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The Impact of Varying Numbers of Quadrivalent HPV Vaccine Doses on Anogenital Warts in the US: A Database Study

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Abstract

Objective—To investigate the effects of 3 quadrivalent human papillomavirus (HPV) vaccine doses on anogenital warts in both males and females in the US.

Methods—We conducted a retrospective database study that included males and females aged 9–26 years who received varying numbers of vaccine doses between 2006 and 2015. The primary outcome was the incidence of anogenital warts starting 3 months after the last dose of the HPV vaccine. Proportional hazard regression models were used to examine the association between the number of HPV vaccine doses and the incidence of anogenital warts. The Kaplan-Meier method was used to estimate the proportion of subjects.

Results—A total of 440,532 females and 133,394 males were included in the study. We found a significant 2-way interaction ($P < .0001$) between the number of doses and age. For the group between 15 and 19 years of age, the hazard ratio of anogenital warts for the 3-dose vaccine was 0.58 (95% CI; 0.49, 0.70), whereas it was 0.65 (95% CI; 0.49, 0.85) and 0.67 (95% CI; 0.51, 0.89) for the 1- and 2-dose groups, respectively.

Conclusions—Our findings showed that 1, 2, and 3 doses of the quadrivalent HPV vaccine were similarly effective against anogenital warts in 15–19-year-old adolescents, irrespective of gender.

Keywords

quadrivalent HPV vaccine; vaccine effectiveness; anogenital warts; single dose; 2 doses; 3 doses

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Disclosure statement

The authors declare no conflict of interest.

Introduction

The first human papillomavirus (HPV) vaccine was available in the US in 2006 (1). Since then, efforts have been directed toward the creation of implementation programs to increase the vaccine coverage rate despite significant barriers (2). The quadrivalent HPV vaccine contains virus-like particles derived from the L1 capsid proteins of HPV types 6, 11, 16, and 18, and, so far, it has been found to be strongly efficacious for type-specific diseases, such as cervical dysplasia and genital warts (3). HPV types 16 and 18 are responsible for 70% of cervical cancer cases, and HPV types 6 and 11 are responsible for approximately 90% of condylomas (4). Because the development of high-grade cervical dysplasia and cervical cancer takes many years, condyloma accuminatum could be the first measurable HPV-related disease endpoint post vaccination due to its short incubation time (5).

The HPV vaccine was initially recommended to be administered in 3 doses; however, in early 2014, the European Medicines Agency (EMA) approved the 2-dose schedule to be given at least 6 months apart for both boys and girls 9–13 years of age (6). This change was based on a phase III study on the immunogenicity of the 2-dose schedule (7). In October 2016, the Centers for Disease Control and Prevention (CDC) also updated its guidelines, recommending the 2-dose schedule for girls 9–14 years of age in the US (8). However, a recent systematic review and meta-analysis, which investigated the immunogenicity of 2- vs 3-dose HPV immunizations in preadolescent girls, found inconclusive evidence for noninferiority (9). In another study comparing the immunogenicity of 2 doses in younger adolescents with 3 doses in young women, noninferiority could not be reached for HPV type 6 by month 36, raising concerns about the long-term effectiveness of the 2-dose schedule (10). Since the threshold for the quantitative antibody level that protects against natural HPV infection has not yet been defined, it is currently not clear how inferior antibody levels or waning antibody response translates into disease prevention. Also, the question of whether the reduced dose schedule could be extended to people older than 15 years is still a matter of debate. To shed light on these issues, we investigated the impact of different numbers of quadrivalent HPV vaccine doses on the incidence of anogenital warts in the US.

Methods

We conducted a retrospective cohort study using health insurance claims from the Clinformatics™ Data Mart (CDM) Database (Optum, Eden Prairie, MN). This database is mainly used for research and includes longitudinal patient data for over 56 million enrollees from one of the largest insurance companies in the US. The database does not contain information on patients' socioeconomic status or race / ethnicity but it does contain geographic location. We used medical tables, which have claims for medical services, and the member table, which includes the demographic and enrollment information for enrollees. Since this study was a secondary data analysis using deidentified data, Institutional Review Board approval was not required.

Quadrivalent HPV vaccinated subjects

As with all vaccines recommended by the Advisory Committee on Immunization Practices (ACIP), HPV vaccines are covered by individuals' insurance companies in the US.

