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Safety of the 9-Valent Human Papillomavirus Vaccine

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Abstract

BACKGROUND: The 9-valent human papillomavirus vaccine (9vHPV) was approved for females and males aged 9 to 26 years in 2014. We analyzed postlicensure surveillance reports to the Vaccine Adverse Event Reporting System (VAERS).

METHODS: We searched VAERS data for US reports of adverse events (AEs) after 9vHPV from December 2014 through December 2017. We calculated reporting rates and conducted empirical Bayesian data mining to identify disproportional reporting. Physicians reviewed reports for selected prespecified conditions.

RESULTS: VAERS received 7244 reports after 9vHPV: 31.2% among females, 21.6% among males, and for 47.2%, sex was not reported. Overall, 97.4% of reports were nonserious. Dizziness, syncope, headache, and injection site reactions were most commonly reported; the most commonly reported AEs were similar between females and males. Two reports of death after 9vHPV were verified; no information in autopsy reports or death certificates suggested a causal relationship with vaccination. Approximately 28 million 9vHPV doses were distributed during the study period; crude AE reporting rates were 259 reports per million 9vHPV doses distributed for

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all reports and 7 per million doses distributed for serious reports. Syncope (a known AE associated with human papillomavirus vaccination) and several types of vaccine administration errors (eg, administered at wrong age) exceeded the statistical threshold for empirical Bayesian data mining findings.

CONCLUSIONS: No new or unexpected safety concerns or reporting patterns of 9vHPV with clinically important AEs were detected. The safety profile of 9vHPV is consistent with data from prelicensure trials and from postmarketing safety data of its predecessor, the quadrivalent human papillomavirus vaccine.

The 9-valent human papillomavirus vaccine (9vHPV) Gardasil9 (Merck & Co) was licensed by the US Food and Drug Administration (FDA) in December 2014 for use in females and males for prevention of vaccine type–associated cervical and other anogenital cancers, precancerous or dysplastic lesions, and genital warts.[1] The 9vHPV is the third human papillomavirus (HPV) vaccine licensed in the United States, following quadrivalent human papillomavirus vaccine (4vHPV) (Merck & Co) in 2006 and bivalent HPV vaccine (GlaxoSmithKline Biologicals) in 2009; however, since 2016, 9vHPV is the only HPV vaccine distributed in the United States. The 9vHPV is a virus-like particle (VLP) vaccine manufactured by using a similar process to its predecessor, 4vHPV; but, 9vHPV has more aluminum-containing adjuvant, more antigen content for some of the 4 VLP types in 4vHPV, and 5 additional VLP types.[2]

The Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination at 11 or 12 years of age, although vaccination can be started at age9 years, with catch-up vaccination through age 26 years for women and 21 years for men. Men 22 to 26 years of age may also be vaccinated.[2–4] ACIP recommends 9vHPV as a 2-dose series for most persons starting the series before their 15th birthday or as a 3-dose series for teens and young adults who start the series at ages 15 years or older and for immunocompromised persons.[2,3] The 9vHPV was FDA approved for individuals aged 9 to 26 years until October 2018, when the age range was expanded to 27 to 45 years.[5] In June 2019, 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.[6]

The safety profile of 4vHPV (the first licensed HPV vaccine) is well established, with postlicensure monitoring and research having provided a substantial body of evidence from the United States and globally.[7–14] From 2006 to 2015, almost all HPV vaccines used in the United States was 4vHPV (>80 million doses distributed). When 9vHPV was studied in multiple prelicensure clinical trials, adverse events (AEs) observed were similar to those for 4vHPV, except for more-frequent reports of injection site swelling and erythema.[1,15–18] We analyzed reports to the Vaccine Adverse Event Reporting System (VAERS) after 9vHPV during its first 3 years of licensure in the United States.

METHODS

Study Population

VAERS is a national spontaneous reporting system for AEs after US-licensed vaccines.[19] It is coadministered by the Centers for Disease Control and Prevention (CDC) and FDA.

