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No evidence found for an increased risk of long-term fatigue following human papillomavirus vaccination of adolescent girls

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ABSTRACT

Introduction: In 2013, the Netherlands Pharmacovigilance Center Lareb published an overview of reports of long-lasting fatigue following bivalent HPV-vaccination (2vHPV). After an update of this overview in 2015, concerns regarding the safety of 2vHPV was picked up by the media, which led to further reports of long-lasting fatigue. Therefore, the Dutch National Institute for Public Health and the Environment (RIVM) investigated a possible association between HPV-vaccination and long-term fatigue.
Methods: In this retrospective cohort study conducted in the Integrated Primary Care Information database, we investigated the occurrence of chronic fatigue syndrome (CFS), fatigue ≥6 months and 3–6 months in all girls born in 1991–2000 during the follow-up period January 1st 2007-December 31st 2014 (2007–2008 pre-vaccination and 2009–2014 post-vaccination). Patients with certain fatigue ≥6 m were asked for consent to link their primary care information with vaccination data. Incidence rates per 10,000 person years (PY) for 12–16-year-old girls were compared between pre- and post-HPV-vaccine era. A self-controlled case series (SCCS) analysis was performed using consenting vaccinated cases. A primary high-risk period of 12 months after each dose was defined.
Results: The cohort consisted of 69,429 12–16-year-old girls accounting for 2758 PY pre-vaccination and 57,214 PY post-vaccination. Differences between pre- and post-vaccination incidences (CFS: 3.6 (95% CI 0.5–25.7)/10,000 PY and 0.9 (0.4–2.1); certain fatigue ≥6 m: 7.3 (1.8–29.0) and 19.4 (16.1–23.4); certain fatigue 3–6 m: 0.0 and 16.6 (13.6–20.3), respectively) were not statistically significant. SCCS analyses in 16 consenting vaccinated cases resulted in an age-adjusted RR of 0.62 (95%CI 0.07–5.49).
Conclusions: Fatigue ≥6 m and 3–6 m was frequently found among adolescent girls, but CFS was rarely diagnosed. No statistically significant increased incidence rates were found post-vaccination compared to similar age groups of girls pre-vaccination. The SCCS analysis included a low number of cases but revealed no elevated risk of certain fatigue ≥6 m in the high-risk period.

1. Introduction

Since 2006, the bivalent HPV vaccine (2vHPV) has been licensed for the prevention of cervical cancer. In the Netherlands, routine 2vHPV vaccination of 12-year-old girls was introduced in the National Immunization Program (NIP) in 2010 (born from 1997 onwards). In 2009, a catch-up campaign was carried out for girls born between 1993 and 1996. Vaccination coverage of the catch-up campaign was 52.3%. Coverage among the regular campaign increased from 56.0% in 2010 to 61.0% in 2013/2014 but declined again to 53.4% in 2015 [1].

Several years after the introduction of HPV-vaccination, various publications raised concerns regarding adverse events (AE) [2–5]. From 2013 onwards, the Danish Health and Medicines Authority received a number of reports regarding suspected postural orthostatic tachycardia syndrome (POTS) after vaccination with the quadrivalent vaccine (4vHPV) and informed the European

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Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) in September 2013. Taking into account all available information, the PRAC concluded in November 2015 that the evidence did not support the theory that HPV-vaccines caused POTS [6], although this conclusion was criticized by the Nordic Cochrane Center [7].

A frequent and major comorbidity of POTS is chronic fatigue syndrome (CFS) [8,9]. These two conditions frequently appear together [10], and the majority of patients with POTS also fulfill the criteria for CFS [11]. Fatigue is a well-known symptom in adolescence and often lasts for several months. In 1997, the CFS prevalence was estimated at approximately 10 per 10,000 GP patients and 1–2 per 10,000 teenagers [12–14]. In 2005, van der Linden et al. reported that the incidence of GP consultation for fatigue (ICPC-code A04 (fatigue/weakness), independent of duration) was 10 per 1000 for girls around the age of 10 years, and increased to a peak of 48 per 1000 for girls at the age of 15 [15]. Ter Wolbeek et al. performed a school-based study with questionnaires among adolescents and found that 20% of girls reported severe fatigue [16]. In 2011, Nijhof et al. found a CFS incidence of 12 per 100,000 adolescents per year as diagnosed by a GP or pediatrician [17].

