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Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink☆

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ABSTRACT

Background: In 7 large managed care organizations (MCOs), we performed a post-licensure safety assessment of quadrivalent human papillomavirus vaccine (HPV4) among 9–26 year-old female vaccine recipients between August 2006 and October 2009.
Methods: Sequential analyses were conducted weekly to detect associations between HPV4 exposure and pre-specified outcomes. The pre-specified outcomes identified by ICD-9 codes using computerized data at the participating MCOs included: Guillan–Barré Syndrome (GBS), stroke, venous thromboembolism (VTE), appendicitis, seizures, syncope, allergic reactions, and anaphylaxis. For rare outcomes, historical background rates were used as the comparison group. For more common outcomes, a concurrent unexposed comparison group was utilized. A standardized review of medical records was conducted for all cases of GBS, VTE, and anaphylaxis.
Results: A total of 600,558 HPV4 doses were administered during the study period. We found no statistically significant increased risk for the outcomes studied. However, a non-statistically significant relative risk (RR) for VTE ICD-9 codes following HPV4 vaccination of 1.98 was detected among females age 9–17 years. Medical record review of all 8 vaccinated potential VTE cases in this age group revealed that 5 met the standard case definition for VTE. All 5 confirmed cases had known risk factors for VTE (oral contraceptive use, coagulation disorders, smoking, obesity or prolonged hospitalization).
Conclusions: In a study of over 600,000 HPV4 vaccine doses administered, no statistically significant increased risk for any of the pre-specified adverse events after vaccination was detected. Further study of a possible association with VTE following HPV4 vaccination is warranted.

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1. Introduction

In June 2006, the Food and Drug Administration (FDA) licensed the quadrivalent human papillomavirus (HPV) vaccine (Gardasil®; Merck & Co. Inc., Whitehouse Station, New Jersey) for females aged 9–26 years. Gardasil®, or HPV4, is a virus-like particle vaccine composed of the major L1 capsid protein for HPV types 6, 11, 16, and 18 and an aluminum-containing adjuvant. The vaccine, administered in a series of three doses, is recommended by the Advisory Committee on Immunization Practices (ACIP) for routine use among females ages 11–12 years, permitted for girls as young as nine years of age, and recommended for females 13–26 years of age not previously vaccinated [1]. Prelicensure clinical trials have shown no evidence for any major safety problems [2,3]. However, prelicensure studies were not adequately powered to detect rare adverse events. Because of this limitation, post-licensure monitoring of HPV4 safety using large population-based cohorts is needed.

The Vaccine Safety Datalink (VSD) is a collaboration of managed care organizations (MCOs) in the United States which collects medical information on more than 9 million people each year [4]. The VSD has developed a near real-time surveillance system, called Rapid Cycle Analysis (RCA), to monitor potential adverse events following licensure of new vaccines [5]. The purpose of this study was to determine whether HPV4 is associated with an increased risk of

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pre-specified clinically well-defined and severe adverse events in a large, nationally representative population.

2. Methods

2.1. Design and study population

Seven VSD sites, including Group Health Cooperative (Seattle, WA), Harvard Pilgrim Health Care and Harvard Vanguard Medical Associates (Boston, MA), HealthPartners Research Foundation (Minneapolis, MN), Kaiser Permanente of Colorado (Denver, CO), Kaiser Permanente of Northern California (Oakland, CA), Marshfield Clinic (Marshfield, WI) and Kaiser Permanente Northwest (Portland, OR) participated in this prospective cohort study. Females aged 9–26 years, identified at the participating sites from August 2006 to October 2009 formed the base population. Weekly standardized datafiles, containing demographic, immunization, and ICD-9 diagnosis data from medical encounters in outpatient clinics, emergency department, and hospital settings were generated.

The Institutional Review Boards at all participating MCOs approved this study.

