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Association between quadrivalent human papillomavirus vaccination and selected syndromes with autonomic dysfunction in Danish females: population based, self-controlled, case series analysis

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ABSTRACT

OBJECTIVE

To evaluate the association between quadrivalent human papillomavirus vaccination and syndromes with autonomic dysfunction, such as chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome.

DESIGN

Population-based self-controlled case series.

SETTING

Information on human papillomavirus vaccinations and selected syndromes with autonomic dysfunction (chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome) identified using ICD-10 (international classification of diseases, revision 10) diagnostic codes from Danish nationwide registers.

PARTICIPANTS

869 patients with autonomic dysfunction syndromes from a cohort of 1 375 737 Danish born female participants aged 10 to 44 years during 2007-16.

MAIN OUTCOME MEASURES

Self-controlled case series rate ratios (95% confidence intervals) of the composite outcome of chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome, adjusted for age and season, comparing female participants vaccinated and unvaccinated with the quadrivalent human papillomavirus vaccine. Chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome were also considered separately in secondary analyses.

RESULTS

During 10 581 902 person years of follow-up, 869 female participants with syndromes of autonomic dysfunction (136 with chronic fatigue syndrome, 535 with complex regional pain syndrome, and 198 with postural orthostatic tachycardia syndrome) were identified. Quadrivalent human papillomavirus vaccination did not statistically significantly increase the rate of a composite outcome of all syndromes with autonomic dysfunction in a 365 day risk period following vaccination (rate ratio 0.99, 95% confidence interval 0.74 to 1.32) or the rate of any individual syndrome in the risk period (chronic fatigue syndrome (0.38, 0.13 to 1.09), complex regional pain syndrome (1.31, 0.91 to 1.90), or postural orthostatic tachycardia syndrome (0.86, 0.48 to 1.54)).

CONCLUSIONS

When vaccination is introduced, adverse events could occur in close temporal relation to the vaccine purely by chance. These results do not support a causal association between quadrivalent human papillomavirus vaccination and chronic fatigue syndrome, complex regional pain syndrome, or postural orthostatic tachycardia syndrome, either individually or as a composite outcome. An increased risk of up to 32% cannot be formally excluded, but the statistical power of the study suggests that a larger increase in the rate of any syndrome associated with vaccination is unlikely.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Anecdotal links between human papillomavirus vaccination and syndromes with autonomic dysfunction, such as chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome, have been reported

Concerns about human papillomavirus vaccine persist and challenge cancer prevention in several countries through disappointing uptake of the vaccine

WHAT THIS STUDY ADDS

Our study did not support the hypothesis that quadrivalent human papillomavirus vaccine increases the risk of selected syndromes with autonomic dysfunction (chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome) in Danish girls and women

A moderate to large increase in the rate (more than 32%) of any syndrome associated with vaccination is unlikely given the statistical power of our study

Introduction

Human papillomavirus vaccines have been used in national immunisation programmes worldwide for more than a decade, with great success.[1] In countries such as Denmark, Japan, and Ireland, however, national immunisation programmes have had serious setbacks owing to concerns about safety.[2 3] These concerns have originated from anecdotal links between human papillomavirus vaccines and syndromes with autonomic dysfunction, such as chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and complex regional pain syndrome.[4-6] Rapid spread on social media and sensationalist media coverage have fuelled these concerns.

Chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and complex regional pain syndrome are complex disorders characterised by autonomic dysfunction, and present with many unspecific symptoms, such as headache, dizziness, and nausea.[7-9] Consequently, these syndromes, especially chronic fatigue syndrome and postural

orthostatic tachycardia syndrome, could individually have a wide range of unique presentations, and also considerable clinical overlap.[5 10]

In 2015, the European Medicines Agency concluded that there was no evidence that the human papillomavirus vaccine caused postural orthostatic tachycardia syndrome and complex regional pain syndrome.[11] This conclusion was echoed in a 2019 statement from the American Autonomic Society.[12] Most observational studies on the association of human papillomavirus vaccines and syndromes with autonomic dysfunction have evaluated chronic fatigue syndrome, including studies from the United Kingdom, Norway, Finland, and the Netherlands, which all reported no such association.[13-16] The Finnish study also evaluated postural orthostatic tachycardia syndrome and complex regional pain syndrome. This study's results again suggested no increased risk associated with human papillomavirus vaccination.[15] The clinical overlap between syndromes does support extrapolation and provides reassurance of the safety of human papillomavirus vaccines for autonomic dysfunctions. More evidence is needed, however, and examination of the association between human papillomavirus vaccination and complex regional pain syndrome and postural orthostatic tachycardia syndrome specifically, would be valuable. Furthermore, only the Norwegian study evaluated the quadrivalent human papillomavirus vaccine, whereas the three other studies evaluated the bivalent vaccine.