Vaccinated subjects included males and females who were 9–26 years old when they received their first dose of the quadrivalent HPV vaccine between 2006 and 2015 (N = 1,014,830; Table 1). Claims for the quadrivalent HPV vaccine were identified by Current Procedural Terminology (CPT) code 90649. We selected those who had continuous enrollment 12 months before and 18 months after the first dose (N = 335,262). The 18-month post period was used to determine whether or not the subject finished all 3 doses of the vaccine. We excluded those who had any claim for the 9-valent HPV vaccine (CPT code 90651) and those who received more dose(s) of the quadrivalent HPV vaccine after the 18-month period, leaving 291,002 subjects. Then, we identified the date of the last dose within 18 months of the initial dose. This date served as the index date, and the follow-up started 3 months after this date. After we selected those who had continuous enrollment 12 months before and 3 months after the index date and excluded those who had anogenital warts in this period, 288,870 subjects remained. Lastly, we removed those who resided in Puerto Rico, resulting in 288,774 subjects in this initial cohort. We classified the subjects into 3 groups based on the number of doses they received within 18 months of the first dose. Since age at vaccination has been previously shown to alter vaccine effectiveness (11), 3 age groups (< 15, 15–19, 20) were further analyzed for the hazard ratios of varying numbers of vaccine doses. These age groups were determined based on the available immunogenicity evidence, which showed a 2-dose schedule (0, 6–12 months) has an efficacy equivalent to a 3-dose schedule (0, 1–2, 6 months) if the HPV vaccination series is initiated before the patient's 15th birthday (12). The mean age of first sexual intercourse (16–17 years for males and 16–18 years for females) in the US is also taken into consideration since the vaccine is very efficacious in HPV-naïve cohorts (13).

Matching vaccinated and unvaccinated subjects

We first selected all CDM members without any bivalent (CPT code 90650), quadrivalent, or 9-valent HPV vaccinations (N = 58,645,435). Then, we selected those who were born between 1980 and 2006 (N = 22,249,117). The vaccinated subjects received the vaccine between 2006 and 2015 when they were aged 9–26 years. Therefore, we selected those who were eligible for vaccination between 2006 and 2015. The matching process started with taking the dates of the first and last doses of the first subject. These 2 dates were assigned to all eligible unvaccinated subjects so that we could identify those who (i) had continuous enrollment 12 months before and 18 months after the first date; (ii) had continuous enrollment 12 months before and 3 months after the second date, the “index date”; and (iii) did not have anogenital warts 12 months before and 3 months after the index date. From these subjects, we randomly selected one who matched the age, gender, region, sexually transmitted disease (STD) history, and length of enrollment prior to the index date of a vaccinated subject. We repeated this process for 288,774 times to match the 288,774 vaccinated subjects. In the end, we were able to identify matching unvaccinated counterparts for 286,963 (99.4%) vaccinated subjects. The majority of the unmatched vaccinated subjects (70.4%) were from the Northeast.

Variables

The year of birth, gender, census region of residence, and enrollment period were obtained from the CDM member table. The ages of subjects and their unvaccinated counterparts were

calculated by subtracting the year of birth from the index year. We used the claims in the year before the index date to identify history of sexual transmitted diseases, chlamydia, and gonorrhea. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for identifying chlamydia and gonorrhea can be found in the appendix.

Study Outcome

The outcome of this study was the incidence of anogenital warts starting 3 months after the last dose of the quadrivalent HPV vaccine. The claims with anogenital wart diagnosis were identified using the ICD-9-CM code 078.11 or A63.0. Study subjects were censored when they lost insurance coverage or at the end of 5 years of follow-up visits.

Statistical analysis

We used analysis of variance (ANOVA, for continuous variable) and a Chi-square test (for categorical variables) to examine the difference in the patient characteristics among the dose groups. For each age group, we used the Kaplan-Meier method to estimate the proportion of those developing anogenital warts among the unvaccinated subjects and among vaccinated subjects with 1, 2, or 3 doses. The results were presented in Figure 1 and Table 3. We used proportional hazard regression models to examine the association between the number of HPV doses and the incidence of anogenital warts while adjusting for age group, gender, region of residence, and history of STDs. Due to the significant interaction between the number of doses and age groups, we presented the hazard ratios of HPV doses by age group. Dunnett's method (14,15) was used for multiple comparison adjustment. All statistical analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC).

