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High-risk HPV prevalence among women undergoing cervical cancer screening: Findings a decade after HPV vaccine implementation in British Columbia, Canada

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ABSTRACT

Background: British Columbia (BC) introduced a publicly funded, school-based human papillomavirus (HPV) immunization program in 2008 with the quadrivalent vaccine. In 2010/2011, a baseline evaluation of HPV prevalence was conducted among women undergoing cervical cancer screening. After 10 years of publicly funded HPV vaccination, HPV-type prevalence was re-evaluated.

Methods: From August 2017 to March 2018, 1107 physicians were invited to return cytobrushes used during routine Pap screening to the Cervical Cancer Screening Laboratory for HPV testing. Only age or year of birth was collected. Specimens were screened for high-risk HPV (hrHPV) and positive samples were genotyped. HPV type prevalence was compared for females 15–22 yrs (those eligible for the school-based vaccination) and 23+ yrs (ineligible for school-based vaccination) for the 2010/2011 and the 2017/2018 data.

Results: There were 3309 valid samples received for testing; of these, 3107 were included in the analysis. The overall hrHPV prevalence was 12.2% (95% CI 11.3–13.3) in 2010/11, and 12.0% (95% CI 10.9–13.2) in 2017/18. For the 15–22 age group, the prevalence for any hrHPV was 26.8% (95% CI 23.1–30.8) in 2010/11 and 25.4% (95% CI 15.3–37.9) in 2017/18. For those aged 15–22, HPV16 prevalence in 2010/11 was 8.8% (95% CI 6.5–11.5) and in 2017/18 was 6.3% (95% CI 1.8–15.5), with corresponding figures for HPV18 3.7% (95% CI 2.3–5.7) and 0% (95% CI 0.0–5.7), respectively. For all hrHPV types, there were no statistically significant differences between the 2010/11 and 2017/18 periods.

Conclusions: This study illustrates the prevalence of hrHPV in BC over time in women undergoing cervical cancer screening, where an indication of a decline in HPV16/18 is seen in vaccine eligible women.

1. Background

It has been well established that persistent infection with an oncogenic human papillomavirus (HPV) type is necessary for the development of cervical cancer [1,2]. All currently available HPV vaccines prevent against at least HPV oncogenic type 16 and 18, responsible for approximately 70% of invasive cervical cancer cases worldwide, in addition to 50–80% of cases of vulvovaginal, penile, anal and oropharyngeal cancers [3]. The 4-valent HPV vaccine has been found to be approximately 95% effective at reducing the risk of developing cervical intraepithelial neoplasia (CIN) grade 3 (CIN3) caused by HPV16/18 in HPV-naïve women, compared to unvaccinated women [4]. In addition, meta-analyses and mathematical models predict a substantial decrease in overall HPV-related disease burden within the next few decades, with anticipated high cost-effectiveness of vaccination programs [5–7].

The 4-valent HPV vaccine was licensed for use in Canada in 2006. Thereafter, publicly funded HPV vaccination began in school-based programs across Canada for school-aged girls [8]. In British Columbia (BC), the vaccination program was initiated with

