Observational Study of Routine Use of 9-Valent Human Papillomavirus Vaccine: Safe in More Than 140,000 Individuals

John Hansen[1], Arnold Yee[1], Ned Lewis[1], Se Li[2], Christine Velicer[2], Patricia Saddier[2], Nicola P. Klein[1]

[1] Kaiser Permanente Vaccine Study Center, Oakland, CA, USA. [2] Pharmacoepidemiology Department, Merck & Co., Inc., Kenilworth, NJ, USA.

John Hansen, MPH / Kaiser Permanente Vaccine Study Center
1 Kaiser Plaza 16B, Oakland, CA 94612 USA
Tel: (510) 267-7525 Fax: (510) 267-7524
Email: john.hansen@kp.org Registration ID: 3588

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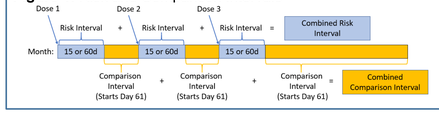
BACKGROUND

- The nine-valent[1] human papillomavirus (HPV) vaccine (9vHPV, GARDASIL®9) was licensed in the United States in December 2014.
- We conducted this study as part of the manufacturer's post-licensure commitment to monitor 9vHPV vaccine safety.
- At licensure 9vHPV vaccine had a recommended 3-dose schedule (0, 2, 6m). In October 2016, ACIP changed the recommendation for 9-14 year olds to a 2-dose schedule (0, 6-12m).
- This was a retrospective cohort study in Kaiser Permanente Northern California (KPNC) which evaluated the safety of 9vHPV among individuals who had not received any prior HPV vaccine.

METHODS

- **Study Setting:** KPNC is an integrated healthcare delivery system with approximately 4.2 million members. KPNC's complete electronic medical record contains all healthcare encounters and diagnoses, vaccines, demographics, and other clinical data.
- **Study period:** October 2015 through September 2017, which included the change in ACIP recommendations from 3 to 2 doses for 9-14 years olds.
- **Study cohort:** KPNC members who received their first dose of 9vHPV in the study period, with no prior HPV vaccination.
- **Events:** Post-vaccination emergency room visits and hospitalizations. All deaths in study period. Day of vaccination syncope and allergic reactions.
- **HCUP[2]:** All events were classified into meaningful categories with HCUP clinical classification software (overall 152 categories, with 17 level-1 categories and 135 level-2 sub-categories).
- **Analyses**: Self-controlled risk interval design analyzing all ED and hospital diagnoses with conditional logistic regression with further multiplicity adjustment (DFDR method[3])
  - —**Risk Intervals:** 15 day (days 0-14) and 60 day (days 1-60)
  - —**Comparison Intervals:** 15 day (days 61-75) and 60 day (days 61-120) (**Figure 1**)

Figure 1. Risk and Comparison Intervals



  - —**Combined Series:** Events in risk interval (light blue) are combined and compared with events in combined comparison intervals (orange). First events were counted in each observation period.
  - —**By Dose:** Events in risk interval after each dose compared with events in immediate comparison interval prior to a next dose.
  - —**Deaths:** Reviewed and summarized. Comparison with published rates.
  - —**Day of vaccination syncope and allergic reactions:** Reviewed and summarized. Comparison with published rates.
- **Investigation of significantly elevated event categories**: 1) assessed events for post-vaccination temporal clustering and; 2) medical record review.
- **Safety Review Committee:** An independent Safety Review Committee evaluated potential safety signals.

RESULTS

- 140,628 subjects initiated 9vHPV series in the study period (**Table 1**).
- Most subjects received their first dose of 9vHPV as 11-year olds (**Figure 2**).

Table 1. Study Population Features

	N (%)
Total N	140,628
Female	69,818 (49.6%)
Male	70,810 (50.4%)
Doses of 9vHPV	
At least 2 doses	69,027 (49.1%)
At least 3 doses	29,901 (21.3%)
Concomitant vaccine w dose 1	77.1%
Concomitant vaccine w dose 2	19.5%
Concomitant vaccine w dose 3	22.2%

Figure 2. Age at First 9vHPV in Study

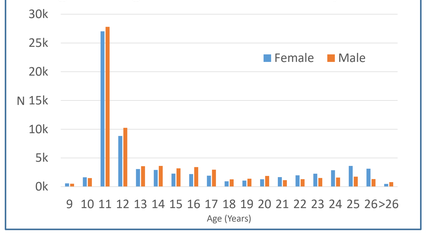


Table 2. Event Categories and Sub-Categories with Significantly Elevated Odds Ratios

