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Very Low Prevalence of Vaccine Human Papillomavirus Types Among 18- to 35-Year Old Australian Women 9 Years Following Implementation of Vaccination

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Introduction. A quadrivalent human papillomavirus vaccination program targeting females aged 12–13 years commenced in Australia in 2007, with catch-up vaccination of 14–26 year olds through 2009. We evaluated the program's impact on HPV prevalence among women aged 18–35 in 2015.

Methods. HPV prevalence among women aged 18–24 and 25–35 was compared with prevalence in these age groups in 2005–2007. For women aged 18–24, we also compared prevalence with that in a postvaccine study conducted in 2010–2012.

Results. For the 2015 sample, Vaccination Register-confirmed 3-dose coverage was 53.3% (65.0% and 40.3% aged 18–24 and 25–35, respectively). Prevalence of vaccine HPV types decreased from 22.7% (2005–2007) and 7.3% (2010–2012), to 1.5% (2015) (P trend < .001) among women aged 18–24, and from 11.8% (2005–2007) to 1.1% (2015) (P = .001) among those aged 25–35.

Conclusions. This study, reporting the longest surveillance follow-up to date, shows prevalence of vaccine-targeted HPV types has continued to decline among young women. A substantial fall also occurred in women aged 25–35, despite lower coverage. Strong herd protection and effectiveness of less than 3 vaccine doses likely contributed to these reductions.

Keywords. human papillomavirus; HPV infection; prevalence; vaccine impact; surveillance; women.

Infection with human papillomavirus (HPV) is the underlying cause of cervical cancer and other types of anogenital cancers in both males and females [1, 2]. A government funded national program using the quadrivalent HPV vaccine (protection against types 6, 11, 16, and 18) was introduced in Australia in 2007 for females, and in 2013 extended to males. The vaccine has high protective efficacy when administered to people without existing infection [3].

Between 2007 and 2009, all females aged 12–26 years were eligible to receive 3 doses of the vaccine free of charge. The program was delivered through schools and community providers. In that period, an estimated 83% of adolescent girls and 55% of women received at least 1 vaccine dose; with 70% and 32%, respectively, having all 3 doses [4, 5]. Vaccination of children aged 12–13 years through schools continued and has achieved high coverage each year, with over 70% of school-based cohorts receiving all 3 doses [6]. All female residents of Australia born on or after 30 June 1980 were eligible for free vaccination in the catch-up program. The result of this coverage includes striking reductions in HPV infections, genital warts, and cervical high-grade lesions, with the greatest impact observed among the youngest cohorts [7–10].

The catch-up program provided the opportunity for individuals to be vaccinated at ages older than routinely recommended. Indeed, a decline in both genital warts and cervical lesions in females aged up to 30 years has recently been observed, as vaccinated cohorts age and new infections are prevented in these groups [11, 12]. These findings suggest that the population-level prevalence of vaccine-targeted HPV types has significantly declined across all cohorts who have been offered vaccination. This is despite the lower vaccine coverage among older groups, as well as the likelihood that a substantial proportion of these older women would have been previously exposed to vaccine HPV types at the time of vaccination.

We previously reported on the substantial decline in vaccine-targeted HPV types in a repeat cross-sectional study that compared cervical HPV prevalence among females aged 18–24 years before the introduction of vaccination with prevalence among females of the same age group recruited 4–5 years

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after program implementation [13, 14]. These data provided the first evidence of the population-level benefit of the program, both direct and through herd protection [13]. The program's impact on HPV infections among older vaccine-eligible females has not been described to date using this repeat cross-sectional study methodology.

In this follow-up repeat cross-sectional study, we compared prevalence of vaccine-targeted HPV types among women in the age groups 18–24 and 25–35 recruited in 2015, with prevalence among women in the same age groups recruited in 2005–2007. For women aged 18–24, we also compared prevalence with that in a postvaccine study conducted in 2010–2012 [13], extending the results of a previous study.

METHODS

Study Population

For this report, the prevaccine sample consisted of women aged 18–35 years who attended urban family planning clinics in Victoria and New South Wales (NSW), Australia, for cervical screening, between November 2005 and April 2007. This was a subset of women who participated in the national Women, Human Papillomavirus Prevalence, Indigenous, Non-Indigenous, Urban, Rural Study (WHINURS) [15, 16], previously described. There were 2 postvaccine-implementation samples made up of women who attended family planning clinics in the same metropolitan areas in Victoria and NSW: the first consisted of the Victoria and NSW subset of women aged 18–24 years, recruited between 2010 and 2012 from clinics in 3 States (NSW, Victoria, and Western Australia), as described previously [13]; the second consisted of a subset of women aged 18–35 years, recruited between January and October 2015. For the 2015 sample, only women born on or after 30 June 1980 (vaccine catch-up program eligible) were included. As previously described [14], there were some changes in the number of participating clinics and in clinic location between the pre- and first postvaccine implementation samples, but no further changes prior to the second post vaccine sample. Under Australian guidelines before December 2017, cervical screening using cytology began at age 18 years or 2 years after first intercourse. There were not changes to this recommendation between 2005 and 2015.

Approval to undertake this study was obtained from ethics committees associated with each study site, and all participants provided written, informed consent.

