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No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England

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ABSTRACT

Objective: To investigate the risk of Guillain-Barré syndrome (GBS) after human papilloma virus (HPV) vaccine given to 12–18 year old girls in England.
Methods: Hospital Episode Statistics (HES) were searched using data to March 2016 to identify incident cases of GBS in female patients aged from 11 to 20 years eligible to have received the HPV vaccine since its introduction as a 3 dose schedule in September 2008. Diagnosis was confirmed by the case's general practitioner (GP) who also provided HPV vaccination dates. The risk of admission within 3 months (primary risk window) 6 and 12 months of any dose was assessed using the self-controlled case-series (SCCS) method in vaccinated girls with age, season and time-period adjustment. The risk before and after the change in 2012 from bivalent vaccine to quadrivalent vaccine was also assessed.
Results: A total 244 episodes were initially identified which reduced to 101 episodes in 100 girls when just including cases where the GP could be contacted, at least one vaccine dose was given, and GBS was confirmed or classed as probable. Nine, 14 and 24 GBS admissions occurred within 3, 6, 12 months of a dose respectively. The relative incidence (RI) for the 3 month risk period was 1.04 (95% confidence interval 0.47–2.28), for the 6 month period 0.83 (0.41–1.69) and for the 12 month period 1.10 (0.57–2.14). When restricting to 79 confirmed cases the RI in the 3 month risk period was 1.26 (0.55–2.92) and the RI 1.61 (0.39–6.54) for quadrivalent vaccine compared to 0.84 (0.30–2.34) for bivalent.
Conclusion: We found no evidence of an increased risk of GBS following HPV vaccination in England and, based on the upper end of the 95% CI for the RI and the number of HPV vaccine doses given in England, can exclude a risk of about 1 per million doses.

1. Introduction

Guillain-Barré syndrome (GBS) is an autoimmune disease that is usually preceded by a viral or bacterial infection. It is the commonest cause of acute neuromuscular paralysis in the United Kingdom (UK) with symptoms of progressive weakness that can lead to respiratory failure requiring ventilatory support [1]. Diagnosis is by a neurologist based on clinical, laboratory and electrophysiological features.

Human papilloma virus (HPV) vaccine was introduced into the routine immunisation schedule in the UK in September 2008 with a 3 dose schedule (0, 1, 12 months) of the bivalent vaccine, Cervarix ® (GlaxoSmithKline) for girls aged 12/13 years. From 2008 to 2010 a catch-up programme was used to vaccinate girls up to the age of 18 with the same schedule. In September 2012 the two dose quadrivalent vaccine Gardasil ® (Merck) replaced the bivalent vaccine, Cervarix ® and from September 2014 the schedule was changed with the second dose given 6 to 24 months apart. The programme is mainly administered in schools with the intention that records should be passed to general practitioners to be recorded in the girl's notes. In England the coverage of the vaccine is high at 91% for one dose and 87% for all doses [2].

The concern around GBS and vaccination gained impetus following an increased risk seen after the 1976 swine influenza vaccine programme in the US which was subsequently suspended [3]. Since then there has been inconsistent evidence about the association with other influenza vaccinations including seasonal trivalent vaccines and the 2009 pandemic vaccines [4–6]. Although GBS is the most common passively reported neurological condition after influenza vaccination [7], no signal has been seen specifically for HPV vaccine. In the US a study using passive reports initially suggested a signal for The quadrivalent vaccine but this was later examined in more detail with further data from the same passive

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reporting system and not confirmed [8–10]. Epidemiological studies assessing a range of autoimmune and neurological events for the quadrivalent vaccine have been published from the United States, France and Scandinavia with none finding any GBS cases in post vaccination risk periods [11–13]. However in 2015 the findings of a cohort study, carried out by the French Agency for the Safety of Health Products, were made public in an online report in which 14 autoimmune events were assessed and for which there was a signal of an association when assessing the risk of GBS in the period at any time after the first dose (relative risk 4.0, 95% confidence interval (CI) 1.8–8.7) [14]. These findings were discussed by the WHO Global Advisory Committee on Vaccine Safety who recommended further studies are done [15]. We instigated this study to assess the risk of GBS following HPV vaccination in England.