		ORs (95% CI)	
HCUP Event Categories	**Combined Series or by Dose**	**1-60d Risk Interval**	**0-14d Risk Interval**
3.2 Diabetes mellitus	Combined Series	**1.66 (1.01, 2.74)**	1.64 (0.72, 3.71)
5.4 Delirium	Dose 3	**NE (1.11, NE)**	NE (0.27, NE)
6 Nervous system disorders	Dose 1	0.96 (0.83, 1.11)	**1.33 (1.02, 1.72)**
6.5 Headache	Dose 1	0.90 (0.70, 1.15)	**1.82 (1.17, 2.85)**
6.6 Coma, stupor, brain damage	Dose 1	**NE (1.67, NE)**	NE (0.43, NE)
9 Digestive disorders	Dose 1	**1.21 (1.03, 1.41)**	1.19 (0.90, 1.57)
9.2 Disorders of teeth & jaw	Dose 2	**2.38 (1.14, 4.98)**	1.55 (0.26, 9.29)
9.5 Abdominal hernia	Combined Series	**1.73 (1.06, 2.80)**	0.62 (0.21, 1.80)
	Dose 1	**2.63 (1.28, 5.42)**	1.15 (0.31, 4.34)
9.6 Lower GI disorders	Dose 1	**1.53 (1.01, 2.32)**	1.12 (0.56, 2.24)
9.10 GI hemorrhage	Combined Series	**2.18 (1.19, 4.00)**	2.50 (0.89, 7.02)
	Dose 1	**2.32 (1.02, 5.29)**	2.10 (0.53, 8.35)
	Dose 2	**3.80 (1.07, 13.46)**	**NE (1.70, NE)**
10.2 Male genital disease	Combined Series	**1.44 (1.04, 1.98)**	1.57 (0.89, 2.78)
	Dose 1	**1.60 (1.04, 2.46)**	1.61 (0.78, 3.29)
12 Skin disorders	Combined Series	1.04 (0.88, 1.23)	**1.40 (1.02, 1.92)**
	Dose 2	1.31 (0.94, 1.83)	**1.88 (1.00, 3.53)**
12.1 Skin & subcutaneous infections	Combined Series	1.09 (0.85, 1.39)	**1.86 (1.15, 3.01)**
	Dose 2	1.33 (0.82, 2.16)	**2.90 (1.04, 8.04)**
14.4 Congenital anomalies, nervous system	Dose 1	**5.01 (1.10, 22.83)**	NE (0.43, NE)
17. Symptoms; signs; & ill-defined conditions & factors influencing health status	Dose 1	**1.13 (1.02, 1.26)**	**1.36 (1.13, 1.64)**
17.1 Symptoms; signs; & ill-defined conditions	Dose 1	**1.16 (1.03, 1.30)**	**1.47 (1.20, 1.80)***

Bold OR and CI indicates the category is significantly elevated. * Category remains significant after adjustment for multiple comparisons. NE: not estimable.

RESULTS (continued)

- **Risk Interval Analyses:** Eight significantly elevated event categories were observed (**Table 2**). Only the category "Symptoms, Signs & Ill-defined conditions" remained significant after DFDR adjustment for multiple comparisons.
- After investigating these significantly elevated event categories (per Methods), only "skin disorders" was considered potentially related to receipt of 9vHPV or concomitant vaccination. Many elevated event categories appeared to be the result of follow-up care generated at the vaccination event or pre-existing conditions.
- "Symptoms, Signs & Ill-defined conditions" is a broad category and within it only syncope appeared to be temporally associated with vaccination.
- **Deaths:** There were 20 deaths, none considered related to vaccination. Rate of 14.11 per 100,000 person-years was similar to NCHS rates of same period[4].
- **Day of vaccination allergic reactions and syncope:** Observed rates of these conditions were similar to prior studies of HPV vaccine or other vaccines among populations at same age[5,6] (**Table 3**). Most subjects had 1-3 concomitant vaccines.
  - –On review, some allergy events preceded vaccination and all syncope events were post-vaccination.
  - –Confirmed post-vaccination allergy events were in 5 subjects: 2 hives, 2 non-specific allergic reactions, 1 anaphylactic reaction.
  - –Allergic reaction and syncope have previously been found to be associated with 9vHPV and are in the vaccine label[7].

Table 3. Examination of Allergic Reactions and Syncope on Day of Vaccination

	N	Incidence per Million Doses (95% CI)	Medical Record Review: N of Post-Vaccination Events
Allergic Reactions	8	33.4 (14.4, 65.8)	5
Syncope	14	58.4 (32.0, 98.1)	14

CONCLUSION

- ➢ This study of individuals vaccinated only with 9vHPV vaccine did not identify any new safety events related to 9vHPV administration.
- ➢ Most findings were previously known, preceded vaccination, or were better explained by other medical history.
- ➢ This study provides reassuring evidence of the favorable safety profile of 9vHPV administered as part of routine clinical care.

[1] 9vHPV targets HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58.
[2] HCUP = Healthcare Cost and Utilization Project (HCUP) using Clinical Classifications Software Refined (CCSR) for ICD-10-CM Diagnoses (https://www.hcup-us.ahrq.gov/toolssoftware/ccsr/ccs_refined.jsp)
[3] Double false discovery rate (DFDR) method. Mehrotra, D, Adewale, A. Statist. Med. 2012, 31 1918–1930, https://doi.org/10.1002/sim.5310
[4] Murphy, Xu, Kochanek, Curtin, and Arias, Division of Vital Statistics. Deaths: Final Data for 2015 (Supplemental Tables). National Vital Statistics System (NVSS).
[5] Bohlke K, et al. Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics. 2003;112(4):815–20.
[6] MMWR. Syncope After Vaccination. May 2, 2008 / 57(17);457-460.
[7] GARDASIL®9 package insert: https://www.fda.gov/media/90064/download

Conflicts of Interest: Authors employed by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA may hold Merck & Co., Inc., Kenilworth, NJ, USA stock and stock options. Nicola Klein reports grants from Pfizer, Sanofi Pasteur, GlaxoSmithKline, Merck & Co, MedImmune, and Protein Science, outside the submitted work. John Hansen, Arnold Yee, and Ned Lewis have nothing to disclose.
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Contact: John Hansen, MPH (john.hansen@kp.org)

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