

# Safety of the 9-Valent Human Papillomavirus Vaccine

Tom T. Shimabukuro, MD, MPH, MBA,<sup>a</sup> John R. Su, MD, PhD, MPH,<sup>a</sup> Paige L. Marquez, MSPH,<sup>a</sup> Adamma Mba-Jonas, MD, MPH,<sup>b</sup> Jorge E. Arana, MD, MPH,<sup>a</sup> Maria V. Cano, MD, MPH<sup>a</sup>

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 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.



<sup>a</sup>Division of Healthcare Quality Promotion, Immunization Safety Office, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; and <sup>b</sup>Division of Epidemiology, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland

Drs Shimabukuro, Su, Mba-Jonas, Arana, and Cano contributed substantially in the development of the methodological concept and the design of the review, acquisition of data, statistical analysis, interpretation of results, and drafting and revising the manuscript; Ms Lewis contributed substantially in the development of the methodological concept and the design of the review, acquisition of data, statistical analysis, interpretation of results, and drafting and revising the manuscript and performed statistical programming; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Dr Arana's current affiliation is Clinical Safety and Risk Management, Merck Research Laboratories, Merck & Co, North Wales, PA.

The findings and conclusions in this paper 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. The use of product trade names is for identification purposes only.

**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.

**To cite:** Shimabukuro TT, Su JR, Marquez PL, et al. Safety of the 9-Valent Human Papillomavirus Vaccine. *Pediatrics*. 2019;144(6):e20191791

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.<sup>1</sup> 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.<sup>2</sup>

The Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination at 11 or 12 years of age, although vaccination can be started at age 9 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.<sup>2-4</sup> 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.<sup>2,3</sup> 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.<sup>5</sup> 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.<sup>6</sup>

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.<sup>7-14</sup> 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.<sup>1,15-18</sup> 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.<sup>19</sup> 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.<sup>20</sup> 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.<sup>21</sup> 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.<sup>19</sup>

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.<sup>7-14,22</sup> 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.<sup>23,24</sup> 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.<sup>25-31</sup> 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.<sup>32</sup> We used published methods and criteria<sup>33,34</sup> 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 [ $EB05 \geq 2$ ]) 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 to 17 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. In 74.7% 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 acellular 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).

**TABLE 1** Characteristics of 9vHPV Reports to VAERS, 2014–2017

Report Characteristics	Female	Male	Unknown Sex	Total Reports
Total reports, <i>n</i>	2258	1566	3420	7244
Serious reports <sup>a,b</sup>	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, <i>n</i> (%)				
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, <i>y</i> , <i>n</i> (%)				
<9 <sup>c</sup>	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 <sup>c</sup>	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), <i>d</i> <sup>d</sup>	0 (0–527)	0 (0–610)	0 (0–751)	0 (0–751)

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

<sup>b</sup> Includes 4 reports of death in females, 2 reports of death in males, and 1 report of death in an individual of unknown sex.

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

<sup>d</sup> Day 0 is the day of vaccination.

## Clinical Review of Reports of Prespecified Conditions

### Anaphylaxis

We identified 9 reports of anaphylaxis<sup>23</sup>: 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<sup>24</sup>: 4 in females, 2 in males, and in 2, sex was

**TABLE 2** Most Commonly Reported AEs After 9vHPV to VAERS, 2014–2017

Report Characteristics	<i>n</i> (%)		<i>n</i> (%)
All 9vHPV Reports			
Nonserious	7058	Serious <sup>a</sup>	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 <sup>a</sup>	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 <sup>a</sup>	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).

<sup>a</sup> As defined in 21CFR600.80.<sup>21</sup>

**TABLE 3** Crude AE Reporting Rates (per 1 Million 9vHPV Doses Distributed) in VAERS, 2014–2017

Report Type or AE	<i>n</i> (Reporting Rate per 1 Million Doses Distributed <sup>a</sup> )
Report type	
All reports	7244 (259)
Serious reports <sup>b</sup>	186 (7)
AE <sup>c,d</sup>	
Syncope	722 (26)
POTS	17 (0.6)
Autoimmune disorders	13 (0.5)
Anaphylaxis <sup>e</sup>	9 (0.3)
GBS <sup>e</sup>	8 (0.3)
Venous thromboembolism	8 (0.3)
Death <sup>e</sup>	7 (0.3)
POI	3 (N/A) <sup>f</sup>
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.

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

<sup>b</sup> As defined in 21CFR600.80.<sup>21</sup>

<sup>c</sup> A single report may contain more than 1 AE (ie, not mutually exclusive).

<sup>d</sup> See Supplemental Table 4 for MedDRA Preferred Terms used to identify prespecified conditions.

