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Human papillomavirus vaccination of adult women and risk of autoimmune and neurological diseases

A. Hviid[1], H. Svanström[1], N. M. Scheller[1], O. Grönlund[2], B. Pasternak[1,3] & L. Arnheim-Dahlström[2]

From the [1]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark; [2]Department of Medical Epidemiology and Biostatistics; and [3]Department of Medicine Solna, Clinical Epidemiology Unit, Karolinska Institutet, Stockholm, Sweden

Abstract. Hviid A, Svanström H, Scheller NM, Grönlund O, Pasternak B, Arnheim-Dahlström L (Statens Serum Institut, Copenhagen, Denmark; Karolinska Institutet, Stockholm, Sweden). Human papillomavirus vaccination of adult women and risk of autoimmune and neurological diseases. *J Intern Med* 2018; **283**: 154–165.

Background. Since 2006, human papillomavirus (HPV) vaccines have been introduced in many countries worldwide. Whilst safety studies have been reassuring, focus has been on the primary target group, the young adolescent girls. However, it is also important to evaluate safety in adult women where background disease rates and safety issues could differ significantly.

Objective. We took advantage of the unique Danish and Swedish nationwide healthcare registers to conduct a cohort study comparing incidence rate

Results. The study cohort comprised 3 126 790 women (1 195 865 [38%] Danish and 1 930 925 [62%] Swedish) followed for 16 386 459 person-years. Vaccine uptake of at least one dose of qHPV vaccine was 8% in the cohort: 18% amongst Danish women and 2% amongst Swedish. We identified seven adverse events with statistically significant increased risks following vaccination—Hashimoto's thyroiditis, coeliac disease, localized lupus erythematosus, pemphigus vulgaris, Addison's disease, Raynaud's disease and other encephalitis, myelitis or encephalomyelitis. After taking multiple testing into account and conducting self-controlled case series analyses, coeliac disease (RR 1.56 [95% confidence interval 1.29–1.89]) was the only remaining association.

Conclusion. Unmasking of conditions at vaccination visits is a plausible explanation for the increased risk associated with qHPV in this study because

ratios (RRs) of 45 preselected serious chronic diseases in quadrivalent HPV (qHPV)-vaccinated and qHPV-unvaccinated adult women 18–44 years of age.

Methods. We used Poisson regression to estimate RRs according to qHPV vaccination status with two-sided 95% confidence intervals (95% CIs).

coeliac disease is underdiagnosed in Scandinavian populations. In conclusion, our study of serious adverse event rates in qHPV-vaccinated and qHPV-unvaccinated adult women 18–44 years of age did not raise any safety issues of concern.

Keywords: Cohort study, Epidemiology, Human papillomavirus, Vaccine Safety.

Since 2006, human papillomavirus (HPV) vaccines have been introduced in many countries worldwide including all of North America and most of Western Europe [1]. The peak incidence of HPV infection occurs soon after sexual debut, and to increase vaccine effectiveness, national immunization programmes target the youngest adolescent girls of 9–12 years of age. Consequently, the majority of postlicensure evidence of the safety of HPV vaccines comes from young adolescents [2]. However, adult women are also getting HPV vaccinated through catch-up programmes or by choice at their own expenses. Indeed, the Advisory Committee on Immunization Practices recommends HPV vaccination of females through the age of 26 years, and recent estimates indicate that amongst HPV-vaccinated women aged 19–26 years approximately 20% received their first vaccine dose at the age of 19 or older [3, 4]. In adult women, evidence of vaccine safety is limited to primarily prelicensure phase II/III randomized clinical trials including women 15–26 years of age [5]. These studies have been reassuring, but only statistically powered to evaluate common adverse events such as local

reactions and general symptoms such as fever and nausea. In addition, randomized trials are being conducted in women older than 25 years of age with favourable vaccine efficacy estimates against infection and cervical abnormalities up to 45 years of age, suggesting that the age indication might be expanded in future [6, 7].

When a large population is vaccinated, cases of serious and rare chronic disease are expected to occur in temporal relationship to vaccination purely by chance [8]. Despite this fact, sensationalist reporting of such cases in traditional and social media channels is frequently the source of public concern and anti-vaccine sentiment [9]. To properly address vaccine safety concerns and contribute relevant safety data to help inform clinical practice and assessment by drug authorities, carefully designed and well-conducted postlicensure studies are vital. Furthermore, many chronic diseases, such as autoimmune or neurological diseases, that are often allegedly linked to HPV vaccination occur at markedly different rates in young girls and adult women. Thus, it is also important to evaluate HPV vaccine safety in all target groups and not just the primary group of young girls.

We took advantage of the unique Danish and Swedish nationwide healthcare registers to conused to access information in national registers [11]. We used this identifier to obtain information on HPV vaccination status, serious chronic disease and possible confounders for all women in the cohort.

HPV vaccination

The qHPV vaccine (Gardasil; Sanofi Pasteur MSD SNC, Lyon, France) was licensed in Europe in September 2006. In Denmark, the qHPV vaccine has been included in the national vaccination programme since 2009 for 12-year-old girls, with catch-up vaccination of girls 13–15 years of age from October 2008 and of young women 20–27 years of age from August 2012. In Sweden, the qHPV vaccine was available from May 2007 as a subsidized vaccine for 13- to 17-year-old girls outside the national programme. In January 2012, the vaccine was included in the national vaccination programme for 10- to 12-year-old girls together with catch-up vaccination of 13- to 18-year-old girls. Since licensure, the qHPV vaccine has also been available in both countries for adult women at their own expense.

