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Declines in HPV vaccine type prevalence in women screened for cervical cancer in the United States: Evidence of direct and herd effects of vaccination

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ABSTRACT

Background: Human papillomavirus (HPV) vaccine has been recommended in the United States since 2006 for routine vaccination of girls at age 11–12 years and through age 26 years for women not previously vaccinated. Changes in vaccine-type HPV (VT) prevalence can be used to evaluate vaccine impact, including herd effects.

Methods: We determined type-specific HPV in cytology specimens from women aged 20–29 years screened for cervical cancer at Kaiser Permanente Northwest in 2007 and in two vaccine era periods: 2012–2013 and 2015–2016. Detection and typing used L1 consensus PCR with hybridization for 37 types, including quadrivalent vaccine types (HPV 6/11/16/18).

Results: Among 20–24 year-olds in 2012–2013 and 2015–2016, 44% and 64% had a history of ≥1-dose vaccination. VT prevalence decreased from 13.1% in 2007 to 2.9% in 2015–2016 (prevalence ratio [PR] = 0.22; 95% confidence interval [CI] 0.17–0.29). HPV 31 prevalence was also lower in the vaccine periods compared with 2007. VT prevalence in 2015–2016 among 20–24 year-olds was lower in both vaccinated, 1.3% (PR = 0.10; 95% CI 0.06–0.16), and unvaccinated women, 5.8% (PR = 0.45; 95% CI 0.33–0.61). Among 25–29 year-olds, 21% and 32% had a history of ≥1-dose vaccination. VT prevalence decreased from 8.1% in 2007 to 5.0% in 2015–2016 (PR = 0.62; 95% CI 0.50–0.78). Non-VT high risk prevalence was higher in the vaccine periods compared with the pre-vaccine era in both age groups, however, not in 2015–2016 compared with 2012–2013.

Conclusion: Within 9–10 years of vaccine introduction, VT prevalence decreased 78% among 20–24 year-olds and 38% in 25–29 year-olds. There were declines in both vaccinated and unvaccinated women, showing evidence of direct and herd protection.

1. Background

After human papillomavirus (HPV) vaccine introduction in the United States and other countries, vaccination impact has been demonstrated on cervicovaginal HPV prevalence, genital warts and cervical precancers [1–5]. In the United States, HPV vaccine was first recommended in 2006 for females and in 2011 for males [6]. Routine vaccination is recommended at age 11 or 12 years. Vaccination is also recommended for females through age 26 years and for males through age 21 years who were not previously vaccinated. Almost all vaccine administered in the United States was quadrivalent vaccine (4vHPV) through 2015. In 2015, there was a gradual transition to 9-valent HPV vaccine (9vHPV); after the end of 2016, 9vHPV has been the only vaccine available in the United States. National vaccination coverage in 13–17 year-old females has increased over time and reached 65% for at least 1 dose and 43% for 3 doses in 2016; 50% were up-to-date based on the current 2 dose or 3 dose recommendations [7,8].

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Several studies were established in the United States to evaluate HPV vaccination impact, including studies of HPV prevalence, the first outcome for which impact was expected [1,9]. The National Health and Nutrition Examination Survey (NHANES) is one study examining HPV prevalence. While prevalence monitoring in a national survey has the advantage of being representative of the entire country, there are limitations including a fixed number of subjects in each age group and reliance on self-reported HPV vaccination status. In addition, initially it was not clear if the magnitude of vaccine impact would be large enough to be observed within the national survey. To supplement those data, prevalence monitoring was also initiated using specimens from women receiving cervical cancer screening [9,10]. From that study, we previously reported findings from vaccine era years 2012–2013, compared with 2007 (defined here as pre-vaccine era, as few women receiving screening had received vaccine and the analysis was restricted to unvaccinated women) [9]. There was a 42% decline in HPV types targeted by 4vHPV in 20–29 year-olds, from 10.6% to 6.2% [9]. Higher non-VT prevalence in the vaccine era was also observed. In the current analysis, we report data from additional years and compare prevalence in two vaccine time periods, 2012–2013 and 2015–2016, approximately 6–7 and 9–10 years after national vaccine introduction, with prevalence in 2007. We report prevalence separately for 20–24 and 25–29 year-olds and also evaluate evidence of herd protection by comparing prevalence among unvaccinated women in the vaccine years with prevalence in 2007.

