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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine

Per Magnus[a,*], Nina Gunnes[a], Kari Tveito[b], Inger Johanne Bakken[a], Sara Ghaderi[a], Camilla Stoltenberg[a], Mady Hornig[c], W. Ian Lipkin[c], Lill Trogstad[a], Siri E. Håberg[a]

[a] Norwegian Institute of Public Health, 4404 Nydalen, 0403 Oslo, Norway
[b] Journal of the Norwegian Medical Association, Oslo, Norway
[c] Center for Infection and Immunity, Columbia University, NY, NY, USA

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ABSTRACT

Background: Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated to infections and it has been suggested that vaccination can trigger the disease. However, little is known about the specific association between clinically manifest influenza/influenza vaccine and CFS/ME. As part of a registry surveillance of adverse effects after mass vaccination in Norway during the 2009 influenza A (H1N1) pandemic, we had the opportunity to estimate and contrast the risk of CFS/ME after infection and vaccination.

Methods: Using the unique personal identification number assigned to everybody who is registered as resident in Norway, we followed the complete Norwegian population as of October 1, 2009, through national registries of vaccination, communicable diseases, primary health, and specialist health care until December 31, 2012. Hazard ratios (HRs) of CFS/ME, as diagnosed in the specialist health care services (diagnostic code G93.3 in the International Classification of Diseases, Version 10), after influenza infection and/or vaccination were estimated using Cox proportional-hazards regression.

Results: The incidence rate of CFS/ME was 2.08 per 100,000 person-months at risk. The adjusted HR of CFS/ME after pandemic vaccination was 0.97 (95% confidence interval [CI]: 0.91–1.04), while it was 2.04 (95% CI: 1.78–2.33) after being diagnosed with influenza infection during the peak pandemic period.

Conclusions: Pandemic influenza A (H1N1) infection was associated with a more than two-fold increased risk of CFS/ME. We found no indication of increased risk of CFS/ME after vaccination. Our findings are consistent with a model whereby symptomatic infection, rather than antigenic stimulation may trigger CFS/ME.

1. Introduction

Mass vaccination, as done in several countries during the novel influenza A (H1N1) pandemic in 2009, is a public health action where the benefit is assumed to outweigh the risk of adverse events. Surveillance of adverse reactions is needed for an appraisal of the balance between benefit and risk, and to ensure both appropriate use of vaccines and public confidence in vaccine safety. After 2009, narcolepsy and Guillain–Barré syndrome have been linked to H1N1 vaccines, although the final verdicts concerning causality have not yet been made [1–6]. The two diseases are considered to be autoimmune, possibly triggered by infection or immunization [7–10].

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a debilitating disorder, characterized by severe fatigue of unknown cause. In addition to fatigue, CFS/ME is associated with a wide range of symptoms, including post-exertional malaise, pain, unrefreshing sleep, and cognitive impairment [11]. Alterations in both the innate and acquired immune systems have been reported [12–17]. Disease clustering and even small epidemics have been described [18–24]. It has been proposed that autoimmune mechanisms may play a role [25–27], and that, in addition to infections, immunizations could be involved in the onset or continuation of the pathophysiological process.

* Corresponding author. Tel.: +47 92683119.
E-mail address: per.magnus@fhi.no (P. Magnus).

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In the fall of 2009, a decision was made to offer vaccination, free of charge, to all citizens in Norway, using an H1N1 vaccine with an AS03 adjuvant. Utilizing nationwide registries, a surveillance program to monitor effects and side effects of vaccination was established [28]. Although many influenza infections may be asymptomatic, and only a proportion of symptomatic subjects will seek health care, a sufficient number of subjects with influenza infections were included in Norwegian primary care and communicable disease registries in the peak pandemic period October–December 2009, to provide an opportunity to prospectively estimate and compare effects of vaccination and influenza infection on the risk of CFS/ME.

2. Methods

In Norway, a few cases of novel influenza A (H1N1) infection were registered from July 2009, but the majority of laboratory-confirmed cases were noted in a peak period from October 1 through December 31, 2009 [28]. In October 2009, two vaccines became available: Pandemrix (GlaxoSmithKline), containing the squalene-based adjuvant AS03, and Celvapan (Baxter), which did not. The vaccinations coincided with the peak time period of the pandemic wave.

