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Research Article

Change in Population Prevalences of Human Papillomavirus after Initiation of Vaccination: The High-Throughput HPV Monitoring Study

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Abstract

Background: Organized human papillomavirus (HPV) vaccination was introduced in Sweden in 2012. On-demand vaccination was in effect from 2006 to 2011. We followed the HPV prevalences in Southern Sweden from 2008 to 2013.

Methods: Consecutive, anonymized samples from the *Chlamydia trachomatis* screening were analyzed for HPV DNA for two low-risk types and 14 high-risk types using PCR with genotyping using mass spectrometry. We analyzed 44,146 samples in 2008, 5,224 in 2012, and 5,815 in 2013.

Results: Registry-determined HPV vaccination coverages of the population in Southern Sweden increased mainly among 13- to 22-year-old women. Most analyzed samples contained genital swabs from women and the HPV6 prevalence in these samples decreased from 7.0% in 2008 to 4.2% in 2013 [−40.0%; $P < 0.0005$ (χ^2 test)]. HPV16 decreased from 14.9% to 8.7% (−41.6%; $P < 0.0005$) and HPV18 decreased from 7.9% to 4.3% (−45.6%; $P < 0.0005$) among 13- to 22-year-old women. There were only small changes in vaccination coverage among 23- to 40-year-old women. In this age group, HPV18 decreased marginally (−19.6%; $P = 0.04$) and there were no significant changes for HPV6 or HPV16. Two nonvaccine HPV types (HPV52 and HPV56) were increased among 13- to 22-year-old women, both in 2012 and 2013.

Conclusions: A major reduction of HPV6, 16, and 18 prevalences is seen in the age groups with a concomitant increase in HPV vaccination coverage. The minor changes seen for nonvaccine types will require further investigation.

Impact: Monitoring of type-specific HPV prevalences may detect early effects of HPV vaccination. *Cancer Epidemiol Biomarkers Prev; 23(12); 2757–64. ©2014 AACR.*

Introduction

Vaccination against human papillomavirus (HPV) is highly effective for prevention of HPV infection and cervical disease (1, 2). HPV vaccination programs have been found to result in a decrease in the prevalence of genital warts among young women (3, 4). Vaccination also affects oral HPV 16/18 infections (5). HPV vaccination programs have been implemented in many countries, particularly in North America, Australia, and Europe (6). Modes of administration and organization vary between countries (6). In Sweden, a public subsidy for on-demand vaccination of 13- to 17-year-old girls was in effect between 2006 and 2011 (7). In 2012, organized, publicly funded HPV vaccination of 10- to 18-year-old girls using the quadrivalent vaccine (that contains HPV6, 11, 16, and 18) was launched. Therefore, the vaccine coverage in Sweden started to increase already before the organized vaccination was launched (excerpt from the Swedish HPV vaccination registry).

Monitoring of how HPV prevalences change after implementation of HPV vaccination programs serves several purposes (8). Clinical trials can only measure effect of vaccination at the individual level, whereas the effectiveness of population-based vaccination is also affected by population immunity ("Herd immunity"). This would typically increase the effectiveness compared with the individual-level efficacy, but alternative scenarios are possible, for example, the size of herd immunity effects is dependent on sexual mixing patterns, which differ markedly between different populations. Also, different vaccination strategies may reach different strata of the population (4), and there is a risk that the most sexually active groups may not be reached. Rapid evaluation of which vaccination strategies work best to reduce the spread of the HPV infection is therefore potentially useful for exchanging experiences of which HPV

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vaccination strategies that work best. Finally, there is a possibility that eradication of HPV vaccine types may result in an increase of nonvaccine HPV types, so-called type replacement (9). Conversely, cross-protection against HPV types not included in the vaccine may result in declines also of nonvaccine types (10). However, monitoring nonvaccine HPV types requires very large sample sizes, and thus requires development of high-throughput HPV monitoring technology (11).

In 2008, we performed a study of type-specific HPV prevalences in southern Sweden to establish prevalences of 16 HPV types at a time when the vaccination coverage was still low (11). To evaluate (i) whether the program was effective in preventing the circulation of vaccine-type HPV infections and (ii) whether it was associated with changes in prevalences of nonvaccine types, we compared the 2008 baseline HPV prevalences in southern Sweden with the HPV prevalences in southern Sweden in 2012 and 2013, two time points after the launch of the organized vaccination program when the HPV vaccination coverages in southern Sweden had increased.

