

Trends in Human Papillomavirus Vaccine Types 16 and 18 in Cervical Precancers, 2008–2014

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Abstract

Background: The impact of human papillomavirus (HPV) vaccination has been observed in the United States through declining cervical precancer incidence in young women. To further evaluate vaccine impact, we described trends in HPV vaccine types 16/18 in cervical precancers, 2008–2014.

Methods: We analyzed data from a 5-site, population-based surveillance system. Archived specimens from women age 18–39 years diagnosed with cervical intraepithelial neoplasia grades 2–3 or adenocarcinoma *in situ* (CIN2+) were tested for 37 HPV types. We described the proportion and estimated number of cases of CIN2+ by HPV-type groups over time. Trends in HPV16/18-positive CIN2+ were examined, overall and by vaccination status, age, histologic grade, and race/ethnicity, using Cochran–Armitage tests.

Results: In 10,206 cases, the proportion and estimated number of cases of HPV16/18-positive CIN2+ declined from

52.7% (1,235 cases) in 2008 to 44.1% (819 cases) in 2014 ($P < 0.001$). Declining trends in the proportion of HPV16/18-positive CIN2+ were observed among vaccinated (55.2%–33.3%, $P < 0.001$) and unvaccinated (51.0%–47.3%, $P = 0.03$) women; ages 18–20 (48.7%–18.8%, $P = 0.02$), 21–24 (53.8%–44.0%, $P < 0.001$), 25–29 (56.9%–42.4%, $P < 0.001$), and 30–34 (49.8%–45.8%, $P = 0.04$) years; CIN2 (40.8%–29.9%, $P < 0.001$) and CIN2/3 (61.8%–46.2%, $P < 0.001$); non-Hispanic white (59.5%–47.9%, $P < 0.001$) and non-Hispanic black (40.7%–26.5%, $P < 0.001$).

Conclusions: From 2008–2014, the proportion of HPV16/18-positive CIN2+ declined, with the greatest declines in vaccinated women; declines in unvaccinated women suggest herd protection.

Impact: The declining proportion of HPV16/18-positive CIN2+ provides additional evidence of vaccine impact in the United States.

Introduction

The human papillomavirus (HPV) vaccine was introduced in the United States in 2006 for the primary prevention of HPV-associated morbidity and mortality (1). Three HPV vaccines are currently licensed and recommended in the United States, all of which target HPV types 16 and 18, responsible for approximately 70% of cervical cancers worldwide (2, 3). Nearly all vaccine administered in the United States from 2006–2015 was the quadrivalent HPV vaccine (4vHPV) that additionally targets HPV types 6 and 11, types that cause most anogenital warts and recurrent respiratory papillomatosis cases. The 9-valent HPV

vaccine (9vHPV) that targets five additional oncogenic HPV types (31/33/45/52/58) was licensed in 2015 and became the only HPV vaccine available in the United States in 2017. In females, HPV vaccine is recommended routinely for 11- to 12-year-olds and for catch-up vaccination through age 26 years, in a 2- or 3-dose schedule depending on age of initiation (1). Coverage of ≥ 1 HPV vaccine dose was 65.1% in 13- to 17-year-old girls in 2016, and 49.5% were up to date on all the recommended doses (4). Among women 19–26 years old, ≥ 1 dose coverage has steadily increased to 41.6% in 2015 (5).

Although HPV vaccination coverage remains moderate, the impact of vaccination programs has already been observed in the United States. Within 4 to 6 years of vaccine introduction, declines were observed in early outcomes of HPV infections and anogenital warts (6, 7), and within 8 years, declines were observed in the intermediate outcome of cervical precancer in young women (8, 9). Cervical precancer is the most proximal outcome to cervical cancer, typically developing within years of HPV infection and is detected through routine cervical cancer screening. In the United States, data from the HPV Vaccine Impact Monitoring Project (HPV-IMPACT), a population-based, active surveillance system, is used to monitor trends in cervical precancer incidence, including HPV typing on archived diagnostic specimens from women age 18–39 years (8). Since vaccine introduction, cervical precancer incidence has declined 56% among 18–20 year olds and 39% among 21–24 year olds reported to HPV-IMPACT (10).