Procedures

As previously described, the procedures to recruit participants were identical for the prevaccine and postvaccine samples [13, 16]. Clinic staff identified all consecutive age-eligible women attending health services for routine cervical screening. Invitation to participate was dependent on the clinician's judgment that there was sufficient time to discuss the study. At the time of Papanicolaou test, exfoliated cervical cells were collected in PreservCyt (Hologic Corporation, Bedford, MA) for HPV testing. Information on age, smoking status, and residential postcode was collected from routine records. Information on sexual practices was sought from women recruited in the 2 postvaccine samples, including age at first sexual intercourse, number of male sexual partners (lifetime and in the previous 12 months), and whether or not they had received HPV vaccination. Written consent was collected to obtain vaccination status from the National HPV Vaccination Program Register (hereafter referred to as the Register) [17].

HPV testing was performed as previously described [13, 16], with one modification. For specimens collected in 2015 the cobas HPV test (Roche Diagnostics, Indianapolis, IN) was used as the initial screening assay, with the results used for clinical follow-up, replacing the Roche Amplicor HPV (AMP) [13]. High concordance has been reported between AMP and cobas in several studies [18, 19]. Briefly, 1 mL of the PreservCyt specimen was tested for the presence of 14 high-risk HPV types using the cobas HPV test. A second 1-mL aliquot of the original sample was peleted and resuspended in 200 μL of phosphate buffered saline (PBS) [20] to use for DNA extraction (MagNA Pure 96 DNA and Viral Nucleic Acid Small Volume Kit, Pathogen Universal 200 protocol; Roche Molecular Diagnostics), then eluted in 100 μL. All extracted DNA was assessed for adequacy by quantitative polymerase chain reaction (PCR) amplification of a 260-bp segment of the human β-globin gene [21]. Extracted DNA (20 μL of extract) from samples negative or invalid on cobas were analyzed for the presence of mucosal HPV type DNA by an PGMY09-PGMY11-based HPV consensus PCR/enzyme-linked immunosorbent assay (ELISA) using a set of biotin-labeled probes, as previously described [21–24]. Extracted DNA (50 μL of extract) from samples positive for HPV by either test (cobas or PCR/ELISA) were genotyped using the Linear Array HPV genotyping test (Roche Molecular Diagnostics) according to manufacturer's instructions, with minor modifications as previously reported [13, 25]. Due to possible cross-reactivity of the HPV52 probe with types 33, 35, and 58 amplicons, samples positive for the HPV52 probe in the presence of 1 or more of these 3 probes were further tested for HPV52 using a type-specific PCR assay [26].

Statistical Analyses

Vaccine doses are known to be underreported to the Register, particularly among women vaccinated in the community [4]. In view of this, classification of vaccination status was based on a composite measure of self-reported and registry reported doses, as previously described [13]. Women were classified as fully vaccinated if they had 3 doses of the vaccine recorded on the Register. Unvaccinated women were those reporting not being vaccinated who also had no Register record of vaccination. If consent to access the Register was not obtained,

self-report of nonvaccination was accepted. Women who had received 1 or 2 doses of vaccine as confirmed by the Register, or had self-reported doses that could not be verified on the Register, were classified as being partly vaccinated. The latter category included women who reported doses, but did not provide consent for access to Register-recorded vaccination status [13]. Each individual's residential postcode was used to assign socioeconomic status (upper or lower 50th centile based on the Australian Bureau of Statistics Index of Relative Socioeconomic Disadvantage [12]) and area of residence (major city or regional/remote based on the Accessibility/Remoteness Index of Australia classification from the 2011 census [13]).

HPV prevalence estimates and 95% confidence intervals (CIs) were calculated using the exact binomial method in the following categories: vaccine-targeted HPV types (HPV6/11/16/18); any of the 5 additional HPV types covered by the 9-valent vaccine (HPV31/33/45/52/58) [27]; any high-risk HPV types other than 16/18 (HPV31/33/35/39/45/51/52/56/58/59/68); any high-risk HPV types (HPV16/18/31/33/35/39/45/ 51/52/56/58/59/68); any 1 of 37 HPV types identified by Linear Array; and any 1 of 37 HPV types excluding 6/11/16/18. Chi-square tests were used to examine differences in characteristics between study periods, and within subgroups of vaccination status. Binomial log linear regression was used to estimate prevalence ratios (PRs) and 95% CIs for each grouping of HPV types between the study periods, adjusted for sociodemographic characteristics that varied between the groups. PRs were also estimated for each vaccine subgroup (unvaccinated, partly vaccinated, and fully vaccinated) in the 2015 sample, compared with the prevaccine sample. We performed logistic regression to investigate the relationship between HPV, vaccination status, and a range of sociodemographic and behavioral characteristics among women recruited in 2015. Variables that were associated with each outcome at $P < .10$, along with vaccination status and age, were included in the adjusted models. Data analyses were performed using STATA version 14 (Stata Corporation, College Station, TX).

RESULTS

Between January and October 2015, we recruited 381 women aged 18–35 (Table 1). Compared with the prevaccine sample (n = 275), women recruited in 2015 were younger ($P < .001$), and less likely to be smokers ($P = .04$). One in 7 (n = 54; 14.2%) were unvaccinated and just over half (n = 203; 53.3%) were fully vaccinated. The remaining 124 (32.6%) were partly vaccinated: 21 (5.5%) had documented receipt of 1 or 2 doses, 101 (26.5%) reported receiving doses or were unsure of their status, but had no Registry record of being vaccinated, and 2 (0.5%) women reported that they had been vaccinated but did not provide consent to verify their status with the Register.

