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Infectious Diseases

Encephalitis after influenza and vaccination: a nationwide population-based registry study from Norway

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Abstract

Background: Influenza is known to be associated with various neurological complications, including encephalitis. We conducted a registry-based study to assess the risk of encephalitis after influenza and A(H1N1)pdm09 vaccine.

Methods: Data from Norwegian national health registries during 2008–14 were linked using the unique personal identifiers given to all Norwegian residents ($N = 5\,210\,519$). Cox proportional-hazard models with time-varying variables were fitted to estimate hazard ratios (HRs) of encephalitis after influenza and A(H1N1)pdm09 vaccine, using the risk windows 0–7, 0–14, 0–30, 0–60, 0–90 and 0–180 days.

Results: In Norway, 684 172 individuals received an influenza diagnosis and 2793 patients were hospitalized with encephalitis during 2008–14. The risk of encephalitis increased after influenza: HR, 7-day risk window: 47.8 (95% confidence interval (CI): 35.8–63.8), and the HR decreased for longer risk windows; HR, 180-day risk window: 3.8 (95% CI: 3.1–4.7). HR of encephalitis after influenza during the 2009 main pandemic wave using a 7-day risk window was 30.0 (95% CI: 10.8–83.2). We found no differences in the risk of encephalitis after the seasonal influenza compared with influenza during the 2009 main pandemic wave; HR, 7-day risk window: 1.3 (95% CI: 0.4–4.3). A(H1N1)pdm09 vaccine was not associated with the risk of encephalitis: HR, 14-day risk window: 0.6 (95% CI: 0.2–2.1).

Conclusions: There was an increased risk of encephalitis following influenza but not after A(H1N1)pdm09 vaccine. The risk of encephalitis was highest in the first few weeks after influenza.

Key words: Encephalitis, meningitis, influenza, pandemic influenza, A(H1N1)pdm09 vaccination, Norway

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Key Messages

- Influenza was associated with an increased risk of encephalitis.
- The A(H1N1)pdm09 vaccine was not associated with risk of encephalitis.
- We found no differences in risk of encephalitis after seasonal influenza compared with influenza during the 2009 main pandemic wave.

Introduction

Influenza is known to be associated with neurological complications, such as seizures, encephalopathy and Guillain-Barré syndrome.[1, 2] Influenza and other infectious agents which trigger either acute inflammation or an immunological response may cause encephalitis after a lag period.[3]

Influenza-associated encephalopathy has been reported in several studies.[1,4–8] Some studies have compared the risk of acute encephalopathy following the 2009 influenza pandemic season with seasonal influenza,[6,7] and others have focused on influenza-associated encephalopathy after infection during the pandemic season in 2009.[1]

Encephalitis is a rare disease. To our knowledge, previous studies on the association of influenza infection and encephalitis have mainly been limited to case reports.[9–14] Few studies have been population-based.[1,4,5] In Norway, national health databases provide dates of hospital diagnoses, seasonal influenza (seasons other than the 2009 main pandemic wave) and influenza diagnosis during the 2009 main pandemic wave in primary care, and A(H1N1)pdm09 vaccines for the entire population. Data from these registries are linked on an individual level, and information includes dates of influenza and encephalitis diagnoses for all residents in Norway during 2008–14. Using such data enabled us to study the occurrence of encephalitis in more detail than has been possible earlier. Our main aim was to assess the association between the seasonal influenza or influenza during the 2009 main pandemic wave [A(H1N1)pdm09 influenza] and risk of encephalitis. Furthermore, we explored whether there was an increased risk after A(H1N1)pdm09 vaccine.

Methods

Our study cohort included the entire Norwegian population as registered in the National Registry during 2008–14 ($N = 5\,210\,519$). The National Registry holds demographic information (date of birth, place of residence, date of emigration or death etc.) based on the unique 11-digit personal identification number (PIN) provided to all Norwegian residents.

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

Data sources

The PIN enabled us to link data from national health registries and databases. The Norwegian Patient Registry (NPR)[15] is an administrative database covering all Norwegian hospitals. Reporting of data on hospitalizations and outpatient visits is mandatory and linked to the reimbursement system. The NPR provided data on hospitalizations with encephalitis [International Classification of Diseases, Version 10 (ICD-10): A86, A87.9, A89, G03.9, G04.0, G04.8 and G04.9] and influenza (ICD-10 codes: J09, J10, and J11) during 2008–14.