Materials and Methods

We used consecutive series of all samples collected for *Chlamydia trachomatis* screening in a defined region of Sweden (the Skåne region in Southern Sweden with 1.27 million inhabitants). All *C. trachomatis* testing for this population is performed in a single laboratory and a very large proportion of the adolescent and young female population participate in this screening program (11) For example, during a single year 23% of all 19-year-old girls resident in the region are screened (11). The exact coverage statistics per age group and sex have been previously presented (11). The HPV analysis was performed on the residual material that remained after DNA extraction and analysis for *C. trachomatis*. All samples were anonymized. The Ethical Review Board in Lund, Sweden, decided that informed consent was not required.

The baseline HPV prevalence for the study area was established using the consecutive samples collected in 2008, and the samples for follow-up of the baseline study were all the samples that had been collected for *C. trachomatis* screening in the same population in Southern Sweden from September 1 to 30, 2012, and from March 1 to 31, 2013. The details of sample collection, sample analysis, and the characteristics of the study population in the baseline study are the same as for the samples collected for follow-up in 2012 and 2013 and are described elsewhere (11). In short, the baseline study samples were all the samples collected for *C. trachomatis* screening in Southern Sweden during March to November 2008 and the follow-up samples were also all the samples collected for *C. trachomatis* screening in Southern Sweden, but during September 2012 and March 2013. Male samples were mostly first-void urine, but also a small number of samples from rectum, urethra, pharynx, eye, and other sites, as described previously (11). Female samples were mostly genital swabs (either alone or immersed in urine), but there were also urine samples and a low number of swabs from other sites (11). Previous validation studies have found that urine samples had a low sensitivity and that the genital swab samples from females were the most informative (11). As all samples were anonymized, it is not known whether the same individuals may have been screened multiple times. Variables that were, by the Ethical Review Board, allowed to be maintained after anonymization were age, sex, sampling date, sample type, and sampling location. The samples were analyzed for HPV6, 11, 16, 18, 31, 33, 35, 39, 45 51, 52, 56, 58, 59, 66, and 68 by PCR with genotyping by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry. This method was proficient in the 2010 WHO Global HPV LabNet HPV DNA typing proficiency panel (12). Because the system shows a slight cross-reaction between HPV68 and HPV70 as well as between HPV11 and HPV89, confirmative testing of all samples positive for HPV68 and HPV11 was performed using secondary HPV DNA analysis on the Luminex platform, which also had the capacity to distinguish HPV68A (GenBank accession number DQ080079) and HPV68B (GenBank accession number M73258 for the original sequence ME180; refs. 11, 13).

HPV vaccination coverages for Southern Sweden (the same population that the samples were derived from) were determined using a comparison of registry excerpts from the Swedish HPV vaccination registry, maintained at the Public Health Agency of Sweden, and the population registry of Sweden, maintained at the Swedish Tax Office. The population coverages were determined for the same calendar periods when the samples were collected and for each sex and specific age group. Subsequently, age groups with high (13–22-year-olds) or low (23–40-year-olds) vaccination coverages were analyzed together.

Statistical analysis

Statistical analyses were performed using SPSS version 20 (IBM). Differences in prevalence between groups were tested using the χ^2 test. P values less than 0.05 were considered significant.

Results

The total number of analyzed samples was 44,146 in 2008, 5,224 in September 2012, and 5,815 in March 2013, and most samples were from women 18 to 23 years of age (Table 1). There were about four times as many samples from women as from men. The vaccination coverage for each female birth cohort of the entire population in the catchment area is given in Table 1. The highest coverage was seen among women younger than 23 years.

The most common sample type collected from women was a genital swab sample (by itself or immersed in first-void urine). Our previous validation studies have shown that swab samples were more sensitive compared with urine samples for detection of HPV infection (11). In 2008, 2012, and 2013 genital swabs constituted 63.3%, 85.5%,

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Table 1. The age- and gender-specific distribution of samples at 2008 (baseline), 2012, and 2013, compared with the vaccination coverage (given only for female birth cohorts in the catchment area population; data on vaccinations derived from the Swedish HPV vaccination registry)