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

<sup>f</sup> Not able to calculate reporting rates because of the inability to determine doses distributed for female versus male use;

N/A = not available

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,<sup>25</sup> 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 to 114 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.<sup>27,28</sup> 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<sup>26</sup>: 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.<sup>29</sup> 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 leptomenigeal 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<sup>30</sup> or CIDP.<sup>31</sup>

### 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  $EB05 \geq 2$ . Syncope is a known AE for 9vHPV<sup>1</sup> and for injectable vaccines in general,<sup>35</sup> 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).<sup>7,36–39</sup> For 9vHPV, 97.4% of reports to the VAERS were classified as nonserious (versus 94.2% 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.<sup>7</sup>

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<sup>40</sup> and febrile seizures in young children after inactivated influenza vaccine.<sup>41</sup> 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.<sup>19</sup> 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.<sup>42,43</sup> Furthermore, nonspecific safety concerns have evolved over time since 4vHPV was first licensed in 2006 and could continue to evolve.<sup>44</sup> 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.<sup>45</sup> 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.<sup>46</sup> 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<sup>45,47–49</sup>; 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.<sup>50</sup> 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.<sup>7,22,36,49,51</sup> Recently, in a large epidemiologic study in the CDC’s Vaccine Safety Datalink, researchers found no association between receipt of 4vHPV and POI.<sup>52</sup>

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.<sup>7</sup> 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,<sup>35</sup> and recommendations exist for preventing syncope and AEs resulting from syncope.<sup>53</sup> 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,<sup>17</sup> reassuring results from postlicensure near real-time sequential monitoring by the CDC's Vaccine Safety Datalink on ~839 000 doses administered,<sup>54</sup> 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.<sup>7-14</sup>

## ACKNOWLEDGMENT

We thank Dr Lauri Markowitz of the CDC for her valuable technical assistance with the analysis and for her helpful comments during the drafting of this article.

## 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

**DOI:** <https://doi.org/10.1542/peds.2019-1791>

Accepted for publication Aug 1, 2019

Address correspondence to Tom T. Shimabukuro, MD, MPH, MBA, Immunization Safety Office, Centers for Disease Control and Prevention (CDC), 1600 Clifton Rd, MS D-26, Atlanta, GA 30329. E-mail: [tshimabukuro@cdc.gov](mailto:tshimabukuro@cdc.gov)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2019 by the American Academy of Pediatrics

**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** No external funding.

**POTENTIAL CONFLICT OF INTEREST:** Dr Arana currently works in Clinical Safety and Risk Management, Merck Research Laboratories, Merck & Co, on matters unrelated to the content of this article. During the time he worked on this article, he was employed by the Centers for Disease Control and Prevention. His work on the article ceased before his employment with Merck; the other authors have indicated they have no potential conflicts of interest to disclose.

**COMPANION PAPER:** Companions to this article can be found online at [www.pediatrics.org/cgi/doi/10.1542/peds.2019-1808](http://www.pediatrics.org/cgi/doi/10.1542/peds.2019-1808) and [www.pediatrics.org/cgi/doi/10.1542/peds.2019-2345](http://www.pediatrics.org/cgi/doi/10.1542/peds.2019-2345).

