ONLINE FIRST

Safety of Quadrivalent Human Papillomavirus Vaccine Administered Routinely to Females

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Objective: To assess the safety of the quadrivalent human papillomavirus vaccine (HPV4) in females following routine administration.

Design: In a cohort of vaccinated females, we compared the risk of emergency department visits and hospitalizations during the interval soon after vaccination with risk during a comparison interval more remote from vaccination.

Setting: Kaiser Permanente in California.

Participants: All females who received the HPV4 vaccine.

Main Exposure: One or more doses of HPV4 between August 2006 and March 2008.

Main Outcome Measures: Outcomes were emergency department visits and hospitalizations, grouped into predefined diagnostic categories. Within diagnostic groups, we used odds ratios (ORs) to estimate whether each subject had any outcome in postvaccination risk intervals (days 1-60, days 1-14, and day 0), compared with a control interval distant in time from vaccination.

Results: One hundred eighty-nine thousand six hundred twenty-nine females received at least 1 dose and 44 001 received 3 HPV4 doses. Fifty categories had significantly elevated ORs during at least 1 risk interval. Medical record review revealed that most diagnoses were present before vaccination or diagnostic workups were initiated at the vaccine visit. Only skin infections during days 1 to 14 (OR, 1.8; 95% CI, 1.3-2.4) and syncope on day of vaccination (OR, 6.0; 95% CI, 3.9-9.2) were noted by an independent Safety Review Committee as likely associations with HPV4.

Conclusions: The quadrivalent human papillomavirus vaccine was associated with same-day syncope and skin infections in the 2 weeks after vaccination. This study did not detect evidence of new safety concerns among females 9 to 26 years of age secondary to vaccination with HPV4.

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HUMAN PAPILLOMAVIRUS (HPV) is a family of small DNA viruses. Infections with this viral family are the most commonly detected sexually transmitted infection in women. Although most HPV infections cause no symptoms and are self-limited, persistent genital HPV infection can cause cervical cancer in women, as well as other anogenital cancers and genital warts in both men and women.[1] Human papillomavirus is estimated to cause more than half a million new cancers every year, most of which affect women in developing countries.[2]

In June 2006, the US Food and Drug Administration approved the quadrivalent HPV vaccine (HPV4) (GARDASIL; Merck and Co Inc) for females between the ages of 9 and 26 years for prevention of a range of diseases attributed to HPV types 6, 11, 16, and 18, including genital warts, cervical cancer, cervical adenocarcinoma in situ, cervical intraepithelial neoplasia, and high-grade vulvar and vaginal intraepithelial neoplasia. More recently, HPV4 was also approved for females 9 to 26 years old for the prevention of vaginal and vulvar cancer, males 9 to 26 years old for the prevention of genital warts, and males and females 9 to 26 years old for the prevention of anal intraepithelial neoplasia and anal cancer.

In the clinical trials of females prior to licensure, HPV4 was found to be safe, generally well tolerated, and highly immunogenic. Following HPV4 licensure, we undertook the current study with the primary aim to evaluate the safety of HPV4 administered to females during the course of routine clinical care.

METHODS

COHORT STUDIED

This study was a postlicensure commitment to the Food and Drug Administration and the European Medicines Agency after initial licensure in females. We conducted this retrospective, observational cohort study within the large, integrated health care delivery systems of Northern and Southern California Kaiser Permanente, which each have more than 3 million members generally representative of the racial and ethnic composition of the Northern and Southern California populations. Each Kaiser member has a unique medical record number that links information across services for the same individual over time. All vaccine administration, all medical use, demographics, and health plan membership information are stored electronically in clinical and administrative databases. The study was reviewed and approved by the health plan institutional review boards.

This study included all females who received at least 1 dose of HPV4 during routine clinical care. Subject accrual began following the first administration of HPV4 (August 2006) and continued until 44 000 female members aged 9 to 26 years at first dose had received 3 HPV4 doses within 12 months with at least (per recommendations) 28 days between doses 1 and 2 and 12 weeks between doses 2 and 3. Accrual completed in March 2008. This population will be referred to as the "3-dose" population. We also evaluated a larger safety population, referred to as the "any-dose" population, comprising females of any age irrespective of membership who received at least 1 HPV4 dose between August 2006 and March 2008. This population includes individuals in the 3-dose population, as well as females who received 3 HPV4 doses but not according to the 3-dose population required schedule.

SAFETY OUTCOMES

This study's primary aim was to assess safety in females following HPV4 by monitoring all postvaccination emergency department (ED) and hospitalization events identified by *International Classification of Diseases, Ninth Revision* codes in the electronic medical records. We categorized all codes into the hierarchical (4-level), clinically meaningful groups developed by the Healthcare Cost and Utilization Project (HCUP).[3] Health outcomes in level 4 are the most specific, whereas levels 3, 2, and 1 are increasingly less specific; health outcomes represented in an HCUP level 4 category are also represented in the corresponding levels 3, 2, and 1. We included all 18 level 1 HCUP categories and selected level 2 through 4 subcategories for categories for which biological plausibility warranted greater specificity.