We took advantage of the unique Danish nationwide registers and evaluated the association between the quadrivalent human papillomavirus vaccine and chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome in a self-controlled case series analysis nested in a nationwide cohort of Danish female participants aged 10-44 years in 2007-16.

Methods

Study cohort

Denmark has a longstanding tradition of nationwide population based registers facilitating high quality epidemiological research. The key administrative and demographic register in Denmark is the Civil Registration System.[17] This register contains information on date of birth and familial links, together with daily updated information on vital status, civil status, and place of residence for every person residing in Denmark. This information is indexed by a unique identifier, which is used in all national registers and permits the construction of large nationwide cohorts with individual level information from many different sources. We constructed a study cohort of all Danish-born female participants aged 10-44 years in the period 2007-16 with information on human papillomavirus vaccination status and possible diagnoses of chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and complex regional pain syndrome. The study was approved by the Danish Data Protection Agency (approval No 2015-57-0102). Ethical approval is not required for register based research in Denmark.

Vaccination

We obtained information on dates of human papillomavirus vaccination in the study cohort from the Danish vaccination register.[18] The quadrivalent human papillomavirus vaccine (Gardasil, Merck Sharp and Dohme) was licensed in Europe in September 2006. In Denmark, universal vaccination of girls aged 12 with the quadrivalent human papillomavirus vaccine was started in January 2009, with catch-up vaccination of girls aged 13-15 starting in October 2008. Vaccination of women aged 20-27 was started in August 2012. Three doses of the vaccine in total were originally given, with the second and third doses administered two and six months, respectively, after the first dose. A schedule requiring two doses was introduced in August 2014 for girls given the first dose at age 12-13. The bivalent vaccine (Cervarix, GlaxoSmithKline) replaced the quadrivalent vaccine in February 2016.

The Danish vaccination register comprises human papillomavirus vaccinations administered as part of the free national childhood vaccination programme and also vaccinations privately purchased and given to those not eligible for the national programme.

Selected syndromes with autonomic dysfunction

Denmark healthcare is financed by tax payers, and general practitioners act as gatekeepers for referrals to specialists.[19] Our information on syndromes with autonomic dysfunction, in the form of chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome, was obtained from the Danish National Patient Register.[20] This register comprises information on all hospital patients in Denmark, including dates of admission and discharge, the care setting (that is, inpatient, outpatient, and emergency department services), diagnoses, procedures, and operations. Diagnoses are coded using ICD-10 (international classification of diseases, 10th revision).

As primary outcomes in the study, we included those with the following ICD-10 codes: postviral fatigue syndrome G93.3 and G93.3A for chronic fatigue syndrome; algoneurodystrophy M89.0 for complex regional pain syndrome (the recommended code for complex regional pain syndrome according to Danish guidelines); and supraventricular tachycardia, postural orthostatic tachycardia syndrome I47.1J for postural orthostatic tachycardia syndrome (this code is a Danish ICD-10 modification not present in the standard ICD-10). As a secondary outcome we included F45 and F48.0 (somatoform disorders and neurasthenia). We included both inpatients and outpatients and patients at emergency departments. Only the first outcome diagnosis was included, and thus, individuals are included only once in our analyses.

Statistical analysis

We followed up individual female participants in the study cohort from age 10 or 1 January 2007, whichever event came later, until the 45th birthday, 1 January 2017, emigration, death, or disappearance from the Civil Registration System, whichever event came first. Human papillomavirus vaccination was considered to be a time dependent variable with the possibility that both unvaccinated and vaccinated individuals could contribute to follow-up. Female participants who received human papillomavirus vaccines other than the quadrivalent human papillomavirus vaccine were censored. Chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome were analysed as a composite outcome in the main analysis, but each was also considered separately in secondary analyses.

The number of cases and person time of follow-up were aggregated according to vaccination status, age, and calendar period, and used to calculate incidence rates. In this descriptive analysis, any primary study outcome diagnosis was a censoring event.