2.2. Outcome definitions and ascertainment

Prespecified adverse events (outcomes) were selected based on safety data from prelicensure clinical trials and reports to the Vaccine Adverse Event Reporting System (VAERS) [6]. The outcomes monitored were clinically well defined with relatively acute onset, serious enough to result in a medical visit, and represent a biologically plausible association with vaccination. Outcomes included Guillain–Barré Syndrome (GBS), stroke, venous thromboembolism (VTE), appendicitis, anaphylaxis, seizure, syncope, and allergic reaction. Outcomes were identified by ICD-9 codes. To avoid counting multiple visits for the same illness episode, case ascertainment was limited to the first episode in a particular time period. Table 1 lists definitions used and time windows for outcomes under surveillance. Given the serious nature of VTE and GBS and elevated concern in early VAERS reports, we decided *a priori* to perform medical record review of potential cases to facilitate more rapid confirmation or exclusion of identified cases of these diseases. Medical record review for all anaphylaxis cases was conducted due to concerns about a lack of specificity of the selected ICD-9 codes [7]. Medical record review instruments were developed for each of these outcomes and referenced the respective Brighton Collaboration definitions for GBS and anaphylaxis [8,9]. We used a case definition that included confirmed duplex ultrasound for VTE, consistent with definitions used in other population-based epidemiologic studies [10,11].

2.3. Exposure and covariate assessment

Females receiving at least one dose of HPV4 were considered vaccine-exposed and followed for each adverse outcome for the risk periods defined in Table 1. We collected information on date of vaccination, days to the specified adverse event outcome, age (in years), and VSD site.

2.4. Unexposed comparison groups

A historical comparison group not vaccinated with HPV4 was used for less common outcomes, including GBS, VTE, stroke, and appendicitis. Background rates were calculated without regard to vaccination status. For this study, we defined less common outcomes as those with a background incidence rate of less than 150 cases per 100,000 person-years based on rates calculated from the time period prior to HPV4 licensure (Table 2). When possible, we calculated background rates using automated VSD data from January 2000 to June 2006, although in some cases the date range varied based on data availability at participating sites. Outcome ascertainment was limited to the first episode in the period specified in Table 1, and site specific rates were calculated. A larger data source, the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS), was used to obtain more stable background rates for GBS [12]. Generally, we stratified analyses by youth (9–17 years) and adult (18–26 years) age groups, but because rates of GBS and VTE vary widely by age, analyses were adjusted by finer age categories (in years) as follows: for VTE, 9–13, 14–17, and 18–26; for GBS, 9–10, 11–14, 15–17, and 18–26 (Table 2).

A concurrent unexposed comparison group was used for more common outcomes: allergic reactions, syncope, and seizures. For seizures, women who had a preventive care visit were included to compare the risk of seizures following HPV4 to the general risk of seizures in the population. For syncope and allergic reactions, vaccination visits without concomitant HPV4 vaccine were included to compare the risk following HPV4 with the risk following other vaccines, as these outcomes have been known to occur following vaccination. We defined preventive care visits as a routine child health check, a routine general medical exam at a health care facility, or a routine gynecological exam. Vaccination visits were defined as receipt of any of the following adolescent vaccines received during the surveillance period: Tdap, Td, meningococcocal, or varicella vaccine. Comparison visits were matched on age, site and date of vaccination/preventive care visit. Follow-up for each outcome used pre-specified risk windows and other criteria defined in Table 1.

No formal statistical comparison was performed for anaphylaxis due to concern over a low predictive value of a positive test for ICD-9 code for this outcome [7]. Instead, we describe the incidence of anaphylaxis following HPV4 vaccination for confirmed cases.