VAERS accepts reports from patients, parents, health care providers, vaccine manufacturers, and others. The report form includes information on the vaccinated individual, vaccines administered, and the AE(s) experienced. AEs are coded by using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology.[20] A single VAERS report may be assigned more than 1 MedDRA Preferred Term; MedDRA Preferred Terms are not necessarily medically confirmed diagnoses. Multiple (duplicate) reports on the same person for the same AE are detected by using algorithms and consolidated into a single report for the purpose of analysis. A report is classified as "serious" based on the Code of Federal Regulations if any of the following are documented: hospitalization, prolongation of existing hospitalization, permanent disability, life-threatening illness, congenital anomaly or birth defect, or death.[21] Except for reports submitted by vaccine manufacturers, medical records are routinely requested for reports classified as serious; for reports of death, autopsy reports and death certificates are also requested to ascertain cause of death. Manufacturers are required to conduct appropriate follow-up on their reports, including obtaining and reviewing medical records for serious reports, and to report all AEs that come to their attention to VAERS.[19]

We included US reports received by the VAERS of individuals vaccinated with 9vHPV from December 1, 2014, through December 31, 2017. VAERS is used to conduct routine surveillance as a public health function and is exempt from institutional review board review.

Analytic Design

We conducted descriptive analyses, estimated crude 9vHPV AE reporting rates using vaccine doses distributed, performed clinical reviews of reports for selected prespecified conditions of interest, and conducted disproportionality screening using empirical Bayesian (EB) data mining. Dose number in a vaccination series is often missing or inconsistently reported in VAERS; therefore, we did not analyze 9vHPV data by dose number.

Outcome Measures and Statistical Methods

Data Analysis—We summarized characteristics of reports by serious status, type of reporter, patient age, and time from vaccination to onset of AE symptoms. We stratified by sex and assessed the most common symptoms documented in 9vHPV reports, including reports where other simultaneous vaccinations were given and reports where 9vHPV was administered alone.

AE Reporting Rates for 9vHPV—We calculated crude 9vHPV AE reporting rates for all reports and serious reports by dividing the number of reports by the total number of doses of 9vHPV distributed in the United States from 2014 through 2017. We also calculated crude AE reporting rates for the following prespecified conditions of interest: syncope, anaphylaxis, autoimmune disorders, venous thromboembolism, Guillain-Barré syndrome (GBS), pancreatitis, stroke, postural orthostatic tachycardia syndrome (POTS), complex regional pain syndrome (CRPS), acute disseminated encephalomyelitis (ADEM), transverse myelitis, chronic inflammatory demyelinating polyneuropathy (CIDP), and death (see Supplemental Table 4 for search strategy). Because we were not able to determine doses

distributed for a particular sex, we could not calculate a reporting rate by sex for any AE or for any sex-specific conditions.

Clinical Review of Reports of Selected Prespecified Conditions—Prespecified conditions for clinical review were chosen on the basis of AEs of general interest for vaccine safety, of information from previous HPV vaccine postlicensure studies and surveillance, and of concerns expressed among health care providers and the general public regarding HPV vaccine safety.[7–14,22] Physicians reviewed all reports of anaphylaxis, GBS, POTS, primary ovarian insufficiency (POI) (also known as premature menopause), CRPS, ADEM, transverse myelitis, CIDP, and death (Supplemental Table 4). Reports suggestive of anaphylaxis and GBS were verified by using the Brighton Collaboration criteria.[23,24] Reports suggestive of POTS (hallmark of which is orthostatic symptoms of unknown etiology), CRPS (a rare, poorly understood chronic pain condition), and other selected prespecified conditions were evaluated by using established diagnostic criteria.[25–31] Cause of death was determined from information documented in the autopsy report, death certificate, or medical records.

EB Data Mining—EB data mining is used to address the inherent limitation of absent denominator data (eg, number of overall relevant doses administered) in VAERS by screening for statistically significant disproportional reporting for specific vaccine-AE pairings (ie, 9vHPV–MedDRA Preferred Term pairings). It is the standard method FDA uses to identify disproportional reporting of vaccine-AE pairings.[32] We used published methods and criteria[33,34] to identify vaccine-AE pairings reported at least twice as frequently as expected after 9vHPV in the VAERS database (ie, lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05 ≥2]) compared with all other vaccine-AE pairings in the VAERS database (for US-licensed vaccines only). Clinical reviews were conducted for AEs that exceeded this data mining threshold and had not previously been assessed or identified and characterized in prelicensure clinical trials or other postmarketing studies.

