Journal of Adolescent Health 61 (2017) 577–582

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Original article

Reports of Postural Orthostatic Tachycardia Syndrome After Human Papillomavirus Vaccination in the Vaccine Adverse Event Reporting System

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Article history: Received May 12, 2017; Accepted August 1, 2017

Keywords: Human papillomavirus (HPV); Human papillomavirus (HPV) vaccine; Postural orthostatic tachycardia syndrome (POTS); Vaccine Adverse Event Reporting System (VAERS); Vaccine safety; Vaccine adverse event

A B S T R A C T

Purpose: Human papillomavirus (HPV) vaccination prevents infections with HPV strains that cause certain cancers. Reports of postural orthostatic tachycardia syndrome (POTS) following HPV vaccination have raised safety concerns. We reviewed POTS reports submitted to the Vaccine Adverse Event Reporting System (VAERS).

Methods: We searched the VAERS database for reports of POTS following any type of HPV vaccination (bivalent, quadrivalent, or nonavalent) from June 2006 to August 2015. We reviewed reports and applied established POTS diagnostic criteria. We calculated unadjusted POTS case reporting rates based on HPV vaccine doses distributed and conducted empirical Bayesian data mining to screen for disproportional reporting of POTS following HPV vaccination.

Results: Among 40,735 VAERS reports following HPV vaccination, we identified 29 POTS reports that fully met diagnostic criteria. Of these, 27 (93.1%) were in females and mean age was 14 years (range 12–32). Median time from vaccination to start of symptoms was 43 days (range 0–407); most (18, 75.0%) had onset between 0 and 90 days. Symptoms frequently reported concomitantly included headache (22, 75.9%) and dizziness (21, 72.4%). Twenty (68.9%) reports documented a history of pre-existing medical conditions, of which chronic fatigue (5, 17.2%), asthma (4, 13.8%), and chronic headache (3, 10.3%) were most common. Approximately one POTS case is reported for every 6.5 million HPV vaccine doses distributed in the United States. No empirical Bayesian data mining safety signals for POTS and HPV vaccination were detected.

IMPLICATIONS AND CONTRIBUTION

Human papillomavirus (HPV) vaccines prevent infection with certain oncogenic HPV types. A rare condition called postural orthostatic tachycardia syndrome (POTS) has emerged as a vaccine safety concern among the public, despite limited epidemiologic evidence. This review found no evidence to suggest a safety problem with POTS following HPV vaccination.

Financial Disclosure: No authors have a conflict of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Conflicts of Interest: None of the authors have any financial or personal relationships to disclose or any conflict of interest.

Statement: This paper contains original unpublished work and is not being submitted for publication elsewhere. Some of the data have been presented at the 19th Annual Conference on Vaccine Research in Baltimore, Maryland, April 2016.

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 (CDC) or the U.S. Food and Drug Administration (FDA). Mention of a product or company name does not constitute endorsement by the CDC or FDA.

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1054-139X/Published by Elsevier Inc. on behalf of Society for Adolescent Health and Medicine.
https://doi.org/10.1016/j.jadohealth.2017.08.004

Conclusions: POTS is rarely reported following HPV vaccination. Our review did not detect any unusual or unexpected reporting patterns that would suggest a safety problem.

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Human papillomavirus (HPV) vaccination prevents infections with HPV strains that cause certain cancers in women and men [1,2]. Three HPV vaccines are currently available: bivalent (types 16 and 18) (2vHPV, Cervarix, 2009); quadrivalent (types 6, 11, 16, 18) (4vHPV, Gardasil, 2006); and nonavalent (types 6, 11, 16, 18, 31, 33, 45, 52, 58) (9vHPV, Gardasil9, 2014). In the United States, vaccination was recommended at age 11 or 12 years for girls in 2006 and for boys in 2011. Most other countries have had female-only vaccination programs. In the United States 4vHPV was the predominant vaccine used (compared to 2vHPV); 9vHPV, licensed in 2014, has since replaced 4vHPV in the United States. Through August 2015, 84,758,822 million doses of HPV vaccines had been distributed in the United States, of which 94.5% was 4vHPV (personal communication, Merck & Co. and GlaxoSmithKline). More than 200 million HPV vaccine doses have been distributed globally [3].