STATISTICAL METHODS

This study was a risk interval design. That is, we compared the odds of ED visits and hospitalizations during intervals soon after vaccination (risk interval) with odds during a comparison interval more remote from vaccination (control interval). We used postvaccination risk intervals of days 1 to 60, days 1 to 14, or day 0 (day vaccine administered). For the 3-dose population, the control interval was a 180-day period that began 91 days after the subject's last HPV4 dose (**Figure**). The 180-day control interval was selected because it was equivalent to the sum of the 3 postvaccination 60-day risk intervals. For the any-dose population, the control interval was 60 days for those who received 1 HPV4 dose, 120 days for those who received 2 doses, and 180 days for those who received 3 doses. We identified the first occurrence of the outcome for each subject during the risk and control intervals.

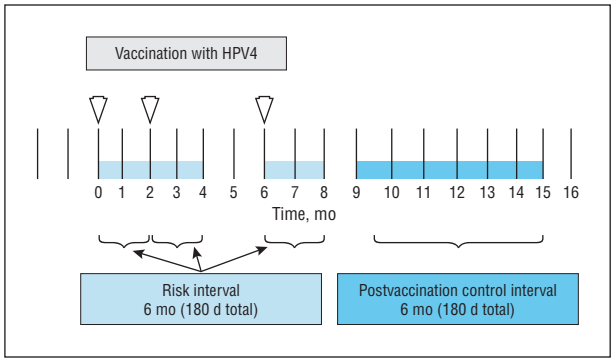

Figure. General safety risk and comparison intervals after the quadrivalent human papillomavirus vaccine (HPV4). Each month signifies 30 days. This example shows the risk- and control-length intervals for females who received 3 doses. Females who received only 1 dose had 2-month (60-day) risk and control intervals. Females who received 2 doses had 4-month (120-day) risk and control intervals.

For day 0 analyses to assess events occurring immediately after vaccination, we prespecified evaluating HCUP categories of allergic events/anaphylaxis, syncope, epilepsy or convulsion, and coma, stupor, or brain damage.

We monitored for deaths in the any-dose population through the end of the control interval using information from inpatient and ED medical records, claims data, notification by family members, and coroner reports.

We calculated incidence rates and separately computed odds ratios (ORs) using conditional logistic regression models. The risk interval and the control interval for each vaccinated female were treated as a matched pair (ie, conditioned on the individual). We separately conducted subanalyses by age (9-26, 9-15, and 11-12 years) and by setting (ED or hospitalization), as well as by dose analyses within the any-dose population. Age stratifications represent the indicated age range (9-26 years), recommended ages (11-12 years), and a larger subset of younger females (9-15-years) because of the limited HPV4 uptake in 11- to 12-year-olds.

For completeness, we reported all ORs and confidence intervals. Because of concern that conducting thousands of comparisons would lead to a significant finding due to chance alone and to provide perspective on such findings, the study prespecified performing multiple-comparisons adjustment using the double false discovery rate (FDR) method[4,5] (limited to HCUP levels 1 and 2) using an α 1 (first-stage FDR limit) of α/A and α 2 (second-stage FDR limit) of α. *A* equaled the average number of HCUP level 2 categories under each HCUP level 1 category; α was the designated upper limit of the overall FDR and set at .05. Multiplicity adjustment was not performed for day 0 events because of the small number of categories analyzed. Multiple-comparisons adjustment did not change ORs and confidence intervals. We used SAS version 9.13 (SAS Institute) for all analyses.

MEDICAL RECORD REVIEW

We reviewed the electronic medical records of selected diagnoses demonstrating a significantly elevated OR postvaccination to clarify the nature of the outcome or to determine whether it was present prior to vaccination; all outcomes remained in the analyses regardless of whether they were preexisting. Selection of categories for review was based on the significance of findings (regardless of multiplicity adjustment), biological plausibility, and consistency between analyses. Among diag-

Table 1. Age Distribution of Any-Dose and 3-Dose Population, August 2006 to March 2008

Age, y[a]	Any-Dose Population, No. (%)[b]			3-Dose Population, Sample Size[d]
	Dose 1	Dose 2[c]	Dose 3[c]	
All ages	189 629	105 412 (55.6)	51 931 (27.4)	Not applicable
9-26	187 905	104 747 (55.7)	51 603 (27.5)	44 001
9-15	96 839	56 007 (57.8)	28 443 (29.4)	24 558
11-12	33 334	18 736 (56.2)	9341 (28.0)	8146

Abbreviation: HPV4, quadrivalent human papillomavirus vaccine.
[a] Age at first dose.
[b] "Any dose" refers to the population of females who received at least 1 dose of HPV4 between August 2006 and March 2008. See the "Methods" section for further details. All HPV4 doses shown in the Table were administered at Kaiser Permanente.
[c] For the any-dose population, counts from the respective row in the Dose 1 column were used as the denominator.
[d] "3-Dose" population refers to individuals 9 to 26 years old who received all 3 doses of HPV4 according to the recommended schedule. See the "Methods" section for further details.

noses selected, all medical records in the risk interval were reviewed except that the following were sampled because of resource limitations: infectious and parasitic disease cases (HCUP categories 1, 1.1, and 1.3), mental illness (HCUP category 5), ear conditions (HCUP category 6.8), chronic obstructive pulmonary disease/bronchitis (HCUP category 8.2), musculoskeletal system and connective tissue diseases (HCUP categories 13, 13.3, and 13.8), and intracranial injury cases (HCUP 16.4). Selected 3-dose population medical records were also reviewed.