RESULTS

During the analytic period, VAERS received 7244 US reports after 9vHPV (Table 1). Females accounted for 2258 (31.2%) reports, males accounted for 1566 (21.6%) reports, and in 3420 (47.2%) reports, sex was unknown or not reported. Overall, 97.4% of reports were nonserious. In reports in which age was documented (n = 3764), most (n = 2992, 79.5%) described persons aged 9 to17 years. By source of report, 64.2% of reports were submitted to VAERS by the vaccine manufacturer, and 26.8% were submitted by health care providers. Median time from receipt of the 9vHPV to start of symptoms was day 0 (the day of vaccination) and ranged up to 2 years. In74.7% of reports, 9vHPV was given alone. The most frequently coadministered vaccines were meningococcal conjugate (n = 1028 reports); tetanus and diphtheria (Td) or tetanus, diphtheria, and a cellular pertussis (Tdap) (n = 673); and hepatitis A (n = 434). Dizziness, syncope, and headache were the most commonly reported symptoms in nonserious reports (Table 2). Injection site reactions (ie, various combinations of pain, swelling, and erythema) were noted in 17.5% of reports describing female patients, and 18.0% of reports describing male patients. Headache (33.9%),

dizziness(26.9%), and nausea (25.8%) were commonly reported symptoms in serious reports.

AE Reporting Rates for 9vHPV

During the analytic period, 27 996 934 9vHPV doses were distributed in the United States (Merck & Co Inc, personal communication, 2018). The overall crude reporting rate to VAERS was 259 reports per million 9vHPV doses distributed; for serious reports, crude reporting rate was 7 per million. The crude reporting rate for syncope was 26 reports per million doses distributed, and for all other conditions, rates were <1 per million (Table 3).

Clinical Review of Reports of Prespecified Conditions

Anaphylaxis—We identified 9 reports of anaphylaxis[23]: 5 in males and 4 in females. In 5 reports, 9vHPV was given alone; the remaining reports involved simultaneous administration of at least 1 other vaccine, including meningococcal conjugate ($n = 3$); hepatitis A ($n = 2$); tetanus, diphtheria, and pertussis ($n = 1$); and varicella ($n = 1$). Two cases met Brighton criteria level 1 (the highest level of diagnostic certainty) and one met level 2; all had a history of nonanaphylactic hypersensitivity reactions to food or environmental allergens. The remaining reports did not meet Brighton criteria or did not contain sufficient information to make a determination for a diagnosis of anaphylaxis. In 7 of 8 reports in which onset interval was documented, symptoms occurred the day of vaccination.

GBS—We identified 8 reports of GBS[24]: 4 in females, 2 in males, and in 2, sex was not specified. Of these 8 reports, 4 did not meet Brighton criteria for a diagnosis of GBS or did not contain sufficient information to make a determination. The remaining 4 met either Level 1 ($n = 1$) or Level 2 ($n = 3$) Brighton criteria for GBS; all were females with symptom onset in the 1- to 42-day postvaccination window of biological plausibility. The median onset interval from vaccination to start of neurologic symptoms in these 4 cases was 12 days (range: 4–31 days); in 2 reports, 9vHPV was given alone. Three of the 4 reports described a viral respiratory or gastrointestinal illness is described in the 1 to 4 weeks prior to presentation with GBS symptoms.

POTS—We identified 17 reports of POTS,[25] 12 (70.6%) of which did not meet diagnostic criteria or did not contain sufficient information to confirm a diagnosis of POTS. The remaining 5 (29.4%) reports partially met the diagnostic criteria; 4 were in females, median age was 12 years (range: 11–22 years), and median onset interval was 19 days (ranging from the day of vaccination to114 days after vaccination). Comorbid conditions commonly reported included anxiety, chronic headache, attention-deficit/hyperactivity disorder, and thyroid disease.

POI—There were 3 reports that met the search criteria for POI.[27,28] However, all were “hearsay” (ie, secondhand or indirect) reports and had insufficient information to confirm a POI diagnosis.

CRPS—We identified 1 report of a possible case of CRPS[26]: a 13-year-old girl with history of anxiety who experienced perisacral pain that spread to her back and lower extremities the

day after vaccination with 9vHPV. At the time of the report, she continued to experience severe pain and bilateral decreased range of motion and weakness in her lower extremities.

