CBER SENTINEL/PRISM FINAL REPORT

A SAFETY STUDY OF 9-VALENT HUMAN PAPILLOMA VIRUS VACCINE (GARDASIL 9) USING SEQUENTIAL ANALYSIS IN THE CBER PRISM/SENTINEL PROGRAM

Prepared by: W. Katherine Yih, PhD, MPH,[1] Adamma Mba-Jonas, MD, MPH,[2] Lingling Li, PhD,[1] Grace Lee, MD, MPH,[1] Meghan Baker, MD, ScD,[1] Genna Panucci, MPH,[1] Zilu Zhang, MS,[1] Azadeh Shoaibi, PhD, MHS,[2] Judith C. Maro, PhD, MS[1]

Author Affiliations: 1. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; 2. Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD

November 28, 2018

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

CBER Sentinel/PRISM Final Report

A Safety Study of Gardasil 9 in PRISM/Sentinel Using Sequential Analysis: Interim Results

Table of Contents

I. INTRODUCTION

As part of the Food and Drug Administration's (FDA's) ongoing post-licensure vaccine safety surveillance activities, this study was designed to provide safety data on the human papillomavirus vaccine Gardasil 9 (HPV9) from the Post-licensure Rapid Immunization Safety Monitoring (PRISM) component of Sentinel, the largest vaccine safety surveillance system in the U.S. We intended to monitor the safety of this vaccine with respect to four pre-specified health outcomes of interest, using sequential analysis methods.

After conducting two rounds of sequential analysis, monitoring the accumulation of vaccine doses administered since the vaccine approval in December 2014 and its first significant uptake in summer 2015, and factoring in that all available data for this study at any given time are about 9-12 months old, the Center for Biologics Evaluation and Research (CBER) decided to discontinue this study as of December 2017. The uptake rate of HPV9 vaccine has been slower in the population than CBER anticipated at the time of the design of this study. The study protocol stated that surveillance was to continue until three million doses were included in analysis. Hence, according to the protocol, the study would end after accumulation of three million doses of vaccine if no statistically significant results were detected for any of the outcomes prior to that date. However, based on the observed rate of vaccine accumulation, it would have taken several more years to accumulate three million doses of the vaccine in the data. Even if three million doses had accumulated, power calculations indicated that the statistical power to detect elevated risks would have been sub-optimal for two of the four outcomes to be analyzed unless relative risks were at least 5. In addition, the Global Advisory Committee on Vaccine Safety (GACVS) has conducted several reviews of the safety of HPV vaccines and has published a recent safety update.[1] The GACVS continues to conclude that HPV vaccines are safe.

This report presents the rationale for selecting the four outcomes; the methods, which are described in greater detail in the surveillance plan;[2] and the results for the two sequential analyses completed as of the termination of the surveillance activity.

II. HEALTH OUTCOMES OF INTEREST

FDA's post-licensure safety monitoring for Gardasil 9 had not identified any safety issues between the time of licensure and the initiation of this surveillance activity. However, FDA sought to make use of the PRISM/Sentinel's sequential analysis capability to conduct surveillance for the following potential adverse events:

- **Complex regional pain syndrome (CRPS):** CRPS is a clinical syndrome that affects one or more extremities and is characterized by persistent pain and swelling disproportionate to any known inciting event, and at least one sign of autonomic dysfunction in the affected limb(s). The pathogenesis of this syndrome is poorly understood, but its onset is often precipitated by a physical injury, such as minor trauma, fracture, infection, or a surgical procedure. Published literature suggests that time between the precipitating event and CRPS symptom onset can vary widely; however, a review of available studies indicated that symptom onset typically occurs within 6 months of the injury.[3] In June 2013, the Japanese Ministry of Health, Labor, and Welfare suspended its recommendation of routine immunization with HPV vaccine in girls and women following post-vaccination reports of serious chronic pain and concern about a possible association with HPV vaccine; such reports occurred after both bivalent HPV (Cervarix, GSK,

Brentford, UK) and quadrivalent HPV (Gardasil, Merck, Whitehouse Station, US) vaccines.[4] In early November 2015, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee completed a detailed scientific review of the evidence related to a possible association between HPV vaccines (Cervarix, Gardasil, and Gardasil 9) and CRPS. The Committee concluded that the evidence did not support a causal link between the vaccines and the syndrome.[5] Although U.S. vaccine safety information sources such as the Vaccine Adverse Event Reporting System (VAERS) have not suggested an increased risk of CRPS following HPV vaccination either, some post-HPV-vaccine cases have been reported to VAERS.

- **Uveitis:** Uveitis is characterized by inflammation of the uvea, the pigmented layer of the eye lying beneath the sclera and cornea. Frequently occurring in association with systemic medical conditions such as infections and inflammatory diseases, uveitis has been noted in the literature as occurring sporadically following HPV vaccination. In a case series of 24 such reports published in 2014, the median time to symptom onset was 30 days after Gardasil vaccination, with a range of 0-476 days.[6] Two earlier population-based observational studies evaluated the risk of uveitis[7] or "eye disorders"[8] after Gardasil vaccination and found no association.
- **Acute disseminated encephalomyelitis (ADEM):** ADEM is a demyelinating disease of the central nervous system that typically follows an infection. Clinical features include multifocal neurologic signs, including motor, sensory, cranial nerve, and brainstem deficits, as well as nonspecific symptoms such as headache, malaise, and altered mental status. Onset of ADEM following certain vaccines has been described previously.[9] Reports of ADEM following HPV vaccination (with both Cervarix and Gardasil) are present in the VAERS database. A 2014 publication summarizing case reports of demyelinating syndromes occurring after various vaccinations, including Gardasil, noted a mean symptom onset interval of 14 days; however, in some cases onset of the clinical presentation was observed up to and beyond three weeks following vaccination.[10] Four population-based observational studies examined the risk of ADEM after Gardasil vaccination and found no association.[7,11,12,13]
- **Pericarditis:** Pericarditis is characterized by inflammation of the pericardium; clinical features can include chest pain, electrocardiogram abnormalities, a pericardial friction rub, and a new or worsening pericardial effusion.[14] Cases of pericarditis following vaccination have been documented in the literature, with mean time to symptom onset after vaccination noted as 11 days (range 2-42 days).[15] Klein et al. evaluated the risk of "diseases of the heart" after Gardasil vaccination and found no association.[8] Spontaneous reports of pericarditis following HPV vaccination (with both Cervarix and Gardasil) are present in the VAERS database.

