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Surveillance of Autoimmune Conditions following Routine Use of Quadrivalent Human Papillomavirus Vaccine

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Running Title: Autoimmune safety of HPV vaccine

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Abstract

Objective: An observational safety study of the quadrivalent human papillomavirus vaccine (HPV4) in females was conducted. This report presents findings from autoimmune surveillance.

Design: Subjects were followed for 180 days after each HPV4 dose for new diagnoses of 16 pre-specified autoimmune conditions.

Setting: Two managed care organizations in California.

Subjects: 189,629 female who received ≥1 dose of HPV4 between 08/2006 - 03/2008.

Outcome: Potential new-onset autoimmune condition cases among HPV4 recipients were identified by electronic medical records. Medical records of those with ≥12 months health plan membership prior to vaccination were reviewed by clinicians to confirm the diagnosis and determine the date of disease onset. The incidence of each autoimmune condition was estimated for unvaccinated females at one study site using multiple imputation, and compared to that observed in vaccinated females. Incidence rate ratios (IRR) were calculated. Findings were reviewed by an independent Safety Review Committee (SRC).

Results: Overall, 1,014 potential new-onset cases were electronically identified; 719 were eligible for case review; 31%-40% were confirmed as new-onset. Of these, no cluster of disease onset in relation to vaccination timing, dose sequence or age was found for any autoimmune condition. None of the estimated IRR was significantly elevated except Hashimoto's disease [IRR=1.29, 95% confidence interval: 1.08-1.56]. Further investigation of temporal relationship and biological plausibility revealed no consistent evidence for a safety signal for autoimmune thyroid conditions. The SRC and the investigators identified no autoimmune safety concerns in this study.

Conclusions: No autoimmune safety signal was found in females vaccinated with HPV4.

Keywords: human papillomavirus; human papillomavirus vaccine; vaccination; vaccine safety;

post-licensure safety study; autoimmune conditions

Introduction

Vaccination with the quadrivalent human papillomavirus (HPV) vaccine, HPV4, presents an opportunity to reduce the burden of cervical cancer and other conditions caused by HPV types 6, 11, 16 and 18[1-4]. HPV4 demonstrated high efficacy in preventing clinical outcomes associated with new infection of HPV vaccine types[1-5]. The antigen presented in HPV4 is the L1 major capsid proteins of the four HPV vaccine types. HPV4 uses aluminum-containing adjuvant but does not contain thimerosal or antibiotics[6]. In June 2006, HPV4 was approved by the US Food and Drug Administration (FDA) as a regimen of three injections given over 6 months to females between the ages of 9 and 26

years. The Advisory Committee on Immunization Practices subsequently recommended routine HPV4 vaccination for girls 11-12 years old[6].

Between 2006 and 2010, a safety surveillance study of HPV4 in routine use among females was conducted as a post-licensure commitment to the FDA, the European Medicines Agency, and other regulatory authorities. This study was conducted in collaboration between two managed care organizations, Kaiser Permanente Southern California (KPSC) and Kaiser Permanente Northern California (KPNC), as a retrospective analysis of information from medical records and other databases. The study objectives were to monitor (1) general safety, (2) pregnancy outcomes, and (3) new onset of autoimmune conditions following HPV4 vaccination. Autoimmune reactions have been a long-standing concern surrounding vaccination[7-9]. However, most speculated associations have stemmed from case reports lacking confirmation by large, controlled epidemiologic studies[9]. Thus, well-designed post-licensure safety studies for newly approved vaccines facilitate proper evaluation of their autoimmune safety. This report presents findings from the autoimmune surveillance component of the post-licensure safety study of HPV4 in females.

Methods

Study population

KPSC and KPNC serve over 6.6 million ethnically and socioeconomically diverse members in California. The study population for the autoimmune surveillance included 189,629 females of all ages who received at least one dose of HPV4 between 08/2006

and 03/2008. The majority (99%) of these females were in the indicated age range (9-26 years). Females in the autoimmune surveillance were followed up to 180 days (referred to as the risk period, excluding day of vaccination) after each dose of HPV4 to identify new-onset autoimmune conditions (Figure 1). This study was approved by the Kaiser Permanente Institutional Review Boards.

Autoimmune conditions of interest

Autoimmune conditions of interest were pre-specified and composed of three groups: (1) rheumatologic/autoimmune disorders, including immune thrombocytopenia (ITP), autoimmune hemolytic anemia, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and juvenile rheumatoid arthritis (JRA); (2) autoimmune endocrine conditions, including type 1 diabetes, Hashimoto's disease and Graves' disease; and (3) autoimmune neurological/ophthalmic conditions, including multiple sclerosis (MS), acute disseminated encephalomyelitis, other demyelinating diseases of the central nervous system, vaccine-associated demyelination, Guillain-Barré syndrome, neuromyelitis optica, optic neuritis, and uveitis.