The Norwegian Directorate of Health reimburses consultations in emergency outpatient clinics and general practice, for which reporting includes date of consultation and the diagnostic code(s) using the International Classification of Primary Care, Second Edition (ICPC-2). Dates of physician consultations were used for those individuals receiving an influenza diagnosis [ICPC-2 code R80 ('influenza-like illness')]. The criteria for receiving a diagnosis with R80 code are muscle pains and cough with no abnormal findings on examination of the airway other than inflammation of the nasal mucosa and throat. In addition, three or more of the following symptoms must be present: rapid onset (within 12 h), chills/fever, fatigue, influenza in the community, ongoing influenza epidemic or confirmed influenza virus infection by culture or serology.[16]

The Norwegian Surveillance System for Communicable Diseases, which is a nationwide registry for surveillance of infectious diseases,[17] provided dates of laboratory-confirmed influenza A(H1N1)pdm09 infection. Reporting to this registry was mandatory for positive influenza A (H1N1)pdm09 tests only during the 2009 main pandemic wave.

Influenza was defined as registration of the ICPC-2 code R80 ('influenza-like illness'), ICD-10 codes J09, J10 and J11, and/or laboratory-confirmed influenza A(H1N1)pdm09. The dates of A(H1N1)pdm09 vaccinations (Pandemrix®) from late 2009 through 2014 were obtained from the Norwegian Immunization Registry.[18] In Norway, the Pandemrix® (GlaxoSmithKline) vaccine was offered to the general population free of charge during the 2009 main pandemic wave. Registration of A(H1N1)pdm09 vaccinations was mandatory. The vaccination campaign began on 19 October 2009, and more than

97% of the A(H1N1)pdm09 vaccines were administered before31 December 2009.

Case definition of encephalitis

We aimed to study the risk of encephalitis after recent influenza. Only diagnostic codes that are likely to be used with viral encephalitis were included, and encephalitis diagnoses with other known agents were excluded. We included the following ICD-10 codes in the case definition of encephalitis:

- A86: Unspecified viral encephalitis;
- A87.9: Viral meningitis, unspecified;
- A89: Unspecified viral infection of the central nervous system;
- G03.9: Meningitis, unspecified;
- G04.0: Acute disseminated encephalitis and encephalomyelitis (ADEM);
- G04.8: Other encephalitis, myelitis and encephalomyelitis;
- G04.9: Encephalitis, myelitis and encephalomyelitis, unspecified.

Due to the rare occurrence of each diagnosis, and since they all may be used for both encephalitis and meningitis triggered or caused by influenza, any of the ICD-10 codes above defined an individual as an encephalitis case. Only the dates of hospitalizations with acute encephalitis (obtained from the NPR) were considered, and all follow-up visits were disregarded. There were no cases of with ICD-10 code A87.8 or G05.1 (with or without combination with influenza ICD-10 codes J10.8/J11.8/J09).

Influenza seasons

We defined the respective peak periods of seven influenza seasons in 2008–14 in Norway based on the Norwegian Institute of Public Health's influenza surveillance. In Norway, the main pandemic influenza wave occurred between 1 October and 31 December 2009.[16] Details of each peak period are summarized in Table 1.

Table 1. Peak periods of influenza seasons in Norway (2008–14) based on influenza surveillance by the Norwegian Institute of Public Health

Influenza season	Date
Season 1	01.02.2008–13.03.2008
Season 2	26.12.2008–26.02.2009
Season 3[a]	01.10.2009–31.12.2009
Season 4	17.12.2010–03.03.2011
Season 5	27.01.2012–22.03.2012
Season 6	14.12.2012–14.03.2013
Season 7	25.01.2014–11.04.2014

[a]The 2009 main pandemic wave.

Statistical analysis

We estimated the risk of encephalitis (following individuals diagnosed with influenza or receiving the A(H1N1)pdm09 vaccination) by conducting six separate analyses with different risk windows (0–7, 0–14, 0–30, 0–60, 0–90 and 0–180 days).