We used the self-controlled case series method to compare the incidence rate of syndromes in a predefined risk period after vaccination with the quadrivalent human papillomavirus vaccine and the incidence rate in all other periods of follow-up for individual female participants with a study outcome.[21] In the self-controlled case series analysis, follow-up was not censored at diagnosis of any syndrome, and individuals contributed to the risk period of interest every time they received a dose of the vaccine. The "self-controlling" aspect of this approach provides implicit adjustment for all time independent covariates.

Three key assumptions must be fulfilled for the self-controlled case series to provide valid estimates.[22] Firstly, study outcomes must be either recurrent and independent or unique. Secondly, outcomes must not be fatal. Thirdly, experiencing an outcome must not influence future risk of exposure. Rate ratios (with 95% confidence intervals) comparing incidence rates according to vaccination status were estimated using conditional Poisson regression (conditional on the individual female participants). Unless otherwise specified, we adjusted rate ratios for age (ages 10-35 in one year intervals, 36-41 in two year intervals, 42-44 years of age) and season (January-March, April-June, July-September, October-December). We predefined a risk period of 365 days after the last vaccination for our main analysis to allow for a possible insidious onset and delayed clinical investigation owing to the complex nature of the study outcomes. The risk period was re-entered for each additional dose of vaccine received. Thus an individual receiving three doses of vaccine with two and four month intervals between the doses, contributed 18 months (2+4+12 months) of follow-up to the one year risk period (supplementary fig S1).

In sensitivity analyses, we explored alternative risk periods (0-91 days, 92-181 days, 182-365 days, 366 or more days after the last vaccination), excluded the periods immediately before and after vaccination (seven days before and seven days after last vaccination), compared the main risk period (0-365 days after the last vaccination) only with the later vaccinated period (more than 365 days after the last vaccination), and conducted stratified analyses of the main risk period effect in strata according to age and calendar period. We also evaluated the association between quadrivalent human papillomavirus vaccination and a secondary study outcome (somatoform disorders and neurasthenia). Finally, we also estimated the rate ratio for any syndrome comparing the 365 day risk period with referent period rates in the full cohort using Poisson regression, with adjustment for age, calendar period, and season.

Previous studies have shown a link between healthcare use and later diagnosis of chronic fatigue syndrome or reporting of serious adverse events after human papillomavirus vaccination.[14 23] We estimated the risk of being diagnosed with an autonomic dysfunction syndrome conditional on healthcare use at baseline and evaluated the association between quadrivalent human papillomavirus vaccination and any syndrome in the resulting risk strata (details of methods and results are given in the supplementary material).

Data management and statistical analyses were conducted using R version 3.5.1 (R Core Team, 2017). Analyses were conducted using the SCCS package. For data manipulation and plots we used the packages eeptools, data.table, plyr, ggsci, ggplot2, and gridExtra. All packages available from https://cran.r-project.org/web/packages/.

Patient and public involvement

Our study was conducted in response to public concerns about vaccine safety. The inclusion of specific outcomes in our study was informed by public and patient anecdotal information.

Results

Our study cohort included 1 375 737 Danish-born female participants aged 10-44 years during the 2007-16 study period. During 10 581 092 person years of follow-up, 23 493 study participants were lost to follow-up (19 273 due to emigration, 4069 to death, 151 to disappearance) and 11 931 were censored owing to vaccination with other human papillomavirus vaccines. In the study cohort, 529 547 female participants received at least one dose of the quadrivalent human papillomavirus vaccine. Among girls aged 10-17, vaccines were given at a median age of 12.6 years (interquartile range 2.0), and among women aged 18-44 at a median age of 24.3 years (4.9). We observed chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome in 869 participants of the study cohort, corresponding to an incidence rate of 8.21 per 100 000 person years. Complex regional pain syndrome was the most common syndrome, occurring in 535 participants, followed by postural orthostatic

tachycardia syndrome in 198 and chronic fatigue syndrome in 136.

The incidence rates for all syndromes increased throughout the study period, being especially marked for postural orthostatic tachycardia syndrome and also reflected in the composite outcome of any syndrome (table 1). For all syndromes, the incidence rates were highest among adolescent girls. The incidence rates for postural orthostatic tachycardia syndrome declined markedly with increasing age, whereas those for chronic fatigue syndrome and complex regional pain syndrome showed a U shape with slight increases in older women (table 1). The median age at diagnosis of any syndrome was 14.0 years (interquartile range 3.6) among girls aged 10-17, and 33.3 years (13.5) among women aged 18-44 (table 2). Among individuals with any syndrome, the median age at first vaccination was 12.3 years (interquartile range 0.8) among girls aged 10-17, and 21.9 years (9.8) among women aged 18-44 (table 2).

