Association between Human Papillomavirus (HPV) Vaccination and Autonomic Dysfunction: A Self-Controlled Case Series Analysis

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Background

Although the human papillomavirus (HPV) vaccine prevents papillomavirus infection and subsequent cervical cancer, limited research suggests the development of autonomic dysfunction (AD) subsequent to immunological stressors, including HPV vaccination.

Objective

To investigate the association between receipt of HPV vaccination and development of autonomic dysfunction in girls and young women.

Methods

DATA and STUDY COHORT

A 25% random sample of IQVIA PharMetrics® Plus for Academics claims database from 2016-2020 of 1,654 commercially-insured girls and young women aged 9-26 years who received their first HPV vaccine between 1 January 2017 and 31 December 2019 and experienced an AD outcome during the study period.

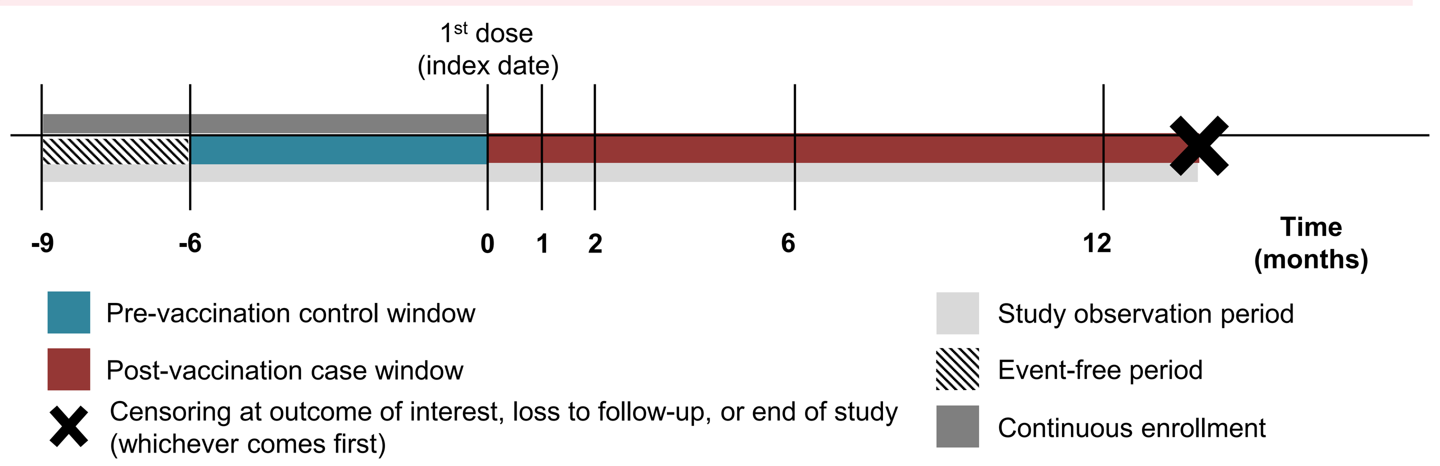
MEASURES

CPT-codes to measure HPV vaccine administration; ICD-10-CM codes based on previously defined symptom clusters and conditions to define AD **(Table 1)**.

ANALYSES

A ***self-controlled case series study*** was used to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) over a maximum case post-vaccination period of 36 months compared to a six-month within-person control pre-vaccination period. In addition to adjusting for age as a time-varying covariate, we conducted analyses stratifying by age (9-17 versus 18-26 years) and number of HPV vaccines received (**Figure 1**).

Figure 1. Illustration of time-window for self-controlled case series



Results

Table 1. Autonomic dysfunction diagnoses: definitions and frequencies pre- and post- vaccine

ICD-10-CM	Definition	Pre-vaccine event, N (%)	Post-vaccine event, N (%)
G90.8	Other disorders of autonomic nervous system	2 (0.5)	4 (0.3)
G90.9	Disorder of autonomic nervous system, unspecified	3 (0.8)	20 (1.5)
I95.1	Orthostatic hypotension	35 (9.3)	127 (9.5)
I47.1	Supraventricular tachycardia	6 (1.6)	36 (2.7)
R00.0	Tachycardia, unspecified	156 (41.4)	570 (42.5)
R00.2	Palpitations	122 (32.4)	510 (38.1)
I47.1 + R00.0 &/or R00.2		12 (3.2)	14 (1.0)
I951 + R00.0 &/or R00.2		12 (3.2)	23 (1.7)
R00.0 + R00.2		29 (7.7)	36 (2.7)

Abbreviations: ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Table 2. Self-controlled Case Series Analysis: Association between first HPV vaccination with autonomic dysfunction

	Post-vaccination case window			Pre-vaccination control window			IRR post- vs. pre-event rate (95% CI)	Adjusted IRR post- vs. pre-event rate[a] (95% CI)
	No. of events	Person-days	Event rate per 10,000 person-days	No. of events	Person-days	Event rate per 10,000 person-days		
Autonomic dysfunction cohort	1340	710,649	18.9	377	266,298	14.2	**1.33 (1.19-1.49)**	**1.23 (1.08-1.41)**
Age 9-17	879	494,418	17.8	242	175,408	13.8	**1.29 (1.12-1.49)**	1.14 (0.97-1.35)
Age 18-26	461	216,231	21.3	135	90,890	14.9	**1.44 (1.18-1.74)**	**1.40 (1.12-1.75)**

Abbreviations: CI, confidence interval; **HPV**, human papillomavirus; **IRR**, incidence rate ratio; **No.**, number. [a]Controlling for age as time-varying covariate .

- Of 1654 girls and young women, 1089 (65.8%) were aged 9-17 and 565 (34.2%) were aged 18-26. The majority (69.2%) received 1 dose; 23.6% received 2 doses, and 7.2% received 3 doses before end of follow-up.
- Tachycardia, palpitations, and orthostatic hypotension were the most common diagnoses pre- and post- vaccination. The number of individuals with 2+ diagnoses was higher in pre-vaccination period but comprised <15% of all diagnoses (**Table 1**).
- There was a statistically significant association between HPV vaccination and AD, with the post-vaccination event rate of 18.9/10,000 person days exceeding the pre-vaccination event rate of 14.2/10,000 person-days, yielding an unadjusted IRR of 1.33 (95% CI: 1.19-1.49) (**Table 2**).
  - After age-adjustment, the overall IRR decreased but remained statistically significant (IRR=1.23; 95% CI: 1.08-1.41). Age-stratified IRRs of the 18-26 year-old and the 9-17 year-old groups varied, with those aged 18-26 experiencing higher risk.
- When stratified by number of doses, only receipt of 1 dose achieved statistical significance (1.49; 95% CI: 1.30-1.70).

Conclusions

- Using a rigorous self-controlled design, our study supports an association between HPV vaccination and subsequent AD in girls and young women.
- Future research should include recently-added POTS diagnostic code, as well as control for other vaccine and drug exposures.
- Patients and their caregivers should consult with their primary healthcare providers to discuss both benefits and risks of HPV vaccination.

Acknowledgements

We express our gratitude to Pharmaceutical Research Computing at the University of Maryland Baltimore for analytic support.
Funded in part by the UMB Institute for Clinical and Translational Research and National Center for Advancing Translational Sciences Award.

Paper Link