ORIGINAL ARTICLE

Pandemic H1N1 Vaccination and Incidence of Acute Disseminated Encephalomyelitis in Manitoba

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ABSTRACT: ***Background:*** An increased incidence of hospital admissions coded as acute disseminated encephalomyelitis (ADEM) was noted in Winnipeg, Manitoba, Canada, during the second wave of the influenza pandemic from October 2009 to March 2010. However, it was not clear whether this was due to heightened awareness of potential neurological complications of influenza or influenza vaccination or an actual increase in the number of cases. ***Methods:*** We extracted data from the charts of 139 patients hospitalized with an International Classification of Diseases-10 discharge code indicating ADEM (G04.0) or unspecified noninfectious encephalitis or myelitis (G04.8, G04.9) between January 2006 and December 2012. Clinical and laboratory data were reviewed by a neurologist, and diagnoses were determined using the Brighton criteria. ***Results:*** Over the entire study period, there were 22 cases of ADEM. During the peak pandemic period (April-December 2009), seven patients were hospitalized with ADEM, corresponding to a rate of 7.8/million/year; 4.7 (95% confidence interval: 1.9-11.4) times higher than the rate before or after the pandemic period. Only one patient with ADEM had received the monovalent A(H1N1)pdm09 vaccine within 12 weeks of hospitalization. ***Conclusions:*** We have found an increased incidence of ADEM during the pandemic period that may be related, at least in part, to the increased incidence of influenza during that period. However, there was no temporal relationship with the administration of A(H1N1)pdm09 or seasonal influenza vaccines. Our study provides reassurance that use of these vaccines was not associated with increased risk of ADEM.

RÉSUMÉ: Vaccination H1N1 en période de pandémie et incidence d'encéphalomyélite disséminée aiguë au Manitoba. ***Contexte:*** Une augmentation de l'incidence des hospitalisations dont le code consigné au dossier indiquait que le patient souffrait d'une encéphalomyélite disséminée aiguë (EMDA) a été notée à Winnipeg, Manitoba, Canada, pendant la deuxième vague de la pandémie d'influenza, soit d'octobre 2009 à mars 2010. Cependant, il n'était pas clair si ceci était dû à une prise de conscience des complications neurologiques potentielles de l'influenza ou à la vaccination contre l'influenza ou d'une véritable augmentation du nombre de cas. ***Méthodologie:*** Nous avons extrait les données des dossiers de 139 patients hospitalisés entre janvier 2006 et décembre 2012 dont le code indiquait que le patient souffrait d'une EMDA (G04.0) ou d'une encéphalite ou d'une myélite non infectieuse non spécifiées (G04.8, G04.9) selon la Classification internationale des maladies-10 au moment du congé hospitalier. Les données cliniques et de laboratoire ont été revues par un neurologue et les diagnostics ont été établis selon les critères de Brighton. ***Résultats:*** Au cours de la période de l'étude, il y a eu 22 cas d'EMDA. Au moment du point culminant de la pandémie (avril à décembre 2009), sept patients atteints d'une EMDA ont été hospitalisés, ce qui correspond à un taux de 7,8/million/année, soit 4,7 fois plus élevé (intervalle de confiance à 95% : 1,9 à 11,4) que le taux avant ou après la période de pandémie. Seulement un patient atteint d'EMDA avait reçu le vaccin monovalent A(H1N1)pdm09 au cours des douze semaines précédant l'hospitalisation. ***Conclusions:*** Nous avons constaté une incidence accrue d'EMDA pendant la pandémie ce qui pourrait être en relation, du moins en partie, à une incidence accrue d'influenza pendant cette période. Cependant, il n'existait pas de relation temporelle avec l'administration de A(H1N1)pdm09 ou de vaccins saisonniers contre l'influenza. Notre étude montre que l'utilisation de ces vaccins n'était pas associée à un risque accru d'EDMA, ce qui est rassurant.