2.5. Sequential analysis for real-time surveillance

In order to detect promptly any significant increases while maintaining an overall Type I error rate of 0.05, we analyzed data weekly using sequential analysis methods [5]. In brief, these methods call for weekly analyses until a pre-defined “upper limit” is reached; if analyses were continued beyond the upper limit, the risk of type I error would be >0.05. Depending on the sequential method used, the upper limit may be expressed as a number of HPV4 doses to be monitored or the number of expected outcome events (calculated by multiplying the expected rate by the expected number of HPV4 doses). We calculated upper limits based on a prespecified number of approximately 350,000 doses for youth and 150,000 doses for adults. If the upper limit was reached and there was no signal, the null hypothesis of no association between HPV4 and adverse event was accepted. If a signal was detected, the null hypothesis would be rejected, and further evaluation conducted to determine the likely importance of this positive finding. For each outcome, results from the sequential analyses are presented at the time that the upper limit was reached, a signal was detected, or the end of the study period (October 2009), whichever came first.

We used Poisson based maximized sequential probability ratio test (maxSPRT) to analyze rare outcomes using the historical comparison group [13]. Using historical background incidence rates, we calculated age and site adjusted expected numbers of adverse events based on the distribution of HPV4 doses administered compared with the number of events actually observed in the HPV4 vaccinated population, and calculated a relative risk (observed/expected). A log likelihood ratio test statistic at each time period (LLR(t)) was used to determine if elevated risks were statistically significant. The null hypothesis of no excess risk is rejected and a statistical signal is generated if and when the LLR(t) exceeds

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Table 1
Definitions of potential adverse events following quadrivalent human papillomavirus (HPV4) vaccination, relevant comparison groups, and observation window under surveillance after vaccination, Vaccine Safety Datalink, 2006–2009.

Adverse event	ICD9 codes	Comparison group	Post-vaccination observation window (days)	Medical setting	First episode in what period?
Anaphylaxis	995.0, 999.4	No comparison visit	0–2	Outpatient, inpatient, ED[b]	First in 2 days
Allergic reactions	995.1, 995.3, 708.0, 708.1, 708.9	Concurrent vaccination visit	0–2 for inpatient and ED[b] 1–2 for outpatient	Outpatient, inpatient, ED[b]	First in 42 days
Appendicitis	540.[a]	Historic VSD background rate	0–42	Inpatient, ED[b]	First in 42 days
Guillain–Barré syndrome	357.0	Historic background rate using HCUP data	1–42	Outpatient, inpatient, ED[b]	First in 42 days
Seizures	345[a], 789.3[a]	Historic VSD background rate	0–42	Inpatient, ED[b]	First in 42 days
First ever seizures	345[a], 789.3[a]	Concurrent preventative care visit	0–42	Inpatient, ED[b]	First since joining the health plan
Stroke	433.[a], 434.[a], 435.0, 435.1, 435.8, 435.9, 436.[a], 437.1	Historic VSD background rate	0–42	Inpatient, ED[b]	First in 42 days
Syncope	780.2	Concurrent vaccination visit	0	Outpatient, inpatient, ED[b]	First in 2 days
Venus Thromboembolism	415.1[a], 453[a]	Historic VSD background rate	1–42	Outpatient, inpatient, ED[b]	First in 1 year

[a] Includes all 4th and 5th digits within an ICD-9 code.
[b] Emergency department visit.

Table 2
Background incidence rates for outcomes used in the Poisson maximum sequential probability ratio test analyses, Vaccine Safety Datalink, 2006–2009.

Outcome	Comparison window (days)	Chosen data source	Age group (yrs)	Incidence rate (per 100,000 PY)
Guillain–Barré syndrome	1–42	HCUP[a]	9–10	0.945
			11–14	1.257
			15–17	2.130
			18–26	2.251
Appendicitis	0–42	VSD[b]	9–17	133.440
			18–26	124.427
Stroke	0–42	VSD[b]	9–17	2.656
			18–26	7.454
Venus Thromboembolism	1–42	VSD[b]	9–13	3.221
			14–17	13.428
			18–26	73.642

[a] Heath care utilization project data from 1991 to 2004.
[b] VSD data from 2000 to June 2006.