III. METHODS

A. OVERVIEW OF STUDY DESIGNS AND SEQUENTIAL ANALYSIS METHODS

We used a cohort design for CRPS and uveitis because the long putative risk interval relative to the typical spacing of Doses 1 and 2 (2 months) makes the self-controlled risk interval (SCRI) design unfeasible. For these outcomes, the comparison was between HPV9 vaccinees and concurrent controls receiving tetanus-diphtheria-acellular-pertussis combination vaccine (Tdap) and/or meningococcal (groups A, C, Y, and W-135) conjugate vaccine (MCV4). For ADEM and pericarditis, we used a SCRI design, and the comparison was between exposed and unexposed person-time for the same HPV9 vaccinees. The health outcomes of interest are listed, with their respective study designs, comparison groups, and sequential analysis methods, in Table 1:

Table 1. Design and analysis methods

Outcome	Design	Intervals compared	Confounding adjustment	Sequential analysis method
1) Complex Regional Pain Syndrome (CRPS) 2) Uveitis	Cohort	Days 1-56 after HPV9 vs. Days 1-56 after tetanus-diphtheria-acellular pertussis vaccine (Tdap) or meningococcal conjugate vaccine (MCV4)	By means of stratification by covariates of interest	Conditional sequential sampling procedure (CSSP), group sequential with a pre-specified number and frequency of interim tests[16,17]
3) Acute Demyelinating Encephalomyelitis (ADEM) 4) Pericarditis	Self-controlled risk interval (SCRI)	Days 1-28 vs. Days 29-56 after HPV9; each vaccinee contributes both periods	By means of self-controlled design	Binomial maximized sequential probability ratio test (maxSPRT),[18] group sequential[19,20]

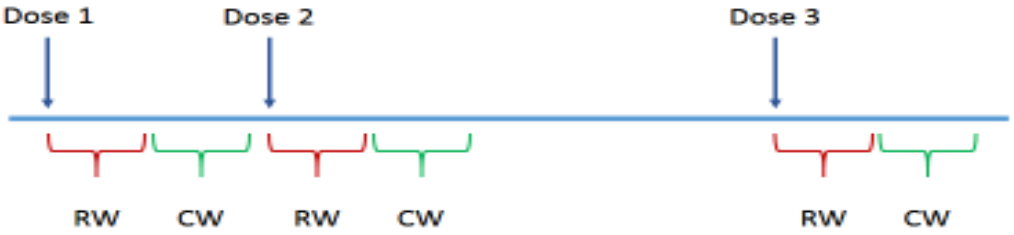
1. Cohort Design

For CRPS and uveitis, we used a cohort design with concurrent controls. We compared the rate of each outcome occurring during Days 1-56 after HPV9 vaccination (whether with or without other vaccines) to the rate in the same period after Tdap or MCV4 vaccination without HPV9 vaccine. (Tdap and MCV4 were considered equivalent for the purposes of this analysis.) We adjusted for confounding bias by stratifying by Data Partner, sex, and age group (9-11, 12-14, 15-17, 18-20, 21-23, 24-26 years of age). Within each stratum (defined by unique combination of Data Partner, sex, and age group), the number of incident events (i.e., cases of CRPS or of uveitis) among HPV9 vaccinees follows a binomial distribution, with the number of trials being the total number of events among all those vaccinated with HPV9, Tdap, or MCV4. Under the null hypothesis of no elevated risk, the binomial probability equals the proportion of eligible HPV9 doses among all the eligible HPV9, Tdap, and MCV4 doses. If the observed number of events among HPV9 vaccinees were statistically significantly larger than the expected number of events under the null hypothesis, it would indicate a potentially elevated risk due to HPV9 vaccination.

2. Self-Controlled Risk Interval (SCRI) Design

For ADEM and pericarditis, we used a self-controlled risk interval (SCRI) design,[21,22] shown schematically in Figure 1. This design makes use of only vaccinated cases occurring in pre-specified risk or control windows. A particular strength of self-controlled designs is that they control for fixed potential confounders (e.g., sex, genetic factors, socio-economic status), whether they are known or not, since individuals serve as their own controls. In addition, in using only vaccinated cases the SCRI design avoids the bias that can affect cohort studies when vaccinated subjects are misclassified as unvaccinated. The null hypothesis is that the risk of the outcome in question on an average day during the pre-defined risk interval after HPV9 is the same as the risk of the outcome on an average day during the pre-defined control interval.

Figure 1. Self-controlled risk interval (SCRI) design. Paired risk and comparison windows (RW and CW) follow each dose. Each vaccinee contributes person-time in both intervals. Only vaccinated cases occurring in these intervals are used in the analysis.