Cox proportional hazard regression models were applied, with the number of days since the start of the study (1 January 2008) as the time metric. Exposure to influenza (ICPC-2 code R80, laboratory-confirmed influenza A (H1N1) diagnosis, or ICD-10 codes J09, J10 and J11), overall or during the respective peak periods of the influenza seasons during 2008–14, and exposure to the A(H1N1)pdm09 vaccine, were treated as binary time-varying variables. An individual was considered as exposed from the date of influenza/A(H1N1)pdm09 vaccination through the length of the risk window in question. All models were adjusted for sex and year of birth (dichotomized as <1980 or ≥ 1980). For each risk window, we estimated crude and adjusted hazard ratios (HRs) of encephalitis, with associated 95% confidence intervals (CIs), after influenza and A(H1N1)pdm09 vaccination. Individuals were followed from the start of the study or from birth, whichever occurred latest, until hospitalization with acute encephalitis, death, emigration or the end of study on 31 December 2014, whichever occurred first.

Four approaches were used to estimate the HR of encephalitis after a diagnosis of influenza. First, the overall HR of encephalitis following a diagnosis of influenza was estimated, disregarding whether or not the diagnosis occurred during the peak period of any influenza seasons. Second, we estimated the HR of encephalitis after a diagnosis of influenza during the peak period of each influenza season under study. Six separate analyses for each risk window were fitted and, in each analysis, variables indicating diagnosis during all seven seasons were included simultaneously. Third, we considered an individual exposed to seasonal influenza if the diagnoses occurred during the peak of the influenza seasons except the 2009 main pandemic wave. We compared the risk of encephalitis after diagnosis with seasonal influenza with the risk after influenza during the 2009 main pandemic wave. Fourth, we applied a model restricted to influenza during the 2009 main pandemic wave, in which we also included the A(H1N1)pdm09 vaccine as an exposure, since reliable vaccination data were available only for this season. In the latter approach, indicators of influenza during the 2009 main pandemic and the

Table 2. Characteristics of the study sample comprising the entire Norwegian population during 2008–14

	All individuals[a]		Individuals with influenza				Cases of encephalitis	
			Overall[b]		Peak periods of influenza seasons			
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Total	5210519	100	684172	13.1	359859	6.9	2793	0.1
Sex								
Male	2603523	50.0	311438	12.0	162306	6.2	1441	0.1
Female	2607996	50.0	372734	14.3	197553	7.6	1352	0.1
Year of birth								
<1980	3079721	59.1	404851	13.2	199600	6.5	1683	0.1
≥1980	2130798	40.9	279321	13.1	160259	7.5	1110	0.1

[a]All individuals included in the study period (2008–14).
[b]All individuals with an influenza episode during the study period 2008–14, regardless of influenza seasons.

A(H1N1)pdm09 vaccine were included simultaneously as time-varying variables in the adjusted model.

In addition, we performed a sensitivity analysis with a stricter definition of encephalitis, ignoring ICD-10 codes related to unspecified meningitis (A87.9 and G03.9) and ADEM (G04.0). All analyses were performed using the Stata 14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

Results

During 2008–14, 2793 individuals were registered with a diagnosis with acute encephalitis in Norway. The mean age at diagnosis was 39.4 years (standard deviation: 23.2 years), with a similar occurrence in males and females (Table 2). The crude overall incidence rate of encephalitis was 8.3 per 100 000 person-years. A total of 5 210 519 individuals were eligible for the analysis.

Overall

The proportion of the Norwegian population hospitalized with acute encephalitis during 2008–14 was 0.1 % (Table 2). Table 3 displays the number of encephalitis cases among individuals with and without influenza in the period 2008–14, for the different risk windows. The risk of encephalitis following influenza was elevated for all risk windows; however, the HR decreased as the length of the risk window increased (Figure 1). The adjusted HR of encephalitis for influenza was 47.7 (95% CI: 35.7–63.6) using a risk window of 7 days,and the adjusted HR using a 180-day risk window was 3.8 (95% CI: 3.1–4.7).

Approximately half of the cases had ICD-10 codes related to unspecified meningitis and ADEM. However, when these codes were excluded from the case definition of encephalitis in our sensitivity analysis, the results were similar to those from the main analysis, although the point estimates were reduced. The adjusted HR from the sensitivity analysis was 31.74 (95% CI: 20.33–49.54).