## REFERENCES

- Merck & Co, Inc. *Gardasil 9 [Package Insert]*. Whitehouse Station, NJ: Merck & Co, Inc; 2014
- Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination - updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2016; 65(49):1405–1408
- Petrosky E, Bocchini JA Jr, Hariri S, et al; Centers for Disease Control and Prevention (CDC). Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2015; 64(11):300–304
- Markowitz LE, Dunne EF, Saraiya M, et al; Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP) [published correction appears in *MMWR Recomm Rep*. 2014;63(49):1182]. *MMWR Recomm Rep*. 2014;63(RR):1–30
- US Food and Drug Administration. Gardasil 9 [approval letter]. 2018. Available at: [www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM622718.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM622718.pdf). Accessed July 23, 2019
- Meites E, Szilagyi PG, Chesson HW, et al. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;68(32):698–702
- Arana JE, Harrington T, Cano M, et al. Post-licensure safety monitoring of quadrivalent human papillomavirus vaccine in the Vaccine Adverse Event Reporting System (VAERS), 2009–2015. *Vaccine*. 2018;36(13):1781–1788
- Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA*. 2009; 302(7):750–757
- Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. *Vaccine*. 2011;29(46):8279–8284
- Arnheim-Dahlström L, Pasternak B, Svanström H, Sparén 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
- Vichnin M, Bonanni P, Klein NP, et al. An overview of quadrivalent human papillomavirus vaccine safety: 2006 to 2015. *Pediatr Infect Dis J*. 2015;34(9): 983–991
- 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
- Scheller NM, Svanström 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
- Gee J, Weinbaum C, Sukumaran L, Markowitz LE. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. *Hum Vaccin Immunother*. 2016;12(6):1406–1417
- Joura EA, Giuliano AR, Iversen OE, et al; Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;372(8):711–723
- Van Damme P, Olsson SE, Block S, et al. Immunogenicity and safety of a 9-valent HPV vaccine. *Pediatrics*. 2015;136(1). Available at: [www.pediatrics.org/cgi/content/full/136/1/e28](http://www.pediatrics.org/cgi/content/full/136/1/e28)
- Moreira ED Jr, Block SL, Ferris D, et al. Safety profile of the 9-valent HPV vaccine: a combined analysis of 7 phase III clinical trials. *Pediatrics*. 2016;138(2): e20154387
- Merck & Co, Inc. *Gardasil [package insert]*. Whitehouse Station, NJ: Merck & Co, Inc; 2006
- Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*. 2015;33(36): 4398–4405
- Medical Dictionary for Regulatory Activities. MedDRA. Available at: [www.meddra.org/](http://www.meddra.org/). Accessed July 23, 2019
- US Food and Drug Administration. Code of Federal Regulations title 21, volume 7 (21CFR600.80). Available at: [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.80](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.80). Accessed July 23, 2019
- European Medicines Agency. (EMA/762033/2015) Pharmacovigilance Risk Assessment Committee. Assessment report: review under article 20 of regulation (EC) No 726/2004, human papillomavirus (HPV) vaccines. 2015. Available at: [https://www.ema.europa.eu/documents/variation-report/silgard-h-c-732-a20-1421-epar-assessment-report-article-20\\_en.pdf](https://www.ema.europa.eu/documents/variation-report/silgard-h-c-732-a20-1421-epar-assessment-report-article-20_en.pdf). Accessed July 23, 2019
- Rüggeberg JU, Gold MS, Bayas JM, et al; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5675–5684
- Sejvar JJ, Kohl KS, Gidudu J, et al; Brighton Collaboration GBS Working Group. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine*. 2011;29(3):599–612
- Raj SR. Postural tachycardia syndrome (POTS). *Circulation*. 2013;127(23): 2336–2342
- Goebel A, Bisla J, Carganillo R, et al. *A Randomised Placebo-Controlled Phase III Multicentre Trial: Low-Dose Intravenous Immunoglobulin Treatment for Long-Standing Complex Regional Pain Syndrome (LIPS Trial)*. Southampton, United Kingdom: NIHR Journals Library; 2017
- Committee opinion no. 605: primary ovarian insufficiency in adolescents and young women. *Obstet Gynecol*. 2014;124(1):193–197
- Nelson LM. Clinical practice. Primary ovarian insufficiency. *N Engl J Med*. 2009;360(6):606–614