RW: risk window
CW: control window

B. STUDY POPULATION AND ENROLLMENT CRITERIA

The study population consisted of females and males enrolled with medical coverage in Aetna, Harvard Pilgrim Health Care, HealthCore, Humana, and Optum, who were 9-26.99 years of age at the time of vaccination. To be included in analysis, a vaccine dose must have occurred on or after 1/1/2015, have been preceded by ≥ 183 days of continuously enrolled time, and have been followed by ≥ 70 days of continuously enrolled time. (We required 70 days instead of only 56 days, in the event that we needed to obtain claims profiles of case-patients for signal follow-up—requiring 70 days of post-exposure enrollment would have provided 2 weeks more of post-diagnosis time in which to examine claims, which could have been useful, especially for cases occurring toward the end of the Days 1-56 period.) In determining "continuously enrolled time," apparent gaps in enrollment of up to 45 days duration were bridged, i.e., treated as continuously enrolled time.

C. EXPOSURES

HPV9, Tdap, and MCV4 vaccine exposures were ascertained by means of CPT codes 90651, 90715, and 90734, respectively, in claims data as well as by means of NDC codes (not listed because proprietary). All HPV9 doses meeting the criteria in Section B were included in analysis as HPV9-exposed, regardless of whether other vaccines were given on the same day, unless there was a dose of any HPV vaccine (CPT codes 90649, 90650, or 90651 and NDC codes) given in the prior 56 days. All doses of Tdap or MCV4 meeting the criteria in Section B were included in analysis as the comparison group, unless (a) the dose was given on the same day as HPV9, (b) there was a dose of any HPV vaccine given in the prior 56 days, or (c) the dose was followed by HPV9 within 56 days.

All eligible HPV9 doses were included in analysis and treated as equivalent; no dose-specific analyses were done.

D. OUTCOMES AND RISK AND COMPARISON INTERVALS

Algorithms and risk and control intervals for the four outcomes are shown in Table 2. For CRPS and uveitis, which were studied using the cohort design, we used a risk interval of Days 1-56 after vaccination ("Day 0" is the day of vaccination). If there were an association between HPV9 vaccination and either of these outcomes, this Days 1-56 interval may not have captured all of the vaccine-associated cases (see Section II), but since the comparison was between Days 1-56 after HPV9 and the same period after the comparison vaccines, the design had the capability of detecting an increased risk after HPV9 as long as at least part of the period of increased risk was during Days 1-56. (It was not

practical to use a longer risk interval because of the typical 2-month spacing between Doses 1 and 2.) Only instances of CRPS and uveitis that were the first-ever to occur in all enrolled time (with a minimum requirement of 183 days of enrolled time prior to HPV9 vaccination) were included in analysis. For ADEM and pericarditis, which have shorter putative risk intervals and were studied using the SCRI design, we used a risk interval of Days 1-28 and a control interval of Days 29-56 after vaccination. If there were an association between HPV9 vaccination and either of these outcomes, the Days 1-28 risk interval would be expected to capture most of the vaccine-associated cases (see Section II). To the extent that a vaccine-associated risk of either outcome were to extend beyond Day 28, there would be some attenuation of the risk detected. Only instances of ADEM and pericarditis that were the first to occur in a 183-day period of time were included in analysis.

Table 2. Algorithms and risk and control intervals (RW and CW) for the health outcomes of interest (HOIs) to be monitored. ICD-9 and ICD-10 diagnosis codes used in case-finding algorithms are shown in the Appendix.

#	HOI	Exclusions	Settings	First in what period	RW	CW
1	Complex regional pain syndrome (reflex sympathetic dystrophy) (CRPS)	None	Inpatient, ED, outpatient	First ever	Days 1-56	Days 1-56 after Tdap or MCV4
2	Uveitis	None	Inpatient, ED, outpatient	First ever	Days 1-56	Days 1-56 after Tdap or MCV4
3	Acute disseminated encephalo-myelitis (ADEM)	ICD10 code G35 or ICD9 code 340*: multiple sclerosis, ever, in all previous enrolled time (including beyond (i.e., before) -183 days) through 56 days post-exposure	Inpatient, ED	183 d	Days 1-28	Days 29-56
4	Acute pericarditis	None	Inpatient	183 d	Days 1-28	Days 29-56

E. DATA EXTRACTION

The Sentinel Cohort Identification and Descriptive Analysis (CIDA) tool, version 3.3.6, was used to extract the data for analysis.

The surveillance plan entailed extracting data each time a PRISM Data Partner updated their data, i.e., produced a new batch of data that was quality-checked and approved as part of the Sentinel infrastructure. For CRPS and uveitis, we ran conditional sequential sampling procedure (CSSP) analyses if and only if the number of doses of HPV9 accrued was approximately equal to or greater than 250,000 more than at the last look and there were new cases of the respective outcome. For ADEM and pericarditis, we planned to run the first binomial maxSPRT analyses if and only if there were at least 4 total cases accumulated in Days 1-56 after HPV9 vaccination. We planned to run subsequent binomial maxSPRT analyses if and only if new cases of the respective outcome had appeared in the data since the previous analysis. Thus, analyses for the four outcomes occurred on somewhat different schedules.

