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Short communication

Impact of a mass vaccination campaign against Serogroup B meningococcal disease in the Saguenay-Lac-Saint-Jean region of Quebec four years after its launch

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ABSTRACT

In the Saguenay-Lac-Saint-Jean region of Quebec, 83% of the population ≤20 years (n ≅ 59,500) was immunized in 2014 with the four-component Serogroup B meningococcal vaccine to control a long-lasting outbreak caused by a virulent ST-269 Serogroup B *Neisseria meningitidis* clone. Following the campaign, invasive meningococcal B disease (B-IMD) incidence fell sharply in the target population from 11.4/100,000 in 2006–2014 to 0.4/100,000 in 2014–2018 ($p < 0.0001$). Five B-IMD cases occurred in the region from July 2014 to June 2018, including one vaccinated child, one unvaccinated young adult and 3 unvaccinated elderly adults. Estimate of direct vaccine protection was 79% [95%CI:−231%;99%]. The overall campaign impact in the region taking into account the decrease in B-IMD incidence at provincial level was a 86% [95%CI:−2%;98%] decrease in B-IMD risk. The campaign impact was mostly seen in the target age-group suggesting no herd effect among unvaccinated older adults.

1. Introduction

An increase in the incidence of Serogroup B invasive meningococcal disease (B-IMD) started in the province of Quebec, Canada, in 2003. This was caused by the emergence of a Sequence-Type (ST) 269 *Neisseria meningitidis (Nm)* clone [1,2]. The Saguenay-Lac-Saint-Jean (SLSJ) region was particularly affected with an average B-IMD rate of 3.4 per 100,000 person-years in 2006–2013, compared to 0.6/100,000 in other regions [3]. In May 2014, an immunization campaign was launched in this region, using the four-component protein-based meningococcal vaccine (MenB-4C). By the end of the campaign, 83% of the 59 500 SLSJ residents between 2 months and 20 years of age had been vaccinated [4]. A first evaluation of the impact of the campaign was performed shortly after its completion [3]. The objective of the present study was to evaluate the impact of the campaign four years after its initiation, allowing an exploration of the direct protection provided by MenB-4C, the indirect (herd) protection to unvaccinated individuals in the region and the overall impact of the campaign taking into account the decrease in B-IMD incidence in other regions during the period 2014–2018. There is no published data on the effectiveness of MenB-4C in individuals 2–20 years of age.

2. Methods

Details on the methodology was described in previous publications [3,4]. The study period extends from July 1st 2006 to June 30th 2018 (12 years). The vaccination campaign in the SLSJ region started in early May 2014 and by the end of June, most of first MenB-4C doses had been administered, subsequent doses being administered during the fall of 2014. The study period was arbitrarily divided into a pre-campaign period (July 2006 to June 2014) and a post-campaign period (July 2014 to June 2018). Serogroup B invasive meningococcal disease (B-IMD) cases reported to public health authorities and confirmed by culture or PCR were included in the analysis and information on their phenotypic and genotypic characteristics were provided by the provincial and

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national reference laboratories. The immunization status of B-IMD cases was ascertained by regional public health authorities. Denominators data by age-group, region of residence and year were provided by the Quebec Statistics Institute ('Institut de la Statistique du Québec'). B-IMD rates in the SLSJ and other regions of Quebec during the pre- and post-campaign periods were compared using rate differences and ratios. The number of vaccinated residents in the SLSJ was extracted from the regional immunization registry. B-IMD rates among unvaccinated and vaccinated individuals in the target population of SLSJ were compared to estimate the direct protection provided by MenB-4C during the post-campaign period (vaccine effectiveness = 1 minus rate ratio). P-values of rate differences and ratios and their confidence intervals were computed assuming a Poisson distribution (GENMOD procedure in SAS 9.3 software). In order to assess the overall impact of the campaign, B-IMD risk during the 2006–2018 study period was analyzed by multivariate Poisson regression models, adjusting for age (5 categories), region of residence (SLSJ *vs* other regions) and epidemic year (12 categories extending from July 1st to June 30th). A variable representing the overall impact of the campaign in the vaccinated cohort (direct protection + herd effect) was introduced in the model, taking a value of 1 in vaccinated persons during the post-campaign years and 0 in all the other strata (including unvaccinated individuals only). Another variable representing the indirect (herd) effect of the campaign was also introduced, taking the value of 1 among unvaccinated individuals residing in the SLSJ region during the post-campaign years and 0 in all other strata (including all individuals not vaccinated and not targeted in other regions and the target population in the SLSJ region before the campaign).