In analyses stratified by age group (Table 1), women aged 18–24 in 2015 (n = 200) were older ($P < .001$), and less likely to be smokers ($P = .03$), than those recruited in the first postvaccine sample (n = 688) and the prevaccine sample (n = 88) [13]. They were also more likely to be fully vaccinated ($P < .001$), compared with women in the first postvaccine sample; 21 (10.5%) were unvaccinated, 130 (65.0%) were fully vaccinated, and 49 (24.5%) were partly vaccinated. Women aged 25–35 in 2015 (n = 181) were younger ($P = .02$) than women recruited in the prevaccine sample (n = 187) [16]. Overall, 33 (18.2%) were unvaccinated, 73 (40.3%) were fully vaccinated, and 75 (41.4%) were partly vaccinated.

The combined prevalence of vaccine-targeted HPV types among women aged 18–35 decreased from 15.3% (42/275) in 2005–2007, to 1.3% (5/381) in 2015; aPR = 0.08 (95% CI, 0.03–0.20) compared with the prevaccine sample; $P < .001$ (Table 2). Of the 5 samples positive for vaccine-targeted HPV types in 2015, 4 were positive for HPV16 and 1 for HPV18. There were no cases of HPV6 or HPV11 detected. In analyses stratified by age group (Table 2 and Figure 1), prevalence of vaccine-targeted HPV types among women aged 18–24 decreased from 22.7% in 2005–2007 and 7.3% in 2010–2012, to 1.5% in 2015; aPR = 0.40 (95% CI, 0.25–0.63) and 0.08 (95% CI, 0.02–0.26), respectively, compared with the prevaccine sample; P trend < .001. A significant decline in vaccine-targeted HPV types was also observed among women aged 25–35, from 11.8% in 2005–2007 to 1.1% in 2015; aPR = 0.10 (95% CI, 0.02–0.41); $P = .001$. No significant reductions in detection of nonvaccine-targeted HR-HPV types were observed. However, we noted a significantly lower prevalence of nonvaccine HPV types (excluding 6/11/16/18) overall, among women recruited in 2015 compared with the prevaccine sample (31.5% [95% CI, 27.0–36.4] vs 43.3% [95% CI, 37.5–49.2], respectively, aPR = 0.70 [95% CI, 0.57–0.85]) (Supplementary Table S1).

Next, results from 54 unvaccinated, 124 partly vaccinated, and 203 fully vaccinated women recruited in 2015 were compared with those of 275 women recruited in the prevaccine sample [13]. Fully vaccinated women were younger ($P < .001$), and more likely to have been born in Australia ($P < .001$), but were otherwise similar for other measured characteristics (Supplementary Table S2). Prevalence of vaccine-targeted HPV types was significantly lower than the prevaccine sample in all vaccine-eligible subgroups recruited in 2015: aPR = 0.13 (95% CI, 0.02–0.91) for unvaccinated; aPR = 0.10 (95% CI, 0.02–0.41) for partly vaccinated; and aPR = 0.06 (95% CI, 0.01–0.24) for fully vaccinated women (Table 3). No significant reductions in detection of nonvaccine-targeted HR-HPV types were observed among each vaccine-eligible subgroup, compared with the prevaccine sample (Table 3). Again, we noted small but significant reductions in the prevalence of nonvaccine HPV types overall (Supplementary Table S1).

Among women recruited in 2015, there was a higher crude prevalence of nonvaccine-targeted HPV types among fully vaccinated women compared with those who were unvaccinated or partly vaccinated. In univariate analyses, detection of any HPV

Table 1. Cohort Characteristics Among Australian Females Attending for Cervical Cytology Screening, According to Study Period and Age Group