The risk of CFS in relation to the 2vHPV and the 4vHPV vaccine was investigated in UK and Norway, respectively. No increased risk of fatigue syndromes for vaccinated girls was found [18–20].

In 2013, the Netherlands Pharmacovigilance Center Lareb published an overview of the reports of long-lasting fatigue possibly associated with 2vHPV [21]. After an update of this overview in 2015, concerns about the safety of the HPV-vaccine was picked up by the Dutch media. In the month following this media attention, Lareb received more than one hundred reports concerning AEs following 2vHPV. In total, Lareb received 256 reports concerning long-lasting fatigue (≥2 months) between January 1, 2009 and October 31, 2016, the majority of which were received after the increased media attention in 2012 and 2015. Based on the analysis of these reports, Lareb concluded that a causal relation between 2vHPV and long-lasting symptoms could not be confirmed nor excluded [22]. Recent figures regarding background incidences of fatigue and CFS in the Netherlands are not available. In addition, no data in the Netherlands was available stratified by HPV-vaccination status. Therefore, following the recommendation of Lareb, the National Institute for Public Health and the Environment (RIVM) investigated a possible association between 2vHPV and long-term fatigue.

2. Methods

2.1. Study design

A retrospective cohort study among adolescent girls was conducted to study the possible association between HPV-vaccination and CFS or long-term fatigue symptoms with a duration of ≥6 months and 3–6 months. A cohort analysis was performed on the entire study cohort, to avoid selection and to get power. Within this cohort, cases with diagnosed CFS or certain fatigue ≥6 m were asked for informed consent to collect their HPV-vaccination status. Data from the cases that provided consent was analyzed using a self-controlled case series approach. In this analysis only vaccinated cases were included; cases act as their own controls in order to correct for time-independent confounders.

2.2. Setting

The study was conducted using the Integrated Primary Care Information (IPCI) database (Erasmus Medical Center, the Netherlands). The IPCI-database is a longitudinal collection of electronic patient records from Dutch GPs into a central research database established since 1989. At present, the database contains information on more than 1,500,000 patients [23].

2.3. Cohort definition

The study cohort comprised all girls born between 1991 and 2000 for the study period January 1st 2007–December 31st 2014. The calendar years 2007–2008 were classified as the pre-vaccination era, and the years 2009–2014 were classified as post-vaccination. The first date of follow-up was January 1st 2007, or the date at which 1 year of valid data history in the IPCI-database was accumulated, whatever was the latest. The end of follow-up was December 31st 2014 or the end of registration of the patient, death or last IPCI data delivery.

2.4. Outcome selection

Cases were identified from the electronic records if they met the following criteria: the International Classification of Primary Care (ICPC) code A04.01 (chronic fatigue syndrome (CFS)) or ICPC-codes A04/A04.00 (fatigue/weakness) or 'moe' (Dutch for fatigue) in the free text. This Dutch word covers all synonyms (such as 'moeheid' and 'vermoeidheid') for fatigue syndromes and thus was considered as a robust search term. Cases who met any of the following criteria were excluded: words containing 'moe' but it had nothing to do with fatigue (e.g., moeder = mother). In addition, we excluded fatigue cases with a concomitant diagnosis other than those that presented in the inclusion criteria on the same consultation date. Thereafter, selected cases were manually validated and coded for the onset and duration of the fatigue and concomitant symptoms included in the case definition of CFS [24].

We defined different levels of evidence for long-term fatigue symptoms:

1. ICPC-code A04.01 (CFS)
2. ICPC-code A04/A04.00 (fatigue/weakness) or 'fatigue' in the free text, with a duration of fatigue longer than 6 months and at least 4 of the following symptoms [24]: malaise after exertion lasting at least 24 h; unrefreshing sleep; significant deterioration of short-term memory or concentration; joint pain without swelling or redness; headaches of a new type, pattern or severity; tender lymph nodes in the neck or armpit; and regularly or frequently a sore throat.
3. ICPC-code A04/A04.00 or 'fatigue' in the free text, with a duration of fatigue ≥6 months or as stated by the GP as 'chronic' and 2–3 of the symptoms (see point 2).
4. ICPC-code A04/A04.00 or 'fatigue' in the free text with a duration of fatigue ≥6 months or as stated by the GP as 'chronic' and <2 of the symptoms (see point 2).
5. ICPC-code A04/A04.00 or 'fatigue' in the free text with a duration of fatigue possibly ≥6 months (i.e., multiple fatigue consults over time but unknown if the complaints continued over time or were independent events).
6. ICPC-code A04/A04.00 or 'fatigue' in the free text with a duration of the fatigue 3–6 months or as stated by the GP as 'long lasting'.
7. ICPC-code A04/A04.00 or 'fatigue' in the free text with a duration of the fatigue possibly 3–6 months (see also point 5) or as stated by the GP as 'long lasting'.