SAFETY REVIEW COMMITTEE

We assembled a 5-member Safety Review Committee comprising external medical experts responsible for reviewing the interim and final safety data for potential safety signals. The safety committee was independent from both the Kaiser Study Team and Merck and Co (study sponsor). The committee approved the study methods, HCUP categories assessed, and the standard operating procedures related to this study. The committee had full access to summarized medical record information and all analyses and substantially contributed to decisions regarding which diagnoses underwent medical record review.

RESULTS

A total of 189 629 females received at least 1 HPV4 dose between August 2006 and March 2008 and were included in the any-dose population; of these, 44 001 met criteria for inclusion in the 3-dose population (**Table 1**). Most subjects (>99%) were between 9 and 26 years of age at first dose, with approximately half being 9 to 15 years old at first dose. A total of 346 972 HPV4 doses were administered within the any-dose population of 189 629 females.

Overall, we analyzed 265 HCUP categories and conducted 7551 comparisons. Prior to multiplicity adjustment, the ORs for 50 HCUP categories were significantly elevated in at least 1 risk interval (day 0, days 1-14, or days 1-60) of at least 1 analysis population (any dose or 3 dose), including subanalyses stratified by age, care setting, or dose. As would be expected in such a study conducting multiple comparisons, there were also many statistically significantly decreased ORs (79 HCUP categories); after multiplicity adjustment, the ORs for 10 HCUP categories remained significantly increased while 12 categories remained significantly decreased.

Of the 50 HCUP categories with elevated ORs, 40 were in the days 1 to 14 risk interval and 26 were in the days 1 to 60 risk interval, with some overlap, for a total of 47 HCUP categories during the days 1 to 14 and 1 to 60 risk intervals. The HCUP categories with significantly elevated ORs in specific subanalyses (age and care setting; data not shown) showed no important differences compared with those in all ages combined (**Table 2** and **Table 3**).

COMBINED ED/HOSPITAL ANALYSES

Combined ED and hospital analyses in the any-dose and/or 3-dose populations revealed that 21 HCUP categories had elevated ORs during at least 1 risk interval (Table 2), while 59 HCUP categories were significantly decreased (data not shown). The HCUP categories corresponding to attention-deficit disorder, ear conditions, and congenital anomalies among vaccinees (represents anomalies in the vaccine recipients, not offspring) were the only significantly elevated ORs prior to multiple-comparison adjustment during both the days 1 to 60 and days 1 to 14 risk intervals (Table 2).

Following multiple comparison adjustments, only skin infections (OR, 1.8; 95% CI, 1.3-2.4) in the any-dose population and congenital anomalies in both the any-dose (OR, 3.6; 95% CI, 2.0-6.3) and 3-dose (OR, 5.1; 95% CI, 2.2-11.9) populations for postvaccination days 1 to 14 remained significantly elevated (Table 2). The ORs for these 2 outcomes also remained significantly elevated after adjustment for multiple comparisons in certain stratified days 1 to 14 analyses (any dose: ED only and 9- to 15-year-olds) and congenital anomalies (any dose: hospital only and 9- to 15-year-olds; data not shown).

BY-DOSE ANALYSES

Following dose 1, 15 HCUP categories had significantly elevated ORs in days 1 to 60 and/or days 1 to 14 analyses; 4 categories remained elevated for days 1 to 14 analysis after multiple-comparison adjustments (viral, bacterial, and skin infections and other congenital anomalies). Analyses during days 1 to 60 and/or days 1 to 14 noted increased ORs for 15 HCUP categories following dose 2

Table 2. Summary of HCUP Categories With Elevated ORs Following HPV4 Vaccination in the Combined ED/Hospital Setting, All Doses Combined