Key words: A (H1N1) pdm09 vaccine, Encephalomyelitis, Epidemiology, Influenza, Vaccine

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Influenza A viruses infect a variety of mammals and avian species. Genetic reassortant viruses can cause epidemics that may spread rapidly and widely enough to be classified as a pandemic. The 1918 influenza A/H1N1 pandemic was responsible for about 40 million deaths[1] and was associated with unique neurologic syndromes, including encephalitis lethargica and postencephalitic

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parkinsonism.[2] By comparison, the 2009 pandemic, caused by a novel influenza A/H1N1 virus—A(H1N1)pdm09—had a milder course but was still associated with significant mortality and morbidity across the globe.[3]

Many cases of central nervous system demyelination and encephalomyelitis have been reported to be due to influenza A infection or after influenza vaccination.[4-7] Although there are many case reports, there is uncertainty about the exact risk of neurological complications as a consequence of influenza vaccination. Postmarketing surveillance showed an increased incidence of hospital admissions coded as acute disseminated encephalomyelitis (ADEM) in Winnipeg, the capital and largest urban center in the Canadian province of Manitoba during the second wave of the pandemic. During the 6-month period from October 2009 to March 2010, ten hospitalizations were coded as ADEM, whereas only about one or two were expected based on the literature. We conducted a public health investigation to confirm the presence of the signal and to explore possible links to the administration of the A(H1N1)pdm09 or seasonal influenza vaccines used during the pandemic.

Methods

We used the Hospital Abstracts Database of Manitoba Health to identify all patients who were admitted to Winnipeg hospitals with an International Classification of Diseases-10 code indicating ADEM (G04.0) or unspecified noninfectious encephalitis or myelitis (G04.8, G04.9) between January 2006 and December 2012 (about 3 years before and after the pandemic period). Manitoba Health is a publicly funded agency that provides comprehensive health insurance, including hospital and vaccination services, to the province's 1.2 million residents. Coverage is universal, without regard to age or income, and participation rates are very high.

An experienced nurse-auditor extracted relevant clinical and laboratory information from the charts of 141 patients using a standard form developed by the Brighton Collaboration.[5] Two charts were excluded because of insufficient information. An experienced neurologist (ACJ) reviewed the data, without knowledge of patient vaccination status, and used the Brighton criteria[5] to classify cases into ADEM (Table 1) or "other diagnosis." We obtained information on all vaccines received by participants up to 3 years before the index admission date from the Manitoba Immunization Monitoring System, a population-based province-wide registry of all vaccines administered in Manitoba residents since 1988.[8] This information was needed because the clinical charts may not include accurate information on all vaccines received by these patients.

The study was approved by the University of Manitoba Health Research Ethics Board and the Government of Manitoba Health Information Privacy Committee.

Results

Of the 139 charts reviewed, only 22 (15.8%) cases met the Brighton criteria for ADEM. The remaining were classified as encephalitis/myelitis of unspecified etiology (56), non-ADEM demyelinating (DM) disorder (6), central nervous system infection (24), and other conditions (31) (Table 2). During the pandemic period (April-December 2009), seven patients were hospitalized with ADEM corresponding to a rate of ~7.8/million/year (95% confidence interval [CI]: 3.1-16.0), compared with an average rate of ~1.7/million/year (95% CI: 0.9-2.7) before and after the pandemic. The rate ratio was 4.7 (95% CI: 1.9-11.4; p = 0.005). None of the 7 ADEM patients had a relevant medical history. In particular, none of them tested positive for pandemic or other influenza. Compared with ADEM patients diagnosed outside of the pandemic period, these patients were slightly younger (9 vs 15 years). Otherwise, they had similar presentations, laboratory findings, and outcomes.

Table 1: Acute disseminated encephalomyelitis: level 1 of diagnostic certainty

(A) Demonstration of diffuse or multifocal areas of demyelination by histopathology.
OR
(B) Focal or multifocal findings referable to the central nervous system, including **one or more** of the following:
1. Encephalopathy,
2. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
3. Cranial nerve abnormality/abnormalities,
4. Visual field defect/defects,
5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
6. Motor weakness (either diffuse or focal; more often focal),
7. Sensory abnormalities (either positive or negative; sensory level),
8. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes), or
9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus,
AND
(C) Magnetic resonance imaging findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted, or fluid-attenuated inversion recovery sequences (± gadolinium enhancement on T1 sequences),
AND
(D) Monophasic pattern to illness (i.e. absence of relapse within a *minimum* of 3 months of symptomatic nadir).
Case definition as per the Brighton Collaboration[5] in the highest of three levels of diagnostic certainty.