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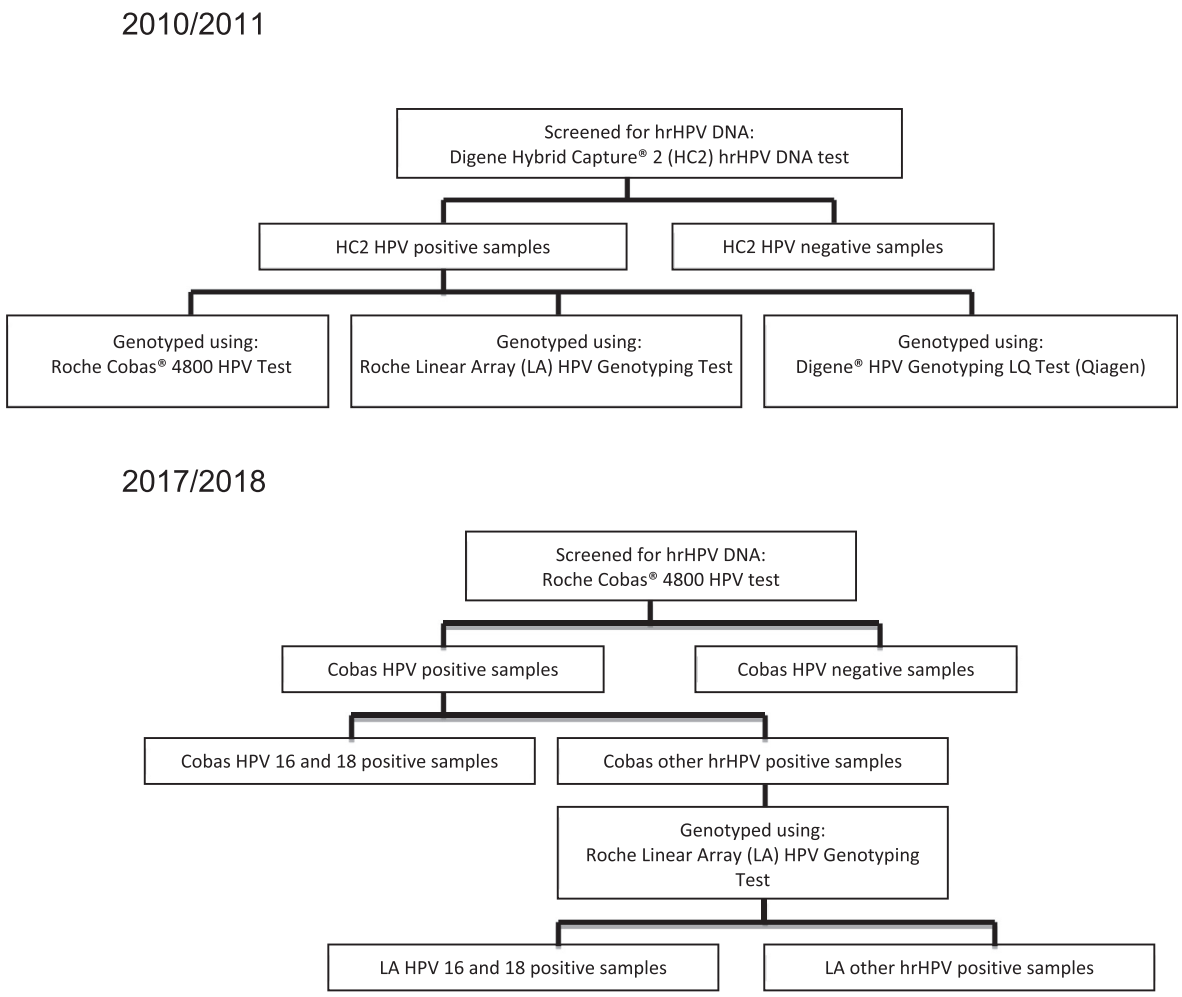

Fig 1. Comparison of laboratory assessment of samples between 2010/11 and 2017/18.

the 4-valent HPV vaccine and commenced in September 2008 for girls in Grade 6 or born in 1994 or later. The 4-valent vaccine was then replaced with the 9-valent vaccine in 2017 for girls and for the first time, boys were also included in the program. HPV vaccine uptake rates in school-based HPV vaccination programs are variable across Canadian provinces [9]. In 2019, 66% of grade 6 (11–12 years old) female students in BC had received both doses of the HPV vaccine program [10].

The school-based HPV vaccination program in BC is now entering its second decade, allowing for the assessment of long-term population impact of the vaccine. BC has comprehensive and ongoing monitoring and surveillance activities in place to evaluate the effect of the school-based HPV vaccination program. An initial study that provided baseline information for HPV prevalence in the province prior to the vaccination program was performed in 2010/2011 [11]. Recently, studies have reported a decline in rates of cervical intraepithelial neoplasia and anogenital warts in birth cohorts eligible for vaccination in BC [12–14]. In addition, a data-linkage study indicated that vaccinated women had a lower risk of high-grade squamous intraepithelial lesion (HSIL) cytology and histologically confirmed CIN2+, with respective RR of 0.53 (95 % CI 0.43–0.64) and 0.42 (95 %CI 0.31–0.57) [15]. Given that HPV prevalence trends can provide valuable information to support the monitoring and surveillance of HPV infections in the province, this current paper assesses the prevalence of HPV genotypes among women undergoing cervical cancer screening in British Columbia, 10 years after implementation of the provincial HPV vaccination program.

