Epilepsy in Children After Pandemic Influenza Vaccination

Siri E. Håberg, MD, PhD,[a] Kari M. Aaberg, MD,[a,b] Pål Surén, MD, PhD,[a,b] Lill Trogstad, MD, PhD,[a] Sara Ghaderi, MSc, PhD,[a] Camilla Stoltenberg, MD, PhD,[a,c] Per Magnus, MD, PhD,[a,d] Inger Johanne Bakken, MSc, PhD[a]

abstract

OBJECTIVES: To determine if pandemic influenza vaccination was associated with an increased risk of epilepsy in children.

METHODS: Information from Norwegian registries from 2006 through 2014 on all children <18 years living in Norway on October 1, 2009 was used in Cox regression models to estimate hazard ratios for incident epilepsy after vaccination. A self-controlled case series analysis was used to estimate incidence rate ratios in defined risk periods after pandemic vaccination.

RESULTS: In Norway, the main period of the influenza A subtype H1N1 pandemic was from October 2009 to December 2009. On October 1, 2009, 1 154 113 children <18 years of age were registered as residents in Norway. Of these, 572 875 (50.7%) were vaccinated against pandemic influenza. From October 2009 through 2014 there were 3628 new cases of epilepsy (incidence rate 6.09 per 10 000 person-years). The risk of epilepsy was not increased after vaccination: hazard ratio: 1.07; 95% confidence interval: 0.94–1.23. Results from the self-controlled case series analysis supported the finding of no association between vaccination and subsequent epilepsy.

CONCLUSIONS: Pandemic influenza vaccination was not associated with increased risk of epilepsy. Concerns about pandemic vaccination causing epilepsy in children seem to be unwarranted.

[a]*Norwegian Institute of Public Health, Oslo, Norway;* [b]*The National Center for Epilepsy, Oslo University Hospital, Oslo, Norway;* [c]*Department of Global Public Health and Community Care, University of Bergen, Bergen, Norway; and* [d]*Institute of Health and Society, University of Oslo, Oslo, Norway*

Dr Håberg conceptualized and designed the study, was responsible for the data collection and the analytics plan, and drafted the initial manuscript; Dr Bakken contributed to the data collection and the analytics plan, conducted the analyses, and reviewed and revised the manuscript; Drs Trogstad, Magnus, and Stoltenberg contributed to the conceptualization and design of the study, and the interpretation of results, and critically reviewed the manuscript; Drs Ghaderi, Surén, and Aaberg contributed to the interpretation of results, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Siri E. Håberg, MD, PhD, Norwegian Institute of Public Health, PO Box 4404 Nydalen, 0403 Oslo, Norway. E-mail: siri.haberg@fhi.no

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WHAT'S KNOWN ON THIS SUBJECT: Influenza vaccination has been associated with an increased risk of febrile seizures in children. There is a link between febrile seizures, particularly complex febrile seizures, and an increased risk of later epilepsy.

WHAT THIS STUDY ADDS: Concerns about pandemic vaccination increasing the risk of epilepsy in children seem to be unwarranted.

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Seizures, including febrile seizures, are the most commonly reported neurologic complication of influenza infection.[1–10] Influenza vaccinations have also been associated with an increased risk of febrile seizures in children.[11–14] We have previously shown that vaccination against pandemic influenza increased the risk of febrile seizures in children, although to a lower degree than influenza infection,[1] and there have been concerns about an association with later epilepsy. There has been increasing focus on the role of infections and immunologic factors, not only in febrile seizures, but also in the etiology of epilepsy.[15–17]

Epilepsy is defined by the occurrence or high risk of recurrent, unprovoked seizures.[18] Childhood epilepsy has many different causes, but in most cases the causal mechanisms are not identified.[19] However, there is a clear link between febrile seizures, particularly complex febrile seizures, and increased risk of later epilepsy.[20–26] The role of influenza infection as a causal trigger of epilepsy is not clear. In one matched case-control study, which included people of all ages, the authors found no increased risk of epilepsy after influenza infection.[27] In other studies, authors have found neurologic complications such as meningitis and encephalitis in relation to influenza infections,[3–6,8,9,28,29] and these complications may in turn increase the risk of later epilepsy.