Only one ADEM patient received the A(H1N1)pdm09 vaccine within 12 weeks before hospital admission (Figure 1). This patient developed neurological symptoms 18 days following receiving an adjuvanted A(H1N1)pdm09 vaccine and was hospitalized 25 days after receiving the vaccine. The Canadian-manufactured Arepanrix (GlaxoSmithKline Biologicals), an AS03-adjuvanted monovalent split virion vaccine containing 3.75 µg hemagglutinin per 0.5 mL dose, was the only adjuvanted vaccine used in Manitoba during the immunization campaign that began on October 26, 2009.[9] Three other ADEM patients developed symptoms later than 12 weeks after receiving the same product. Another patient developed non-ADEM encephalitis symptoms 43 days after vaccination. None of the other cases received a pandemic vaccine. Throughout the study period, no patient developed ADEM within 12 weeks of seasonal influenza vaccination.

Discussion

Although we observed nearly a five-fold increase in ADEM rates during the pandemic period in Manitoba, only one of seven cases (14.3%) occurred within an etiologically plausible interval

Table 2: Diagnoses for the 117 non-ADEM cases

Diagnosis	CNS infection	Encephalitis	Myelitis	DM disorder	Other
Acute cerebellitis	1				
Bacterial meningitis	8				
Bacterial ventriculitis	1				
Brain abscess	5				
Cerebritis	2				
Cervical paravertebral abscess	1				
Disseminated varicella-zoster virus infection	1				
Spinal cord compression from *Staphylococcus aureus* epidural infection	1				
Ventriculoperitoneal shunt infection	4				
Encephalitis level 1 of diagnostic certainty		2			
Encephalitis level 2 of diagnostic certainty		43			
Encephalitis level 3 of diagnostic certainty		7			
Myelitis level 1 of diagnostic certainty			1		
Myelitis level 2 of diagnostic certainty			2		
Myelitis level 3 of diagnostic certainty			1		
Demyelination without evidence of ADEM				1	
Isolated tumefactive demyelinating disease				1	
Multiple sclerosis				4	
Anti-NMDA receptor autoimmune encephalitis					1
Central nervous system diffuse large B-cell lymphoma					1
Cerebral infarction					1
Pineal tumor					1
Diffuse cerebral gliomatosis					1
Encephalopathy					5
Intracranial hemorrhage					1
Meningeal lymphoma					1
Metastatic diffuse large B-cell lymphoma to brain and spinal cord					1
Myelopathy					1
Periventricular leukomalacia					2
Hypertensive encephalopathy					1
Ruptured cerebral aneurysm					2
Seizures					8
Traumatic brain injury					2
Viral syndrome					1
Voltage-gated potassium channel receptor autoimmune encephalitis					1
Total	24 (20.5)	52 (44.4%)	4 (3.4%)	6 (5.1%)	31 (26.5%)

(12 weeks) of vaccination with the adjuvanted A(H1N1)pdm09 vaccine and none following vaccination with a seasonal influenza vaccine.

The scientific literature on the relationship between ADEM and the monovalent A(H1N1)pdm09 vaccine, and influenza vaccination in general, is quite limited. In China, 89.6 million doses of A(H1N1)pdm09 vaccine were administered between September 2009 and March 2010, and there were only 8067 adverse events (rate of 90.0 per 1 million doses), including only two cases of ADEM and no cases of encephalitis.[10] A meta-analysis of 18 randomized clinical trials of A(H1N1)pdm09 vaccines showed only three serious vaccine-related adverse events out of 22,826 vaccinated subjects; none was neurological and all resolved with 10 days.[11] Similarly, a large surveillance study showed a low rate of adverse events after A(H1N1)pdm09 vaccination in the United States.[12] In Japan, a postmarketing study by the Kitasato Institute found only three cases of ADEM following more than 38 million doses of seasonal influenza vaccines administered in Japan between 1994 and 2004.[13] Although it has been estimated that up to 5% to 20% of