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Although a declining cervical precancer incidence is consistent with the impact of HPV vaccination, the interpretation of this decline is complicated by changes to cervical cancer screening guidelines since vaccine introduction, such as delayed initiation of screening and longer screening intervals (11). Because precancers are detected through routine cervical screening, these changes may also lead to a decreased precancer incidence. A reduction in HPV vaccine types detected in cervical precancers would provide more specific evidence that vaccine is impacting disease. If the number of cervical precancers due to vaccine types is declining, and those due to nonvaccine HPV types are not changing, the relative proportion of cervical precancers due to vaccine types would be observed to decrease. Early evidence of a reduction in the proportion of cervical lesions due to HPV types 16 or 18 (16/18) in 2008–2012 was observed by HPV-IMPACT among women receiving ≥ 1 dose of HPV vaccine (12). To update these findings and further evaluate vaccine impact, we described trends in the proportion of cervical precancers positive for HPV types 16/18 from 2008 through 2014. We also evaluated vaccine impact in population subgroups. In addition to vaccination status, we evaluated trends by age group and histologic grade of lesion, in which we expected to observe differential trends based on observations of precancer incidence, and by race/ethnicity, in which baseline differences in HPV 16/18 prevalence have been observed (13).

Materials and Methods

Study design/population

HPV-IMPACT was established in 2008 by the Centers for Disease Control and Prevention (CDC) in collaboration with five sites in the Emerging Infections Program: California, Connecticut, New York, Oregon, and Tennessee. Each site has a defined county or zip code–based catchment area that includes a population of females aged ≥ 18 years ranging from about 230,000 to 330,000. HPV-IMPACT was determined to be public health surveillance, and exempt from CDC and most sites' institutional review board (IRB) review. IRB approval was obtained from one site as required (14).

All histopathology laboratories serving the catchment areas reported cases of cervical intraepithelial neoplasia (CIN) grades 2, 2/3, 3, and adenocarcinoma *in situ* (AIS), collectively referred to as CIN2+, to each site. Cases were identified using standard classification systems and nomenclature and deduplicated at the surveillance site. Demographic and clinical data were collected from medical chart review, vaccine registries, or patient interview.

A detailed description of laboratory methods has been described previously (15). Among females aged 18–39 years, CDC obtained an archived diagnostic specimen, representing the highest grade lesion, for HPV typing. The presence of a CIN2+ lesion was verified by a pathologist at CDC. HPV DNA was extracted from the tissue and tested for 37 different HPV types with a HPV genotyping assay using nucleic acid–amplification methods. Specimens with inadequate or HPV-negative results were retested using a different genotyping assay (16). Specimens negative for HPV and the genomic control probe in both genotyping assays were considered inadequate and excluded from analysis.

Study variables

This analysis was restricted to HPV-IMPACT cases identified in women ages 18–39 years, diagnosed with CIN2+ in 2008–2014

that had valid HPV typing results. HPV vaccination status was categorized as vaccinated (≥ 1 dose received before the screening test that triggered evaluation of the lesion), unvaccinated (vaccinated on or after trigger screen test or medical record documentation of no vaccination), or unknown. Women who were vaccinated, but had unknown timing of vaccination in relation to trigger screen test, were excluded from vaccination analyses ($n = 432$). Age was categorized into five groups: 18–20, 21–24, 25–29, 30–34, and 35–39 years. Specimens were classified on the basis of the diagnostic pathology report and by histologic grade [CIN2, CIN2/3, CIN3, AIS; (AIS = AIS \pm CIN)]. Race/ethnicity was categorized as non-Hispanic white (NHW), non-Hispanic black (NHB), Hispanic, Asian, "other," and unknown. For descriptive analyses, HPV types were classified hierarchically into five mutually exclusive categories. The five categories, starting with the highest in the hierarchy were HPV 16/18; other high-risk (HR) vaccine types (31/33/45/52/58); other HR-HPV types (35/39/51/56/57/66/68); and other HPV types (6/11/26/40/41/42/53/54/55/61/62/64/67/69/70/71/72/73/81/82/83/84/89/IS39) or no HPV. Hierarchical classification attributes individual lesions to a single type group even if multiple types were detected; for example, if a lesion tests positive for HPV types 16 and 35, the case would be classified as attributable to the HPV16/18 group. For the trends analyses, HPV types were classified solely on the basis of detection of HPV 16 and/or 18 (HPV 16/18 or no HPV 16/18).

Statistical analysis

Demographic and clinical characteristics were described in cases with and without typing results available. Among cases with typing results, the proportions of CIN2+ lesions attributed to each hierarchical HPV-type category was calculated for each year. The total number of cases by HPV-type category was estimated for each year, by multiplying the total number of cases reported by the proportion of cases in each HPV-type category. Cochran–Armitage trend tests were used to evaluate significant trends over time (2008–2014) in the proportion of CIN2+ positive for HPV16/18, overall and stratified by vaccination status, age group, histologic grade, and race/ethnicity (excluding "other" and unknown race). The distribution of age, histologic grade of diagnosis, time period of diagnosis, and vaccination status were compared by race/ethnicity using χ^2 tests. Statistical significance was set at $P < 0.05$ for all tests. All analyses were conducted in SAS version 9.4 (SAS Institute).

