Supplemental Information

ANALYTICAL METHODS

The following is a detailed description of analytical methods used for this study .

MAXSPRT

The Poisson-based MaxSPRT analyses used the historical general VSD population as the unexposed comparison group. A subgroup-specific RR was computed every week based on the observed rate of a specific adverse event in the risk interval after 9vHPV vaccination, and the expected rate for that subgroup derived from the comparison group. The test statistic to assess the one-sided statistical significance of the RR was the log-likelihood ratio. If the test statistic exceeded a predefined critical value, the null hypothesis of no elevated risk was rejected, which was termed a "signal" in this study.[22] The maximum length of surveillance ("upper limit") was expressed in terms of the expected number of events under the null hypothesis and was derived from person-time-based background rates and estimated 9vHPV doses during the surveillance period.[22] On the basis of experience from previous VSD RCA studies, the upper limit used in the analyses was the computed upper limit inflated by 20%. This step was undertaken to reduce the likelihood that the upper limit would be reached without signaling before the end of the study period. Formal analysis continued until (1) the test statistic exceeded the critical value (ie, a signal), (2) the total number of observed adverse events in the risk interval reached the upper limit, or (3) the study period ended.

CMAXSPRT

CMaxSPRT, which was used for analyses employing the historical vaccinated VSD population, was developed as an extension of MaxSPRT. In addition to accounting for the uncertainty in the surveillance population and preserving the type I error rate, it further accounts for uncertainty in estimating the historical comparator rates instead of treating them as known.[23] CMaxSPRT analyses was used to compare adverse events in the risk window after 9vHPV with adverse events in the risk window for comparator vaccines administered during the historical period. CMaxSPRT analyses were precluded in subgroups in which there were no events in the risk window in the historical period; this was mainly observed for CIDP but also 1 subgroup each for anaphylaxis and GBS.

ESA

All adverse events under study were evaluated by using ESA with a concurrent comparison group. This method was employed for the sequential analysis of more-common adverse events and has been used previously in the VSD.[12,24] ESA was conducted weekly for each age group, sex, and dose subgroup for each adverse event. Within each subgroup, analytic strata defined by age (in 1-year increments), site, sex, and week of the vaccination visit were created. Each analysis was conditioned on the number of adverse events identified within the strata up to that point. ESA includes all available exposed and unexposed subjects. The exposed versus unexposed breakdown of adverse events is analyzed such that the adverse events are treated as independent Bernoulli trials with the probability of an unexposed event equal to the proportion of persons in the given stratum who were unexposed. A signal is declared when the 1-sided binomial *P* value is equal to or less than a threshold value on the basis of an α spending plan that accounts for multiple analyses of data that accumulate during the study period.[39] For this analysis, we computed Mantel Haenszel RRs from the counts in the exposed and unexposed groups.

SUPPLEMENTAL TABLE 4 ICD-10 Codes Used To Identify Potential Adverse Events Associated With 9vHPV Administration in the VSD

Adverse Event	ICD-10 Code[a]	Code Description
Allergic reactions	L50.0	Allergic urticaria
	L50.1	Idiopathic urticaria
	L50.9	Urticaria, unspecified
	T50.905	Adverse effect of unspecified drugs, medicaments, and biological substances
	T50.B95	Adverse effect of other viral vaccines
	T50.Z95	Adverse effect of other vaccines and biological substances
	T78.3	Angioneurotic edema
	T78.4	Other and unspecified allergy
Anaphylaxis	T78.2	Anaphylactic shock, unspecified
	T88.6	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered
	T80.52	Anaphylactic reaction due to vaccination
Appendicitis	K35	Acute appendicitis
	K37	Unspecified appendicitis
	K36	Other appendicitis
	K38.8	Other specified diseases of appendix
CIDP	G61.81	Chronic inflammatory demyelinating polyneuritis
GBS	G61.0	Guillain-Barre syndrome
Injection site reactions	L02.413	Cutaneous abscess of right upper limb
	L02.414	Cutaneous abscess of left upper limb
	L02.419	Cutaneous abscess of limb, unspecified
	L02.423	Furuncle of right upper limb
	L02.424	Furuncle of left upper limb
	L02.429	Furuncle of limb, unspecified
	L02.433	Carbuncle of right upper limb
	L02.434	Carbuncle of left upper limb
	L02.439	Carbuncle of limb, unspecified
	L02.91	Cutaneous abscess, unspecified
	L02.92	Furuncle, unspecified
	L02.93	Carbuncle, unspecified
	L03.113	Cellulitis of right upper limb
	L03.114	Cellulitis of left upper limb
	L03.119	Cellulitis of unspecified part of limb
	L03.123	Acute lymphangitis of right upper limb
	L03.124	Acute lymphangitis of left upper limb
	L03.129	Acute lymphangitis of unspecified part of limb
	L03.818	Cellulitis of other sites
	L03.898	Acute lymphangitis of other sites
	L03.9	Cellulitis and acute lymphangitis, unspecified
	L04.2	Acute lymphadenitis of upper limb
	L04.8	Acute lymphadenitis of other sites
	L04.9	Acute lymphadenitis, unspecified
	L08.9	Local infection of the skin and subcutaneous tissue, unspecified
	M79.89	Other specified soft tissue disorders
	M79.601	Pain in right arm
	M79.602	Pain in left arm
	M79.603	Pain in arm, unspecified
	M79.609	Pain in unspecified limb
	M79.62	Pain in upper arm
	M79.63	Pain in forearm
	I88.8	Other nonspecific lymphadenitis
	I88.9	Nonspecific lymphadenitis, unspecified
	R59	Enlarged lymph nodes
Nonspecific reactions	T80.29	Infection following other infusion, transfusion, and therapeutic injection
	T88.0	Infection following immunization
	T88.1	Other complications following immunization, not elsewhere classified
	T88.7	Unspecified adverse effect of drug or medicament
	T88.9	Complication of surgical and medical care, unspecified
	T50.905	Adverse effect of unspecified drugs, medicaments, and biological substances
	T50.995	Adverse effect of other drugs, medicaments, and biological substances
	T50.B95	Adverse effect of other viral vaccines