2. Methods

Patients were identified using the Hospital Episode Statistics (HES) database which contains details of all admissions to National Health Service hospitals in England [16]. Admissions between 01/09/2007 and 31/03/2016 with any mention of the ICD-10 code for GBS (G610) in any of the 20 diagnosis fields were identified for girls born between 01/09/1990 and 31/08/2002. An admission for GBS within 180 days of a previous one was treated as the same episode. To ascertain vaccination history the GP of each case was identified where possible and a questionnaire sent asking for dates of all HPV vaccinations. Where this was unavailable from the GP the provider of the community child health information system (CHIS) for the case was contacted as an alternative source of vaccination data collected from schools. In the questionnaire the GP was also asked to confirm the GBS diagnosis, provide an onset date and to send supporting documentation such as a discharge summary or a hospital letter. Diagnosis certainly levels were assigned as confirmed (by the GP/hospital letters), probable (lacking confirmatory data from the GP), or not GBS (GP confirms not an incident GBS episode). The GBS event date was derived from the earliest date identified either from the GP questionnaire, the supporting documentation, or the date of hospital admission from HES. The manufacturer of the vaccine was assigned according to the date of vaccination.

The self-controlled case-series method (SCCS) [17] was used to estimate the relative incidence (RI) of GBS in the 3 month (0–91 day, with day 0 the day of vaccination) period after any dose of HPV vaccine compared to other periods outside this window. The SCCS method automatically controls for time invariant confounding and has been used in previous studies of GBS and vaccination [5,6]. A pre-vaccination low risk period of 28 days before the first dose to allow for possible deferred vaccination due to GBS was investigated but not included in the model as it was not significant. Adjustment was made for the possible time varying confounders of age in years, period (September to August of 2007/08, 08/09, 09/10, 10/11, 11/12, 12/13, 13/14, September 2014-March2016) and season (September-November, December-February, March-May, June-August). The following sensitivity analyses were performed: i) risk periods of 92–183, 184–365, 0–183, and 0–365; ii) only including confirmed cases; and iii) stratification by vaccine manufacturer. Where the risk period after a dose overlapped the risk period after the next dose it was censored at the time of the next dose. The statistical analysis plan was completed before data analysis with the 0–91 day period selected as the primary risk window.

The sample size was dictated by available data; however initial assessment of GBS numbers in HES indicated that about 40 cases may be expected to occur in the same year as a vaccine dose (either first second or third dose). With follow up one year before the first dose to at least one year after the third dose it was calculated that there would be at least 90% power to detect a relative incidence of 2.0 for the 3 month risk period.

The maximum attributable risk was calculated based on the number of attributable cases required to give a relative incidence equal to that seen at the upper end of the 95% CI around the observed RI. This number was then divided by the estimated number of doses given to the English population during the study period based on coverage data and England population estimates data [18,19].

3. Results

A total of 244 admissions in 209 girls were identified in the period 01/09/2007 to 31/03/2016 born from 01/09/1990 to 31/08/2002 and aged 11 to 19 years at time of admission for GBS. Information on vaccine history (or absence of vaccination) could be obtained for 200/209 (95.7%) girls of which 178 records came from the GP and 22 from CHIS. Of these 200 girls 85 (42.5%) were dropped because they had no record of having received vaccination and a further15 girls were excluded based on their GP confirming that the HES GBS episode was not an incident event in the study period. The remaining 100 girls had 106 episodes, however after review 5 of the 6 second episodes were found not to actually be a new episode leaving 101 episodes in 100 girls. For these 101 episodes a hospital discharge letter confirming the diagnosis was sent by the GP for 62, and for a further 17 the GP confirmed the diagnosis but did not provide a letter. For 22 episodes in 22 girls we ascertained vaccination history but did not get further confirmation of the GBS diagnosis, so classified these as probable (Table 1). For 63/101 episodes an onset date earlier than the hospital admission date was ascertained from the GP or hospital letter, with the majority having onset close to admission (mean interval 5 days).