Table 3. Number of encephalitis cases according to status of influenza (regardless of season) for different risk windows, based on the entire Norwegian population with follow-up in 2008–14

Risk window	Exposure	Encephalitis cases
0–7 days	Influenza	
	No	2741
	Yes	48
0–14 days	Influenza	
	No	2732
	Yes	57
0–30 days	Influenza	
	No	2723
	Yes	66
0–60 days	Influenza	
	No	2712
	Yes	77
0–90 days	Influenza	
	No	2707
	Yes	82
0–180 days	Influenza	
	No	2691
	Yes	98

Influenza seasons

There was an increased risk of encephalitis after influenza during the peak period of influenza seasons (Figure 2). Detailed results for all seasons and risk windows are presented in Supplementary Table 1, available as Supplementary data at *IJE* online. In the early 2008 season, the adjusted HR using a 7-day risk window was 92.2 (95% CI: 28.6–296.7) and the adjusted HR for influenza

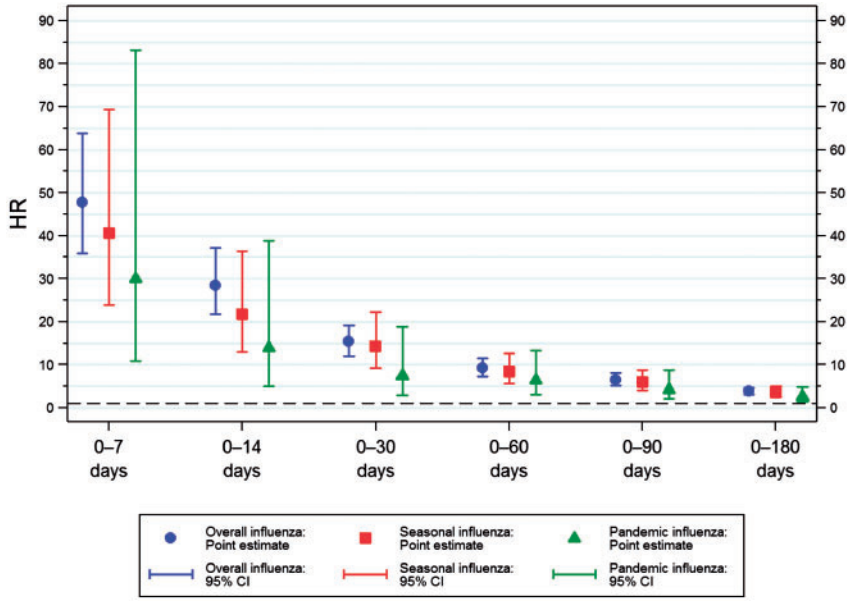

Figure 1. Adjusted hazard ratios (HRs) of encephalitis, with 95% confidence intervals (CIs), for overall influenza, seasonal influenza and influenza during the 2009 main pandemic wave (pandemic influenza), respectively, for different risk windows, using Cox proportional-hazards regression based on the Norwegian population with follow-up in 2008–14. Separate analyses were conducted for each risk window: 0–7 days, 0–14 days, 0–30 days, 0–60 days, 0–90 days and 0–180 days. All estimates have been adjusted for sex and year of birth (<1980 or ≥1980). The estimates corresponding to the 2009 main pandemic wave (pandemic influenza) were adjusted in addition for A(H1N1)pdm09 vaccine. The horizontal dashed black line indicates HR equal to 1.