The date of onset was obtained from the first fatigue record in the GP-database, in case a clear date of the start of the fatigue symptoms was indicated in the record. Because the date of onset

of fatigue was largely unknown or vague, the date of first fatigue record in the GP database was used as the index date for statistical analyses. The duration of fatigue symptoms was defined as the time of the existence of fatigue as indicated by the patient in the first fatigue consult by the GP plus the duration of the fatigue symptoms indicated by the follow-up consults in the GP-database, i.e., up to the last fatigue consult.

GPs of validated cases with certain fatigue ≥6 m (level 1–4) who were eligible for HPV-vaccination, i.e., girls born in 1993–2000, received an invitation letter to contribute to the study. If the GP was willing to participate, the selected girls from his/her practice received an information letter and an informed consent form through this GP. The informed consent form asked for permission to link their primary care information with the HPV-vaccination data. For girls younger than 18 years, permission of her parents/guardians was also required.

2.5. Vaccination status

In the Netherlands, an electronic national immunization register called 'Præventis' was implemented in 2005 [25]. Præventis is primarily used for NIP-invitations and to register and validate administered vaccinations. In addition, Præventis allows for the production of (sub)national vaccination coverage estimates with high accuracy and additional research, for instance, on vaccine safety, by linking it with disease registers. The HPV-vaccination status and dates of vaccine administration were obtained from this registry for all girls who gave consent for linkage.

2.6. Statistical analysis

Incidence rates (IRs) of long-term fatigue among 12–16-year-old girls were calculated for 2007–2008 (pre-vaccination) and for 2009–2013 (post vaccination) by level of evidence (see above) or a combination of these levels:

- CFS chronic fatigue syndrome (level 1);
- CF6 certain fatigue ≥6 months (level 1–4);
- PF6 possible and certain fatigue ≥6 months (level 1–5);
- CF3 certain fatigue 3–6 months (level 6);
- PF3 possible and certain fatigue 3–6 months (level 6–7).

IRs for 2014 were not computed to correct for the need to have a certain follow-up after the start of fatigue in order to be classified as long-term fatigue. Incidence rate ratios (IRRs) for the post- versus pre-vaccination period were calculated and adjusted for age using Poisson regression.

Within the CF6 cases who provided consent, were HPV-vaccinated and had sufficient follow-up to capture high- and non-high-risk time, a self-controlled case series (SCCS) analysis was conducted to estimate the relative incidence of CF6 following HPV-vaccine exposure in high-risk periods compared to non-high-risk periods (Fig. 1), adjusted for age. A primary high-risk period of 12 months following each dose was defined. In this analysis, the last 6 months of the study period were censored in order to correct for the need of a certain follow-up for case ascertainment. Since the potential risk period to develop fatigue after HPV-vaccination is not clear, sensitivity analyses were performed using two different high-risk periods, i.e., 6 and 18 months, and one using cases only for which a date of onset of fatigue symptoms was known.

2.7. Ethical approval

This research was exempted from review by the medical ethics committee of Erasmus Medical Center, Rotterdam, the Netherlands (protocol number MEC-2015-629).

3. Results

3.1. Incidences

The cohort consisted of 69,429 12–16-year-old girls accounting for 2759 PY pre-vaccination and 57,214 PY post-vaccination.

IRs of CF6 were the lowest, whereas IRs of PF6 and PF3 were much higher. Post-vaccination, IRs increased with age, peaking at 14–16 years of age and declining thereafter (Fig. 2). The age-related IR was similar in the pre- and post-vaccination periods, although the pre-vaccination incidence at 17 years was relatively high (as were the confidence intervals).

IRs per 10,000 PY of CF6 for 12–16-year-old girls declined slightly between 2007 and 2009 (13.2 (95%CI 1.9–93.6) and 5.1 (1.3–20.3), respectively) but increased slightly in 2010 to 24.3 (14.9–39.6) and stayed stable up to 2013 (Fig. 3). The IRs of PF6 increased from 2007 up to 302.5 (252.1–362.8) in 2009 and declined thereafter to 119.8 (105.2–136.4) in 2013. IRs of PF3 remained more or less stable since 2008.