Results

From 2008–2014, 14,637 CIN2+ cases diagnosed among women ages 18–39 years were reported to HPV-IMPACT. Representative archived diagnostic specimens were available for 10,277 cases (69.8%); 10,206 (99.3%) had valid HPV typing results. Overall, mean age of women was 28 years and the majority were NHW (53.0%), diagnosed with a CIN2 lesion (50.6%), and diagnosed in 2008–2011 (60.2%; Table 1). Few women with CIN2+ were vaccinated (10.2%), but the majority had unknown vaccination status (57.7%). Women with and without typed lesions were similar with respect to most characteristics. Compared with women without typed lesions, women with typed lesions had a slightly higher proportion of CIN3 (31.8% vs. 28.9%) and vaccination (10.8% vs. 8.8%). Of the 1,065 women with typed lesions who were vaccinated, 84% were at least 18 years old at time of vaccination and only one was vaccinated at a

Table 1. Characteristics of 18–39 year-old women with CIN2±, with and without typing data, 2008–2014

	Overall N (%)	Typed n (%)	Not typed n (%)
Total	14,637	10,206 (69.7%)	4,431 (30.3%)
Age(years)			
Mean (SD)	28.2 (5.1)	28.1 (5.1)	28.4 (5.1)
18–20	545 (3.7)	391 (3.8)	154 (3.5)
21–24	3,451 (23.6)	2,464 (24.1)	987 (22.3)
25–29	5,091 (34.8)	3,553 (34.8)	1,538 (34.7)
30–34	3,540 (24.2)	2,452 (24.0)	1,088 (24.8)
35–39	2,010 (13.7)	1,346 (13.2)	664 (15.0)
Race/ethnicity			
Non-Hispanic white	7,759 (53.0)	5,526 (54.1)	2,233 (50.4)
Non-Hispanic black	2,079 (14.2)	1,458 (14.3)	621 (14.0)
Hispanic	1,961 (13.4)	1,334 (13.1)	627 (14.2)
Asian	590 (4.0)	451 (4.4)	139 (3.1)
Other	672 (4.6)	394 (3.9)	278 (6.3)
Missing	1576 (10.8)	1043 (10.2)	533 (12.0)
Histologic grade of lesion			
CIN2	7,411 (50.6)	5,071 (49.7)	2,340 (52.8)
CIN2/3	2,431 (16.6)	1,723 (16.9)	708 (16.0)
CIN3	4,521 (30.9)	3,242 (31.8)	1,279 (28.9)
AIS	274 (1.9)	170 (1.7)	104 (2.3)
Time period of diagnosis			
2008–2011	8,811 (60.2)	6,137 (60.1)	2,674 (60.3)
2012–2014	5,826 (39.8)	4,069 (39.9)	1,757 (39.7)
HPV Vaccination status*			
Vaccinated	1,445 (10.2)	1,065 (10.8)	380 (8.8)
Not vaccinated	4,554 (32.1)	3,280 (33.1)	1,274 (29.6)
Unknown	8,206 (57.7)	5,555 (56.1)	2,651 (61.6)

*Women with unknown timing of vaccination were excluded (n = 432); CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ with or without CIN.