2. Methods

2.1. Study description

Data collection methods in this integrated health care delivery system were previously reported [9,10]. Consecutive residual SurePath (TriPath Imaging, Burlington, NC, USA) liquid cytology cervical specimens from women aged 20–29 years undergoing routine cervical cancer screening at Kaiser Permanente Northwest (KPNW) were retained until target numbers in each age group were obtained (age groups: 20–24 year-olds and 25–29 year-olds). Sample size calculations indicated that 2000 specimens in each of the two age groups were needed to detect a 40% reduction of HPV 16/18 with 80% power. Dates of specimen collection varied slightly by year: May–December 2007 (baseline, unvaccinated only), and April–July 2012, March–July 2013, December 2014–March 2015, and January–May 2016. Retrieved specimens were stored for <37 days at ambient temperature and shipped to the Centers for Disease Control and Prevention (CDC). In 2007, data on age group and cervical cytology results were linked to each specimen. In 2012–2013 and 2015–2016, additional data on vaccination (administration dates, number of doses) and demographics were linked to each specimen. This study was approved by the Institutional Review Board at KPNW and was reviewed at CDC, where it was given a determination of non-engagement.

2.2. Laboratory methods

After receipt at CDC, SurePath specimens (approximately 3 ml) were stored at 4 °C until testing. Specimens were processed and extracted as previously reported [9]. As noted, the ABI Prism 6100 Nucleic Acid Prep Station and NucPrep reagents (Applied Biosystems, Carlsbad, CA) were used in 2007 and changed in 2012 to an automated magnetic bead system, Chemagic MSM1 (Chemagen, Baesweiler, Germany). Four water blanks were used with each set of 96 samples to control for cross-contamination.

HPV genotypes were determined using the Research Use Only Linear Array (LA) HPV Genotyping Test (Roche Molecular Diagnostics, Indianapolis, IN) and HPV 52 quantitative PCR as previously described [11]. The LA provides type-specific results for 37 HPV types (6/11/16/18/26/31/33/35/39/40/42/45/51/XR [52], 53/54/55/56/58/59/61/62/64/66/67/68/69/70/71/72/73/81/82/83/84/89/IS39). We considered specimens that were HPV negative and failed to amplify the cellular positive control (beta-globin) as inadequate and excluded them from the analysis; <0.3% of specimens were inadequate in each time period.

2.3. Data collection and analysis

Patient characteristics, including race and ethnicity, were obtained from administrative and electronic health records in 2012–2013 and 2015–2016. Family poverty was assigned based on geocoded Census tract information. Family poverty was dichotomized as patients living in a Census tract where <20% of households fall below the poverty line and patients living in a Census tract where ≥20% of households fall below the poverty line. Information about HPV vaccination was extracted from the electronic health record as well as the Oregon state immunization registry. We only counted vaccination doses administered ≥30 days before specimen collection. We compared characteristics of women in the two vaccine periods (2012–2013 and 2015–2016) by age group and by vaccination history (receipt of ≥1 vaccine dose) using chi-square tests. A p-value of <0.05 was considered significant.

To evaluate impact of the vaccination program, we determined HPV prevalence among 20–24 and 25–29 year-olds in three time periods: 2007, 2012–2013 and 2015–2016. Prevalence was analyzed in the following HPV type categories: any 4vHPV type (VT; HPV 6/11/16/18), HPV 16/18, HPV 6/11, 3 types for which potential cross-protection from HPV vaccines has been reported (HPV 31/33/45), non-VT high risk (non-VT HR; HPV 31/33/35/39/45/51/52/56/58/59/66/68), and any of 37 HPV types detected by LA except HPV 6/11/16/18 (non-VT).

Comparisons between 2007 and each of the vaccine periods, as well as comparisons between the two vaccine periods, were conducted for 20–24 and 25–29 year-olds, overall and by history of vaccination for each HPV type category. We also determined prevalence of individual HPV types. To compare HPV prevalence in 2012–2013 and 2015–2016 with 2007, and between the two vaccine periods, we calculated prevalence ratios (PRs) and 95% confidence intervals (CI) assuming binomial distribution using loglinear models. Analyses comparing the two vaccine periods were adjusted to account for the significant differences in population characteristics between the two periods; this did not change results and only unadjusted PRs are presented. All analyses were conducted using SAS version 9.3; prevalence, PR, and corresponding 95% CI estimates were calculated using PROC GENMOD.

3. Results

3.1. Population characteristics

Overall, 12,788 specimens were included in this analysis; at least 2000 from each age group (20–24 and 25–29 year-olds) in 2007, 2012–2013 and 2015–2016. In both vaccine periods and age groups, 69–72% of specimens were from non-Hispanic white women, which is consistent with the racial and ethnic characteristics of the health plan membership (Table 1). There were small but statistically significant differences in race/ethnicity between the vaccine periods in both age groups. These differences were mainly due to improved documentation of this information over time in the electronic health record.

Table 1
Characteristics of study population, 2012–2013 and 2015–2016, by age group.