Post-vaccination IRs of CF6 for 12–16-year-old girls were slightly higher, although not statistically significant, than in the pre-vaccination period (IRR = 2.70 (0.67–10.9); Table 1). When comparing IRs of PF6, post-vaccination rates were much lower than the pre-vaccination rates (IRR = 0.76 (0.60–0.96)). For CF3, a higher post-vaccination IR was found than for pre-vaccination, where no cases were found. Post-vaccination IRs for PF3 were only slightly higher than in the pre-vaccination period (IRR = 1.72 (0.76–3.87)).

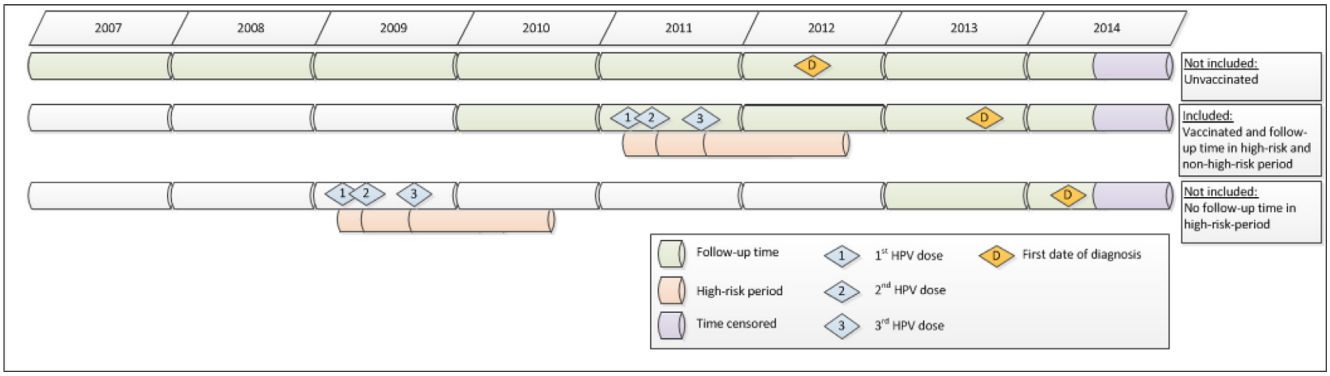

Fig. 1. Inclusion criteria for the SCCS analysis.

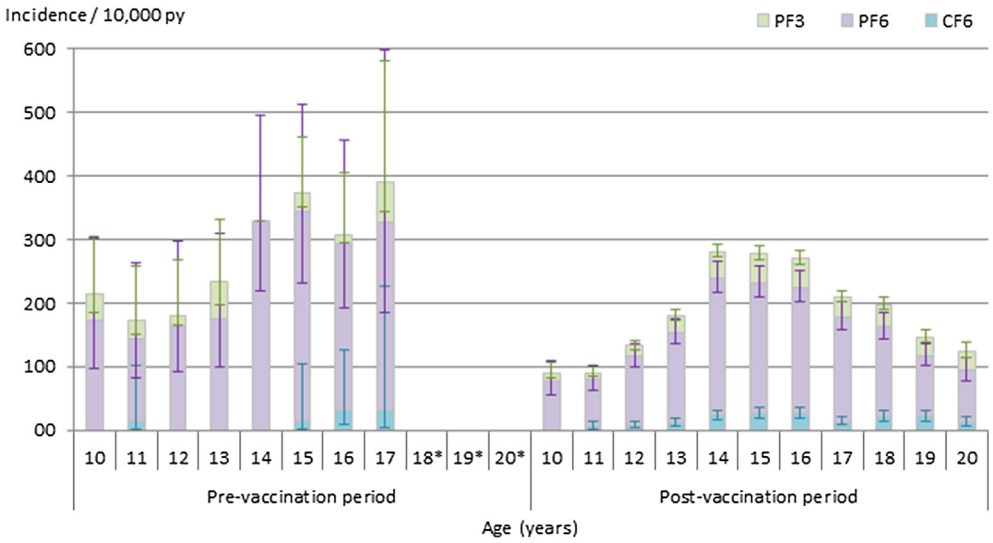

Fig. 2. Age distribution of certain and possible fatigue ≥6 months and 3–6 months in the pre- and post-vaccination period. PY = person years, CF6 = certain fatigue ≥6 months (criteria 1–4), PF6 = possible and certain fatigue ≥6 months (criteria 1 to 5), PF3 = possible and certain fatigue 3–6 months (criteria 6–7). *not estimated, due to restriction of birth cohorts to 1991–2000.

