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Initial Dose of a Multicomponent Serogroup B Meningococcal Vaccine in the Saguenay–Lac-Saint-Jean Region, Québec, Canada: An Interim Safety Surveillance Report

Québec

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Direction des risques biologiques et de la santé au travail

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List of Abbreviations and Acronyms

4CMenB	Four component meningococcal serogroup B vaccine
AEFI	Adverse Event Following Immunization
CIQ	Comité sur l'immunisation du Québec (Québec Immunization Committee)
CSSS	Centre de santé et de services sociaux (Health and Social Service Centre)
DSP	Direction de santé publique (Public Health Unit)
ESPRI	Effets secondaires possiblement reliés à l'immunisation *(AEFI passive* surveillance)
INSPQ	Institut national de santé publique du Québec
MSSS	Ministère de la Santé et des Services sociaux (Ministry of Health and Social Services)
RAMQ	Régie d'assurance maladie du Québec (Québec Health Insurance Board)
RSS	Région sociosanitaire (Health Region)
V09	Provincial electronic database for meningococcal disease vaccination

Summary

Introduction

To control the spread of the meningococcal serogroup B disease in the Saguenay–Lac-Saint-Jean region which has had a higher incidence rate compared with the rest of the province since 2004, a vaccination campaign was undertaken and targeted individuals 20 years and younger residing in or attending an educational institution in this region. An enhanced surveillance system was implemented to monitor the onset of adverse events following immunization (AEFI) in real time in order to be able to promptly notify the Ministère de la Santé et des Services sociaux (MSSS, Ministry of Health and Social Services) and the Direction de la santé publique (DSP, public health unit) of the Saguenay–Lac-Saint-Jean Health Region (RSS 02) about the occurrence of a safety issue in connection with this new quadrivalent serogroup B Meningococcal vaccine (4CMenB).

Methodology

This report covers the experiences of individuals residing in region 02 who received their first dose of 4CMenB between May 5 and June 17, 2014. Both active surveillance and passive surveillance were used to track the occurrence of AEFIs. Active surveillance was performed via electronic questionnaire sent to all vaccinees who provided an email address, whereas passive surveillance was done via the reporting to the AEFI surveillance system already in place in Québec and known as the ESPRI surveillance. For active surveillance, all vaccinees who had provided their email address on the vaccination consent form received an email seven days post-vaccination inviting them to complete an electronic questionnaire.

Results

Between May 5 and June 17, 2014, a total of 43,740 individuals between the age of 2 months and 20 years residing in RSS 02 received a first dose of the 4CMenB vaccine. Of this number, 29,853 (68%) provided an email address and 12,332 (28% of all vaccinees, 44% of those who had a valid email address and received the questionnaire) completed the electronic questionnaire by July 2, 2014. Of these, nine percent (9%) reported the onset of fever within 48 hours following vaccination and 1.9% reported fever within 3 to 7 days. The incidence of fever was higher in children under the age of 2 years (14–15%) than in children between 2 to 4 years old (12%) and those 5 years of age or older (6–8%). In children under the age of 2 years, antipyretic prophylaxis reduced the probability of fever in the first 48 hours by approximately 50% compared with children who were not given these drugs. Overall, 6% of respondents experienced a health problem within seven days post-vaccination that resulted in absenteeism of the person vaccinated or a parent and 1.2% consulted a physician. The most frequently reported problems were general malaise (56%), local reactions (49%), gastrointestinal problems (34%) and respiratory problems (24%). A single case of febrile convulsion was identified and no vaccine-related hospitalizations were reported. The estimated rates of absenteeism attributable to local reactions, fever or general malaise with onset within 48 hours post-vaccination were 3.1% for children between the ages of 2 and 4 years and 4.4% for those between the ages of 5 and 16 years. Open-ended comments were provided by 20% of respondents, of whom 83% reported pain at the injection site.

Of the 12,332 individuals who completed the questionnaire, 99% stated that they likely or definitely intended to receive the second dose of the vaccine, whereas this dropped to 92% in the 764 individuals who reported absenteeism or a medical consultation.

