Near Real-Time Surveillance to Assess the Safety of the 9-Valent Human Papillomavirus Vaccine

James G. Donahue, DVM, PhD,[a] Burney A. Kieke, MS,[a] Edwin M. Lewis, MPH,[b] Eric S. Weintraub, MPH,[c] Kayla E. Hanson, MPH,[a] David L. McClure, PhD,[a] Elizabeth R. Vickers, MPH,[a] Julianne Gee, MPH,[c] Matthew F. Daley, MD,[d] Frank DeStefano, MD,[c] Rulin C. Hechter, MD, PhD,[e] Lisa A. Jackson, MD, MPH,[f] Nicola P. Klein, MD, PhD,[b] Allison L. Naleway, PhD,[g] Jennifer C. Nelson, PhD,[f] Edward A. Belongia, MD[a]

BACKGROUND AND OBJECTIVES: Human papillomavirus is the most common sexually transmitted infection in the United States and causes certain anogenital and oropharyngeal cancers. The 9-valent human papillomavirus vaccine (9vHPV) provides protection against additional types not included in the quadrivalent vaccine. We conducted near real-time vaccine safety surveillance for 24 months after the vaccine became available in the Vaccine Safety Datalink.

METHODS: Immunizations and adverse events were extracted weekly from October 2015 to October 2017 from standardized data files for persons 9 to 26 years old at 6 Vaccine Safety Datalink sites. Prespecified adverse events included anaphylaxis, allergic reaction, appendicitis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, injection site reaction, pancreatitis, seizure, stroke, syncope, and venous thromboembolism. The observed and expected numbers of events after 9vHPV were compared weekly by using sequential methods. Both historical and concurrent comparison groups were used to identify statistical signals for adverse events. Unexpected signals were investigated by medical record review and/or additional analyses.

RESULTS: During 105 weeks of surveillance, 838 991 doses of 9vHPV were administered. We identified unexpected statistical signals for 4 adverse events: appendicitis among boys 9 to 17 years old after dose 3; pancreatitis among men 18 to 26 years old; and allergic reactions among girls 9 to 17 years old and women 18 to 26 years old after dose 2. On further evaluation, which included medical record review, temporal scan analysis, and additional epidemiological analyses, we did not confirm signals for any adverse events.

CONCLUSIONS: After 2 years of near real-time surveillance of 9vHPV and several prespecified adverse events, no new safety concerns were identified.

abstract

[a]*Marshfield Clinic Research Institute, Marshfield, Wisconsin;* [b]*Kaiser Permanente Northern California, Oakland, California;* [c]*Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia;* [d]*Kaiser Permanente Colorado, Aurora, Colorado;* [e]*Kaiser Permanente Southern California, Pasadena, California;* [f]*Kaiser Permanente Washington, Seattle, Washington; and* [g]*Kaiser Permanente Northwest, Portland, Oregon*

WHAT'S KNOWN ON THIS SUBJECT: Human papillomavirus (HPV) is a common sexually transmitted infection that can cause cancer and other illnesses. Clinical trials of the 9-valent HPV vaccine have demonstrated efficacy and safety, but population-based studies are needed to evaluate its safety profile.

WHAT THIS STUDY ADDS: In this postlicensure study, we documented ~839 000 9-valent HPV doses administered from 2015 to 2017 among persons 9 to 26 years old in the Vaccine Safety Datalink; no new safety concerns were identified. With these findings, we add to the safety profile established in prelicensure clinical trials.

ARTICLE

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States.[1] Although most of the 14 million infections that occur each year in the United States are transient, HPV is a known cause of certain anogenital and oropharyngeal cancers and accounts for 3% of all cancers among women and 2% of all cancers among men.[1,2] The Advisory Committee on Immunization Practices (ACIP) first recommended the quadrivalent vaccine (4-valent human papillomavirus vaccine [4vHPV], Gardasil; Merck and Co) in 2006 for routine vaccination of 11- to 12-year-old girls with catchup through age 26 years[3]; recommendations for boys followed in 2011.[4] In February 2015, the ACIP recommended 3 doses (0, 1–2, and 6 months) of the recently licensed 9-valent human papillomavirus vaccine (9vHPV) (Gardasil 9; Merck and Co) be routinely administered to boys and girls starting at the age of 11 to 12 years. Vaccination was also recommended for females 13 to 26 years and males 13 to 21 years, if not previously vaccinated, and through age 26 for men in specific risk groups.[5] The ACIP changed its recommendation in October 2016 from 3 doses to 2 doses (0, 6–12 months) for those who begin the series before the age of 15 years.[6,7] In June 2019, the ACIP recommended shared clinical decision-making for HPV vaccination in individuals aged 27 to 45 years but did not extend the recommended catch-up age group beyond age 26 years.[8] Compared with the quadrivalent vaccine (4vHPV), 9vHPV has more than twice the amount of an aluminum-based adjuvant and protects against an additional 5 HPV types.[5]