Safety Review Committee

Review of all safety data emerging from this study was carried out by an independent scientific committee, the Safety Review Committee (SRC). The SRC consisted of five experts who were external to the investigator team conducting the study and to the sponsor, and included: a general pediatrician/clinical epidemiologist, a

perinatologist/teratologist, a vaccinologist, a pediatric rheumatologist, and a pharmacoepidemiologist.

Electronic case identification

Potential new autoimmune diagnoses were identified among the vaccinated cohort in Kaiser Permanente's electronic health records. The method for case identification was designed to be highly sensitive to capture any potential cases, in order to address potential undercoding or miscoding in the early course of an autoimmune condition. To this end, ICD-9 diagnosis codes, abnormal laboratory results or pharmacy prescriptions possibly indicative of autoimmune conditions occurring from the first HPV4 dose to 180 days after the last HPV4 dose were captured. Both the disease specific ICD-9 codes (original codes) and general, expanded ICD-9 codes (e.g., general diabetes code 250 was considered an expanded code for type 1 diabetes) were identified in the electronic outpatient, emergency room and hospitalization records. The specific electronic case identification criteria for each autoimmune condition are listed in Appendix A-C. Electronically identified cases who had the ICD-9 codes, abnormal lab value or pharmacy prescription in the electronic records anytime between January 2004 and date of first dose of HPV4 were excluded, as their disease was likely a pre-existing condition.

Case review

In-depth case review was conducted for potential new-onset cases who had been health plan members for ≥12 months prior to receiving their first dose of HPV4. De-identified medical records were reviewed by three clinician expert panels (KPSC physicians)

referred to as the Case Review Committee (CRC). The Rheumatology CRC consisted of one pediatric and two adult rheumatologists. The Endocrinology CRC consisted of three endocrinologists. The Neurology/Ophthalmology CRC consisted of one ophthalmologist with neurology specialization and two neurologists. The CRC reviewed medical records dating back to 12 months prior to the first dose of HPV4, performed diagnosis confirmation using their clinical judgment (i.e., no pre-established diagnostic criteria were provided to the CRC), and where appropriate, determined the date of disease onset. The CRC also rated the level of diagnostic certainty as either strong or weak. CRC members were masked to the dates of HPV4 vaccination. Prior to the review by the CRC, if one of the study Principal Investigators confirmed that there was a diagnosis of the autoimmune condition in the chart note prior to HPV4 vaccination, the subject was removed from the case review process and categorized as a pre-existing case.

Due to the large number of potential new-onset cases identified for SLE, RA, JRA, Hashimoto's and Graves' disease, a random sample of potential cases for these conditions was included for case review. The random sampling was stratified based on the method of case identification (i.e., ICD-9 diagnosis codes, lab value or pharmacy prescription), as detailed in Appendix D. For the other autoimmune conditions, all eligible potential new-onset cases were reviewed.

The disposition of all reviewed cases was tabulated, along with a listing of subjects who were electronically identified but not reviewed, including those with <12 months Kaiser Permanente membership prior to vaccination. Confirmed autoimmune condition cases whose date of disease onset occurred within the 180-day risk period were summarized as

new-onset cases. For these, the dose sequence of HPV4, the median number of days to disease onset after vaccination, and the median age at disease onset were tabulated. Cases whose disease onset was in-between risk periods for those with >1 dose of HPV4 were also tabulated to provide additional perspective on the timing of autoimmune disease onset.

Background incidence rates comparison from population at KPSC

The "background" incidence rates of the autoimmune conditions in the unvaccinated female population 9-26 years old were estimated to compare to the observed incidence in the vaccinated females, using the population at KPSC only. Observed incidence in the vaccinated females at KPSC was calculated among those with ≥12 months prior membership. The accrual of person-time began with first HPV4 vaccination and ended at health plan disenrollment or 180 days after the last dose of HPV4. For the unvaccinated population (which includes members who will later become part of the vaccinated population), the accrual of person-time began at the later of 12 months after KPSC enrollment (to rule out pre-existing cases as was done in the vaccinated population) or August 2006, and ended at KPSC disenrollment, first HPV4 vaccination, or end of September 2008 (~180 days after the last possible dose in the vaccinated cohort), whichever came first.

The same electronic case identification algorithm was used to identify potential new-onset autoimmune conditions in the unvaccinated population. Since case review was not conducted for unvaccinated potential cases, Rubin's multiple imputation[10] was used to

estimate the rates of new-onset autoimmune conditions by treating the actual status of new-onset as missing data for the un-reviewed potential cases. The imputation for new onset status was done for all unvaccinated potential cases identified at KPSC, as well as for those not sampled, vaccinated potential cases at KPSC of the five autoimmune conditions for which only a random sample was included for case review. Five hundred imputed samples were generated using the PROC MI procedure in SAS statistical software version 9. Autoimmune condition, age, and how the condition was identified (original or expanded ICD-9 codes, lab data or prescriptions) were included as predictors in the model for the imputation. Both KPSC and KPNC reviewed vaccinated cases were included to inform the imputation model as new-onset case confirmation rates were similar between KPSC and KPNC (overall rates were 37% and 32%, respectively). Separate models were created for each disease grouping (rheumatologic, endocrine and neurologic). The median of the 500 imputed samples was used as the estimated incidence rate and ratio, and the 2.5^{th} and 97.5^{th} percentiles were used to estimate the 95% confidence interval. Incidence rate ratios (IRR) for the vaccinated group were considered significantly elevated if the lower bound of the confidence interval was greater than 1.0.