Characteristic	20–24 years 2012–2013 N = 2057 n (%)	20–24 years 2015–2016 N = 2059 n (%)	p-value	25–29 years 2012–2013 N = 2114 n (%)	25–29 years 2015–2016 N = 2420 n (%)	p-value
Median age, years (IQR)	22 (21–23)	22 (21–24)		27 (26–28)	27 (26–28)	
Race/ethnicity						
NH white	1424 (69.2)	1473 (71.5)	<0.01	1494 (70.7)	1715 (70.9)	<0.01
NH Asian	70 (3.4)	94 (4.6)		114 (5.4)	166 (6.9)	
NH black	78 (3.8)	91 (4.4)		64 (3.0)	91 (3.8)	
Hispanic	177 (8.6)	256 (12.4)		173 (8.2)	261 (10.8)	
Other	62 (3.0)	78 (3.8)		60 (2.8)	76 (3.1)	
Unknown	246 (12.0)	67 (3.3)		209 (9.9)	111 (4.6)	
Family poverty						
≥20% below	484 (24.0)	521 (25.4)	0.28	533 (25.8)	654 (27.1)	0.34
<20% below	1536 (76.0)	1528 (74.6)		1534 (74.2)	1764 (73.0)	
HPV vaccination history[a]						
≥1 dose	898 (43.7)	1323 (64.3)	<0.01	433 (20.5)	775 (32.0)	<0.01
3 doses	612 (29.8)	1060 (51.5)	<0.01	251 (11.9)	498 (20.6)	<0.01
Median age at first dose, years (IQR)	17 (16–18)	15 (14–17)	<0.01	23 (21–24)	20 (18–23)	<0.01

IQR, interquartile range; NH, non-Hispanic; Family poverty, assigned based on geocoded Census tract information from household income.
Numbers do not add to total N in some categories due to exclusion of women with unknown characteristics.
p-value from Chi-square test.
[a] Includes vaccine doses administered 30 or more days before specimen collection.

In 2012–2013 and 2015–2016, 44% and 64% of women aged 20–24 years had received ≥1 HPV vaccine dose; 30% and 52% had received 3 doses. The median age at first dose was 17 years in 2012–2013 and 15 years in 2015–2016. Among women aged 25–29 years, 21% and 32% had received ≥1 dose in the two vaccine periods; 12% and 21% had received 3 doses. The median age at first dose was 23 and 20 years (Table 1).

3.2. Changes in HPV prevalence

Among 20–24 year-olds, VT prevalence decreased from 13.1% in the pre-vaccine era to 5.5% in 2012–2013 (PR = 0.42; 95% CI 0.34–0.52) and 2.9% in 2015–2016 (PR = 0.22; 95% CI 0.17–0.29) (Table 2 and Fig. 1). Compared with 2007, prevalences of HPV 16/18 and HPV 6/11 were each statistically lower in the vaccine periods. VT prevalence was lower in 2015–2016 than in 2012–2013. Prevalence of HPV 31/33/45 was lower in the vaccine periods compared with 2007; this was statistically significant in 2012–2013, (PR = 0.69, 95% CI 0.51–0.94). Non-VT HR and non-VT prevalences were higher in the vaccine periods compared with the pre-vaccine era; however, there were no differences in prevalence of these HPV type categories between 2012–2013 and 2015–2016.

Among 25–29 year-olds, VT prevalence was 8.1% in 2007, 6.9% in 2012–2013 (PR = 0.85; 95% CI 0.69–1.05) and 5.0% in 2015–

Table 2
HPV prevalence among women aged 20–24 and 25–29 years, 2007, 2012–2013 and 2015–2016.