		Prevaccine Sample	Vaccine-Eligible Samples		
		2005–2007	2010–2012	2015	
		n (%)	n (%)	n (%)	*P* value[a]
18–35 years old		**N = 275**	…	**N = 381**	
Age	Median (IQR)	27 (23–30)	…	24 (22–27)	<.001
	Mean (SD)	26.8 (4.5)	…	25.2 (4.0)	<.001
Current smoker	No	25 (74.5)	…	309 (81.1)	.04
	Yes	70 (25.5)	…	72 (18.9)	
Socioeconomic status	Less disadvantaged	235 (85.5)	…	308 (80.8)	.12
	More disadvantaged	40 (14.5)	…	73 (19.2)	
Area of residence	Major city	269 (97.8)	…	373 (97.9)	.94
	Regional/remote	6 (2.2)	…	8 (2.1)	
Vaccination status[c]	Unvaccinated	…	…	54 (14.2)	
	Partly vaccinated	…	…	124 (32.6)	
	Fully vaccinated	…	…	203 (53.3)	
18–24 years old		**n = 88**	**n = 688[b]**	**n = 200**	
Age	Median (IQR)	22 (20–23)	21 (20–23)	22 (21–23)	<.001
	Mean (SD)	21.6 (1.8)	21.3 (1.8)	22.1 (1.5)	<.001
Current smoker	No	60 (68.2)	470 (69.3)	157 (78.5)	.03
	Yes	28 (31.8)	208 (30.7)	43 (21.5)	
Socioeconomic status	Less disadvantaged	78 (88.6)	573 (83.4)	165 (82.5)	.40
	More disadvantaged	10 (11.4)	114 (16.6)	35 (17.5)	
Area of residence	Major city	87 (98.9)	669 (97.4)	196 (98.0)	.64
	Regional/remote	1 (1.1)	18 (2.6)	4 (2.0)	
Completed high school	No	…	26 (3.8)	11 (5.5)	.28
	Yes	…	662 (96.2)	189 (94.5)	
Country of birth	Australia	…	589 (85.6)	168 (84.0)	.572
	Other	…	99 (14.4)	32 (16.0)	
Age at first vaginal sex	≤16 years old	…	359 (53.4)	100 (50.0)	.40
	> 16 years old	…	313 (46.6)	100 (50.0)	
Lifetime number of sexual partners	1–2	…	134 (19.5)	39 (19.5)	.53
	3–4	…	141 (20.5)	34 (17.0)	
	≥5	…	413 (60.0)	127 (63.5)	
Number of sexual partners in the previous 12 months	0–1	…	327 (47.5)	99 (49.8)	.58
	≥2	…	361 (52.5)	100 (50.3)	
Vaccination status[c]	Unvaccinated	…	86 (12.5)	21 (10.5)	<.001
	Partly vaccinated	…	250 (36.3)	49 (24.5)	
	Fully vaccinated	…	352 (51.2)	130 (65.0)	
25–35 years old		**n = 187**	…	**n = 181**	
Age	Median (IQR)	29 (26–32)	…	28 (25–31)	.02
	Mean (SD)	29.3 (3.1)	…	28.5 (3.2)	.03
Current smoker	No	145 (77.5)	…	152 (84.0)	.12
	Yes	42 (22.5)	…	29 (16.0)	
Socioeconomic status	Less disadvantaged	157 (84.0)	…	143 (79.0)	.22
	More disadvantaged	30 (16.0)	…	38 (21.0)	
Area of residence	Major city	182 (97.3)	…	177 (97.8)	.77
	Regional/remote	5 (2.7)	…	4 (2.2)	
Vaccination status[c]	Unvaccinated	…	…	33 (18.2)	
	Partly vaccinated	…	…	75 (41.4)	
	Fully vaccinated	…	…	73 (40.3)	

[a] *P* values presented are score test of homogeneity between the study periods.

[b] Some numbers do not add up to 688 due to missing data.

[c] Women were classified as fully vaccinated if they had 3 doses of the vaccine recorded on the National HPV Vaccination Program Register. Unvaccinated women were those reporting not being vaccinated who also had no Register record of vaccination. If consent to access the Register was not obtained, self-report of nonvaccination was accepted. Women who had received 1 or 2 doses of vaccine as confirmed by the Register, or had self-reported doses that could not be verified on the Register, were classified as being partly vaccinated.

Abbreviations: IQR, interquartile range; SD, standard deviation.

Table 2. Crude Prevalence and Prevalence Ratios for Human Papillomavirus (HPV) Detected among Australian Females Attending for Cervical Cytology Screening, According to Study Period and Age Group, in Unadjusted and Adjusted Analyses