Age	Gender	2008 *N* = 44,146 (%)	2012 *N* = 5,224 (%)	2013 *N* = 5,815 (%)	Vaccination coverage 2008 (%)	Vaccination coverage 2012 (%)	Vaccination coverage 2013 (%)
0–12	Women	70 (0.2)	8 (0.2)	5 (0.1)	0.028	6.4	4.8
	Men	56 (0.5)	1 (0.08)	3 (0.24)	—	—	—
13	Women	14 (0.04)	1 (0.03)	3 (0.07)	1.8	63.6	77.6
	Men	1 (<0.01)	0 (0)	0 (0)	—	—	—
14	Women	130 (0.4)	17 (0.4)	6 (0.1)	7.8	47.7	77.7
	Men	15 (0.1)	3 (0.2)	0 (0)	—	—	—
15	Women	563 (1.7)	49 (1.2)	42 (0.9)	12.5	49.4	53.5
	Men	46 (0.4)	5 (0.4)	2 (0.2)	—	—	—
16	Women	982 (3.0)	93 (2.4)	80 (1.8)	15.1	50.6	54.2
	Men	202 (1.8)	12 (0.9)	8 (0.6)	—	—	—
17	Women	1,715 (5.2)	173 (4.4)	126 (2.8)	17.1	51.3	53.4
	Men	327 (3.0)	38 (2.9)	18 (1.4)	—	—	—
18	Women	2,313 (7.0)	221 (5.6)	177 (3.9)	16.1	59.4	53.2
	Men	546 (5.0)	43 (3.3)	25 (2.0)	—	—	—
19	Women	2,300 (6.9)	240 (6.1)	192 (4.2)	5.6	57.2	59.0
	Men	697 (6.3)	57 (4.4)	50 (4.0)	—	—	—
20	Women	2,237 (6.8)	266 (6.8)	259 (5.7)	3.2	36.0	56.1
	Men	763 (6.9)	95 (7.3)	54 (4.3)	—	—	—
21	Women	2,051 (6.2)	272 (6.9)	312 (6.8)	2.3	29.5	35.0
	Men	765 (6.9)	87 (6.7)	88 (7.0)	—	—	—
22	Women	2,039 (6.2)	264 (6.7)	308 (6.8)	1.6	17.8	28.9
	Men	791 (7.2)	109 (8.4)	93 (7.4)	—	—	—
23–25	Women	4,842 (14.6)	635 (16.2)	778 (17.1)	1.2	5.9	10.8
	Men	1,974 (17.9)	243 (18.7)	237 (18.9)	—	—	—
26–30	Women	5,984 (18.1)	731 (18.6)	932 (20.4)	0.47	2.3	3.1
	Men	2,164 (19.7)	263 (20.2)	276 (22.0)	—	—	—
31–35	Women	3,829 (11.6)	455 (11.6)	619 (13.6)	0.063	0.65	0.91
	Men	1,121 (10.2)	144 (11.1)	159 (12.7)	—	—	—
36–40	Women	2,181 (6.6)	269 (6.9)	399 (8.8)	0.037	0.31	0.38
	Men	615 (5.6)	76 (5.8)	93 (7.4)	—	—	—
41–45	Women	1,060 (3.2)	120 (3.1)	160 (3.5)	0.028	0.23	0.27
	Men	372 (3.4)	41 (3.2)	56 (4.5)	—	—	—
46–50	Women	467 (1.4)	63 (1.6)	90 (2.0)	0.0080	0.073	0.12
	Men	208 (1.9)	50 (3.8)	37 (2.9)	—	—	—
51+	Women	360 (1.1)	46 (1.2)	72 (1.6)	0	0.0055	0.0067
	Men	346 (3.1)	34 (2.6)	56 (4.5)	—	—	—
Total	Women	33,137 (75.1)	3,923 (75.1)	4,560 (78.4)	1.2	6.6	7.5
	Men	11,009 (24.9)	1,301 (24.9)	1,255 (21.6)	—	—	—

and 86.7% of all samples, respectively. Among women, urine samples constituted 32.7%, 12.4%, and 11.7% of samples in 2008, 2012, and 2013, respectively. The majority of male samples were urine. In 2008, 2012, and 2013 this sample type constituted 89.0%, 86.3%, and 85.6% of all male samples, respectively.

