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Risk of Guillain-Barré Syndrome following quadrivalent human papillomavirus vaccine in the Vaccine Safety Datalink

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Abstract

Objective: Describe the Vaccine Safety Datalink's (VSD) Guillain Barré Syndrome (GBS) surveillance following quadrivalent HPV vaccine (4vHPV) from 2006 through 2015.

Methods: Among 4vHPV vaccinated persons aged 9–26, ICD-9 coded GBS was identified in VSD's electronic data. Medical records were reviewed and adjudicated to confirm GBS. We calculated incidence rates of confirmed GBS within 1–42 days following 4vHPV with a one-sided 95% confidence interval.

Results: Following 2,773,185 4vHPV doses, we confirmed 1 case of GBS in a male and no cases among females. The incidence rate of medical record confirmed GBS within 42 days following 4vHPV vaccine was 0.36 cases per million 4vHPV doses administered (1-sided 95% CI 1.71), which was less than the background rate.

Conclusion: We found no evidence of an increased risk of GBS following 4vHPV. With an upper 95% confidence limit, we estimate that, if an increased risk exists, we would expect at most 1.08 additional cases of GBS per million people vaccinated with 4vHPV.

Keywords

Human papillomavirus vaccine; Vaccine Safety; Guillain Barré Syndrome

1. Background

Guillain Barré Syndrome (GBS) is a rare, serious autoimmune disorder of the peripheral nerves characterized by muscle weakness and loss of reflexes [1]. Estimated GBS incidence ranges from0.8 to 1.9 cases per 100,000 person-years; the rate is higher in males and increases with age [2]. The exact cause of GBS is unknown; however, molecular mimicry is hypothesized to be the mechanism for antigenic stimulation with resulting autoimmune demyelination and damage to peripheral nerves [3,4]. Approximately two-thirds of patients with GBS describe symptoms of gastrointestinal (e.g., *Campylobacter jejuni*) or respiratory

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infection within few weeks prior to onset [5]. Rarely, GBS occurs following vaccination. During the 1976 swine influenza vaccination program, GBS was found to be increased in the six weeks following vaccination [6]. Since then, findings for post-vaccination GBS have been inconsistent for influenza vaccines and reassuring for other vaccines [7–10]. Because of this history, GBS is an outcome of interest for vaccine safety surveillance, particularly when new vaccines are licensed and recommended.

Since 2006, human papillomavirus vaccine (HPV) vaccine has been routinely recommended in the United States for girls aged 11 or 12 and through age 26 years for those not previously vaccinated. In 2011, the recommendation was expanded to include routine vaccination of males. Through 2015, almost all HPV vaccine used in the United States was 4vHPV. To date, no safety concerns for GBS following HPV vaccines have been observed in the US spontaneous monitoring system, the Vaccine Adverse Event Reporting System [11,12]. Large population-based studies in the US, France, England, and Scandinavia have found no increased risk of GBS following HPV vaccination [13–16]. In 2017, however, the French National Agency for Medicines and Health Products Safety published findings from a retrospective cohort study using healthcare administrative databases and no medical record review evaluating 14 autoimmune conditions. This study detected robust statistical associations with GBS following HPV vaccination in girls in their general analyses and several sensitivity analyses [17].

The Vaccine Safety Datalink (VSD), a collaboration between CDC and several integrated health care plans, has been a cornerstone of U.S. population-based vaccine safety surveillance for over 25 years [18]. VSD links health outcome and vaccination data to monitor vaccine safety in near-real-time using a rapid cycle analysis (RCA) method, which has been described elsewhere [19]. VSD conducted 4vHPV RCA from August 2006 through October 2009 and observed 0 GBS cases following 600,558 doses among females 9–26 years of age. Because GBS is rare, the power to detect a risk was limited. Therefore, VSD continued long term surveillance. The objective of this report is to describe the findings of VSD's GBS surveillance following 4vHPV from 2006 through 2015.

2. Methods

Six VSD sites contributed data to this prospective 4vHPV surveillance of GBS. The population under surveillance included males and females aged 9–26 years who received 4vHPV at participating sites between August 1, 2006-December 31, 2015 (after which 9vHPV replaced 4vHPV). One VSD site began contributing data starting April 2008. Among 4vHPV vaccine recipients, we identified all potential electronic ICD-9 coded cases of GBS using the following definition: diagnostic ICD-9 code 357.0 within 1–42 days post-vaccination (whereas day 0 is day of vaccination), in either the inpatient, outpatient, or emergency department settings. An incident case of GBS following 4vHPV was defined as the first diagnosis in the preceding 42 days.

We conducted medical record reviews for potential cases of GBS. VSD medical epidemiologists conducted adjudication using Brighton Collaboration case definition criteria to classify cases [1]. Diagnostic certainty is higher for cases assigned a Brighton

Collaboration case definition of level 1. The Institutional Review Boards at all participating sites approved this study.

We calculated medical record confirmed incidence rates of GBS within 1–42 days following 4vHPV. We then calculated a one-sided 95% confidence interval using the exact Poisson method around these rates. Using the exact Poisson method, we obtained the upper bound of the one-sided 95% confidence interval for the attributable risk of GBS per million vaccinations. Using a published background rate of 0.55 chart-confirmed GBS cases per 100,000 person years among a population aged 11–18 years, we calculated the expected number of cases per 1 million vaccine doses [20]. In order to produce the upper bound of the one-sided 95% confidence interval for the attributable risk of GBS per 1 million 4vHPV vaccinations, we subtracted the expected number of cases from the upper bound of the confidence interval for the incidence rate of GBS. We also performed this calculation on all cases identified from electronic data.