The study population of this nationwide cohort study is the resident population on October 1, 2009, as registered in the Norwegian population registry [29] (n = 4840,084). Data from the Norwegian Immunization Registry [30], the reimbursement data from primary care physicians, the Norwegian Surveillance System for Communicable Diseases [31], and the national specialist health care register (Norwegian Patient Register—NPR) were linked to the study base using the unique 11-digit personal identification number provided to all residents. Subjects with missing or invalid information in the population registry (n = 7873), subjects who had received a diagnosis of CFS/ME prior to October 1, 2009, as registered in the NPR (n = 1951), subjects who had been vaccinated with Celvapan but not with Pandemrix (n = 481), and subjects who were vaccinated but who lacked registration of the date of vaccination (n = 2573), were excluded. In total, 4827,209 subjects were eligible for the present study. This registry-based study was approved by the Regional Committee for Medical and Health Research Ethics for South-Eastern Norway (reference number: 2010/2583).

The vaccination registry provided information on the two influenza vaccines against the A(H1N1)pdm09 strain used in Norway. One dose of Pandemrix was recommended by the Norwegian Institute of Public Health. Vaccinations were offered from October 19, 2009, and all vaccinations from this date until the early months of 2010 were included in the analyses.

Information on infection with the H1N1 influenza virus was obtained from two different sources. One source was from consultations in primary health care and emergency outpatient clinics, where all consultations must be reported to obtain reimbursement. Diagnoses are reported with codes from the International Classification of Primary Care, Second Edition (ICPC-2). The code for influenza-like illness (R80) was taken as a measure of H1N1 infection when the diagnosis was made during the pandemic peak period (October 1 through December 31, 2009). We considered R80 codes outside this period as insufficiently specific to be used as evidence for exposure to H1N1, as other infections may have caused similar symptoms. The other source of information on influenza infection was registrations in the Norwegian Surveillance System for Communicable Diseases of a confirmed antigenic test for H1N1 as reported from microbiology laboratories. The majority of these infections were reported during the peak period. However, due to the high specificity of these tests, reports from outside the peak period were included.

Table 1
Characteristics of subjects with follow-up time* (n = 4822,337), all residents of Norway as of October 1, 2009.

	n	%
Year of birth		
<1940	518,118	10.7
1940–1949	503,836	10.4
1950–1959	612,885	12.7
1960–1969	698,012	14.5
1970–1979	672,069	13.9
1980–1989	604,677	12.5
1990–1999	634,351	13.1
2000–2009	583,261	12.1
Sex		
Male	2410,311	49.9
Female	2416,898	50.1
Vaccinated with Pandemrix		
No	2931,549	60.7
Yes, during peak period*	1841,982	38.2
Yes, other time period	53,678	1.1
Influenza diagnosis in primary care in peak period		
No		
Yes	4713,230	97.6
	113,979	2.4
Laboratory-confirmed influenza		
No	4814,155	99.7
Yes, during peak period	10,582	0.2
Yes, other time period	2472	0.1

* Exclusions: 7873 subjects with missing or invalid status in the population register; 481 subjects who were vaccinated with Celvapan but not with Pandemrix; 2573 subjects with missing date of first vaccination with Pandemrix; 1951 subjects who had been diagnosed with CFS/ME prior to October 1, 2009.

The specialist health care register (NPR) includes diagnostic information (International Classification of Diseases, Version 10—ICD-10) for outpatient consultations and hospitalizations in the specialized health services. All cases of CFS/ME (ICD-10 code G93.3) were included. In addition, the population registry provided information about potential confounders, such as sex and year of birth. Year of birth was categorized into 10-year groups, with all persons born prior to 1960 merged into one group.

Crude incidence rates were estimated as the number of new cases of CFS/ME divided by the sum of person-months at risk, both overall and by exposure. Hazard ratios (HRs) of CFS/ME, with associated 95% confidence intervals (CIs), were estimated using Cox proportional-hazards regression, with number of whole months since the start of the study (October 1, 2009) as the time metric. Subjects were followed until diagnosis of CFS/ME, death, emigration, or end of the study (December 31, 2012), whichever occurred first. By default, observations from 4872 subjects with zero follow-up time (due to emigration, death, or diagnosis of CFS/ME in October 2009) were excluded, leaving 4822,337 subjects in the analysis. Indicator variables of vaccination (yes/no) and influenza infection (yes/no) were included as time-varying covariates. Subjects were considered as being exposed to vaccination from the month of first vaccination with Pandemrix and as exposed to infection from the month of first influenza diagnosis. The infection and vaccination exposure status persisted until the end of follow-up. Data were analyzed using the Stata 13 software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.).

