

Nephrotic syndrome following the four component meningococcal serogroup B vaccine (4CMenB) in Quebec

Presented by: Marie-Claude Gariépy

Gaston De Serres,
Marie-Noëlle Billard,
Eveline Toth, Monique Landry,
Chantale Bilodeau, Sylvie Belley
Marie-Claude Roy, François Boucher

Disclosure Statement

- I have no affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.



Saguenay–Lac-Saint-Jean
Population: 270 000

High IMD-B endemicity

Mass vaccination campaign in SLSJ region with 4CMenB vaccine

- Target: \approx 59 000 persons 2 months - 20 years
- Immunization schedule
 - 2-5 months : 4 doses
 - 6-11 months : 3 doses
 - 12 months and older : 2 doses
- Campaign
 - First dose: May-June 2014
 - Second dose : September-October 2014
 - End of campaign : December 31, 2014
- Offered in schools and public health clinics

Source: http://www.inspq.qc.ca/pdf/publications1801_Infections_Invasives_Meningocoque.pdf

Vaccine coverage

Age at the 1 st dose	Target population Number	1 dose %	2 doses %
<2 years	~6500	92	88
2-4 years	~8 000	86	80
5-16 years	~31400	94	90
17-20 years	~12100	48	34
Overall	~59 000	83	77

Enhanced safety surveillance

- Passive VAERS already in place
 - AEFI reporting is mandatory for all physicians
- Electronic active surveillance
 - Email one week after each dose with a link to a web-based questionnaire
 - Outcomes: AEFI of sufficient severity to cause absenteeism or a medical consultation during the 7 days post vaccination
 - **Another questionnaire six months after the last dose**
 - **Outcome: Serious Adverse Events (SAE)**
- Nurse contacted participants reporting SAE to validate information.

Participation in active surveillance

- 70% of vaccinees provided an email address
- Participation rate
 - 1st dose: 39% among those sent an email message
27% among all vaccinees
 - 2nd dose : 31% among those sent an email message
22% among all vaccinees
 - **6 months post last dose:**
 - 23% among those sent an email message**
 - 16% among all vaccinees**



Contents lists available at [ScienceDirect](#)

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Short-term safety of 4CMenB vaccine during a mass meningococcal B vaccination campaign in Quebec, Canada

Gaston De Serres^{a,b,c,*}, Marie-Noëlle Billard^b, Marie-Claude Gariépy^b, Isabelle Rouleau^b, Eveline Toth^d, Monique Landry^d, Nicole Boulianne^{a,b}, Hélène Gagné^e, Vladimir Gilca^{a,b}, Geneviève Deceuninck^b, Manale Ouakki^a, Danuta M Skowronski^f

Serious Adverse Events

	During the four months between dose 1 and 2	During the 6 months following the last dose	All reported SAE
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

Nephrotic syndrome rate

- Disease usually rare
 - Incidence: 2 to 4 per 100 000 person-years
- With three cases for ~10 000 respondents, this corresponds to a rate of 60 per 100 000 person-years (3/10 000 x 6 months)
 - 15 to 30 times higher than expected

Nephrotic syndrome (NS)

- Glomerular permeability disorder causing kidney loss of proteins in urine.
- **Case definition** : Simultaneous presence of:
 - Generalized edema
 - Hypoalbuminemia $<30\text{g/L}$
 - Proteinuria $\geq 3\text{ g/L}$
 - First episode

Etiologies according to age

- Infants <1 y-o
 - NS cases generally linked to genetic abnormalities of the basal glomerular membrane.
- Children 1-9 y-o
 - **~90% of NS is idiopathic (INS)**
- Adolescents and adults
 - NS usually secondary to systemic diseases.
 - Renal biopsy necessary to determine the cause of NS.

Idiopathic Nephrotic Syndrome (INS)

- Cause unknown but sometimes follows URTI or allergic reaction
- Typical onset between 2-7 y-o
- In patients 1-9 y-o:
 - presumptive diagnosis of INS made without indication for renal biopsy when satisfactory clinical response to systemic steroids
- INS may persist for several years
 - relapses are frequent
 - outcome generally favourable with full recovery
 - no longterm sequelae

Epidemiological investigation

- Objective:
 - Identify risk factors linked to excess of INS cases
 - Return to cases to see their evolution:
 - Other risk factors, recurrences, sequelae, etc.
- Search for other vaccinated cases
 - Hospitalization database Med-ECHO (ICD-10 N04)
 - Emergency room consultation database
 - Vaccination status in the vaccine registry