HPV types/Years	20–24 years N	% (95% CI)	PR (95% CI)	PR (95% CI)[a]	25–29 years N	% (95% CI)	PR (95% CI)	PR (95% CI)[a]
VT								
2007	2057	13.1 (11.7–14.6)	1.00	NA	2081	8.1 (7.0–9.4)	1.00	NA
2012–2013	2057	5.5 (4.6–6.6)	0.42 (0.34–0.52)	1.00	2114	6.9 (5.9–8.1)	0.85 (0.69–1.05)	1.00
2015–2016	2059	2.9 (2.3–3.7)	0.22 (0.17–0.29)	0.53 (0.39–0.71)	2420	5.0 (4.2–6.0)	0.62 (0.50–0.78)	0.73 (0.58–0.92)
16/18								
2007	2057	10.6 (9.4–12.1)	1.00	NA	2081	7.2 (6.1–8.4)	1.00	NA
2012–2013	2057	4.5 (3.7–5.5)	0.42 (0.34–0.54)	1.00	2114	5.8 (4.9–6.9)	0.81 (0.64–1.02)	1.00
2015–2016	2059	2.5 (1.9–3.3)	0.24 (0.18–0.32)	0.56 (0.40–0.78)	2420	4.6 (3.8–5.5)	0.64 (0.50–0.81)	0.79 (0.62–1.02)
6/11								
2007	2057	3.1 (2.4–3.9)	1.00	NA	2081	1.5 (1.1–2.1)	1.00	NA
2012–2013	2057	1.4 (1.0–2.0)	0.46 (0.30–0.71)	1.00	2114	1.3 (0.9–1.9)	0.86 (0.51–1.43)	1.00
2015–2016	2059	0.5 (0.3–1.0)	0.17 (0.09–0.33)	0.38 (0.19–0.76)	2420	0.5 (0.3–0.9)	0.36 (0.19–0.69)	0.42 (0.22–0.81)
31/33/45								
2007	2057	4.7 (3.9–5.7)	1.00	NA	2081	3.8 (3.1–4.7)	1.00	NA
2012–2013	2057	3.3 (2.6–4.1)	0.69 (0.51–0.94)	1.00	2114	4.0 (3.2–4.9)	1.05 (0.77–1.41)	1.00
2015–2016	2059	3.5 (2.8–4.4)	0.75 (0.56–1.01)	1.09 (0.79–1.51)	2420	3.3 (2.6–4.1)	0.86 (0.63–1.17)	0.82 (0.61–1.11)
Non-VT HR								
2007	2057	20.3 (18.6–22.1)	1.00	NA	2081	14.8 (13.4–16.5)	1.00	NA
2012–2013	2057	25.6 (23.8–27.6)	1.26 (1.13–1.41)	1.00	2114	18.6 (17.0–20.4)	1.26 (1.10–1.44)	1.00
2015–2016	2059	25.7 (23.9–27.7)	1.27 (1.13–1.42)	1.00 (0.91–1.11)	2420	15.7 (14.4–17.3)	1.06 (0.92–1.22)	0.84 (0.74–0.96)
Non-VT								
2007	2057	32.9 (30.9–35.0)	1.00	NA	2081	24.4 (22.6–26.3)	1.00	NA
2012–2013	2057	41.6 (39.5–43.8)	1.26 (1.17–1.37)	1.00	2114	32.8 (30.9–34.9)	1.34 (1.22–1.48)	1.00
2015–2016	2059	40.6 (38.5–42.8)	1.24 (1.14–1.34)	0.98 (0.91–1.05)	2420	29.0 (27.3–30.9)	1.19 (1.08–1.31)	0.88 (0.81–0.96)

VT, quadrivalent vaccine types; Non-VT, non-quadrivalent vaccine types; HR, high risk; N, number tested; PR, prevalence ratio; CI, confidence interval; NA, not applicable.
[a] Prevalence ratio comparing 2015–2016 with 2012–2013.

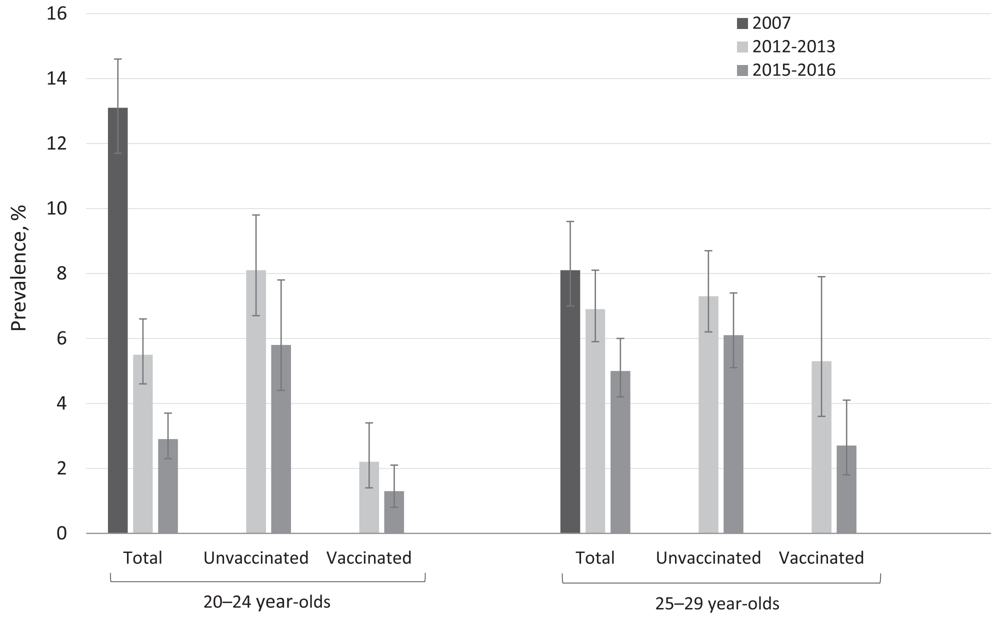

Fig. 1. Vaccine-type HPV prevalence (HPV 6/11/16/18) among women aged 20–24 years and 25–29 years, 2007, 2012–2013 and 2015–2016, overall and by vaccination status. Vaccinated, receipt of at least one HPV vaccine dose 30 or more days before specimen collection. Error bars represent 95% confidence intervals.