Two sensitivity analyses were conducted for this background incidence rates comparison. One employed a direct comparison of electronically identified potential cases, without the use of the new onset confirmation rate from CRC review. The other sensitivity analysis examined the original ICD-9 diagnosis codes only (without the use of expanded ICD-9 code, lab or pharmacy data), incorporating the new onset confirmation rates. In addition,

a combined analysis of thyroid conditions (Hashimoto's and Graves' diseases together) was conducted due to potential similarities in their pathogenesis, as requested by the SRC.

Additional graphic analysis and medical record review request by the SRC

After reviewing the background rate comparisons, the Safety Review Committee requested additional graphic analysis for three autoimmune endocrine conditions to evaluate the timing of disease onset in relationship to each HPV4 dose. There were 5 Graves' cases whose disease onset was within 14 days following a dose of HPV4. Additional medical record review was conducted for these 5 Graves' disease cases. Additional medical record review was also conducted for conditions with elevated IRR in the background rate comparisons (regardless of statistical significance, namely ITP, MS, and optic neuritis) to clarify the timing of disease symptom onset with respect to timing of vaccination.

Results

Among the 189,629 females in the autoimmune surveillance, 1,014 potential new autoimmune diagnoses were identified electronically. A total of 149,306 females met the 12-month membership criteria and were eligible for case review. Of these, 719 potential new-onset cases were identified, and 347 were sampled for case review (80 rheumatologic/autoimmune, 167 endocrine, and all of the 100 neurologic/ophthalmic, Table 1).

Case review findings

Rheumatologic/autoimmune conditions

Overall, 25 of 80 sampled cases (31%) were confirmed as new-onset (Table 1). Of the 25 confirmed cases, the CRC indicated a strong level of diagnostic certainty for 19 cases (Table 2). Nineteen of the confirmed cases had 1 single dose of HPV4 prior to first diagnosis. The median time after HPV4 vaccination to disease onset of these conditions was 55 days (range: 1-176 days). The average age at disease onset of these conditions was 16 years (range: 11-23 years). No potential cases of autoimmune hemolytic anemia were identified.

Endocrine conditions

Overall, 67 of 167 sampled cases (40%) were confirmed as new onset (Table 1). Of the 67 confirmed cases, the CRC indicated a strong level of diagnostic certainty for 48 cases (Table 2). Thirty-seven of the confirmed cases had 1 single dose of HPV4 prior to first diagnosis. The median time from HPV4 vaccination to disease onset of these conditions was 56 days (range: 1-175 days). The average age at disease onset of these conditions was 16 years (range: 11-25 years).

Neurologic/ophthalmic conditions

Overall, 32 of the 100 eligible cases (32%) were confirmed as new onset (Table 1). Of the 32 confirmed cases, the CRC indicated a strong level of diagnostic certainty for 21 cases (Table 2). Nineteen of the confirmed cases had 1 single dose of HPV4 prior to first diagnosis. The median time after HPV4 vaccination to disease onset of these conditions

was 46.5 days (range: 1-161 days). The average age at disease onset of these conditions was 16 years (range: 12-27 years). No potential Guillain-Barré syndrome or neuromyelitis optica cases were identified.

Background incidence rates comparison (KPSC population only)

At KPSC, there were 117,761 eligible vaccinated females with 87,771 accrued person-years and 412,151 eligible unvaccinated females with 561,050 accrued person-years. Observed incidence rates in the vaccinated females ranged from 1.14/100,000 person-years for other demyelinating diseases of the central nervous system to 104.82/100,000 person-years for Hashimoto's disease (Table 3). For the non-vaccinated females, estimated rates ranged from 1.60 to 81.10 per 100,000 person-years for the same two conditions. None of the estimated IRR was significantly elevated except for Hashimoto's disease [IRR=1.29, 95% confidence interval: 1.08-1.56] (Table 3). In the sensitivity analyses, the IRR of Hashimoto's disease was again significantly elevated when the original ICD-9 code was used as the only case identification method, but not in analysis focused only on electronic case identification with no incorporation of new onset confirmation rate. Type 1 diabetes and JRA, on the other hand, showed an IRR significantly less than 1.0 in these analyses.