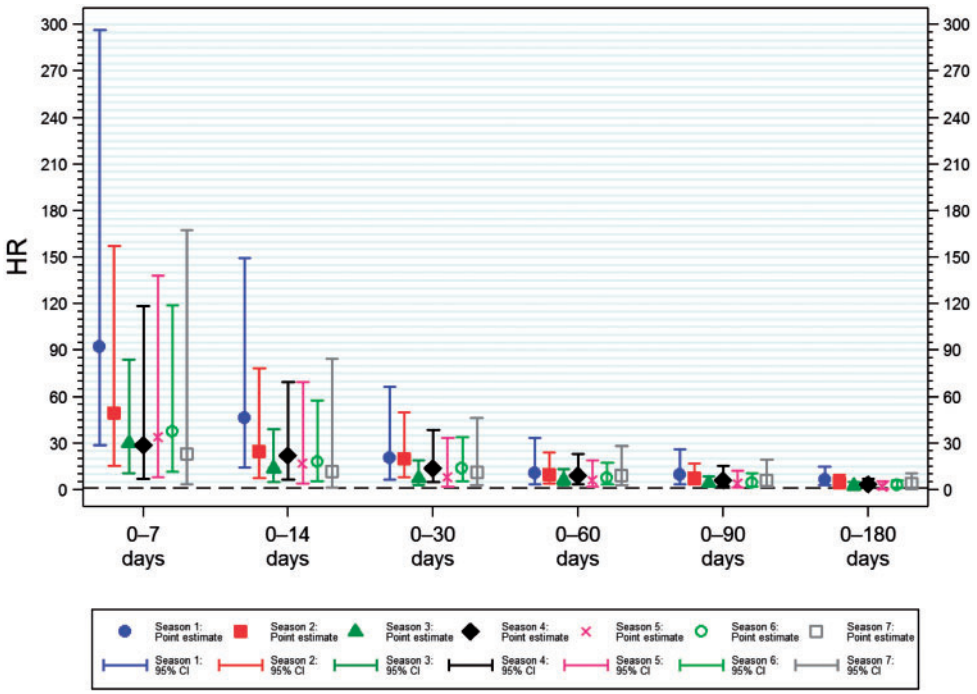

Figure 2. Adjusted hazard ratios (HRs) of encephalitis with associated 95% confidence intervals (CIs) for influenza during seven influenza seasons, for different risk windows, using Cox proportional hazards regression based on the Norwegian population with follow-up in 2008–14. Separate analyses were conducted for each risk window: 0–7 days, 0–14 days, 0–30 days, 0–60 days, 0–90 days and 0–180 days. All estimates have been adjusted for sex and year of birth (<1980 or ≥1980). Season 3 is the 2009 main pandemic wave. The horizontal dashed black line indicates HR equal to 1.

during the 2009 main pandemic wave using a 7-day risk window was 30.2 (95% CI: 10.9–83.7). Similarly to the overall estimates, the HR of encephalitis when using all influenza seasons except the 2009 main pandemic wave as exposure decreased with increasing length of the risk window in separate analyses (Figure 1).

Seasonal versus pandemic influenza

In order to compare seasonal and pandemic influenza, we estimated the HR of encephalitis for seasonal influenza, including individuals with influenza during the 2009 main pandemic wave as the reference group. For a 7-day risk window, the adjusted HR of encephalitis after the seasonal influenza compared with influenza during the 2009 main pandemic wave was 1.3 (95% CI: 0.4–4.3). The differences between influenza during the 2009 main pandemic wave and seasonal influenza were minor and results are based on low numbers. These results are presented in Table 4.

Influenza during the 2009 main pandemic wave and A(H1N1)pdm09 vaccination

There was an increased risk of encephalitis after influenza during the 2009 main pandemic wave (Table 5). The highest risk was shortly after the influenza diagnosis: adjusted HR, 7-day risk window: 30.0 (95% CI: 10.8–83.2). The A(H1N1)pdm09 vaccine was not associated with the risk of encephalitis in any risk windows: adjusted HR, 14-day risk window: 0.6 (95% CI: 0.2–2.1). There was no cases of encephalitis within the 7-day risk window after A(H1N1)pdm09 vaccination.

Table 4. Adjusted[a] hazard ratios (HRs) of encephalitis with associated 95% confidence intervals (CIs) for seasonal influenza as compared with influenza during the 2009 main pandemic wave (reference group), for different risk windows, using Cox proportional hazards regression based on the entire Norwegian population with follow-up in 2008–14

Risk window	Exposure	Encephalitis cases	Adjusted[a] HR (95% CI)
0–7 days	Influenza		
	Pandemic[b]	4	1
	Seasonal[c]	14	1.3 (0.4–4.3)
0–14 days	Influenza		
	Pandemic[b]	4	1
	Seasonal[c]	15	1.6 (0.5–4.9)
0–30 days	Influenza		
	Pandemic[b]	5	1
	Seasonal[c]	21	2.2 (0.7–6.8)
0–60 days	Influenza		
	Pandemic[b]	8	1
	Seasonal[c]	25	1.3 (0.6–3.1)
0–90 days	Influenza		
	Pandemic[b]	8	1
	Seasonal[c]	25	1.4 (0.6–3.2)
0–180 days	Influenza		
	Pandemic[b]	10	1
	Seasonal[c]	37	1.4 (0.7–2.8)

[a]Adjustment for sex and year of birth (<1980 or ≥1980).
[b]An influenza diagnosis during the 2009 main pandemic wave only.
[c]An influenza diagnosis in any influenza season except the 2009 main pandemic wave.