2016 (PR = 0.62; 95% CI 0.50–0.78) (Table 2 and Fig. 1). In the later vaccine period, prevalences of HPV 16/18 and HPV 6/11 were each statistically lower than in 2007. Prevalences of non-VT HR and any non-VT were higher in the first vaccine period compared with the pre-vaccine era, but only any non-VT was higher in the later vaccine period. Prevalence of these non-VT categories did not increase between the two vaccine periods.

3.3. Population characteristics and HPV prevalence by vaccination status

Characteristics of women were compared across vaccine periods for both vaccinated and unvaccinated; there were small differences in race/ethnicity and family poverty (among vaccinated) that were statistically significant among 20–24 years-olds and in race/ethnicity among 25–29 year-olds. Differences were also observed between vaccinated and unvaccinated women within each vaccine period (Supplementary Tables 1 and 2).

VT prevalence was significantly lower in both unvaccinated and vaccinated 20–24 year-olds in the two vaccine periods compared with 2007 (Table 3 and Fig. 1). VT prevalence was 13.1% in 2007; in 2015–2016, VT prevalence was 5.8% (PR = 0.45; 95% CI 0.33–0.61) among unvaccinated and 1.3% (PR = 0.10; 95% CI 0.06–0.16) among vaccinated women. Prevalences of non-VT HR and any non-VT were higher in both unvaccinated and vaccinated women in the vaccine periods compared with 2007; there was no difference in non-VT prevalence between the two vaccine periods. In 25–29 year-olds, significantly lower VT prevalence was also observed in 2015–2016 compared with 2007 among unvaccinated, 6.1% (PR = 0.76; 95% CI 0.60–0.96), and vaccinated women, 2.7% (PR = 0.33; 95% CI 0.21–0.52) (Table 4 and Fig. 1). Differences in non-VT prevalence between the pre-vaccine and vaccine periods were similar to those observed in the younger age group.

3.4. Individual HPV type prevalence

To further explore changes in HPV type categories, we evaluated prevalence of individual HPV types (Supplementary Figs. 1, 2 and Supplementary Tables 3, 4). Among 20–24 year-olds, in addition to the declines in HPV 6, 16 and 18, HPV 31 prevalence was significantly lower in 2012–2013 (PR = 0.45; 95% CI 0.29–0.71) and 2015–2016 (PR = 0.63; 95% CI 0.42–0.95) compared to the pre-vaccine era. Prevalences were higher for non-VT HR types 35, 51, 52, 58 and 59 and 10 non-VT non-HR types in at least one vaccine period. Between the two vaccine periods, there were no increases in prevalence of any individual HR type. Among 25–29 year-olds, prevalences were higher for non-VT HR types 39, 51 and 59, and 10 non-VT non-HR types in at least one vaccine period. The HPV types with increases were generally the same in both vaccinated and unvaccinated women (data not shown).

4. Discussion

In this evaluation of women screened for cervical cancer in an integrated health plan in the United States we found large decreases in VT prevalence among 20–24 year-olds in the vaccine era. There was a 58% reduction in VT prevalence by 6–7 years after vaccine introduction and a 78% reduction by 9–10 years. Among women in this age group, only 44% and 64% had received at least 1 vaccine dose. There was evidence of both direct and herd protection from vaccination with prevalence 90% lower among vaccinated women and 55% lower among unvaccinated women in 2015–2016 compared with 2007. Among 25–29 year-olds, there was a smaller but significant 38% reduction 9–10 years after introduction; 32% of women in this age group had received at least 1 vaccine dose. Almost all women in both age groups had received vaccine as part of catch-up vaccination.

Other studies from the United States and other countries have demonstrated reductions in VT prevalence after introduction of HPV vaccine [12]. In the United States, a nationally representative survey found a 56% reduction in VT prevalence in females aged 14–19 years within 4 years of the start of the vaccine program and a 34% reduction in 20–24 years-olds within 6 years [1,2]. By 8 years after vaccine introduction, a 61% reduction was observed among 20–24 year-olds [3]. The current study, with larger decreases in this age group at 9–10 years after introduction, is consistent with national U.S. data. Of note, women in this analysis differ from those in the general U.S. population and are likely to have higher HPV vaccine coverage and compliance with screening due to their participation in an integrated health care delivery system. Countries

Table 3
HPV prevalence among 20–24 year-old women, 2007, 2012–2013 and 2015–2016, by vaccination status.