Although prelicensure clinical trials of the 9-valent vaccine did not detect any important safety concerns, these studies were not powered to detect uncommon adverse events; population-based monitoring of 9vHPV is warranted.[9,10] Several months after the ACIP recommendation for 9vHPV, the Vaccine Safety Datalink (VSD) initiated near real-time surveillance to assess the risks of prespecified adverse events after receipt of 9vHPV.

METHODS

Study Design and Population

The VSD was established in 1990 as a collaborative project between several integrated health care organizations and the Centers for Disease Control and Prevention to monitor vaccine safety.[11] Six integrated health care organizations in the VSD contributed data for this surveillance: Kaiser Permanente Northern California, Southern California, Colorado, Oregon, and Washington and Marshfield Clinic (Marshfield, Wisconsin). The study population consisted of persons 9 to 26 years old during the study period (October 4, 2015 through October 7, 2017). Standardized electronic data files were generated weekly and contained information on demographics, vaccinations, and medical encounters. Data were aggregated to create prospective cohorts that were followed for up to 180 days from the date of vaccination.

This study was approved by institutional review boards at all participating sites.

Ascertainment of Adverse Events

Adverse events were prespecified on the basis of reports from clinical trials, the Vaccine Adverse Event Report System, or other published investigations including a VSD safety study of 4vHPV.[12] Adverse events were identified by using *International Classification of Diseases, 10th Revision* (ICD-10) codes assigned during inpatient, outpatient, or emergency department (ED) encounters (Supplemental Table 4); only diagnoses assigned in event-specific, postvaccination exposure windows and settings were included in the analysis (Table 1). A 10-week lag was applied before each weekly analysis to permit administrative corrections to the electronic data, enhance data completeness, and ensure that sufficient time had passed to cover postvaccination risk windows.[13]

The adverse events included both common and uncommon diseases. Primary analyses for uncommon diseases used large historical comparison groups, whereas common diseases were analyzed with a smaller concurrent comparison group; both are described below. To be consistent with the earlier study of 4vHPV,[12] we considered the following adverse events to be uncommon in the age groups of interest: anaphylaxis, appendicitis, Guillain-Barré syndrome (GBS), pancreatitis, seizures, stroke, and venous thromboembolism (VTE). Chronic inflammatory demyelinating polyneuropathy (CIDP), not evaluated previously, was also considered an uncommon event. Injection site reactions, allergic reactions (evaluated separately in the outpatient, ED, and inpatient settings), syncope, and nonspecific reactions (eg, adverse effect of viral vaccines) were considered common (Table 1).[14]

Exposure Ascertainment

Individuals were considered exposed if electronic medical records indicated receipt of 9vHPV during the study period. Doses given within 42 days of a previous dose in the same person were excluded from the analysis to prevent overlapping risk windows.

Unexposed Comparison Groups

Comparison groups were age-comparable persons observed in either historical or concurrent periods of time relative to 9vHPV uptake who were unexposed to 9vHPV vaccine. Person-time rates

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TABLE 1 Characteristics of Prespecified Adverse Events