In both Denmark and Sweden, we obtained information on qHPV vaccinations primarily from the national prescription registers (Anatomic Therapeutic Chemical [ATC] code J07BM01) [12, 13].

duct a postlicensure cohort study comparing rates of serious chronic disease in quadrivalent HPV (qHPV)-vaccinated and qHPV-unvaccinated adult women 18–44 years of age.

Materials and methods

We designed a register-based cohort study including all Danish and Swedish women 18–44 years of age in the period from 1 October 2006 to 30 June 2013 for Danish women and to 31 December 2012 for Swedish women (we did not have access to Swedish data beyond this date). We accomplished this using register data from the Danish Civil Registration System and Statistics Sweden, respectively [10]. These registers contain basic demographic information such as date of birth, date of potential loss to follow-up by, for example, emigration or death and a unique personal identifier for each resident. Both Denmark and Sweden keep nationwide registers of demographic and health-related information on all residents. In both countries, a unique personal identifier is assigned to all residents and is

Both registers contain individual-level information on all prescriptions filled at Danish and Swedish pharmacies, respectively. We supplemented this with information on catch-up vaccinations of young women given within the national vaccination programmes. We obtained this information from national vaccination registers. In Denmark, we used the Childhood Vaccination Database, which contains information on all vaccinations administered in the national childhood vaccination programme [14]. In Sweden, we used the Swedish HPV vaccination register, which was launched in parallel with the start of opportunistic HPV vaccination [15]. For vaccinations identified through prescription data, we defined the date of vaccination as the date of filling the prescription plus 2 days, which was the average time to administration amongst a subset of vaccinations with registrations in both prescription and national registers. Because the use of the bivalent HPV vaccine is rare in both Denmark and Sweden (given to <1% of all vaccines), it was not evaluated in the present study. The 9-valent HPV vaccine was not in use during the study period.

Serious adverse events

Before conducting the study, we predefined a number of serious chronic disease outcomes using International Classification of Diseases 10th revision (ICD-10) codes—see Table S1 for all study outcomes with corresponding ICD-10 codes. We included a wide range of autoimmune diseases because these are often claimed to be adverse effects of vaccinations. We also included a selection of neurological diseases, mainly based on recent reports of increased risks of neurological diseases such as Guillain–Barré syndrome and narcolepsy after pandemic influenza vaccination. In addition, many of the predefined outcomes have been linked with vaccination in traditional and social media channels in reports of disease occurring in the immediate time-period following vaccination. Finally, the selected study outcomes are similar to what has previously been included in studies of HPV vaccine safety [16]. In total, we evaluated 45 outcomes.

In both Denmark and Sweden, we used hospital patient registers to obtain the predefined diagnoses (coded using ICD-10 with dates of hospital contacts) for all women in the cohort [17, 18]. Both registers contain nationwide individual-level information on all hospital contacts in the study period including inpatient and outpatient visits. We had age, calendar year, qHPV vaccination status and country of residence. We then used Poisson regression (log-linear regression of the counts with the logarithm of person-time as offset) to estimate incidence rate ratios (RRs) according to qHPV vaccination status with two-sided 95% confidence intervals (95% CIs). QHPV vaccination status was a time-varying variable; each woman could contribute person-time as both unvaccinated and vaccinated if applicable. All study outcomes were analysed separately so that one woman could contribute with more than one study outcome during follow-up; i.e. women were not censored due to outcomes not under study in one particular analysis. Women with the study outcome before beginning of follow-up for that outcome were not eligible for that particular analysis; i.e. prevalent disease cases were excluded. When identifying the first hospitalization for a given outcome, we considered hospitalization register data in the preceding 10 years. RRs were adjusted for age (categories 18–24, 25–29, 30–34, 35–39 and 40–44 years of age), calendar year (2-year intervals) and country of residence (Denmark or Sweden).

We subdivided all follow-up times as qHPV vaccinated into two risk periods: an acute period comprising the first 179 days after vaccination and a long-term period comprising all vaccinated follow-up times in the study after the first 180 days.

no information from primary health care. However, in both countries, primary health care acts as a gatekeeper to further care within specialized departments in the hospital setting.

Statistical methods

Study follow-up started on the date of becoming 18 years of age or 1 October 2006, whichever came last. Women who received their first vaccination prior to this date were excluded from the study cohort. We chose this new user design to remove women with a history of HPV vaccination without any adverse events as they might have a lower risk of developing adverse events after subsequent HPV vaccinations. Follow-up ended on the date of loss to follow-up (emigration, death or disappearance), vaccination with the bivalent HPV vaccine, first hospitalization with the outcome under study, 45 years of age or end of follow-up (1 July 2013 for Danish women or 1 January 2013 for Swedish), whichever came first. For each disease, this yielded outcome counts together with the corresponding number of person-years of follow-up, according to

These periods were defined according to the latest date of vaccination. Thus, after each dose, the vaccinated women re-entered the acute risk period. The duration of the acute period was defined as such to allow for the insidious onset of disease together with diagnostic investigation. This is similar to risk periods after HPV vaccination in comparable studies. We estimated adjusted RRs for the acute period, the period after the first 180 days and the combined period following qHPV vaccination.