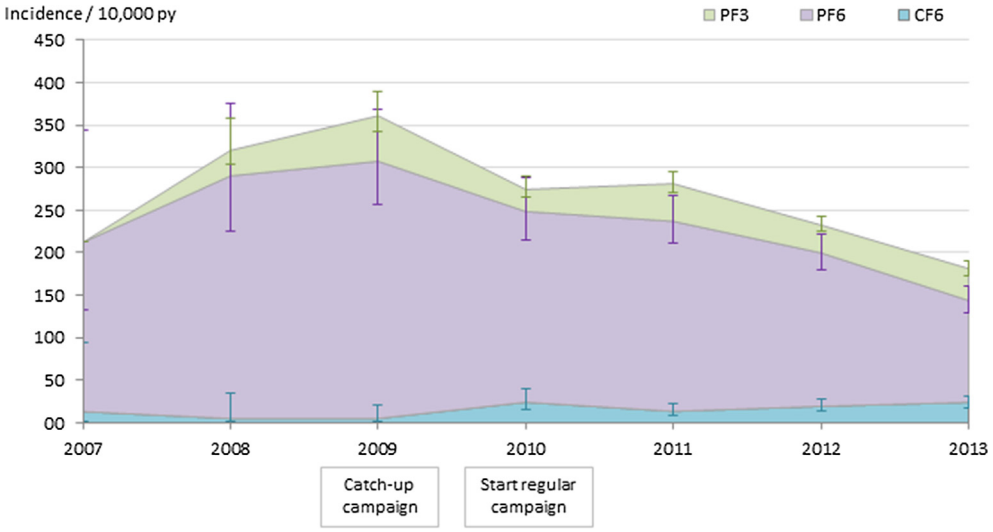

Fig. 3. Incidences of certain and possible fatigue ≥6 months and 3–6 months per year for 12–16-year-old girls. PY = person years, CF6 = certain fatigue ≥6 months (criteria 1–4), PF6 = possible and certain fatigue ≥6 months (criteria 1–5), PF3 = possible and certain fatigue 3–6 months (criteria 6–7).

Table 1
Pre- and post-vaccination period incidences of long-term fatigue for 12–16-year-old girls.

Criteria*		Pre-vaccination period (2007–2008)			Post-vaccination period (2009–2013)			Adjusted IRR# post vs. pre (95% CI)
		N events (%)	PY	Incidence/10,000 PY (95% CI)	N events (%)	PY	Incidence/10,000 PY (95% CI)	
1	CFS	1 (0.03)	2758	3.6 (0.5–25.7)	5 (0.01)	57,214	0.9 (0.4–2.1)	0.24 (0.03–2.09)
1–4	CF6	2 (0.05)	2758	7.3 (1.8–29.0)	111 (0.17)	57,092	19.4 (16.1–23.4)	2.70 (0.67–10.9)
1–5	PF6	73 (1.91)	2715	268.9 (213.7–338.2)	1117 (1.74)	55,286	202.0 (190.5–214.2)	0.76 (0.60–0.96)
6	CF3	0 (0.00)	2759	0.0	95 (0.15)	57,101	16.6 (13.6–20.3)	NA
6–7	PF3	6 (0.16)	2755	21.8 (9.8–48.5)	212 (0.32)	56,924	37.2 (32.6–42.6)	1.72 (0.76–3.87)

PY = person years, CI = confidence interval, CFS = chronic fatigue syndrome (criteria 1), CF6 = certain fatigue ≥6 months (criteria 1–4), PF6 = possible and certain fatigue ≥6 months (criteria 1–5), CF3 = certain fatigue 3–6 months (criteria 6), PF3 = possible and certain fatigue 3–6 months (criteria 6–7), IRR = incidence rate ratio.
* According to the criteria described in the methods.
# Adjusted for age.

3.2. SCCS

Two hundred six GPs (for 484 cases) were contacted to ask for participation, and 52% responded positively (Table 2). Participating and non-participating GPs were geographically distributed throughout the country and comparable regarding practice size. Slightly more participating GPs are male than non-participating GPs (73% versus 66%). Consent to allow for linkage was received

Table 2
Participation for data linkage between primary care data and vaccination data (A) and age distribution of cases included in the SCCS analysis (B).