	Medical Setting	Postvaccination Risk Window, d	First Episode in What Period?	Primary Comparison Group[a]
Uncommon or rare adverse event				
Anaphylaxis	ED, inpatient	0–2	First in 42 d	Historic
Appendicitis	ED, inpatient	1–42	First in 42 d	Historic
Pancreatitis	ED, inpatient	1–42	First ever	Historic
GBS	Outpatient, ED, inpatient	1–42	First in 42 d	Historic
CIDP	Outpatient, ED, inpatient	1–180	First ever	Historic
Seizure	ED, inpatient	0–42	First in 42 d and first ever	Concurrent
Stroke	ED, inpatient	0–42	First in 42 d	Historic
VTE	Outpatient, ED, inpatient	1–42	First in 1 y	Historic
Common adverse event				
Allergic reactions	Outpatient, ED, inpatient	0–2 for ED and inpatient, 1–2 for outpatient	First in 42 d	Concurrent
Injection site reactions	Outpatient, ED, inpatient	1–6	First in 42 d	Concurrent
Nonspecific reactions	Outpatient, ED, inpatient	0–6	First in 42 d	Concurrent
Syncope	Outpatient, ED, inpatient	Day 0	First in 2 d	Concurrent

[a] Concurrent comparison group: visits during which comparator vaccines were administered, with analytic strata defined by age (in 1-y increments), site, sex, and week of the vaccination visit. Two historic comparison groups (2007–2014) were used: general VSD population and vaccinated VSD population, vaccinated with comparator vaccines.

based on the general population provide increased stability for rare adverse events but may introduce bias because of systematic differences in exposed and unexposed groups. In contrast, data based on comparator vaccines, both historical and concurrent, were derived from smaller populations with risk estimates that are less stable, but exposed and unexposed groups are more likely to be similar. For the analysis of common adverse events, we used a concurrent comparison group. For uncommon events, the primary analytic method used 2 complementary historical comparison groups, but we also evaluated uncommon events (eg, pancreatitis and seizures) using the concurrent comparison group because the analytic infrastructure for uncommon events was under development at the start of the study.

Data for both historical comparison groups were derived from persons 9 to 26 years of age from 2007 through 2014. One group was the general VSD population that was used to estimate (via modeling) general background person-time rates by sex, site, and single-year of age; there was no exclusion based on 4vHPV vaccination. The rates were multiplied by the observed number of 9vHPV doses to produce expected counts, which were prorated to the length of the postvaccination risk window (Table 1). For informational and comparison purposes, the rates summarized across subgroups (but not prorated to the length of the postvaccination risk window) are provided in Supplemental Table 5. The other historical group consisted of persons with visits at which comparator vaccines routinely given to this age group (tetanus, diphtheria; tetanus, diphtheria, acellular pertussis; meningococcal conjugate; hepatitis A; varicella) were administered. Visits in which 4vHPV was administered were not included in this group. The number of events observed in postvaccination risk windows for comparator vaccine visits and the number of comparator vaccine doses administered in the historical period were incorporated into the analyses.

The concurrent comparison group was defined in the same manner as the historical comparator vaccine group, except that the visits among the VSD population occurred during the study period. Across analytic strata defined by age, site, sex, and week of the vaccination visit, exposed versus unexposed comparisons were performed.

Analytic Methods

We used the Rapid Cycle Analysis (RCA) methodology and near real-time data to compare adverse event rates in a recently vaccinated group with rates from an unvaccinated group.[15] The VSD has investigated multiple vaccines using the RCA approach, including 4vHPV.[12,15–21]

To estimate the relative risk (RR) for prespecified adverse events, we used the Poisson-based maximized sequential probability ratio test (MaxSPRT) for analyses in which the historical general VSD population comparison group was used,[22] the conditional maximized sequential probability ratio test (CMaxSPRT) for analyses in which the historical vaccinated VSD population was used,[23] and the exact sequential analysis (ESA) for analyses in which the concurrent comparison group was used.[12,24] We conducted the analyses in the overall study population as well as in subgroups defined by age group and sex. Analyses for more-common outcomes (eg, syncope) were dose specific, whereas others (eg, GBS) pertain to 1 or more doses (ie, any dose). Because data were analyzed on a weekly basis, sequential methods were used to maintain an overall 1-sided type I error rate of 0.05 across the multiple tests performed for each adverse

event, subgroup, and statistical method combination. Sequential methods periodically compare the number of cases of each adverse event among the exposed with the number of cases observed or expected among a comparison group unexposed to 9vHPV.[12,22–24] A preliminary statistical signal was generated if a test statistic from an analysis exceeded a predetermined threshold. A more-detailed description of the analytical methods used in this study is provided in the Supplemental Information.