Sensitivity analyses

For each significantly increased RR (lower bound of 95% CI > 1.0), we (i) reanalysed the association using the self-controlled case series (SCCS) method to take potential confounding by all unmeasured time-invariant confounders into account [19], (ii) compared RRs between Denmark and Sweden for consistency of association and (iii) recalculated the confidence interval using the Bonferroni correction to take multiple testing into account. For any associations that remained after these three

criteria were applied, we additionally assessed clustering of events in time by plotting cases according to time since vaccination.

For the SCCS analysis, we used the cases and follow-up from the cohort analysis, except that when becoming a case, follow-up was not terminated but continued until any of the other conditions for terminating follow-up in the cohort analysis were met. We then used a conditional Poisson model to derive incidence ratios (IRs) by comparing the rate of events during the period under investigation with the rate of events in the unvaccinated period for each case. The IRs derived from the SCCS analysis were adjusted for age and calendar year periods similar to the main analysis.

Given the large number of study outcomes and two risk periods under investigation, we conducted a significant number of separate analyses (n = 3*45). However, as different risk period analyses for a given study outcome cannot be assumed statistically independent, we conservatively used the number of study outcomes (n = 45) for Bonferroni-corrected confidence intervals corresponding to 1−(0.05/45)% confidence intervals.

Results

The study cohort comprised 3 126 790 women (1 195 865 [38%] Danish and 1 930 925 [62%] Swedish) aged 18–44 years with a mean age of entry into the study of 29.8 years (Table 1).

Table 1 *Descriptive characteristics of Danish and Swedish women 18–44 years of age in the period from 1 October 2006 to 30 June 2013 for Danish women or 31 December 2012 for Swedish women*[a]

	Overall (n = 3 126 790)	Denmark (n = 1 195 865)	Sweden (n = 1 930 925)
Person-years of follow-up	16.386.459	6.536.547	9.849.913
Age at entry, mean (SD)	29.8 (8.7)	30.2 (8.6)	29.6 (8.7)
Year of study entry			
2006	2 708 683 (87)	1 057 223 (88)	1 651 460 (86)
2007	101 127 (3)	38 369 (3)	62 758 (3)
2008	94 342 (3)	35 538 (3)	58 804 (3)

2009	77 239 (2)	29 345 (2)	47 894 (2)
2010	66 038 (2)	24 845 (2)	41 193 (2)
2011	43 151 (1)	4911 (<0.5)	38 240 (2)
2012	34 509 (1)	3933 (<0.5)	30 576 (2)
2013	1701 (<0.5)	1701 (<0.5)	0 (0)
Age at vaccination, mean (SD)	24.6 (4.9)	25.1 (4.7)	21.2 (4.8)
Vaccinated with quadrivalent HPV			
First dose	242 720 (8)	211 188 (18)	31 532 (2)
Second dose	201 965 (6)	176 196 (15)	25 769 (1)
Third dose	135 885 (4)	116 806 (10)	19 079 (1)
Year of vaccination			
2006	342 (<0.5)	119 (<0.5)	223 (1)
2007	8385 (3)	3947 (2)	4438 (14)
2008	13 927 (6)	9879 (5)	4048 (13)
2009	12 915 (5)	9787 (5)	3128 (10)
2010	7755 (3)	5968 (3)	1787 (6)
2011	12 184 (5)	8936 (4)	3248 (10)
2012	132 756 (55)	118 096 (56)	14 660 (46)
2013	54 456 (22)	54 456 (26)	0 (0)

[a]Values are numbers (percentages) unless otherwise stated.

Vaccine uptake of at least one dose of qHPV vaccine was 8% in the cohort: 18% amongst Danish women and 2% amongst Swedish. Amongst Danish women, 10% received all three doses, and amongst Swedish women, 1% received all three doses during the study period. The mean age at vaccination was 25.1 years in Denmark and 21.2 years in Sweden. For both Denmark and Sweden, the majority of all vaccinations were administered in 2012 (56% and 46%, respectively).

We followed women in the cohort for 16 386 459 person-years according to qHPV vaccination status: 319 298 years amongst vaccinated and 16 067 162 years amongst unvaccinated. During the study period, 150 629 women were lost to follow-up (emigration $N = 142\ 127$, death $N = 7281$ or unexplained disappearance from the source registers $N = 1221$) and 591 were vaccinated with the bivalent HPV vaccine and consequently censored. This yielded crude incidence rates for 45 autoimmune and neurological study outcomes amongst qHPV-vaccinated and qHPV-unvaccinated women (Fig. 1).

We identified seven adverse events with statistically significant increased RRs associated with qHPV vaccination compared with four adverse events with statistically significant reduced RRs (Table 2). RRs for Hashimoto's thyroiditis were