Among 433 individuals with a syndrome diagnosis vaccinated during the study period (55 with chronic fatigue syndrome, 223 with complex regional pain syndrome, and 155 with postural orthostatic tachycardia syndrome), most received a diagnosis after vaccination; this diagnosis was especially marked for chronic fatigue syndrome and postural orthostatic tachycardia syndrome (fig 1A) and particularly pronounced in the later study period (fig 1B).

In the self-controlled case series analysis, chronic fatigue syndrome occurred in four individuals, complex regional pain syndrome in 49, and postural orthostatic tachycardia syndrome in 19 within the one year risk period after vaccination. Follow-up in the one year risk period was primarily composed of contributions from adolescent girls vaccinated according to schedule (supplementary fig S2). No statistically significantly increased rate was found between quadrivalent human papillomavirus vaccination and any syndrome (rate ratio 0.99, 95% confidence interval 0.74 to 1.32), chronic fatigue syndrome (0.38, 0.13 to 1.09), complex regional pain syndrome (1.31, 0.91 to 1.90), or postural orthostatic tachycardia syndrome (0.86, 0.48 to 1.54) (table 3). We conducted a number of sensitivity analyses of the association between quadrivalent human papillomavirus vaccination and any syndrome (table 4). No association was found between quadrivalent human papillomavirus vaccination and any syndrome in girls aged 10-17 (rate ratio 0.81, 95% confidence interval 0.56 to 1.18) or in women aged 18-44 (1.36, 0.87 to 2.12), in the period before 1 January 2015 (1.00, 0.73 to 1.36) or after (0.80, 0.37 to 1.71) (table 4).

Removing the seven day period just before and after vaccination or removing unvaccinated follow-up from the reference period had little effect (rate ratio 1.02, 95% confidence interval 0.76 to 1.37 and 0.96, 0.68 to 1.35, respectively, table 4). When a number of additional risk periods were examined no increased rates were found (0-91 days: rate ratio 0.81; 92-181 days: 1.00; 182-365 days: 1.32; all estimates statistically non-significant; table 4). We analysed a secondary outcome (somatoform disorders and neurasthenia) and found no increased rate in the one year risk period after vaccination (rate ratio 0.95, 95% confidence interval 0.79 to 1.14). Comparison of the 365 day risk period and referent period rates in the full cohort using Poisson regression, with adjustment for age, calendar period, and season, yielded a rate ratio for any syndrome of 0.90 (95% confidence interval 0.67 to 1.18).

Discussion

Principal findings

In a self-controlled case series analysis of 869 cases nested in a large nationwide cohort comprising 1.4 million Danish female participants, we observed no association between quadrivalent human papillomavirus vaccination and the rates of chronic fatigue syndrome, postural orthostatic tachycardia syndrome, or complex regional pain syndrome.

Comparison with other studies

The pathophysiology of chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and complex regional pain syndrome is poorly understood.[24 25] Human papillomavirus vaccination

Table 1 | Incidence rates (95% confidence intervals) per 100 000 years of follow-up of selected syndromes with autonomic dysfunction among 1 375 737 female participants aged 10-44 years, born in Denmark between 2007 and 2016

