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RESEARCH ARTICLE

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Extended surveillance to assess safety of 9-valent human papillomavirus vaccine

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ABSTRACT

The safety of 9-valent HPV vaccine (9vHPV) has been established with regard to common and uncommon adverse events. However, investigation of rare and severe adverse events requires extended study periods to capture rare outcomes. This observational cohort study investigated the occurrence of three rare and serious adverse events following 9-valent human papillomavirus (9vHPV) vaccination compared to other vaccinations, in US individuals 9–26 years old, using electronic health record data from the Vaccine Safety Datalink (VSD). We searched for occurrences of Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and stroke following 9vHPV vaccination from October 4, 2015, through January 2, 2021. We compared the risks of GBS, CIDP, and stroke following 9vHPV vaccination to risks of those outcomes following comparator vaccines commonly given to this age group (Td, Tdap, MenACWY, hepatitis A, and varicella vaccines) from January 1, 2007, through January 2, 2021. We observed 1.2 cases of stroke, 0.3 cases of GBS, and 0.1 cases of CIDP per 100,000 doses of 9vHPV vaccine. After observing more than 1.8 million doses of 9vHPV, we identified no statistically significant increase in risks associated with 9vHPV vaccination for any of these adverse events, either combined or stratified by age (9–17 years of age vs. 18–26 years of age) and sex (males vs. females). Our findings provide additional evidence supporting 9vHPV vaccine safety, over longer time frames and for more serious and rare adverse events.

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Introduction

Human papillomavirus (HPV) is a sexually transmitted virus that causes cervical, oropharyngeal, vulvar, vaginal, anal, and penile cancers.[1] A quadrivalent vaccine against HPV (4vHPV) was recommended in the United States in 2006 for females 11–12 years old and females 13–26 years old who were not previously vaccinated against HPV;[2] in 2011, this recommendation was extended to males aged 13–21 years.[3] In 2015, a 9-valent HPV vaccine (9vHPV) was recommended for use in the same populations and in 2017, this vaccine became the sole HPV vaccine available in the United States.[4,5]

Compared to the 4vHPV vaccine, 9vHPV vaccine has more than twice the amount of an aluminum-based adjuvant, and contains antigens against five additional HPV serotypes.[4] Pre-licensure clinical trials of 9vHPV identified no safety concerns, but these studies were not adequately powered to detect uncommon adverse events.[6,7] A post-licensure observational study conducted in the Vaccine Safety Datalink (VSD) identified no safety concerns for uncommon adverse events over a 24-month period.[8] However, among the rare events assessed in that analysis, there were sparse data available for chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barré syndrome (GBS), and stroke due to very low background incidence rates for these outcomes. There was an additional interest in investigating stroke to rule out a potential synergistic effect with oral contraceptives. To investigate further safety following 9vHPV vaccination, we extended our previous VSD study to increase the data available to evaluate these rare events in particular. We used a longer study period of October 2015 to January 2021 to capture additional vaccinations, and included both males and females aged 9–26 years.

Methods

Study design and population

The VSD was established in 1990 and is a collaboration between 9 integrated health-care organizations and the US Centers for Disease Control and Prevention (CDC).[9] VSD conducts vaccine safety analyses using a distributed data model, allowing each member organization to maintain its own data on a secure server at the member's site, rather than transferring data to a central location. Additionally, to further ensure confidentiality, each individual in VSD is assigned a unique and randomized VSD study identification number.

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The VSD study identification number serves as a link between demographic information and medical services information. Existing investigations of the demographic characteristics in the VSD suggest that the VSD population is generalizable to the United States population.[10]

The data used to conduct this analysis were provided by six VSD sites: five Kaiser Permanente organizations (Colorado, Northern California, Northwest, Southern California, and Washington) and Marshfield Clinic Health System. Each site provided standardized electronic data files containing information on participant demographics, vaccinations, and diagnosis codes assigned during medical encounters; data were aggregated to create cohorts followed up to 180 days after vaccination. The data were gathered in a prospective manner with the index date being the date of vaccination, in an observational cohort study design. The study population consisted of males and females aged 9–26 years old during the study period, who were members of one of the six VSD sites in this analysis. This study was approved by institutional review boards at all participating sites with a waiver of informed consent.