3. Results

From November 1, 2009 through 2012, 3737 new cases of CFS/ME were registered in the specialist health care register. Among these, 138 were registered in November and December 2009, 1092 in 2010, 1258 in 2011, and 1249 in 2012. Nearly 40% were vaccinated with Pandemrix (Table 1). More than 97% of these vaccinations were given during the peak pandemic period. Table 1

Table 2
Incidence rates and hazard ratios (HRs) of CFS/ME, with associated 95% confidence intervals (CIs), according to pandemic vaccination and influenza infection. Follow-up time from October 1, 2009, through December 31, 2012 for 4822,377 residents of Norway born 1899–2009.

Year of birth		No. of person-months at risk	No. of cases	Incidence rate*	Crude	Adjusted**	
					HR	HR	95% CI
1899–2009	*Influenza*						
	Yes	4422,760	227	5.13	2.55	2.04	1.78–2.33
	No	175,460,422	3510	2.00	1.0	1.0	
	Vaccinated						
	Yes	69,375,157	1408	2.03	0.95	0.97	0.91–1.04
	No	110,508,025	2329	2.11	1.0	1.0	
1899–1979	*Influenza*						
	Yes	2033,877	94	4.62	2.49	1.65	1.34–2.03
	No	109,159,893	2020	1.85	1.0	1.0	
	Vaccinated						
	Yes	42,335,444	781	1.84	0.95	0.89	0.82–0.98
	No	68,858,326	1333	1.94	1.0	1.0	
1980–2009	*Influenza*						
	Yes	2388,883	133	5.57	2.46	2.45	2.05–2.92
	No	66,300,529	1490	2.25	1.0	1.0	
	Vaccinated						
	Yes	27,039,713	627	2.32	0.94	1.08	0.98–1.20
	No	41,649,699	996	2.39	1.0	1.0	

* Number of new cases per 100,000 person-months at risk.
** Stratified Cox analysis with separate baseline hazards functions for each year-of-birth category and adjusted for sex and the other variable in the table.

Table 3
Incidence rates and hazards ratios (HRs) of CFS/ME, with associated 95% confidence intervals (CIs), according to exposure to pandemic vaccination and influenza infection. Follow-up time from October 1, 2009, through December 31, 2012, for 4822,377 residents of Norway born 1899–2009.

		No. of person-months at risk	No. of cases	Incidence rate*	Adjusted**	
Vaccinated	Infected				HR	95% CI
No	No	107,475,182	2165	2.01	1.0	
Yes	No	67,985,240	1345	1.98	0.98	0.91–1.05
No	Yes	3032,843	164	5.41	2.08	1.78–2.44
Yes	Yes	1,389,917	63	4.53	1.88	1.46–2.42

* Number of new cases per 100,000 person-months at risk.
** Stratified Cox analysis with separate baseline hazards functions for each year-of-birth category and adjusted for sex.

shows that 2.4% of the population was registered with an influenza infection in primary health care consultations, while only about 0.3% had a verified antigenic diagnosis from a microbiology laboratory.

Among eligible subjects for follow-up (n = 4822,337), the crude incidence rate of CFS/ME was 2.08 per 100,000 person-months (3737 cases and 179,883,182 person-months). The adjusted HR of CFS/ME after influenza infection was 2.04 (95% CI: 1.78–2.33), while it was 0.97 (95% CI: 0.91–1.04) after vaccination (Table 2). The HR of CFS/ME after influenza infection was higher for subjects who were below 30 years of age in 2009 (born in 1980–2009, lower part of Table 2) compared to older subjects. The same pattern of associations between CFS/ME and the two exposures was found when the regression analysis was performed separately for males and females (results not shown). Table 3 shows the joint effects of influenza infection and vaccination. In the absence of influenza infection, the incidence rates were about the same for vaccinated and unvaccinated subjects. The rates were increased for infected subjects, independent of vaccination status.