	Crude Prevalence	Comparison of Vaccine-Eligible Sample With Prevaccine Samples			
	n (%; 95% CI)	PR (95% CI)	*P* value	aPR[a] (95% CI)	*P* value
18–35 years old					
HPV 6, 11, 16, 18					
Prevaccine sample (2005–2007)	42 (**15.3**; 11.5–20.0)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	5 (**1.3**; 0.5–3.1)	0.09 (0.03–0.21)	<.001	0.08 (0.03–0.20)	<.001
HPV 31, 33, 45, 52, 58					
Prevaccine sample (2005–2007)	30 (**10.9**; 7.7–15.2)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	47 (**12.3**; 9.4–16.0)	1.13 (0.73–1.74)	.58	1.01 (0.65–1.56)	.98
HR-HPV types other than 16 and 18					
Prevaccine sample (2005–2007)	67 (**24.4**; 19.6–29.8)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	86 (**22.6**; 18.6–27.1)	0.93 (0.70–1.22)	.59	0.83 (0.63–1.10)	.20
Any HR-HPV type					
Prevaccine sample (2005–2007)	85 (**30.9**; 25.7–36.6)	*1.00 (ref)*		*1.00 (Ref)*	
Vaccine-eligible sample (2015)	89 (**23.4**; 19.4–27.9)	0.76 (0.59–0.97)	.03	0.69 (0.53–0.89)	.004
Any HPV type					
Prevaccine sample (2005–2007)	129 (**46.9**; 41.1–52.8)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	123 (**32.9**; 27.8–37.2)	0.69 (0.57–0.83)	<.001	0.66 (0.54–0.80)	<.001
18–24 years old					
HPV types 6, 11, 16, 18					
Prevaccine sample (2005–2007)	20 (**22.7**; 15.1–32.7)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2010–2012)	50 (**7.3**; 5.5–9.5)	0.32 (0.20–0.51)	<.001[b]	0.40 (0.25–0.63)	<.001[b]
Vaccine-eligible sample (2015)	3 (**1.5**; 0.5–4.6)	0.07 (0.02–0.22)		0.08 (0.02–0.26)	
High-risk HPV types 31, 33, 45, 52, 58					
Prevaccine sample (2005–2007)	13 (**14.8**; 8.7–23.9)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2010–2012)	131 (**19.0**; 16.3–22.2)	1.29 (0.76–2.18)	.75[b]	1.38 (0.82–2.33)	.80[b]
Vaccine-eligible sample (2015)	31 (**15.5**; 11.1–21.2)	1.05 (0.58–1.91)		1.09 (0.60–1.97)	
High-risk HPV other than 16 and 18					
Prevaccine sample (2005–2007)	29 (**33.0**; 23.9–43.5)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2010–2012)	251 (**36.5**; 33.0–40.2)	1.11 (0.81–1.52)	.27[b]	1.12 (0.82–1.53)	.46[b]
Vaccine-eligible sample (2015)	59 (**29.5**; 23.6–36.2)	0.90 (0.62–1.29)		0.94 (0.65–1.35)	
Any HR-HPV type					
Prevaccine sample (2005–2007)	36 (**40.9**; 31.1–51.5)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2010–2012)	269 (**39.1**; 35.5–42.8)	0.96 (0.73–1.25)	.03[b]	0.98 (0.75–1.27)	.05[b]
Vaccine-eligible sample (2015)	60 (**30.0**; 24.0–36.7)	0.73 (0.53–1.02)		0.76 (0.55–1.05)	
Any HPV type					
Prevaccine sample (2005–2007)	47 (**53.4**; 42.9–63.6)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2010–2012)	355 (**51.6**; 47.9–55.3)	0.97 (0.78–1.19)	.002[b]	0.98 (0.80–1.20)	.005[b]
Vaccine-eligible sample (2015)	76 (**38.0**; 31.5–44.9)	0.71 (0.55–0.93)		0.73 (0.56–0.95)	
25–35 years old					
HPV types 6, 11, 16, 18					
Prevaccine sample (2005–2007)	22 (**11.8**; 7.9–17.3)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	2 (**1.1**; 0.3–4.3)	0.09 (0.02–0.39)	.001	0.10 (0.02–0.41)	.001
High-risk HPV types 31, 33, 45, 52, 58					
Prevaccine sample (2005–2007)	17 (**9.1**; 5.7–14.2)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	16 (**8.8**; 5.5–14.0)	0.97 (0.51–1.87)	.93	0.94 (0.49–1.81)	.85
High-risk HPV other than 16 and 18					
Prevaccine sample (2005–2007)	38 (**20.3**; 15.1–26.7)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	27 (**14.9**; 10.4–20.9)	0.73 (0.47–1.16)	.18	0.70 (0.44–1.10)	.12
Any HR-HPV type					
Prevaccine sample (2005–2007)	49 (**26.2**; 20.4–33.0)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	29 (**16.0**; 11.3–22.1)	0.61 (0.41–0.92)	.02	0.58 (0.38–0.88)	.01
Any HPV type					
Prevaccine sample (2005–2007)	82 (**43.9**; 36.9–51.1)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	47 (**26.0**; 20.1–32.9)	0.59 (0.44–0.80)	<.001	0.57 (0.42–0.77)	<.001

[a]Adjusted for age and smoking status.

[b]Score test for trend, else the *P* values presented are score test of homogeneity between the study periods.

Abbreviations: aPR adjusted PR; CI, confidence interval; HPV, human papillomavirus; HR-HPV, high-risk HPV; PR, prevalence ratio.