	Days 1-60 Risk Interval			Days 1-14 Risk Interval			Postvaccination Control Interval	
HCUP Category[a]	No. of Events	Incidence/1000 PY	Days 1-60 Risk vs Control Interval OR (95% CI)	No. of Events	Incidence/1000 PY	Days 1-14 Risk vs Control Interval OR (95% CI)	No. of Events	Incidence/1000 PY
				Any-Dose Population (n = 189 629)[b]				
1.3 Viral infection	210	3.7	1.1 (0.9-1.3)	71	5.3	1.5 (1.2-2.0)[c]	200	3.5
5.3 Attention-deficit, conduct, and disruptive behavior disorders	127	2.2	1.5 (1.2-2.0)[c]	29	2.2	1.5 (1.0-2.3)	84	1.5
6 Disease of nervous system and sense organs	1036	18.3	1.0 (0.9-1.1)	279	21.0	1.2 (1.0-1.3)[c]	1012	17.8
6.8 Ear conditions	282	5.0	1.2 (1.0-1.5)[c]	79	5.9	1.5 (1.1-1.9)[c]	230	4.0
6.9.1 Disorders of peripheral nervous system	24	0.4	2.1 (1.0-4.2)[c]	6	0.5	2.1 (0.8-5.7)	12	0.2
7 Diseases of circulatory system	499	8.8	1.1 (1-1.3)	128	9.6	1.2 (1.0-1.5)[c]	442	7.8
7.2 Diseases of heart	375	6.6	1.1 (0.1-1.3)	98	7.4	1.3 (1.0-1.6)[c]	333	5.9
8.2 COPD and bronchiectasis	62	1.1	1.5 (1-2.2)	18	1.4	1.8 (1.1-3.2)[c]	42	0.7
8.3 Asthma	570	10.0	1.2 (1.1-1.4)[c]	137	10.3	1.21 (1-1.47)	477	8.4
12 Disease of skin and subcutaneous tissue	290	5.1	1.0 (0.8-1.1)	107	8.1	1.5 (1.2-1.9)[c]	300	5.3
12.1 Skin and subcutaneous tissue infections	165	2.9	1.1 (0.9-1.4)	62	4.7	1.8 (1.3-2.4)[d]	149	2.6
12.1.1 Cellulitis and abscess	128	2.3	1.1 (0.8-1.4)	47	3.5	1.6 (1.2-2.3)[c]	122	2.2
13 Diseases of musculoskeletal system and connective tissue	647	11.4	1.1 (1-1.2)	172	12.9	1.2 (1.0-1.4)[c]	608	10.7
13.3 Spondylosis, disc intervertebral disorders, back problems	250	4.4	1.1 (0.9-1.3)	71	5.3	1.4 (1.0-1.8)[c]	223	3.9
14 Congenital anomalies	79	1.4	1.6 (1.1-2.3)[c]	29	2.2	2.5 (1.6-4.0)[c]	49	0.9
14.5 Other congenital anomalies	44	0.8	1.8 (1.1-3.0)[c]	21	1.6	3.6 (2.0-6.3)[d]	25	0.4
17.1.2 Fever of unknown origin	136	2.4	1.1 (0.9-1.4)	42	3.2	1.5 (1.0-2.1)[c]	121	2.1
17.1.3 Lymphadenitis	27	0.5	1.0 (0.6-1.8)	14	1.1	2.3 (1.2-4.4)[c]	26	0.5

(continued)

Table 2. Summary of HCUP Categories With Elevated ORs Following HPV4 Vaccination in the Combined ED/Hospital Setting, All Doses Combined (continued)

HCUP Category[a]	Days 1-60 Risk Interval			Days 1-14 Risk Interval			Postvaccination Control Interval	
	No. of Events	Incidence/1000 PY	Days 1-60 Risk vs Control Interval OR (95% CI)	No. of Events	Incidence/1000 PY	Days 1-14 Risk vs Control Interval OR (95% CI)	No. of Events	Incidence/1000 PY
				3-Dose Population (n = 44 001)[e]				
3.2 Diabetes mellitus	26	1.2	2.2 (1.1-4.4)[c]	7	1.4	2.5 (1.0-6.4)	12	0.6
5.3 Attention-deficit disorder	48	2.2	1.7 (1.1-2.8)[c]	14	2.8	2.1 (1.1-4.1)[c]	28	1.3
5.9 Personality disorders	26	1.2	1.8 (0.9-3.4)	10	2.0	2.8 (1.3-6.4)[c]	15	0.7
9.2 Disorders of teeth and jaw	20	0.9	1.1 (0.6-2.1)	11	2.2	2.6 (1.2-5.6)[c]	18	0.8
14 Congenital anomalies	36	1.7	1.7 (1.0-2.8)	14	2.8	2.7 (1.4-5.3)[c]	22	1.0
14.5 Other congenital anomalies	23	1.1	2.3 (1.1-5.0)[c]	12	2.4	5.1 (2.2-11.9)[d]	10	0.5

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; HCUP, Healthcare Cost and Utilization Project; HPV4, quadrivalent human papillomavirus vaccine; OR, odds ratio; PY, person-years.

[a] The HCUP categories are hierarchical. For example, a person with a diagnosis represented in level 2 category 14.5 is also represented in level 1 category 14.

[b] Risk interval was compared with 60-, 120-, or 180-day postvaccination control interval, depending on the number of doses of vaccine received.

[c] Statistically significantly elevated ORs. The ORs approximate relative risks in this analysis.

[d] Statistically significantly increased ORs after multiplicity adjustment. The ORs approximate relative risks in this analysis.

[e] Risk interval was compared with 180-day postvaccination control interval.

and 12 HCUP categories following dose 3; none remained significant after multiple-comparisons adjustment (Table 3).