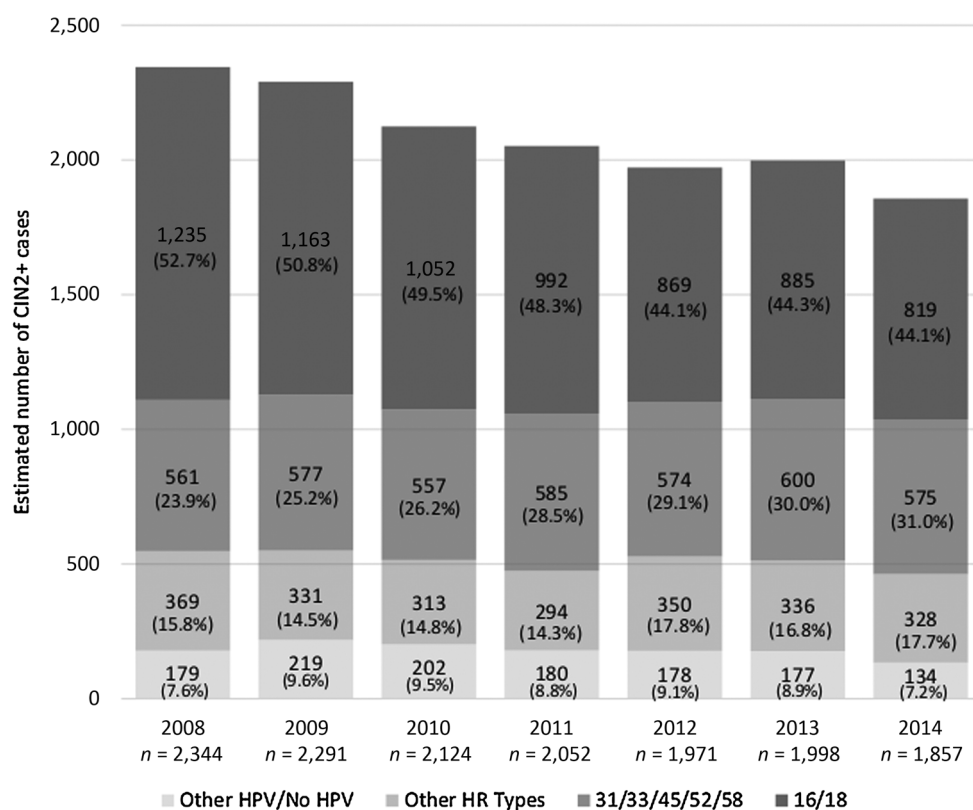


Figure 1. Total reported CIN2+ cases, proportion and estimated number of cases by HPV type category, 2008–2014. CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HR, high-risk. Estimated number of CIN2+ cases in each HPV type category = total cases (typed + nontyped) × proportion of typed cases with types in respective type categories.

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routine age (11 or 12 years). The proportion of vaccinated women who were vaccinated before age 18 increased from 1.9% in 2008 to 25.9% in 2014.

HPV types detected in CIN2+

Of the 10,206 specimens with valid HPV typing results, 9,948 (97.5%) were positive for HPV. The majority of specimens (77.8%) had a single HPV type detected. Among specimens with multiple HPV types detected, most included two types (77.7%), with a range of 2–14 types detected; 53.9% of multiple-type infections included HPV16/18.

The number of cases of CIN2+ reported to HPV-IMPACT declined 21%, from 2,344 cases in 2008 to 1,857 cases in 2014 (Fig. 1). In all years, the majority or plurality of cases were HPV16/18-positive. The proportion of typed cases that were positive for HPV 16/18 declined from 52.7% in 2008 to 44.1% in 2014 ($P < 0.001$). Correspondingly, the estimated number of all reported cases attributed to HPV 16/18 declined from 1,235 cases in 2008 to 819 cases in 2014. The proportion of cases attributed to HPV 31/33/45/52/58 increased from 23.9% in 2008 to 31.0% in 2014 ($P < 0.001$). However, when applying this proportion to the declining overall incidence, the estimated number of cases