ADEM—We identified 2 reports of ADEM.[29] One report described a boy aged 11 years with no notable medical history who developed fever, dizziness, lethargy, and difficulty walking ~3 weeks after vaccination; MRI scan revealed lesions in the brain and spinal cord consistent with ADEM. Approximately 1 year after the initial report, this patient had recovered from ADEM. The other report described a boy aged 12 years who developed headache, nausea, vomiting, and altered consciousness, but no paralysis or difficulty walking; MRI revealed leptomeningeal inflammation, which (considering his symptoms) was more consistent with aseptic meningitis than ADEM. Per medical records, this patient had improved markedly over the course of his hospital admission and was recovering at time of discharge.

Transverse Myelitis and CIDP—We did not identify any reports of transverse myelitis[30] or CIDP.[31]

Deaths—We identified 7 reports of death after 9vHPV. Five were hearsay reports that did not include any medical information or other documentation that could confirm a death occurred; 9vHPV was the only vaccine reportedly given in these 5 hearsay reports. The remaining 2 death reports were verified by autopsy report or death certificate: a girl aged 14 years who also received simultaneous influenza vaccination and died after dissection of the thoracic aorta 7 days after vaccination, and a boy aged 16 years who received simultaneous hepatitis A vaccination and died of a cerebellar hemorrhage 4 days after vaccination. There was no information in either of these 2 death reports and accompanying documentation to suggest that 9vHPV caused or contributed to the deaths.

EB Data Mining

The MedDRA Preferred Term “syncope” paired with 9vHPV exceeded the EB data mining threshold of EB05 ≥2. Syncope is a known AE for 9vHPV[1] and for injectable vaccines in general,[35] and this finding was not evaluated further. Some other MedDRA Preferred Terms exceeded the threshold (eg, drug administered to patient of inappropriate age and other administration errors) but represent medical errors rather than AEs potentially related to the inherent properties of 9vHPV. No other data mining findings were detected.

DISCUSSION

In our review of 9vHPV reports to VAERS during its first 3 years of licensure (December 2014 to December 2017), we did not detect any unexpected or concerning patterns. The safety profile observed for 9vHPV is consistent with data from the vaccine’s prelicensure clinical trials and is similar to postlicensure safety monitoring data for 4vHPV and bivalent HPV vaccine and for other vaccines administered in this age group (eg, tetanus, diphtheria, and acellular pertussis; meningococcal conjugate; and influenza vaccines).[7,36–39] For 9vHPV, 97.4% of reports to the VAERS were classified as nonserious (versus94.2% for 4vHPV); crude AE reporting rates for all reports and serious reports were 259 and 7 reports per million doses distributed, respectively (versus 327 and 19 reports per million,

respectively, for 4vHPV); and the most frequently reported AEs (dizziness, syncope, headache, nausea, and injection site reactions) were similar to those observed for 4vHPV.[7]

VAERS is a critical early warning system to detect possible safety problems in US-licensed vaccines and is a key component of the US vaccine safety monitoring infrastructure. VAERS has successfully detected clinically important safety signals such as intussusception among recipients of the subsequently discontinued RotaShield rotavirus vaccine[40] and febrile seizures in young children after inactivated influenza vaccine.[41] However, VAERS is subject to the limitations of spontaneous reporting systems in general, which include underreporting, reporting biases, inconsistent quality and completeness of reports, lack of a denominator, and lack of an unbiased and unvaccinated comparison group.[19] Because of such limitations, VAERS data cannot be used to assess risk of AEs and generally cannot be used to determine if a vaccination caused an AE. Crude AE reporting rates using vaccine doses distributed should be interpreted with caution because the actual number of doses administered is not known and the amount of underreporting of AEs is also not known. Limitations notwithstanding, VAERS is a valuable monitoring system to detect potential vaccine safety concerns that might require further assessment in more robust systems.