4. Discussion

This study shows that CFS/ME occurring after the influenza A (H1N1) pandemic was associated with a diagnosis of influenza-like illness. We found no evidence of an association between pandemic influenza vaccination and CFS/ME. This suggests that development of CFS/ME may be a reaction to fever, malaise, and general activation of the immune system, rather than the more restricted antigenic stimulation from a vaccine.

An advantage of this study is that the whole nation formed the cohort, reducing the potential for selection bias. Another advantage is that the registration of exposures (vaccination and infection) was made before and independently of the registration of the endpoint (CFS/ME). A limitation of registry data is that the classifications of exposures and the disease outcomes are not designed for research purposes. There is some degree of misclassification of the variables. During the pandemic, a web-based, electronic reporting form for registration of influenza vaccinations into the immunization registry was set up. A comparison between the number of vaccines distributed to local communities and the number of registered vaccinations indicates that as many as 200,000 subjects (about 4% of the population) could have been vaccinated without registration [32].

CFS/ME is a heterogeneous disorder and different case definitions have been used [11]. The diagnosis of CFS/ME is based on the presence of a constellation of subjective symptoms, obtained through patient interviews as well as the exclusion of other conditions that may result in chronic fatigue. There are no objective signs or biomarkers for this disease. It is a weakness of registry data that diagnoses are not based on strict criteria from a research protocol. We did not perform in-depth case validation as part of this study.

The registrations of influenza from primary health care were restricted to the peak pandemic period in Norway. We assume that the majority of subjects with influenza-like symptoms who received an R80 code in the period October–December 2009 were infected with the H1N1 influenza virus rather than another respiratory pathogen. No other influenza virus was known to be circulating in the population at this time. The reporting of diagnoses from

primary health care consultations is believed to be complete as it is required for reimbursements from the government. However, many patients with influenza symptoms will not seek medical care during an influenza season. Only 2.4% of the study population received a physician diagnosis of influenza during the peak pandemic period. Presumably, patients with more severe symptoms seek medical care. The proportion of the population with clinical influenza infection during the pandemic has been estimated to be 20–30% [33,34], implying that a substantial number of the subjects categorized as uninfected in this study, actually were infected and therefore misclassified. Non-differential misclassification of exposures and end-points in a prospective study usually leads to underestimation of the effect of the exposure on the outcome, in this case influenza infection on later CFS/ME occurrence, suggesting that the true relative risk may be higher than estimated by us.

In Norway, two distinct age peaks in the incidence of CFS/ME have been reported. The first peak is in the age group 10 to 19 years, and the second peak is in the age group 30 to 39 years [35]. In the present study, a slightly stronger effect of influenza infection was found for subjects below the age of 30 years, as compared to subjects aged 30 years or older. However, the possibility that this difference may be due to illness behavior (the proportion of ill persons who seek medical care) should be kept open.

There is still a lack of large, well-characterized cohort studies with CFS/ME as endpoint. Studies in general practice suggest that prolonged fatigue is not specifically related to features of common viral illnesses [36,37]. By following subjects with either acute Epstein–Barr virus infection, Q fever or Ross river virus infection in a rural region of Australia, it was found that 11% had prolonged illness with disabling fatigue [20]. A cohort of subjects with infectious mononucleosis (IM), influenza or tonsillitis, but without a comparison group free of infections, found the odds of clinically diagnosed fatigue to be 4.4 times higher when IM was compared to influenza and 6.6 times higher when IM was compared to tonsillitis [38]. Our finding of a significantly increased risk of CFS/ME in the general population after influenza infection is novel and needs confirmation. Fatigue was found to be frequent in the weeks after having suffered from the Asian influenza during the winter of 1957–58 [39], and a case report of CFS/ME after the recent pandemic has been published [40], but we are not aware of other population-based studies.

It is reassuring that no evidence for increased risk of CFS/ME was found among vaccinated subjects. Studies of the effect of influenza vaccination on immune function in subjects with CFS/ME have not suggested excess early reactions or altered antibody responses [41–43]. Also an earlier Norwegian study showed no relation between vaccination against meningococcal disease and CFS/ME [44].

5. Conclusions

In conclusion, pandemic influenza vaccination in a mass campaign does not increase the risk of CFS/ME. The findings suggest that clinically manifest influenza-like illness may play a causal role for the development of at least a proportion of cases of this disorder.

Conflict of interest statement

None.

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