Discussion

In this nationwide registry-based study from Norway, we found an increased risk of encephalitis after both seasonal and pandemic influenza. We found no differences in risk of encephalitis after the seasonal influenza compared with influenza during the 2009 main pandemic wave. There was no indication that the A(H1N1)pdm09 vaccination was associated with the risk of encephalitis.

Strengths and weaknesses

A major strength of the current study was the availability of national health data from the entire Norwegian population of more than 5.2 million individuals, which minimize the risk of differential reporting and potential selection bias. By linking individual-level data from independent registries of primary care consultations and hospitalizations across the whole country, we had the unique opportunity to study the impact of influenza on the risk of encephalitis.

In Norway, the public health care system is financed through government funding, and all hospitalizations are free of charge. We believe that registration of encephalitis is likely to be complete since this is a serious condition that requires medical attention and is expected to be treated in hospitals. As hospitals are reimbursed through mandatory reporting to the NPR, it is probable that all cases of encephalitis are registered.

A major limitation of this study is the lack of data on microbial agents. These data are not available in national registries and it is not feasible to obtain them for a large study populations such as ours. However, a limited number of microbial agents are found in the Norwegian climate, and cultures of bacteria and a panel of 4–5 viruses are routinely investigated using polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) [herpes simplex virus 1,2 (HSV 1,2), varicella, enteroviruses].[3] We only had information on the ICD-10 diagnosis codes, in this registry-based study. Information on results from analysis of cerebrospinal fluid and neurological imaging were not available in national registries. Only a limited proportion of influenza episodes were confirmed by microbiology, and

Table 5. Crude and adjusted[a] hazard ratios (HRs) of encephalitis, with associated 95% confidence intervals (CIs), for influenza during the 2009 main pandemic wave (pandemic influenza) and A(H1N1)pdm09 vaccine, respectively, for different risk windows, using Cox proportional hazards regression based on the Norwegian population with follow-up in 2008–14

Risk window	Exposure	Encephalitis cases	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
0–7 days	Pandemic influenza			
	No	2785	1	1
	Yes	4	30.2 (10.9–83.7)	30.0 (10.8–83.2)
	A(H1N1)pdm09 vaccine			
	No	2789	1	1
	Yes	0	0.00 (—)	0.00 (—)
0–14 days	Pandemic influenza			
	No	2785	1	1
	Yes	4	14.0 (5.1–38.9)	14.0 (5.0–38.8)
	A(H1N1)pdm09 vaccine			
	No	2786	1	1
	Yes	3	0.63 (0.2–2.0)	0.6 (0.2–2.1)
0–30 days	Pandemic influenza			
	No	2784	1	1
	Yes	5	7.5 (3.0–18.8)	7.5 (3.0–18.8)
	A(H1N1)pdm09 vaccine			
	No	2781	1	1
	Yes	8	0.7 (0.4–1.5)	0.7 (0.4–1.6)
0–60 days	Pandemic influenza			
	No	2781	1	1
	Yes	8	6.4 (3.1–13.2)	6.4 (3.1–13.2)
	A(H1N1)pdm09 vaccine			
	No	2770	1	1
	Yes	19	0.9 (0.6–1.6)	1.0 (0.6–1.6)
0–90 days	Pandemic influenza			
	No	2781	1	1
	Yes	8	4.3 (2.1–8.8)	4.3 (2.1–8.8)
	A(H1N1)pdm09 vaccine			
	No	2761	1	1
	Yes	28	0.9 (0.6–1.4)	1.0 (0.6–1.5)
0–180 days	Pandemic influenza			
	No	2779	1	1
	Yes	10	2.6 (1.4–5.0)	2.6 (1.4–4.9)
	A(H1N1)pdm09 vaccine			
	No	2736	1	1
	Yes	53	0.8 (0.6–1.1)	0.8 (0.6–1.1)