2. Methods

2.1. Cervical screening in British Columbia

Cervical cancer screening in BC is managed through the BC Cancer Cervix Screening Program, the first population-based cancer screening program in the world [16]. The organized cervical cancer screening program is responsible for the provincial guidelines on screening frequency and coordinates the recall and reminder system. All cytology specimens are processed and interpreted at the Cervical Cancer Screening Laboratory (CCSL), a centralized laboratory, and all program results (complete cytology, colposcopy, treatment and histopathology) for any women participating in the program are captured in a single registry.

As part of the comprehensive HPV vaccine monitoring program, an HPV prevalence study in women presenting for routine cervical cancer screening was conducted in 2010/2011 [11]. This study published by Ogilvie et al. (2013) provided a baseline measure of HPV prevalence in screened, unvaccinated women in the province. At the time of the baseline study, guidelines recommended screening via cytology (conventional Pap smear) commencing at age 21

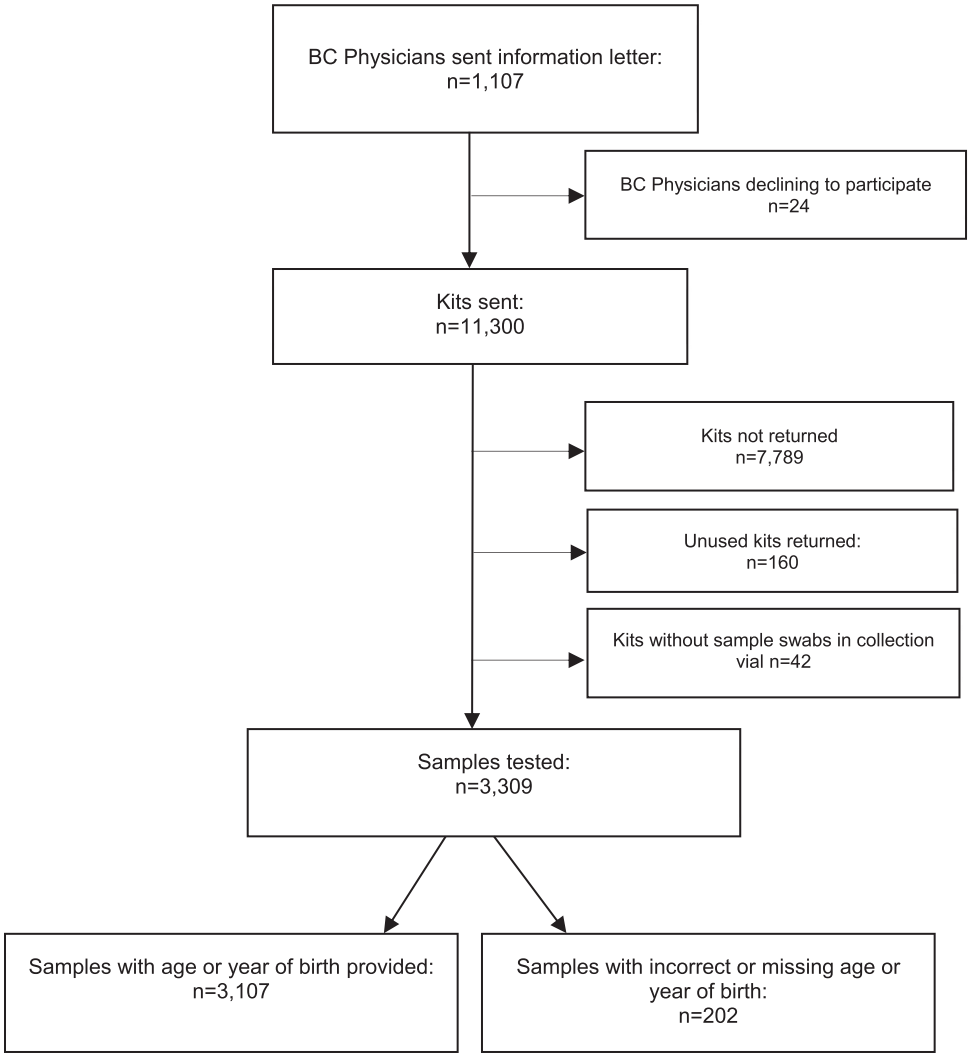

Fig. 2. Flow diagram.

or approximately 3 years after the first sexual contact, whichever occurred first. Screening was performed at 12-month intervals until 3 consecutive negative screens, after which it was recommended every 24 months until the age of 69. In June 2016, the guidelines were updated and cytology-based (Pap) screening for average risk women is now recommended every 3 years, from age 25–69, regardless of age of first sexual contact [17].