We conducted the first analytic run for ESA in week 25, which encompassed data from October 4, 2015 (week 1), to March 20, 2016. We conducted the first analytic run for MaxSPRT and CMaxSPRT in week 53, which encompassed data from October 4, 2015, to October 2, 2016. All subsequent analyses were conducted at weekly intervals. For reporting purposes, signals detected on the first analytical runs were arbitrarily designated as having occurred in weeks 25 (ESA) and 53 (MaxSPRT and CMaxSPRT), respectively. The analyses were delayed to allow for development of the analytic infrastructure.

Signal Investigations

In general, follow-up of a signal entailed 1 or more additional evaluations to determine if the signal was an indicator of increased risk. These included data quality assessments, use of temporal scan statistics,[25] medical record reviews to validate the adverse event, and a self-controlled risk interval (SCRI) analysis.[26] No follow-up investigations were conducted for syncope, injection site reactions, and nonspecific reactions because associations were expected based on 9vHPV clinical trials[27] and clinical or observational studies of 4vHPV.[28,29]

All analyses were conducted by using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Study Population

Over the 2-year study period, we observed 838 991 doses of 9vHPV vaccine administered among the VSD population. Of 638 947 (76.2%) doses administered among individuals aged 9 to 17 years, 47.6% of doses were administered among girls. Of 200 044 (23.8%) doses administered among persons aged 18 to 26 years, 64.4% of doses were administered among women. Doses administered to 9- to 17-year-olds increased sharply during August of each year; the counts for 18- to 26-year-olds are relatively constant during the study period (Fig 1).

Historical Comparisons Using MaxSPRT and CMaxSPRT

No signals were observed in the MaxSPRT or CMaxSPRT analyses for anaphylaxis, appendicitis, CIDP, GBS,

seizure, stroke, or VTE (Tables 1, 2, and 3, and Suplemental Tables 4 and 5). In week 71, the MaxSPRT analysis identified a statistical signal for pancreatitis among men 18 to 26 years old after any dose. There were 8 exposed cases of pancreatitis in this subgroup; the RR was 3.1 ($P <$ .05, Table 2). No pancreatitis statistical signal was observed in the CMaxSPRT analysis (RR = 1.9, $P >$ .05). Pancreatitis was also evaluated using ESA; the RR was elevated but not statistically significant (RR = 4.7, $P =$ .47).

Medical record review determined that 7 of the 8 pancreatitis cases were either not incident ($n = 2$) or were attributed to causes other than vaccination ($n = 5$). The one confirmed case had no known risk factors for pancreatic disease. Consequently, the pancreatitis statistical
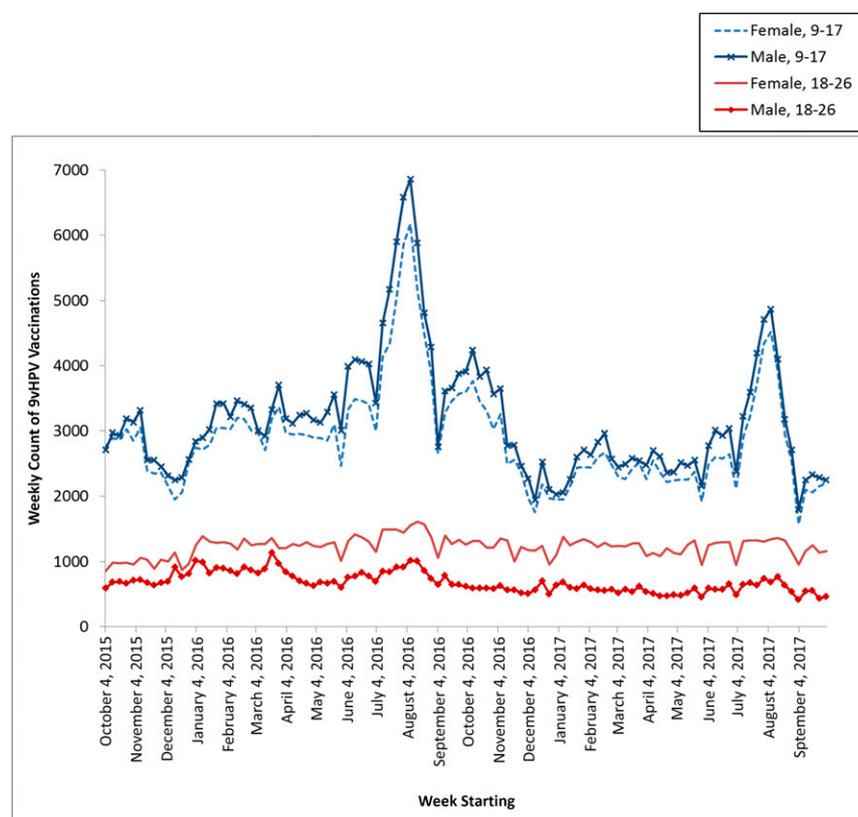