Additional graphic analysis and medical record review for autoimmune endocrine conditions

The graphic analysis of type 1 diabetes and Hashimoto's disease in relation to the timing of HPV4 vaccination showed mostly a random pattern of disease onset distributed evenly

across days since vaccination (Figure 2). The graphic analysis of Graves' disease showed 5 Graves' cases whose disease onset was shortly after vaccination. Additional medical record review of these 5 cases found that 3 cases had their diagnostic lab drawn on the date of HPV4 vaccination. The remaining two were likely pre-existing cases as Graves' related symptoms (i.e., eyes popping, weight loss, fatigue, tachycardia) were found to precede HPV4 vaccination.

Additional medical record review for ITP, MS and optic neuritis

Additional medical record review for confirmed ITP, MS and optic neuritis cases found that 3 of 11 ITP cases and 1 of 5 MS cases had disease-related symptom onset prior to HPV4 vaccination. Review of the remaining new-onset cases revealed no apparent pattern to timing of symptom onset with respect to HPV4 vaccination; 3 of the 8 new-onset ITP cases were found to have potential causes unrelated to vaccination (e.g., prior viral illness, drug reaction). The SRC reviewed all findings and independently reached consensus on this conclusion.

Discussion

There was no clear evidence of safety signal for autoimmune conditions following vaccination with HPV4 in this study. This conclusion was based on the finding that no pre-specified autoimmune condition examined demonstrated any cluster of disease onset in relation to vaccination timing, dose sequence or age. The five Graves' disease cases that clustered shortly after HPV4 vaccination were found to be pre-existing cases. In

addition, most conditions showed no significant elevation in IRR for the vaccinated females in the background rates comparison analyses.

An elevated IRR was seen for Hashimoto's disease, a relatively common autoimmune condition in young females. After carefully considering all available safety data, the SRC and the investigator team interpreted this as unlikely a true signal of concern. This conclusion was based on the lack of consistent evidence for a safety signal for autoimmune thyroid conditions, e.g., disease onset was mostly randomly distributed in relation to the vaccination timing; there was no consistent elevation in incidence for autoimmune thyroid conditions in the vaccinated cohort [IRR=0.72 (0.50-1.01) for Graves' disease, Table 3]; and several confirmed new-onset autoimmune thyroid condition cases were likely pre-existing cases at the time of vaccination.

The initial presentation of autoimmune conditions often involves general symptoms, and there is often a lag between initial symptom onset and the correct assignment of diagnosis. To address this issue, several strategies were used in this study: (1) a 180-day risk period was used to accommodate lag time for clinical work-up, (2) broad, highly sensitive case identification criteria were used; (3) expert panels were employed to confirm the diagnosis and date of disease onset; and (4) only females with ≥12 months membership prior to vaccination were included to allow reasonable assessment by the expert panels. With these approaches, half of the potential Hashimoto's disease cases identified by laboratory test alone were confirmed to be new-onset cases. Furthermore, the case review process excluded 30% of the sampled potential cases as pre-existing cases. These

findings emphasize the limitation of ICD-9 diagnosis code-based approaches for assessing the timing of autoimmune condition onset, and the need for in-depth medical record review in studies using electronic health information.

There are some potential limitations that should be considered when interpreting the study results: (1) The CRC evaluated the date of disease onset, but the actual timing of initial symptom onset was not always clearly determined. Several cases classified as new onset after vaccination may actually have been pre-existing cases, as found by additional chart review for the Graves' disease, ITP and MS cases. (2) Analyses for many autoimmune conditions were based on a small number of cases, which gave the study limited power in examining temporal patterns or estimating IRR for these conditions. (3) The multiple imputation approach was not a standard method for estimating background incidence rates. Furthermore, only the reviewed vaccinated cases were used to inform the imputation for new onset status among the unvaccinated potential cases. If the true new onset confirmation rate was lower in the unvaccinated population, this may have biased the IRR estimates. There was also no adjustment for potential confounders when estimating the IRR, although most autoimmune conditions lack established risk factors. It should be noted that this study was based on early adopters of the HPV4 and their medically attended events. We did not evaluate potential effect modification by demographic or medical factors, or the risk of recurrence among vaccinated females with pre-existing autoimmune conditions.

Despite the potential limitations, the present investigation is based on a large, ethnically and socioeconomically diverse study population that received HPV4 through routine clinical care, and involved both in-depth case review and simulation modeling. Thus, this study provides important complementary knowledge on the safety profile of HPV4 as related to autoimmune condition risk, in addition to data from other resources such as clinical trials[11] and the Vaccine Adverse Event Reporting System[12, 13]. In conclusion, this observational surveillance study offers some assurance that among a large and likely generalizable female population, no safety signal for autoimmune conditions was found following HPV4 vaccination in routine clinical use.

Conflict of Interest Statement

This study was funded by Merck & Co.

Chao C, Jacobsen SJ and Slezak JM received research funding from Merck & Co for another study related to the quadrivalent human papillomavirus vaccine.

Chao C also receives research funding from Merck & Co, Pfizer and Amgen for other unrelated studies.

Jacobsen SJ served as an unpaid consultant to Merck & Co.

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Velicer CM and Liaw KL are employees at Merck Research Laboratories.

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Figure 1. Risk period after each dose of HPV4 for autoimmune condition surveillance.