Despite the comprehensive monitoring and research that have contributed to characterizing the favorable safety profile of HPV vaccines, concerns about AEs continue to be expressed by some members of the public, and even by some health care providers, and could be contributing to suboptimal HPV vaccination coverage.[42,43] Furthermore, nonspecific safety concerns have evolved over time since 4vHPV was first licensed in 2006 and could continue to evolve.[44] Apprehensions about POI, POTS, CRPS, and putative autoimmune or autoinflammatory syndrome induced by adjuvants (ASIA) and their potential associations with HPV vaccination emerged after substantial reassuring postlicensure safety data for 4vHPV were already available.[45] Reports of these late-coming concerns largely originated from outside the mainstream medical community and were amplified among sections of the public through the Internet and social media.[46] However, evidence of serious safety problems from such reports has been decidedly lacking, consisting of temporally associated case reports with a lack of biological plausibility or only weak theoretical plausibility[45,47–49]; for example, autoimmune or autoinflammatory syndrome induced by adjuvants, as proposed, is an ill-defined constellation of general symptoms and disparate illnesses and is not a medically recognized diagnosis.[50] Conversely, public health investigations, surveillance reviews, and epidemiologic studies to date have not confirmed any link between HPV vaccination and several of these emerging safety concerns.[7,22,36,49,51] Recently, in a large epidemiologic study in the CDC's Vaccine Safety Datalink, researchers found no association between receipt of 4vHPV and POI.[52]

Our review of 9vHPV reports to the VAERS revealed that POI, POTS, CRPS, and autoimmune disorders were rarely reported after 9vHPV (Table 3); most reported events did not meet diagnostic criteria or did not contain sufficient information to make a determination on the diagnosis. We did not detect any unusual or unexpected reporting patterns for these conditions or other prespecified conditions of interest; reporting rates were actually lower for 9vHPV compared with a previous 4vHPV analysis.[7] Although we identified a substantial number of reports of syncope, and syncope in association with 9vHPV exceeded the EB data

mining threshold, syncope is a known adverse reaction to HPV vaccination and to any injectable vaccination,[35] and recommendations exist for preventing syncope and AEs resulting from syncope.[53] We identified 2 confirmed deaths after 9vHPV, both of which had causes of death that were not related to vaccination.

CONCLUSIONS

The body of evidence on the safety of 9vHPV now includes prelicensure clinical trial data on >15 000 study subjects,[17] reassuring results from postlicensure near real-time sequential monitoring by the CDC's Vaccine Safety Datalink on ~839 000 doses administered,[54] and our review of VAERS reports over a 3-year period, during which time ~28 million doses were distributed in the United States. We did not identify any unusual or unexpected safety concerns in our review of 9vHPV reports to the VAERS; most (97.4%) reports were nonserious, and AEs were analogous to those observed in the prelicensure clinical trials. The most common types of reported AE symptoms were similar between females and males. The safety profile of 9vHPV is favorable and comparable to that of its predecessor, 4vHPV, produced by the same manufacturer and studied extensively in the United States and abroad.[7–14]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ADEM	acute disseminated encephalomyelitis
AE	adverse event
CDC	Centers for Disease Control and Prevention
CIDP	chronic inflammatory demyelinating polyneuropathy
CRPS	complex regional pain syndrome
EB	Empirical Bayesian
FDA	US Food and Drug Administration
GBS	Guillain-Barré syndrome
HPV	human papillomavirus
MedDRA	Medical Dictionary for Regulatory Activities

POI	primary ovarian insufficiency
POTS	postural orthostatic tachycardia syndrome
VAERS	Vaccine Adverse Event Reporting System
VLP	virus-like particle
4vHPV	quadrivalent human papillomavirus vaccine
9vHPV	9-valent human papillomavirus vaccine

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WHAT'S KNOWN ON THIS SUBJECT:

The 9-valent human papillomavirus vaccine (9vHPV), licensed in 2014, was tested on 15 703 volunteers in prelicensure clinical trials. Its safety profile was similar to the quadrivalent human papillomavirus vaccine (made by the same manufacturer), with slightly more injection site swelling and erythema.

WHAT THIS STUDY ADDS:

Initial postlicensure monitoring of 9vHPV during 2014 through 2017, when ~28 million doses were distributed, did not identify any new or unexpected safety concerns. Health care providers, parents, and patients should be reassured about the safety of 9vHPV.