Table 3
Relative risks (RR) of selected outcomes following HPV4 vaccination in analyses using historical comparison group, Vaccine Safety Datalink, 2006–2009.

Outcome	Youth/adult	Upper limit	Last week of analysis[a]	Doses administered	Observed events	Expected events under H0	RR	Log likelihood ratio (LLR)	Critical value of LLR	Signal
Guillain–Barré syndrome	Youth[b]	1	164	416,942	0	0.80	0.00	–	2.81	No
	Adult[b]	1	164	183,616	1	0.48	2.10	0.22	2.86	No
Appendicitis	Youth	60	79	203,890	50	32.80	1.52	3.88	3.86	Yes
	Adult	25	120	139,746	33	25.03	1.32	1.15	3.68	No
Stroke	Youth[b]	1.5	164	416,942	0	1.35	0.00	–	2.97	No
	Adult	1.5	98	112,619	2	1.50	1.33	0.07	2.97	No
Venus Thromboembolism	Youth	4	110	292,302	8	4.04	1.98	1.51	3.25	No
	Adult	15	156	176,194	11	15.00	0.73	–	3.57	No

[a] The earliest of the following: upper limit reached, signal occurred or end of study.
[b] Upper limit not reached – results from the last available week of analysis.
Week 1 defined as August 20, 2006.

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Table 4
Summary of confirmed venous thromboembolism (VTE) cases among 9–17 year olds, Vaccine Safety Datalink, 2006–2009.

Case number	Age	Days to VTE diagnosis	Type of VTE[a]	Risk factor
1	17	32	PE	Antiphospholipid syndrome, hormonal contraceptive use, overweight, smoker
2	16	7	DVT	Car accident with spinal cord injury and paralysis, Factor V leiden
3	17	3	DVT	Hormonal contraceptive use
4	14	2	DVT	Lupus anticoagulant positive, protein S deficiency
5	17	3	PE	Hormonal contraceptive use

[a] PE = pulmonary embolism, DVT = deep vein thrombosis.

a predefined critical value. We required at least 2 exposed cases before investigating a signal.

We used exact sequential analysis (ESA) to analyze more common outcomes using the concurrent comparison group [14]. For this analysis, we compared the exposed group to the unexposed group, matching on age in years, site, and vaccination date. This method is similar to binomial maxSPRT, but allows for more efficient use of the data through a flexible matching ratio of exposed to unexposed subjects within each stratum and uses an exact binomial test. For each outcome, we defined a unique threshold *p*-value for signaling that was more stringent than 0.05 in order to ensure that the total chance of a Type 1 error was below 0.05 over all of our analyses of the accumulating data. We followed an alpha-spending plan which specified for each outcome a nominal *p*-value required for a signal that was nearly constant over time [15]. At the time of each analysis, we determined the exact *p*-value required for a signal based on our pre-specified alpha-spending plan, the number of outcome events in each stratum to date, the ratio of exposed to unexposed in each stratum, and the probability (under the null hypothesis) that no signal has yet occurred.

2.6. Additional investigations

All statistical signals and instances of elevated relative risks from weekly sequential analyses were followed-up [16]. Follow-up included additional data quality checks; temporal scan statistics using SaTScan™ software to evaluate clustering of events at time intervals after vaccination; adjustments for possible additional confounders using non-sequential analyses, or other methodologies such as the case-centered analysis, which allows for finer adjustment of confounding [17–19].

3. Results

Monitoring of HPV4 occurred for 164 weeks during which a total of 600,558 doses were administered in the VSD population. 416,942 doses were administered to youth and 183,616 doses to adults.