	Unvaccinated women				Vaccinated women			
HPV types/Years	N	% (95% CI)	PR (95% CI)	PR (95% CI)[a]	N	% (95% CI)	PR (95% CI)[b]	PR (95% CI)[a]
VT								
2007	2057	13.1 (11.7–14.6)	1.00	NA	–	–	1.00	NA
2012–2013	1159	8.1 (6.7–9.8)	0.62 (0.50–0.78)	1.00	898	2.2 (1.4–3.4)	0.17 (0.11–0.27)	1.00
2015–2016	736	5.8 (4.4–7.8)	0.45 (0.33–0.61)	0.72 (0.51–1.02)	1323	1.3 (0.8–2.1)	0.10 (0.06–0.16)	0.58 (0.30–1.10)
16/18								
2007	2057	10.6 (9.4–12.1)	1.00	NA	–	–	1.00	NA
2012–2013	1159	6.7 (5.4–8.3)	0.63 (0.49–0.81)	1.00	898	1.7 (1.0–2.8)	0.16 (0.09–0.26)	1.00
2015–2016	736	5.0 (3.7–6.9)	0.47 (0.34–0.66)	0.75 (0.51–1.09)	1323	1.1 (0.7–1.9)	0.11 (0.06–0.18)	0.68 (0.33–1.38)
6/11								
2007	2057	3.1 (2.4–3.9)	1.00	NA	–	–	1.00	NA
2012–2013	1159	2.0 (1.3–3.0)	0.65 (0.40–1.04)	1.00	898	0.7 (0.3–1.5)	0.22 (0.09–0.50)	1.00
2015–2016	736	1.2 (0.6–2.3)	0.40 (0.20–0.80)	0.62 (0.29–1.32)	1323	0.2 (0.0–0.6)	0.05 (0.01–0.20)	0.23 (0.05–1.12)
31/33/45								
2007	2057	4.7 (3.9–5.7)	1.00	NA	–	–	1.00	NA
2012–2013	1159	3.2 (2.3–4.4)	0.68 (0.47–0.98)	1.00	898	3.3 (2.3–4.7)	0.71 (0.47–1.06)	1.00
2015–2016	736	3.9 (2.8–5.6)	0.84 (0.56–1.25)	1.23 (0.77–1.99)	1323	3.3 (2.5–4.4)	0.71 (0.50–1.00)	1.00 (0.63–1.57)
Non-VT HR								
2007	2057	20.3 (18.6–22.1)	1.00	NA	–	–	1.00	NA
2012–2013	1159	25.5 (23.1–28.1)	1.26 (1.10–1.43)	1.00	898	25.8 (23.1–28.9)	1.27 (1.11–1.47)	1.00
2015–2016	736	23.9 (21.0–27.2)	1.18 (1.01–1.38)	0.94 (0.80–1.10)	1323	26.8 (24.5–29.3)	1.32 (1.17–1.49)	1.04 (0.90–1.19)
Non-VT								
2007	2057	32.9 (30.9–35.0)	1.00	NA	–	–	1.00	NA
2012–2013	1159	41.3 (38.6–44.3)	1.26 (1.15–1.38)	1.00	898	41.9 (38.8–45.2)	1.27 (1.15–1.41)	1.00
2015–2016	736	37.5 (34.2–41.2)	1.14 (1.02–1.28)	0.91 (0.81–1.02)	1323	42.3 (39.7–45.1)	1.29 (1.18–1.41)	1.01 (0.92–1.12)

Vaccinated, includes women who received first HPV vaccine dose at least 30 days before specimen collection; N, number tested; PR, prevalence ratio; CI, confidence interval; VT, quadrivalent HPV vaccine types; Non-VT, non-quadrivalent vaccine type; HR, high risk; NA, not applicable.
[a] Prevalence ratio comparing 2015–2016 with 2012–2013.
[b] Referent group for vaccinated and unvaccinated women are women in 2007 (all unvaccinated).

Table 4
HPV prevalence among 25–29 year-old women, 2007, 2012–2013 and 2015–2016, by vaccination status.