Fifteen girls had received the quadrivalent vaccine and 85 the bivalent vaccine with the number of doses shown in Table 1 along with the distribution of age at admission. No cases aged 11 years old were seen. The quadrivalent vaccinated cases are younger because there has been less time to see older cases. Over the study period there was an increase in the number of GBS episodes (Fig. 1). The usual seasonal pattern of GBS was observed with fewer episodes in the summer months (17 in June–August compared to 27–29 in the other quarters).

The results of the SCCS analysis are shown in Table 2. There were 9 episodes in the 0 to 91 day risk period after any dose of vaccine with no significant increased risk (RI, 1.04; 95% CI, 0.47–2.28).

Table 1
Description of the 101 episodes included in the SCCS analysis.

Factor	Level	Bivalent HPV (Cervarix ®) (N = 86)	Quadrivalent HPV (Gardasil ®) (N = 15)	Total (N = 101)
Age at admission	11	0	0	0
	12	3	9	12
	13	6	3	9
	14	5	2	7
	15	9	1	10
	16	9	0	9
	17	17	0	17
	18	21	0	21
	19	16	0	16
Diagnosis	Confirmed	70	9	79
	Probable	16	6	22
Doses of vaccine recorded in the study period[a]	1	7	6	13
	2	10	2	12
	3	68	7	75

[a] The case with 2 episodes is only counted once for vaccine doses.

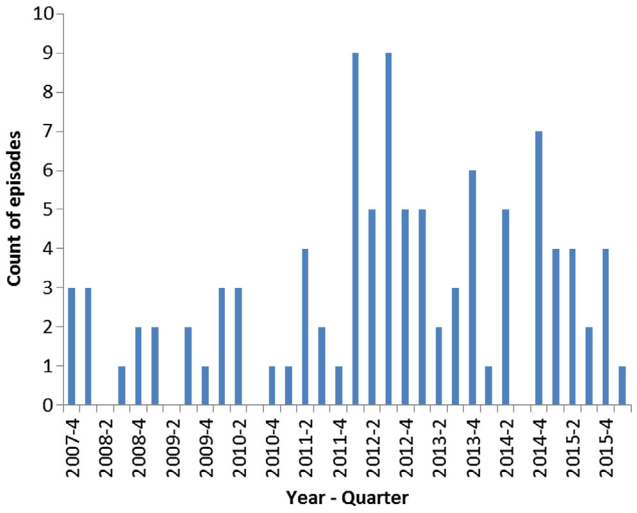

Fig. 1. Quarter of onset for the 101 GBS episodes included in the SCCS analysis.

Table 2
Relative incidence of GBS in risk periods following any dose of HPV vaccine.

Analysis (total episodes)	Risk period (days)	Episodes in the risk period	RI[a] (95% CI)
Primary (101)	0–91	9	1.04 (0.47–2.28)
Alternative risk windows (101)	92–183	5	0.78 (0.27–2.21)
	184–365	10	1.41 (0.61–3.22)
	0–183	14	0.83 (0.41–1.69)
	0–365	24	1.10 (0.57–2.14)
Just confirmed cases (79)	0–91	9	1.26 (0.55–2.92)
Quadrivalent HPV (15)	0–91	4	1.61 (0.39–6.54)
Bivalent HPV (86)	0–91	5	0.84 (0.30–2.34)

[a] Adjusted for age, period and season.

Of these 9 events 4, 2 and 3 were after the first, second and third doses respectively. No increased risk was seen in 6 month or 12 month risk windows or between 3 and 6 or 6 and 12 months. All the 9 cases in the 3 month risk window were confirmed giving a slightly higher estimate when just including confirmed cases (RI, 1.26; 95% CI, 0.55–2.92). When the data were stratified by manufacturer there was no significant difference in the relative incidence estimates (quadrivalent vaccine RI 1.61 (CI 0.39–6.54) and the bivalent vaccine RI 0.84 (CI 0.30–2.34)) and no significant increased risk for either manufacturer (Table 1).