DAY 0 ANALYSES

The ORs were significantly elevated for events that occurred the same day as vaccination (day 0) in 3 HCUP categories: syncope, epilepsy, and allergic reactions (**Table 4**). For the any-dose population, there were 23 total day 0 syncope cases occurring in the combined ED or hospital setting, 21 of which were identified in the ED. There were 3 events each in the epilepsy/convulsions and allergic events categories; based on review of all available clinical details, the safety committee concluded that there was no association between day 0 epilepsy/convulsions and allergic/anaphylactic outcomes and HPV4.

MEDICAL RECORD REVIEW

We also reviewed medical records of 28 HCUP categories shown in Table 2 and/or Table 3 with elevated ORs in the days 1 to 14 and 1 to 60 analyses. Record review revealed most diagnoses were either present before administration of HPV4, had diagnostic workups initiated at the vaccine visit, or had obvious etiologies not associated with vaccination (**Table 5**). Review of skin infection diagnoses suggested that some may have been local injection site reactions, although the medical records contained insufficient detail to exclude acute infections.

Taking into account all the analyses, subanalyses, and relevant record reviews, the safety committee noted that there may be an association between HPV4 vaccination and both day 0 syncope and skin infections during the 2 weeks after immunization.

There were 14 deaths that occurred in the any-dose population. The causes were Burkitt tumor or lymphoma (n = 1); cardiorespiratory arrest, probably secondary to congenital heart disease (n = 3); drug overdose (n = 1); motor vehicle collision (n = 2); respiratory arrest (n = 1); suicide (n = 4); systemic lupus erythematosus (n = 1); and pneumonia (n = 1). The causes of death appeared consistent with national data for this age group.[7] The safety committee found no relationship between deaths and vaccination with HPV4.

COMMENT

In this large study assessing the safety of 346 972 HPV4 doses administered as part of routine clinical care to 189 629 females, we evaluated all postvaccination ED and hospitalization events and identified significantly elevated ORs in 50 HCUP categories. Although only 4 HCUP categories remained elevated after multiple-comparisons adjustment, in the interest of a thorough safety evaluation, we reviewed medical records of HCUP categories with significantly elevated ORs without regard for the multiplicity adjustment. Based on those findings, we observed an association between HPV4 and same-day syncope and skin infections.

The association between HPV4 and syncope was not unexpected. Immunization and injections in general have a known association with syncope (particularly in this

Table 3. Summary of HCUP Categories With Elevated ORs Following HPV4, by Dose Administered, in the Combined Hospital/ED Setting, Any-Dose Population[a]