	Unvaccinated women				Vaccinated women			
HPV types/Years	N	% (95% CI)	PR (95% CI)	PR (95% CI)[a]	N	% (95% CI)	PR (95% CI)[b]	PR (95% CI)[a]
VT								
2007	2081	8.1 (7.0–9.4)	1.00	NA	–	–	1.00	NA
2012–2013	1681	7.3 (6.2–8.7)	0.90 (0.72–1.13)	1.00	433	5.3 (3.6–7.9)	0.65 (0.43–1.00)	1.00
2015–2016	1645	6.1 (5.1–7.4)	0.76 (0.60–0.96)	0.84 (0.65–1.08)	775	2.7 (1.8–4.1)	0.33 (0.21–0.52)	0.51 (0.29–0.91)
16/18								
2007	2081	7.2 (6.1–8.4)	1.00	NA	–	–	1.00	NA
2012–2013	1681	6.1 (5.0–7.3)	0.85 (0.66–1.08)	1.00	433	4.6 (3.0–7.1)	0.65 (0.41–1.02)	1.00
2015–2016	1645	5.6 (4.6–6.8)	0.78 (0.61–1.00)	0.92 (0.70–1.21)	775	2.5 (1.6–3.8)	0.34 (0.21–0.55)	0.53 (0.29–0.98)
6/11								
2007	2081	1.5 (1.1–2.1)	1.00	NA	–	–	1.00	NA
2012–2013	1681	1.4 (1.0–2.1)	0.96 (0.56–1.63)	1.00	433	0.7 (0.2–2.1)	0.47 (0.14–1.51)	1.00
2015–2016	1645	0.7 (0.4–1.2)	0.45 (0.23–0.89)	0.47 (0.23–0.95)	775	0.3 (0.1–1.0)	0.17 (0.04–0.72)	0.37 (0.06–2.22)
31/33/45								
2007	2081	3.8 (3.1–4.7)	1.00	NA	–	–	1.00	NA
2012–2013	1681	3.9 (3.0–4.9)	1.02 (0.74–1.41)	1.00	433	4.4 (2.8–6.8)	1.16 (0.71–1.89)	1.00
2015–2016	1645	3.1 (2.4–4.1)	0.82 (0.58–1.15)	0.80 (0.56–1.15)	775	3.6 (2.5–5.2)	0.95 (0.62–1.45)	0.82 (0.47–1.46)
Non-VT HR								
2007	2081	14.8 (13.4–16.5)	1.00	NA	–	–	1.00	NA
2012–2013	1681	17.8 (16.1–19.8)	1.20 (1.04–1.39)	1.00	433	21.7 (18.2–26.0)	1.46 (1.19–1.80)	1.00
2015–2016	1645	14.2 (12.6–16.0)	0.95 (0.82–1.12)	0.79 (0.68–0.93)	775	19.1 (16.5–22.1)	1.29 (1.08–1.54)	0.88 (0.70–1.11)
Non-VT								
2007	2081	24.4 (22.6–26.3)	1.00	NA	–	–	1.00	NA
2012–2013	1681	30.6 (28.5–32.9)	1.25 (1.13–1.39)	1.00	433	41.6 (37.2–46.5)	1.70 (1.49–1.95)	1.00
2015–2016	1645	26.8 (24.8–29.0)	1.10 (0.98–1.23)	0.88 (0.79–0.98)	775	33.7 (30.5–37.2)	1.38 (1.22–1.56)	0.81 (0.70–0.94)

Vaccinated, includes women who received first HPV vaccine dose at least 30 days before specimen collection; N, number tested; PR, prevalence ratio; CI, confidence interval; VT, quadrivalent HPV vaccine types; Non-VT, non-quadrivalent vaccine types; HR, high risk; NA, not applicable.
[a] Prevalence ratio comparing 2015–2016 with 2012–2013.
[b] Referent group for vaccinated and unvaccinated women are women in 2007 (all unvaccinated).

that achieved higher coverage than the United States have reported even greater decreases in VT prevalence. For example, in Australia coverage reached over 80% in the target age group (girls aged 12–13 years) with high coverage also in the catch-up population (women through age 26 years) soon after vaccine introduction. In 18–24 year-old women, VT prevalence declined from 29% to 7%

at 4–5 years after vaccine introduction and to 1.5% at 9 years, a decline of 95% [13]. In Scotland, another country with high coverage in the routine target age group (>90%) and with catch-up vaccination through age 18 years, prevalence was monitored in women aged 20–21 years [14]. Within 7 years after bivalent vaccine introduction, HPV 16/18 prevalence declined from 28.9% to 4.8%. The age groups and time in which declines will be observed depend on vaccination coverage and the extent of the catch-up vaccination program, as a wider catch-up age group will decrease the time needed to observe impact [15].

We also explored prevalence of 3 types, HPV 31/33/45, for which other post-introduction studies have reported evidence of cross protection, particularly in countries that introduced 2vHPV [14,16]. We found lower HPV 31/33/45 prevalence compared with 2007 among 20–24 year-olds, which was significant in the first vaccine period. For individual types, only HPV 31 prevalence was significantly lower in both vaccine periods compared with 2007. Cross-protection against HPV 31 was found in the 4vHPV trials and in some vaccine effectiveness studies [6,17].