Under the passive surveillance reporting system, 56 cases of AEFI were reported through the ESPRI surveillance: 46% were an allergic-like event, 29% fever and 19% a large local reaction. One case of febrile seizure was reported.

Conclusion

This surveillance did not identify any serious or unexpected health problems associated with the vaccine. It did, however, confirm a significant incidence of painful local reactions, fever and general malaise that caused absenteeism.

Executive Summary

Introduction

To control the spread of the meningococcal serogroup B disease in the Saguenay–Lac-Saint-Jean region which has had a higher incidence rate compared with the rest of the province since 2004, the Comité sur l'immunisation du Québec (CIQ) issued a recommendation for the targeted vaccination against this meningococcal disease of young people 20 years-old and under residing in or attending an educational institution in this region.[1] The CIQ stated that this public health intervention, with its time and space limitations, should be rigorously evaluated so that the lessons learned could help define the future use of this vaccine. The evaluation plan to assess the impact of this targeted vaccination involved several components, including the surveillance of adverse events following immunization (AEFI). This interim report presents the post-vaccination surveillance results after the first dose of a quadrivalent meningococcal B vaccine (4CMenB, Bexsero® from Novartis).

Objectives

The overall objective of this surveillance was to monitor the occurrence of AEFI in real time in order to be able to promptly notify the Ministère de la santé et de services Sociaux (MSSS) and the Direction de santé publique (DSP) of RSS 02 about the emergence of a vaccine-related safety issue.

Safety monitoring of the 4CMenB vaccine included active surveillance via electronic questionnaires sent to all vaccinees who provided an email address and passive surveillance of AEFI through the ESPRI reporting system already in place for all vaccines administered given in Québec.

The primary objective of active surveillance was to estimate the real-time incidence of AEFIs resulting in absenteeism (either in vaccinated individuals or a parent) or medical consultations attributable to the 4CMenB vaccine. The intent was to estimate the following for a 7-day period after vaccination with 4CMenB:

1) Incidence of high fever (≥ 40.5°C);
2) Protective effect of antipyretic prophylaxis on the incidence and severity of fever in children under 2 years of age;
3) Incidence of febrile convulsions;
4) Incidence of severe transient arthralgia;
5) Impact of AEFI on the intention to receive the second dose of 4CMenB or other regularly scheduled vaccinations.

Methodology

The surveillance of AEFI in this report describes the experiences of individuals residing in RSS 02 who received their initial dose of 4CMenB during the first wave of the campaign, i.e. between May 5 and June 17, 2014.

All vaccinated individuals were invited to provide their email address on the vaccination consent form. The email address as well as information about vaccination such as vaccination date and vaccine lot number, were entered into the provincial electronic vaccination database (V09). Seven days post-vaccination, a personalized email was sent to all vaccinees who provided an email address. This message was personalized for each vaccinated individual and included a brief description of the surveillance. The vaccinee or the vaccinee's parent were invited to complete an electronic questionnaire by clicking onto a secured link that would direct them to the questionnaire.

Results

Between May 5 and June 17, 2014, a total of 43,740 individuals between the ages of 2 months and 20 years residing in the RSS 02 received an initial dose of the 4CMenB vaccine. Of these, 29,853 (68%) provided email addresses, of which 1,349 (4.5%) were invalid or incorrect. Data capture was too late for 609 vaccinees (2.0%) to take part in the survey. Of the 27,895 vaccinees with a valid address to whom an email was sent, 12,332 (44.2%) completed the electronic questionnaire as of July 2, 2014, i.e. 28.2% of all persons vaccinated.

Active Surveillance

Of the 12,332 participants in active surveillance, 1,346 (10.9%) reported a fever within 7 days after vaccination. Onset occurred within 48 hours of the vaccination in 9% (1,154) of vaccinees and within 3 to 7 days in 1.9% (n= 191, $p < 0.001$).

Although fever prophylaxis medication was recommended in children under 2 years of age, 70% of all respondents reported using prophylaxis (67% of vaccinees > 2 years). However, this varied by age, ranging from 93% in children under 2 years of age to 43% in those ≥17-year-old (Chi-square test for trend, $p < 0.001$). Acetaminophen was the drug most used in all age groups.