29. Pohl D, Alper G, Van Haren K, et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. *Neurology*. 2016;87(9 suppl 2):S38–S45
30. Scott TF, Frohman EM, De Seze J, Gronseth GS, Weinschenker BG; Therapeutics and Technology Assessment Subcommittee of American Academy of Neurology. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2011;77(24):2128–2134
31. Sander HW, Latov N. Research criteria for defining patients with CIDP. *Neurology*. 2003;60(8 suppl 3):S8–S15
32. Martin D, Menschik D, Bryant-Genevier M, Ball R. Data mining for prospective early detection of safety signals in the Vaccine Adverse Event Reporting System (VAERS): a case study of febrile seizures after a 2010-2011 seasonal influenza virus vaccine. *Drug Saf*. 2013; 36(7):547–556
33. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Stat*. 1999;53(3): 177–190
34. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf*. 2002;25(6): 381–392
35. Institute of Medicine. Injection-Related Adverse Events. In: Clayton EW, Rusch E, Ford A, Stratton K, eds. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: The National Academy Press; 2012:620–624
36. Suragh TA, Lewis P, Arana J, et al. Safety of bivalent human papillomavirus vaccine in the US Vaccine Adverse Event Reporting System (VAERS), 2009-2017. *Br J Clin Pharmacol*. 2018;84(12): 2928–2932
37. Chang S, O'Connor PM, Slade BA, Woo EJUS. U.S. Postlicensure safety surveillance for adolescent and adult tetanus, diphtheria and acellular pertussis vaccines: 2005-2007. *Vaccine*. 2013;31(10):1447–1452
38. Myers TR, McNeil MM, Ng CS, et al. Adverse events following quadrivalent meningococcal CRM-conjugate vaccine (Menveo<sup>®</sup>) reported to the Vaccine Adverse Event Reporting System (VAERS), 2010-2015. *Vaccine*. 2017; 35(14):1758–1763
39. Haber P, Moro PL, Lewis P, et al. Post-licensure surveillance of quadrivalent inactivated influenza (IIV4) vaccine in the United States, Vaccine Adverse Event Reporting System (VAERS), July 1, 2013-May 31, 2015. *Vaccine*. 2016;34(22): 2507–2512
40. Centers for Disease Control and Prevention (CDC). Intussusception among recipients of rotavirus vaccine—United States, 1998-1999. *MMWR Morb Mortal Wkly Rep*. 1999; 48(27):577–581
41. Leroy Z, Broder K, Menschik D, Shimabukuro T, Martin D. Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the Vaccine Adverse Event Reporting System. *Vaccine*. 2012;30(11):2020–2023
42. Hanson KE, Koch B, Bonner K, McRee AL, Basta NE. National trends in parental human papillomavirus vaccination intentions and reasons for hesitancy, 2010-2015. *Clin Infect Dis*. 2018;67(7): 1018–1026
43. Lindley MC, Jeyarajah J, Yankey D, et al. Comparing human papillomavirus vaccine knowledge and intentions among parents of boys and girls. *Hum Vaccin Immunother*. 2016;12(6): 1519–1527
44. Markowitz LE, Gee J, Chesson H, Stokley S. Ten years of human papillomavirus vaccination in the United States. *Acad Pediatr*. 2018;18(2S):S3–S10
45. Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K. Safety of human papillomavirus vaccines: an updated review. *Drug Saf*. 2018;41(4): 329–346
46. Kata A. Anti-vaccine activists, Web 2.0, and the postmodern paradigm—an overview of tactics and tropes used online by the anti-vaccination movement. *Vaccine*. 2012;30(25): 3778–3789
47. Hawkes D, Buttery JP. Human papillomavirus vaccination and primary ovarian insufficiency: an association based on ideology rather than evidence. *Curr Opin Obstet Gynecol*. 2016;28(1):70–72
48. Butts BN, Fischer PR, Mack KJ. Human papillomavirus vaccine and postural orthostatic tachycardia syndrome: a review of current literature. *J Child Neurol*. 2017;32(11):956–965
49. Ameratunga R, Gillis D, Gold M, Linneberg A, Elwood JM. Evidence refuting the existence of autoimmune/ autoinflammatory syndrome induced by adjuvants (ASIA). *J Allergy Clin Immunol Pract*. 2017;5(6):1551–1555.e1
50. Mackay IR. Cameos: Candidates and Curiosities. In: Rose NR, Mackay IR, eds. *The Autoimmune Diseases*. San Diego, CA: Academic Press; 2013:1127–1128
51. Arana J, Mba-Jonas A, Jankosky C, et al. Reports of postural orthostatic tachycardia syndrome after human papillomavirus vaccination in the Vaccine Adverse Event Reporting System. *J Adolesc Health*. 2017;61(5): 577–582
52. Naleway AL, Mittendorf KF, Irving SA, et al. Primary ovarian insufficiency and adolescent vaccination. *Pediatrics*. 2018;142(3):e20180943
53. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General best practice guidelines for immunization: best practices guidance of the Advisory Committee on Immunization Practices (ACIP). Available at: [www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf](http://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf). Accessed July 23, 2019
54. Donahue JG, Kieke BA, Lewis EM, et al. Near real-time surveillance to assess the safety of the 9-valent human papillomavirus vaccine. *Pediatrics*. 2019;144(6):e20191808

## Safety of the 9-Valent Human Papillomavirus Vaccine

Tom T. Shimabukuro, John R. Su, Paige L. Marquez, Adamma Mba-Jonas, Jorge E. Arana and Maria V. Cano

*Pediatrics* 2019;144;

DOI: 10.1542/peds.2019-1791 originally published online November 18, 2019;

### Updated Information & Services

including high resolution figures, can be found at:  
<http://pediatrics.aappublications.org/content/144/6/e20191791>

### References

This article cites 43 articles, 5 of which you can access for free at:  
<http://pediatrics.aappublications.org/content/144/6/e20191791#BIBL>

### Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):  
**Infectious Disease**  
[http://www.aappublications.org/cgi/collection/infectious\\_diseases\\_sub](http://www.aappublications.org/cgi/collection/infectious_diseases_sub)  
**Vaccine/Immunization**  
[http://www.aappublications.org/cgi/collection/vaccine:immunization\\_sub](http://www.aappublications.org/cgi/collection/vaccine:immunization_sub)

### Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://www.aappublications.org/site/misc/Permissions.xhtml>

### Reprints

Information about ordering reprints can be found online:  
<http://www.aappublications.org/site/misc/reprints.xhtml>

# American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Safety of the 9-Valent Human Papillomavirus Vaccine**

Tom T. Shimabukuro, John R. Su, Paige L. Marquez, Adamma Mba-Jonas, Jorge E. Arana and Maria V. Cano

*Pediatrics* 2019;144;

DOI: 10.1542/peds.2019-1791 originally published online November 18, 2019;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/144/6/e20191791>

Data Supplement at:

<http://pediatrics.aappublications.org/content/suppl/2019/11/15/peds.2019-1791.DCSupplemental>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2019 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