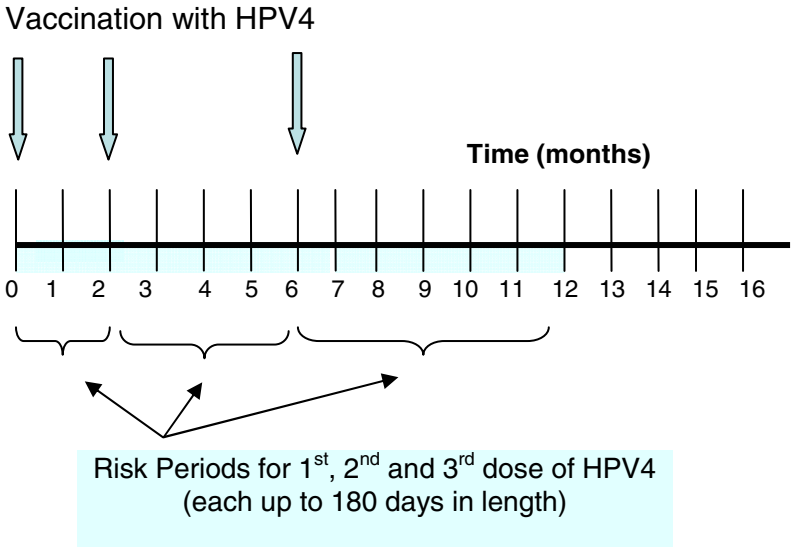
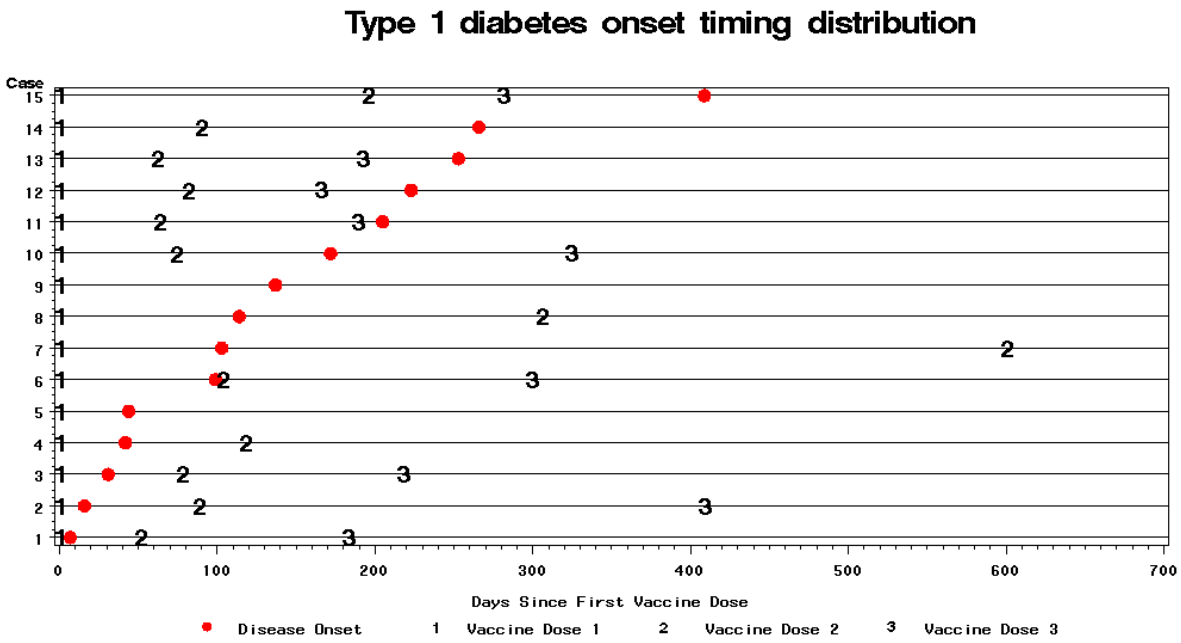


Figure 2. Distribution of date of disease onset for confirmed new-onset Type 1 diabetes, Hashimoto's disease and Graves' disease cases by doses of HPV4 (*date of disease onset as specified by the Case Review Committee)*