3. Results

During the 2006–2018 study period, a total of 535B-IMD cases were recorded in the province of Quebec, 80 of which in the SLSJ region (15% of total), this region representing only 3.4% of the Quebec population (2011 census: 275,000/7,903,000). B-IMD rates during the pre- and post-campaign periods are shown in Table 1. During the 2006–2014 period of sustained circulation of the ST-269 clone In the SLSJ, B-IMD rate was 3.4/100,000 person-years and fell to 0.5/100,000 following the mass immunization campaign (87% decrease; $p < 0.0001$). In the other regions, there was also a decrease in incidence but of lower magnitude, from 0.6 to 0.3/100,000 (58% decrease; $p < 0.0001$). In the SLSJ, the decrease was particularly marked in the age-group targeted by the campaign with a 96% decrease from 11.4 to 0.4/100,000 to ($p < 0.0001$), compared with a 59% decrease from 1.1 to 0.5/100,000 ($p = 0.1$) in older adults. In the other regions, the magnitude of the decrease was similar in younger (minus 58%) and older (minus 56%) age-groups.

During the 4-year post-campaign period July 2014 to June 2018, five B-IMD cases occurred among SLSJ residents. Information on these cases is shown in Table 2. The 6 year-old child received two MenB-4C doses in 2014 at the age of two years. Three cases were culture-confirmed and the strains involved had been typed as ST-269 or ST-11386 with *fHbp* and *nhba* genes predicted to encode FHBP14 and NHBA21 peptides respectively. The other two cases were diagnosed by PCR with one case confirmed to be caused by strain ST-269 and the other by strain ST-7064 (single locus variant of ST-269).

Among persons targeted by the campaign and observed from July 1st 2014 to June 30th 2018, B-IMB rate was 0.51/100 000 [95%CI: 0.01 to 2.83] in vaccinated (1 case) and was 2.45/100 000 [95%CI: 0.06 à 13.7] in unvaccinated persons (1 case), giving a vaccine effectiveness estimate of 79% [95%CI: −231% à 99%].

Results of the multivariate Poisson regression models using the whole dataset showed an effect of age with the highest B-IMD risk in the 0–4 years age-group followed by the 12–17 years age-group, and the lowest in adults > 20 years (details in supplementary material). Residing in SLSJ was a strong risk factor (RR: 5.69; 95% CI: 4.44 to 7.29) compared with other regions. Adjusting for these factors and temporal variation in B-IMD incidence in the province, the overall effect of the campaign in the vaccinated SLSJ cohort was of borderline significance (RR: 0.14: 95% CI: 0.02 to 1.02; $p = 0.05$), meaning a disease risk reduction of 86% (95%CI: −2% to 98%). The factor representing the indirect effect of the campaign among unvaccinated individuals in the SLSJ region was not significant (RR: 0.48; 95%CI: 0.17 to 1.35; $p = 0.17$).

4. Discussion

Our results provides some evidence of the effectiveness of a mass campaign using MenB-4C to control an outbreak of Serogroup B meningococcal disease: B-IMD incidence markedly dropped in the SLSJ region (minus 87%), more than in other regions of Quebec (minus 57%). Before the campaign, the average number of B-IMD cases was close to 10 per year in the SLSJ region (75 cases over the 8-year 2006–2014) and was only one per year following the campaign (5 cases over 4 years), which is close to what was observed before the emergence of the ST-269 clone (13 cases over the 10-year period 1996–2006) [4].

To be effective, MenB-4C should cover the *Nm* strains causing the outbreak. Using the Meningococcal Antigen Typing System (MATS), a study on Serogroup B ST-269 strains identified in Canada in 2006–2009 predicted at least 85% coverage by MenB-4C [5]. *Nm* strains causing the outbreak in SLSJ and sporadic cases occurring after the mass campaign (Table 2) belonged to the clonal complex 269 and commonly expressed two surface proteins (FHBP and NHB) closely related to the antigens contained in MenB-4C [1,4].