A. Participation	N
GPs who received an invitation letter	206
Consent GPs	107
Potential patients to invite	484
Invited patients	240
Consent patients	49
Vaccinated	37
Follow-up time within the high-risk period	16
B. Age distribution	**N**
12–13 yr.	0
14–15 yr.	8
16–17 yr.	6
18–19 yr.	1
20–21 yr.	1

for 49 CF6 cases, of which 37 (76%) were vaccinated against HPV (Table 2). Of them, 16 vaccinated cases had a follow-up time in the high- and non-high-risk periods and therefore could be included in the SCCS analysis (Table 2). Five of them were vaccinated in the catch-up campaign (birth cohort 1993–1996) and 11 through the regular NIP (birth cohort 1997–2000).

One case had a fatigue diagnosis before she received the first vaccine dose, and for the other 15 cases the median time between the most recent vaccine dose and the date of first fatigue recorded in the GP database was 765 days (range 191–1872 days). A lower risk of fatigue was found in the high-risk period versus the non-high-risk period (adjusted RR 0.62, 95%CI 0.07–5.49; Table 3). This lower risk was sustained in the sensitivity analysis with different high-risk periods and analysis of only cases with a known date of onset of the fatigue symptoms (Table 3).

Table 3
SCCS analysis with a high-risk period of 12 months after each dose and sensitivity analysis.

	Crude	Adjusted for age (12–13, 14–15, 16–17, 18–19, 20–21 yrs)
High-risk period 12 months		
Within high-risk period		
N events	2	
N person time (days)	5469	
Non-high-risk period		
N events	14	
N person time (days)	24,749	
RR (95% CI)	0.51 (0.11–2.41)	0.62 (0.07–5.49)
High-risk period 6 months		
Within high-risk period[*]		
N events	0	
N person time (days)	2937	
Non-high-risk period		
N events	16	
N person time (days)	27,281	
RR (95% CI)	NA	NA
High-risk period 18 months		
Within high-risk period[*]		
N events	2	
N person time (days)	8104	
Non-high-risk period		
N events	14	
N person time (days)	22,114	
RR (95% CI)	0.27 (0.06–1.24)	0.17 (0.02–1.52)
Cases for which date of symptoms is known, high-risk period 12 months		
Within high-risk period[*]		
N events	2	
N person time (days)	5469	
Non-high-risk period		
N events	11	
N person time (days)	24,749	
RR (95% CI)	0.29 (0.03–2.52)	

4. Discussion

This cohort and SCCS analysis showed no significant increased association between long-term fatigue and bivalent HPV-vaccination. Fatigue ≥6 m and 3–6 m occurred frequently among adolescent girls, but CFS was rarely diagnosed by the GP. The cohort analysis had the most power and no selection and consistently showed that the IRs of CFS, fatigue ≥6 m (CF6 and PF6) and 3–6 m (CF3 and PF3) were not statistically significantly elevated in the post-vaccination period compared to the pre-vaccination period. There was no indication that the age pattern, peaking at age 14–16 years of age, have changed between the pre- and post-vaccination period, although a somewhat higher incidence at 17 years of age in the pre-vaccination period. The SCCS analysis, where HPV-vaccination status was linked on a personal level, did not show an increased risk of certain fatigue ≥6 m (CF6) within 12 months after HPV doses, but because of the low response for consent of data linkage, this analysis had little power.

Several case reports have been published that described symptoms of POTS and/or CFS in relation to 4vHPV [3,26,27]. However, two observational studies found no association [19,20]. In the UK, an SCCS approach was applied among 187 vaccinated girls with CFS to estimate their risk in the 12 months after HPV-vaccination. No association was found between vaccination with 2vHPV and CFS [19]. Similarly, in Norway, no indication of an increased risk of CFS/ME (myalgic encephalomyelitis) following HPV-vaccination was observed among girls in the first six birth cohorts offered 4vHPV through the NIP [20]. Although study designs differ, our results are in accordance with the results in the UK and Norway. Thus, the signals raised by several case reports were not confirmed in observational studies. In addition, three reviews also did not detect any unusual reporting of POTS after HPV-vaccination that would suggest a safety problem [28–30]. Overall, the Global Advisory Committee on Vaccine Safety (GACVS) concluded that there is still no evidence to suggest a causal association between HPV-vaccine and POTS or other diverse symptoms [31].