Graves' disease onset timing distribution

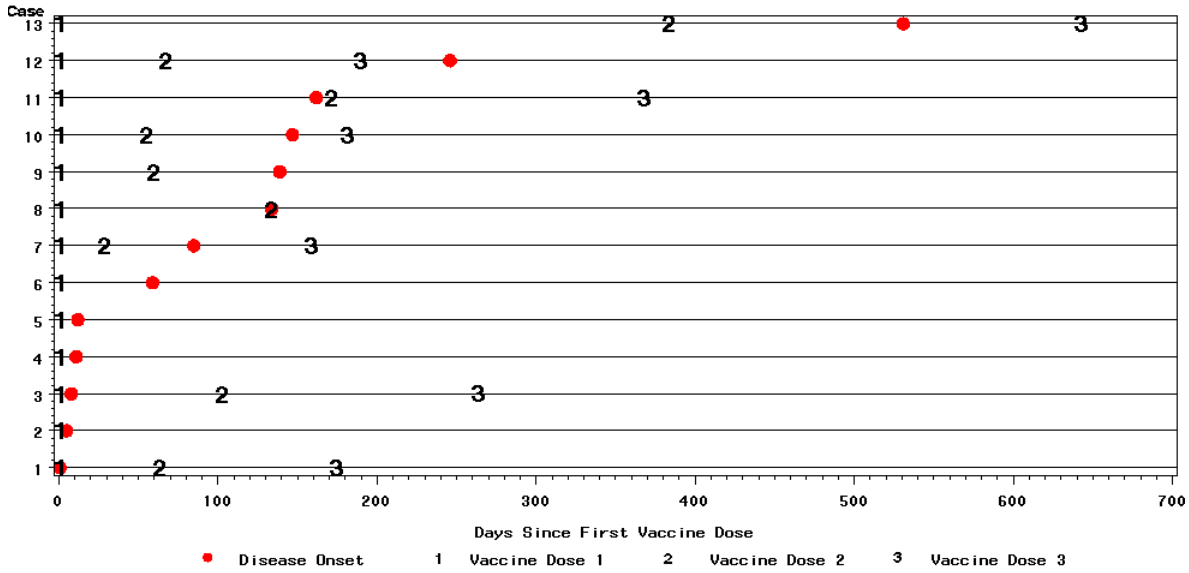


Table 1. Summary of autoimmune condition case review results for potential new-onset cases among vaccinated females at Kaiser Permanente Southern California and Northern California.

Condition	A. Electronically identified potential new-onset cases	B. Potential new-onset cases with ≥12 mos health plan membership [*]	C. Potential new-onset cases sampled for Case Review Committee review of medical records[§]	D. Potential new-onset cases reviewed by Case Review Committee[†]	E. Cases confirmed as new-onset cases after HPV4 by Case Review Committee[‡]	F. Proportion confirmed among those with ≥12 mos health plan membership (n=149,306)
	n	n	n (% among those eligible for Case Review Committee review from B)	n	n (% among potential cases sampled from C)	Confirmed new-onset cases per 100,000 females
Rheumatologic/Autoimmune	165	116	80	71	25 (31%)	NA, sampling was applied
Immune thrombocytopenia	32	24	24 (100%)	20	11 (46%)	7.4
Autoimmune hemolytic anemia	1	1	1 (100%)	0	0 (NA)	0
Systemic lupus erythematosus	57	44	25 (57%)	24	8 (32%)	NA, sampling was applied
Rheumatoid arthritis	37	27	17 (63%)	16	3 (18%)	NA, sampling was applied
Juvenile rheumatoid arthritis	38	20	13 (56%)	11	3 (23%)	NA, sampling was applied
Endocrine	718	503	167	155	67 (40%)	NA, sampling was applied
Type 1 diabetes	46	32	32 (100%)	30	15 (47%)	10.0
Hashimoto's disease	564	401	101 (25%)	93	39 (39%)	NA, sampling was applied
Graves' disease	108	70	34 (49%)	32	13 (38%)	NA, sampling was applied
Neurologic/Ophthalmic	131	100	100	92	32 (32%)	32 (0.02)
Multiple sclerosis	13	10	10 (100%)	10	5[¶] (50%)	3.3
Acute disseminated encephalomyelitis	4	3	3 (100%)	2	3[¶](100%)	2.0
Other demyelinating diseases of the central nervous system	10	8	8 (100%)	8	3[¶](38%)	2.0
Guillain-Barré syndrome	1	0	0 (NA)	0	0 (NA)	0
Neuromyelitis optica	2	2	2 (100%)	0	0 (NA)	0
Optic neuritis	17	12	12 (100%)	10	6[**] (50%)	4.0
Uveitis	84	65	65 (100%)	62	15 (23%)	10.0

Left to right – in order of appearance by each row

[*]Excluded due to <12 months Kaiser Permanente membership or pre-existing condition (not new-onset case).
[†]Sampled cases excluded by study Principal Investigators as pre-existing were not reviewed by Case Review Committee.
[‡]Cases confirmed as new onset include those cases with diagnosis confirmed by the Case Review Committee, for which the study team then confirmed that the date of disease onset, as determined by the average of the estimates for the date of disease onset indicated by the Case Review Committee members, was within 180 days after the date of vaccination.
[§]For specific sampling algorithm and sampling scheme, see Appendix D.
[¶]Three additional subjects were electronically identified as "other demyelinating disease of the central nervous system" and after case review, 1 was acute disseminated encephalomyelitis, 1 was multiple sclerosis, and the third (not counted in this table) was multiple sclerosis with diagnosis prior to vaccination date.
[**]One optic neuritis case is also a multiple sclerosis case; that case is included in both rows of this table.