Outcomes

Diagnosis codes (ICD-9 and ICD-10; International Classification of Diseases, 9th and 10th revisions respectively) were used to identify GBS, CIDP, and stroke. These outcomes were chosen as a result of our previous analysis, which investigated these outcomes but observed very few instances, thereby making it statistically challenging to draw firm conclusions about vaccine safety. The original analysis pre-specified analysis of these events based on reports from clinical trials, the Vaccine Adverse Event Reporting System, and other published investigations of HPV vaccine safety, including a prior VSD safety study of quadrivalent HPV vaccination.[8,11] Increasing the number of immunizations observed in this analysis allowed us to investigate these outcomes with greater statistical power. We screened for codes corresponding to these conditions in the emergency department, inpatient, or outpatient settings (for GBS and CIDP) or emergency department or inpatient settings only (for stroke) (Table S1). Only the codes that occurred in the specified risk periods were considered to be post-vaccination events (Table 1). To exclude prevalent cases, defined as administrative codes identified in the post-vaccination period that may have been associated with an outcome that occurred before vaccination, events were required to be the first observed in 42 days (for GBS and for stroke), or the first ever in an individual's lifetime, as documented in VSD data (for CIDP). We required 'prevalent' cases to occur in the same settings as the outcomes (Table 1). We did not exclude otherwise eligible individuals from contributing person-time to this analysis if they had underlying risk factors such as cardiovascular disease.

Comparison of events after 9vHPV and after comparator vaccines

We compared outcomes occurring after receipt of a 9vHPV vaccine (Table 1) and outcomes occurring after receipt of a comparator vaccine. Comparator vaccines were defined as vaccines that were routinely administered to persons in this age group, including tetanus-diphtheria (Td), tetanus-diphtheria-acellular pertussis (Tdap), meningococcal conjugate ACWY (MenACWY), hepatitis A and varicella vaccines. If an individual received more than one comparator vaccine at any given clinical visit, the subsequent person-time was only counted once in the historical comparator value. These comparator vaccines have robust safety profiles with no associations reported with outcomes of interest included in this analysis.[12–14] Therefore, comparisons with these vaccines are functionally similar to comparisons with background rates of these outcomes.

For this analysis, outcomes were only counted if they occurred in individuals 9–26 years old at the time of vaccination; for 9vHPV, vaccines were included if they were received from 4 October 2015 through 2 January 2021. Comparator vaccines were included if they were received from 1 January 2007 through 2 January 2021.

Statistical analysis

We compared the number of events occurring after administration of 9vHPV vaccines per 100,000 9vHPV doses to the number of events occurring after administration of comparator vaccines per 100,000 comparator vaccine doses, stratified by age and sex. Events were compared using a 1-sided Fisher's exact test where the alternative hypothesis was that the probability of being a case is greater for 9vHPV doses than comparator vaccine doses. The 95% confidence limits on the ratio of cases per 100,000 9vHPV doses to cases per 100,000 comparator vaccine doses were estimated using exact logistic regression analysis. Since the events in these analyses are very rare, the odds ratio closely approximated the relative risk value.

We then established the number of outcome events needed to occur after 9vHPV vaccination to generate a statistical vaccine safety "signal," given fixed numbers of 9vHPV doses, comparator vaccine doses, and events occurring after comparator vaccine doses. We did this by creating a table of vaccine type (9vHPV or comparator) by outcome (present or absent) and varying the table cell containing the number of potential 9vHPV vaccine events while keeping the quantities listed above fixed. The number of potential 9vHPV vaccine events was

Table 1. Criteria for determining adverse events.

Adverse event	Medical setting	Post-vaccination risk period	First episode in which period?
GBS[a]	Outpatient, inpatient, emergency department	1–42 days	First in 42 days
CIDP[b]	Outpatient, inpatient, emergency department	1–180 days	First ever
Stroke	Inpatient, emergency department	0–42 days	First in 42 days

[a]Guillain-Barré syndrome.
[b]Chronic inflammatory demyelinating polyneuropathy.

initially set to zero and incrementally increased until the p-value for the corresponding 1-sided Fisher's exact test was less than 0.05. The number of potential events that caused the p-value to cross this threshold was deemed the number of outcome events that would have been needed to elicit a "signal." This number provided additional context for the actually observed number of events occurring after 9vHPV vaccination. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Over the study period, we observed 1,835,789 9vHPV doses and 3,814,009 comparator vaccine doses administered within this VSD population. The mean (SD) age was 16.1 (5.0) years; 9vHPV recipients were slightly younger [mean (SD) age: 14.7 (4.6) years] than comparator vaccine recipients [mean (SD) age: 16.8 (5.1) years]. Of the 9vHPV doses administered, 1,407,380 (76.7%) were administered to individuals 9–17 years of age, and 968,570 (52.8%) were administered to females. In the comparator vaccine group, there were 2,370,428 doses (62.2%) administered to individuals 9–17 years old; 1,853,331 doses (48.6%) were administered to females.