Children under 2 years of age had a higher incidence of fever than children between 2 and 4 (14–15% and 12% respectively) and in those 5 years of age and older (6–8%). In the under 2-year-old age group, the proportion of children who developed fever within the first 48 hours was lower in children who received the meningococcal serogroup B vaccine alone than in those who received it at the same time as other pediatric vaccines, but this was not statistically different (13% vs. 19%, $p = 0.09$). Overall, the mean maximum temperature was 38.9°C and was similar in children under 2 years of age (38.8°C) and those in the 2–20 year-old age group (39°C). The percentage of children reporting a high grade fever (≥ 40.5°C) was < 1%. The mean duration of fever with onset within 48 hours post-vaccination was 1.8 days; the median duration was 2 days.

In children under the age of 2 years, the use of antipyretics reduced the probability of fever within the first 48 hours by approximately 50% compared with children who did not receive these drugs (2-11 months 14% vs. 31%; 12–23 months 13% vs. 23%, $p < 0.001$). The effect of the prophylaxis was more pronounced in children who received other vaccines concomitantly than in those who received 4CMenB alone. The reduction in the risk of fever was greater in individuals who received two or more doses of antipyretic prophylaxis than in those who received only one.

In total, 764 respondents (6.2%) reported a health problem resulting in absenteeism, either on the part of the vaccinee or another person, or a medical consultation within seven days post-vaccination. Overall, absenteeism was reported by 6% and 1.2% consulted a physician. When a vaccinee was absent, in 46% of cases another person also had to be absent to take care of the vaccinee. This percentage was inversely proportional to the age of the vaccinated person: 56% of absences in children under 5 years of age also involved the absence of another person whereas this value was 48% in children aged 5–11 years, 25% in the 12- to 16-year-old category, and 12.5% in those ≥ 17 years of age. The most frequently reported problems were general malaise (56%), local reactions (49%), gastrointestinal problems (34%) or respiratory problems (24%).

Of these 764 cases, 290 had more serious problems requiring a nurse telephone interview for validation. Among individuals contacted by a nurse, the most commonly reported problems were systemic reactions lasting ≥ 4 days (114), local reactions lasting ≥ 4 days (79), respiratory problems (13), allergic-like (8) or non-allergic- like (2) skin problems, and arthralgia (5). A single case of febrile seizure was identified in a 1-year-old child. Of the 8 patients who reported hospitalization, four had a

visit to the emergency room that lasted <12 hours and one was hospitalized outside the observation period (for otitis that began on day 7 with hospitalization on day 10). The three other hospitalizations were attributable to respiratory problems and did not appear related to vaccination.

The estimated rates of absenteeism attributable to local reactions, fever or general malaise with onset within 48 hours post-vaccination by age group were, 4.4% (5–16 years), 3.1% (2–4 years), 0.9% (2-11 months), 2.2% (12–23 months), and 1% (17–20 years).

The questionnaire included a section for open-ended comments that was completed by 20% (2,440) of respondents. Nearly 90% reported a health problem that did not result in absenteeism or a medical consultation. The most common complaint was pain at the injection site (83%), whereas fever and general malaise were mentioned in 32% of cases.

Of the 12,332 individuals who completed the questionnaire, 99% stated that they likely or definitely would receive the next dose of the vaccine, whereas this dropped to 92% in the 764 individuals who reported absenteeism or medical consultation.

With regard to passive surveillance, 56 cases of AEFI were reported to the ESPRI surveillance between May 5 and July 2, 2014, including 49 that had been investigated as of July 7. Data on 39 had been entered in the ESPRI database, and 37 were in the age group targeted by the mass vaccination campaign (0 to 20 years). Of the reported cases entered, 46% (n = 17) were for an allergic-like event, 30% (n = 11) for a fever, and 19% (n = 7) for a large local reaction. One case each of arthralgia and febrile seizure (infant <6 months) were reported.

Discussion and Conclusion

Although only one quarter of the vaccinated individuals participated in active surveillance following the initial dose of the vaccine, these 12,322 young people nevertheless represent a larger group than the total number of participants in all the Novartis clinical trials conducted pre-licensure.[1] This surveillance did not reveal any serious or unexpected health problems associated with the vaccine but did confirm a significant incidence of painful local reactions, fever and general malaise severe enough to result in absenteeism. Despite this, virtually all of vaccines expressed their intention to receive the second dose.