Table 2. Exposure to HPV4 doses, diagnostic certainty and timing of disease onset among Case Review Committee confirmed new-onset autoimmune condition cases.

Condition	A. Case Review Committee confirmed new-onset cases[*]	B. Exposed to 1 dose prior to disease onset	C. Exposed to 2 doses prior to disease onset	D. Exposed to 3 doses prior to disease onset	E. Strong level of diagnostic certainty[†]	F. Days to disease onset since 1st dose of HPV4[‡]	G. Age (yrs) at disease onset
	n	n (% of confirmed cases from A)				Median (range[§])	Median (range[§])
Rheumatologic/Autoimmune	25	19 (76%)	5 (20%)	1 (4%)	19 (76%)	55 (1-176)	16 (11-23)
Immune thrombocytopenia	11	6 (55%)	4 (36%)	1 (9%)	8 (73%)	36 (1-176)	16 (11-18)
Autoimmune hemolytic anemia	0	‖	‖	‖	‖	‖	‖
Systemic lupus erythematosus[**]	8	8 (100%)	0 (0%)	0 (0%)	8 (100%)	44.5 (3-140)	16.5 (13-23)
Rheumatoid arthritis[**]	3	3 (100%)	0 (0%)	0 (0%)	3 (100%)	62 (62-106)	18 (16-18)
Juvenile rheumatoid arthritis[**]	3	2 (67%)	1 (33%)	0 (0%)	0 (0%)	55 (15-139)	14 (14-14)
Endocrine	67	37	20	9	48 (72%)	56 (1-175)	16 (11-25)
Type 1 diabetes[¶]	15	9 (60%)	2 (13%)	3 (20%)	11 (73%)	56 (7-175)	14 (11-20)
Hashimoto's disease[**]	39	20 (51%)	14 (36%)	5 (13%)	30 (77%)	52 (1-162)	16 (11-25)
Graves' disease[**]	13	8 (62%)	4 (31%)	1 (8%)	7 (54%)	56 (1-162)	17 (15-23)
Neurologic/Ophthalmic	32	19 (59%)	9 (28%)	4 (13%)	21 (66%)	46.5 (1-161)	16 (12-27)
Multiple sclerosis	5[††]	3 (60%)	1 (20%)	1 (20%)	4 (80%)	73 (14-92)	17 (15-26)
Acute disseminated encephalomyelitis	3[††]	2 (67%)	1 (33%)	0 (0%)	2 (67%)	46 (14-62)	16 (15-16)
Other demyelinating diseases of the central nervous system	3[††]	1 (33%)	2 (67%)	0 (0%)	3 (100%)	38 (3-67)	17 (14-26)
Guillain-Barré syndrome	0	‖	‖	‖	‖	‖	‖
Neuromyelitis optica	0	‖	‖	‖	‖	‖	‖
Optic neuritis	6	3 (50%)	1 (17%)	2 (33%)	6 (100%)	65.5 (14-144)	15.5 (14-24)
Uveitis	15	10 (67%)	4 (27%)	1 (7%)	5 (33%)	45 (1-161)	17 (12-27)

Left to right – in order of appearance by each row

[*]New onset within 180 days post HPV4 vaccination.

[†]At least two Case Review Committee members indicated strong level of diagnostic certainty.

[‡]Based on the estimated date of disease onset indicated by the Case Review Committee members.

[§]For each confirmed case, the date of disease onset indicated by each Case Review Committee member was averaged to give the averaged date of disease onset for this case. The median and range for all confirmed cases was then calculated based on the averaged date of disease onset for each case.

‖Not applicable because no cases were confirmed as new onset after vaccination.

[¶]One confirmed type 1 diabetes case had 4 HPV4 doses prior to disease onset.
[**]Potential cases of 5 conditions were randomly sampled for case review: systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, Hashimoto's disease and Graves' disease.
[††]Three additional subjects were electronically identified as "other demyelinating disease of the central nervous system" and after case review, 1 was acute disseminated encephalomyelitis, 1 was multiple sclerosis, and the third (not counted in this table) was multiple sclerosis with diagnosis prior to vaccination date.

Table 3. Incidence rate ratio (IRR) and 95% confidence interval (CI) of select autoimmune conditions in the vaccinated vs. non-vaccinated female populations of similar age in Kaiser Permanente Southern California.