Results suggest direct protection provided by MenB-4C over a 4-year period among children and teenagers, although the confidence interval of the vaccine effectiveness estimate is very large. This result is in line with results of the routine immunization program for infants in the United Kingdom: 83% effectiveness of two MenB-4C doses against all B-IMDs during the first 10 months of the program [6]. The duration of protection conferred by MenB-4C is not known and is difficult to extrapolate from immunogenicity studies [7–9]. It may be well that the duration of protection is longer in adolescents and young adults than in infants as suggested

Table 1
Characteristics of cases and strains of serogroup B meningococcal disease reported in the Saguenay-Lac-Saint-Jean Region during the post-vaccination campaign period July 1st 2014 to June 30th 2018.

Date of onset	Age in years	Clinical presentation	Outcome	Diagnostic method	Serotype	Subtype	Genomic sequence type	Clonal complex
March 2015	44	Meningococcemia	Recovery	Culture	17	P1.19	ST-269	269
April 2015	62	Meningococcemia	Death	Culture	17	P1.19	ST-11386	269
September 2015	65	Meningitis	Recovery	PCR	ND	ND	ST-7064	269
February 2017	21	Meningococcemia and meningitis	Recovery	Culture	17	P1.19	ST-269	269
April 2018	6	Meningitis	Recovery	PCR	ND	ND	ST-269	269

Table 2
Number of cases and incidence rate (IR per 100,000 person-years) of Serogroup B invasive meningococcal disease in the province of Québec before (July 2006–June 2014) and after (July 2014–June 2018) the initiation of the mass vaccination campaign in the Saguenay-Lac-Saint-Jean (SLSJ), according to region and age-group.

Age group	Region	July 2006–June 2014		July 2014–June 2018		Rate difference and 95%CI			% change	Rate ratio	p value
		Cases	IR/100 000	Cases	IR/100 000	Difference	Inf.	Sup			
All	Province	448	0.71	87	0.26	−0.45	−0.53	−0.36	−63%	0.37	<0.0001
	SLSJ region	75	3.40	5	0.45	−2.95	−3.81	−2.08	−87%	0.13	<0.0001
	Other regions	373	0.61	82	0.26	−0.36	−0.44	−0.27	−58%	0.42	<0.0001
≤20 years	Province	294	2.00	51	0.70	−1.30	−1.60	−1.00	−65%	0.35	<0.0001
	SLSJ region	56	11.35	1	0.44	−10.91	−14.01	−7.82	−96%	0.04	0.0013
	Other regions	238	1.68	50	0.71	−0.97	−1.26	−0.68	−58%	0.42	<0.0001
>20 years	Province	154	0.32	36	0.14	−0.18	−0.25	−0.11	−56%	0.44	0.0001
	SLSJ region	19	1.11	4	0.45	−0.65	−1.32	0.01	−59%	0.41	0.1
	Other regions	135	0.29	32	0.13	−0.16	−0.23	−0.10	−56%	0.44	<0.0001

by immunogenicity data but this would have to be investigated further [7–9].

Our results are not supporting the hypothesis of indirect herd protection to the unvaccinated fraction of the SLSJ population, mainly older adults. B-IMD risk among persons > 20 years in the SLSJ was reduced by 59% following the campaign, compared with 56% in the other regions where no vaccination took place. Absence of herd effect may be explained by two factors. Studies on asymptomatic meningococcal carriage showed that 17–24 year-old persons constitute the main reservoir for transmission in the whole population [10]. Vaccine uptake in the 17–20 years age-group in SLSJ was 47%, compared with ≥ 86% in younger age-groups [3]. Reaching adolescents, many of whom are not attending school on a full time basis and convincing them to receive a vaccine is particularly challenging [11]. The proportion of vaccinated individuals in this age-stratum was probably too low in the SLSJ region to generate a herd effect. The second factor is the weak effectiveness of 4CMenB on the carriage and acquisition of Serogroup B *Nm* strains as shown in a study among university students in the UK [12].

In conclusion, results of our study on the direct protection provided by MenB-4C, along with reassuring safety data presented in another study [13], support the current recommendations for MenB-4C use for controlling outbreaks caused by clones covered by the vaccine.

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Declaration of Competing Interest

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.06.021.

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