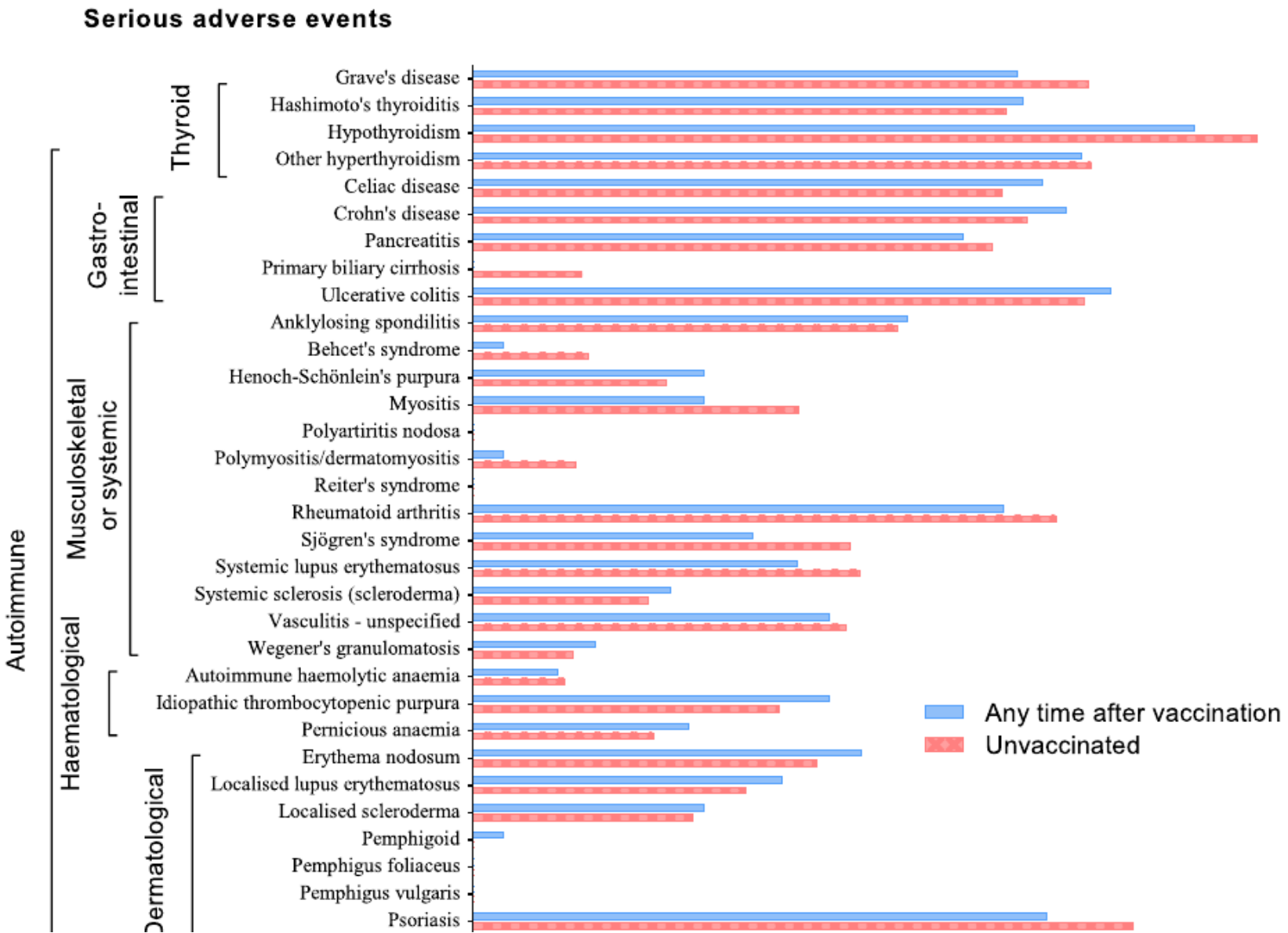
We conducted a number of sensitivity analyses (Table 3). Taking multiple testing into account and comparing the original cohort estimates with estimates derived from the SCCS method, only coeliac disease was still associated with qHPV vaccination. The RR was 1.56 (1.29–1.89) and 1.65 (1.20–2.27) for the period any time after vaccination for the cohort method and the SCCS method, respectively. This association was present throughout the vaccination period and appeared to be stronger in Denmark (1.74, 1.35–2.25) than in Sweden (1.21, 0.87–1.68). The crude incidence rates for coeliac disease in Denmark were 13.9 and 31.1 per 100 000 person-years for the unvaccinated and vaccinated periods, respectively. The corresponding Swedish rates were 34.2 and 50.9 per 100 000 person-years. In Fig. 2, we present coeliac cases occurring after vaccination ordered according to timing. Visual inspection reveals clustering in the first year after the first dose.

Discussion

In this large cohort study comprising more than 3 million Danish and Swedish adult women, we evaluated possible associations between qHPV vaccination and 45 preselected autoimmune and neurological outcomes. Comparing incidence rates in qHPV-vaccinated and qHPV-unvaccinated women, we identified seven adverse events with

increased for both the period any time after vaccination (RR 1.35, 95% confidence interval 1.10–1.67) and the more than 180 days after vaccination period (1.42, 1.08–1.88). RRs for coeliac disease were increased for both the period any time after vaccination (RR 1.56, 1.29–1.89), the first 179 days (1.54, 1.16–2.03) and the more than 180 days after vaccination period (1.58, 1.22–2.05). The RR for localized lupus erythematosus was increased for the period any time after vaccination (1.70, 1.01–2.86). For pemphigus vulgaris, the RR for the first 179 days was increased (8.75, 1.04–73.99), whereas the RR for Addison's disease was increased in the more than 180 days after vaccination period (2.25, 1.10–4.59) and the RR for Raynaud's disease was increased for the period any time after vaccination (1.46, 1.02–2.09). Finally, the RR for other encephalitis, myelitis or encephalomyelitis was increased in the more than 180 days after vaccination period (4.27, 1.00–18.35). The associations with pemphigus vulgaris, Addison's disease and other encephalitis, myelitis or encephalomyelitis were based on few vaccinated cases (n = 1, 2 and 8, respectively, Table 2).

