.8)

N: number; CI: Confidence intervals.
HR-HPV (high-risk HPV) includes types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.
Statistically significant values are marked in bold.
** Adjusted for age and number of new sexual partners in the last 12 months.

value of 86% (95% CI: 71–93%) [45]. The VE of 4vHPV vaccine was 73% (95% CI: 70–76%) against receiving a diagnosis of genital warts in another study conducted among participants of 10–44 years, five years after the implementation of the Swedish program of vaccination against HPV [46].

It is important to stress that vaccine effectiveness is not expected to be 100% among women vaccinated after their sexual debut. According to a study conducted in Scotland, the risk of being infected with HPV 16 and 18 increases with the age at the time of the vaccination (adjusted OR: 1.70 (95% CI: 1.22–2.38), 2.38 (95% CI: 1.67–3.40) and 5.31 (95% CI: 3.28–8.48) for participants vaccinated at 17, 18 and beyond 18 years, respectively, compared to those immunized between 15-16 years) [47]. In our study, the mean age at vaccination was 23.4 years (SD +/- 6.2) and only 12.7% of vaccinated women were vaccinated before the onset of sexual activity (data not shown). This leads to a lower potential for vaccine effectiveness. HPV vaccines are prophylactic and not therapeutic, thus will have no effect for prevalent infections.

The vaccine effectiveness of 4vHPV against HPV-31, 33 and 45 estimated in our study was 57.0% (95% CI: -47.7–92.0%). There is a potential cross-protection effect of the 4vHPV vaccine against HPV-31, 33, and 45 although the results in our study were not statistically significant. The Australian post-vaccination study [45] showed similar results regarding cross-protection for HPV-31, 33 and 45 with an adjusted VE for these types of 58% (95% CI: 26–76%). A study conducted in England [35], among women aged 16–24 years with 2vHPV had also suggested a cross-protection for HPV-31, 33 and 45 for women aged 16–18 with an adjusted VE of 50% (20–70%).

In our study we also show some possible herd effect. The prevalence of HPV-6, 11, 16 and 18 in unvaccinated women recruited during the second recruitment period was lower (although not statistically significant) compared to those recruited during the first period (adjusted OR = 0.8 (95% CI: 0.4–1.8)). Our analysis also suggests a non-statistically significant reduction of 20% in the prevalence of HPV-31, 33 and 45 in 2015–2016 among the unvaccinated participants compared to 2010–2012 (adjusted OR = 0.8 (95% CI: 0.3–1.7)). This was similar to the finding of another study that reported that the prevalence of HPV-31, 33 and 45 in unvaccinated women in United States, 6 years after the introduction of the vaccine program, was reduced, although also not statistically significant (OR = 0.80 (0.46–1.37)) [44]. For HPV-31 alone, we found a statistically significant reduction of 70% (10–90%). Finally, the prevalence of HR-HPV other than 16, 18, 31, 33, 45 was comparable between the two time points, which indicates that the prevalence of HPV types not targeted by the 4vHPV vaccine stayed constant between the two study periods.

It is possible that the herd effect regarding HPV-6, 11, 16 and 18 and HPV-31, 33, and 45 would have been stronger if we had recruited younger participants since vaccine coverage is higher in younger age groups. Indeed, others have found the herd effect to be strongest among unvaccinated groups of similar age as the vaccine program targeted cohorts [48, 49]. Also, we used two time-points after implementation of vaccination (approximately 2 years post-implementation compared to 7 years post-implementation). This may have underestimated herd effect in our cohort. It would have been preferable to compare HPV prevalence between pre and post-vaccination periods. The period 2010–2012 was used in our study as a proxy for the prevalence of HPV in the pre-vaccination era. This is likely an underestimate of the herd effect, as the prevalence of HPV in 2010–2012 may have had already started to decline following the vaccination program implementation in 2008.

There are some limitations to our study, one of them being the statistical power, especially in order to stratify the results based on the age at vaccination. Although there is a benefit in vaccinating older women, very high vaccine efficacy [~100%] would only be expected in cohorts vaccinated before sexual debut. Furthermore, generalizability of our results to the effectiveness of the school based program may be limited, as participants were not necessarily representative of the women vaccinated as part of the school based vaccination program. Moreover, many variables were self-reported, including vaccination status, resulting into a potential risk for information bias. However, we expect self-report of HPV vaccination to be reliable as sensitivity and specificity for self-reported HPV vaccination status was 91% (95% CI: 87–95) and 76%

(95% CI: 70–82), respectively in the study undertaken in a similar population [50]. Despite its limitations, HERITAGE is a large study including women typically not targeted by vaccination programs. Even though most vaccinated participants were immunized after sexual debut, we demonstrated high vaccine effectiveness against HPV-16 and 18. These results suggest vaccine protection well beyond groups that were targeted by the school-based vaccination program.

Declarations

Author contribution statement

El Hadji Malick Sarr: Analyzed and interpreted the data, Wrote the paper.

Marie-Hélène Mayrand, Helen Trottier: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

François Coutlée: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Joseph Niyibizi, Louise Laporte, Patricia Monnier, Ana Maria Carceller, Jacques Lacroix, François Audibert, Marie Josée Bédard, Isabelle Girard, Paul Brassard, William D. Fraser: Performed the experiments; Wrote the paper.

The HERITAGE study group: Conceived and designed the experiments.

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Competing interest statement

Helen Trottier has received occasional lecture or consultation fees from GlaxoSmithKline Biologicals and Merck.

Marie-Hélène Mayrand was a site PI for a Merck clinical trial on HPV vaccination.

François Coutlée has received grants through his institution from Merck and Roche.

Additional information

No additional information is available for this paper.

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