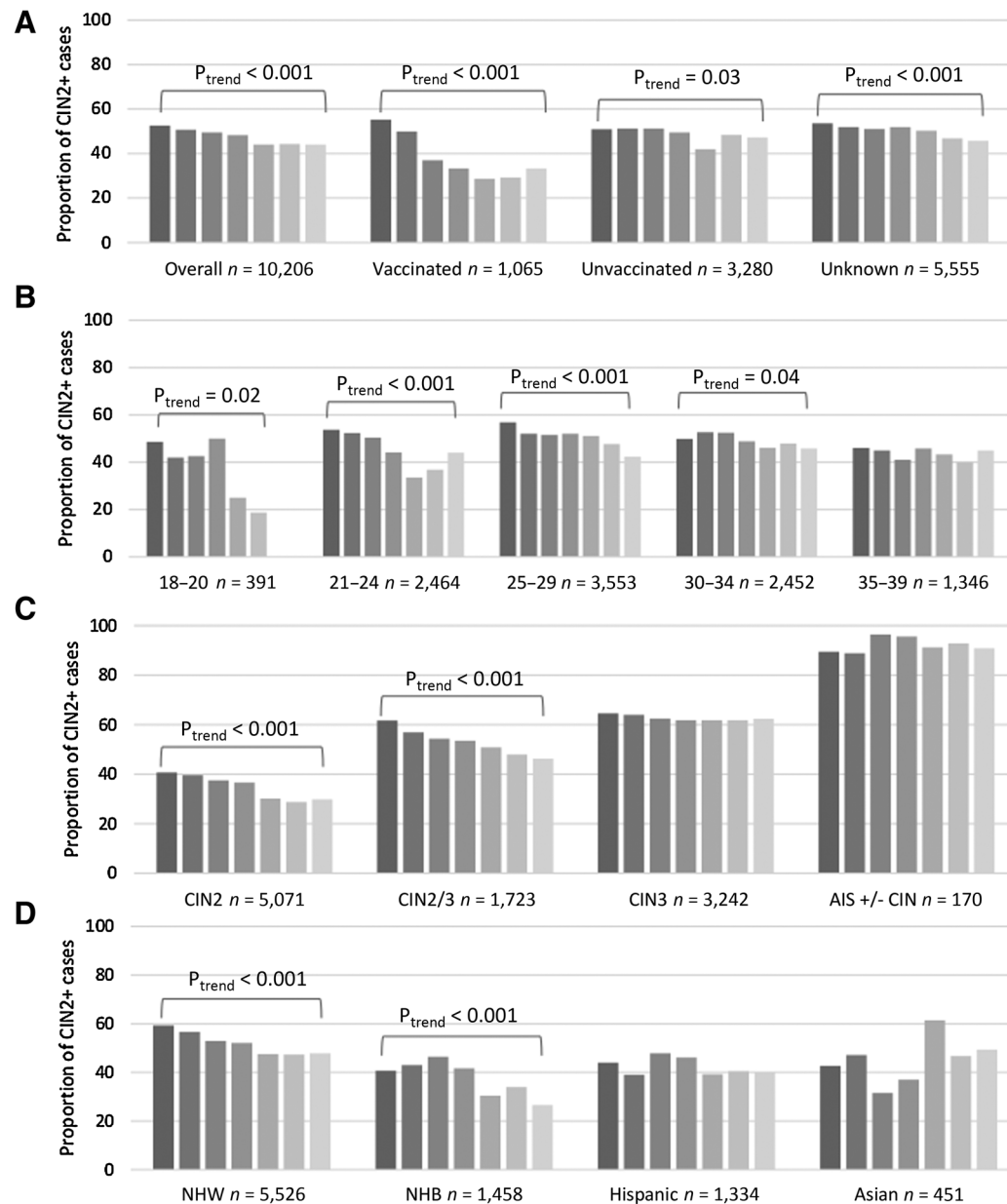


Figure 2.

Proportion of CIN2+ cases among 18- to 39-year-old women that were HPV 16/18-positive, 2008–2014, by vaccination status, age group, histologic grade, and race/ethnicity. **A**, vaccination status, women with unknown timing of vaccination were excluded ($n = 306$) **B**, age group, **C**, histologic grade, and **D**, race/ethnicity. Gray bars indicate HPV 16/18-positive cases and sequential years from 2008 (darkest gray) to 2014 (lightest gray). CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ with or without CIN.

Table 2. Characteristics of 18–39 year-old women with CIN2+ by race/ethnicity^a with valid HPV typing results

	Non-Hispanic white n (%)	Non-Hispanic black n (%)	Hispanic n (%)	Asian n (%)
Total	5,526 (63.0%)	1,458 (16.6%)	1,334 (15.2%)	451 (5.1%)
Age (years) ^b				
Mean (SD)	28.0 (5.0)	27.3 (5.1)	28.4 (5.2)	30.6 (5.0)
18–20	209 (3.8)	79 (5.4)	49 (3.7)	3 (0.7)
21–24	1,326 (24.0)	436 (29.9)	305 (22.9)	51 (11.3)
25–29	1,992 (36.0)	466 (32.0)	430 (32.2)	140 (31.0)
30–34	1,310 (23.7)	317 (21.7)	344 (25.8)	140 (31.0)
35–39	689 (12.5)	160 (11.0)	206 (15.4)	117 (25.9)
Histologic grade of lesion ^b				
CIN2	2,679 (48.5)	810 (55.6)	641 (48.1)	205 (45.5)
CIN2/3	910 (16.5)	234 (16.0)	213 (16.0)	81 (18.0)
CIN3	1,814 (32.8)	405 (27.8)	460 (34.5)	156 (34.6)
AIS	123 (2.2)	9 (0.6)	20 (1.5)	9 (2.0)
Time period of diagnosis ^b				
2008–2011	3246 (58.7)	876 (60.1)	800 (60.0)	229 (50.8)
2012–2014	2280 (41.3)	582 (39.9)	534 (40.0)	222 (49.2)
HPV Vaccination status ^{b,c}				
Vaccinated	646 (12.2)	179 (12.5)	91 (6.9)	32 (7.3)
Not vaccinated	1,824 (34.3)	519 (36.3)	399 (30.3)	113 (25.7)
Unknown	2,844 (53.5)	733 (51.2)	829 (62.9)	294 (67.0)

^a“Other” and unknown excluded from analysis (*n* = 1,437, 14.1%); CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ with or without CIN.

