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# HPV vaccination and risk of chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide register-based study from Norway

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ABSTRACT

*Background:* Vaccination has been suggested to be involved in the aetiology of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). HPV vaccine was introduced in the Norwegian Childhood Immunisation Programme and offered 12 year old girls from 2009. We studied the association between HPV vaccination and risk of CFS/ME and also assessed medical history in relation to both risk of CFS/ME and HPV vaccine uptake.

*Methods:* Individual data from national registries, including the Norwegian Population Registry, the Norwegian Patient Registry and the Norwegian Immunisation Registry were linked using the unique personal identification number. Yearly incidence rates of CFS/ME for 2009–2014 were calculated among the 824,133 boys and girls, aged 10–17 living in Norway during these 6 years. A total of 176,453 girls born 1997–2002 were eligible for HPV vaccination and included in further analyses. Hazard ratios (HRs) of CFS/ME were estimated using Cox regression. Risk differences (RDs) of vaccine uptake were estimated with binomial regression.

*Results:* A similar yearly increase in incidence rate of CFS/ME was observed among girls and boys, IRR = 1.15 (95% confidence interval (CI) 1.10–1.19) and 1.15 (95% CI 1.09–1.22), respectively. HPV vaccination was not associated with CFS/ME, HR = 0.86 (95% CI 0.69–1.08) for the entire follow-up period and 0.96 (95% CI 0.64–1.43) for the first two years after vaccination. The risk of CFS/ME increased with increasing number of previous hospital contacts, HR = 5.23 (95% CI 3.66–7.49) for 7 or more contacts as compared to no contacts. Girls with 7 or more hospital contacts were less likely to be vaccinated than girls with no previous hospital contacts, RD = −5.5% (95% CI −6.7% to −4.2%).

*Conclusions:* No indication of increased risk of CFS/ME following HPV vaccination was observed among girls in the first 6 birth cohorts offered HPV vaccine through the national immunisation programme in Norway.



## 1. Introduction

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a complex clinical condition characterized by persistent severe and disabling unexplained fatigue [1]. The aetiology of CFS/ME is unknown. There are no biomarkers for the disease and no validated laboratory test for diagnosis. Altered cognitive function, autonomic dysfunction, neuroendocrine abnormalities and alterations in the immune system, including abnormal cytokine patterns, deficiencies in natural killer cell function and poorly responsive T cells, are reported in CFS/ME patients [1–8]. Also, higher frequencies of autoantibodies have been described, and autoimmune mechanisms may be involved [2,9–11]. Autoimmunity might be triggered by infections, and CFS/ME is often precipitated by a long-lasting viral infection, such as glandular fever [1,11–13]. Recently, a slight impairment of B cell differentiation and development combined

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with activation of anti-viral innate immunity was suggested from gene expression studies, further suggesting a possible pathophysiological role for viral infections [14].

Vaccines have also been suggested to play a role in the development of CFS/ME, but no associations between vaccination and CFS/ME have been found for the vaccines studied, including the bivalent HPV vaccine [12,15–18]. The risk of CFS/ME after vaccination with the quadrivalent HPV vaccine has not been studied.

Concerns have been raised about a possible relationship between HPV vaccination and two syndromes with symptoms that partly overlap with CFS/ME, namely postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS) [19–26]. Moreover, clinical manifestations with CFS/ME-like symptoms reported after HPV vaccination have been referred to as 'HPV vaccination associated neuro immunopathic syndrome (HANS)' and 'human papillomavirus vaccination syndrome' [27,28]. However, studies comparing vaccinated and unvaccinated girls have not been performed. Reviews performed by the European Medicines Agency (EMA) and the WHO Global Advisory Committee on Vaccine Safety (GACVS) found no evidence to support a causal link between HPV vaccination and development of CRPS or POTS [29,30]. However, the body of evidence is limited, and the conclusion in EMA's report has been discussed [31–34]. Thus, further research is still warranted.

In Denmark, girls and women reporting severe adverse events following HPV vaccination, including POTS and other CFS/ME-like symptoms, had been seeking healthcare more often in the two years prior to vaccination than vaccinees not reporting adverse events [35]. Underlying conditions that predispose for medical outcomes suspected to be adverse vaccine reactions have been linked to lower vaccine uptake [36]. This may result in healthy vaccinee bias [37,38]. Thus, it is important to consider medical history when studying adverse events following vaccination [35,36]. Whether conditions associated with increased risk of CFS/ME-like symptoms are linked to lower uptake of HPV vaccine was not addressed in the Danish study.