Characteristics	No of person years of follow-up (100 000 years)	Any syndrome		Chronic fatigue syndrome		Complex regional pain syndrome		Postural orthostatic tachycardia syndrome	
		No of cases	IR (95% CI) (per 100 000 years)	No of cases	IR (95% CI) (per 100 000 years)	No of cases	IR (95% CI) (per 100 000 years)	No of cases	IR (95% CI) (per 100 000 years)
Overall	105.81	869	8.21 (7.68 to 8.77)	136	1.29 (1.08 to 1.51)	535	5.06 (4.64 to 5.50)	198	1.87 (1.62 to 2.14)
Period:									
2007-08	21.80	100	4.59 (3.75 to 5.55)	22	1.01 (0.64 to 1.49)	77	3.53 (2.80 to 4.38)	1	0.05 (0.003 to 0.20)
2009-10	21.49	102	4.75 (3.88 to 5.73)	16	0.74 (0.44 to 1.17)	80	3.72 (2.97 to 4.60)	6	0.28 (0.11 to 0.57)
2011-12	21.16	163	7.70 (6.58 to 8.95)	23	1.09 (0.70 to 1.59)	112	5.29 (4.37 to 6.34)	28	1.32 (0.89 to 1.88)
2013-14	20.86	240	11.51 (10.11 to 13.03)	39	1.87 (1.34 to 2.52)	131	6.28 (5.27 to 7.42)	70	3.36 (2.63 to 4.21)
2015-16	20.51	264	12.87 (11.38 to 14.49)	36	1.76 (1.24 to 2.39)	135	6.58 (5.53 to 7.76)	93	4.53 (3.67 to 5.52)
Age (years):									
10-17	25.21	323	12.81 (11.47 to 14.26)	43	1.71 (1.25 to 2.27)	167	6.62 (5.67 to 7.68)	113	4.48 (3.71 to 5.36)
18-24	20.70	128	6.18 (5.17 to 7.32)	15	0.72 (0.42 to 1.16)	68	3.29 (2.56 to 4.13)	45	2.17 (1.60 to 2.87)
25-34	26.83	175	6.52 (5.60 to 7.54)	31	1.16 (0.79 to 1.61)	115	4.29 (3.55 to 5.12)	29	1.08 (0.73 to 1.52)
35-44	33.07	243	7.35 (6.46 to 8.31)	47	1.42 (1.05 to 1.87)	185	5.59 (4.83 to 6.44)	11	0.33 (0.17 to 0.57)

Table 2 | Descriptive characteristics of 869 cases of autonomic dysfunction syndrome among female participants aged 10-44 born in Denmark during 2007-16. Results are shown as median (interquartile range)

Characteristics	Any syndrome	Chronic fatigue syndrome	Complex regional pain syndrome	Postural orthostatic tachycardia syndrome
Age at study entry (years):				
All patients with a syndrome diagnosis	17.76 (19.72)	21.05 (19.18)	23.14 (22.34)	10.00 (6.27)
Girls aged 10-17	10.00 (0.00)	10.00 (2.01)	10.00 (0.00)	10.00 (0.00)
Women aged 18-44	27.59 (14.07)	27.93 (12.88)	29.06 (12.37)	17.18 (9.57)
Age at first vaccination (years)*:				
All patients with a syndrome diagnosis	13.04 (8.39)	15.48 (9.35)	13.28 (9.46)	12.52 (2.47)
Girls aged 10-17	12.25 (0.76)	13.04 (2.73)	12.23 (0.75)	12.21 (0.46)
Women aged 18-44	21.91 (9.79)	22.33 (6.89)	23.37 (6.25)	16.76 (8.91)
Age at diagnosis (years):				
All patients with a syndrome diagnosis	24.11 (21.08)	28.44 (20.74)	29.26 (22.71)	16.87 (8.52)
Girls aged 10-17	13.99 (3.55)	14.66 (4.03)	13.20 (3.10)	14.60 (2.99)
Women aged 18-44	33.31 (13.54)	35.00 (11.84)	35.07 (11.79)	24.46 (8.44)
Time from first vaccination to diagnosis (years)*:				
All patients with a syndrome diagnosis	1.86 (3.89)	2.17 (5.08)	1.05 (3.63)	2.95 (3.22)
Girls aged 10-17	1.52 (3.51)	1.92 (4.30)	0.73 (3.33)	2.15 (2.25)
Women aged 18-44	2.53 (5.47)	2.63 (7.09)	1.62 (4.34)	4.63 (3.62)

*Among vaccinated patients with a syndrome diagnosis (n=433).

has been proposed to increase the risk of syndromes with autonomic dysfunction through autoimmune mechanisms.[26] Autoantibodies have been described in patients with chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and complex regional pain syndrome, and viral infections precipitating the onset of chronic fatigue syndrome have been reported.[27-30] Complex regional pain syndrome has been seen after vaccination with other vaccines, such as hepatitis B vaccine and rubella vaccine in adolescent girls, possibly provoked by needle trauma.[31 32]