Because there was a strong increasing trend over time in the use of genital swabs for Chlamydia screening and because it has been well documented that this sample type is better for HPV detection that urine samples, a bias with improved ability to detect HPV over time would have been introduced if analysis had been based on all samples. Therefore, we restricted the analyses to a stratified analysis of only a single sample type. In analyses restricted to urine samples (without swabs) collected from women, the prevalence of at least one of the vaccine HPV types HPV6, 16 and 18, with or without concomitant infection with nonvaccine types was significantly lower in 2012 and 2013 than in 2008 (Table 2). Nonvaccine types tended to also be somewhat lower in

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Table 2. HPV prevalence in all samples from men and in urine samples from women

HPV	Gender	2008: Women 10,840, men 11,009 (%; 95% CI)	2012: Women 487, men 1,301 (%; 95% CI)	2013: Women 532, men 1,255 (%; 95% CI)	*P*: 2008 vs. 2012	*P*: 2008 vs. 2013
At least one of HPV 6/16/18[a]	Women	1,250 (11.5; 10.9–12.1)	32 (6.6; 4.4–8.8)	30 (5.6; 3.6–7.6)	$P = 0.001$	$P < 0.0005$
	Men	523 (4.8; 4.4–5.2)	28 (2.2; 1.4–3.0)	28 (2.2; 1.4–3.0)	$P < 0.0005$	$P < 0.0005$
At least one nonvaccine HPV type	Women	1,616 (14.9; 14.2–15.6)	63 (12.9; 0.29–2.3)	66 (12.4; 9.6–15.2)	$P = 0.2$	$P = 0.1$
	Men	678 (6.2; 5.7–6.7)	55 (4.2; 3.1–5.3)	52 (4.1; 3.0–5.2)	$P = 0.005$	$P = 0.004$

Abbreviation: CI, confidence interval.

[a]The vaccine type HPV11 is not included because of too few observations.

the samples taken after launch of organized vaccination, but not significantly so (Table 2).

The sensitivity for HPV detection in urine samples from men is known to be very low, and we did find only a very low number of positive observations among men. The HPV prevalences among men appeared to have decreased both for vaccine and nonvaccine HPV types (Table 2).

In the predominant and most adequate sample type (genital swab samples from women, with or without urine), we had sufficient number of observations to assess also the prevalences of individual HPV types (Table 3). The type-specific prevalences for HPV6, 16, and 18 were all significantly lower at both time points after launch of the organized vaccination program (Table 3). There were only few observations for the vaccine type HPV11, but also this type was decreased in the follow-up samples (Table 3). The only nonvaccine type that tended to decrease continuously from 2008 to 2013 was HPV31, but this tendency was not statistically significant. Several nonvaccine HPV types had increased prevalences in one of the time points after launch of organized vaccination. Because 16 different HPV types were tested and at several different time points, we considered that changes that were not reproducibly detected at both time points tested after launch of organized vaccination might have been due to chance. In 2012, the prevalence of nine types were significantly different compared with in 2008, but only six of these changes (for HPV6, 11, 16, 18, 52, and 56) were consistently seen for both the 2012 and 2013 surveys. Two nonvaccine HPV types (HPV52 and HPV56) were significantly increased both in the 2012 sample series and in the 2013 sample series, compared with the 2008 baseline. Among women ages 13 to 22 years, HPV52 increased from 6.5% to 9.1% (+40.0%; $P < 0.0005$) and HPV56 increased from 6.0% to 7.3% (+21.7%; $P = 0.05$). Among women ages 23 to 40, there was a very small increase of HPV52 [from 4.9% to 5.3% (+8.2%; $P = 0.5$)] whereas HPV56 was increased also in this age group [from 3.8% to 4.9% (+28.9%; $P = 0.01$)].

For the vaccine types HPV6, 16, and 18, the prevalence was strongly decreased mostly among women younger than 23 years (Figs. 1–3). In the age group 13 to 22 years, the prevalence of HPV6 decreased from 7.0% in 2008 to 4.2% in 2013 (−40.0%). For HPV16 the prevalence decreased from 14.9% in 2008 to 8.7% in 2013 (−41.6%). The decrease was so strong that it was statistically significant for most of the birth cohorts (women born during a certain calendar year) ages 14 to 22 years. For HPV18 the prevalence decreased from 7.9% in 2008 to 4.3% in 2013 (−45.6%). Among women ages 23 to 40 years, there was a decline of HPV18 that was of borderline significance [$P = 0.04$; a decrease from 4.6% to 3.7% (−19.6%)]. There were nonsignificant tendencies for HPV6 [increase from 2.9% in 2008 to 3.2% in 2013 (+10.3%)] and HPV16 [decrease from 9.7% to 8.7% (−10.3%)].