F. STATISTICAL ANALYSIS

1. Cohort Design

With the cohort design with concurrent controls, we used the conditional sequential sampling procedure (CSSP) for sequential analysis.[16,17] This is a group sequential analytic method to test whether there is an elevated risk for a selected adverse outcome (CPRS or uveitis in this case) following exposure to the vaccine of interest (HPV9) compared to selected comparator vaccine(s) (Tdap, MCV4). The CSSP adjusts for possible confounding bias between the two exposure groups by stratifying on important covariates (Data Partner, sex, and age group). The test statistic is the cumulative number of events among HPV9 vaccinees, which is the sum across all covariate strata from the beginning of surveillance through the current interim test. Within each covariate stratum, the number of new events among HPV9 vaccinees added at each interim look follows a binomial distribution with the number of trials being the number of newly added events from both the exposure and control groups. The binomial probability under the null hypothesis is the proportion of eligible HPV9 doses among the number of eligible HPV9, Tdap, and MCV4 doses.

Three inputs to the sequential analysis were pre-specified: 1) the alpha level, which we set at 0.05; 2) the upper limit on surveillance, defined as the maximum number of interim looks, which we set at 12; and 3) the alpha spending function, which allocates the overall alpha of 0.05 among the interim tests, which we specified as linear.

At each interim test, the probability of observing "more or equally extreme" scenarios under the null hypothesis was calculated via Monte Carlo simulation, as the distribution of the test statistic does not exist in simple, analytic form. This conditional probability was compared to a cut-off p-value that was determined by the overall alpha level and the alpha spending function. If the conditional probability were less than or equal to the cut-off p-value, then the possibility of an elevated risk of the outcome following HPV9 vaccination would be raised. At that point, surveillance for the outcome in question would formally end, in keeping with the dictates of sequential analysis.

One-tailed tests were used since we were looking only for elevated risks from vaccination rather than for protective effects.

2. SCRI Design

For the sequential SCRI analyses, we used the maximized sequential probability ratio test (maxSPRT) for binomial data to compare the cumulative numbers of events in risk and control intervals.[18] The maxSPRT adjusts for the repeated looks at the accumulating data entailed in sequential analysis. The test statistic is the log-likelihood ratio (LLR). We used group sequential analysis[19,20] rather than continuous sequential analysis, since the data were expected to arrive in large chunks.

Three inputs to the sequential analysis were pre-specified: 1) The alpha level: We set this at 0.05. 2) The upper limit on surveillance: In contrast to the cohort/CSSP method above, for the SCRI/binomial maxSPRT method the upper limit is the cumulative number of observed cases in risk and control intervals combined at which surveillance will end. The concept is the same, however, namely that if surveillance were to continue beyond our pre-specified upper limit, then our chance of getting a false positive (Type I error) over the course of surveillance would exceed 0.05. We choose upper limits based on the approximate cumulative number of cases that were expected to occur in the risk plus control intervals over the planned duration of surveillance (i.e., until 3 million doses had been administered to the study population). The upper limit for ADEM was 20 and for uveitis 12. The critical value of the LLR is the signaling threshold, expressed as the cumulative number of cases needed in the risk window in

order to reject the null hypothesis, which changes with each sequential analysis. The critical value is dictated by the matching ratio (ratio of risk interval length to control interval length, 1 in our case), the alpha level, and the upper limit. 3) The minimum number of cases needed in order to conduct the first analysis: For a binomial maxSPRT with equal-length risk and control intervals, no signal is possible with fewer than 6 total cases in the two intervals. However, one may wish to conduct an analysis with fewer than 6 cases in order to monitor the LLR and RR. In this surveillance, we planned to begin SCRI analysis when there were at least 4 cases in risk and control intervals combined.

The null hypothesis was that the risk on an average day in the risk interval is the same as the risk on an average day in the control interval. The null hypothesis would be rejected if, in a sequential analysis, the LLR reached the critical value. The null hypothesis would not be rejected if the upper limit of observed cases in risk and control intervals were surpassed without a statistically significant result arising, or if surveillance ended without this upper limit being surpassed.

As with the CSSP, one-tailed tests were used, since we were looking only for elevated risks from vaccination, not protective effects.

3. Comment on Alpha Levels Shown in Tables

We were running these tests in a rare-events setting, so, due to the discreteness of the test statistics, the actual alpha spent could have been lower than the allocated alpha (also sometimes called "nominal" or "target" alpha). If we had continued surveillance, the number of events would have gotten larger and larger, and we would have expected the actually spent alpha and the allocated alpha to converge. It is helpful to keep track of the alpha spent, because if, for example, the alpha actually spent by the end of surveillance is appreciably less than the nominal level, it would mean the test was quite conservative in the setting.

IV. RESULTS

All five Data Partners extracted data for surveillance, providing approximately 855,000 eligible HPV9 doses for analysis. Considering the five Data Partners collectively, the maximum period of HPV9 doses included is 1/1/2015-7/31/2016. The Data Partner-specific periods during which HPV9 doses were ascertained are shown in Table 3. The number of cases of CRPS, uveitis, ADEM, and acute pericarditis ascertained in Days 1-56 after the approximately 855,000 doses were 21, 65, 5, and 1, respectively. The cumulative number of HPV9 doses administered and the cumulative number of cases in the post-vaccination observation period as of each look at the data are shown in Table 4a and 4b. The number of doses varies somewhat by outcome for two reasons: (1) The enrollment and exclusion criteria vary by outcome (Table 2). (2) In the CSSP analyses, if a patient vaccinee had one of the health outcomes of interest (CRPS or uveitis), all subsequent doses of HPV9, Tdap, and MCV4 were censored, because the first-ever requirement for those outcomes meant that no subsequent event would have been eligible for analysis.