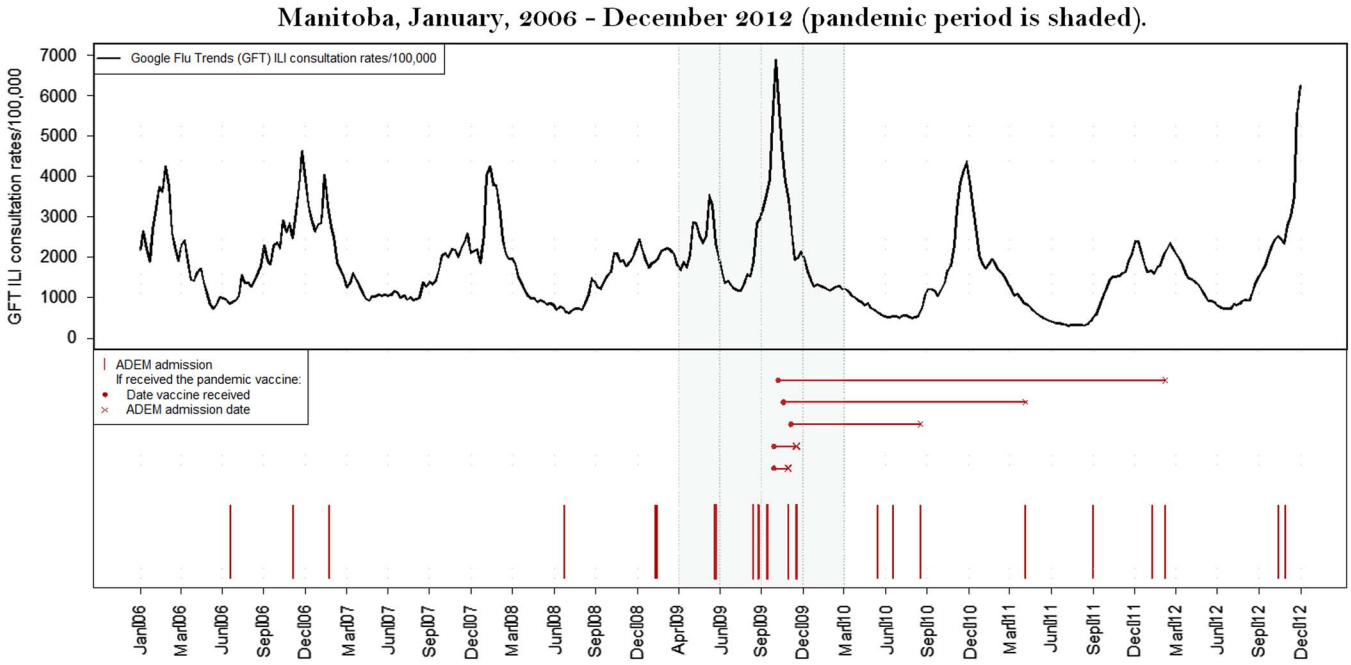

Figure 1: *Timing of admission with ADEM in relation to influenza disease activity (Google Flu Trends ILI consultation rates) and pandemic vaccine administration in Manitoba, January 2006-December 2012 (pandemic period is shaded).*

ADEM cases occur within 1 month of vaccination,[14,15] reports of ADEM following influenza vaccination are quite rare.[4,6,7]

The reasons for the higher incidence of ADEM during the pandemic in Winnipeg are not clear, and a role for infection with A(H1N1)pdm09 cannot be ruled out. In a recently published systematic review of large ADEM cohort studies, 67% of ADEM cases had a preceding vaccination or infection.[14] Although cases of A(H1N1)pdm09 infection associated with ADEM have been reported, information on the frequency of this occurrence on a population level is lacking.[16-18] A systematic review of all case reports that mentioned neurological complications related to A(H1N1)pdm09 disease found more reports of neurological complications from the infection itself than to vaccination.[7] None of the patients in our study had a laboratory evidence of prior A(H1N1)pdm09 virus infection, but we do know from the literature and from our own A(H1N1)pdm09 seroprevalence studies that laboratory confirmation was available for only a very small percentage of infected patients, possibly $<1\%$.[19,20]

In summary, we have found an increased incidence of ADEM during the pandemic period that may be related, at least in part, to the increased incidence of influenza. However, there was no temporal relationship with the administration of A(H1N1) pdm09 or seasonal influenza vaccines. Our study provides reassurance that use of these vaccines was not associated with increased risk of ADEM and supports the results of previous observational studies indicating that neurological disorders, including ADEM, are fortunately very rare consequences of influenza vaccination.

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