statistically significant increased risks following vaccination—Hashimoto's thyroiditis, coeliac disease, localized lupus erythematosus, pemphigus vulgaris, Addison's disease, Raynaud's disease and other encephalitis, myelitis or encephalomyelitis. These increased risks were offset by four adverse events with significantly reduced risks. After sensitivity analyses, the association between qHPV vaccination and coeliac disease was the most robust; the remaining six associations with increased risks were not statistically significant when taking multiple testing into account or when using a case-only analytical approach. The observed association of a 56% increased risk of coeliac disease after qHPV vaccination was strong, and the increase was strikingly similar in both risk periods after vaccination. We did not see any evidence of consistency of effect because the increase was only observed in Denmark. However, a plot of the timing of coeliac diagnoses in relation to HPV vaccination dates reveals clustering extending beyond the first 179 days of the acute risk period. In our study, approximately half of all coeliac cases occurring after vaccination occurred



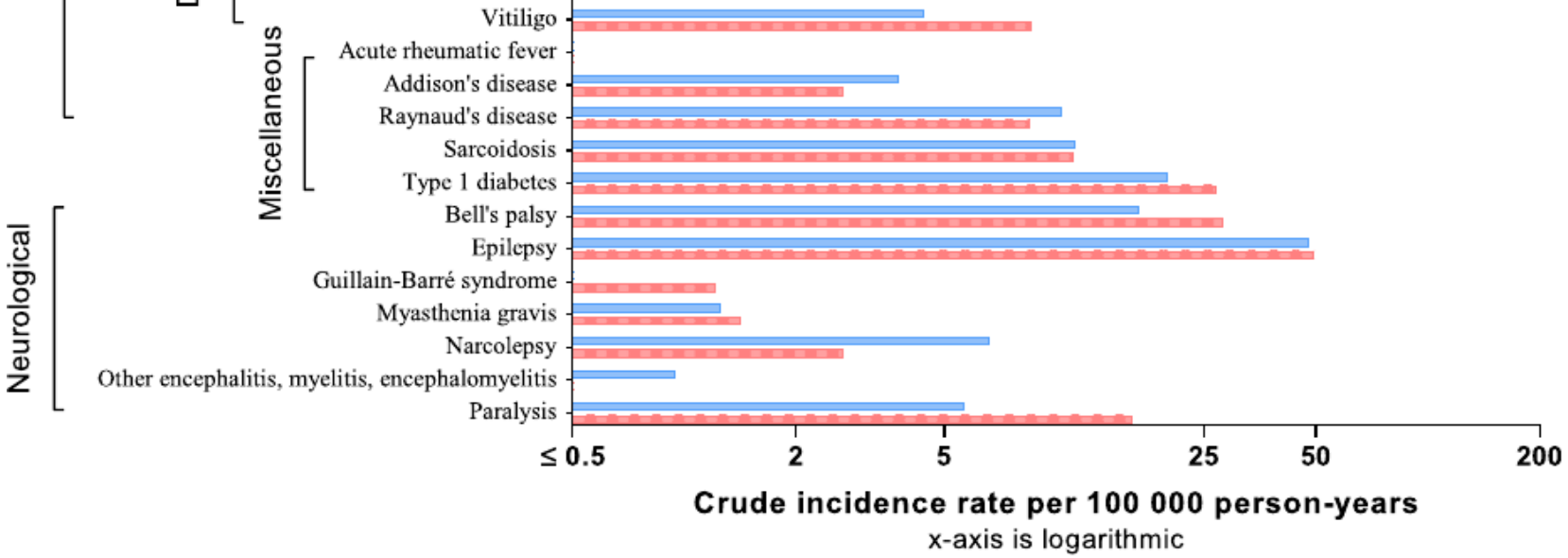


Fig. 1 *Crude incidence rates for 45 autoimmune and neurological study outcomes amongst qHPV vaccinated and unvaccinated in a cohort of Danish and Swedish women 18–44 years of age in the period from 1 October 2006 to 30 June 2013 for Danish women and 31 December 2012 for Swedish women.*

within 1 year of the first dose. To our knowledge, no previous study has linked qHPV vaccination and coeliac disease. Coeliac disease is an autoimmune condition triggered by dietary gluten in susceptible individuals with an estimated prevalence of 1% worldwide [20]. Scandinavia is

nan papillomavirus vaccination status in a cohort of Danish and Swedish women 18–3 for Danish women or 31 December 2012 for Swedish women