Table 3. Date ranges for HPV9 exposure ascertainment, by Data Partner

Sequential analysis no.	Data Partner	Start date	End date
Analysis 1	1	1/1/2015	7/31/2016
	2	1/1/2015	3/31/2016
	3	1/1/2015	4/30/2016
	4	1/1/2015	3/31/2016
Analysis 2	5	1/1/2015	7/31/2016

Table 4a. For complex regional pain syndrome and uveitis, cumulative number of HPV9 and of Tdap/MCV4 doses administered and cumulative number of cases in post-vaccination follow-up period (Days 1-56 post-vaccination) as of each look at the data, by health outcome. These two outcomes were studied using a cohort design and the conditional sequential sampling procedure. The overall exposure assessment period was 1/1/2015 - 7/31/2016.

Row # (for reference)	Vaccine	Analysis #	Data Partner(s) (code no.)	Cumulative Number of Index Doses	Cumulative Number of Events in Follow-Up Period (Days 1-56)
Complex regional pain syndrome (CRPS)					
1	***HPV9***	Analysis 1	1-4	504,774	12
2		Analysis 2	5	854,948	21
3		…			
4		Analysis 12			
5	***Tdap or MCV4***	Analysis 1	1-4	951,644	36
6		Analysis 2	5	1,536,141	57
7		…			
8		Analysis 12			
Uveitis					
9	***HPV9***	Analysis 1	1-4	504,034	42
10		Analysis 2	5	853,576	65
11		…			
12		Analysis 12			
13	***Tdap or MCV4***	Analysis 1	1-4	949,935	90
14		Analysis 2	5	1,533,274	149
15		…			
16		Analysis 12			

Table 4b. For acute demyelinating encephalomyelitis and acute pericarditis, cumulative number of HPV9 doses administered and cumulative number of cases in risk interval (Days 1-28 post-vaccination) and control interval (Days 29-56 post-vaccination) as of each look at the data, by health outcome. The self-controlled risk interval design and the binomial maximized probability ratio test were the methods selected to study these two outcomes. The overall exposure assessment period was 1/1/2015 - 7/31/2016.

Row # (for reference)	Vaccine	Analysis #	Data Partner(s) (code no.)	Cumulative Number of Index Doses	Cumulative Number of Events in Risk Window (Days 1-28)	Cumulative Number of Events in Control Window (Days 29-56)	Cumulative Total Events
Acute demyelinating encephalomyelitis (ADEM)							
17	***HPV9***	Pre-analysis	1-4	504,977	3	0	3
18		Analysis 1	5	855,248	4	1	5
19		…					
20		Analysis 12					
Acute pericarditis							
21	***HPV9***	Pre-analysis	1-4	505,111	0	1	1
22		Pre-analysis	5	855,488	0	1	1
23		Analysis 1					
24		…					
25		Analysis 12					

Two CSSP analyses were performed for CRPS and uveitis (Table 4a), and one SCRI analysis was done for ADEM (Table 4b). The results are presented in Table 5-7. No analysis was performed for acute pericarditis, given that only 1 case had been ascertained as of the termination of the surveillance activity. Descriptive results for acute pericarditis are shown in Table 8. No statistically significant elevated risk for any of the four outcomes was detected in these analyses. The only outcome for which there appeared to be an elevated relative risk (RR=4) was ADEM (Table 7), but this result was not statistically significant.

Table 5. Conditional sequential sampling procedure inputs and results regarding risk of complex regional pain syndrome in Days 1-56 after current HPV9 compared with risk in Days 1-56 after concurrent Tdap or MCV4 (cohort design)

			Cumulative							
Analysis	Cases after HPV9	Cases after Tdap/ MCV4	Cases after HPV9	Cases after Tdap/ MCV4	HPV9 doses/ total doses of HPV9, Tdap, MCV4	Incidence rate ratio (IRR)	Cases after HPV9 needed to signal	Alpha allocated	Alpha actually spent	H_0 rejected
1	12	36	12	36	0.35	0.63	25	0.00833	0.00351	No
2	9	21	21	57	0.36	0.66	38	0.01250	0.00968	No
…										
12										

Parameter settings: 12 looks, one-tailed tests, alpha (Type I error allowance) = 0.05, alpha spending function = linear.
HPV9 doses/total doses of HPV9, Tdap, MCV4: number of HPV9 doses divided by the total number of doses of HPV9, Tdap , and MCV4 (
The target alpha and allocated alpha are the same thing; it is the nominal alpha level, i.e., the maximum amount of alpha tha t could be spent at each particular interim test.

Table 6. Conditional sequential sampling procedure inputs and results regarding risk of uveitis in Days 1-56 after current HPV9 compared with risk in Days 1-56 after concurrent Tdap or MCV4 (cohort design)

			Cumulative							
Analysis	Cases after HPV9	Cases after Tdap/ MCV4	Cases after HPV9	Cases after Tdap/ MCV4	HPV9 doses/ total doses of HPV9, Tdap, MCV4	Incidence rate ratio (IRR)	Cases after HPV9 needed to signal	Alpha allocated	Alpha actually spent	H_0 rejected
1	42	90	42	90	0.35	0.88	57	0.00833	0.00627	No
2	23	59	65	149	0.36	0.78	85	0.01250	0.01164	No
…										
12										

Parameter settings: 12 looks, one-tailed tests, alpha (Type I error allowance) = 0.05, alpha spending function = linear.