In the present study, we found slightly higher but not statistically significant post-vaccination IRs of CF6 and CF3 than in the pre-vaccination period (CF6: 19.4 vs. 7.3, IRR = 2.70 (0.67–10.9); CF3: 16.6 vs. 0.0). When we compared incidences of fatigue ≥6 m and 3–6 m including possible cases (PF6 and PF3), the pre- and post-vaccination incidences were comparable. The number of CF6 and CF3 were very low, especially in the pre-vaccination period (2 and 0, respectively per 2758 PY, vs. 111 and 95 per 57,214 PY in the post-vaccination period), since there was only limited follow-up time in the pre-vaccination period. Media attention on safety concerns about HPV-vaccination, which have been raised frequently in the Netherlands (i.e. especially in 2009, March 2012, November 2013, March 2015 and November 2016), often on chronic fatigue symptoms, could have increased awareness about this syndrome. This might possibly have led to more GP consultations in those periods leading to a higher estimate of the incidence compared to periods with no media attention. This could explain the relatively high incidence of fatigue PF6 in 2009. However, no increased incidence of PF6 was seen in 2012 and 2013. Of the patients included in the SCCS analysis, one was diagnosed within 3 months after such increased media attention, however

this patient was not vaccinated yet at that time. The other patients were diagnosed at least 6 months following increased media attention. Therefore, we think that the impact of this media attention was low in this analysis.

Classification of cases using routine health care records was difficult. For several girls, there were several fatigue consults over time. However, in most cases, it was unknown if the complaints persisted over time or whether these were independent events. These cases were defined as possible cases. Therefore, we assumed that the incidence of certain cases is an underestimation and the incidence of possible cases an overestimation of the true incidence. This assumption seems to be confirmed when the incidences found in our study were compared with other Dutch estimations of GP consultations for fatigue and CFS among adolescents [15,17]. Incidences of possible and certain fatigue ≥6 m (7.3–268.9 per 10,000 PY) were, despite a wide range, in line with incidences of GP consultations for fatigue (ICPC-code A04, independent of duration) found by Van der Linden et al. in 2005 (one-year incidence 20.1/1000 girls <18 years) [15]. Post-vaccination CFS incidences were comparable with the CFS incidence found in the pre-vaccination period by Nijhof et al. using GP-data from 2008 (12/100,000 adolescents per year) [17]. Our study also showed that the incidence of fatigue ≥6 m and 3–6 m increased with year of age to peak at 14–16 years and declined again thereafter. This same pattern with a peak at 15 years of age was seen among girls in studies conducted before the introduction of HPV-vaccination in the Netherlands, such as by M. ter Wolbeek et al. among approximately 3400 high school students in 2002–2005 (personal communication), by S. Nijhof et al. among 135 adolescent CFS patients in 2008–2010 [32] and Van der Linden et al. GP consultations for fatigue in 2005 [15]. However, in our study, the pre-vaccination incidence at 17 years of age was relatively high. This finding might be explained by the low amount of person time and cases in the pre-vaccination period, which resulted in estimations with a wide confidence interval.

Overall, the incidence of fatigue is relatively high in adolescents, particularly among girls [16]. Life-style characteristics such as sleep and physical activity, and depression, anxiety and chronic fatigue-related symptoms are associated with the onset and persistence of fatigue [16,33]. In girls, early menarche and medication use also play a role [16]. In contrast, CFS is a relatively rare but disabling disorder, which often results in considerable absence from school leading to long-term consequences for the patients' educational and social development [17].

A comprehensive description of CFS is the bio-psycho-social approach, which distinguishes between predisposing, precipitating and perpetuating factors at both the biological (such as genetic or physical vulnerability, trauma or physical stress and disturbed sleep-wake cycles or disordered food intake) and the psychosocial level (such as anxiety, depression, personality disorders, somatization, stress and physiological trauma) [34]. Changes in social influences, such as somatization of the parents, a family member with physical or mental diseases, life events, isolation or excessive medication consumption, might also be a cause of the increasing incidence of long-term fatigue symptoms and/or an increase in healthcare use due to long-term fatigue symptoms [34].

In a nationwide hospital register-based study in Norway, it was found that between 2009 and 2014 the incidence rate of CFS increased annually [20]. However, a similar increase was found among girls as well as among boys despite only girls being vaccinated with the 4vHPV vaccine [20]. In contrast, in the UK no change in CFS incidence was observed among girls in the three years following the introduction of 2vHPV [19]. Conversely, a decreasing trend in fatigue syndromes was observed for boys. This trend was probably natural random variation, as no other explanation was found [19].