FIGURE 1
Histogram of weekly counts of 9vHPV vaccinations administered in the VSD population from the week starting on October 4, 2015, through the week starting on October 1, 2017, by age and sex.

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TABLE 2 Summary of Uncommon Adverse Events in Selected Subgroups Evaluated With Historical Comparison Groups Using MaxSPRT and CMaxSPRT

AE	Type of SPRT Analysis[a]	Subgroup, Sex, Age Group in y	No. Observed Vaccinations	No. Observed AE	No. Comparator Vaccinations, Historical Period	No. AEs in the Historical Period	No. Expected AEs	RR	Test Statistic	Critical Value[b]	Signal
Anaphylaxis	Maximized	Male, 9–17	334 381	0	—	—	0.9	0	0	2.7	No
	CMax	Male, 9–17	334 381	0	1 053 642	2	—	0	0	2.6	No
Appendicitis	Maximized	Male, 9–17	78 885	33	—	—	25.6	1.3	0.97	3.5	No
	CMax	Male, 9–17	78 885	33	1 053 642	312	—	1.4	1.6	3.8	No
GBS	Maximized	Female, 18–26	128 645	0	—	—	0.6	0	0	2.6	No
	CMax	Female, 18–26	128 645	0	431 401	3	—	0	0	2.7	No
Pancreatitis	Maximized	Male, 18–26	51 944	8	—	—	2.6	3.1	3.7	2.9	Yes
	CMax	Male, 18–26	51 944	8	349 966	29	—	1.9	1.1	3.4	No
Seizures	Maximized	Female, 9–17	304 384	44	—	—	115.2	0.4	0	3.8	No
	CMax	Female, 9–17	304 384	44	698 263	105	—	1.0	0	3.7	No
Stroke	Maximized	Female, 18–26	128 645	5	—	—	4.9	1.0	0	2.9	No
	CMax	Female, 18–26	128 645	5	431 401	11	—	1.5	0.3	2.9	No
VTE	Maximized	Female, 18–26	128 645	8	—	—	9.8	0.8	0	3.1	No
	CMax	Female, 18–26	128 645	8	431 401	54	—	0.5	0	3.4	No

Results were extracted from the final report (week starting October 1, 2017) for all events except for pancreatitis, which comes from the week when it first signaled (week 71). CIDP was not included because there were no events during the study period. AE, adverse event; CMax, conditional maximized; SPRT, sequential probability ratio test; —, not applicable.

[a] MaxSPRT: analyses were conducted in combination with the general VSD population historic comparison group (2007–2014). CMaxSPRT: analyses were conducted in combination with the historic VSD population vaccinated with comparator vaccines (2007–2014).

[b] Critical values are threshold values of the test statistic above, in which the null hypothesis would be rejected.

signal was classified as a false-positive.

Concurrent Comparisons Using ESA

A total of 12 statistical signals were identified for 5 types of adverse events in the ESA analysis: appendicitis, allergic reaction, injection site reaction, syncope, and nonspecific reactions (Table 3). No signals were detected for anaphylaxis, CIDP, GBS, pancreatitis, seizure, stroke, or VTE.

Appendicitis

A statistical signal for appendicitis was observed in week 84 among boys 9 to 17 years old after the third dose of 9vHPV (RR = 2.1, P = .03). Medical record reviews were performed for patients vaccinated with 9vHPV, and all 30 were confirmed to be acute appendicitis within 42 days postvaccination. A temporal scan analysis revealed no statistically significant clustering within the 42-day postvaccination risk interval (Fig 2); the P value for the various scan widths ranged from .78 to .98. RRs for appendicitis ranged from 1.4 to 1.5 among other dose-specific subgroups, but none were statistically significant

(Table 3). There were no statistical signals for appendicitis in either the MaxSPRT or CMaxSPRT analyses.