me after vaccination		0–179 days since vaccination		≥180 days since vaccination	
s	Adjusted RR (95% CI)	Events	Adjusted RR (95% CI)	Events	Adjusted RR (95% CI)
	0.79 (0.64–0.97)	53	0.93 (0.71–1.22)	40	**0.65 (0.48–0.89)**
	1.35 (1.10–1.67)	45	1.28 (0.94–1.72)	52	**1.42 (1.08–1.88)**
	0.88 (0.79–0.98)	120	**0.65 (0.54–0.78)**	228	1.07 (0.94–1.23)
	1.04 (0.88–1.22)	71	0.98 (0.77–1.25)	79	1.09 (0.87–1.36)
	1.56 (1.29–1.89)	53	**1.54 (1.16–2.03)**	60	**1.58 (1.22–2.05)**
	1.07 (0.90–1.28)	77	1.22 (0.97–1.54)	57	0.93 (0.71–1.21)
	0.86 (0.66–1.11)	31	0.87 (0.61–1.24)	31	0.85 (0.59–1.21)
	–	0	–	0	–
	1.09 (0.94–1.26)	100	1.16 (0.95–1.42)	87	1.02 (0.82–1.26)
	1.20 (0.87–1.65)	17	1.00 (0.62–1.63)	24	1.39 (0.93–2.09)
	0.62 (0.15–2.56)	2	–	0	–
	0.90 (0.46–1.79)	7	1.40 (0.64–3.04)	2	0.41 (0.10–1.65)
	0.76 (0.39–1.47)	4	0.71 (0.26–1.92)	5	0.79 (0.33–1.92)
	0.74 (0.10–5.59)	1	–	0	–
	0.68 (0.17–2.83)	2	–	0	–
	1.96 (0.24–15.92)	0	–	1	3.85 (0.49–30.58)
	0.98 (0.79–1.22)	38	0.92 (0.66–1.27)	46	1.04 (0.77–1.39)
	1.25 (0.72–2.19)	7	1.48 (0.70–3.15)	6	1.07 (0.48–2.39)
	0.80 (0.50–1.28)	8	0.73 (0.36–1.47)	10	0.87 (0.46–1.63)
	1.83 (0.84–3.99)	4	2.13 (0.77–5.91)	3	1.54 (0.49–4.88)
	1.03 (0.68–1.58)	11	1.01 (0.55–1.85)	12	1.05 (0.59–1.87)
	1.44 (0.52–4.04)	1	0.72 (0.10–5.27)	3	2.15 (0.67–6.90)
	1.36 (0.42–4.42)	2	1.89 (0.45–7.92)	1	0.88 (0.12–6.39)
	1.38 (0.90–2.12)	14	1.70 (0.98–2.94)	9	1.07 (0.55–2.09)
	1.57 (0.76–3.27)	5	2.04 (0.82–5.10)	3	1.15 (0.36–3.63)

Table 2 *Rate ratios of adverse events according to quadrivalent hum*
44 years of age in the period from 1 October 2006 to 30 June 201

	Unvaccinated	Any ti
Adverse events	Events	Events
Autoimmune		
Thyroid		
Grave's disease	7923	93
Hashimoto's thyroiditis	4329	97
Hypothyroidism	28 023	348
Other hyperthyroidisms	8117	150
Gastrointestinal		
Celiac disease	4204	113
Crohn's disease	5048	134
Pancreatitis	3898	62
Primary biliary cirrhosis	182	0
Ulcerative colitis	7727	187
Musculoskeletal or systemic		
Ankylosing spondylitis	1919	41
Behcet's syndrome	190	2
Henoch–Schönlein's purpura	341	9
Myositis	918	9
Polyarteritis nodosa	74	1
Polymyositis/dermatomyositis	173	2
Reiter's syndrome	29	1
Rheumatoid arthritis	6251	84
Sjögren's syndrome	1342	13
Systemic lupus erythematosus	1447	18
Systemic sclerosis (scleroderma)	297	7
Vasculitis—unspecified	1301	23
Wegener's granulomatosis	171	4
Haematological		
Autoimmune haemolytic anaemia	159	3
Idiopathic thrombocytopenic purpura	797	23
Pernicious anaemia	310	8

me after vaccination		0–179 days since vaccination		≥180 days since vaccination	
s	Adjusted RR (95% CI)	Events	Adjusted RR (95% CI)	Events	Adjusted RR (95% CI)
	1.26 (0.86–1.85)	17	1.50 (0.92–2.46)	12	1.04 (0.58–1.84)
	1.70 (1.01–2.86)	8	1.71 (0.84–3.51)	8	1.69 (0.83–3.44)
	1.44 (0.73–2.85)	6	2.07 (0.90–4.75)	3	0.90 (0.29–2.84)
	2.48 (0.57–10.71)	1	2.80 (0.37–21.47)	1	2.22 (0.30–16.55)
	–	0	–	0	–
	3.42 (0.42–27.81)	1	**8.75 (1.04–73.99)**	0	–
	0.96 (0.80–1.16)	57	1.06 (0.82–1.38)	59	0.88 (0.68–1.14)
	1.00 (0.59–1.71)	10	1.78 (0.94–3.34)	4	0.48 (0.18–1.29)
	0.50 (0.07–3.75)	0	–	1	–
	1.71 (0.94–3.12)	4	1.15 (0.42–3.14)	8	**2.25 (1.10–4.59)**
	1.46 (1.02–2.09)	17	1.56 (0.96–2.56)	16	1.37 (0.83–2.26)
	1.31 (0.93–1.85)	16	1.18 (0.72–1.95)	20	1.44 (0.92–2.25)
	0.93 (0.72–1.19)	28	0.85 (0.58–1.24)	35	1.00 (0.71–1.39)
	0.72 (0.55–0.95)	21	**0.59 (0.39–0.92)**	32	0.84 (0.59–1.19)
	0.91 (0.77–1.07)	84	1.01 (0.81–1.25)	67	0.81 (0.63–1.03)
	–	0	–	0	–
	1.07 (0.39–2.96)	1	0.55 (0.07–3.96)	3	1.57 (0.49–4.98)
	1.42 (0.89–2.24)	10	1.34 (0.70–2.57)	11	1.49 (0.81–2.74)
	3.40 (0.99–11.75)	1	2.38 (0.31–18.40)	2	**4.27 (1.00–18.35)**
	0.52 (0.32–0.83)	7	**0.42 (0.20–0.89)**	11	0.61 (0.34–1.10)

esidence. Significant associations are in bold

Table 2 (*Continued*)