Based on the 95% confidence interval for the relative incidence in the primary analysis we can exclude as unlikely a value above 2.28. To generate a RI of 2.28 we would have required approximately 20 cases in the risk window with 11.2 ($20 \times 1.28/2.28$) attributable.

Using COVER data from England [2] the number of doses given to the population from which we obtained our cases is approximately 10.4 million. Therefore, even if there is a risk, we can exclude it being above 11.2/10.4 million which is a 1.1 per million doses.

4. Discussion

This is the largest study to date to assess the risk of GBS following HPV vaccination with 101 GBS episodes ascertained from a population given approximately 10.4 million HPV vaccine doses. We found no evidence of an increased risk in the first 3 months, 6 months or 12 months following an HPV dose and can exclude a risk in the order of 1 per million doses. The results are for the English population, mostly vaccinated with the bivalent vaccine aged 12–13, but with some girls vaccinated up to the age of 18 and some with the quadrivalent vaccine. These results are in accordance with the lack of a signal from passive surveillance reports [10,20] or active monitoring in the US Vaccine Safety Datalink [21], and the lack of any GBS cases associated temporally with vaccination in three published epidemiological studies from the US, France and Scandinavia [11–13]. The largest of these published studies [13] was a cohort study in Denmark and Sweden of nearly 1 million girls receiving 696,000 doses of the quadrivalent vaccine. This study assessed 53 outcomes, but despite its size was of lower power than our study, with a total of only 28 GBS cases seen, all outside the 6 month risk window following an HPV vaccine dose. The findings of the cohort study from France that instigated our study were not supported by our results [14], although this study was primarily based on quadrivalent vaccine and ours on bivalent vaccine. In this cohort study, which included 2.25 million children aged 13 to16 given 2.1 million doses (93% of doses the quadrivalent vaccine, 7% the bivalent vaccine), the primary analysis assessed the risk at any time after the first dose for 14 autoimmune conditions and found a significantly raised hazard ratio of 4.0 (95% CI, 1.8–8.7) for GBS. The report shows elevated risks at all times after HPV vaccination which may indicate bias, although the timing of the 19 GBS events relative to vaccination is given in figure 3 of the report and appears to indicate some evidence of clustering within 3 months, but this would need further analysis to be confirmed.

The main strengths of our study are its size, the use of the SCCS method with implicit confounder adjustment, the independent verification of vaccination history and the confirmation of the HES diagnosis for 79% of GBS episodes. There are some limitations however. Firstly it was only possible to include vaccinated girls because of the likelihood that vaccination records may not be passed to the GP or be included in the CHIS. The fact that 42.5% did not have a vaccination recorded is evidence of this when compared to population coverage data of about 90%, however there is no reason to expect bias, which would require that missing vaccination history is be associated with the timing of GBS relative to vaccination. Even within those vaccinated it is possible that some of those recorded as 1 or 2 doses had further doses not captured, which could lead to a small bias towards the null due to misclassification bias. Almost all of the children with apparent multiple GBS episodes only had a single event with the entries in the HES diagnostic fields at later dates simply recording the fact there had been a previous episode, however none of the probable episodes included in the final analysis were recurrent so this is unlikely to affect the results. Whilst date of hospitalisation is a reasonable proxy for the onset date, for 63% of cases an earlier date (by a mean of 5 days) was obtained from the GP. This is why we considered risk windows extending to a year after vaccination. Finally, the data are limited for assessing the risk for the quadrivalent vaccine as this was only introduced in 2012 and is used at an age when there are fewer GBS cases.

Our study provides further data on the safety profile of HPV vaccines with no evidence of an association with GBS. Another epidemiological study in the UK assessing HPV vaccine and chronic fatigue syndrome also showed no evidence of an association [22]. Continued surveillance and epidemiological studies will be required as new HPV vaccines are developed and used.

5. Conflicts of interest

None

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