Consistent with the previous report from this project, we found higher any non-VT prevalence in the vaccine periods compared with pre-vaccine era. In our first publication, results were reported for 20–29 year-olds combined and only data from 2012–2013 were available [9]. The current analysis includes data from subsequent years using the same sampling method. Factors that may have impacted non-VT prevalence include changes in laboratory methods and risk behavior of women attending screening. There were some differences in laboratory specimen processing starting in 2012, including a more consistent interval from specimen collection to freezing and changes in the extraction methods to improve sensitivity. We do not have data on how these changes impacted our findings, but it is possible that increased sensitivity contributed to the higher non-VT prevalence observed in the vaccine era. Higher sensitivity also would have resulted in an underestimate of impact on VT prevalence and a decreased ability to detect cross protection against some non-vaccine types. Similar effects on VT and non-VT prevalence relative to the pre-vaccine era could have occurred if higher risk women were attending cervical cancer screening during the vaccine era. Because we did not have data on sexual behavior in this study, we cannot determine if higher risk woman were attending screening in 2012 and later compared with 2007. National surveys of women in the United States have not reported an increase in sexual risk behavior in this age group [18], but there could have been differences in the screened populations.

Reports from other countries have also noted higher non-VT prevalence in the vaccine compared with the pre-vaccine era but no differences between years in the vaccine era. Such findings were observed in Scotland and England, where bivalent HPV vaccine was introduced [14,16]. In the England study, an assay change between the pre-vaccine and vaccine era could have contributed to the findings. Similar to our study, no change was observed in non-VT prevalence within the vaccine era as VT prevalence continued to decline [16]. Although there have been investigations of possible type replacement after HPV vaccine introduction, no definitive evidence has been found [17]. In contrast to findings from this report, no significant increases in non-VT prevalence have been observed in national monitoring in the United States through NHANES [3].

Herd effects from HPV vaccination have been observed in other countries with high coverage; however, there are less data in low coverage settings [3,12,19]. In the United States, herd effects have been shown among 14–24 year-olds in a nationally representative survey, where coverage of at least one dose was 51% [3]. To explore evidence of herd protection in our study we evaluated prevalence by vaccination status. VT prevalences in 2015–2016 among vaccinated 20–24 and 25–29 year-old women were 90% and 67% lower than in 2007. In those unvaccinated, the declines were 55% and 24%, respectively. While the lower prevalence among unvaccinated women compared with 2007 suggests evidence of herd protection, we also considered whether the declines could have been due to lower risk behavior. Non-VT prevalence was higher in both vaccinated and unvaccinated women compared with 2007 suggesting no decrease in sexual exposure. Moreover, among 20–24 year-olds, non-VT HPV prevalence was similar among vaccinated and unvaccinated women in the vaccine periods, suggesting that exposure to HPV and sexual risk behavior did not differ by vaccination status. In contrast, among 25–29 year-olds, non-VT prevalence was lower in unvaccinated compared with vaccinated women. Based on these findings, we feel confident that the lower VT prevalence among unvaccinated 20–24 year-olds in the vaccine eras compared with 2007 indicates herd effects; however, we cannot be certain about herd effects among 25–29 year-olds.

There are several limitations to this assessment. First, our population included women screened for cervical cancer. Although cervical cancer screening adherence is high within KPNW, the women may not be representative of all women enrolled in the integrated healthcare delivery system. Second, we lacked demographic data from women in the pre-vaccine era and data on sexual behavior in all years, which limited some of our analyses. Third, during the time period of this study, cervical cancer screening recommendations changed in the United States, with recommendations to start screening at age 21 and for less frequent screening [20]. Our pre-vaccine era assessment included 20 year-olds, and we included 20 year-olds in our assessments going forward; women screened at age 20 might have been at higher risk than those in 2007. Fourth, although we conducted this study in an integrated health care delivery system in order to have access to documented HPV vaccination records, it is possible that women could have received vaccine outside of the system. Under ascertainment of vaccination would have resulted in an over estimation of herd effects. Finally, as discussed earlier, there was a change in laboratory specimen processing starting in 2012, which could have led to increased sensitivity for HPV detection.

In summary, this assessment of HPV prevalence in an insured population of 20–24 and 25–29 year-old women in the Northwest United States found decreasing VT HPV prevalence over time in the vaccine era. In addition, despite $\geq$1 dose vaccination coverage of only 44% and 64% in the two vaccine periods among 20–24 years-olds, there was evidence of herd effects among unvaccinated women. These data add to the strong evidence accumulating on impact of the HPV vaccination program in the United States.

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Conflict of interest disclosures

A Naleway has received research funding from Pfizer, Takeda, MedImmune, and Merck for unrelated studies. No other authors have conflicts of interest to disclose.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.099.

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