Table 7. Binomial maximized sequential probability ratio test inputs and results regarding risk of acute demyelinating encephalomyelitis in Days 1-28 compared with risk in Days 29-56 (self-controlled risk interval design)

			Cumulative								
Analysis	Cases in risk interval (Days 1-28)	Cases in control interval (Days 29-56)	Cases in risk interval (Days 1-28)	Cases in control interval (Days 29-56)	Expected cases under H_0	Relative risk	Log-likelihood ratio (LLR)	Alpha allocated	Alpha actually spent	Critical value of LLR	H_0 rejected
1	4	1	4	1	2.50	4.00	0.963724	0.0312	0	n.a.	No
2											
...											
12											

Parameter settings and definitions: N = 20, one-tailed tests, alpha= 0.05, zp= 1, and M= 4. N is the upper limit, or the total number of events in risk and control windows needed to end surveillance when failing to reject the null hypothesis. It represents a stopping boundary for sequential surveillance. Alpha is the overall Type I error allowance, zp is the ratio of the length of the control window to the length of the risk window, and M is the minimum number of events to conduct the first test.

Table 8. Binomial maximized sequential probability ratio test inputs and descriptive results regarding risk of acute pericarditis in Days 1-28 compared with risk in Days 29-56 (self-controlled risk interval design). No sequential analysis was conducted for this outcome, because the minimum number of cases to conduct the first test, pre-specified as 4, had not been reached as of the point when surveillance was discontinued.

			Cumulative								
Analysis	Cases in risk interval (Days 1-28)	Cases in control interval (Days 29-56)	Cases in risk interval (Days 1-28)	Cases in control interval (Days 29-56)	Expected cases under H_0	Relative risk	Log-likelihood ratio (LLR)	Alpha allocated	Alpha actually spent	Critical value of LLR	H_0 rejected
0	0	1	0	1	0.50	0.00					
1											
2											
...											
12											

Parameter settings and definitions: N = 20, one-tailed tests, alpha= 0.05, zp= 1, and M= 4. N is the upper limit, or the total number of events in risk and control windows needed to end surveillance when failing to reject the null hypothesis. It represents a stopping boundary for sequential surveillance. Alpha is the overall Type I error allowance, zp is the ratio of the length of the control window to the length of the risk window, and M is the minimum number of events to conduct the first test.

V. CONCLUSION

This study performed two sequential analyses for outcomes CRPS and uveitis and one analysis for ADEM. Due to occurrence of too few (only one case) cases of acute pericarditis, no analysis could be performed for this outcome. As of the last analyses conducted before the activity was terminated, approximately 855,000 doses of HPV9 had accumulated in the surveillance data, and no statistically significant elevated risk of any of the four outcomes had been detected.

Post-licensure sequential analysis for vaccine safety surveillance can be a useful method to monitor the risks of outcomes too rare to fully assess in pre-licensure clinical trials.[23,24] The study designs—a cohort design comparing HPV9 vaccines with a concurrent group receiving Tdap or MCV4 vaccines and the self-controlled risk interval design—are more robust against confounding than cohort designs using current-vs.-historical comparison, which have been associated with false positive results in other studies,[25] and the statistical method used for the cohort design (CSSP) is novel, having been developed for this project.

VI. REFERENCES

1. http://www.who.int/vaccine_safety/committee/topics/hpv/en/
2. https://www.sentinelinitiative.org/sites/default/files/PRISM/Sentinel_PRISM_HPV9-Sequential-Analysis_Surveillance-Plan.pdf
3. Martin, CW and the WorkSafeBC Evidence-Based Practice Group. Complex Regional Pain Syndrome (CRPS): What does the literature report regarding the time interval between the inciting trauma and its subsequent diagnosis? April 2011. http://www.worksafebc.com/health_care_providers/Assets/PDF/CRPSDiagnosisLatency.pdf
4. Kinoshita T, Abe RT, Hineno A, Tsunekawa K, Nakane S, Ikeda S. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. Intern Med. 2014;53:2185-200.
5. European Medicines Agency. Review concludes evidence does not support that HPV vaccines cause CRPS or POTS. 2015. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Human_papillomavirus_vaccines/human_referral_prac_000053.jsp&mid=WC0b01ac05805c516f
6. Holt HD, Hinkle DM, Falk NS, Fraunfelder FT, Fraunfelder FW. Human papilloma virus vaccine associated uveitis. Curr Drug Saf. 2014;9:65-8.
7. Chao C, Klein NP, Velicer CM et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med 2012;271(2):193-203.
8. Klein NP, Hansen J, Chao C et al. Safety of quadrivalent human papillomavirus vaccine administered routinely to females. Arch Pediatr Adolesc Med 2012;166(12):1140-1148.
9. Menge T, Hemmer B, Nessler S, Wiendl H, Neuhaus O, Hartung PH, Kieseier BC, Stüve O. Acute Disseminated Encephalomyelitis: An Update. Arch Neurol. 2005;62(11):1673-1680
10. Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. Autoimmun Rev. 2014;13:215-24.
11. Arnheim-Dahlstrom L, Pasternak B, Svanstrom H, Sparen P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013;347:f5906.
12. Langer-Gould A, Qian L, Tartof SY et al. Vaccines and the Risk of Multiple Sclerosis and Other Central Nervous System Demyelinating Diseases. JAMA Neurol 2014.
13. Scheller NM, Svanstrom H, Pasternak B et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015;313(1):54-61.
14. Troughton RW, Asher CR, Klein AL. Pericarditis. Lancet. 2004;363:717-27.
15. Morgan J, Roper MH, Sperling L, Schieber RA, Heffelfinger JD, Casey CG, Miller JW, Santibanez S, Herwaldt B, Hightower P, Moro PL, Hibbs BF, Levine NH, Chapman LE, Iskander J, Lane JM, Wharton M, Mootrey GT, Swerdlow DL. Myocarditis, pericarditis, and dilated cardiomyopathy after smallpox vaccination among civilians in the United States, January-October 2003. Clin Infect Dis. 2008;46 Suppl 3:S242-50.