Discussion

Analysis of anonymized samples from the *C. trachomatis* screening program was found to be a powerful approach for evaluation of the effects of the HPV vaccination programs on the circulation of type-specific HPV infections. The fact that these samples are collected from sexually active subjects implies that a relevant target population likely to be affected by HPV infections was analyzed. We consider it essential that monitoring studies should make an effort to include the most sexually active women, as it is possible that vaccination programs may preferentially reach women from high socioeconomic groups that may be at low risk for HPV infection (4), resulting in that effectiveness of HPV control cannot be directly inferred from vaccination coverages. We monitored 16 different HPV types, but only the four vaccine HPV types were significantly decreased after the launch of the organized vaccination program. The decline was seen for all of the vaccine HPV types (HPV6, 11, 16, and 18). The fact that the decline was seen only among women in the analyzed age groups with high vaccination coverage (below 23 years of age) suggests that the decline is a result of the vaccination. None of the nonvaccine types showed any significant decrease in prevalence, suggesting that the cross-protection known to be induced by vaccination was less effective for reducing the HPV spread in this population (14). The effect of HPV vaccination programs on the population is not only dependent on protection of vaccinated

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Table 3. Type-specific prevalence among women in 2008, 2012, and 2013 in genital swab samples with or without urine for all ages and for 13- to 22-year-olds

HPV	2008 $N = 20,960$ (%; 95% CI)	2012 $N = 3,354$ (%; 95% CI)	2013 $N = 3,953$ (%; 95% CI)	*P*: 2008 vs. 2012	*P*: 2008 vs. 2013	2008 13–22 years $N = 9,644$ (%; 95% CI)	2012 13–22 years $N = 1,433$ (%; 95% CI)	2013 13–22 years $N = 1,383$ (%; 95% CI)	*P*: 2008 vs. 2012, 13–22 years	*P*: 2008 vs. 2013, 13–22 years
6	981 (4.7; 4.4–5.0)	114 (3.4; 2.8–4.0)	135 (3.4; 2.8–4.0)	$P = 0.001$	$P < 0.0005$	678 (7.0; 6.5–7.5)	52 (3.6; 2.6–4.6)	58 (4.2; 3.1–5.3)	$P < 0.0005$	$P < 0.0005$
11	124 (0.59; 0.49–0.69)	7 (0.21; 0.055–0.36)	10 (0.25; 0.094–0.41)	$P = 0.005$	$P = 0.008$	76 (0.79; 0.61–0.97)	2 (0.14; −0.054 to 0.33)	3 (0.22; −0.027 to 0.47)	$P = 0.006$	$P = 0.02$
16	2,451 (11.7; 11.3–12.1)	264 (7.9; 7.0–8.8)	326 (8.2; 7.3–9.1)	$P < 0.0005$	$P < 0.0005$	1,433 (14.9; 14.2–15.6)	128 (8.9; 7.4–10.4)	120 (8.7; 7.2–10.2)	$P < 0.0005$	$P < 0.0005$
18	1,253 (6.0; 5.7–6.3)	145 (4.3; 3.6–5.0)	145 (3.7; 3.1–4.3)	$P < 0.0005$	$P < 0.0005$	761 (7.9; 7.4–8.4)	68 (4.7; 3.6–5.8)	59 (4.3; 3.2–5.4)	$P < 0.0005$	$P < 0.0005$
31	1,273 (6.1; 5.8–6.4)	187 (5.6; 4.8–6.4)	213 (5.4; 4.7–6.1)	$P = 0.3$	$P = 0.1$	688 (7.1; 6.6–7.6)	101 (7.0; 5.7–8.3)	81 (5.9; 4.7–7.1)	$P = 0.9$	$P = 0.08$
33	596 (2.8; 2.6–3.0)	87 (2.6; 2.1–3.1)	107 (2.7; 2.2—3.2)	$P = 0.4$	$P = 0.6$	360 (3.7; 3.3–4.1)	45 (3.1; 2.2–4.0)	54 (3.9; 2.9–4.9)	$P = 0.3$	$P = 0.8$
35	410 (2.0; 1.8–2.2)	51 (1.5; 1.1–1.9)	78 (2.0; 1.6–2.4)	$P = 0.09$	$P = 0.9$	153 (1.6; 1.3–1.9)	21 (1.5; 0.87–2.1)	16 (1.2; 0.63–1.8)	$P = 0.7$	$P = 0.2$
39	905 (4.3; 4.0–4.6)	166 (4.9; 4.2–5.6)	195 (4.9; 4.2–5.6)	$P = 0.1$	$P = 0.08$	491 (5.1; 4.7–5.5)	92 (6.4; 5.1–7.7)	77 (5.6; 4.4–6.8)	$P = 0.04$	$P = 0.5$
45	776 (3.7; 3.4–4.0)	106 (3.2; 2.6–3.8)	157 (4.0; 3.4–4.6)	$P = 0.1$	$P = 0.4$	352 (3.6; 3.2–4.0)	49 (3.4; 2.5–4.3)	60 (4.3; 3.2–5.4)	$P = 0.7$	$P = 0.2$
51	1,444 (6.9; 6.6–7.2)	253 (7.5; 6.6–8.4)	279 (7.1; 6.3–7.9)	$P = 0.2$	$P = 0.7$	949 (9.8; 9.2–10.4)	171 (11.9; 10.2–13.6)	147 (10.6; 9.0–12.2)	$P = 0.01$	$P = 0.4$
52	1,154 (5.5; 5.2–5.8)	228 (6.8; 5.9–7.7)	254 (6.4; 5.6–7.2)	$P = 0.003$	$P = 0.02$	630 (6.5; 6.0–7.0)	121 (8.4; 7.0–9.8)	126 (9.1; 7.6–10.6)	$P = 0.007$	$P < 0.0005$
56	976 (4.7; 4.4–5.0)	184 (5.5; 4.7–6.3)	220 (5.6; 4.9–6.3)	$P = 0.04$	$P = 0.01$	575 (6.0; 5.5–6.5)	115 (8.0; 6.6–9.4)	101 (7.3; 5.9–8.7)	$P = 0.003$	$P = 0.05$
58	605 (2.9; 2.7–3.1)	116 (3.5; 2.9–4.1)	123 (3.1; 2.6–3.6)	$P = 0.07$	$P = 0.4$	317 (3.3; 2.9–3.7)	58 (4.0; 3.0–5.0)	48 (3.5; 2.5–4.5)	$P = 0.1$	$P = 0.7$
59	619 (3.0; 2.8–3.2)	133 (4.0; 3.3–4.7)	116 (2.9; 2.4–3.4)	$P = 0.002$	$P = 0.9$	384 (4.0; 3.6–4.4)	85 (5.9; 4.7–7.1)	51 (3.7; 2.7–4.7)	$P = 0.001$	$P = 0.6$
66	1,223 (5.8; 5.5–6.1)	228 (6.8; 5.9–7.7)	252 (6.4; 5.6–7.2)	$P = 0.03$	$P = 0.2$	747 (7.7; 7.2–8.2)	140 (9.8; 8.3–11.3)	129 (9.3; 7.8–10.8)	$P = 0.008$	$P = 0.04$
68	216 (1.0; 0.87–1.1)	51 (1.5; 1.1–1.9)	44 (1.1; 0.77–1.4)	$P = 0.01$	$P = 0.6$	92 (1.0; 0.80–1.2)	17 (1.2; 0.64–1.8)	14 (1.0; 0.48–1.5)	$P = 0.4$	$P = 0.8$