Postural orthostatic tachycardia syndrome (POTS) is characterized by orthostatic intolerance, with variable symptoms of cerebral hypoperfusion upon standing, which are relieved by recumbency [4]. Dizziness, lightheadedness, palpitations, weakness, and fainting are common. The causes of POTS are not known. It occurs more frequently in females and onset tends to be in adolescence to early adulthood [5]. Recent case reports and case series descriptions of POTS occurring in temporal association with HPV vaccination have raised safety concerns with the public, despite a lack of epidemiologic evidence or a biologically plausible mechanism for causality [6–11]. In response, the European Medicines Agency (EMA) conducted a safety review to assess the relationship between HPV vaccination and POTS. In its report published in November 2015, the EMA concluded that the available evidence does not support a causal association between HPV vaccination and POTS [12–14]. To further evaluate this issue, the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) conducted a review of reports of POTS following HPV vaccination submitted to the Vaccine Adverse Event Reporting System (VAERS).

Methods

VAERS is the U.S. spontaneous (i.e., passive) reporting system, co-administered by the CDC and FDA, for monitoring adverse events (AEs) following vaccination [15]. VAERS accepts reports from patients, parents, health-care providers, vaccine manufacturers, and others. Signs and symptoms of AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) terms, a clinically validated, internationally standardized medical terminology [16]. Each VAERS report is reviewed by certified MedDRA coders and a report may be assigned one or more MedDRA Preferred Terms, which are distinct descriptors for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic [17]. Reports are classified as serious based on the Code of Federal Regulations if at least one of the following are reported: death, life-threatening illness, hospitalization, prolongation of hospitalization or permanent disability [18]. For serious nonmanufacturer reports, medical records are routinely requested by VAERS personnel. VAERS is used to conduct routine surveillance as a public health function and does not meet the definition of research; therefore, it is not subject to Institutional Review Board review and informed consent requirements.

We searched the VAERS database from June 1, 2006 through August 31, 2015 for reports of POTS following 2vHPV, 4vHPV, or 9vHPV. The search criteria encompassed MedDRA Preferred Terms "postural orthostatic tachycardia syndrome," "dizziness postural," and "postural reflex impairment." We included domestic (U.S.) and foreign source (non-U.S.) reports.

Review of POTS reports following HPV vaccination

CDC and FDA physicians reviewed POTS reports following HPV vaccination (and medical records if available) identified in the initial VAERS database search. We used diagnostic criteria for POTS established by Raj [19] to determine if the reported event met the case definition for POTS, defined as follows:

(1) A sustained increase in heart rate of ≥30 beats per minute from lying down to a standing-up position (within 10 minutes), in the absence of orthostatic hypotension (for those aged 12–19 years old, this increase should be ≥40 beats per minute);
(2) Symptoms that get worse with standing and improve with recumbence (e.g., rapid palpitations, lightheadedness, chest discomfort, dyspnea, headache, nausea, blurred vision, exercise intolerance, and fatigue);
(3) Presence of orthostatic symptoms lasting for at least 6 months; and
(4) Absence of other overt cause of orthostatic symptoms or tachycardia (e.g., active bleeding, acute dehydration, medications).

Physician reviewers then categorized reports as follows:

(a) Fully met diagnostic criteria (POTS case definition criteria 1, 2, 3, and 4 were met);
(b) Partially met diagnostic criteria (any combination of case definition criteria 1, 2, and 3 met, but insufficient information to assess 4);
(c) Did not meet diagnostic criteria (case definition criteria 4 was not met; or 1, 2, and 3 were not met and there was insufficient information to assess 4);
(d) Insufficient information to establish "fully met," "partially met," or "did not meet" diagnostic criteria for POTS.

We calculated descriptive statistics focused on reports that fully met diagnostic criteria for POTS. We analyzed the data by age, sex, reporter type, U.S. or foreign source report, HPV vaccine type, other vaccinations received, and onset interval from time of HPV vaccination to the start of symptoms. Dose number in a vaccination series is often missing or inconsistently reported in VAERS; therefore, we did not analyze the data by dose number.