Condition	Main comparison				Sensitivity analysis 1 Direct comparison with electronic case identification only (not incorporating new-onset confirmation rate obtained from case review)				Sensitivity analysis 2 Case identification with original ICD-9 codes only* (incorporating new-onset confirmation rate obtained from case review)			
	Vaccinated	Unvaccinated			Vaccinated	Unvaccinated			Vaccinated	Unvaccinated		
	# Observed cases† (Incidence‡)	# Estimated cases (Incidence‡)	IRR	95% CI	# Observed cases† (Incidence‡)	# Estimated cases (Incidence‡)	IRR	P-value§	# Observed cases† (Incidence‡)	# Estimated cases (Incidence‡)	IRR	95% CI
Rheumatologic/Autoimmnue												
Immune thrombocytopenia	6 (6.8)	33 (5.9)	1.16	(0.85-1.83)	10 (11.4)	56 (10.0)	1.14	0.70	6 (6.8)	31 (5.5)	1.24	(0.91-2.02)
Autoimmune hemolytic anemia	-	-	-	-	-	-	-	-	-	-	-	-
Systemic lupus erythematosus	10 (11.4)	58 (10.3)	1.07	(0.69-1.60)	31 (35.3)	157 (28.0)	1.26	0.24	8 (9.1)	46 (8.2)	1.10	(0.71-1.66)
Rheumatoid arthritis	4 (4.6)	39 (7.0)	0.71	(0.39-1.45)	8 (9.1)	95 (16.9)	0.54	0.09	3 (3.4)	31 (5.5)	0.70	(0.41-1.60)
Juvenile rheumatoid arthritis	3 (3.4)	43 (7.7)	0.48	(0.26-0.91)	11 (12.5)	106 (18.9)	0.66	0.20	2 (2.3)	38 (6.8)	0.36	(0.14-0.71)
Endocrine												
Type 1 diabetes	9 (10.3)	101 (18.0)	0.57	(0.47-0.73)	12 (13.7)	139 (24.8)	0.55	0.05	8 (9.1)	95 (16.9)	0.54	(0.45-0.70)
Hashimoto's disease†	92 (104.8)	455 (81.1)	1.29	(1.08-1.56)	241 (274.6)	1406 (250.6)	1.10	0.19	27 (30.8)	85 (15.2)	2.02	(1.65-2.60)
Graves' disease†	16 (18.2)	145 (25.8)	0.72	(0.50-1.01)	44 (50.1)	348 (62.0)	0.81	0.18	6 (6.8)	51 (9.1)	0.76	(0.42-1.10)
Combined Hashimoto's and Graves' disease†,¶	108 (123.1)	601 (107.1)	1.15	(0.97-1.36)	285 (324.7)	1754 (312.6)	1.04	0.55	33 (37.6)	137 (24.4)	1.54	(1.27-1.92)
Neurologic/Opthalmic												
Multiple sclerosis	3 (3.4)	14 (2.5)	1.37	(0.74-3.20)	7 (8.0)	39 (7.0)	1.15	0.74	3 (3.4)	14 (2.5)	1.37	(0.74-3.20)
Acute disseminated encephalomyelitis	-	-	-	-	-	-	-	-	-	-	-	-
Other demyelinating diseases of central nervous system	1 (1.1)	9 (1.6)	0.71	(0.38-2.13)	2 (2.3)	23 (4.1)	0.56	0.43	1 (1.1)	9 (1.6)	0.71	(0.38-2.13)
Guillain-Barré syndrome[e]	-	-	-	-	-	-	-	-	-	-	-	-
Neuromyelitis optica‖	-	-	-	-	-	-	-	-	-	-	-	-
Optic neuritis	5 (5.7)	22 (3.9)	1.45	(1.00-2.91)	8 (9.1)	45 (8.0)	1.14	0.74	5 (5.7)	22 (3.9)	1.45	(1.00-2.91)
Uveitis	7 (8.0)	67 (11.9)	0.67	(0.49-1.02)	37 (42.2)	212 (37.8)	1.12	0.54	1 (1.1)	5 (0.9)	1.28	(0.53-6.39)

[*]Case identification using original ICD-9 diagnosis codes only - no expanded ICD-9 diagnosis code (e.g., general ICD-9 code 250 for diabetes without specifying code for type 1 diabetes), lab or prescription codes were used for case identification.
[†]Observed number of cases and incidence for vaccinated females at Kaiser Permanente Southern California for all autoimmune conditions, except systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, Hashimoto's disease and Graves' disease, for which estimated number of cases and incidence are presented. Since sampling was applied in the case review process for these 5 conditions, the number of cases and incidence are estimated using the multiple imputation approach for these conditions for the vaccinated females, as for the unvaccinated females. Note that the observed number of cases in this table varied from Table 1 as these are cases from the Kaiser Permanente Southern California vaccinated female population only.
[‡]Per 100,000 person-years.
[§]New-onset case confirmation rates obtained from the process of medical record review by the Case Review Committee were not applied. As a result, only p-value was calculated for these comparisons.
[‖]Autoimmune hemolytic anemia, Guillain-Barré syndrome and neuromyelitis optica were excluded from the background rates comparison analysis because no confirmed cases were found in the vaccinated female population at both Kaiser Permanente Southern and Northern California. Acute disseminated encephalomyelitis was excluded because no confirmed vaccinated case was found at Kaiser Permanente Southern California.
[¶]The combined Hashimoto's and Graves' disease analysis was conducted per the Safety Review Committee's request after reviewing the individual results for Hashimoto's disease and Graves' disease, due to potential similarities in their pathogenesis.