^b*P* < 0.05.

^cWomen with unknown timing of vaccination were excluded (*n* = 266)

attributed to these types remained similar over time, 561 cases in 2008 and 575 cases in 2014. The proportions and estimated numbers of cases attributed to other high-risk HPV types and other HPV/no HPV remained relatively constant over time. Further trend analyses focus on the proportion of cases positive for HPV 16/18 among cases that were typed.

Trends in HPV 16/18 by vaccination status, age, histologic grade, and race/ethnicity

From 2008 through 2014, the proportion of CIN2+ cases that were HPV16/18-positive declined among vaccinated women (55.2%–33.3%, *P* < 0.001). This was seen to a lesser degree in unvaccinated women (51.0%–47.3%, *P* = 0.03), and in those with unknown vaccination status (53.7%–45.8%, *P* < 0.001; Fig. 2A). Significant declines in the proportion of CIN2+ cases that were HPV 16/18-positive were also observed in women aged 18–20 years (48.7%–18.8%, *P* = 0.03; 2014 data excluded because case count <10), 21–24 years (53.8%–44.0%, *P* < 0.001), 25–29 years (56.9%–42.4%, *P* < 0.001), and 30–34 years (49.8%–45.8%, *P* = 0.04; Fig. 2B). No declines were observed among 35–39 year olds (46.1%–45.0%, *P* = 0.54). Declines were observed in CIN2 (40.8%–29.9%, *P* < 0.001) and CIN2/3 (61.8%–46.2%, *P* < 0.001), but not in CIN3 (64.7%–62.4%, *P* = 0.28) or AIS (89.5%–90.9%, *P* = 0.83; Fig. 2C). Because declines in CIN3 incidence have been observed in HPV-IMPACT, (10) CIN3 was further stratified by vaccination status. Of 256 women who received at least 1 dose of HPV vaccine prior to diagnosis of CIN3, the proportion of HPV 16/18-positive cases declined from 76.0%–55.9% (*P* = 0.01).

By race and ethnicity, declines in the proportion of CIN2+ cases that were HPV16/18-positive were observed among NHW (59.5%–47.9%, *P* < 0.001) and NHB (40.7%–26.5%, *P* < 0.001), but not Hispanic (44.0%–40.1%, *P* = 0.38) or Asian (42.6%–49.3%, *P* = 0.13) women (Fig. 2D). To better understand possible reasons for the differential trends by race/ethnicity, we evaluated the distribution of other characteristics by race/ethnicity (Table 2). Differences were observed by age, histologic grade of lesion, and vaccination status. Asian women also had the

highest mean age (30.6 years), and both Asian and Hispanic women had a higher proportion of CIN3 diagnoses than NHW and NHB women (34.6% and 34.5% vs. 32.8% and 27.8%, respectively). Percentage of CIN2+ cases in women known to be vaccinated was lower in Hispanic (6.9%) and Asian (7.3%) compared with NHW (12.2%) and NHB (12.5%) women (*P* < 0.001), although the median age at vaccination was similar among all race/ethnicities (22 or 23 years).

Discussion

The findings of this analysis complement and extend prior evidence of HPV vaccine impact in the United States by documenting a decreasing trend in the proportion of CIN2+ due to HPV vaccine types 16 and 18. Overall, we observed an 8.6 percentage-point decrease in HPV16/18-positive CIN2+ from 2008 to 2014, and a 21.9 percentage-point decrease among women who had received at least 1 dose of the HPV vaccine before diagnosis of CIN2+. A decrease in HPV16/18-positive CIN2+ was also observed among unvaccinated women, suggesting for the first time, herd protection for CIN2+ in the United States. The decreasing trend in the proportion of HPV16/18-positive CIN2+ among 25–34 year olds is the first observation of vaccine impact in these older ages in the United States. As a result of the decrease in proportion of HPV vaccine types, the proportion of nonvaccine types increased. However, because the sample was population-based, we were also able to estimate the number of cases due to specific HPV types to show that the increasing proportion of nonvaccine HPV types actually represented a near-constant number of cases, whereas the declining proportion of vaccine types represented a large decline in the number of cases.