3.1. Results using a historical comparison group

Poisson maxSPRT results for youth and adults are presented in Table 3. Among youth, no cases of GBS or stroke were identified. There were 8 cases of VTE identified through ICD9 codes in the sequential analyses compared with the 4 expected at the upper limit; yielding a relative risk (RR) of 1.98; however, the critical value needed to reject the null hypothesis was not reached. Five of the eight cases were confirmed as VTE by medical record review, of which all had other risk factors for VTE such as hormonal contraceptive use, hypercoagulable disorders, smoking and/or obesity (Table 4). Of the other 3 cases not confirmed as VTE, 2 were miscoded diagnoses and one suspected case was ruled out after diagnostic testing.

In week 79, appendicitis signaled among youth when the LLR of 3.9 exceeded the established critical value of 3.86 (RR = 1.5). When evaluating this statistical signal, we discovered that coding practices for appendicitis at one of our MCOs had changed due to a modification of the electronic medical record system resulting in lower background rates. A temporal scan did not find any statistically significant clusters. A logistic regression analysis using a concurrent comparison controlling for sex, age, and seasonality yielded a non-significant association (Odds Ratio (OR) = 1.13, 95% CI: 0.79, 1.64). Further a case-centered analysis also showed no association between vaccination and subsequent appendicitis (RR = 1.03, 95% CI: 0.84–1.26).

Among the adults, there was one case of GBS identified following HPV4. Medical record review revealed this was not an incident GBS case. Two cases of stroke among adults were observed following HPV4, generating a non-statistically significant RR of 1.33. There was no statistically significant increased risk observed for appendicitis or VTE among the adult population.

3.2. Results using concurrent comparison group

Using ESA, we did not see a statistically significant increased risk of seizures, new-onset seizures, allergic reactions, or syncope following HPV4 for either youth or adults (Table 5). Upper limits were reached for youth at week 138 and for adults at week 142.

3.3. Anaphylaxis results

During the 164 weeks, 27 anaphylaxis cases (18 youth; 9 adults) were identified following HPV4. Medical chart review confirmed one vaccine-related case in a 26 year old. The majority of the other cases were visits for food allergies or routine refill of epinephrine autoinjectors (89%). Based on one confirmed case, the rate of anaphylaxis following HPV4 in this study was 1.7 cases per million doses (95% CI: 0.04, 9.3).

4. Discussion

With over 600,000 doses administered, this is the largest population-based, post-licensure study of HPV4 safety in the United States. We confirmed no statistically significant increased risk between HPV4 and Guillain–Barré Syndrome (GBS), stroke, venous thromboembolism (VTE), appendicitis, anaphylaxis, seizure, syncope, or allergic reaction. While we did not confirm any statistically significant signals, an elevated RR of 1.98 for VTE among the youth was observed when the upper limit was reached. All of the 5 confirmed VTE cases were found to have other risk factors for VTE. However, in our study we were unable to determine whether the VTE observed were attributable to these common risk factors, or these were effect modifiers of the association between HPV4 and VTE. In pre-licensure trials, equal numbers of cases of VTE were observed in both treatment arms suggesting no evidence of a safety concern for this outcome [20]. While published VAERS findings indicate increased reporting for VTE, these cases occurred over a wide range of time intervals after immunization, making an association with vaccination less likely; as in our study, all exposed cases reported a known risk factor for VTE [6]. Depending on their age, females may have other risk factors for VTE which

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Table 5
Relative risks (RR) of selected outcomes following HPV4 vaccination in analysis using concurrent comparison group, Vaccine Safety Datalink, 2006–2009.

Outcome	Youth/adult	Upper limit (100 K HPV doses)	Last week of analysis[a]	Doses administered	# of comparison visit	Exposed cases	Un-exposed cases	RR	Signal
Seizure	Youth	350	138	351,706	206,045	47	23	1.02	No
	Adult	150	142	150,603	283,666	22	37	1.13	No
Syncope	Youth	350	138	351,630	146,833	610	202	0.86	No
	Adult	150	142	150,544	54,584	170	95	0.54	No
Allergic reactions	Youth	350	138	351,630	146,833	54	29	0.77	No
	Adult	150	142	150,544	54,584	37	8	1.48	No

[a] The earliest of the following: upper limit reached, signal occurred or end of study.
Week 1 defined as August 20, 2006.

cannot be adequately controlled for in passive surveillance and rapid active surveillance studies; therefore, additional studies are being developed within VSD to better control for confounding and explore potential effect modification of the HPV4 and VTE association [21–24].