The role of vaccination as a causal factor or trigger of epilepsy is still unclear.[30–32] In several studies, including a study from Sweden on the Pandemrix vaccine (GlaxoSmithKline, Brentford, United Kingdom), authors found there was no increased risk of epileptic seizures after vaccination.[30,33,34] Other studies conclude that vaccines may trigger seizures in children with underlying susceptibility.[30–32] It has previously been shown that children were at an increased risk of seizures, including febrile seizures, after pandemic influenza vaccination.[1] Increased seizure risk has also been described after administration of other vaccines,[35,36] but the association with later epilepsy is less clear. In some studies of epilepsy onset after vaccination, genetic or structural etiologies were found in most children with onset of epilepsy around the time of vaccination, supporting the view of vaccinations as possible precipitating factors of first seizures in susceptible children, rather than as primary, causal factors.[31,32]

In several studies, authors conclude that pandemic vaccination may influence the risk of other neurologic conditions, such as Guillain-Barré syndrome, encephalopathies, and narcolepsy,[6–9] suggesting there is a potential influence on the brain when the immune system has been triggered by vaccination.[37,38] However, no association with narcolepsy was found in a study of a nonadjuvanted pandemic influenza vaccine used in the United States.[39]

During the 2009 influenza pandemic, Pandemrix, a monovalent AS03-adjuvanted influenza A(H1N1) pmd09 vaccine, was offered free of charge to all citizens in Norway. We investigated the risk of epilepsy after pandemic influenza vaccination in children by linking individual level information from several national health registries that cover the entire Norwegian population.

METHODS

The study was approved by the Regional Committee for Medical and Health Research Ethics, located in southeast Norway.

Data Sources

Norway has a nationwide public health care system in which access to specialist care requires referral from a general practitioner.[40] Hospitals and outpatient clinics are financed through government funding, and health care is free of charge for children up to age 16. Outpatients older than 16 years pay a minor fee, whereas hospitalization is free of charge for all citizens. Norway has several nationwide, mandatory registries and health databases with individual-level data. The unique identification numbers given to all residents at birth or at immigration enables linkage of information. We linked data from the National Registry[41] (census information), the Norwegian Patient Registry[42] (specialist health care data and hospitalizations), the Norwegian Immunization Register[43] (information on pandemic vaccinations), and the national primary care reimbursement system.[44] The Norwegian Patient Registry contains individual-level data from all Norwegian hospitals and outpatient clinics from 2008 onwards, including dates of discharge from the hospital or outpatient visit, and diagnoses reported as *International Classification of Diseases, 10th Revision* codes. Reporting is mandatory and linked to the reimbursement system. Information from primary care was retrieved from the reimbursement system and included dates of consultation and diagnostic codes based on the *International Classification of Primary Care, Second Edition*.

Study Population

In Norway, the main wave of the pandemic influenza period lasted from October 2009 to December 2009.[45] The study population included all children registered in the National registry on October 1, 2009 who were born after January 1, 1991 (age 0–17 years on October 1, 2009) (N = 1 154 113). The National Registry provided information on sex, date of birth, and dates of emigrations and deaths.

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Exposure: Pandemic Influenza Vaccination

Dates of vaccination with Pandemrix were obtained from the Norwegian Immunization Register. Reporting of all administered vaccines was mandatory. The vaccination period overlapped with the main period of the pandemic, and 98.4% of vaccines to children were given between October 19, 2009 (the first day with available vaccines), and December 31, 2009.