Abbreviation: CI, confidence interval.

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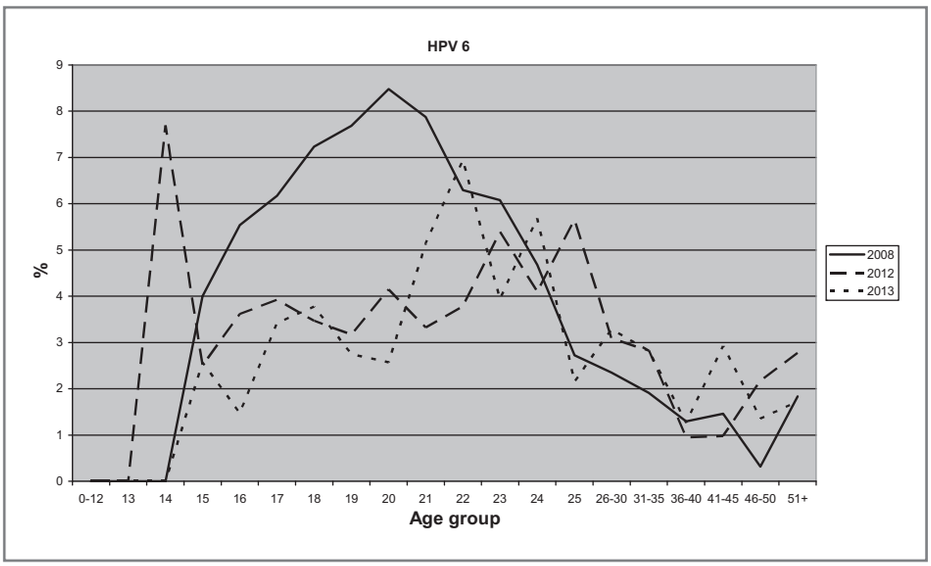

