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Nephrotic syndrome following four-component meningococcal B vaccination: Epidemiologic investigation of a surveillance signal

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ABSTRACT

Background: In May 2014, a mass vaccination campaign with four-component meningococcal serogroup B (4CMenB) vaccine was launched in a localized region of Quebec, Canada experiencing high invasive meningococcal B disease endemicity. Active post-marketing surveillance identified several cases of nephrotic syndrome (NS) among ~49,000 vaccinated individuals aged 2 months to 20 years. We report the epidemiologic investigation of this potential vaccine safety signal.

Methods: Active vaccine safety surveillance was conducted electronically, with participants completing an online questionnaire prompted at 7 days after each dose and 6 months following the last dose. Additional NS cases were sought from provincial hospitalization and emergency room databases.

Results: In the year following the first dose of 4CMenB vaccination, four confirmed NS cases (three hospitalized) were identified among vaccinated children 2–5-years-old with onset several months post-vaccination. None had renal biopsy but given their age, and positive response to steroids, idiopathic NS was presumptively diagnosed. Among vaccinated children 1–9-years-old, the NS incidence in the year post-vaccination was 17.7 per 100,000 (1 per 5650 vaccinees) with an NS hospitalization rate (i.e. excluding the outpatient case) that was 3.6-fold higher (95%CI = 0.7–11.8; p = 0.12) than the rest of the province for the same period, and 8.3-fold greater (95%CI = 1.1–62.0; p = 0.039) than during the eight years preceding the immunization campaign in the affected region.

Conclusion: Active safety surveillance identified an unexpected increase in NS incidence following 4CMenB vaccination. Further epidemiological investigation identified four vaccinated cases in total over a 12 month period of follow up. The greater risk in vaccinees had wide confidence intervals with he lower limit including or just above the nul value, an observation with no or marginal statistical significance. The temporal association with vaccination may be explained by other causes and/or chance clustering of a rare event unrelated to vaccination. To confirm or refute a potential link to vaccination, surveillance in other jurisdictions administering 4CMenB to children 1–9-years-old is needed.

1. Introduction

Nephrotic syndrome (NS) is a glomerular permeability disorder associated with generalized edema, hypoalbuminemia, and proteinuria resulting from loss or altered function of podocytes, that form part of the glomerular filtration apparatus [1–3]. Complications occur in 1–4% of NS cases, mostly when blood albumin levels fall below 20 g/L. In addition to complications related to volume retention and serous effusions, NS complications include infections associated with cellular and humoral immune deficiency secondary to the depletion of circulating IgG, and thrombosis related to the exhaustion of proteins involved in fibrinolysis and hepatic overproduction of coagulation factors.

NS is classified as primary or secondary according to the absence or presence of concurrent systemic disease. In infants less than one year old, two thirds of NS cases are linked to genetic

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abnormalities of the basal glomerular membrane [1–3]. In children 1–9-years-old, 90% of NS cases are considered idiopathic (INS). The annual incidence of INS among children <16-years-old varies between 1 and 3/100,000 for Caucasians, but is higher in Asian or African children [1–5]. Although INS is a primary disease whose causal mechanism and pathophysiology are still unclear, it often follows an upper respiratory tract infection (URTI) or allergic reaction. Patients with INS generally demonstrate normal renal function and blood pressure, no hematuria, and respond well to systemic corticosteroid treatment. While INS may occur at any age, it has typical onset between 2 and 7 years of age. In patients 1–9 years of age, a presumptive diagnosis of INS is made, without indication for renal biopsy, when there is satisfactory clinical response otherwise to systemic steroids. INS may persist for several years and relapses are frequent but the outcome is generally favourable with full recovery and no longterm sequelae. Although INS may also occur in adolescents and adults, in those age groups NS is often related to more severe renal diseases secondary to immunological, infectious or degenerative problems (eg. diabetes), or by protein deposition build-up in tissues (eg. amyloidosis), and a renal biopsy is essential for proper etiologic diagnosis.