16. Li L. A conditional sequential sampling procedure for drug safety surveillance. *Stat Med.* 2009;28:3124-38.

17. Maro JC, Brown JS, Pan GJ, Li L. Orphan therapies: making best use of postmarket data. J Gen Intern Med. 2014;29 Suppl 3:S745-51.

18. Kulldorff M, Davis RL, Kolczak M, Lewis E, Lieu T, Platt R. A maximized sequential probability ratio test for drug and vaccine safety surveillance. Seq Anal. 2011;30:58-78.

19. Silva IR. Composite sequential Monte Carlo test for post-market vaccine safety surveillance. Stat Med. 2015. Epub ahead of print. doi: 10.1002/sim.6805.

20. Silva IR, Kulldorff M. Continuous versus group sequential analysis for vaccine and drug safety surveillance. Biometrics. 2015;71:851-8.

21. Greene SK, Kulldorff M, Lewis EM, Li R, Yin R, Weintraub ES, Fireman BH, Lieu TA, Nordin JD, Glanz JM, Baxter R, Jacobsen SJ, Broder KR, Lee GM. Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. Am J Epidemiol. 2010;171:177-88.

22. Klein NP, Hansen J, Lewis E, Lyon L, Nguyen B, Black S, Weston WM, Wu S, Li P, Howe B, Friedland LR. Post-marketing safety evaluation of a tetanus toxoid, reduced diphtheria toxoid and 3-component acellular pertussis vaccine administered to a cohort of adolescents in a United States health maintenance organization. Pediatr Infect Dis J. 2010;29:613-7.

23. McNeil MM, Gee J, Weintraub ES, Belongia EA, Lee GM, Glanz JM, Nordin JD, Klein NP, Baxter R, Naleway AL, Jackson LA, Omer SB, Jacobsen SJ, DeStefano F. the Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine 2014;32:5390-5398.

24. Weintraub ES, Baggs J, Duffy J, Vellozzi C, Belongia EA, Irving S, Klein NP, Glanz JM, Jacobsen SJ, Naleway A, Jackson LA, DeStefano F. Risk of intussusception after monovalent rotavirus vaccination. N Engl J Med. 2014;370:513-9.

25. Yih WK, Kulldorff M, Fireman BH, Shui IM, Lewis EM, Klein NP, Baggs J, Weintraub ES, Belongia EA, Naleway A, Gee J, Platt R, Lieu TA. Active surveillance for adverse events: The experience of the Vaccine Safety Datalink project. Pediatrics. 2011;127:S54–64.

VII. APPENDIX

Table 9. ICD-10 and ICD-9 codes to be used in case-finding algorithms, including in the look-back to determine incidence (first ever or first-in-183-days occurrence)

ICD10 code	ICD10 code label	ICD9 code	ICD9 code label
Complex regional pain syndrome			
G90.50	Complex regional pain syndrome I, unspecified	337.20 337.21 337.22 337.29	Reflex sympathetic dystrophy, unspecified Reflex sympathetic dystrophy of the upper limb Reflex sympathetic dystrophy of the lower limb Reflex sympathetic dystrophy of other specified site
G90.511	Complex regional pain syndrome I of right upper limb		
G90.512	Complex regional pain syndrome I of left upper limb		
G90.513	Complex regional pain syndrome I of upper limb, bilateral		
G90.519	Complex regional pain syndrome I of unspecified upper limb		
G90.521	Complex regional pain syndrome I of right lower limb		
G90.522	Complex regional pain syndrome I of left lower limb		
G90.523	Complex regional pain syndrome I of lower limb, bilateral		
G90.529	Complex regional pain syndrome I of unspecified lower limb		
G90.59	Complex regional pain syndrome I of other specified site		
Uveitis			
H44.131	Sympathetic uveitis, right eye	360.11 363.00 363.01 363.03 363.04 363.05 363.06 363.07 363.08 363.10 363.11 363.12 363.13 363.14 363.20 364.00 364.01	Sympathetic uveitis Focal chorioretinitis, unspecified Focal choroiditis and chorioretinitis, juxtapapillary Focal choroiditis and chorioretinitis of other posterior pole Focal choroiditis and chorioretinitis, peripheral Focal retinitis and retinochoroiditis, juxtapapillary Focal retinitis and retinochoroiditis, macular or paramacular Focal retinitis and retinochoroiditis of other posterior pole Focal retinitis and retinochoroiditis, peripheral Disseminated chorioretinitis, unspecified
H44.132	Sympathetic uveitis, left eye		
H44.133	Sympathetic uveitis, bilateral		
H44.139	Sympathetic uveitis, unspecified eye		
H20.00	Unspecified acute and subacute iridocyclitis		
H20.011	Primary iridocyclitis, right eye		
H20.012	Primary iridocyclitis, left eye		
H20.013	Primary iridocyclitis, bilateral		
H20.019	Primary iridocyclitis, unspecified eye		
H20.041	Secondary noninfectious iridocyclitis, right eye		
H20.042	Secondary noninfectious iridocyclitis, left eye		
H20.043	Secondary noninfectious iridocyclitis, bilateral		
H20.049	Secondary noninfectious iridocyclitis, unspecified eye		