2.2. Study population

Given that the school-based vaccination program was initiated in 2008 for girls born in 1994 or later, samples obtained in 2010/2011 reflect the prevalence of HPV genotypes prior to the commencement of the vaccination program as people who participated in screening at that time would not have been eligible for vaccination. However, considering vaccine-eligible girls and women would have been 22 years old or younger by January 1, 2017, samples obtained in 2017/2018 as part of opportunistic screening would capture vaccine-eligible women. Therefore, we compared 2 sample groups for analysis: samples obtained in 2010/2011 to samples obtained in 2017/2018. These samples were further stratified by age group, 15–22 years (vaccine-eligible) and 23 years and older (not vaccine-eligible). A comparison was then made between the prevalence of hrHPV between these two time periods and age groups. Finally, we compared the number of HPV types per sample among those testing HPV positive in the 2010/2011 versus 2017/2018 samples, using the Cochrane-Armitage test.

2.3. Study design and specimen collection

A total of 1107 physicians in BC who perform cervical screening were invited to participate in this evaluation 10 years post-vaccine introduction. Physicians were provided with a letter from the research team explaining the study, and those who did not specifically decline to be involved were sent Specimen Transport Medium (STM; Qiagen) collection devices, an information poster to display in their office, and an information brochure to provide to women attending routine screening. Consent from individual participants was not required, as samples were anonymous, but women had the option to decline to be involved. Approval to conduct the study was provided by the University of British Columbia Clinical Research Ethics Board (H16-03414).

Participating clinicians were asked to collect samples from 10 consecutive women undergoing routine screening in their practice between August 2017 and March 2018. Once the routine Pap smear was collected, clinicians were instructed to break off the end of the cytobrush used to collect the Pap smear into a STM vial and label the vial only with the woman's age, or month and year of birth.

Table 1
Prevalence (%) of hrHPV types by age group and comparison pre- and post-vaccination.

	Samples (n)		HPV16		HPV18		HPV31		HPV33		HPV35		HPV39		HPV45		HPV51		HPV52		HPV56		HPV58		HPV59		HPV66		HPV68	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
15–22	537	63	8.8	6.3	3.7	0.0	3.2	3.2	2.8	0.0	0.4	3.2	4.8	1.6	2.6	1.6	6.5	4.8	3.5	4.8	4.1	3.2	0.7	3.2	3.2	4.8	4.7	4.8	0.6	4.8
23+	3793	3044	2.0	2.4	0.7	1.0	1.3	1.5	0.3	0.3	0.3	0.7	1.2	1.3	0.7	0.8	1.3	1.4	0.9	1.8	0.5	0.8	0.6	0.8	0.6	1.0	0.8	1.3	0.4	0.7

"Pre" refers to the data collected between 2010/11, and therefore before the population of interest was eligible for vaccination. "Post" refers to the data collected between 2017/18 including the population vaccinated. People with missing DOB or age were not included in the table.

No other identifiers were collected. STMs were then sent to the CCSL for HPV testing.

The results from this study were then compared to the estimates obtained in 2010/2011, presenting HPV prevalence in British Columbia prior to publicly available HPV vaccination [11].

2.4. Laboratory assessment

Samples from 2010/11 were screened for high-risk HPV (hrHPV) (Fig. 1)DNA using Digene Hybrid Capture Capture® 2 (HC2; Qiagen), which tests for 13 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68), with results classified as positive, negative or invalid. The HC2 positive samples were then genotyped with 3 different tests: Roche Cobas® 4800 (Cobas) HPV test, Roche Linear Array (LA) HPV Genotyping Test and Digene® HPV Genotyping LQ Test (Qiagen). Cobas detects 14 hrHPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and the results are classified as HPV16, HPV18, and/or other-hrHPV positive, negative, or invalid. LA identifies 37 HPV types (including the 14 hrHPV types identified by Cobas) and Qiagen identifies 18 HPV types (including the 14 hrHPV types identified by Cobas).