Dose No.	HCUP Category[b]	Events During Days 1-60 Risk Interval	Days 1-60 Risk vs Control Interval OR (95% CI)[c]	Events During Days 1-14 Risk Interval	Days 1-14 Risk vs Control Interval OR (95% CI)[c]
1	1 Infectious and parasitic diseases	216	1.1 (0.9-1.3)	71	1.5 (1.2-2.0)[d]
	1.1 Bacterial infection	46	1.2 (0.8-1.7)	18	2.0 (1.2-3.4)[e]
	1.3 Viral infection	133	1.2 (1.0-1.5)	48	1.9 (1.4-2.6)[e]
	5.3 Attention-deficit, conduct, and disruptive behavior disorders (ADHD)	70	1.6 (1.1-2.2)[d]	17	1.6 (1.0-2.8)
	6.8 Ear conditions	157	1.2 (1.0-1.5)	47	1.6 (1.1-2.1)[d]
	7 Diseases of circulatory system	276	1.1 (1.0-1.3)	78	1.4 (1.1-1.2)[d]
	7.2 Diseases of heart[f]	199	1.1 (0.9-1.4)	58	1.4 (1.1-1.9)[d]
	8.3 Asthma	301	1.1 (1.0-1.3)	84	1.4 (1.1-1.7)[d]
	12 Disease of skin and subcutaneous tissue	164	1.0 (0.8-1.2)	66	1.7 (1.3-2.3)[d]
	12.1 Skin and subcutaneous tissue infections	92	1.1 (0.9-1.5)	38	2.0 (1.4-2.9)[e]
	12.1.1 Cellulitis and abscess	74	1.1 (0.8-1.5)	33	2.2 (1.4-3.2)[d]
	13 Diseases of musculoskeletal system and connective tissue[f]	352	1.1 (1.0-1.3)	96	1.3 (1.0-1.6)[d]
	14 Congenital anomalies	34	1.3 (0.9-2.1)	16	2.8 (1.6-4.9)[d]
	14.5 Other congenital anomalies	19	1.5 (0.8-2.8)	11	4.0 (1.9-8.2)[e]
	18 Residual codes, unclassified, all E codes	1126	1.1 (1.0-1.2)[d]	246	1.0 (0.9-1.2)
2	3.2 Diabetes mellitus without complication	29	1.8 (1.1-3.0)[d]	7	1.8 (0.8-4.0)
	3.3 Diabetes mellitus with complication	14	1.4 (0.7-2.7)	8	3.3 (1.5-7.5)[d]
	5 Mental illness	391	1.2 (1.0-1.3)[d]	93	1.2 (1.0-1.5)
	5.6 Disorders usually diagnosed in infancy, childhood, or adolescence	9	2.9 (1.1-7.6)[d]	0	NE
	6 Diseases of nervous system and sense organs	330	1.1 (0.9-1.2)	102	1.4 (1.2-1.7)[d]
	6.8 Ear conditions	92	1.4 (1.1-1.8)[d]	26	1.7 (1.1-2.5)[d]
	6.9 Other nervous system disorders	61	1.3 (1.0-1.8)	20	1.8 (1.1-2.9)[d]
	6.9.1 Disorders of the peripheral nervous system	7	2.8 (1.0-7.9)	3	5.1 (1.3-19.6)[d]
	8.2 COPD and bronchiectasis	12	1.0 (0.5-2.0)	7	2.6 (1.1-5.8)[d]
	8.3 Asthma	187	1.3 (1.1-1.5)[d]	35	1.0 (0.7-1.5)
	9.6 Lower gastrointestinal disorders[f]	51	1.1 (0.8-1.5)	18	1.7 (1.0-2.7)[d]
	10.3.9.2 Genital disorders	25	1.0 (0.6-1.6)	13	2.2 (1.2-4.1)[d]
	14 Congenital anomalies	28	1.7 (1.1-2.8)	8	2.1 (1.0-4.5)
	14.5 Other congenital anomalies	16	2.1 (1.1-4.0)	6	3.3 (1.3-8.1)[d]
	17.1.3 Lymphadenitis	12	1.5 (0.7-3.1)	6	3.3 (1.3-8.2)[d]
3	3.4 Other endocrine disorders	10	2.5 (1.1-5.8)[d]	2	2.1 (0.5-9.6)
	3.5 Nutritional deficiency	3	1.3 (0.3-5.0)	3	5.5 (1.4-21.3)[d]
	3.6 Disorders of lipid metabolism[f]	7	3.5 (1.2-10.4)[d]	1	2.1 (0.3-17.8)
	5.3 Attention-deficit, conduct, and disruptive behavior disorders	22	1.8 (1.1-3.1)[d]	7	2.5 (1.1-5.6)[d]
	6.6 Coma, stupor, brain damage	14	2.2 (1.1-4.4)[d]	4	2.7 (0.9-8.0)
	8.3 Asthma	101	1.4 (1.1-1.8)[d]	19	1.1 (0.7-1.8)
	9.8 Liver disease	5	0.8 (0.3-2.2)	5	3.4 (1.3-9.4)[d]
	12 Disease of skin and subcutaneous tissue	45	1.0 (0.7-1.4)	19	1.8 (1.1-3.0)[d]
	12.1 Skin and subcutaneous tissue infections	24	1.0 (0.6-1.5)	13	2.3 (1.3-4.1)[d]
	13.3 Spondylosis: disc disorders, back problems	43	15 (1.0-2.1)[d]	11	1.6 (0.9-3.0)
	14 Congenital anomalies	19	2.0 (1.1-3.6)[d]	5	2.3 (0.9-6.0)
	14.5 Other congenital anomalies	10	1.8 (0.8-4.1)	4	3.2 (1.1-9.1)[d]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COPD, chronic obstructive pulmonary disease; ED, emergency department; HCUP, Healthcare Cost and Utilization Project; HPV4, quadrivalent human papillomavirus vaccine; NE, not estimable because there were 0 events in the days 1 to 14 risk interval; OR, odds ratio.

[a] The any-dose (n = 189 629) population is shown, except when results were statistically significant only in the 3-dose cohort, as footnoted in this Table. Control interval number of events not shown.

[b] The HCUP categories are hierarchical. For example, a person with a diagnosis represented in level 2 category 14.5 is also represented in level 1 category 14.

[c] Risk interval was compared with 60-day postvaccination control interval for each dose. The control interval was 60 days for those who received 1 HPV4 dose, 120 days for those who received 2 doses, and 180 days for those who received 3 doses.

[d] Statistically significantly elevated ORs. The ORs approximate relative risks in this analysis.

[e] Statistically significantly elevated ORs after multiplicity adjustment. The ORs approximate relative risks in this analysis.

[f] The OR was elevated only in the any-dose population subanalysis limited to only those females who received the 3 doses according to the recommended 3-dose schedule as described in the "Methods" section.

Table 4. Summary of Events on Day of Vaccination (Day 0) in the Combined Hospital/ED Setting, All Doses Combined and By Dose Administered

HCUP Category	Population	Dose	Day 0		Control Interval		Day 0 Compared With Control Interval OR (95% CI)
			Events During Day 0	Incidence/ 1000 PY	Events During Control Interval	Incidence/ 1000 PY	
6.4 Epilepsy, convulsions	Any dose	Dose 1	3	5.8	90	1.7	3.7 (1.2-11.7)[a,b]
6.6 Coma, stupor, and brain damage	Any dose	All doses combined	1	1.1	50	0.9	1.2 (0.8-8.7)[c]
17.1.1 Syncope	Any dose	All doses combined	23	24.2	230	4.0	6.0 (3.9-9.2)[a,c]
	3 Dose	All doses combined	5	13.8	104	4.8	2.9 (1.2-7.1)[a,c]
	Any dose	Dose 1	17	32.7	230	4.4	8.9 (5.4-14.7)[a,b]
	Any dose	Dose 2	5	17.3	196	4.9	3.9 (1.6-9.4)[a,b]
17.1.9 Allergic reactions	Any dose	Dose 3	3	21.1	127	5.0	4.2 (1.4-13.3)[a,b]