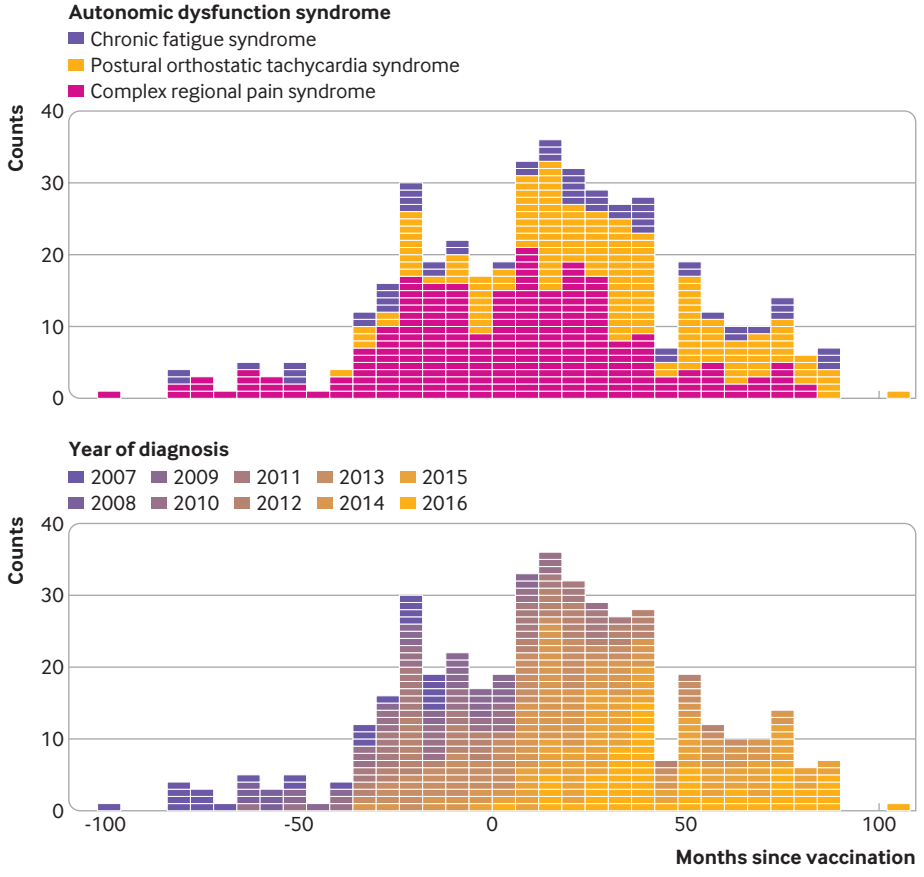

Fig 1 | Frequency of autonomic dysfunction syndrome (chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and complex regional pain syndrome) (A) before and after vaccination and (B) according to year of diagnosis before and after vaccination among Danish female participants aged 10-44 years during 2007-16 (only vaccinated patients with a syndrome diagnosis, n=433)

Table 3 | Self-controlled case series analysis of quadrivalent human papillomavirus vaccination and rate of selected syndromes with autonomic dysfunction in Danish female participants

Risk period	No of cases	No of person years	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)*
Any syndrome:				
Reference period†	797	6735	1 (reference)	1 (reference)
0-365 days after vaccination	72	644	0.87 (0.68 to 1.13)	0.99 (0.74 to 1.32)
Chronic fatigue syndrome:				
Reference period†	132	1100	1 (reference)	1 (reference)
0-365 days after vaccination	4	79	0.41 (0.15 to 1.15)	0.38 (0.13 to 1.09)
Complex regional pain syndrome:				
Reference period†	486	4242	1 (reference)	1 (reference)
0-365 days after vaccination	49	339	1.21 (0.88 to 1.67)	1.31 (0.91 to 1.90)
Postural orthostatic tachycardia syndrome:				
Reference period†	179	1393	1 (reference)	1 (reference)
0-365 days after vaccination	19	226	0.59 (0.37 to 0.96)	0.86 (0.48 to 1.54)

*Adjusted for age in one year categories (except in the older part of the cohort where the groupings 36-37, 38-39, 40-41, and 42-44 are used) and season (January-March, April-June, July-September, October-December).
†Comprising unvaccinated follow-up and follow-up from the period 366 days or more after vaccination.

Several observational studies have evaluated the association between human papillomavirus vaccination and syndromes with autonomic dysfunction. Donegan and colleagues conducted a self-controlled case series analysis of 187 girls with fatigue syndrome (chronic fatigue syndrome/myalgic encephalomyelitis, postviral fatigue syndrome, fibromyalgia, neurasthenia) from the UK Clinical Practice Research Datalink.[13] No association was found in the year after vaccination with the first dose of the bivalent human papillomavirus vaccine (rate ratio 1.07, 95% confidence interval 0.57 to 2.00).