One of the strengths of this study was the ability to include fatigue cases from a large time period, which included two years before and six years after introduction of HPV-vaccination. A large longitudinal database of more than 600 GPs, representative for the Netherlands, including more than 1.5 million inhabitants was used [23]. Another advantage of this GP-database was the availability of free text fields from the GPs. This free text was used to indicate fatigue symptoms and the duration of the fatigue but also to put the fatigue symptoms in context to other complaints or diseases. To use the full potential of this free text, all automatically selected cases were validated and coded manually.

The relationship between HPV-vaccination and fatigue ≥6 m was assessed in two ways: first, an ecological method, comparing population-based incidence rates before and after introduction of HPV-vaccination, and second, by using SCCS analysis. This method was chosen, as it uses only cases, and it controls for confounders that do not vary over time. In addition, the method was most efficient, given that consent was required to be able to link the vaccination status.

Despite its strength, this study also has several limitations, given its observational nature. Misclassification of the outcome may easily occur since the diagnosis of CFS is complex. According to the case definition, additional symptoms to meet the diagnoses and exclusion of other illnesses that could cause similar complaints are required [24]. For this reason, we defined a level of evidence for CFS depending on the duration of fatigue symptoms and the presence of additional symptoms as stated in the case definition. Unfortunately, the presence of these symptoms was largely unknown, as they were rarely reported in the medical records.

CFS is also a rule out diagnosis; in order to be classified as CFS, no other somatic or psychiatric cause for fatigue should be present. We therefore excluded all cases with concomitant diseases on the same consultation date. This approach possibly has resulted in an underestimation of incidences as cases with a concomitant disease that could not explain the fatigue were also excluded. In addition, if CFS was diagnosed by a specialist, not all GPs might have coded this as such in their system and therefore could have been missed. For this reason we chose to select all fatigue diagnoses and thereby prevented that this kind of cases were missed.

Moreover, the date of onset of fatigue symptoms was largely unknown or unclear. We therefore used the date of first fatigue consult as an index date. However, some patients go to their GP within several days after onset of symptoms, while other patients wait for up to several years before going to their GP. Therefore, we performed sensitivity analyses of the cases for which a first date of onset of fatigue symptoms was known, and these analyses did not change the conclusion.

Selection issues may have been a problem in the SCCS analysis. Due to privacy concerns, GP records and vaccination records could not be linked probabilistically in a de-identified manner similar to what we had tested successfully before [35]; instead, we had to approach cases for consent to link their GP data with the vaccination registry data. Within the IPCI database, approaching patients can only be done through their participating GP, who holds the key to identity. Unfortunately, the multiple steps to ask during the consent process resulted in a low participation rate of both GPs (52% of invited GPs) and cases (20% of invited patients). Participating cases were much more likely to be vaccinated than the regular vaccination rate, suggesting potential selection bias. Additionally, the distribution in the date of the first fatigue consult and onset of symptoms did not differ for cases who gave consent compared to those who did not, so we have no indication for response bias in our study. Since the SCCS was only restricted to vaccinated cases, and the estimate was low, we believe that this bias may not have affected our conclusion. Nevertheless, if selection bias is still included this may have led to an overestimation

of the relative risk. Given the loss of information and power and the potential for bias when consent is required, we recommend that other strategies for linkage be investigated in the Netherlands if public health is potentially at stake.

5. Conclusions

In this study, no statistically significantly increased post-vaccination incidence rates of CFS, fatigue ≥6 m or 3–6 m were found compared to the pre-vaccination incidence rates for girls of the same age groups. However, fatigue ≥6 m and 3–6 m were frequently found, but CFS was rarely diagnosed, and its incidence rates were in line with the results of previous studies. Following linkage of primary care information with the vaccination registry, no elevated risk of certain fatigue ≥6 m in the high-risk period of 12 months after each HPV-dose was revealed. We did not find evidence for an increased risk of fatigue syndromes following HPV-vaccination, although the sample size of the present study was small. This may result in a lack of power to detect small differences.

Meetings

These results were presented at the 36th Annual Meeting of the European Society for Paediatric Infectious Diseases in Malmö, Sweden (May 28–June 2, 2018).

Declarations of interest

None.

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