Results

A total of 440,532 females (220,266 subjects with varying numbers of vaccine doses and 220,266 unvaccinated subjects) and 133,394 males (66,697 subjects with varying numbers of vaccine doses and 66,697 unvaccinated subjects) were included in the study. The mean time to final vaccine dose was 6.84 ± 4.69 months for those who received only 2 doses and 8.38 ± 2.99 months for the 3-dose group. Participants were also categorized into 3 groups based on the age at which they received the last dose (< 15, 15–19, 20 years). Participant characteristics are summarized in Table 2. There was a significant 2-way interaction between the number of doses and age ($P < .0001$); therefore, we presented the hazard ratios of the number of doses by age. We also tested interactions between the number of doses and STD history ($P = .5718$), as well as the number of doses and gender ($P = .4969$); however, the results were not significant. For the youngest age group, < 15 years old, there was no significant difference between the unvaccinated and any of the vaccinated groups for the risk of having genital warts (Table 3). In adolescents aged 15 to 19 years, the hazard ratio for the 3-dose group was found to be 0.58 (95% CI; 0.49, 0.70), whereas it was 0.65 (95% CI; 0.49, 0.85) and 0.67 (95% CI; 0.51, 0.89) for the 1- and 2-dose groups, respectively (Table 3, Figure 1). When the vaccinated groups in this age range were compared to each other, we found no significant difference in the vaccine's protective effects (2 vs 1, $P = .67$; 3 vs 1, $P = .49$; 3 vs 2, $P = .21$). We further stratified the 2-dose group based on spacing between the

first and second doses (< 6 months apart vs 6 months apart), and the hazard ratio was nonsignificant in terms of timing 6 months (Table 4). For the older age group (≥ 20 years old), we did not find significant protective effects for any of the vaccinated groups (Table 3).

Discussion

In this study, we sought to evaluate the efficacy of fewer than 3 doses of the quadrivalent HPV vaccine in both males and females. Since there was no significant interaction between number of doses and gender, we presented the results irrespective of gender.

With regard to the youngest age group (< 15 years), many of the cohort subjects were very unlikely to be exposed to HPV or develop anogenital warts by the end of the follow-up period, thus resulting in no difference in cumulative incidence rates between vaccinated and unvaccinated subjects. This result also led to wide confidence intervals of hazard ratios in this age group. For the oldest group (≥ 20 years), there was a selection bias since many of the subjects in this group were very likely to be sexually active before they received the vaccine. Based on the current literature, it is well known that the younger the age of vaccination, the better the outcomes are, not only because the vaccine is very efficacious in HPV-naïve cohorts, but also because it induces a stronger immune response at younger ages (16,17). This latter fact is the rationale for the acceptance of 2-dose schedules for individuals younger than 15 years of age (8,10). Furthermore, real-world vaccine effectiveness in older cohorts is influenced by the vaccine coverage rate at the population level (18,19). The current vaccination coverage rates in the US are increasing: 65% of girls and 56% of boys have received their first dose of the vaccine according to the 2016 National Immunization Survey-Teen (20). However, the rates of series completion are still low nationwide (43%), and this rate is much lower in rural areas.

Young adolescents (15–19 years of age) most accurately showed the effects of varying numbers of vaccine doses in our study since the majority of this group had very likely received the vaccine before being exposed to HPV and become sexually active during the follow-up period. This assumption was based on the fact that the average age of first sexual intercourse in the US is reported to be around 16–17 years for males and 16–18 years for females (13). Our results showed that all vaccine schedules were similarly and significantly effective when compared to unvaccinated subjects. In a recent database study from the US, Hariri et al investigated the effectiveness of varying numbers of quadrivalent HPV vaccine doses in a cohort of insured females (21). While vaccine effectiveness was 68% and 76% in 2-dose (≥ 6-month interval) and 77% and 80% in 3-dose vaccinated groups, compared to unvaccinated subjects, it was not significant in 1-dose and 2-dose (< 6-month interval) groups. The major difference between our study and the one conducted by Hariri et al is that Hariri et al applied 6-month and 12-month buffer periods from the last and first vaccine doses, respectively, to minimize the confounding effects of latent genital warts, but we selected 3 months from the last dose in our study. The reason we applied a 3-month buffer period is because a previous study showed that the cumulative incidence curves for women who received at least 1 dose of the vaccine and unvaccinated women began to diverge after approximately 3 months (22). This time period actually represents the lower limits of the

incubation period, and longer time periods would have led to overestimation of the effect of fewer than 3 vaccine doses.