Feiring and colleagues conducted a survival analysis of 176 453 girls from the Norwegian Patient Registry, including 407 girls with chronic fatigue syndrome/myalgic encephalomyelitis.[14] No association with the quadrivalent human papillomavirus vaccine was found (hazard ratio 0.86, 95% confidence interval 0.69 to 1.08). Norwegian guidelines recommend that chronic fatigue syndrome/myalgic encephalomyelitis in childhood and adolescence should be diagnosed by a paediatrician in a specialised healthcare setting; 73% of adolescents diagnosed as having chronic fatigue syndrome/myalgic encephalomyelitis in Norway fulfilled the Fukuda criteria in another study.[33] Furthermore, the authors argue that in Norway, patients with postural orthostatic tachycardia syndrome are likely to be diagnosed as having chronic fatigue syndrome/myalgic encephalomyelitis. It is noteworthy that the incidence of chronic fatigue syndrome/myalgic encephalomyelitis is about 10-fold higher in Norway than in Denmark. This disparity is unlikely to represent a real difference but is more likely to represent different diagnostic practices and traditions. In Norway, an increase in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis was seen during 2009 to 2014, which was independent of the human papillomavirus vaccine and was seen in both sexes.

In a small Dutch self-controlled case series of 16 vaccinated girls with longlasting fatigue from primary care, no association was found with the bivalent human papillomavirus vaccine (rate ratio 0.62, 95% confidence interval 0.07 to 5.49) in the year after any dose.[16]

In a Finnish cohort of 240 605 girls, Skufca and colleagues evaluated the association between bivalent human papillomavirus vaccine and 38 outcomes identified using the Finnish national hospital discharge register, including chronic fatigue syndrome (n=355), complex regional pain syndrome (n=14), and postural orthostatic tachycardia syndrome (n=37).[15] No increased risk was found to be associated with the vaccine: chronic fatigue syndrome, hazard ratio 0.75 (95% confidence interval 0.59 to 0.95); complex regional pain syndrome, 0.34 (0.11 to 1.05); and postural orthostatic tachycardia syndrome, 0.99 (0.46 to 2.11).

These observational studies used analytical longitudinal study designs and provide reassuring results from different countries and different settings of care (from both general practice and hospitals). Only one of four studies, however, evaluated the quadrivalent human papillomavirus vaccine. Most studied patients with chronic fatigue syndrome or fatigue related illness, and the studies focused on adolescent girls. We provide reassuring support for the safety of the quadrivalent human papillomavirus vaccine also in adult female populations with catch-up vaccination and vaccinations outside the national programme by individual choice. A considerable proportion of reports of serious adverse events after human papillomavirus vaccination have been reported by women.[34] Our study is also by far the largest of the associations between human papillomavirus vaccination and complex regional pain syndrome and postural orthostatic tachycardia syndrome diagnoses.

Table 4 | Sensitivity analyses of the association between human papillomavirus vaccination and rate of any syndrome

	Adjusted rate ratio (95% CI)‡	No of cases in risk period	No of person years
Main analysis of any syndrome*	0.99 (0.74 to 1.32)	72	644
Stratified analyses of the 0-365 days after vaccination v referent period rate ratio			
Risk periods for different age groups:			
Girls aged 10-17	0.81 (0.56 to 1.18)	47	458
Women aged 18-44	1.36 (0.87 to 2.12)	25	187
Risk periods before and after 1 January 2015:			
Before 1 January 2015	1.00 (0.73 to 1.36)	63	593
From 1 January 2015	0.80 (0.37 to 1.71)	9	51
Alternative risk periods and referent periods			
Time after vaccination *v* referent period (days)†:			
0-91	0.81 (0.48 to 1.34)	21	263
92-181	1.00 (0.56 to 1.76)	16	153
182-365	1.32 (0.83 to 2.10)	35	228
≥366 days	1.12 (0.75 to 1.68)	237	1667
Excluding 7 days before and after vaccination from the main analysis	1.02 (0.76 to 1.37)	71	606
0-365 days after vaccination risk period *v* ≥366 days after vaccination	0.96 (0.68 to 1.35)	72	644

*Any syndrome adjusted rate ratio comparing 0-365 days after vaccination with the referent period (table 3).
†Referent period comprising only unvaccinated follow-up.
‡Adjusted for age in one year categories (except in the older part of the cohort where the groupings 36-37, 38-39, 40-41, and 42-44 are used) and season (January-March, April-June, July-September, October-December).