The post-9vHPV vaccination events monitored in this study were exceedingly rare. There were no instances of GBS observed during the post-9vHPV vaccination risk period among all persons aged 18–26 years old, and no instances of CIDP observed for males (all ages) (Table 2).

We identified 22 cases of stroke, 6 cases of GBS, and 2 cases of CIDP occurring after 1,835,789 doses of 9vHPV vaccine. This resulted in 1.2 cases of stroke, 0.3 cases of GBS, and 0.1 cases of CIDP per 100,000 doses of 9vHPV vaccine. When stratifying post-9vHPV vaccine events by age and sex, the highest post-9vHPV vaccine event rates were 4.9 per 100,000 doses (females 18–26 years, for stroke) and 2.1 per 100,000 doses (males 18–26 years, for stroke). All other event rates were <1 per 100,000 doses.

We did not identify any statistically significantly increased risk of the occurrence of events observed in the post-9vHPV vaccine risk period compared to events observed in the post-comparator vaccine risk period (Table 3). The 95% confidence intervals for ratios of cases per 100,000 9vHPV doses/cases per 100,000 comparator vaccine doses included 1 for all outcomes by age and sex, except for stroke in males 9–17 years old (ratio: 0.1; 95% CI: 0.0–0.8) and GBS assessed across age and sex categories (ratio: 0.4; 95% CI: 0.1–0.9).

Discussion

This analysis did not find any statistically significant increase in risk of GBS, CIDP, or stroke after 9vHPV vaccination versus comparator vaccines that are not associated with GBS, CIDP, or stroke, after observing more than 1.8 million doses of 9vHPV over a period of more than 5 years. These findings are in keeping with the existing literature on the safety of 9vHPV vaccines.[6,7,15,16] The current study is an extension of a previous VSD study on the safety of 9vHPV which had a study period of 24 months.[8] In that study, risk estimates for some age/sex groups were not possible to calculate because no adverse events were observed in those groups during the 24-month study period. Due to a longer study period, the current study was able to identify adverse events in those groups (males 9–26 and females 9–17 for GBS and stroke) and report corresponding risk estimates. This analysis reports results from a comparative analysis between 9vHPV and other vaccines commonly given in childhood/adolescence. Our findings should be interpreted as measures of relative safety compared to other vaccines commonly given to individuals aged 9–26 years.

Point estimates of the risk of stroke after 9vHPV vaccine, compared to the risk of stroke after comparator vaccines, were below 1 in males 9–26 and females 9–17 years old. However, 95% confidence intervals were consistent with no statistically significant relationship for all groups except males 9–17 years old, where a protective effect was seen. A small number of

Table 2. Comparison of events after 9vHPV vaccine and after comparator vaccine populations in the Vaccine Safety Datalink, from October 4, 2015 (9vhpv vaccine) or January 1, 2007 (comparator vaccines) to January 2, 2021 (both 9vhpv and comparator vaccines).

Adverse event	Sex/age category[a]	Number of 9vHPV doses	Number of events in the post-9vHPV risk period	Events in the post-9vHPV risk period per 100,000 9vHPV doses	Number of comparator vaccine doses	Number of events in the post-comparator vaccine risk period	Events in the post-comparator vaccine risk period per 100,000 comparator vaccine doses
GBS[b]	F 9–17 years	680,795	3	0.4	1,029,301	7	0.7
	F 18–26 years	287,775	0	0	824,030	8	1.0
	M 9–17 years	726,585	3	0.4	1,341,127	10	0.8
	M 18–26 years	140,634	0	0	619,551	7	1.1
	Overall	1,835,789	6	0.3	3,814,009	32	0.8
CIDP[c]	F 9–17 years	680,795	1	0.2	1,029,301	1	0.1
	F 18–26 years	287,775	1	0.4	824,030	0	0
	M 9–17 years	726,585	0	0	1,341,127	0	0
	M 18–26 years	140,634	0	0	619,551	1	0.2
	Overall	1,835,789	2	0.1	3,814,009	2	0.1
Stroke	F 9–17 years	680,795	4	0.6	1,029,301	7	0.7
	F 18–26 years	287,775	14	4.9	824,030	30	3.6
	M 9–17 years	726,585	1	0.1	1,341,127	15	1.1
	M 18–26 years	140,634	3	2.1	619,551	26	4.2
	Overall	1,835,789	22	1.2	3,814,009	78	2.1

[a]F: Females. M: Males.
[b]Guillain-Barré syndrome.
[c]Chronic inflammatory demyelinating polyneuropathy.