In the present study of samples from 2017/18, specimens were initially screened for hrHPV using the Cobas HPV test and results were classified as HPV16, 18, and or other hrHPV positive, negative, or invalid. Other-hrHPV positive samples were subsequently genotyped using LA. LA results were classified as either positive or negative for each specific hrHPV genotype tested, or as test invalid. (Fig. 1).

2.5. Statistical analysis

All analyses were carried out using R version 3.5.3 [18]. HPV prevalence rates were calculated and the exact method was used for 95% confidence intervals [19]. In the analysis of the 2010/2011 data, overall hrHPV prevalence for each of the three genotyping methods was defined as the number of positive specimens divided by the total number of specimens with valid HC2 results [11]. Prevalence of individual hrHPV types was defined as the number of specimens positive for each hrHPV type, divided by the total number of specimens with valid HC2 results [11]. Age-specific prevalence for individual hrHPV types was determined by dividing the number of individual hrHPV types identified with each method by the total number of specimens with valid HC2 results in each 5-year age stratum [11].

For the 2017/2018 data, prevalence for any hrHPV was calculated as the number of samples positive by Cobas for either HPV16, HPV18, and/or other hrHPV over the total number of samples with valid results. Prevalence of HPV16 and HPV18 was calculated as the number of Cobas positive for these types, with the addition of any additional LA positive for these types, divided by the total number of samples with valid results. Prevalence of all other individual HPV types was calculated as the number of LA positive samples divided by the total number of samples with valid results.

3. Results

Of the STM kits sent to physicians, 3511 samples (31.1%) were returned to CCSL (Fig. 2). Of these, 42 kits were returned without sample swabs, 160 kits were unused and an additional 202 had missing age or year of birth and were therefore excluded from the study. A total of 3107 samples had appropriate labelling and were used for analysis (Fig. 2). The median age in the total group was 40 (IQR 29–50) in 2010/2011 and 44 (IQR 33–54) in 2017/2018. Among those 15–22 years of age, the median age