SCRI analysis of the appendicitis signal was conducted to further assess its validity. The 1- to 42-day risk interval was compared with the control interval of 43 to 84 days postvaccination within the same person. Of the 30 cases that were identified and reviewed from the control interval, 2 cases were not confirmed and 4 were reclassified because onset occurred within the 1- to 42-day risk interval. The rate ratio of appendicitis after 9vHPV was 1.4 (95% confidence interval = 0.8–2.6). The appendicitis statistical signal was classified as a false-positive because 2 of 3 sequential analytic methods did not signal, there was no temporal clustering, and SCRI analysis failed to confirm the association.

Allergic Reaction

We separately assessed allergic reactions occurring in the outpatient setting and in ED and inpatient settings. The first of 3 statistical

signals was observed in the ED or inpatient setting after any 9vHPV dose among girls 9 to 17 years old (RR = 2.7, P = .04). Medical record review identified a possible vaccine-related allergic reaction in 8 (31%) of 26 cases. The most common reasons for nonconfirmation of the diagnosis included injection site reaction (n = 7) and miscoding (n = 4). There was no analogous signal in the outpatient setting (RR = 0.85, P = .75).

The second statistical signal for allergic reactions followed the second dose of 9vHPV among women 18 to 26 years old in the outpatient setting (RR = 1.9, P = .04). Medical records were reviewed for 14 of 15 vaccinated cases, and 6 (43%) were determined as possibly vaccine related. There was no analogous signal for allergic reaction in the ED or inpatient setting (RR = 0.4, P = .75).

The third allergic reaction statistical signal was in the ED or inpatient setting after the first dose of 9vHPV among girls 9 to 17 years old (RR = 2.8, P = .04). This signal included 17 vaccinated cases. Medical record reviews were not conducted for this

TABLE 3 Summary of Common Adverse Events Using ESA in Subgroups Evaluated With the Concurrent Comparison Group

Adverse Event	Subgroup, Sex, Age Group in y, 9vHPV Dose	Week When First Signaled	No. 9vHPV Vaccinations in Subgroup	No. Total Cases[a]	No. Exposed Cases[a]	RR	P
Allergic reaction[b]	Female, 9–17, ED or inpatient, any	82	242 726	33	26	2.7	.04
	Female, 9–17, outpatient, any	No signal[c]	242 726	86	60	0.8	.75
	Female, 9–17, ED or inpatient, dose 1	94	109 896	26	17	2.8	.04
	Female, 9–17, outpatient, dose 1	No signal[d]	109 896	82	50	1.2	.28
	Female, 18–26, outpatient, dose 2	86	33 118	38	15	1.9	.04
	Female, 18–26, ED or inpatient, dose 2	No signal[e]	33 118	8	1	0.4	.92
Appendicitis[f]	Male, 9–17, dose 3	84	73 122	50	30	2.1	.03
	Male, 9–17, any	No signal[g]	271 679	103	81	1.5	.09
	Male, 9–17, dose 1	No signal[g]	106 741	47	25	1.4	.23
	Male, 9–17, dose 2	No signal[g]	91 156	47	26	1.5	.23
Injection site reaction	Male, 9–17, dose 3	26	23 409	29	18	2.5	.03
Nonspecific reaction	Male, 18–26, dose 3	25	4054	3	2	95.0	.04
	Male, 18–26, dose 1	34	13 228	14	9	11.1	.04
	Female, 18–26, dose 1	50	26 711	71	34	1.7	.03
	Female, 18–26, any	105	128 806	215	126	1.3	.04
Syncope	Female, 18–26, any	25	28 234	98	67	1.8	.007
	Female, 18–26, dose 1	25	12 245	65	35	2.0	.004
	Female, 18–26, dose 2	31	10 924	60	25	1.7	.04

Results were extracted from the report for the week when the adverse event first signaled. NS, no signal.

[a] Cases in a specific subgroup are only counted for analytic strata with ≥1 case (either exposed or not), ≥1 9vHPV vaccine, and ≥1 comparator vaccine, in which analytic strata are defined by age (in 1-y increments), site, sex, and week of the vaccination visit.