Some large cohort studies from different countries previously reported on the effect of various numbers of HPV vaccine doses on genital warts. In a Swedish cohort study that included individuals aged 10–16 years at first vaccination, receipt of 3 doses was associated with an incidence rate ratio (IRR) of 0.18 (95% CI, 0.15–0.22), whereas it was 0.29 (95% CI, 0.21–0.40) for 2 doses and 0.31 (95% CI, 0.20–0.49) for 1 dose (22). In this study, the incidence rate difference was 384 cases (95% CI, 305–464) per 100 000 person-years for 1 dose, compared with no vaccination, and the number of prevented cases between 3 vs 2 doses was 59 per 100 000 person-years. A recent cohort study from Spain showed similar results. This study found the relative risk of genital warts after 3 doses of the vaccine to be 0.24 (95% CI, 0.15–0.34), whereas it showed 0.36 (95% CI, 0.14–0.68) in 2-dose and 0.39 (95% CI, 0.13–0.8) in 1-dose recipients (23). In a nationwide study from Denmark that included a cohort of females aged 13–27 years, Blomberg et al found that genital warts occurred less frequently with each additional dose (24). The IRR for 1 dose vs no vaccine was 0.51 (95% CI, 0.46–0.56), whereas it was 0.44 (95% CI, 0.37–0.51) and 0.46 (95% CI, 0.39–0.54) for 2 vs 1 and 3 vs 2, respectively (24). A cohort study from Belgium including 106,579 women aged 10–21 years, showed an age-adjusted vaccine effectiveness of 36% for 1 dose, 65% for 2 doses, and 85.9% for 3 doses of the vaccine (25). The observed median interval between doses was 63 days (about 2 months) among those who received 2 doses. Although these population studies have many limitations due to their retrospective nature, they all suggest that the maximum benefit is seen with 3 doses. However, unlike these studies, we did not find a significant difference in the hazard ratios of 1, 2, and 3 doses of the vaccine in our study, suggesting a similar effectiveness, even with just one dose. This finding raises the question of whether the reduced dose schedule could be extended to people older than 15 years. Apparently, appropriately designed prospective randomized trials are needed to answer this question, but the only observational prospective cohort study in the literature showed no difference between any vaccine dosing schedules (1-dose group; 2-dose default group, vaccinated on days 1 and 60; 2-dose group, vaccinated on days 1 and 180; or 3 dose-group, vaccinated on days 1, 60, 180) in terms of incidental / persistent HPV infections with vaccine types and antibody avidity indices at a median follow-up of 4.7 years (26).

Our study has some limitations. First, information on outcomes came from diagnosis codes and relied on insurance claims for outpatient and hospitalization services. These diagnoses are not always accurate or complete. Second, the database contains a higher percentage of white (73% vs 63%), young (aged 21–39 years, 32% vs 26%), and middle-aged adults (aged 40–64 years, 34% vs 27%), as well as residents from the Midwest (26% vs 21%) and South (44% vs 37%) than what is present in the overall US population, so the findings are only applicable to those with private insurance but not those with public insurance or without insurance (27). Third, our database lacked information that may influence the risk of anogenital warts, such as the number of partners and sexual behavior of participants. Fourth, the longer follow-up periods in vaccinated cohorts might have underestimated the impact of vaccination. Fifth, subjects with STDs were rare in our sample. Among the 288,774 vaccinated subjects before matching, only 0.3% had a history of STD. Due to the low

prevalence of STDs, it was difficult to find matches for those with STDs. Among those unmatched subjects, 24.7% had a history of STD. However, when we compared the matched and unmatched subjects with STD histories, they were similar in age with a difference less than 1 year.

This study, however, has strengths. The database is helpful for studying cumulative incidence rates for diseases because it includes a significant number of participants, which allows for the estimation of vaccine effects in a real-world context. The database also contains longitudinal tracking at the patient level, which provides long-term follow-up data.

Overall, our findings showed similar and significant effectiveness of fewer than 3 doses of the quadrivalent HPV vaccine on anogenital warts in adolescents between 15 and 19 years of age. Our study also supports starting the vaccine series before the first sexual intercourse. Randomized controlled trials, including 1-dose arms with long-term follow-up data, are needed to make definitive conclusions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

HPV	Human Papilloma Virus
EMA	European Medicines Agency
CDC	Centers for Disease Control and Prevention
CDM	Clinformatics™ Data Mart

CPT	Current Procedural Terminology
ACIP	Advisory Committee on Immunization Practices
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
STD	Sexually transmitted disease

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Figure 1.

Table 1

Initial case selection

	N	% of prior step
1. All subjects who ever received quadrivalent HPV vaccine between 2006 and 2015.	1,032,204	
2. Included those aged 9–26 at the 1st dose.	1,014,830	98.3
3. Included those with continuous enrollment 12 months before and 18 months after the 1st dose.	335,262	33.0
4. Excluded those who ever had any claim for the 9-valent vaccine.	330,118	98.5
5. Excluded those who had their 2nd or 3rd dose after 18 months.	291,002	88.2
6. Identified the date of the last dose within 18 months of the initial dose. Selected those with continuous enrollment in the 12 months before and 3 months after the last dose.	290,411	99.8
7. Excluded those who had viral warts in the year before or in the 3 months after the last dose.	288,870	99.5
8. Excluded those who resided in Puerto Rico or US territories.	288,774	100.0

Table 2

Patient characteristics by dose of HPV vaccine received.

