Post-licensure Surveillance of 9-Valent Human Papillomavirus Vaccine (9vHPV) in the Vaccine Adverse Event Reporting System (VAERS), United States 2014–2017

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INTRODUCTION

- In December 2014, the Food and Drug Administration (FDA) licensed the 9-valent human papillomavirus vaccine (9vHPV)
- The Advisory Committee on Immunization Practices (ACIP) recommended routine use of 9vHPV for females and males aged 9-26 years; ACIP recommends routine vaccination at 11-12 years (can be started at age 9 years), and through age 26 for women and 21 for males [a]
- 9vHPV is similar to the previous available quadrivalent HPV (4vHPV) vaccine; they are both virus-like particle (VLP) vaccines and the process is similar
- 9vHPV was studied in multiple pre-licensure clinical trials and was well-tolerated; adverse events observed were similar to those for 4vHPV, except for more injection site-reactions that were mild to moderate in intensity [b]

[a] MMWR Recomm Rep. 2015, 64(11):300-304
[b] Food and Drug Administration. Product approval information-–package insert: Gardasil 9 (Human papillomavirus 9-valent vaccine, recombinant), US Food and Drug Administration; 2014

OBJECTIVE

To assess the safety of 9vHPV in the Vaccine Adverse Event Reporting System (VAERS), a U.S. national spontaneous reporting system [a]

METHODS

- **VAERS US reports received after 9vHPV**
  - Analytic period: Dec 1, 2014 – Dec 31, 2017
- **Signs, symptoms, and diagnoses coded using Medical Dictionary for Regulatory Activities (MedDRA)**
  - MedDRA code = Preferred Term (PT)
- **Serious reports classified based on Code of Federal Regulations: death, life threatening, hospitalization, prolonged hospitalization, permanent disability, or congenital anomaly/birth defect [21CFR312.32]**
- **Reports and available medical records for pre-specified conditions (anaphylaxis, Guillain-Barré syndrome [GBS], postural orthostatic tachycardia syndrome, complex regional pain syndrome, primary ovarian insufficiency, and death) after 9vHPV were reviewed by physicians**
  - Reports suggestive of anaphylaxis and GBS were classified according to Brighton Collaboration criteria
  - Cause of death verified by autopsy report/death certificate

[a] Shimabukuro T et al. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015;33(36):4398-405

RESULTS

Table 1. Characteristics of 9-valent human papillomavirus vaccine (9vHPV) reports to VAERS among persons vaccinated December 1, 2014 through December 31, 2017

Characteristics	No. (%)
Total reports	7,244
Female	2,258 (31)
Male	1,566 (22)
Unknown	3,420 (47)
Classified as serious [a]	186 (3)
Deaths	7 (<1)
9vHPV given alone	5,411 (75)
Median onset interval [range] [b]	0 days [0-751]
Median age [range]	14 years [0-73]
Type of reporter	
Vaccine manufacturer	4,650 (64)
Healthcare provider	1,942 (27)
Patient/parent	200 (3)
Other	452 (6)

[a] Defined as a report of death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability.
[b] Vaccination day is day 0.

Table 2. Most commonly reported adverse events[a] following 9-valent human papillomavirus vaccine (9vHPV) in VAERS among persons vaccinated December 1, 2014 through December 31, 2017

All	N (%) (n=7,244)	Non-serious	N (%) (n=7,058)	Serious[b]	N (%) (n=186)
Dizziness	579 (8)	Dizziness	529 (7)	Headache	63 (34)
Syncope	517 (7)	Syncope	488 (7)	Dizziness	50 (27)
Headache	418 (6)	Headache	355 (5)	Nausea	48 (26)
Nausea	361 (5)	Injection site pain	316 (4)	Fatigue	42 (23)
Injection site pain	324 (4)	Injection site erythema	314 (4)	Pyrexia (fever)	35 (19)
Pyrexia (fever)	318 (4)	Nausea	313 (4)	Asthenia (weakness)	34 (18)
Injection site erythema	317 (4)	Pyrexia (fever)	283 (4)	Vomiting	33 (18)
Loss of consciousness	299 (4)	Loss of consciousness	273 (4)	Syncope	29 (16)
Injection site swelling	268 (4)	Injection site swelling	266 (4)	Abdominal pain	26 (14)
Pallor	252 (3)	Pallor	235 (3)	Loss of consciousness	26 (14)

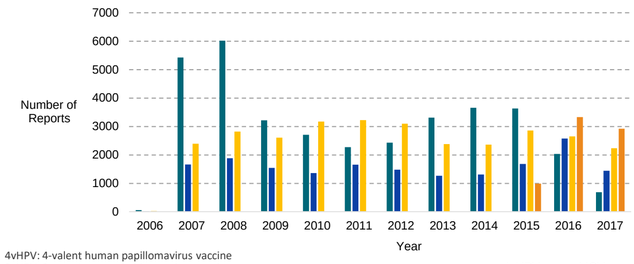
[a] Based on Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms; a single report may be assigned more than one MedDRA Preferred Term (i.e., not mutually exclusive; one report may contain more than one PT name).
[b] Defined as a report of death, life-threatening illness, hospitalization, prolongation of hospitalization, permanent disability, or congenital anomaly/birth defect. [21CFR312.32]

Table 3. Reports of selected pre-specified conditions after 9-valent human papillomavirus vaccine (9vHPV), Vaccine Adverse Event Reporting System (VAERS), 2010-2017

Conditions of historical interest	N	Conditions of recent interest	N
Anaphylaxis Confirmed [a] (3)	9	Postural orthostatic tachycardia syndrome (POTS) Partially met diagnostic criteria [c] (5)	17
Guillain-Barré Syndrome (GBS) Confirmed [b] (4)	8	Primary ovarian insufficiency (POI) Did not met diagnostic criteria [d] (3)	3
Death Verified by autopsy or death certificate (2)	7	Complex regional pain syndrome (CRPS) Possible CRPS [e]; insufficient information	1

[a] Ruggeberg et al. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data Vaccine. 2007 Aug 1;25(31):5675-84
[b] Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011 Jan 10;29(3):599-612
[c] Arana et al. Reports of Postural Orthostatic Tachycardia Syndrome After Human Papillomavirus Vaccination in the Vaccine Adverse Event Reporting System. J Adolescent Health. 2017 Nov;61(5):577-582
[d] The American College of Obstetricians and Gynecologist. Committee on Adolescent Health. Primary Ovarian Insufficiency in Adolescents and Young Adults. Committee Opinion. July 2014 Number 605
[e] Harden et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain. 2010; 150(2):268-274

Figure 1. Reports to VAERS following human papillomavirus, meningococcal, and Tdap vaccines, 2006-2017



4vHPV: 4-valent human papillomavirus vaccine
9vHPV: 9-valent human papillomavirus vaccine
MCV: meningococcal conjugated vaccine
Tdap: tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine

SUMMARY AND CONCLUSIONS

- VAERS received 7,244 reports following 9vHPV; most (97%) were non-serious
- Most frequently reported adverse events after 9vHPV were dizziness, syncope, headache and injection site reactions
- The safety profile of 9vHPV is consistent with data from pre-licensure trials and post-licensure data on 4vHPV
- No new safety signals or unexpected patterns were observed

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the US Food and Drug Administration.

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