Beginning in May 2014, ~49,000 individuals aged 2 months-20 years living in the Saguenay-Lac-Saint-Jean region of the province of Quebec, Canada were vaccinated during a mass campaign with the four component meningococcal serogroup B vaccine (4CMenB, Bexsero®, previously Novartis Vaccines now GSK) in order to control the high endemicity of invasive serogroup B meningococcal disease (IMD-B) affecting this region [6]. Three cases of NS were reported following their second dose of 4CMenB through active vaccine safety surveillance conducted during this campaign. We report here the results of the legally mandated epidemiological investigation conducted to assess in more detail this surveillance signal given the rarity of this syndrome.

2. Methods

2.1. Identification of the signal: vaccination campaign and active safety surveillance

The vaccination campaign started May 5, 2014. Eligible individuals were born between May 6, 1993 and December 31, 2014 and were residents of or attended an educational institution of the Saguenay-Lac-Saint-Jean region (targeted population ~59 000). Vaccination was administered in schools for individuals aged 5–20 years, and in public health clinics for others. The recommended schedule comprised 4 doses for infants 2–5 months of age, 3 doses for those 6–11 months old and 2 doses for children ≥12 months old, with successive doses separated by at least 2 months [6].

To assess the safety of this vaccine, active post-marketing surveillance was conducted using a methodology previously developed and carried out for the surveillance of influenza vaccine [7,8]. On the vaccination consent form, parents or vaccinees aged ≥14 years were all invited to provide an email address to participate in this active 4CMenB vaccine safety surveillance. Those who did provide an email address later received a personalized email invitation briefly describing the surveillance and containing a secure link to an online questionnaire. These questionnaires were sent seven days after each dose and six months following the last dose. The final questionnaires were sent on April 21, 2015 and nearly all responses had been received by April 30, 2015. The active surveillance period therefore covered one year from May 2014–April 2015. This surveillance assessed AEFIs with acute onset (within 7 days post-immunization) for which a separate report has been prepared [9]. The current study reports serious adverse events (SAEs) that occurred at any time point between doses and during the six months after the last dose. SAEs were defined as any of the following occurring between administration of the first vaccine dose and six months following the last dose: hospitalizations lasting ≥24 h; life-threatening events; or events causing permanent disabilities. A nurse contacted participants reporting any SAE to validate the information.

2.2. Epidemiological investigation of the surveillance signal

To define the baseline (pre) and post immunization incidence of NS in the age-relevant groups, we identified in the provincial hospitalization database [10], all patients aged ≤20 years hospitalized for the first time with NS (ICD-10 codes N04.0–N04.9) recorded as their primary or one of their first three secondary diagnoses between April 1, 2006 and March 31, 2016 (10 years). The emergency room (ER) database which records the reason for consultation and medical diagnosis for all ER visits in the province was also searched to identify cases that would have consulted between May 2014 and December 2015 [11]. The vaccination status of cases was retrieved from the provincial immunization registry. No validation of the diagnosis was done except for vaccinated cases whose medical charts were reviewed. A diagnosis of NS was confirmed when a patient met all three of the following criteria: generalized edema, hypoalbuminemia at <30 g/L and proteinuria ≥3 g/L. As INS relapses are frequent, only first episodes of NS were included in this investigation.

The rate of first hospitalization for NS was calculated for the province and the Saguenay-Lac-St-Jean region by dividing the number of NS cases by the number of person-years during the observation period using population data reported by the Quebec Statistical Institute [12]. Hospitalization rate ratios (HRRs) and their 95% confidence intervals were estimated with a Poisson regression. As INS rarely affects infants in general and because nearly 92% of vaccinees were children ≥12 months old who received only two doses, the analysis focused on these first two doses.

The active surveillance and the epidemiological investigation were legally mandated by the National Director of Public Health under the authority conferred by the Quebec Public Health Act and did not require approval by a Research Ethics Board.