Previously, vaccine impact on CIN2+ has been observed through a declining incidence among screened young women. Within eight years of vaccine introduction, significant declines in the rate of CIN2+ were observed in a statewide registry among screened 15–19 year olds and 20–24 year olds, (9) and in 15–19 year olds in a large claims database for the privately insured (17). HPV-IMPACT has also observed a decline in rates of CIN2+

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among young women (8, 10, 18). Compared with 2008–2009, 2014–2015 rates were 56% lower for 18–20 year olds and 39% lower for 21–24 year olds, but no declines were observed in 25–39 year olds. These findings are consistent with several other countries that have also reported a declining incidence of CIN2+ among young women (19–23).

A declining CIN2+ incidence supports vaccine impact, but it is not definitive because some CIN2+ is caused by HPV types not targeted by the vaccine. If the incidence of CIN2+ declined while the proportion of CIN2+ caused by HPV vaccine types and nonvaccine types remained constant, the decline could be due to factors other than vaccination, such as changes to cervical cancer screening recommendations and management. In 2012, guidelines from most major medical organizations changed to delay the initiation of cervical cancer screening from age 18 to age 21 years, and to screen less frequently—every 3 years for most women and every 5 years for women ≥ 30 years-old who have a high-risk HPV test. Women >30 years-old are recommended to have a high-risk HPV test performed in addition to cytology (11). Some studies have accounted for these changes by measuring incidence among women screened for cervical cancer (9, 10, 17). Furthermore, observation rather than immediate referral to colposcopy was recommended in 21–24 year olds with low-grade cytology (24). Quantifying the impact of changes in screening and management practices on incidence is difficult. These changes are complex, recommendations have been in flux, and there remains individual and regional variability in whether clinical practices adopt recommendations (25). Despite these changes, our finding of a decreasing trend in the proportion of HPV16/18-positive CIN2+ extends previous findings in HPV-IMPACT and supports the interpretation that the declining incidence is attributable to vaccine impact (12).

Although the overall proportion of CIN2+ due to HPV vaccine types 16/18 declined, trends varied by subgroups. As expected, the greatest decline, a 22 percentage-point reduction, was observed among women who received at least one HPV vaccine dose prior to their diagnosis of CIN2+. Most of these women were vaccinated as part of the catch-up program, which likely explains the finding that one-third of vaccinated women with CIN2+ had HPV 16/18 detected in 2014. Over 80% of women with CIN2+ were vaccinated over the age of 18 years, when the majority of people in the United States are already sexually experienced (26). Because of this, HPV exposure prior to vaccination was likely in many vaccinated women with CIN2+, limiting vaccine impact.

A smaller but significant decline in the proportion of CIN2+ cases that were HPV 16/18-positive among women with unknown vaccination status (4 percentage-points) and in unvaccinated women (8 percentage-points) was also observed suggesting herd protection, or indirect vaccine benefit. Herd protection against early outcomes, including anogenital warts and vaccine type prevalence in genital specimens, was first observed outside of the United States, in countries with high 3-dose vaccine coverage, at or above 80% (27, 28). Herd protection against vaccine type prevalence in genital specimens was also observed among unvaccinated young females in the United States, where at least 1-dose coverage was moderate, at 60% to 70% (29, 30). Although percent vaccinated among the cases in our analysis cannot be estimated because of missing vaccination information, coverage in the catchment areas is assumed to be moderate, between 40% to 60% based on known coverage among 19–26 year olds in the United States, (5, 31) and may have been closer to 70% in some

HPV-IMPACT sites based on regional variation in coverage (31). A significant decline in HPV 16/18 was not observed in unvaccinated women in prior HPV-IMPACT reports (12). Thus, this is the first reported evidence of herd protection on the intermediate outcome of cervical precancers among 18–39 year-old women in the United States.

The observed differences in trends by age group and histologic grade of lesion were expected because of the relatively short time since vaccine introduction. The proportion of CIN2+ cases that were HPV 16/18-positive declined in women aged 18–34 years, with larger declines in younger age groups. No declines were observed in the oldest age group who were not age-eligible to receive the HPV vaccine during the surveillance period in this analysis. In prior studies of CIN2+ incidence, vaccine impact has not yet been observed among women over the age of 24 years, and rates of CIN2+ calculated among screened women in age groups 25 and older have actually increased (9, 10, 17). By histologic grade, declining trends were observed in CIN2 and CIN2/3 only. Although an overall decline in the proportion of 16/18-positive CIN3 was not observed, a decline among the small number of vaccinated women with CIN3 suggests that the declining CIN3 incidence described previously by HPV-IMPACT could be attributable, at least in part, to HPV vaccination (10).