We observed a total of 2 cases of stroke and no confirmed cases of GBS following HPV4 during the entire study period. Prelicensure trials did not identify any stroke cases. Published VAERS findings confirmed 4 reports of cerebrovascular accidents and 2 reports of superior sagittal venous thrombosis, but each of these cases had risk factors for embolic events (oral contraceptive use, smoking, and hypercoaguable disorders) [6]. However, our power to detect very rare events was limited. Therefore, we will continue to monitor stroke and GBS until one million doses of HPV4 have been administered in our study population, since the upper limits were not reached.

As several new vaccines have been introduced into the adolescent vaccine schedule, post-vaccination syncope among adolescents and young adults has been of increased concern, and because of recognized occurrence of syncope following all adolescent vaccines and the potential for subsequent serious injury, ACIP has recommended that providers should consider observing patients for 15 min after vaccination [25,26]. Following HPV4, post-vaccination syncope has been among the most frequently reported adverse events to VAERS compared to other adolescent vaccines. Post-vaccination syncope reports to VAERS increased between 2005 and 2007, primarily among females age 11–18 years [27]. Among the military population, the risk of post-vaccination syncope over a 10 year surveillance period also showed an increase from 1998 to 2007 [28]. While syncope may be relatively common after adolescent vaccination, our study found no increased risk of syncope following HPV4 when compared to the risk of syncope following other adolescent vaccines.

Concerns regarding seizures have been reported following HPV4 vaccine through VAERS and international case reports [29]. We observed no statistical association between HPV4 and seizures whether recurrent or new onset.

Allergic reactions and analphylaxis are well documented adverse events following vaccination [30]. HPV4 is contraindicated in those with a history of hypersensivity, including severe allergic reaction to yeast (a vaccine component) or after a previous dose of HPV4 [20]. Brotherton et al. found an increase rate of anaphylaxis in Australia's school-based HPV4 vaccination program when compared with other vaccines; however, there were several limitations to their study which may have led to imprecise estimates [31]. We found the rate of confirmed anaphylaxis following HPV4 vaccination (1.7 cases per million doses) to be similar to the expected rate of analyphaxis following childhood vaccines (1.5 per million doses) [7].

Although the biologic plausibility of appendicitis following HPV4 is not well substantiated, this outcome was identified as one of the most frequently reported serious adverse events following HPV4 during prelicensure trials when compared to the placebo group (0.03% HPV4 (5 cases) vs. 0.01% placebo (1 case)). We found a statistical signal indicating a potential increased risk of appendicitis following HPV4 vaccination among youth, but further investigation showed it was unlikely to be a true association.

The VSD's RCA has proven to be an important tool for rapidly addressing safety concerns after a vaccine has been introduced into the US market, but it does have certain limitations. These sequential methods are limited in controlling for potential confounders, such as risk factors for VTE. Also, the use of ICD-9 codes and use of historical background rates could lead to false signals or failure to identify a true signal. Additional studies using alternate designs must be used to validate or dismiss statistical signals. Finally, because HPV4 vaccine was administered to a relatively young female population, we had limited power to assess associations between HPV4 and very rare adverse events such as GBS and stroke.

In summary, we conducted the largest postlicensure active surveillance of HPV4 in the United States. Although additional study is warranted for a possible association between HPV4 and VTE, we found no statistically significant associations between HPV4 and VTE or any of the other pre-specified outcomes of interest. A possible association with VTE following HPV4 administration, although not statistically significant, deserves additional study.

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