3. Results

During the campaign, 83% and 77% of the 59,098 eligible individuals received a first and a second dose of 4CmenB, respectively. Among the 70% who provided an email address, 31% and 39% completed the active surveillance questionnaire after the first and second dose respectively (18% and 27% of all vaccinees). Dose 3 had been administered to 3443 infants and dose 4 to 1050.

3.1. SAEs reported by active surveillance

Ten SAEs, all related to hospitalizations, were reported for the 7 day period following immunization: three for bronchospasm, three for bronchiolitis, two for febrile seizures, one for anaphylaxis and one for mesenteric lymphadenitis [9]. During the period between dose1 and dose2 (~four months for children ≥ 1 year old) and the six-month period following the last dose, 272 (115 after dose1 and 157 after dose2) participants respectively reported an SAE (Table 1). Among the 246 (90%) who were successfully reached by a nurse for a telephone interview, 92 (37%) were excluded because they did not meet the SAE definition, including 48 who had been in ER less than 24 h and were therefore not considered hospitalized. The most frequent SAEs were various respiratory problems (34%) and infections (25%) which were considered to

Table 1
Serious adverse events (SAEs) reported through active surveillance during the four months between doses 1 and 2 or during the six months following the last dose of 4CMenB vaccine.

	During the four months between dose 1 and 2	During the 6 months following the last dose	All reported SAE
SAE reported in the on-line questionnaire	**115**	**157**	**272**
Patient impossible to contact by the nurse	12	14	26
Patient reached but reported problem not meeting SAE criteria	32	60	92
Contacted by the nurse and met SAE criteria	**71**	**83**	**154**
Respiratory problems (infection, bronchospasm, …)	21	31	52
Other infections (urinary tract, ocular, dental, …)	16	22	38
Surgery	11	4	15
Trauma (accidents, fracture, …)	7	1	8
Fever and dehydration	3	2	5
Seizures (febrile and afebrile)	2	2	4
Renal lithiasis	0	4	4
Food allergy	2	1	3
Nephrotic syndrome	**0**	**3**	**3**
Anemia	0	3	3
Seizures, epilepsy	1	2	3
Crohn's disease	2	1	3
Diabetes	1	1	2
Other health problems*	5	9	14

* One of each: abdominal migraine, aneurysm, anxiety attack, burn, cancer, constipation, eating disorder, bacterial endocarditis, severe weight loss, migraine, partial bilateral vision loss, paroxysmal torticollis, synovitis, tracheitis.

fall within normal expectations for incidence in this age group (Table 1). It was however unexpected to receive reports for three cases (two hospitalized, one outpatient) of NS diagnosed during the 6-month period following the second dose.

3.2. Nephrotic syndrome baseline and post immunization incidence

In the hospitalization database, 408 individuals ≤ 20-years-old had a first hospitalization for NS during the ten years between April 1, 2006 and March 31, 2016 in the province of Quebec (Table 2). In cases 1–9-years-old, 82% had NS as their main diagnosis. The overall incidence of NS in the province was 2.23 per 100,000 person-years and was highest in children aged between 1 and 5 years, ranging from 3.03 to 7.06 per 100,000. The incidence in children 1–9-years-old and in those 10–20-years-old was 3.5 and 1.4 per 100,000, respectively (Table 3). During the eight years preceding the vaccination campaign (April 2006–March 2014), ten patients (three 2–5 years old and seven 10–20-years-old) were first hospitalized for NS in the Saguenay-Lac-Saint-Jean region for a combined hospitalization rate of 2.03 per 100,000 in those ≤20-years-old, similar to the provincial rate excluding that region (2.29 per 100 000). However the rate among children 1–9 years old in the Saguenay-Lac-St-Jean region was about half the provincial rate (1.6 vs. 3.67 per 100,000, p = 0.18) (Table 3).

The review of the hospitalization and ER database for the 12 month period following the onset of the campaign only identified one additional case to those already reported by the active surveillance.