The HPV vaccine was included in the Norwegian Childhood Immunisation Programme in the autumn of 2009. The quadrivalent vaccine has been offered in a three-dose schedule to girls aged 12 through a school-based programme during 7th grade. The uptake of at least one dose HPV vaccine has increased from 70% among girls born in 1997, the first cohort eligible for vaccination, to 88% among girls born in 2002 [39,40]. A catch-up programme for older girls was first implemented in November 2016.

A Norwegian study found two distinct age peaks in the incidence of CFS/ME, the first among adolescents aged 10–19 years, and a second in the age group 30–39 years [41]. During the last decade, an increase in referrals of children with fatigue has been reported in Norway [42]. If this increase is related to the implementation of the HPV vaccination programme, we would expect to observe a larger increase in CFS/ME incidence among girls than among boys.

The main aim was to study the association between HPV vaccination and risk of CFS/ME among girls eligible for HPV vaccination in the national immunisation programme in Norway. Also, we wanted to describe and compare the incidence of CFS/ME among adolescent girls and boys after introduction of the HPV vaccine in 2009. Finally, we wanted to study medical history in relation to both risk of CFS/ME and uptake of HPV vaccine.

## 2. Material and methods

### 2.1. Data sources

Information on sex and dates of birth, immigration, emigration and death on all residents in Norway, born 1992–2004 was obtained from the Norwegian Central Population Registry.

The Norwegian Patient Registry (NPR) provided information on hospital contacts. The NPR contains information on date and discharge diagnosis of all in- and outpatient visits in specialist healthcare from 2008 onwards [43]. Hospital discharge diagnoses are reported according to the International Classification of Diseases, Version 10 (ICD-10) [44].

Information on vaccinations was extracted from the Norwegian Immunisation Registry. Notification to the immunisation registry is mandatory for all vaccinations within the national childhood immunisation programme [45].

Statistics Norway provided information on parental countries of birth, parental education levels (as of 31 December 2012) and county of residence.

We used the unique personal identification number allocated to all Norwegians to link information from the different national registers.

The study was approved by the Regional Committee for Medical and Health Research Ethics, South East Norway.

### 2.2. Study populations and follow-up

The study population included all individuals born 1992–2004 residing in Norway at any time before December 31, 2012, n = 859,285. Follow-up started from the 10-year birthday, January 1, 2009 or start of residency in Norway, whichever came last. Individuals were followed until diagnosis of CFS/ME (see definition below), death, emigration, their 18-year birthday (corresponding to the age in 2015 of the first cohort offered the HPV vaccine), or December 31, 2014, whichever came first. We excluded individuals who did not reside in Norway during the follow-up period, i.e. individuals who emigrated (n = 25,150) or died (n = 4584) before start of follow-up, and individuals who immigrated after end of follow-up, i.e. after their 18-year birthday (n = 5162). Furthermore, 199 individuals diagnosed with CFS/ME before start of follow-up were excluded. Finally, we excluded 55 individuals missing from the Norwegian Central Population Registry as of December 31, 2014 and 2 emigrated individuals with missing date of emigration. Incidence rates of CFS/ME were calculated among the remaining 824,133 individuals.

All other analyses were further restricted to the subset of girls born 1997–2002 and thus eligible for HPV vaccination through the national immunisation programme, n = 183,569. In analyses of this subset, end of follow-up was defined as described above. However, follow-up started later; September 1, the year the girls turned 12 and were offered HPV vaccine. We excluded girls who emigrated (n = 978), died (n = 31) or were diagnosed with CFS/ME (n = 61) before the start of this new follow-up period. Furthermore, girls who immigrated later than January 1, the year they turned 11 (n = 4291) were excluded to ensure complete information on medical history. Finally, girls with missing information on both parents' country of birth (n = 49), both parents' education level (n = 1292), or county of residence (n = 414) were excluded. Thus, 176,453 girls were included in the analyses. To study whether associations were stronger during the first period after exposure, we performed additional analyses where the girls were censored after 2 years (two-year follow-up).

### 2.3. Study variables

CFS/ME was defined as an in-or outpatient hospital visit with a discharge diagnosis coded as G93.3 in the NPR. The national guidelines on CFS/ME recommend using ICD-10 code G93.3 for CFS/ME, regardless of suspected cause, and that children and adolescents are diagnosed by a paediatrician in the specialized health care [46]. Children and adolescents are usually diagnosed according to guidelines from the Norwegian Paediatric Association [41,47],

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