Outcome: Epilepsy

To reduce the risk of misclassifying prevalent epilepsy as incident, all children with any registration of epilepsy in either primary care (*International Classification of Primary Care, Second Edition* code N88 "epilepsy"), or in specialist care (*International Classification of Diseases, 10th Revision* codes G40 "epilepsy" or G41 "status epilepticus") before October 2009 (the start of the study period) were excluded from the population at risk for incident epilepsy. Information on previously registered epilepsy was available from January 1, 2006, in primary care and from January 1, 2008, in specialist health care. A stricter definition was used to define epilepsy in the study period and required at least 2 records with the codes G40 or G41 in specialist care. This definition has recently been shown to have a positive predictive value for clinical epilepsy of 88%[46] in a Norwegian study based on the same registry data and population as in the current study. For children fulfilling this criterion, and thus were defined as having epilepsy, the first seizure episode was then defined as the date of first registration with either G40, G41, or R56 ("convulsions, not elsewhere classified"). The R56 code was included to identify the first seizure episode because most children do not get the epilepsy diagnosis at first admission with seizures. Children who fulfilled the case criteria for incident epilepsy (at least 2 registrations with G40/G41 during the follow-up period), but with R56 registered before the start of the follow-up period, were reclassified as prevalent cases and excluded from follow-up.

Statistical Analysis

Crude incidence rates were calculated as the number of new cases with epilepsy divided by the sum of person-years at risk, overall and separately for exposed and unexposed time periods. Hazard ratios (HRs) of epilepsy, with associated 95% confidence intervals (CIs), were estimated by using Cox regression analyses with number of days since October 1, 2009, as the time metric. Children were managed until the first episode of epilepsy, until death, emigration, or the end of the study period (December 31, 2014), whichever occurred first. We adjusted for sex and age (on October 1, 2009) in 2 categories (0 to 9 years of age and 10 to 17 years of age). In separate models, we additionally adjusted for the number of specialist health care contacts (outpatient visits and hospitalizations) occurring in the year before the start of the study period (ie, from October 1, 2008 through September 30, 2009) using 3 categories (0, 1–3, and ≥4 contacts). A pandemic vaccination was defined as a time-dependent exposure, and children were considered to be exposed from the day of vaccination. In the Cox regression analyses, incidence rates in exposed time periods were compared with incidence rates in unexposed time periods. We used a risk window of 365 days after vaccination. Analyses were performed for all ages combined and further stratified by below and above 10 years of age.

Additionally, we applied a self-controlled case series (SCCS) analysis to estimate the incidence rate ratio (IRR) of first epileptic episodes in predefined risk periods after influenza vaccination compared with a background period. This method eliminates time-independent confounding because children with epilepsy serve as their own controls.[47,48] For each individual, the observation period was restricted to a period starting 180 days before vaccination or on the day of birth (whichever came last) and ending 180 days after vaccination or on the day of emigration or death (whichever came first). Thus, each individual could contribute with a maximum of 360 observation days. We stratified person-time and events for each individual by the following risk periods: 180 to 15 days pre-exposure, 14 to 0 days pre-exposure, 0 to 6 days postexposure, 7 to 90 days post-exposure, and 91 to 180 days postexposure. The 180 to 15 days pre-exposure and 91 to 180 days postexposure periods were joined together to constitute the background period. IRR estimates were obtained by using conditional Poisson regression.

Testing was 2-sided and $P < .05$ was considered statistically significant. The Stata software package, version 14.1 (StataCorp, College Station, TX) was used for data analysis.

RESULTS

Among the 1 154 113 children below 18 years of age who were registered as residents in Norway on October 1, 2009, 8567 children with prevalent epilepsy were excluded from the study population. This left data for 1 145 546 children eligible for analyses.

From October 2009 to 2014, the total follow-up time was 5 956 513 person-years. There were 3628 new cases of epilepsy, giving an incidence rate of epilepsy of 6.09 per 10 000 person-years. Pandemic influenza vaccines were distributed to 572 875 children (50.7%) (Table 1). The vaccination coverage was higher in children younger than 10 years of age (56.2%)

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than in older children (45.2%). There was no indication of an increased risk of epilepsy in children after pandemic vaccination (overall HR in the fully adjusted model, 1.07, 95% CI, 0.94–1.23), as shown in Table 2. Results were similar in analyses without adjustment for previous health care contacts (Table 2).

Results from the SCCS analyses did not show an increased risk after vaccination in any of the predefined risk periods (Fig 1, Table 3).