Strength and limitations of this study

Our study had a number of limitations. Outcomes defined by diagnostic codes are widely used for

epidemiological research in the Danish National Patient Registry,[35] but the diagnostic validity of the ICD-10 codes used in our study has not been established in Denmark. Diagnosis of these conditions is complex, and the possibility of misclassification and under-ascertainment cannot be discounted. In view of the wide publicity about the safety of vaccination, girls vaccinated with the human papillomavirus vaccine might be more likely to be diagnosed as having syndromes with autonomic dysfunction, resulting in a falsely increased rate ratio, especially in the later periods of the study. More patients have diagnoses after vaccination in our study (fig 1), especially in the later periods. This is not reflected in the adjusted self-controlled case series analyses, including in the stratification by calendar period (table 4). Any misclassification of patients as having chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome could bias the observed associations. Patients most likely to be misclassified are those with at least some of the symptoms specific for chronic fatigue syndrome, complex regional pain syndrome, and postural orthostatic tachycardia syndrome, which may also be valuable to include in a study of syndromes with autonomic dysfunction. Our main period of interest for examination of risk was the year after vaccination with the quadrivalent human papillomavirus vaccine. This period was predefined and allowed for an insidious onset or prolonged diagnostic investigation. The two previous self-controlled case series analyses of bivalent human papillomavirus vaccination and chronic fatigue syndrome from the UK and the Netherlands also used a predefined risk period of one year after vaccination.[13 16] Our sensitivity analyses of alternative risk periods found no increased rates associated with quadrivalent human papillomavirus vaccination.

Our study used a self-controlled case series analysis nested in a nationwide cohort, with independent ascertainment of vaccination and outcome status, thus reducing concerns about selection and information bias. Furthermore, since the self-controlled case series method is designed to eliminate time invariant confounding, lifestyle and socioeconomic factors are unlikely to have biased our results. A number of assumptions must be fulfilled for the self-controlled case series method to produce unbiased estimates.[22] In our study, we believe these assumptions were met, since the outcomes were rare, were non-fatal, and when we removed unvaccinated follow-up from the referent group in sensitivity analyses, results were consistent with the main analysis. We conducted sensitivity analyses, removing the seven days immediately before and after vaccination from the comparison, and using only vaccinated follow-up. All the results were consistent with the main analyses, reducing concern that only girls in good health are vaccinated.

Perspective

When mass vaccination is introduced in a population, individuals will experience adverse events in close temporal relation to the vaccine purely by chance.[36] In particular, chronic fatigue syndrome and postural orthostatic tachycardia syndrome are not uncommon in young adolescent girls and it is thus not surprising that temporal relations have been seen. Mass psychogenic illness has also been suggested to be a contributing factor to concerns about the safety of the human papillomavirus vaccine.[37] In Colombia in 2014, a group of 15 girls from the same school presented with symptoms of autonomic dysfunction after human papillomavirus vaccination.[38] Videos of these girls quickly went viral online on social media and more than 600 individuals with similar symptoms were reported from all over Colombia in the following weeks. The speed with which these putative links can spread, through television, newspapers, and social media, poses a challenge to public health authorities and regulatory agencies. In countries such as Colombia and Japan, uptake rates of human papillomavirus vaccination have dropped to such an extent that lives will be lost to cervical cancer as a consequence.[38 39] Hopefully, studies such as ours and innovative health information campaigns can turn the tide and reduce the damage done to human papillomavirus vaccination programmes worldwide.

Conclusion

In conclusion, our study does not support a causal association between quadrivalent human papillomavirus vaccination and chronic fatigue syndrome, complex regional pain syndrome, or postural orthostatic tachycardia syndrome, either individually or as a composite outcome. Although we cannot formally exclude the possibility of an increased risk of up to 32%, a larger increase in the rate of any syndrome associated with vaccination is unlikely given the statistical power of our study.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the Danish Medicines Agency, Danish Cancer Society, and the Novo Nordisk Foundation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the Danish Data Protection Agency (approval No 2015-57-0102). Ethical approval is not required for register-based research in Denmark.

Data sharing: The data consist of individual histories of events which we cannot share. No additional data available.

AH affirms that the manuscript is an honest, accurate and transparent account of the conducted study; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: We plan to disseminate the results of this study through conference talks and a press release.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Web appendix: Supplementary materials