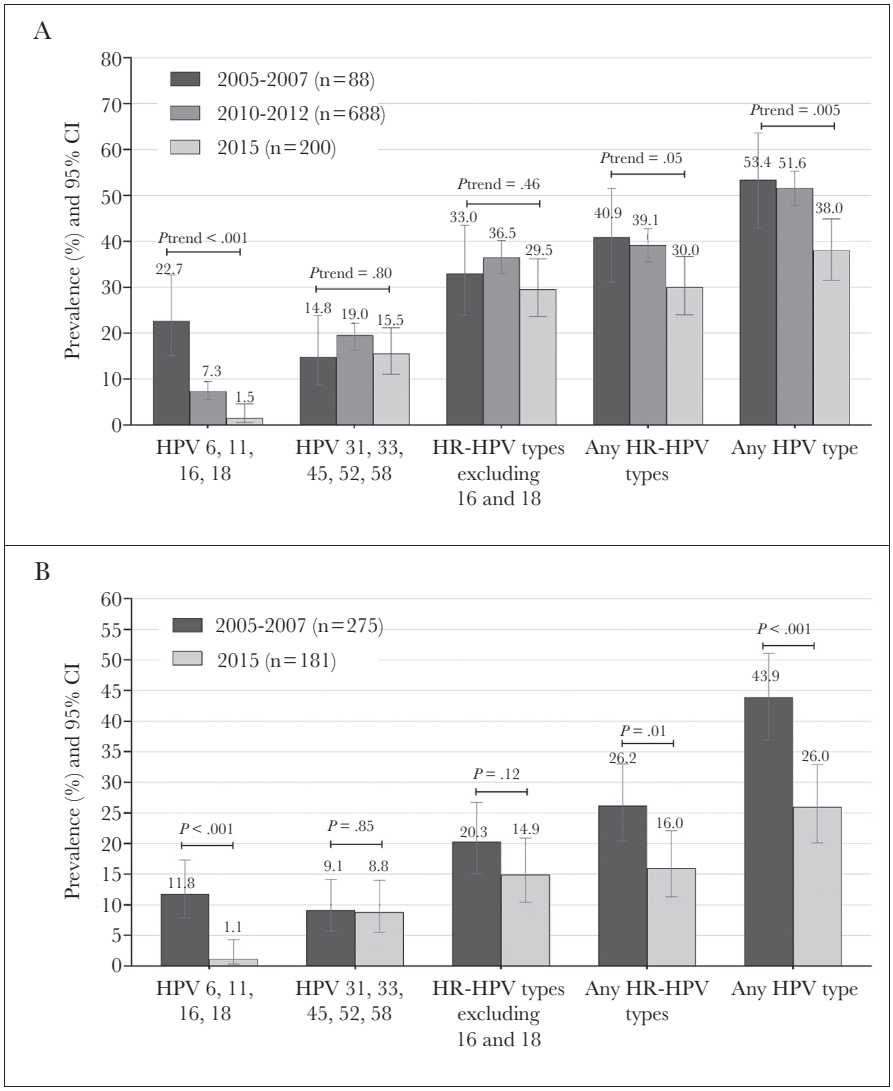

Figure 1. Crude human papillomavirus (HPV) prevalence among Australian females aged 18–24 (*A*) and 25–35 (*B*) years attending for routine cervical cytology screening according to study period. *P* values presented are score test for trend (*A*) or homogeneity (*B*) across the study periods. Abbreviations: CI, confidence interval; HR-HPV, high-risk HPV.

types was associated with younger age ($P = .01$), being born in Australia ($P = .05$), reporting 5 or more lifetime sexual partners ($P < .001$), and 2 or more partners in the previous 12 months ($P < .001$) (Supplementary Table S3 and Supplementary Table S4). In adjusted analysis, only younger age ($P = .03$) and reporting 5 or more lifetime sexual partners ($P < .001$) remained independently associated. Similar results were obtained for all groupings of HPV (Table 4 and Supplementary Table S4), with the exception of vaccine-targeted HPV types, which was not associated with any covariates tested.

DISCUSSION

In this repeat cross-sectional study, we showed that prevalence of cervical HPV types targeted by the quadrivalent vaccine has declined by 92% among women aged 18–35. Even among the subgroup of older women (aged 25–35), who were aged 16–26 when the program began, the prevalence had fallen by 90% compared with prevalence in the same age group prior to the program. This is despite register-recorded 3-dose coverage being only 40% in this group. We also found that prevalence of vaccine-targeted HPV types, which we had already measured 4–5 years after the implementation of the program, has continued to decline in the younger age groups. High and increasing vaccine coverage, strong population-based herd protection, and the effectiveness of less than 3 doses of the HPV vaccine, are likely to be contributing to these reductions in HPV infections.

Our finding, of large reductions in vaccine-targeted HPV types among adult women who were offered vaccine in the catch-up program, is consistent with published ecological data showing significant downward trends in genital warts diagnoses

Table 3. Crude Prevalence and Prevalence Ratios for HPV Detected among Australian Females Attending for Cervical Cytology Screening, Stratified by Vaccination Status in 2015[a], Compared with the Prevaccine Sample, in Unadjusted and Adjusted Analyses

		Crude Prevalence	Comparison of Vaccine-Eligible Sample with Prevaccine Sample			
		n (%; 95% CI)	PR (95% CI)	*P* value	aPR[b] (95% CI)	*P* value
HPV 6, 11, 16, 18						
Prevaccine sample (2005–2007)		42 (**15.3**; 11.5–20.0)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	Unvaccinated (n = 54)	1 (**1.9**; 0.3–12.2)	0.12 (0.02–0.86)	.04	0.13 (0.02–0.91)	.04
	Partly vaccinated (n = 124)	2 (**1.6**; 0.4–6.3)	0.11 (0.03–0.43)	.002	0.10 (0.02–0.41)	.001
	Fully vaccinated (n = 203)	2 (**1.0**; 0.2–3.9)	0.06 (0.02–0.26)	<.001	0.06 (0.01–0.24)	<.001
HPV 31, 33, 45, 52, 58						
Prevaccine sample (2005–2007)		30 (**10.9**; 7.7–15.2)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	Unvaccinated (n = 54)	7 (**13.0**; 6.3–25.0)	1.19 (0.55–2.56)	.66	1.23 (0.57–2.64)	.60
	Partly vaccinated (n = 124)	11 (**8.9**; 5.0–15.4)	0.81 (0.42–1.57)	.54	0.77 (0.40–1.48)	.43
	Fully vaccinated (n = 203)	29 (**14.3**; 10.1–19.8)	1.31 (0.81–2.11)	.27	1.12 (0.68–1.83)	.66
HR-HPV types other than 16 and 18						
Prevaccine sample (2005–2007)		67 (**24.4**; 19.6–29.8)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	Unvaccinated (n = 54)	8 (**14.8**; 7.5–27.1)	0.61 (0.31–1.19)	.15	0.62 (0.32–1.20)	.16
	Partly vaccinated (n = 124)	22 (**17.7**; 11.9–25.5)	0.73 (0.47–1.12)	.15	0.70 (0.45–1.07)	.10
	Fully vaccinated (n = 203)	56 (**27.6**; 21.8–34.2)	1.13 (0.83–1.54)	.43	0.98 (0.72–1.34)	.92
Any HR-HPV type						
Prevaccine sample (2005–2007)		85 (**30.9**; 25.7–36.6)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	Unvaccinated (n = 54)	9 (**16.7**; 8.8–29.2)	0.54 (0.29–1.00)	.05	0.55 (0.30–1.01)	.06
	Partly vaccinated (n = 124)	23 (**18.6**; 12.6–26.4)	0.60 (0.40–0.90)	.01	0.57 (0.38–0.85)	.006
	Fully vaccinated (n = 203)	57 (**28.1**; 22.3–34.7)	0.91 (0.68–1.20)	.51	0.78 (0.59–1.04)	.09
Any HPV type						
Prevaccine sample (2005–2007)		129 (**46.9**; 41.1–52.8)	*1.00 (ref)*		*1.00 (ref)*	
Vaccine-eligible sample (2015)	Unvaccinated (n = 54)	15 (**27.8**; 17.4–41.3)	0.59 (0.38–0.93)	.02	0.60 (0.38–0.94)	.03
	Partly vaccinated (n = 124)	29 (**23.4**; 16.7–31.7)	0.50 (0.35–0.70)	<.001	0.49 (0.35–0.68)	<.001
	Fully vaccinated (n = 203)	79 (**38.9**; 32.4–45.8)	0.83 (0.67–1.03)	.09	0.77 (0.62–0.95)	.02