Abbreviations: ED, emergency department; HCUP, Healthcare Cost and Utilization Project; OD, odds ratio; PY, person-years.
[a] Statistically significantly elevated ORs. Day 0 analyses were not adjusted for multiplicity. The ORs approximate relative risks in this analysis.
[b] For dose-specific analysis, the day 0 risk interval was compared with the 60-day postvaccination control interval.
[c] For the combined ED and hospital analyses, the day 0 risk interval was compared with the 60-, 120-, or 180-day postvaccination control interval, depending on number of doses of vaccine received.

age group).[8-12] Our findings are consistent with a previous study that noted an elevated reporting rate for syncope to the passive Vaccine Adverse Event Reporting System following HPV4.[13] Our results contrast with the recent Vaccine Safety Datalink study, which did not detect an increase in syncope after HPV4 when compared with rates following health care visits for other vaccinations.[14] The difference may be that, within this age group, injections rather than HPV4 specifically could be related to syncope. Future studies will be needed to develop a better understanding of the relationship between injections and/or vaccinations and syncope among adolescents and young adults.

Our study also detected an association between HPV4 and skin infections during the 2 weeks after vaccination. Medical record review suggested that some cases may have been local injection site reactions; however, females who received HPV4 sought increased clinical care for skin conditions following vaccination. That this study detected 2 potentially expected safety signals provides reasonable reassurance this study was a valid approach to uncovering HPV4-associated safety signals.

No other safety signals or potential signals following HPV4 were identified, including hospitalizations/ED visits associated with autoimmune conditions. This is consistent with the findings from our separate analyses that found no evidence of an association between HPV4 and new-onset autoimmune conditions.[6] The current study also did not detect evidence of associations between HPV4 and increased risk for venous embolism, thromboembolic events, other clotting disorders or dysfunction, and anaphylaxis. While some individuals were identified with musculoskeletal system and connective tissue diseases (HCUP category 13), medical record review revealed that the majority were related to arm/limb pain (Table 5). The quadrivalent HPV vaccine was temporally associated with outcomes in a variety of HCUP categories; however, those appeared to be related to increased nonspecific health care use following vaccine visits, a finding that became evident on reviewing numerous medical records. The sequence of events in the medical record clearly demonstrated that the diagnoses were preexisting and not attributable to administration of the vaccine. This type of health care–seeking behavior has been seen in previous studies.[15-17]

This study's strengths include its size, encompassing an ethnically diverse population-based cohort of 189 629 females, 44 001 of whom received all 3 doses within 12 months. Given the large number of vaccine doses, it is likely that the findings herein are representative of larger populations. Kaiser Permanente's integrated health care delivery services are very comprehensive and it is reasonable to assume that subjects received the majority of their health care within Kaiser Permanente's system, providing reassurance that the data represented complete or near-complete medical information. A final strength was that we used a prespecified, validated, clinically meaningful system to categorize all outcomes.

The main strength of using multiple-comparisons adjustment was that it provided some reassurance in a study of this magnitude that safety concerns were not overlooked. To some extent, the multiplicity adjustment also helped direct us toward those elevated ORs that required additional follow-up. However, many of those categories were subsequently found to be preexisting conditions and its usefulness in this regard was limited. The multiple-comparisons method was also unable to adjust for any third- or fourth-level HCUP categories.

This study has limitations. First, we could only detect new-onset conditions requiring ED visits or hospitalizations within 60 days after vaccination; it was not designed to investigate long-term safety outcomes or risk of HPV4-associated recurrence/progression of disease. Second, despite its large size, this study may have had in-

Table 5. Summary of Medical Records Reviewed for HCUP Categories With Elevated ORs for Days 1 to 14 and/or 1 to 60 Risk Periods[a]