Table 3. Comparison of events after 9vHPV vaccine and after comparator vaccine populations in the Vaccine Safety Datalink, stratified by age and sex, from October 4, 2015 (9vHPV vaccine) or January 1, 2007 (comparator vaccines) to January 2, 2021 (both 9vHPV and comparator vaccines).

Adverse event	Sex/age category[a]	Number of 9vHPV doses	Number of events in the post-9vHPV risk period	Number of comparator vaccine doses	Number of events in the post-comparator vaccine risk period	Ratio of cases after 9vHPV to cases after comparator vaccine (exact 95% CI)[b]	1-sided *p*-value for Fisher's exact test	Number of events in the post-9vHPV risk period needed to signal[c]
GBS[d]	F 9–17 years	680,795	3	1,029,301	7	0.7 (0.1, 2.8)	0.8	12
	F 18–26 years	287,775	0	824,030	8	0 (–)	1.0	8
	M 9–17 years	726,585	3	1,341,127	10	0.6 (0.1, 2.2)	0.9	12
	M 18–26 years	140,634	0	619,551	7	0 (–)	1.0	6
	Overall	1,835,789	6	3,814,009	32	0.4 (0.1, 0.9)	1.0	25
CIDP[e]	F 9–17 years	680,795	1	1,029,301	1	1.5 (0.0, 118.7)	0.6	5
	F 18–26 years	287,775	1	824,030	0	–	0.3	3
	M 9–17 years	726,585	0	1,341,127	0	–	–	–
	M 18–26 years	140,634	0	619,551	1	0 (–)	1.0	3
	Overall	1,835,789	2	3,814,009	2	2.1 (0.2, 28.7)	0.4	5
Stroke	F 9–17 years	680,795	4	1,029,301	7	0.9 (0.2, 3.4)	0.7	12
	F 18–26 years	287,775	14	824,030	30	1.3 (0.7, 2.6)	0.2	19
	M 9–17 years	726,585	1	1,341,127	15	0.1 (0.0, 0.8)	1.0	16
	M 18–26 years	140,634	3	619,551	26	0.5 (0.1, 1.7)	0.9	12
	Overall	1,835,789	22	3,814,009	78	0.6 (0.4, 1.0)	1.0	52

[a]F: Females. M: Males.
[b]Calculated as "cases per 100,000 doses" for both 9vHPV vaccines and comparator vaccines.
[c]Number of cases needed to signal calculated by fixing the number of 9vHPV vaccine doses, the number of comparator vaccine doses, and the number of events occurring after comparator vaccine doses. The number of events occurring after 9vHPV vaccine doses was then artificially set to 0 and increased incrementally until a 1-sided Fisher's exact test yielded a p-value < 0.05.
[d]Guillain-Barré syndrome.
[e]Chronic inflammatory demyelinating polyneuropathy.

studies have reported a potential association between HPV infection and the risk of cardiovascular disease, including stroke, in adult women.[17–19] Theoretically, this could implicate HPV vaccination in the prevention of events such as stroke. However, there exists very little information on the potential for this relationship in males or in the pediatric population. It is more likely that our finding is a result of extremely low event numbers or as a result of uncontrolled confounding. Existing evidence suggests that pediatric stroke is more common in older male adolescents (15 years old and up), compared to females or younger adolescents, with congenital heart disease being a common underlying condition.[20] It is possible that HPV vaccination is not prioritized for children with complex medical conditions such as congenital heart disease, which may also account for the statistical association identified in this analysis. Similarly, the point estimate of the risk of GBS after 9vHPV vaccine, compared to the risk of GBS after comparator vaccines, was below 1 when all age and sex categories were combined. This potentially protective effect seems to be driven largely by the absence of GBS in young adults 18–26 years after 9vHPV vaccine. To date, no other studies investigating the relationship of GBS and HPV vaccine have reported a statistically significant protective effect of HPV vaccination on the incidence of GBS in adolescents or young adults. It is therefore likely that this effect is a result of random chance, occurring because of low numbers of GBS in these age groups.