[b] Diagnoses were made in the ED or inpatient setting or in the outpatient setting.

[c] No signal was detected for this subgroup. Data were extracted from the report for the week when allergic reaction signaled for girls 9 to 17 y old with any dose in the ED or inpatient setting.

[d] No signal was detected for this subgroup. Data were extracted from the report for the week when allergic reaction signaled for girls 9 to 17 y old with dose 1 in the ED or inpatient setting.

[e] No signal was detected for this subgroup. Data were extracted from the report for the week when allergic reaction signaled for women 18 to 26 y old with dose 2 in the outpatient setting.

[f] Appendicitis was classified as an uncommon adverse event in this study, but a statistical signal was detected with ESA, and it is therefore included here.

[g] No signal was detected for this subgroup. Data were extracted from the report for the week when appendicitis signaled for boys 9 to 17 y old with dose 3.

subgroup given the low predictive value of allergic reaction diagnosis codes demonstrated in the 2 previous allergic reaction statistical signals, including the first signal, which was also in the ED or inpatient setting and in the same age and sex group. There was no analogous signal in the outpatient setting (RR = 1.2, P = .28).

The allergic reaction statistical signals were classified as false-positives because signals were only observed in ESA analyses; discordant results were observed in outpatient, ED, and inpatient settings; and most cases were not confirmed by record review.

Syncope, Injection Site Reaction, and Nonspecific Reaction

There was a signal for syncope in multiple subgroups of women 18 to 26 years old; the RRs were ≤2.0 in each of these subgroups (Table 3). There was one statistical signal for injection site reaction among boys 9 to 17 years old; the RR was 2.5 (P = .03). There was a signal for nonspecific reactions among several subgroups. Men 18 to 26 years old signaled after dose 3; the RR was 95.0, but there were only 3 cases, 2 of which were exposed. The risk estimates dropped sharply over the subsequent weeks, reaching 2.5 with 6 exposed cases in week 79. The statistical signal among men 18 to 26 years old after dose 1 behaved similarly. No follow-up investigations were conducted for syncope, injection site reaction, or nonspecific reactions because they were expected based on clinical trials of 9vHPV, clinical experience with 4vHPV,[27,30] and because the diagnoses were unlikely to indicate a serious adverse event.

DISCUSSION

After 2 years of surveillance and nearly 839 000 administered doses of 9vHPV in the VSD population, we did not identify any new safety concerns from a group of prespecified adverse events. RCA methodology allows rapid, near real-time assessment to identify potential safety concerns, but it is based on unconfirmed electronic diagnosis coded outcomes. In this framework, false-positive statistical signals are expected and further investigation is conducted to determine if a statistical signal represents a valid safety concern. During the surveillance period, there were several statistical signals, but they were either expected on the basis of prelicensure trials or classified as false-positives after further investigation.

Although pancreatitis has not been identified as a safety concern in any prelicensure studies of 9vHPV, we included it as an adverse event because a temporal association between pancreatitis and 4vHPV was
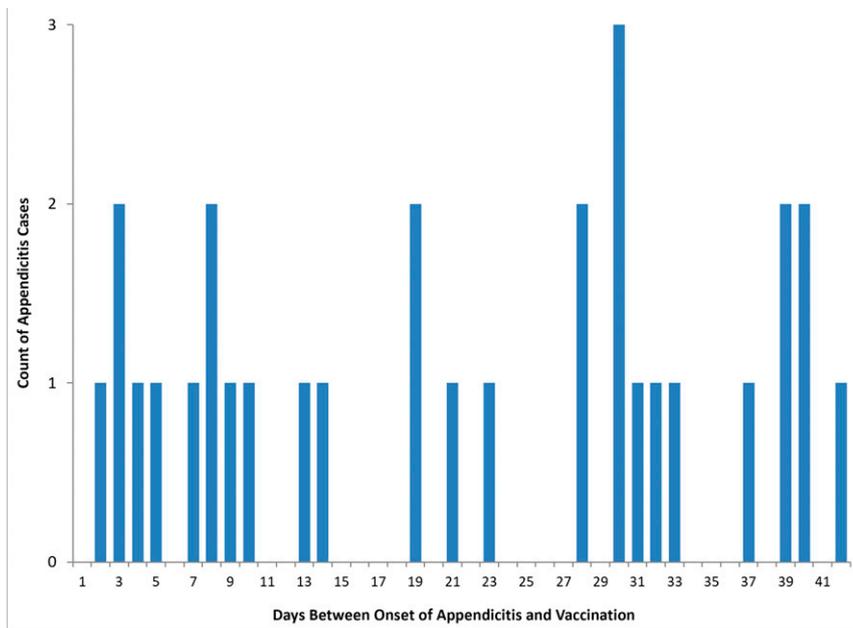
FIGURE 2
Distribution of days to onset of appendicitis in the 42-day risk window after administration of 9vHPV vaccine among boys 9 to 17 years old.