By race/ethnicity, declines in the proportion of HPV 16/18-positive cervical precancers were observed in NHW and NHB, but not in Hispanic or Asian women. These differential trends were unexpected as prelicensure clinical trials found robust immunogenicity in all represented races and ethnicities (32). Differences in vaccination status, age, and histologic grade of lesion are the most likely explanations for the observed trends. Among Hispanic and Asian women with CIN2+ in our study, a lower percentage were known to be vaccinated, 7% compared with 12% among NHB and NHW women. These race differences in percentage vaccinated are consistent with national vaccination coverage estimates. In 2015, the National Health Interview Survey (NHIS) reported that vaccination coverage was lower among Hispanic and Asian women aged 19–26 years compared with NHW and NHB women (5). Furthermore, a higher proportion of cases identified in Asian and Hispanic women were among 35–39 year olds who were not age-eligible for vaccination, 26% and 15%, respectively, compared with 13% and 11% in NHW and NHB women. Hispanic and Asian women also had a higher proportion of CIN3 lesions, in which no declining trend in the proportion of HPV 16/18 was observed. A higher proportion of CIN3 lesions may reflect longer cervical screening intervals in these groups, which is also consistent with NHIS findings (33). Although not relevant to the CIN2+ cases reported here, it is important to note that the racial and ethnic differences in HPV vaccination noted in young adult women are not evident in younger cohorts, and in 2016, vaccination coverages in U.S. 13–17 year olds was highest in Hispanic and Asian adolescents (72% coverage; 4). Therefore, in the future, we expect racial/ethnic disparities in cervical disease to be reduced.

This analysis had a few limitations. The findings reported were proportions of CIN2+ and not incidence rates. To aid in the interpretation of the HPV16/18 proportions in the context of a declining incidence, we applied the overall HPV type proportions over time to the reported number of cases to show that the increasing proportion of nonvaccine types actually represents a near-constant number of cases over time, whereas the declining proportion of 16/18 represents a large decline in the number of cases. Thus, the proportional increase in other HPV types occurs in

the context of steady or declining incidence and does not represent an increase in incidence of lesions attributable to nonvaccine HPV types. Furthermore, the primary purpose of this analysis is descriptive, to show trends in HPV16/18-positive CIN2+. Stratifying results by different subgroups allowed us to explore, but not fully explain, the characteristics associated with the declining trends. In addition, in showing the overall decline in incidence of CIN2+ by HPV type category, we assumed that cases without typing data represented the same frequency distribution as typed cases, as suggested by similar demographic and clinical characteristics. We were unable to confirm vaccination status of approximately 50% of cases, and interpretation of trends in this subgroup is uncertain. We were also unable to determine whether vaccination occurred prior to sexual debut. Some vaccinated women may have already been exposed to HPV, limiting vaccine impact. Because differential trends were observed by race/ethnicity, it is important to note that 10% of women were missing race/ethnicity information. In addition, there is also unknown reliability of race data, as it was collected from medical records and not always verified by self-report. Finally, the number of Asian women was small and the majority were from one site and may not be representative of all Asian women in the United States.

In conclusion, within 8 years of HPV vaccine introduction in the United States, we report an overall declining trend in the proportion and estimated number of cervical precancers caused by HPV vaccine types among 18–39 year-old women. Among vaccinated 18–39 year-old women with CIN2+, the proportion caused by HPV 16/18 dropped by 22 percentage-points between 2008 and 2014. These findings complement the declining incidence of CIN2+ reported previously, demonstrating the impact of the HPV vaccination program in the United States. Examination of HPV typing data extended evidence of vaccine impact into older age groups. For the first time, evidence of herd protection on cervical precancers was observed, suggesting that herd protection reported for early outcomes continues along the natural progression of disease and may also be observed in cervical cancers in the future. We also expect to see declines in the oldest age group and more advanced diagnoses in the future, as more vaccinated people age into these groups. Furthermore, even greater declines are expected in vaccinated people as more and more receive vaccination at routine ages, when the vaccine is most efficacious. Ongoing surveillance is critical to continue to monitor trends in HPV types detected in CIN2+, particularly among different subgroups and with the use of the 9-valent vaccine since 2016. The results of this analysis continue to support the high degree of effectiveness of the HPV vaccine in real-world settings and the rapid reduction of the HPV types that cause 70% of cervical cancers.

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Disclosure of Potential Conflicts of Interest

L.M. Niccolai is a consultant/advisory board member for Merck. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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