[a]Mutual adjustment for influenza during the 2009 main pandemic wave and A(H1N1)pdm09 vaccine in addition to sex and year of birth (<1980 or ≥1980).

other respiratory viruses circulating at the same time may have been wrongly classified as influenza.[3] About 2.6% of individuals with a clinical influenza diagnosis also had a laboratory-confirmed influenza. However, restricting our analyses to laboratory-confirmed influenza yielded results similar to results from the main analysis. Another weakness of the study is the under-reporting of influenza in primary care, as only those seeking a physician for their illness are registered. One motivation for employed adults to seek primary health care services is to obtain documentation and reimbursement for sick leave, whereas younger, older, and unemployed persons may seek primary health care services only when symptoms are severe. It has been estimated that around 30% of the Norwegian population had an influenza A (H1N1)pdm09 during the 2009 main pandemic wave,[19] whereas less than 3% of the population were diagnosed with influenza by a primary care physician. The low number of consultations during the 2009 main pandemic wave can perhaps partly be explained by public advice given during the pandemic. Due to high demands on health clinics, people were advised not to seek medical help for influenza symptoms unless they were in need of urgent care or were at high risk of complications. Consequently, many people with influenza were

incorrectly considered as unexposed in our analyses, which may have led to an underestimation of the effect of influenza in the current study.

Comparison with the literature

In accordance with results from other studies, we observed an association between influenza and risk of encephalitis.[1,4,6]

An American population-based study of neurological manifestations in 2069 individuals with severe or fatal 2009 H1N1 cases reported encephalopathy/encephalitis as an adverse event ($N = 29$).[1] In a Japanese study, risk of acute encephalopathy after the 2009 pandemic influenza was compared with seasonal influenza, and worse outcome was reported among patients 6 years of age or older after 2009 pandemic influenza ($N = 10$) than after seasonal influenza ($N = 51$).[6] Another Japanese study showed that patients with influenza-associated encephalopathy caused by influenza A (H1N1) infection were older compared with patients with seasonal influenza ($N = 8$).[7] In our study, we did not observe any differences in the risk of encephalitis after influenza during the 2009 main pandemic wave compared with seasonal influenza. The differences in our study compared with studies mentioned above may be explained by the considerably larger study sample size (684 172 individuals with influenza and 2793 cases with encephalitis) and the statistical methods used. By applying Cox proportional hazard regression, we were able to include influenza and A(H1N1)pdm09 vaccination as time-varying variables and adjust for the effects of sex and age.

A study from Belgium, based on a case report and summary of the literature review, did not find an elevated risk of acute encephalitis/disseminated encephalomyelitis after A(H1N1)pdm09 vaccine [Pandemrix® (GlaxoSmithKline)], which was similar to our findings.[14]

To our knowledge, studies on the association between influenza vaccination and risk of encephalopathy/encephalitis/encephalomyelitis have mainly been based on case reports or a very small study sample size.[6,7,20–22] The risk of encephalitis has not been studied in large population-based studies. Access to national health registries and application of statistical methods taking the time aspects of influenza, A(H1N1)pdm09 vaccination, and diagnosis of encephalitis, into account have provided us with the unique possibility to study the occurrence of this rare disease following influenza and A(H1N1)pdm09 vaccination.

Conclusion

This nationwide registry-based study supports that the risk of encephalitis was increased after seasonal influenza during 2008–14 and also after influenza during the 2009 main pandemic wave. We found no evidence of any difference in risk of encephalitis after seasonal influenza compared with influenza during the 2009 main pandemic wave. We did not observe any increased risk of encephalitis after the A(H1N1)pdm09 vaccine.

Supplementary Data

Supplementary data are available at *IJE* online.