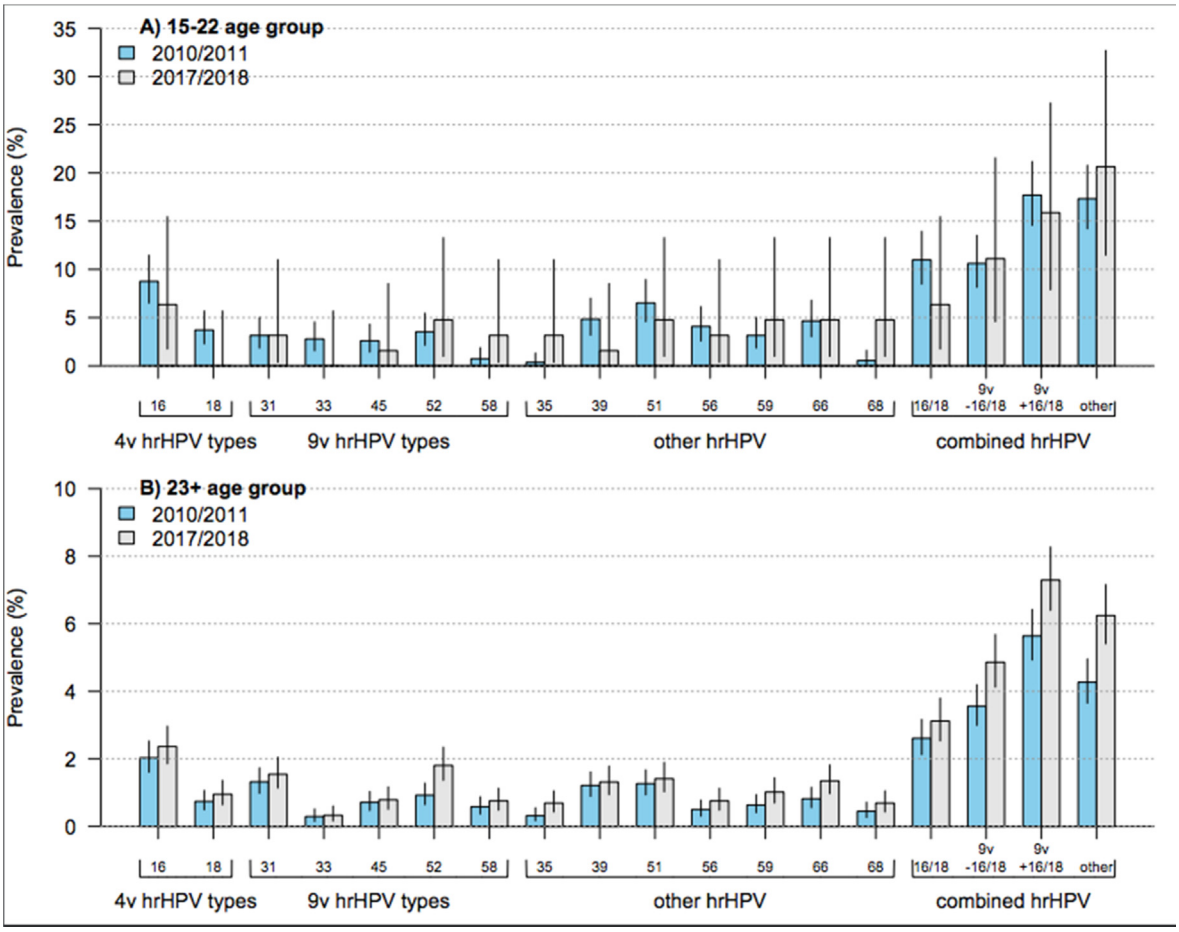

Fig. 3. Prevalence and 95% CI for hrHPV types by age group. Legend: 9v hrHPV types refers to the 5 additional hrHPV types that are not included in the 4v vaccine. 9v – 16/18 is the prevalence for the 5 additional hrHPV types, while 9v + 16/18 is for all 7 hrHPV types in the 9v vaccine. The combined bars indicate prevalence for those samples positive for at least one of the types listed, with samples counted once if positive for more than one type. Bars indicate the observed prevalence (%) and the lines extend to the 95 %CI.

was 20 (IQR 19–22) in the 2010/2011 cohort and 22 (IQR 21–23) in the 2017/18 cohort.

The overall prevalence of hrHPV was 12.2% (95% CI 11.3–13.3) in 2010/11, and 12.0% (95% CI 10.9–13.2) in 2017/18. For the 15–22 age group, the prevalence for any hrHPV was 26.8% (95% CI 23.1–30.8) in 2010/11 and 25.4% (95% CI 15.3–37.9) in 2017/18 (Table 1). The prevalence of HPV16 decreased from 8.8% (95% CI 6.5–11.5) to 6.3% (95% CI 1.8–15.5), and the prevalence of HPV18 decreased from 3.7% (95% CI 2.3–5.7) to 0.0% (95% CI 0.0–5.7) between 2010/11 and 2017/18 respectively in vaccine eligible women. The differences were not statistically significant.

For the age group of 23 and older, the prevalence for all hrHPV increased from 8.3% (95% CI 7.4–9.2) in 2010/11 to 11.4% (95% CI 10.3–12.6) in 2017/18. The prevalence of HPV16 and HPV18 between 2010/11 and 2017/18 increased from 2.0% (95% CI 1.6–2.5) to 2.4% (95% CI 1.9–3.0), and from 0.7% (95% CI 0.5–1.1) to 1.0% (95% CI 0.6–1.4), respectively (Table 1). The differences were not statistically significant.

Fig. 3 displays hrHPV type prevalence for both age groups. In the 15–22 age group, the prevalence of HPV16/18 was 11.0% (95% CI 8.5–13.9%) in 2010/11 and 6.4% (95% CI 1.8–15.5%) in 2017/18. In comparison, the HPV16/18 prevalence in the 23 years and older group pre and post-vaccination program were 2.6% (95% CI 2.1–3.2%) and 3.1% (95% CI 2.5–3.8), respectively. The differences were not statistically significant.