In total, four vaccinated NS cases (all Caucasians) were identified during this investigation, three by active surveillance and

Table 2
Number and incidence (per 100,000 person-years) of first hospitalizations for nephrotic syndrome per year of age in individuals aged ≤20 years for the province of Quebec between April 1st 2006 and March 31st 2016.

Age (years) at admission	Diagnostic code position				Total N	Incidence per 100 000
	Main diagnosis N patients	Secondary 1 N patients	Secondary 2 N patients	Secondary 3 N patients		
0	7	0	2	0	9	1.04
1	20	2	1	3	26	3.03
2	54	2	2	2	60	7.06
3	44	1	3	1	49	5.83
4	35	6	3	0	44	5.30
5	20	3	3	2	28	3.41
6	8	2	2	1	13	1.60
7	13	1	2	0	16	2.00
8	12	1	0	1	14	1.76
9	7	3	0	0	10	1.26
10	12	2	1	1	16	1.99
11	7	4	0	0	11	1.34
12	3	1	0	3	7	0.84
13	8	0	6	1	15	1.74
14	8	2	0	1	11	1.24
15	13	2	1	0	16	1.75
16	9	5	1	0	15	1.59
17	9	5	0	1	15	1.55
18	6	3	2	3	14	1.42
19	7	1	0	1	9	0.89
20	5	1	1	3	10	0.98
Total	307(75%)	47 (12%)	30 (7%)	24 (6%)	408(100%)	2.23

Table 3
Incidence of first hospitalization for nephrotic syndrome in the Province of Quebec and in the region of Saguenay – Lac-Saint-Jean (SLSJ) per period and age group.

	1–9 years	10–20 years	0–20 years
Province of Quebec			
April 2006- March 2016 (10 years)			
Number of hospitalized cases	260 cases	139 cases	408 cases
Person-time	~740 000 × 10y.	~1 004 000 × 10y	~1 830 000 × 10y
Rate per 100 000 (95%CI)	3.5 (3.1–3.95)	1.4 (1.2–1.6)	2.2 (2.0–2.5)
Province of Quebec excluding SLSJ			
April 2006-March 2014 (8 years)			
Cases/Person-time	206/(~702 000 × 8 y)	110/(~986 125 × 8y)	324/(~1 772 000 × 8 y)
Rate per 100 000 (95%CI)	3.67 (3.18–4.20)	1.39 (1.14-1.67)	2.29 (2.04-2.54)
May 2014-April 2015 (1 year)			
Cases/ Person-years	28/(~769 000 × 1 y)	15/(~912 000 × 1 y)	44/(~1,767 000 × 1 y)
Rate per 100 000 (95%CI)	3.64 (2.46–5.20)	1.64 (0.95–2.65)	2.49 (1.84-3.31)
SLSJ			
April 2006-March 2014 (8 years)			
Cases/ Person-years	3/(~23 400 × 8y)	7/(~35 200 × 8y)	10/ (~61 400 × 8y)
Rate per 100 000 (95%CI)	1.6 (0.4–4.4)	2.5 (1.1-4.9)	2.0 (1.0–3.6)
Vaccinated (>1 dose) children			
May 2014-April 2015 (1 year)			
Cases/Person-years	3/(~22 600 × 1 year)	0/~26 400 × 1 year	3/(~49 000 × 1 year)
Incidence per 100 000 (95%CI)	13.3 (3.4–36.1)	0	6.1 (1.5–16.6)
Hospitalization rate ratio (95 %CI)			
Comparing			
2014–15 SLSJ vaccinated children to:			
2006–2014 SLSJ	8.3 (1.1–62.0); p = 0.039	Not applicable	3.0 (0.5–11.7); p = 0.21
2014–2015 Quebec excl. SLSJ	3.6 (0.7–11.8); p = 0.12	Not applicable	2.5 (0.5–7.7); p = 0.27
2006–2014 Quebec excl. SLSJ	3.6 (0.7–10.7); p = 0.105	Not applicable	2.67 (0.5–7.9); p = 0.21

