Guillain-Barré syndrome after HPV vaccine: a self controlled case-series study in England

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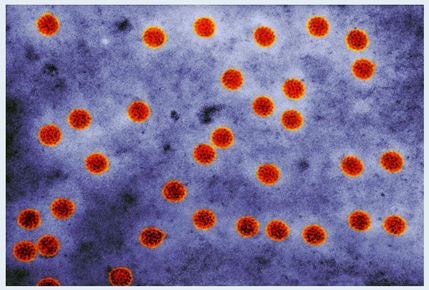
BACKGROUND

- HPV vaccine was introduced in September 2008 to protect girls against their future risk of cervical cancer
- It is given in schools to girls aged 12/13 years of age with a catch up programme used to vaccinate girls up to 18 years of age
- In September 2012 the quadrivalent vaccine Gardasil® replaced the bivalent vaccine Cervarix®
- The vaccine was initially given in 3 doses but this highly effective vaccine is now given as a 2 dose schedule
- Acceptance and coverage of the vaccine has been high with 91% coverage for one dose and 87% for two doses
- GBS was first identified as a potential rare vaccine reaction in the US following an increased risk seen after the subsequently suspended 1976 swine influenza vaccine programme



- This concern around GBS has remained with GBS the most common passively reported neurological condition after influenza vaccination
- GBS following HPV vaccination has been monitored globally in both passive and active surveillance since introduction without signals, however recently in France an unpublished cohort study, which assessed 14 autoimmune events following HPV vaccine, reported a signal.

What is Guillain-Barré syndrome ?

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 with symptoms of progressive weakness that can lead to respiratory failure requiring ventilatory support . Diagnosis is by a neurologist based on clinical, laboratory and electrophysiological features.

METHODS

Cases: Girls born between 01/09/1990 and 31/08/2002 with GBS were identified from the Hospital Episode Statistics (HES) database from 01/09/2007 until 31/03/2016

Vaccine Histories: HPV vaccine histories were ascertained from GP records and regional Child Health Information Systems (CHIS)

Validation:

The GP was asked to complete a questionnaire to confirm the GBS diagnosis, provide an onset of symptoms date and to send supporting documentation such as a discharge summary. Diagnostic certainty levels were assigned without knowledge of the subject's vaccination status using this information. A GBS event date was also derived using the earliest date from the GP questionnaire, the supporting documentation or the admission date in HES. The manufacturer of the vaccine was assigned according to the date of vaccination

Confounding variables: Age, calendar month (individual level confounding automatically controlled for in analysis method).

Analysis: We used the self-controlled case-series (SCCS) method to test the hypothesis of an increased risk of GBS in three risk periods of 0-91, 91-183 and 184-365 days and overall 0-183 and 0-365 days after HPV vaccination. Sensitivity analyses were performed which only included confirmed cases and stratification by vaccine manufacturer.

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% confidence interval (CI) around the observed relative incidence (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

RESULTS

A total 244 episodes were initially identified from HES. A vaccination history was obtained for 95.7% of girls but 42.5% did not have a HPV vaccination recorded. There were 6 girls with a second episode of GBS recorded in HES but 5 of these were found to be referring to the original episode.

After review and validation 101 episodes in 100 girls were analysed and included cases where the GP could be contacted, at least one HPV vaccine dose was given, and GBS was confirmed or classed as probable.

Sixty three of the 101 episodes had an onset of symptoms date recorded before the hospital admission date with the admission dates close to the onset dates with a mean interval of 5 days.

Nine, 14 and 24 GBS admissions occurred within 3, 6 and 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). There was no significant difference in the risk by manufacturer (p= 0.31).

In a vaccine safety study, as the event is often very rare, it is useful to give the risk per dose alongside the risk estimate. As no risk was seen in this study the upper end of the confidence interval can be used to give an attributable risk which the analysis can exclude as unlikely. Using vaccine coverage data from England we can therefore, even if there is a risk, exclude it being above 1.1 per million doses.

Description of the 101 episodes included in the SCCS analysis.

Factor	Level	Cervarix ® (N=86)	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*	1	7	6	13
	2	10	2	12
	3	68	7	75

*The case with 2 episodes is only counted once for vaccine doses.

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 (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)
The bivalent vaccine Gardasil ® (15)	0-91	4	1.61 (0.39-6.54)
The quadrivalent vaccine Cervarix ® (86)	0-91	5	0.84 (0.30-2.34)

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 a HPV dose and can exclude a risk in the order of 1 per million doses.

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 .

The fact that 42.5% did not have a vaccination recorded is evidence of HPV vaccination records not being passed to the GP as the population coverage data is about 90%, however there is no reason to expect bias, which would require that the missing vaccination history is associated with the timing of GBS relative to vaccination.

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.

CONCLUSIONS

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. Our study provides further data on the safety profile of HPV vaccines with no evidence of an association with GBS.

REFERENCES

Public Health England. Vaccine uptake guidance and the latest coverage data, [15/05/2017]. Available from: https://www.gov.uk/government/collections/vaccine-uptake.

L.B. Schonberger, D.J. Bregman, J.Z. Sullivan-Bolyai, R.A. Keenlyside, D.W. Ziegler, H.F. Retailliau, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977 Am J Epidemiol, 110 (2) (1979), pp. 105–123

Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. American journal of epidemiology. 2009;169(3):382-8.

Souayah N, Michas-Martin PA, Nasar A, Krivitskaya N, Yacoub HA, Khan H, et al. Guillain-Barre syndrome after Gardasil vaccination: data from Vaccine Adverse Event Reporting System 2006-2009. Vaccine. 2011;29(5):886-9.

Agence nationale de securite du medicament et des produits de sante. Vaccins anti-HPV et risque de maladies autoimmunes: étude pharmacoépidémiologique, 2015 [04/10/2016]. Available from: http://ansm.sante.fr/content/download/80841/1023043/version/1/file/Ansm_Gardasil-Hpv2_Rapport_Septembre-2015.pdf.

Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. Vaccine. 2017 Mar 23;35(13):1729-1732. doi:10.1016/j.vaccine.2017.01.076. Epub 2017 Feb 27. PubMed PMID: 28245941