ICD10 code	ICD10 code label	ICD9 code	ICD9 code label
H20.9	Unspecified iridocyclitis	364.04	Disseminated choroiditis and chorioretinitis, posterior pole
H30.001	Unspecified focal chorioretinal inflammation, right eye	364.3	Disseminated choroiditis and chorioretinitis, peripheral
H30.002	Unspecified focal chorioretinal inflammation, left eye		Disseminated choroiditis and chorioretinitis, generalized
H30.003	Unspecified focal chorioretinal inflammation, bilateral		Disseminated retinitis and retinochoroiditis, metastatic
H30.009	Unspecified focal chorioretinal inflammation, unspecified eye		Chorioretinitis, unspecified
H30.011	Focal chorioretinal inflammation, juxtapapillary, right eye		Acute and subacute iridocyclitis, unspecified
H30.012	Focal chorioretinal inflammation, juxtapapillary, left eye		Primary iridocyclitis
H30.013	Focal chorioretinal inflammation, juxtapapillary, bilateral		Secondary iridocyclitis, noninfectious
H30.019	Focal chorioretinal inflammation, juxtapapillary, unspecified eye		Unspecified iridocyclitis
H30.021	Focal chorioretinal inflammation of posterior pole, right eye		
H30.022	Focal chorioretinal inflammation of posterior pole, left eye		
H30.023	Focal chorioretinal inflammation of posterior pole, bilateral		
H30.029	Focal chorioretinal inflammation of posterior pole, unspecified eye		
H30.031	Focal chorioretinal inflammation, peripheral, right eye		
H30.032	Focal chorioretinal inflammation, peripheral, left eye		
H30.033	Focal chorioretinal inflammation, peripheral, bilateral		
H30.039	Focal chorioretinal inflammation, peripheral, unspecified eye		
H30.041	Focal chorioretinal inflammation, macular or paramacular, right eye		
H30.042	Focal chorioretinal inflammation, macular or paramacular, left eye		
H30.043	Focal chorioretinal inflammation, macular or paramacular, bilateral		
H30.049	Focal chorioretinal inflammation, macular or paramacular, unspecified eye		
H30.101	Unspecified disseminated chorioretinal inflammation, right eye		

ICD10 code	ICD10 code label	ICD9 code	ICD9 code label
H30.102	Unspecified disseminated chorioretinal inflammation, left eye		
H30.103	Unspecified disseminated chorioretinal inflammation, bilateral		
H30.109	Unspecified disseminated chorioretinal inflammation, unspecified eye		
H30.111	Disseminated chorioretinal inflammation of posterior pole, right eye		
H30.112	Disseminated chorioretinal inflammation of posterior pole, left eye		
H30.113	Disseminated chorioretinal inflammation of posterior pole, bilateral		
H30.119	Disseminated chorioretinal inflammation of posterior pole, unspecified eye		
H30.121	Disseminated chorioretinal inflammation, peripheral right eye		
H30.122	Disseminated chorioretinal inflammation, peripheral, left eye		
H30.123	Disseminated chorioretinal inflammation, peripheral, bilateral		
H30.129	Disseminated chorioretinal inflammation, peripheral, unspecified eye		
H30.131	Disseminated chorioretinal inflammation, generalized, right eye		
H30.132	Disseminated chorioretinal inflammation, generalized, left eye		
H30.133	Disseminated chorioretinal inflammation, generalized, bilateral		
H30.139	Disseminated chorioretinal inflammation, generalized, unspecified eye		
H30.891	Other chorioretinal inflammations, right eye		
H30.892	Other chorioretinal inflammations, left eye		
H30.893	Other chorioretinal inflammations, bilateral		
H30.899	Other chorioretinal inflammations, unspecified eye		

ICD10 code	ICD10 code label	ICD9 code	ICD9 code label
H30.90	Unspecified chorioretinal inflammation, unspecified eye		
H30.91	Unspecified chorioretinal inflammation, right eye		
H30.92	Unspecified chorioretinal inflammation, left eye		
H30.93	Unspecified chorioretinal inflammation, bilateral		
ADEM			
G04.00	Acute disseminated encephalitis and encephalomyelitis, unspecified		
G04.01	Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM)		
G04.02	Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis	323.51	Encephalitis and encephalomyelitis following immunization procedures Myelitis following immunization procedures
G04.30	Acute necrotizing hemorrhagic encephalopathy, unspecified	323.52	
G04.31	Postinfectious acute necrotizing hemorrhagic encephalopathy	323.61	Infectious acute disseminated encephalomyelitis (ADEM)
G04.32	Postimmunization acute necrotizing hemorrhagic encephalopathy	323.62	Other postinfectious encephalitis and encephalomyelitis
G04.39	Other acute necrotizing hemorrhagic encephalopathy	323.81	Other causes of encephalitis and encephalomyelitis
G04.81	Other encephalitis and encephalomyelitis	323.9	Unspecified causes of encephalitis, myelitis, and encephalomyelitis
G04.90	Encephalitis and encephalomyelitis, unspecified		
Pericarditis			
B33.23	Viral pericarditis		
I30.0	Acute nonspecific idiopathic pericarditis	074.21	Coxsackie pericarditis
I30.1	Infective pericarditis	420.90	Acute pericarditis, unspecified
I30.8	Other forms of acute pericarditis	420.91	Acute idiopathic pericarditis
I30.9	Acute pericarditis, unspecified	420.99	Other acute pericarditis