HCUP Category	Medical Record Review Summary[b]
1 Infectious and parasitic diseases, 1.1 bacterial, 1.3 viral infections	Bacterial cases included variety of diagnoses (eg, urinary tract infections) and some sexually transmitted infections contracted prior to first dose of HPV4. Viral cases were acute, majority had no symptoms at vaccination.
3.2, 3.3 Diabetes mellitus, without/with complications	Reviewed as part of separate autoimmune analysis.[6] Some cases preexisting. New-onset cases randomly distributed over 180 d after vaccination. Rates after vaccination were not elevated above background rates in the Kaiser Permanente Southern California population who did not receive the vaccine.[6]
3.5 Nutritional deficiencies	All cases were "protein calibrated malnourished not otherwise specified."
5.3 Attention-deficit, conduct, and disruptive behavior disorders[c]	Preexisting condition in nearly all cases. Diagnosis codes listed in patients with history of attention-deficit/hyperactivity disorder being seen for other conditions.
6.6 Coma, stupor, brain damage[c]	Most cases were intoxication and alteration of consciousness, including ingestion events and alcohol intoxication.
6.8 Ear conditions	Preexisting condition in about 30% of cases. In remaining cases, etiologies either obvious (eg, swimming) or not obvious but routine (eg, ear pain) usually with other viral symptoms.
6.9 Other nervous system	Preexisting condition in about 60% of cases. In remaining cases, etiologies typically obvious (eg, postoperative pain). The few cases without obvious etiology were not similar.
7 Diseases of circulatory system, including 7.2 diseases of heart	Preexisting condition in about 50% of cases. In remaining cases, etiologies typically obvious (eg, anxiety).
8.2 Chronic obstructive pulmonary disease and bronchitis	Routine, acute, new-onset bronchitis evenly distributed among days 9-56 after vaccination.
8.3 Asthma	Preexisting condition in nearly all cases. Many were being seen for other illness. Others had asthma with other diagnoses (eg, flu) or asthma visit (eg, exercise-induced asthma).
9.2 Disorders of teeth and jaw	Reviewed for 3-dose population (no elevated OR in any-dose population). Preexisting condition in most cases (82%) (eg, malocclusion). Remaining cases had obvious etiology (eg, dental abscess).
10.3.9 (10.3.9.1, 10.3.9.2) Female genital pain, genital disorders	Category 10.3.9.1 reviewed for interim study findings (in 3-dose population). Preexisting condition in most cases (eg, pelvic inflammatory disease). Safety committee noted that category 10.3.9.2 was similar to 10.3.9.1; therefore, no additional medical record reviews undertaken.
12, 12.1, 12.1.1 Cellulitis and abscess[c]	Four cases of "cellulitis and abscess of arm" reviewed; all diagnosed postvaccine days 2-11. One was methicillin-resistant *Staphylococcus aureus* infection in the axilla on opposite arm as HPV4 in location where different vaccine received. Detailed medical record notes not available on remaining 3 cases, all of whom received other concomitant vaccinations. Two of these cases were on postvaccine day 2. The third occurred on day 10 in patient with preexisting left wrist pain. Six cases of "other skin and subcutaneous infections" found impetigo, pilonidal cyst, and carbuncle (buttock) on days 1-13.
13 Diseases of musculoskeletal system and connective tissue and 13.8 13.3 Spondylosis	Preexisting condition in most cases. In remaining cases, etiology typically obvious (eg, sports injury) but not in all (eg, limb pain, rib pain). Some limb pain could have been injection site pain. Preexisting condition in about 65% of cases. Remaining cases were typically neck pain (eg, stiff neck on awakening).
14, 14.5 Congenital anomaly[c]	Preexisting condition in all cases. Typically, hospitalizations were planned procedures to repair congenital anomaly. Other cases typically unrelated to congenital anomaly with no clustering of specific symptoms.
16.4 Intracranial injury	Almost all cases were motor vehicle collisions or sports injuries (none with temporal proximity to vaccination). The 1 remaining case was observed in the hospital for intracranial injury secondary to syncope on day of vaccination. This patient had a history of syncopal episodes with a previous negative neurologic workup; the workup findings were also negative for this current event.
17.1.3 Lymphadenitis	Preexisting condition in most cases. The remaining 2 cases had onset on day 2 after vaccination, 1 with abnormal laboratory results on day of vaccination.

Abbreviations: HCUP, Healthcare Cost and Utilization Project; HPV4, quadrivalent human papillomavirus vaccine; OD, odds ratio.

[a] Categories with elevated ORs prior to multiplicity adjustment; please refer to the "Methods" section for further details. Medical records from the "any dose" population (unless stated otherwise); combined hospital/emergency department setting.

[b] Preexisting condition means that diagnosis or symptom onset predated first dose of HPV4.

[c] Medical records from 3 dose population reviewed as part of an interim analysis.

sufficient power to detect very rare conditions. Thus, ongoing monitoring of spontaneous reports and other sources such as the Vaccine Safety Datalink[18] will further contribute to HPV4's safety profile. Third, the ORs were generated from *International Classification of Diseases, Ninth Revision* codes without medical record validation. Assessing such ORs for the purposes of safety signal detection was informative, yet the point estimate of the OR did not necessarily imply an increased risk because unvalidated codes were used. Fourth, our syncope findings were limited to only those events that were serious enough to have required an ED visit. Finally, this study identified numerous outcomes with elevated ORs that were subsequently identified as preexisting conditions or were not plausible as being associated with HPV4 (eg, congenital anomalies). Future studies should consider using algorithms or other methods to avoid extensive "false positives."

In summary, this study of 189 629 females who received HPV4 found that immunization was associated with same-day syncope and skin infections in the 2 weeks after vaccination. The findings from this large, comprehensive study did not detect any evidence of serious safety concerns secondary to HPV4. These findings support the general safety of routine vaccination with HPV4 to prevent cancer.

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