one through hospitalization database review. According to their medical charts, all met the criteria for confirmed NS, with symptoms becoming apparent between October 2014 and February 2015 (Table 4). All were Caucasian between 2 and 5 years of age, 2/4 were boys and 3/4 were hospitalized. None had a prior episode of NS or a pre-existing renal condition likely to increase the risk of NS. While three had acute respiratory illness (ARI) at the time of diagnosis, the NS symptoms preceded their ARI and were the reason for admission. While all were diagnosed after the second dose, two developed initial symptoms before receiving their second dose. All four responded well to steroids but one had several relapses and is receiving long-term immunosuppressive therapy. No child had a renal biopsy, but given their age and response to steroids, INS was the presumptive diagnosis in all cases. Table 4 displays details regarding their clinical presentation and blood test results at the time of diagnosis.

In the Saguenay-Lac-St-Jean region, the incidence of NS among 1–9 year old vaccinees during the year following the start of the vaccination period was 17.7 (95%CI = 5.6–42.7) per 100 000 or 1 NS per 5650 vaccinees with a hospitalization rate (i.e. excluding the ambulatory case) of 13.3 (95%CI = 3.4–36.1) per 100,000. This NS hospitalization rate was more than three-fold higher (HRR = 3.6, 95%CI = 0.7–11.8; p = 0.12) compared to that of the rest of the province for the same period but more than eight-fold higher (HRR = 8.3, 95% CI = 1.1–62.0; p = 0.039) compared to 8-year period preceding the vaccination campaign in the affected region (Table 3). When the comparison of the post and pre-campaign periods within the SLSJ region was restricted to the 2–5 year olds, the HRR was essentially unchanged as 1–9 year old cases in both periods were all between 2 and 5 years of age.

4. Discussion

This investigation identified four confirmed cases of nephrotic syndrome (NS), most likely idiopathic (INS), among children 2–5 years of age previously vaccinated with 4CMenB during a mass immunization campaign in the Saguenay-Lac-Saint-Jean region of Quebec, Canada. While the initial signal from active surveillance suggested that NS occurred following the 2nd dose of 4CMenB, this investigation found that two had their symptom onset before and two after the second dose. The incidence in vaccinated children 1–9 years old from the Saguenay-Lac-Saint-Jean region during the year following the start of the campaign was 17.7 per 100 000 (1 per 5650 vaccinees) with a rate of first NS hospitalization that was 3.6 times higher than the rest of the province during the same period (non-significant) and 8 times greater than during the eight years preceding the immunization campaign in the affected region. The interpretation of these estimates should take into account the wide confidence intervals which, although indicating observations are unlikely due to chance alone, encompass risk estimates ranging from minimally (HR = 1.1) to highly (HR = 62) clinically relevant.

The Saguenay-Lac-St-Jean area has a higher prevalence of some autosomal dominant genetic disorders (myotonic dystrophy, oculopharyngeal dystrophy, hypercholesterolemia type II) or autosomal recessive disorders (cystic fibrosis, haemochromatosis, congenital lactic acidosis, hereditary tyrosinemia, polyneuropathy with or without agenesis of corpus callosum, autosomic spastic recessive ataxia) [13]. These diseases however are not know to be related to NS or to a higher risk of IMB as observed before the campaign. Ultimately, the surveillance signal we report suggesting a greater NS hospitalization rate among vaccinees is predicated on four vaccinated cases accrued over a twelve month follow up period and for which the lower bound of the confidence interval of the association with vaccination includes or is slightly above the null value. As such, the surveillance observation we report may be unrelated to vaccine receipt, but rather due to some other unidentified exposure or the chance clustering of a rare disease. Although INS is known to occur following infection or allergic reaction, in absence of a clear pathophysiological mechanism for this disease, it is not possible to assess the biological plausibility of a causal link with 4CMenB immunization. In published clinical trials, no cases of NS were reported, but most participants were infants or adolescents and adults, outside the 1–9 year age group where INS is most frequent [14–29]. In the 6 clinical studies conducted in the age

Table 4
Characteristics of vaccinated patients with confirmed nephrotic syndrome at the time of diagnosis.