3. Results

From August 2006 through December 31, 2015, 2,773,185 doses of 4vHPV were administered in the study population: 1,900,370 doses among females and 872,815 doses among males. Seven cases of GBS were identified using the electronic case definition prior to medical record review: 4 cases in females and 3 in males. The overall electronic potential GBS case incidence rate was 2.52 cases per million 4vHPV doses administered (95% CI 1.01, 5.20); 2.10 per million doses for females (95% CI: 0.057, 5.39) and 3.44 per million doses for males (95% CI: 0.71, 10.04). After performing medical record review, we observed one incident case of Acute Inflammatory Demyelinating Polyneuropathy, the most common form of GBS. Among the six cases that were not confirmed, five had a prior history of GBS and one was determined not to be GBS (Table 1).

On medical record review, we identified 0 confirmed cases among females and one confirmed case in a male. This single confirmed case met Brighton Collaboration case definition Level 4-reported GBS with insufficient evidence to meet the case definition levels 1–3. The overall incidence rate of medical record confirmed GBS within 42 days for both sexes combined following 4vHPV vaccine was 0.36 cases per million 4vHPV doses administered, which was not higher than the expected background rate. The 1-sided upper 95% confidence limit was 1.71 cases per million doses (Table 2). Based on the upper 95% confidence limit, a potential increased risk of GBS associated with 4vHPV would be at most1.08 cases per million doses.

4. Discussion

To our knowledge, this is the first study to evaluate GBS following 4vHPV in males and females. We identified only one confirmed incident GBS case in a male during the 9 year surveillance period and no cases among females. Among an estimated 1,708,075 vaccinated patients, we found no increased risk of GBS in the 42 days following receipt of 4vHPV.

The capability to exclude a small excess risk of 4vHPV-associated GBS reflects the strength of the VSD, which routinely collects high quality vaccination and health outcome data in a

large population. The ability to access the medical records in VSD allows for well-validated incidence rates to be generated. Had we relied on electronic data alone, our rates of GBS following 4vHPV would have been falsely elevated and potentially misleading. Our medical record reviews confirmed that only 1 of the 7 GBS cases initially identified (among 2,773,185 4vHPV doses administered) was an incident case. Of the remaining cases, 5 had a prior history of GBS and 1 was determined not to be GBS.

With the exception of the French database study [17], no study observed an increased risk of GBS [13–16]. Few of the large population-based studies on HPV vaccines and GBS have employed medical record validation. Based on our GBS case validation findings, it is reasonable to assume that if other large population-based studies had conducted medical record review, the results may have shown lower rates of GBS following exposure. The French study, which analyzed electronic administrative healthcare data on 2.25 million females aged 13–16 years between January 2008 and December 2012 without medical record review, found 19 GBS cases among those vaccinated and 21 cases in unvaccinated females during the overall follow-up period. This study observed a significant association in the first 0–2 months. The strength of the significant association decreased with the longer exposure windows between 2 and 12 months and reached non-significancy > 12 months following vaccination. Some of the chosen risk windows for this study were longer than the traditionally accepted risk window for GBS following vaccination of 1–42 days [6]. This may account for some of the findings; longer risk windows may increase the potential for bias and confounding.

Our study has some limitations. We used a published background rate of GBS among 11–18 year olds from five US health plans [20]. While this rate did not include adolescents aged 9–10 years and 19–26 years, we still considered this rate to be comparable since it involved a similar US adolescent population. Another limitation was potential loss to follow-up among those males and females aged 18–26 years as it is possible that some older members may utilize college based insurance. However given the cost of hospitalization, we would expect that this diagnosis would be reliably captured in our VSD data under the family's primary insurance.

Among an estimated 1,708,075 vaccinees, we confirmed only one incident case of GBS, which is in line with the background rate. Even if we make the conservative assumption that an increased risk may be as high as the upper 95% confidence limit of our estimate, we would expect at most 1.08 additional cases of GBS per million people vaccinated with 4vHPV.

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Table 1

Guillain-Barré syndrome (GBS) cases (N = 7) following quadrivalent human papillomavirus vaccination (4vHPV) identified through ICD-9 coded automated data and confirmatory medical record review, Vaccine Safety Datalink, 2006–2015.

Case number	Sex	Age (years)	4vHPV dose number	Days after vaccination to diagnosis	Incident GBS case (Y/N)	Final determination after medical record review
1	Male	15	1	15	Y	GBS, AIDP type[a]
2	Male	14	2	20	N	GBS diagnosis 4 years prior
3	Male	15	3	35	N	GBS diagnosis 5 years prior
4	Female	16	1	34	N	GBS diagnosis 3 years prior
5	Female	19	2	4	N	GBS diagnosis 3 months prior
6	Female	12	2	18	N	GBS diagnosis 4 years prior
7	Female	14	1	2	N	Fibromyalgia with ruled out GBS

[a]Acute Inflammatory Demyelinating Polyneuropathy; 0 days between onset of symptoms and diagnosis.

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Table 2

Medical record confirmed Guillain-Barré syndrome (GBS) surveillance in the Vaccine Safety Datalink following 4vHPV vaccine among 9–26 year olds, 2006–2015.

	No. of 4vHPV vaccinations	Number of observed GBS cases	Number of GBS cases per 1 million vaccinations		Attributable risk for GBS per 1 million vaccinations	
			Cumulative incidence for 1–42 day interval	One-sided upper 95% CI	Attributable risk	One-sided upper 95% CI
Females	1,900,370	0	0	1.58	0	0.95
Males	872,815	1	1.15	5.44	0.52	4.81
Total	2,773,185	1	0.36	1.71	0	1.08

Background rate based on expected rate of 0.55 per 100,000 person years [20].