TABLE 1 Characteristics of All Children Who Were Residents of Norway as of October 1, 2009

	No. Children		Vaccinated	
	No.	%	No.	%
Total	1 139 715	100	577 579	50.7
Age on October 1, 2009				
0–9 y	569 552	50.0	319 824	56.2
10–17 y	570 163	50.0	257 755	45.2
Sex				
Male	584 445	51.3	293 081	50.1
Female	555 270	48.7	284 498	51.2

DISCUSSION

There are few studies in which epilepsy after pandemic vaccination has been investigated; however, in some studies it has been found to increase risk of febrile seizures after vaccinations, including influenza vaccination.[1,11–13] In this nationwide Norwegian registry-based study, we found no increase in risk of epilepsy after vaccination with the adjuvanted pandemic vaccine.

The main strength of the study was the availability of registry data from the entire Norwegian population, which eliminates selection bias. We used independent data sources and linked individual-level data. Independent data collection minimizes differential information bias in reporting. Also, the public health system in Norway aims at providing similar health services to all citizens, and services are free for all children and at low cost for those over 16 years of age. Thus, availability of vaccines and the availability of health care for children with seizures are similar for all socioeconomic groups. The availability of information on the timing of events allowed for detailed assessment of risk windows. Registration of pandemic vaccinations in the national vaccination registry was mandatory and is considered to be nearly complete. Differential misclassification or selection bias based on vaccine status is therefore unlikely.

Nearly all children with chronic diseases are diagnosed and treated within the public health system in Norway, and thus, registered in the databases used in this study. The definition of epilepsy was based on repeated registrations in specialist health services. Diagnoses were not validated, but our definition of incident epilepsy based on specialist care registrations has been shown to have a high positive predictive value for clinical epilepsy.[46] The overall incidence of epilepsy found in this study is in line with the incidence found in a large cohort study of Norwegian children based on the review of medical records and parental interviews,[46] and also similar to incidences in other high-income countries.[49] As in these other studies, we also found the highest incidence of epilepsy among the youngest children.

Children with epilepsy are managed more frequently by health services and could more likely be vaccinated against influenza. This could inflate associations between influenza vaccinations and epilepsy if incident epilepsy was not well-defined. We therefore made additional efforts to improve the validity of our case definition of incident epilepsy. Children with epilepsy in Norway are usually followed-up at least once a year in specialist services.[50] Those who were diagnosed with epilepsy before the pandemic would most likely have been registered in the Norwegian Patient Registry between

TABLE 2 Incidence Rates and HRs of Epilepsy Within 1 Year After Pandemic Vaccination

Age in 2009	Vaccinated	No. Person-y at Risk[a]	No. Cases	Incidence Rate[b]	Crude		Adjusted[c]		Adjusted[d]	
					HR	95% CI	HR	95% CI	HR	95% CI
0–17 y	Yes	571 048.5	432	5.87	1.16	1.02–1.33	1.12	0.98–1.28	1.07	0.94–1.23
	No	5 311 002.1	3116	7.56	1	—	1	—	1	—
0–9 y	Yes	316 716.8	271	8.56	1.09	0.92–1.31	1.09	0.92–1.31	1.05	0.88–1.26
	No	2 620 757.8	1864	7.11	1	—	1	—	1	—
10–17 y	Yes	254 331.7	161	6.33	1.18	0.96–1.46	1.18	0.95–1.46	1.13	0.92–1.40
	No	2 690 244.3	1252	4.65	1	—	1	—	1	—

—, not applicable.

[a] Follow-up time from October 1, 2009, to December 31, 2014, for 1 145 512 residents of Norway born between 1991–2009. Data for 34 children with 0 follow-up time were excluded from the analyses.

[b] Number of new cases per 10 000 person-years at risk.

[c] Adjusted for sex and age-group.

[d] Adjusted for sex, age-group, and overall number of hospitalizations and outpatient visits in the year before the study.