Fig. 4 shows the proportion of samples by number of HPV types detected pre- and post-vaccination program commencement for the 15–22 and 23 + age groups. For the 15–22 age group, the proportion of samples with 1, 2, 3 and 4 or more types of hrHPV was 49%, 31%, 13% and 8% respectively pre-vaccination, compared to 44%, 38%, 12% and 6% post-vaccination (p = 0.96). For the 23 + age group, the proportion of samples with 1, 2, 3 and 4 or more type of hrHPV was 70%, 22%, 5% and 3% pre-vaccination, compared to 72%, 20%, 6% and 2% post-vaccination respectively (p = 0.57).

4. Discussion

This study illustrates the prevalence of hrHPV in BC over 8 years in people undergoing cervical cancer screening. Overall, small differences in hrHPV prevalence were found between 2010/2011 and 2017/2018 in those eligible for vaccination (15–22 years). The point estimates show a decline in HPV16/18. Prevalence of hrHPV and HPV16/18 in the age group not eligible for vaccination (23+ years) did not vary significantly between the two timepoints. In addition, our study did not find a change in the proportion of hrHPV types in each sample between the two time points.

A recent systematic review and meta-analysis of the population-level impact of HPV vaccination campaigns in 14 high-income countries reported a significant decrease in prevalence of HPV16 and 18 in women aged 24 years or younger,

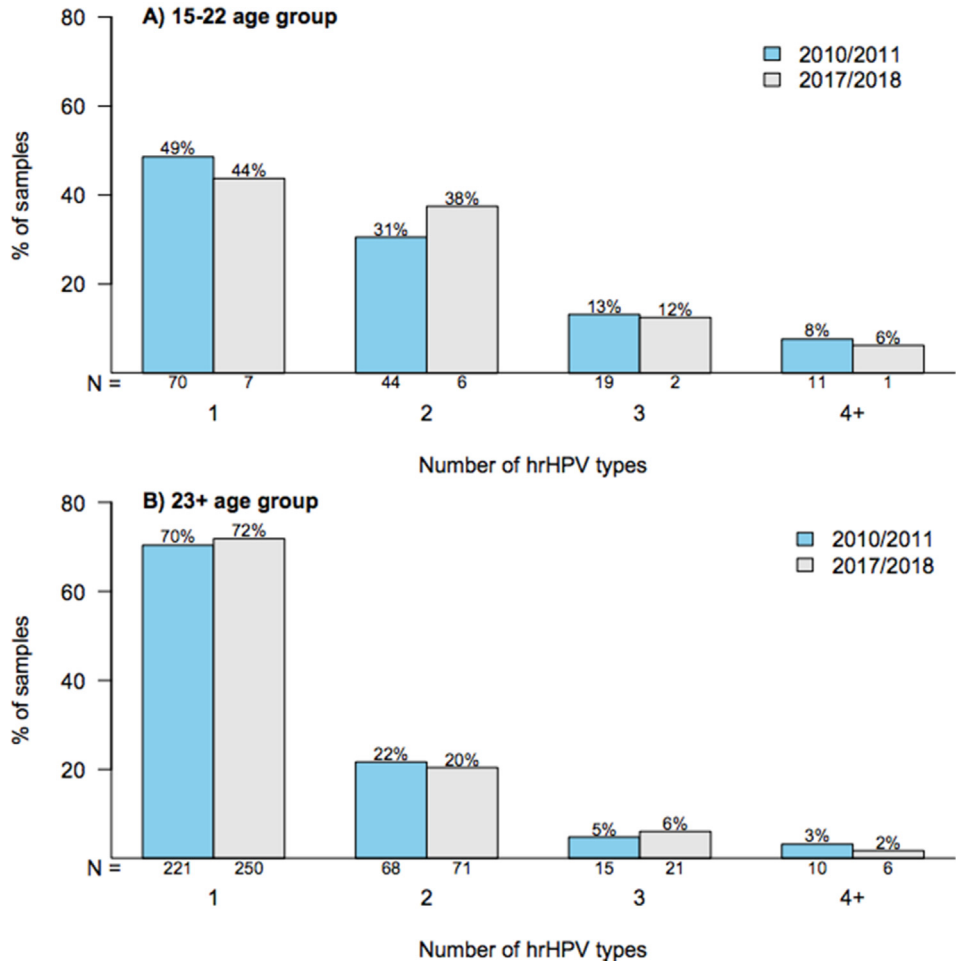

Fig. 4. Proportion of samples classified by number of hrHPV types found in each sample. Legend: The number of samples from 2010 to 2011 was n = 458 and from 2017 to 2018 was n = 385.

cross-protection to HPV31, 33 and 45 and herd effects from girls-only vaccination programs, especially when vaccination coverage was ≥50% of the population [20]. Our study showed a decreased prevalence of HPV vaccine types but the decrease was not as large compared to other jurisdictions. Several factors might have influenced the findings.