	Unvaccinated	Any ti
Adverse events	Events	Events
Dermatological		
Erythema nodosum	1047	29
Localized lupus erythematosus	619	16
Localized scleroderma	418	9
Pemphigoid	75	2
Pemphigus foliaceus	12	0
Pemphigus vulgaris	29	1
Psoriasis	11 138	116
Vitiligo	1382	14
Miscellaneous		
Acute rheumatic fever	72	1
Addison's disease	427	12
Raynaud's disease	1367	33
Sarcoidosis	1784	36
Type 1 diabetes	4318	63
Neurological		
Bell's palsy	4515	53
Epilepsy	7878	151
Guillain–Barré syndrome	194	0
Myasthenia gravis	227	4
Narcolepsy	431	21
Other encephalitis, myelitis, encephalomyelitis	62	3
Paralysis	2574	18

Rate ratios are adjusted for age, calendar period and country of r

Table 3 *Sensitivity analyses. Adjusted rate ratios with 95% confidence intervals for different analytical scenarios*

Association	Original estimate	With Bonferroni correction	Only Danish data	Only Swedish data	Self-controlled data case series method
Hashimoto's thyroiditis					
Any time after vaccination	1.35 (1.10–1.67)	1.35 (0.96–1.91)	1.18 (0.93–1.51)	1.81 (1.20–2.74)	1.30 (0.94–1.80)
≥180 days since vaccination	1.42 (1.08–1.88)	1.42 (0.90–2.26)	1.27 (0.91–1.77)	1.70 (1.02–2.84)	1.30 (0.80–2.11)
Coeliac disease					
Any time after vaccination	1.56 (1.29–1.89)	1.56 (1.13–2.15)	1.74 (1.35–2.25)	1.21 (0.87–1.68)	1.65 (1.20–2.27)
0–179 days since vaccination	1.54 (1.16–2.03)	1.54 (0.97–2.44)	1.66 (1.20–2.31)	1.05 (0.58–1.89)	1.64 (1.17–2.30)
≥180 days since vaccination	1.58 (1.22–2.05)	1.58 (1.03–2.43)	1.85 (1.30–2.61)	1.30 (0.87–1.93)	1.68 (1.06–2.67)
Localized lupus erythematosus					
Any time after vaccination	1.70 (1.01–2.86)	1.70 (0.72–4.03)	1.93 (1.10–3.39)	0.55 (0.08–3.91)	1.95 (0.93–4.08)
Pemphigus vulgaris					
0–179 days since vaccination	8.75 (1.04–73.99)	8.75 (0.25–305.06)	Not estimable	Not estimable	Not estimable
Addison's disease					
≥180 days since vaccination	2.25 (1.10–4.59)	2.25 (0.68–7.38)	2.93 (1.41–6.10)	Not estimable	7.97 (0.81–78.07)

Raynaud's disease					
Any time after vaccination	1.46 (1.02–2.09)	1.46 (0.81–2.65)	1.16 (0.73–1.84)	2.04 (1.14–3.64)	1.17 (0.67–2.05)
Other encephalitis, myelitis, encephalomyelitis					
≥180 days since vaccination	4.27 (1.00–18.35)	4.27 (0.38–48.28)	2.81 (0.34–23.46)	Not estimable	2.79 (0.07–116.95)

considered a high-prevalence area, and it has been suggested that the condition is underdiagnosed in Denmark when using hospital register data for case ascertainment. In a small screening study, Danish colleagues concluded that coeliac disease was markedly underdiagnosed in the general adult population and estimated a prevalence of 0.48% that was several times higher than the registry-based prevalence in Denmark [21]. Unmasking of pre-existing conditions at vaccination visits has been described for adolescents and young adults in the context of qHPV vaccination; the vaccination visit triggers a work-up of symptoms that later result in a diagnosis [22]. Unmasking of an underreported disease such as coeliac disease in qHPV-vaccinated Danish women is a possible explanation for the increased RR and is also consistent with the clustering after the first dose that we observed.

We have previously evaluated the risk of serious chronic disease in qHPV-vaccinated compared to qHPV-unvaccinated girls aged 10–17 in a similar setting [16]. In line with the present study, we found no support for associations between qHPV vaccination and autoimmune and neurological adverse events. To our knowledge, no previous study has evaluated qHPV vaccine safety in women older than 26 years of age [23, 24]. In our study, the mean age at vaccination was 25.1 years, and