described in 2 case reports.[31,32] Additionally, in a Vaccine Adverse Event Report System study, researchers reported 9 cases after 4vHPV vaccination,[33] although the postvaccination reporting rate was not greater than expected. In our analyses, the pancreatitis statistical signal was not confirmed after further investigation.

Appendicitis was the most frequent serious adverse event (excluding fetal loss) in a pivotal prelicensure trial of 9vHPV, although none of the cases were vaccine related.[9,34] Our results are similar to the VSD study of 4vHPV, which also identified a signal for appendicitis, but a causal association was judged unlikely after further analysis.[12]

Preliminary statistical signals for allergic reactions were detected in 3 subgroups. However, we concluded that these signals represented false-positives because medical record reviews failed to confirm most cases. Our findings are consistent with prelicensure clinical trials in which serious allergic reactions were rare.[35]

We detected preliminary statistical signals for syncope in 18- to 26-year-old women, but not in younger girls, a group in which higher rates of syncope have been reported.[36] Our results are in general agreement with both cohort and passive surveillance studies in which researchers have found associations between 4vHPV and vasovagal syncope, particularly among adolescents.[29,33] In contrast, the previous VSD study of 4vHPV, in which researchers used analytic methods and comparison groups similar to ours, did not find an association.[12]

In previous VSD studies, researchers have assessed the risk of VTE after the 4vHPV vaccine. In the RCA analysis, researchers found a nonstatistically significant elevated risk of VTE (RR = 1.98) among girls 9 to 17 years old after receipt of 4vHPV.[12] In a follow-up study, researchers determined that VTE risk among 9- to 26-year-old males and females in the VSD population was not elevated after 4vHPV

exposure.[37] In our analysis of 9vHPV, we observed 4 VTE cases among girls 9 to 17 years old but no signal.

Our study is subject to a number of limitations. Presumptive cases were identified by using coded diagnoses, but the validity of electronic diagnosis codes varies substantially[38]; diagnoses were validated by medical record review for some statistical signals but not for others. Although sequential methods accounted for weekly testing within a subgroup, they did not account for the number of tests performed each week across subgroups (ie, examining many subgroups increases the likelihood of a false-positive signal). We chose to enhance the sensitivity of our analyses with the understanding that it would require additional investigation to rule out false-positives. Finally, despite the large size of the VSD population, this analysis had limited power to detect signals for rare adverse events, such as GBS.

With this large observational study, we contribute reassuring postlicensure data that will help bolster the safety profile of 9vHPV. We documented nearly 839 000 9vHPV doses administered over 2 years and did not identify any new safety concerns. Although we detected several unexpected potential safety signals, none were confirmed after further evaluation. Our findings are consistent with prelicensure clinical trials, which have determined that 9vHPV, similar to 4vHPV, has a favorable safety profile.[9,10,35]

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ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices
CIDP: chronic inflammatory demyelinating polyneuropathy
CMaxSPRT: conditional maximized sequential probability ratio test
ED: emergency department
ESA: exact sequential analysis
GBS: Guillain-Barré Syndrome
HPV: human papillomavirus
ICD-10: *International Classification of Diseases, 10th Revision*
MaxSPRT: maximized sequential probability ratio test
RCA: Rapid Cycle Analysis
RR: relative risk
SCRI: self-controlled risk interval
VSD: Vaccine Safety Datalink
VTE: venous thromboembolism
4vHPV: 4-valent human papillomavirus vaccine
9vHPV: 9-valent human papillomavirus vaccine

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