	Patient 1	Patient 2	Patient 3	Patient 4
Month, year of the 1st 4CMenB dose	May 2014	May 2014	May 2014	May 2014
Month, year of the 2nd 4CMenB dose	November 2014	September 2014	October 2014	October 2014
Month, year of symptom onset	October 2014	February 2015	February 2015	October 2014
Interval (days)				
Between 1st and 2nd dose	180	133	165	164
Between 1st dose and symptom onset	172	278 (145 post-dose2)	281 (116 post dose2)	150
Between symptom onset and hospitalization/consultation	55	10	14	21
Clinical signs, at diagnosis				
Edema	Generalized	Generalized	Generalized	Generalized
Hematuria	Yes (microscopic)	No	No	No
Proteinuria $\geq$ 3 g/L	>3.0	3.0	3.0	$\geq$10
Blood pressure (mm Hg)	117/66	145/73	114/86	106/77
Concomitant infections	URTI	Pneumonia	None	URTI
Hospitalization	Yes	Yes	No	Yes
Response to corticosteroids	Yes	Yes	Yes	Yes
Relapse	No	No	No	Yes
Blood test results (normal values), at time of diagnosis				
Hemoglobin (115–135 g/L)	128	133	126	137
White blood cells x10^9 (5.5–15.5 10^9/L)	10.3	23.8	12.1	10.4
Platelets $\times$ 10^9 (140–440 10^9/L)	384	618	371	268
Sodium (136–145 mmol/L)	135	138	142	139
Potassium (3.0–5.5 mmol/L)	5.8	4.7	4.7	4.9
Chloride (95–110 mmol/L)	110	106	109	108
Glycemia (3.1–6.1 mmol/L)	4.9	6.4	5.2	5.3
Blood urea nitrogen (1.4–6.9 mmol/L)	3.8	2.8	–	7.3
Creatinine (20–70 µmol/L)	<18	17	27	31
Total proteins (63–81 g/L)	32	41	43	39
Albumin (36–52 g/L)	<15	<6	15	7
C3 (0.90–1.80 g/L)	–	–	1.13	–
C4 (0.1–0.4 g/L)	–	–	0.23	–
Triglycerides (0.4–1.3 mmol/L)	3.17	3.7	1.8	4.2
Cholesterol (3.2–4.4 mmol/L)	12.32	11.8	8.0	8.7
LDL (0.0–2.8 mmol/L)	10.1	9.1	–	5.1
Antistreptolysin (ASLO) (0–199 UI/mL)	$\leq$199	$\geq$200	$\geq$200	
C-reactive protein (mg/L)	–	29.8	0.1	8.8
TSH (0.35–5.50 mU/L)	21.58	–	13.87	10
Free T4 (8.0–21.0 pmol/L)	9.1	–	10.6	8.4

group where we found NS, a total of about 1500 children were vaccinated with 4CMenB between 2 and 10 years of age [24–29]. This may have been an insufficient size to detect INS as a potentially serious but rare adverse event following 4CMenB immunization. In the United States, public health authorities have not received domestic notifications of NS following 4CMenB, but the vaccine is currently licensed only for individuals 10–25 years of age. No cases have been reported in the United Kingdom where an infant program (at 2, 4 and 12 months) has been implemented since 2015 [30] or in Germany [31] where it has been administered to a broader age range. However, it may be difficult for parents or clinicians to identify an association between the vaccine and NS given the long interval between vaccination and symptom onset of NS as reported here. Without the long systematic follow-up afforded by our active surveillance, this signal would not have been detected.