Figure 1. HPV6 prevalence according to age in genital swab samples with or without urine from women.

individuals, but is also affected by population immunity (herd immunity). At a vaccination coverage of 80%, the vaccine effectiveness at the population level has been estimated to be 78% for HPV16 and 96% for HPV18 (15). In the age groups with highest coverage, our results are, in principle, in agreement with these predictions. HPV-vaccinated women have been shown to have an about 90% protection against condyloma, a disease that is caused primarily by HPV6 (4). The fact that the present study also found a decline in prevalences of HPV6 in the age groups with high vaccination coverage is in line with the reported decline of condylomas in Sweden.

Indirect protection of unvaccinated men has been predicted to be about 42%, if 80% of all girls are vaccinated (15). Although we did find a decline of HPV vaccine types also among men, the decline among men was based on few observations and was not specific to HPV vaccine types, suggesting that it is not an effect of the vaccination, but due to some other causes.

Our findings of declining prevalences for HPV6, 11, 16, and 18 in the vaccinated age groups of women are in good agreement with reports from other populations. In Australia, the prevalence of HPV16 decreased from 21.3% before vaccination among 18- to 24-year-olds to 4.9% some years after vaccination, the prevalence of HPV6 decreased from 5.5% to 0.5% whereas the prevalence of HPV18 decreased from 8.4% to 2.2% (16). In the present study, the HPV16 prevalence among 18- to 24-year-olds decreased from 15.9% in 2008 to 10.2% in 2013, the HPV6 prevalence decreased from 7.0% to 4.6%, and the HPV18 prevalence decreased from 8.1% to 4.8%. The vaccination coverage in this age group at follow-up was only 35% in

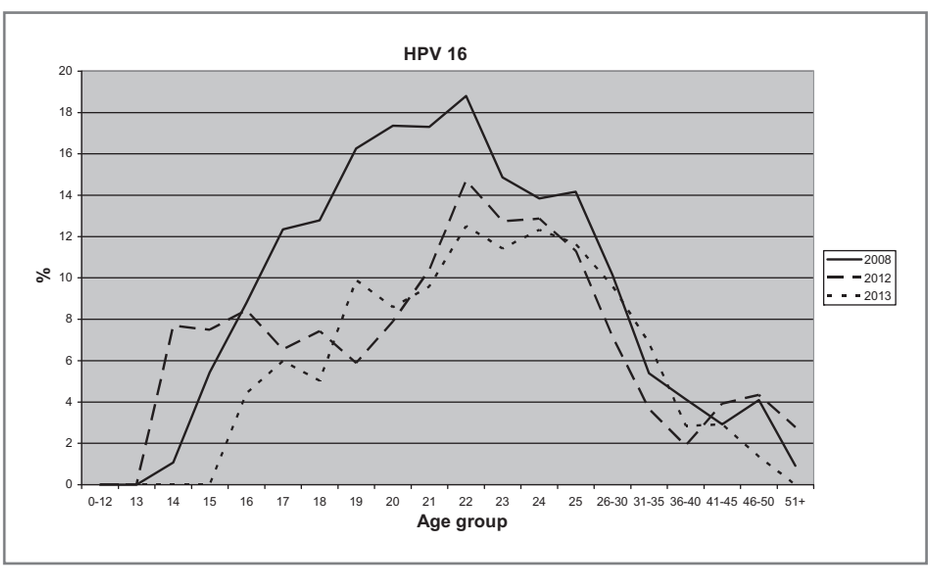

Figure 2. HPV16 prevalence according to age in genital swab samples with or without urine from women.