[a]Women were classified as fully vaccinated if they had 3 doses of the vaccine recorded on the National HPV Vaccination Program Register. Unvaccinated women were those reporting not being vaccinated who also had no Register record of vaccination. If consent to access the Register was not obtained, self-report of nonvaccination was accepted. Women who had received 1 or 2 doses of vaccine as confirmed by the Register, or had self-reported doses that could not be verified on the Register, were classified as being partly vaccinated.

[b]Adjusted for age, smoking status, and area of residence.

Abbreviations: aPR adjusted PR; CI, confidence interval; HPV, human papillomavirus; HR-HPV, high-risk HPV; PR, prevalence ratio.

and occurrence of high-grade cervical abnormalities among women offered vaccine in the catch-up program [11, 28]. Multiple factors are likely to be contributing to these reductions. First, high efficacy of the vaccine in preventing incident HPV infections among fully vaccinated women, including infections newly acquired in the years since vaccination [29]. Additionally, evidence exists from both Australian and international data that less than 3 doses of the vaccine may provide some protection [8, 30–32], therefore suggesting that a proportion of potential incident infections may have been prevented among partly vaccinated women. Finally, the observed reductions are likely to have occurred in part due to herd protection whereby transmission of the virus is interrupted, as vaccinated women do not acquire HPV from, or infect, unvaccinated men and these men in turn do not transmit the virus to future unvaccinated female partners [33].

A key result of the current analyses is our finding of the ongoing reductions in vaccine-targeted HPV types among young women aged 18–24, from 7% in 2010–2012, to less than 2% in the current sample. The results suggest that as the proportion of vaccinated cohorts (both male and female) increase over time, the transmission efficiency of vaccine HPV types in the population may be reduced to almost undetectable levels. Mathematical modeling suggests that elimination of HPV 6, 11, 16, and 18 is possible if 80% coverage in girls and boys is reached, and if high vaccine efficacy is maintained over time [33]. In Australia, 3-dose vaccine coverage by age 15 for girls and boys had in 2016 reached 79% and 73% respectively, with data from the Register suggesting an increasing trend over time [6, 34]. Completion rates may improve further from 2018, when a 2-dose schedule with a 9-valent vaccine replaces the current 3-dose schedule [35].

We observed a higher crude prevalence of nonvaccine HPV types among fully vaccinated women, compared with those who were unvaccinated or partly vaccinated in the 2015 sample. Type-replacement is unlikely to explain these differences because both the relative ecological stability of HPV over time, and recent evidence from published data, argue against such a development [36, 37]. Unmasking of HPV types in the absence of HPV16 is another possible explanation [38]. However, the

Table 4. Multivariate Analyses of Factors Associated with Cervical Human Papillomavirus (HPV) Detection among 381 Australian Females Aged 18–35 Years Attending for Routine Cervical Cytology Screening in 2015

	aOR[a] (95% CI); *P* value			
	Any HPV Type	Any HR-HPV Type	HR-HPV Types Other Than 16 and 18	HPV 31, 33, 45, 52, 58
Vaccination statusb				
Unvaccinated	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
Partly vaccinated	0.68 (0.31–1.46); .32	1.07 (0.45–2.56); .87	1.17 (0.47–2.89); .73	0.60 (0.22–1.68); .33
Fully vaccinated	1.29 (0.62–2.64); .50	1.60 (0.71–3.59); .26	1.77 (0.76–4.13); .18	0.91 (0.36–2.29); .83
Age group				
25–35 years	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
18–24 years	1.67 (1.04–2.69); .03	2.22 (1.31–3.76); .003	2.34 (1.37–4.01); .002	1.95 (0.99–3.84); .05
Country of birth				
Other	*1.00 (ref)*	…	…	…
Australia	1.59 (0.83–3.05); .16	…	…	…
Lifetime number of sexual partners				
1–2	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*	*1.00 (ref)*
3–4	0.99 (0.38–2.56); .99	0.98 (0.33–2.93); .98	1.15 (0.37–3.52); .81	2.35 (0.41–13.40); .33
≥5	3.84 (1.90–7.79); <.001	3.45 (1.55–7.66); .002	3.89 (1.68–9.01); .002	6.97 (1.63–29.78); .009