One of the components of the 4CMenB vaccine is derived from outer membrane vesicles (OMV) of serogroup B meningococcus [32]. Several vaccines containing only OMV have been developed and widely used [33,34]. More than 55 million doses of the combined meningococcal B and C vaccine (VA-MENGOC-BC®, Finlay Institute, Cuba) have been used in several countries and no association with NS has been reported [35]. In Norway, the OMV vaccine targeting only serogroup B (Folkehelsa®) was administered to tens of thousands of young people and no cases of NS were reported [36]. In New Zealand, where 3 million doses of an OMV vaccine specifically prepared for the strain circulating in this country (MeNZB®) were administered to young people <20-years-old, NS was not reported in vaccinees [37]. A review of the experience with vaccines consisting solely of OMV did not identify an association with this syndrome based on national passive vaccine adverse events reporting systems [34]. The safety of each of the other three components of 4CMenB (NadA, FHbp, and NHBA) has not been individually assessed. However one case of NS temporally associated with the bivalent FHbp vaccine (Trumenba®, Pfizer) has been reported to the Vaccine Adverse Event Reporting System (VAERS) in the United States where this vaccine is currently licensed only for individuals 10–25 years of age [38].

This investigation has limitations. The active surveillance was based on parents reporting SAEs. The determination by parents of "a life-threatening event" is subjective and the method could have missed mild NS cases. As the follow-up of SAEs was 6 months after the last dose parents could have also had difficulty identifying permanent disabilities. The main comparison of risk in vaccinated and unvaccinated children 1–9-years-old was based on the hospitalization rate in the Saguenay-Lac-St-Jean region during the eight years preceding the campaign and during the year of follow-up after vaccination. The population in this region is small and for rare diseases, incidence may be unstable. Consequently, it is unclear if the observed lower hospitalization rate for NS in 1–9 year olds in that region during the eight years preceding the campaign, as compared to that in the rest of the province, reflects this instability or a true lower baseline perhaps owing to differences in other associated factors such as infectious causes. Three of our four NS cases had concomitant acute respiratory illness and we cannot rule out their causal role in lieu of, or in addition to, vaccine. There was notable enterovirus/rhinovirus activity (including EV-D68) during the summer/autumn of 2014 followed by a severe influenza

epidemic through the 2014–15 season [39,40]. However, these are unlikely to explain the higher rate of NS in the Saguenay-Lac-St-Jean region in 2014–15 since the NS hospitalization rate was not higher that year compared to the previous eight years in the rest of the province where these respiratory viruses would have also circulated. The vaccinated ambulatory case was excluded from the comparison of risk as we had no means of identifying ambulatory cases during the pre-vaccine period. This exclusion may have underestimated the real risk in vaccinated compared to unvaccinated children. Finally, as the last vaccinated case of INS occurred in February 2015, we could have ended the follow-up period at this month (10 months) rather than April 2015 (12 months). While this would have increased the incidence rate in vaccinees and the hospitalization rate ratio, it would have neither affected the order of magnitude of our estimates, nor the general conclusion of this investigation.

In conclusion, the four confirmed cases of NS, likely idiopathic, in young children vaccinated with 4CMenB corresponding to a rate of 17.7 per 100,000 (1 per 5650 vaccinees) constitutes a potential vaccine safety signal given the rarity of this syndrome otherwise. To confirm or refute this association, other jurisdictions administering 4CMenB to children 1–9 years old should notify clinicians, especially pediatricians, of this possible association, and implement surveillance mechanisms capable of detecting this disease. Even if it were confirmed that 4CMenB causes INS at a frequency in the range of 1 per 6000 vaccinees aged 1–9 years, given the relatively small risk of serious INS sequelae compared to the lethality and severe morbidity of invasive meningococcal infection, this vaccine would continue to be advantageous and justified in periods of high incidence or outbreaks. If the association does prove causal, however, INS would need to be included in the risk-benefit analysis and consent process when considering mass 4CMenB administration. As such, greater awareness and further assessment of this potential safety signal is warranted.

Summary of article's main point

Four confirmed cases of NS, likely idiopathic, were identified in children 2–5-years-old vaccinated with 4CMenB. Representing a rate of 17.7 per 100 000 (1/5650 vaccinees 1–9-years-old), this vaccine safety signal should be assessed in other jurisdictions administering 4CMenB to young children.

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Declaration of Competing Interest

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