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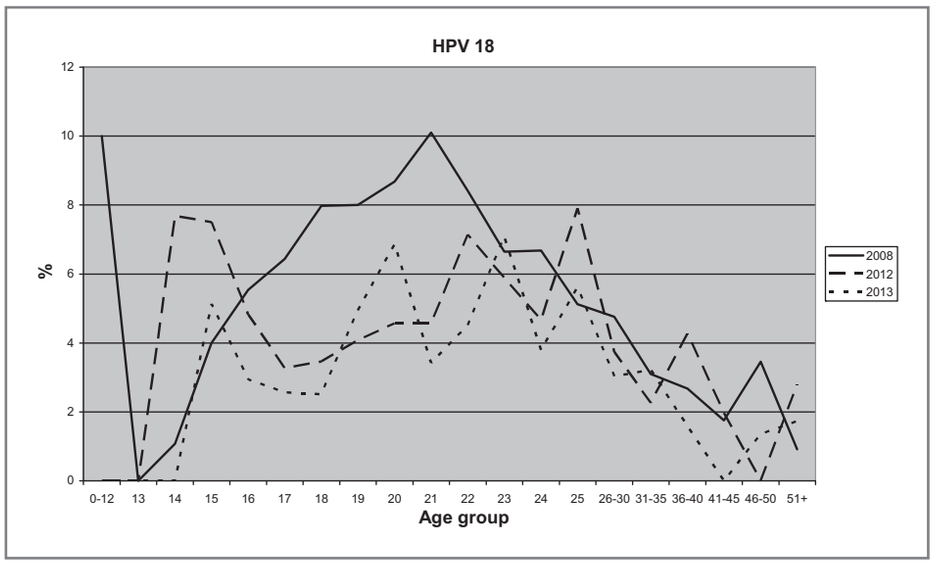

Figure 3. HPV18 prevalence according to age in genital swab samples with or without urine from women.

the Swedish population studied, so our somewhat lower decrease in the prevalences of HPV6, 16, and 18 probably corresponds well with these results. In the United States, there was a reduction of HPV16 and 18 from 7.2% to 3.6% among 14- to 19-year-olds with self-reported vaccine coverage of 34% (17). In Great Britain, there was a decrease of HPV 16/18 from 19.1% to 6.5% among 16- to 18-year-olds (the estimated vaccine coverage was 65%; ref. 18). In the age group targeted by HPV vaccines in Sweden, there has been a 2009 HPV survey among unvaccinated women in a sexual health clinic (19). The HPV prevalences were considerably higher than found in the present study, presumably because a more select group was studied.

HPV31 was the only nonvaccine type that tended to decrease in our study. Although this tendency was not significant, it was only observed in the age groups with high vaccination coverage (women younger than 23 years). The quadrivalent vaccine has significant efficacy against HPV31 (20), but if cross-protection or chance is reason for the tendency for lower HPV31 prevalence will need to be further evaluated.

Two nonvaccine types, HPV52 and HPV56, had significantly higher prevalences in 2012 and 2013 than in 2008. The fact that the increase seen for HPV52 was restricted to the age groups with high vaccination coverage is consistent with an effect that could be related to vaccination, but whether this increase may be a natural variation in prevalence over time or whether it is indeed an early sign of type replacement will need to be studied further.

Our study has several limitations. Only anonymized samples were used, which precluded the collection of data on the individual level on vaccination status and sexual history information. Vaccination status would have been needed to separating direct vaccine effects and population immunity effects. Presently, our study applies only to changes in HPV ecology in the entire population. Change in prevalence of a particular virus type concomitantly with vaccination does not by itself imply a cause–effect relationship. However, the fact that the decline was seen only for the four vaccine types, but not for the 12 nonvaccine types analyzed and was furthermore most pronounced in the age groups with highest uptake of HPV vaccines does suggest that these two concomitant phenomena in the population may be related.

The fact that several different types of samples (with known differences in sensitivity for HPV detection) were collected could be handled by performing only stratified analysis, in which all over-time analyses were restricted to the same type of sample. The fact that urine was the dominant sample from men resulted in unreliable estimates for the HPV epidemiology among men, as this was the sample type with lowest sensitivity. However, there are also some benefits from using anonymous residual samples from the Chlamydia screening program. Extracted, ready-to-analyze sample material from a sexually active population is provided in a suitable plate format and informed consent was not required. Costs were therefore low and logistics were simple. Furthermore, selection biases associated with nonattendance could be minimized as all samples could be tested.

In summary, the established monitoring strategy in Sweden uses anonymous samples collected for Chlamydia testing for the evaluation of the early vaccination impact on type-specific HPV infections. The results suggest that even very early after the launch of the vaccination program, a significant reduction of prevalences of HPV6, 11, 16, and 18 can be seen. Further monitoring will be necessary for further evaluation of indirect protection of unvaccinated individuals as well as for elucidation of whether there is type replacement or cross-protection at the population level.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Söderlund-Strand
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Writing, review, and/or revision of the manuscript: A. Söderlund-Strand, I. Uhnoo, J. Dillner
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Söderlund-Strand
Study supervision: A. Söderlund-Strand, J. Dillner

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