Hospitalizations

Number and incidence (per 100,000 person-years) of first hospitalizations for NS 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

Baseline rate of hospitalization for NS

(April 2006-March 2014= 8 years)

	1-9 years	10-20 years	0-20 years
Quebec without SLSJ	3.67	1.39	2.29
SLSJ	1.60	2.50	2.03

Hospitalization rate ratio comparing vaccinated children from the SLSJ

Comparison group	1 to 9 years	10-20 years	0-20 years
Quebec without SLSJ 2014-15	3.6 (0.7 to 11.8) p=0.12	Not applicable	2.5 (0.5 to 7.7) p=0.27
SLSJ 2006-14	8.3 (1.1 to 62) p=0.039	Not applicable	3.0 (0.5 to 11.7) p=0.21
Quebec without SLSJ 2006-14	3.6 (0.7 to 10.7) p=0.10	Not applicable	2.67 (0.5 to 7.9) p=0.21

Emergency room database

- No new cases

Cases description

- 4 vaccinated NS cases identified during investigation (**3/4 hospitalized**)
 - 3 identified by the active surveillance
 - 1 new case found in the hospitalization database
- Aged between 2 and 5 y-o
- All diagnosed after 2nd dose but for 2 symptom onset before 2nd dose
- All responded well to steroids.
- One had several relapses and is receiving long-term immunosuppressive therapy.
- No child had a renal biopsy: INS = presumptive diagnosis in all cases

Actions taken

- Notification in Canada
 - ESPRI (VAERS in Quebec), CAEFISS, Health Canada
 - GSK: 1 case in Chile
- International notifications
 - UK: No signal : Infant program has been implemented since 2015 (>750 000 vaccinated infants)
 - France: No signal. Limited use.
 - USA: No signal. Vaccine approved for >10y-o. Results were presented to CISA network (CDC).
 - Australia: No signal.

Discussion

- Difficult to observe by passive surveillance
 - Long delay, link not easy to make
- Unable to confirm or deny link with vaccine.
 - Should be observed in the longer term by those who will use this vaccine.
- Clinical trials
 - Too rare to have been observed
 - 7 200 infants ≤ 12 months
 - **113 children aged 40-44 months (3,3-3,5 y-o)**
 - 1 755 adolescents and adults aged 11-50 y-o
- Limited clinical experience for this vaccine with children aged 2-5 y-o.
- Few participants in the affected age group

Conclusion

- 4 confirmed cases of NS, likely idiopathic, in young children vaccinated with 4CMenB
 - Rate of 17.7 per 100,000 (1 per 5650 vaccinees)
 - Constitutes a vaccine safety signal given the rarity of this syndrome otherwise.
- Clinicians, especially pediatricians, should be notified of this possible association
 - Implementation of 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 6 000 vaccinees aged 1-9 years:
 - Relatively small risk of serious INS sequelae compared to lethality/severe morbidity of IMB
 - Vaccine still advantageous and justified in periods of high incidence or outbreaks.
- If association proven causal:
 - INS needs to be included in risk-benefit analysis
 - Consent process when considering mass 4CMenB administration

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

		1 to 9 years	10-20 years	0-20 years
Province of Quebec				
<u>April 2006- March 2016 (10 years)</u>				
	Cases	260	139	408
	Rate per 100 000 (95%CI)	3.5 (3.1 to 3.95)	1.4 (1.2 to 1.6)	2.2 (2.0 to 2.5)
Province of Qc excluding SLSJ				
<u>April 2006-March 2014 (8 y)</u>				
	Cases	206	110	324
	Rate per 100 000 (95%CI)	3.67 (3.18 to 4.20)	1.39 (1.14 to 1.67)	2.29 (2.04 to 2.54)
<u>May 2014-April 2015 (1 year)</u>				
	Cases	28	15	44
	Rate per 100 000 (95%CI)	3.64 (2.46 to 5.20)	1.64 (0.95 to 2.65)	2.49 (1.84 to 3.31)
SLSJ				
<u>April 2006-March 2014 (8 years)</u>				
	Cases	3	7	10
	Rate per 100 000 (95%CI)	1.6 (0.4 to 4.4)	2.5 (1.1 to 4.9)	2.0 (1.0 to 3.6)
<u>Vaccinated (≥1 dose) children May 2014-April 2015 (1 year)</u>				
	Cases	3	0	3
	Incidence per 100 000 (95%CI)	13.3 (3.4 to 36.1)	0	6.1 (1.5 to 16.6)