TABLE 1

Characteristics of 9vHPV Reports to VAERS, 2014–2017

Report Characteristics	Female	Male	Unknown Sex	Total Reports
Total reports, *n*	2258	1566	3420	7244
Serious reports[a,b]	116 (5.1)	65 (4.1)	5 (0.1)	186 (2.6)
9vHPV given alone	1393 (61.7)	736 (47)	3282 (95.7)	5411 (74.7)
Type of reporter, *n* (%)				
Manufacturer	825 (36.5)	432 (27.6)	3393 (99.2)	4650 (64.2)
Health care provider	1071 (47.4)	863 (55.1)	8 (0.2)	1942 (26.8)
Patient or parent	162 (7.2)	92 (5.9)	0	254 (3.5)
Other	200 (8.9)	179 (11.4)	19 (0.6)	398 (5.5)
Age groups, y, *n* (%)				
<9[c]	22 (0.9)	17 (1.1)	45 (1.3)	84 (1.2)
9–17	1434 (63.5)	1165 (74.4)	393 (11.5)	2992 (41.3)
18–26	398 (17.6)	185 (11.8)	48 (1.4)	631 (8.7)
>26[c]	35 (1.5)	13 (0.8)	9 (0.3)	57 (0.8)
Not reported or unknown	369 (16.3)	186 (11.9)	2925 (85.5)	3480 (48)
Median onset from time of vaccination to AE symptoms (range), d[d]	0 (0–527)	0 (0–610)	0 (0–751)	0 (0–751)

[a]Includes hospitalization, prolongation of existing hospitalization, permanent disability, life-threatening illness, congenital anomaly or birth defect, or death as defined in 21CFR600.80.[21]

[b]Includes 4 reports of death in females, 2 reports of death in males, and 1 report of death in an individual of unknown sex.

[c]9vHPV is not approved for children <9 y and was not approved for adults >26 y during the analytic period.

[d]Day 0 is the day of vaccination.

TABLE 2

Most Commonly Reported AEs After 9vHPV to VAERS, 2014–2017

Report Characteristics	*n* (%)		*n* (%)
All 9vHPV Reports			
Nonserious	7058	Serious[a]	186
Dizziness	529 (7.5)	Headache	63 (33.9)
Syncope	488 (6.9)	Dizziness	50 (26.9)
Headache	355 (5.0)	Nausea	48 (25.8)
Injection site pain	316 (4.5)	Fatigue	42 (22.6)
Injection site erythema	314 (4.4)	Pyrexia	35 (18.8)
Females			
Nonserious	2142	Serious[a]	116
Dizziness	303 (14.1)	Headache	41 (35.3)
Syncope	279 (13.0)	Dizziness	37 (31.9)
Headache	211 (9.8)	Nausea	31 (26.7)
Injection site pain	193 (9.0)	Fatigue	29 (25.0)
Nausea	181 (8.4)	Asthenia	27 (23.3)
Males			
Nonserious	1501	Serious[a]	65
Dizziness	213 (14.2)	Headache	21 (32.3)
Syncope	182 (12.1)	Nausea	17 (26.2)
Injection site erythema	153 (10.2)	Vomiting	16 (24.6)
Headache	141 (9.4)	Pyrexia	14 (21.5)
Pyrexia	132 (8.8)	Fatigue	13 (20.0)

Based on MedDRA Preferred Terms; a single report may be assigned more than 1 MedDRA Preferred Term (ie, not mutually exclusive).

[a]As defined in 21CFR600.80.[21]

TABLE 3

Crude AE Reporting Rates (per 1 Million 9vHPV Doses Distributed) in VAERS, 2014–2017

Report Type or AE	*n* (Reporting Rate per 1 Million Doses Distributed[a])
Report type	
All reports	7244 (259)
Serious reports[b]	186 (7)
AE[c,d]	
Syncope	722 (26)
POTS	17 (0.6)
Autoimmune disorders	13 (0.5)
Anaphylaxis[e]	9 (0.3)
GBS[e]	8 (0.3)
Venous thromboembolism	8 (0.3)
Death[e]	7 (0.3)
POI	3 (N/A)[f]
Stroke	2 (0.07)
ADEM	2 (0.07)
CRPS	1 (0.04)
Pancreatitis	1 (0.04)
Transverse myelitis	0 (0)
CIDP	0 (0)

N/A, not applicable.

[a] Estimated 27 996 934 9vHPV doses distributed in the United States from 2014 through 2017 (Merck & Co, Inc, personal communication, 2018).

[b] As defined in 21CFR600.80.[21]

[c] A single report may contain more than 1 AE (ie, not mutually exclusive).

[d] See Supplemental Table 4 for MedDRA Preferred Terms used to identify prespecified conditions.

[e] Confirmed cases after clinical review of reports are as follows: anaphylaxis (*n* = 3), GBS (*n* = 4), death (n = 2).

[f] Not able to calculate reporting rates because of the inability to determine doses distributed for female versus male use; N/A = not available