SUPPLEMENTAL TABLE 4 Continued

Adverse Event	ICD-10 Code[a]	Code Description
	T50.Z95	Adverse effect of other vaccines and biological substances
Pancreatitis	K85.0	Idiopathic acute pancreatitis
	K85.1	Biliary acute pancreatitis
	K85.3	Drug-induced acute pancreatitis
	K85.8	Other acute pancreatitis
	K85.9	Acute pancreatitis, unspecified
	K86.9	Disease of pancreas, unspecified
Seizure	G40.501	Epileptic seizures related to external causes, not intractable, with status epilepticus
	G40.509	Epileptic seizures related to external causes, not intractable, without status epilepticus
	G40.89	Other seizures
	R56.0	Febrile convulsions
	R56.9	Unspecified convulsions
Stroke	G45.0	Vertebro-basilar artery syndrome
	G45.1	Carotid artery syndrome (hemispheric)
	G45.2	Multiple and bilateral precerebral artery syndromes
	G45.8	Other transient cerebral ischemic attacks and related syndromes
	G45.9	Transient cerebral ischemic attack, unspecified
	G46	Vascular syndromes of brain in cerebrovascular diseases
	I63	Cerebral infarction
	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
	I67.2	Cerebral atherosclerosis
	I67.81	Acute cerebrovascular insufficiency
	I67.82	Cerebral ischemia
	I67.84	Cerebral vasospasm and vasoconstriction
	I67.89	Other cerebrovascular disease
	I67.9	Cerebrovascular disease, unspecified
	I68.0	Cerebral amyloid angiopathy
	I68.8	Other cerebrovascular disorders in diseases classified elsewhere
Syncope	R55	Syncope and collapse
	I95.2	Hypotension due to drugs
	I95.81	Postprocedural hypotension
	I95.89	Other hypotension
	I95.9	Hypotension, unspecified
VTE	I26	Pulmonary embolism
	I82.0	Budd-Chiari syndrome
	I82.1	Thrombophlebitis migrans
	I82.210	Acute embolism and thrombosis of superior vena cava
	I82.220	Acute embolism and thrombosis of inferior vena cava
	I82.290	Acute embolism and thrombosis of other thoracic veins
	I82.3	Embolism and thrombosis of renal vein
	I82.4	Acute embolism and thrombosis of deep veins of lower extremity
	I82.6	Acute embolism and thrombosis of veins of upper extremity
	I82.81	Embolism and thrombosis of superficial veins of lower extremities
	I82.890	Acute embolism and thrombosis of other specified veins
	I82.90	Acute embolism and thrombosis of unspecified vein
	I82.A1	Acute embolism and thrombosis of axillary vein
	I82.B1	Acute embolism and thrombosis of subclavian vein
	I82.C1	Acute embolism and thrombosis of internal jugular vein

[a] *International Classification of Diseases* codes include all subcodes.

SUPPLEMENTAL TABLE 5 Background Incidence Rates of Uncommon Adverse Events

Adverse Event	Sex	Age, y	Incidence Rate, per 100 000 PY
Anaphylaxis	Female	9–17	32.0
	Female	18–26	39.9
	Male	9–17	33.3
	Male	18–26	21.0
Appendicitis	Female	9–17	207.4
	Female	18–26	231.0
	Male	9–17	287.1
	Male	18–26	256.1
CIDP	Female	9–10	0.2
	Female	11–14	0.2
	Female	15–17	0.4
	Female	18–26	0.5
	Male	9–10	0.1
	Male	11–14	0.2
	Male	15–17	0.5
	Male	18–26	0.7
GBS	Female	9–10	2.6
	Female	11–14	2.4
	Female	15–17	3.4
	Female	18–26	4.4
	Male	9–10	2.4
	Male	11–14	3.3
	Male	15–17	5.4
	Male	18–26	5.1
Pancreatitis	Female	9–17	19.8
	Female	18–26	80.5
	Male	9–17	14.0
	Male	18–26	48.6
Stroke	Female	9–17	14.4
	Female	18–26	32.6
	Male	9–17	14.4
	Male	18–26	25.3
VTE	Female	9–17	10.0
	Female	18–26	67.6
	Male	9–17	9.1
	Male	18–26	44.1

Rates were derived from the VSD population (ages 9–26 y) over the period of 2007 to 2014. PY, person years.

SUPPLEMENTAL REFERENCES

39. Lan KG, DeMets D. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70:659–663