This analysis has some important limitations. First, despite the longer study period in this study, there were no instances of CIDP identified in post-comparator vaccine risk periods for females 18–26 years old or males 9–17 years old. This prevented the calculation of a ratio of cases after 9vHPV vaccine compared to cases after comparator vaccines, and similarly prevented the calculation of a 95% CI for all groups except for females 9–17 years old, where the 95% CI was wide. Published estimates of the incidence of CIDP range from 0.15 to 1.6 cases per 100,000 person-years,[21] and other studies have determined that CIDP is rare in children [22] with the majority of cases occurring in older adults.[23]

Second, the unit of analysis is vaccine doses, not individuals. As a result, it was possible for two or three separate 9vHPV doses to be received by the same individual at different times. This analysis did not explicitly account for potential correlation within individuals that could have occurred as a result of this. In a previous analysis, we stratified more common outcomes based on dose number, but combined doses for more rare outcomes[1]; identification of the relationship between more common outcomes and vaccines by dose did not appear to differ consistently by dose number. However, if there were intra-person correlation of the risk of rare outcomes, that might result in artificially constricted 95% confidence intervals reported in this analysis.

Third, this analysis focused on the comparative risk of rare events following 9vHPV vaccination specifically. Because of the very rare number of events, we were not able to assess potential differences in risk stratified on individuals who received more than one vaccine at once, or among individuals in categories at higher risk for poor outcomes following HPV infection. For similar reasons, we were not able to stratify results based on race/ethnicity.

Finally, this analysis identified rare adverse events using diagnosis codes without validation by medical record review. On their own, the validity of such codes can vary substantially by provider and clinical site as well as over time.[24] It is possible that chart review and validation of these cases would result in the elimination of some identified cases, but it is also likely that validity does not differ between HPV and comparator vaccines, therefore yielding non-differential misclassification. Additionally, this analysis includes ICD codes identified during the SARS-CoV-2 pandemic; both healthcare-seeking behavior and routine immunizations have been highly impacted during this time. However, the adverse events assessed in this analysis

are serious conditions and therefore not as likely to be influenced by pandemic-related changes in healthcare-seeking behavior. Previous work in VSD has identified optimal methods of identification for GBS,[24,25] and since both GBS and CIDP have only one ICD code (G61.0 and G61.81, respectively, for ICD-10; 357.0 and 357.81, respectively, for ICD-9), the potential for misclassification of these two outcomes may be lower than for other outcomes that are associated with a broader constellation of codes.

Conclusion

During a surveillance period of 5 years, where more than 1.8 million doses of 9vHPV vaccine were administered to individuals aged 9–26 years, no statistically significant increases in risk were observed for GBS, CIDP, and stroke post-9vHPV vaccination. Our longer-term findings support the existing robust literature on 9vHPV vaccine safety. As a result, primary care providers should continue to recommend HPV vaccination to eligible patients.

Abbreviations

CDC	US Centers for Disease Control and Prevention.
CIDP	Chronic inflammatory demyelinating polyneuropathy.
GBS	Guillain-Barré syndrome.
HPV	Human papillomavirus.
4vHPV	4-valent human papillomavirus vaccine.
9vHPV	9-valent human papillomavirus vaccine.
ICD	International Classification of Diseases.
MenACWY	Quadrivalent conjugate meningococcal vaccine.
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2.
Td	Tetanus-diphtheria vaccine.
Tdap	Tetanus, diphtheria, and acellular pertussis vaccine.
VSD	Vaccine Safety Datalink.

Disclosure statement

MES received support from GSK for a feasibility study unrelated to HPV vaccines. BK received support from Janssen and Novavax for studies unrelated to HPV vaccines. NPK received research support from Merck for a HPV9 safety study and research support from Merck, GlaxoSmithKline, Pfizer, Sanofi Pasture and Protein Science (now Sanofi Pasteur) for unrelated studies. JGD reported receiving support from Janssen Vaccines & Prevention for a study unrelated to HPV vaccines. JCN has received grant funding from Moderna and GSK. She has also received statistical consulting fees from Southern California Permanente Medical Group and Harvard Pilgrim Health Care.

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Article summary

Update of previous investigation of 9-valent HPV vaccine safety using a longer study period. No increased risk of rare events associated with 9vHPV identified.

Author contributions statement

Mr. Kieke, Dr. Belongia, and Dr. Donahue conceptualized and designed the original study. Dr. Sundaram drafted the initial manuscript, and reviewed and revised the manuscript including implementing additional analyses and interpreting statistical results. Mr. Weintraub, Ms. Hanson, Dr. Daley, Dr. Hechter, Dr. Klein, Mr. Lewis, Dr. Naleway, and Dr. Nelson provided input on the conceptualization and design of the study, and they, as well as Dr. Donahue, Dr. Belongia, Dr. Sundaram, and Mr. Kieke reviewed and revised the manuscript. Mr. Kieke completed the statistical analyses. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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.

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