[a]For each grouping of HPV, variables significant at $P < .10$ in univariate analyses (see Supplementary Table S2) as well as vaccination status and age group, were included in the multivariate model, except for partners in the previous 12 month, which was not included due to multicollinearity with age and lifetime number of partners. Detection of vaccine-targeted HPV types was not associated with any covariates tested.

[b]Women were classified as fully vaccinated if they had 3 doses of the vaccine recorded on the National HPV Vaccination Program Register. Unvaccinated women were those reporting not being vaccinated who also had no Register record of vaccination. If consent to access the Register was not obtained, self-report of nonvaccination was accepted. Women who had received 1 or 2 doses of vaccine as confirmed by the Register, or had self-reported doses that could not be verified on the Register, were classified as being partly vaccinated.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HR-HPV, high-risk HPV; OR, odds ratio.

extent and severity of this diagnostic artifact on detection of nonvaccine HPV types is not clear. This observed difference is almost certainly an age effect, reflecting underlying differences in the risk of exposure to HPV. Fully vaccinated women in our study were significantly younger than partly vaccinated or unvaccinated women, as younger women are more likely to have received vaccine in the school program, and therefore have completed vaccination doses [6, 34]. Furthermore, substantial research has demonstrated that HPV infection is most common in young women, who have higher numbers of new sexual partners [39]. Our finding of the independent association between nonvaccine HPV types, younger age, and sexual behavior is entirely consistent with this pattern. Furthermore, our conclusions are in line with those of a recent US-based study in which similar increases in nonvaccine-type HPV prevalence in unvaccinated women were noted [40].

A strength of our study is the repeat cross-sectional design and the assessment of HPV prevalence across 3 time points among women in the younger age group, extending the results of a previous study [13]. Additionally, a high proportion of participants gave us permission to obtain HPV vaccination status through the Register. However, the study also has limitations. Findings from a population-based survey suggest that coverage rates for women vaccinated in the community (at age 18–26 years) are underestimated by 5%–15% on the Register [4]. It is therefore likely that that the true coverage rates among women aged 25–35 years, who would largely have received their vaccines in the community, is higher than the estimate reported in this study.

Another limitation of our study is that we did not collect data on sexual behavior in the prevaccine survey, and therefore could not formally adjust for these risk factors of HPV infection across the study periods. In view of this, a better understanding of the observed difference in nonvaccine types between the samples is limited by the lack of data on other factors between the groups (ie, sexual behavior). Nevertheless, we believe that these differences are unlikely to fully explain the effects on vaccine-targeted HPV types for several reasons. First, the observed trends were driven by reductions in low-risk HPV types and the prevalence of nonvaccine high-risk HPV types did not differ significantly between the groups. Furthermore, these reductions were relatively small and of a different magnitude compared with that found between samples for vaccine types (aRP = 0.70 [95% CI, 0.57–0.85] vs aPR = 0.08 [95% CI, 0.03–0.20], respectively). Also, the lower prevalence of smokers in this study is consistent with national data showing declining rates of smoking among this age group over time [41]. Additionally, where data on risk behavior were available (for example among 18 to 24-year-old women in the 2 postvaccine samples), no significant differences in the risk of exposure to HPV were noted. Second, the low prevalence rates reported in our study are consistent with those reported in 2 recent Australian studies, including the COMPASS trial [42] and a surveillance study of young Australian women recruited through Facebook [43]. Another limitation is that the study sample size was limited and was not powered to detect any potential cross-protection of the vaccine on related HPV types. As such, we could not examine any association between the vaccine and

change in prevalence of HPV 31, 33, and 45 as observed in the first repeat cross-sectional study [13]. Recent evidence is compatible with the absence of any sizeable long-lasting effects [44]. Finally, given the sentinel clinic-based design, the results may not be generalizable to all Australian women. Nevertheless, this type of study design does not aim to be representative, but rather reproducible, to allow for the detection of changes over time in similar populations.

In summary, this repeat cross-sectional study demonstrates a marked decline in quadrivalent vaccine-targeted HPV types among women up to the age of 35 years since program implementation. Continued surveillance is needed to determine if these results are sustained or improved in the future. Ongoing monitoring will also serve to assess the impact of 2 doses of the 9-valent vaccine.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. D. A. M. designed the study, performed the data analyses and drafted the manuscript. J. M. B. and J. M. K. contributed to the study design, data interpretation, and writing of the report. D. B., K. M., and M. S. contributed to the study design, participant recruitment, and data interpretation. S. M. G., S. R. S., B. L., A. M. C., and S. N. T. contributed to the study design and data interpretation. All authors reviewed the manuscript for important intellectual content and approved the final version of the manuscript.

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