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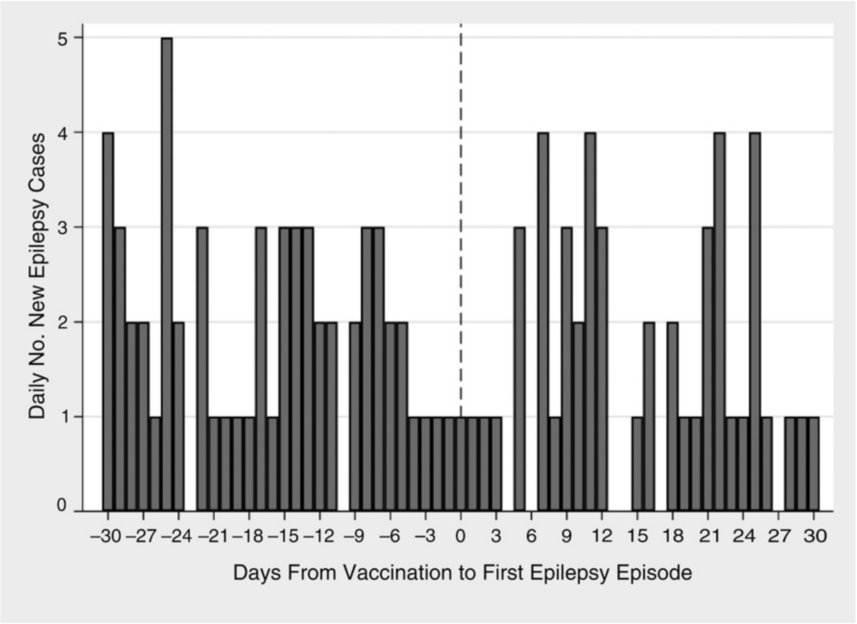

FIGURE 1
Number of days from vaccination to first epileptic episode, in 30 days before and after vaccination.

TABLE 3 IRR of Epilepsy After Pandemic Vaccination Estimated by the SCCS Method

Period	No. Person-d at Risk	No. Events	Incidence Rate per 100 Person-d	IRR (95% CI)
Background period[a]	162 560	471	0.29	1 (ref)
2 wk before vaccination day	8890	26	0.29	1.01 (0.68–1.50)
0–6 d after vaccination	4445	7	0.16	0.54 (0.26–1.15)
7–90 d after vaccination	53 340	131	0.25	0.85 (0.70–1.03)

[a] The 180–15 d pre-exposure and 91–180 d postexposure periods were included in the background period.

January 1, 2008, and October 1, 2009. We also excluded children with any registration of epilepsy in primary health care before the start of the study period. Consequently, the likelihood of bias as a result of misclassification of prevalent cases as incident cases is low.

Another limitation is the lack of detailed information on potential confounding factors, such as underlying conditions that may increase both the likelihood of vaccination and the probability of developing epilepsy. However, SCCS analysis eliminates confounding from factors that do not vary with time and these results supported the results from the Cox analyses.

The biological mechanisms that could explain a connection between inflammatory mechanisms, seizures and epilepsy are not clear,[16] but proinflammatory cytokines have been shown to increase in relation to febrile seizures.[51] Neural inflammation and cytokine release can also be induced by viral infections.[52] Infections, vaccines and fever may trigger seizures, and susceptible individuals may develop epilepsy after febrile seizure episodes.[2,6,8,10,20–24,31,35,53–61] We have previously shown that children were at risk for febrile seizures after pandemic influenza infection, and, to a lower degree, also after pandemic influenza vaccination.[1] Febrile seizures are most often benign, but complex febrile seizures are associated with increased risk of epilepsy.[21–23,61–64] The risk of neurologic conditions, such as Guillain-Barré and narcolepsy, have also been found to be increased after pandemic vaccination.[37,38,65] Concerns about the role of vaccines as cause of neurologic and developmental disorders in children may reduce the willingness to participate in vaccination programs. Low vaccination rates may have consequences for susceptible individuals with higher risk of influenza complications. It is therefore important to perform large population-based studies exploring the risk of neurologic conditions after vaccinations to address such concerns. Our finding of no increased risk of epilepsy after influenza vaccination is reassuring.

CONCLUSIONS

Pandemic influenza vaccination was not associated with an increased risk of epilepsy in children under the age of 18. Concerns about pandemic vaccination causing epilepsy in children seem to be unwarranted.

ABBREVIATIONS

CI: confidence interval
HR: hazard ratio
IRR: incidence rate ratio
SCCS: self-controlled case series

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