Characteristic	Unvaccinated N = 286963	1 Dose N = 54280	2 Doses N = 55632	3 Doses N = 177051	P value [#]	P value ^{\$}
Time to final received dose (months) Mean ± SD	NA	NA	6.84 ± 4.69	8.36 ± 2.99	-	-
Age at the index year, Mean ± SD	16.55 ± 3.61	16.72 ± 3.69	16.75 ± 3.63	16.43 ± 3.57	<.0001	<.0001
Age group, N (column %)						
< 15	94233 (32.84)	16844 (31.03)	17090 (30.72)	60299 (34.06)	<.0001	<.0001
15–19	141662 (49.37)	26543 (48.90)	27884 (50.12)	87235 (49.27)		
20	51068 (17.80)	10893 (20.07)	10658 (19.16)	29517 (16.67)		
Gender						
Female	220266 (76.76)	37347 (68.80)	40202 (72.26)	142717 (80.61)	<.0001	<.0001
Male	66697 (23.24)	16933 (31.20)	15430 (27.74)	34334 (19.39)		
Region, N (column %)						
Midwest	82394 (28.71)	14453 (26.63)	14879 (26.75)	53062 (29.97)	<.0001	<.0001
Northeast	34924 (12.17)	5162 (9.51)	6735 (12.11)	23027 (13.01)		
South	120962 (42.15)	24616 (45.35)	24159 (43.43)	72187 (40.77)		
West	48683 (16.96)	10049 (18.51)	9859 (17.72)	28775 (16.25)		
History of STD, N (%)	446 (0.16)	92 (0.17)	119 (0.21)	235 (0.13)	.0003	<.0001
Follow-up time in months [‡] , Mean ± SD (Median)	28.25 ± 15.65 (23.87)	36.06 ± 14.14 (31.40)	30.76 ± 17.28 (26.63)	33.55 ± 17.95 (29.13)	<.0001	<.0001

[#] ANOVA (for continuous variable) or Chi-square test (for categorical variables). The unvaccinated group was included in the hypothesis testing.

^{\$} ANOVA (for continuous variable) or Chi-square test (for categorical variables). The unvaccinated group was excluded in the hypothesis testing.

[‡] Including the 3 months between the index date and the initiation of the follow-up.

SD: standard deviation; STD: sexually transmitted disease.

Table 3

Effect of the number of doses on the likelihood of viral warts in each age group.

Age group	No. of doses	N	No. of event by year 5	Event rate at year 5 (%)#	Hazard ratio (95% CI) *
< 15	0	94233	48	0.21	Reference
	1	16844	9	0.12	0.80 (0.34, 1.90)
	2	17090	13	0.29	1.36 (0.65, 2.86)
	3	60299	32	0.11	0.78 (0.46, 1.35)
15–19	0	141662	575	0.98	Reference
	1	26543	85	0.61	0.65 (0.49, 0.85)
	2	27884	83	0.70	0.67 (0.51, 0.89)
	3	87235	260	0.61	0.58 (0.49, 0.70)
20	0	51068	367	1.38	Reference
	1	10893	85	1.25	0.96 (0.72, 1.28)
	2	10658	92	1.46	1.15 (0.87, 1.51)
	3	29517	252	1.48	1.11 (0.91, 1.35)

Event rates were estimated by Kaplan-Meier method.

* Hazard ratios were adjusted for gender, region, and the history of sexually transmitted diseases.

CI: confidence interval.

Table 4

Effect of dose spacing on the likelihood of viral warts on subjects aged 15 or older, by age group

Age group	No. of doses	N	Hazard ratio (95% CI)*
15–19	0	141662	Reference
	1	26543	0.61 (0.46, 0.81)
	2, < 6 mo	14597	0.65 (0.45, 0.94)
	2, 6 mo	13287	0.69 (0.44, 1.07)
	3	87235	0.61 (0.50, 0.73)
20	0	51068	Reference
	1	10893	0.93 (0.69, 1.25)
	2, < 6 mo	6955	1.11 (0.79, 1.55)
	2, 6 mo	3703	1.23 (0.76, 1.98)
	3	29517	1.13 (0.92, 1.39)

* Hazard ratios were adjusted for gender, region, and the history of sexually transmitted diseases.

CI: confidence interval.