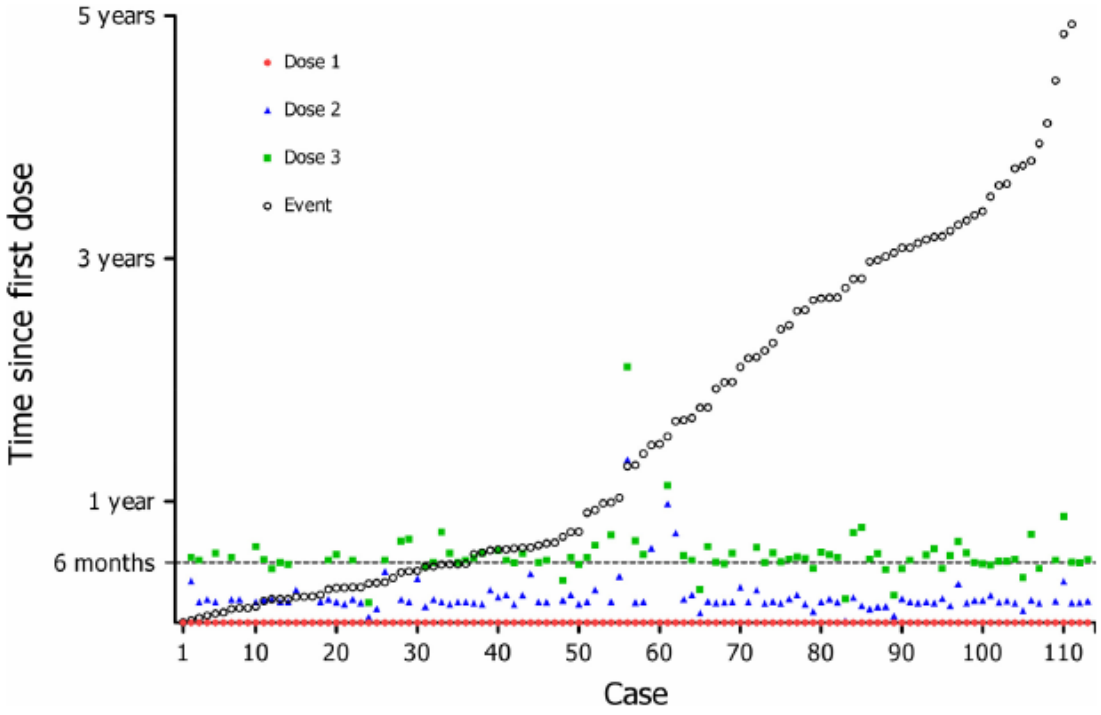


Fig. 2 *Time since first dose of qHPV vaccine for vaccinated coeliac cases in a cohort of Danish and Swedish women 18–44 years of age in the period from 1 October 2006 to 30 June 2013 for Danish women and 31 December 2012 for Swedish women.*

our study is the first to provide extensive safety information in women 26–44 years of age. Baseline disease risks can vary greatly in girls compared to adult women, and it is not unreasonable to expect that different safety issues will arise in different age groups. It should also be noted that HPV vaccination of older women is not primarily an issue in the

bias with seven increased risks and four reduced of 45 possible, we cannot exclude that unmeasured confounding is present in some form. However, we are not aware of any obvious sources of bias.

Our study relies on identifying serious chronic disease through hospital registers. In Scandinavia,

introductory phase of HPV vaccination programmes, but a continuing issue with less than optimal coverage or delayed vaccination because of vaccine safety scares. Consequently, studies such as ours are an important supplement to HPV vaccine safety studies in the younger programme girls.

Our study has a number of strengths. We were able to combine nationwide individual-level data from two Scandinavian countries with similar health care. This not only provided us with an impressive cohort size of more than 3 million women, but also reduced the potential for forms of selection and ascertainment bias seen with, for example, case–control studies. Adult women actively seeking HPV vaccination could be a selected group with respect to comorbidity, socio-economic and lifestyle factors compared to the general population of women. We were able to address confounding by conducting sensitivity analyses with the SCCS method, which takes into account confounding and bias by factors that do not vary during the study period. Although the cohort results do not suggest a clear pattern of serious chronic disease will be diagnosed in the hospital setting and captured in our study if it is diagnosed. We expect the majority of outcomes in our study to be captured in hospital data, but some less severe conditions might only be diagnosed in primary care or remain undiagnosed entirely. All subsidized vaccinations and vaccinations obtained through prescriptions will be captured by the respective vaccination and prescription registers. Exposure ascertainment in this study can thus be considered close to complete. For many of the included outcomes, there will be a delay between onset and diagnosis. We included two risk periods of interest in our study: a 180-day period for outcomes with little delay between onset and diagnosis, and a period following 180 days for outcomes with a more insidious onset. Although our study cohort was large, many of the included outcomes are rare and null findings should be interpreted in the context of statistical power. It will be important to continue to monitor HPV vaccine safety in future when statistical power is increased and more definite conclusions can be reached.

In conclusion, our study of serious adverse event rates in qHPV-vaccinated and qHPV-unvaccinated adult women 18–44 years of age did not raise any safety issues of concern.

Author contributions

Hviid had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Hviid conceived of and designed the study. Scheller, Svanström, Arnheim-Dahlström and Hviid obtained the data. Svanström conducted the statistical analyses. All authors contributed to the interpretation of results. Hviid drafted the manuscript. Scheller, Pasternak, Svanström, Arnheim-Dahlström and Grönlund critically revised the manuscript. Hviid and Arnheim-Dahlström obtained the funding for the study.

Conflict of interest statement

Scheller, Hviid, Svanström, Pasternak have no conflicts of interest to report. Arnheim-Dahlström has obtained funding from MDS Sanofi Pasteur and GlaxoSmithKline for unrelated studies.

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Role of sponsor

The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Correspondence: Anders Hviid MSc, DrMedSci, Statens Serum Institut, Artillerivej 5, Copenhagen S 2300, Denmark.
(fax: +3268 3868; e-mail: aii@ssi.dk).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Study outcomes with ICD-10 codes

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