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References

1. Glaser CA, Winter K, DuBray K *et al*. A population-based study of neurologic manifestations of severe influenza A(H1N1)pdm09 in California. *Clin Infect Dis* 2012;**55**:514–20.
2. Ghaderi S, Gunnes N, Bakken IJ, Magnus P, Trogstad L, Haberg SE. Risk of Guillain-Barre syndrome after exposure to pandemic influenza A(H1N1)pdm09 vaccination or infection: a Norwegian population-based cohort study. *Eur J Epidemiol* 2016;**31**:67–72.
3. Quist-Paulsen E, Kran AM, Dunlop O, Wilson J, Ormaasen V. Infectious encephalitis: a description of a Norwegian cohort. *Scand J Infect Dis* 2013;**45**:179–85.
4. Gu Y, Shimada T, Yasui Y, Tada Y, Kaku M, Okabe N. National surveillance of influenza-associated encephalopathy in Japan over six years, before and during the 2009–2010 influenza pandemic. *PloS One* 2013;**8**:e54786.
5. Hayward AC, Fragaszy EB, Bermingham A *et al*. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. *Lancet Respir Med* 2014;**2**:445–54.
6. Okumura A, Tsuji T, Kubota T *et al*. Acute encephalopathy with 2009 pandemic flu: comparison with seasonal flu. *Brain Dev* 2012;**34**:13–19.
7. Fuchigami T, Imai Y, Hasegawa M *et al*. Acute encephalopathy with pandemic (H1N1) 2009 virus infection. *Pediatr Emerg Care* 2012;**28**:998–1002.
8. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. *Curr Opin Neurol* 2010;**23**:305–11.
9. Akins PT, Belko J, Uyeki TM, Axelrod Y, Lee KK, Silverthorn J. H1N1 encephalitis with malignant edema and review of neurologic complications from influenza. *Neurocrit Caree* 2010;**13**:396–406.
10. Choi SY, Jang SH, Kim JO, Ihm CH, Lee MS, Yoon SJ. Novel swine-origin influenza A (H1N1) viral encephalitis. *Yonsei Med J* 2010;**51**:291–92.

11. Gulati P, Saini L, Jawa A, Das CJ. MRI in H1N1 encephalitis. *Indian J Pediatr* 2013;**80**:157–59.
12. Incecik F, Ozlem Herguner M, Altunbasak S *et al*. Fatal encephalitis associated with novel influenza A (H1N1) virus infection in a child. *Neurol Sci* 2012;**33**:677–79.
13. Ito S, Shima S, Ueda A, Kawamura N, Asakura K, Mutoh T. Transient splenial lesion of the corpus callosum in H1N1 influenza virus-associated encephalitis/encephalopathy. *Intern Med* 2011;**50**:915–18.
14. Ussel IV, Boer W, Parizel P, Cras P, Jorens PG. Encephalitis related to a H1N1 vaccination:Case report and review of the literature. *Clin Neurol Neurosurg* 2014;**124**:8–15.
15. Bakken IJ, Nyland K, Halsteinli V, Kvam UH, Skjeldestad FE. The norwegian patient registry. *Nor J Epidemiol* 2004;**14**:65–9.
16. Haberg SE, Trogstad L, Gunnes N *et al*. Risk of fetal death after pandemic influenza virus infection or vaccination. *N Engl J Med* 2013;**368**:333–40.
17. Health TNIoP. *Norwegian Surveillance System for Communicable Diseases (MSIS)*. 2016. https://www.fhi.no/en/health-in-norway/health-registries/norwegian-surveillance-system-for-communicable-diseases-msis/ (15 July 2016, date last accessed).
18. Trogstad L, Ung G, Hagerup-Jenssen M, Cappelen I, Haugen IL, Feiring B. The Norwegian immunisation register - SYSVAK. *Euro Surveill* 2012;**17**. pii: 20147.
19. Blasio BF, Iversen BG, Tomba GS. Effect of vaccines and antivirals during the major 2009 A(H1N1) pandemic wave in Norwa - -and the influence of vaccination timing. *PloS One* 2012;**7**:e30018.
20. Huynh W, Cordato DJ, Kehdi E, Masters LT, Dedousis C. Post-vaccination encephalomyelitis: literature review and illustrative case. *J Clin Neurosci* 2008;**15**:1315–22.
21. Karussis D, Petrou P. The spectrum of post-vaccination inflammatory CNS demyelinating syndromes. *Autoimmun Rev* 2014; **13**:215–24.
22. Lee ST, Choe YJ, Moon WJ, Choi JW, Lee R. An adverse event following 2009 H1N1 influenza vaccination: a case of acute disseminated encephalomyelitis. *Korean J Pediatr* 2011; **54**:422–24.