First, the samples analyzed in this study come from high volume providers who may have contributed differently to both time points, which in turn may have biased our findings. Nevertheless, in order to systematically compare the results of this study to Ogilvie et al. (2013), this method of collection reduced the risk of bias by recruiting samples from the same geographic locations and many of the same providers as in the earlier period [11].

Second, the screening recommendations in BC changed between the two study periods. Therefore, in 2017/2018, women under the age of 25 may only have been screened based on a clinical indication, increasing the risk for detection of hrHPV [21]. The median age in the group of women screened between 15 and 22 years increased from 20 to 22 between 2010/11 and 2017/18. Since HPV prevalence and type distributions vary by age and peak in the early twenties, this could have also influenced our findings [22,23]. Both the potential increase in risk profile and increase in median age in this study population may have resulted in an underestimation of the true effect of the vaccination program, with the point estimates observed nonetheless indicating a decrease. The sample size for the younger group was small, providing limited power to detect possible differences.

Third, the HPV vaccine series completion rates in BC are approximately 66%. However, we do not have any information regarding the vaccine status of the participants in this study. As indicated previously, a recent data-linkage study has shown a significant impact against HSIL and CIN2+ among vaccinated women in BC. The vaccine effectiveness against these outcomes was 58% and 47% respectively [15]. Previous ecological studies in BC also found a significant impact of the vaccination program, with a 56% reduction in anogenital warts (AGW) post-vaccination, and an 86% reduction in CIN2+, in age groups eligible for vaccination [12,13]. Nevertheless, this study adds to the growing body of evidence observed on the effectiveness of the HPV vaccination program in BC and other jurisdictions.

Finally, the HPV vaccine-type prevalence in BC was lower at the start of the HPV immunization program than in several jurisdictions that have reported substantial declines in vaccine-type HPV prevalence. For example, Australia has documented a drop in prevalence of HPV16 from 21.3 to 4.2% and of HPV18 from 8.4% to 1.9% over 9 years, with the school-based vaccination program reaching a vaccination coverage rate of 70%[24]. The USA, which does not have a nationwide vaccination program, documented a drop in HPV16 and 18 from 13% to 2.9% over 9–10 years, with a 50% vaccination coverage rate [25]. Other studies from England and Sweden, looking at post-vaccination intervals of 5 years or less, also reported significant drops in HPV prevalence [26,27]. The pre-vaccination prevalence of HPV16 and 18 in females aged 15–22 undergoing screening in BC was found to be significantly lower

than in these other studies, 8.8% and 3.7% respectively, and post-vaccination prevalence rates were comparable to the ones documented above. As a result, a statistically significant decline may have been less likely to be observed in the BC data. In addition, the differences in the findings reported by these different jurisdictions may have been influenced by the sensitivity of the assays used for testing and the inherent characteristics and risk factors of the varying study populations.

This study is an initial estimate of the prevalence of HPV among women attending cervical screening 10 years after implementation of school-based HPV vaccination in BC. The comparison of hrHPV prevalence in the province pre- and post-vaccination program commencement was made possible by comparing samples from 2010/2011 and 2017/2018. The point estimates show a decline in HPV16/18 post-vaccination, although not statistically significant. This study therefore adds to the growing body of evidence of the impact of the HPV vaccination program in BC [11–15,20,28,29]. With the program now including boys, the availability of the 9-valent vaccine, and an increasing number of women becoming eligible for the updated cervical screening, future studies will look into ongoing shifts in prevalence rates of hrHPV in BC. Continued surveillance on the impact of the program will offer up-to-date and evidence-based strategies to tackle the burden of HPV-associated diseases in BC.

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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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