In conclusion, surveillance did not identify any worrisome safety signal with the first dose of the 4CmenB vaccine that would call into question the continuation of the vaccination campaign. The campaign will therefore continue as planned with the administration of the second dose and ongoing monitoring to ensure that everything proceeds safely and according to expectations.

1 Introduction

1.1 Background

To control the spread of the meningococcal serogroup B disease in the Saguenay–Lac-Saint-Jean region which has had a higher incidence rate compared with the rest of the province since 2004, the Comité sur l'immunisation du Québec (CIQ) issued a recommendation for the targeted vaccination against this meningococcal disease of young people 20 years-old and under residing in or attending an educational institution in this region.[1] The CIQ stated that this public health intervention, which was limited in time and space would require rigorous evaluation so that the lessons learned could help define the future use of this vaccine. The plan to evaluate the impact of this targeted vaccination involved several components, including the surveillance of adverse events following immunization (AEFI). This interim report presents the post-vaccination surveillance results after the first dose of a quadrivalent meningococcal B vaccine (4CMenB, Bexsero® from Novartis).

1.2 Unexpected Clinical Events with the 4CMenB Vaccine requiring Surveillance

Available 4CMenB vaccine safety data when the Saguenay–Lac-Saint-Jean vaccination campaign was implemented were based on 9 published clinical trials.[1] These studies were conducted in approximately 8,000 individuals, including 4,800 children ≤ 12 months of age, 1,600 children aged 12-24 months, 84 children aged 40- 43 months, and 1,738 adolescents and adults aged 11 to 50 years. Outside these clinical trials, the vaccine has been used in the United States in the context of interventions involving about 5,000 students at Princeton University[2] vaccinated in December 2013 and nearly 9,000 students from the University of California at Santa Barbara[3] vaccinated in February 2014.

Clinical studies with 4CMenB have shown that it caused a higher incidence of fever and local reactions than other pediatric vaccines.[4] The incidence of side effects varies depending on the age group and co-administration with other pediatric vaccines. The CIQ highlighted a number of areas of concern requiring close surveillance including Kawasaki disease, convulsions, high fever, severe transient arthralgia, as well as relatively high absenteeism post-vaccination.[1]

Kawasaki disease (KD) is an immunological disease that causes febrile vasculitis involving the small- and medium-sized arteries. This disease generally has a favourable outcome within 2 to 3 weeks, and effective immunoglobulin-based therapy is available. However, if not detected quickly, the disease can cause heart damage and coronary artery aneurysms. KD is a rare disease that primarily affects children under the age of 5 years. In clinical studies, it was reported in 6 out of 6,403 children who received the 4CmenB vaccine and in 1 out of 1,694 children in the control group (recipients of routine vaccines).[1] In only one of the cases was onset in the week post-vaccination. The risk of KD in these clinical studies was approximately 90 cases per 100,000 person-years (PY) in the subjects who received the 4CMenB vaccine and approximately 60 cases per 100,000 PY in those who received the routine vaccines. Although these incidences were not statistically different and may simply have been the result of random fluctuations in the incidence of the disease, strict monitoring was essential to ensure that the vaccine did not increase the risk of KD.

During the clinical trials with infants, there were 8 reported cases of convulsion among 2,481 children (1/620 infants) who received 4CMenB and no cases were reported in the 1,149 participants who received routine vaccines.[1] Four cases were febrile convulsions occurring within 24 hours of the

vaccination (2 after the first dose and 2 after the second) whereas the other four occurred 2, 6, 8 and 25 weeks after the third vaccine dose. Febrile convulsions would not be surprising given the incidence of fever associated with this vaccine.

A rectal temperature ≥ 38.5°C within 6 hours post-vaccination was reported in 65% of infants vaccinated with 4CMenB compared with 32% of vaccinees who received only the routine vaccines.[5] A fever of ≥ 40°C was reported in 1.2% of infants vaccinated with 4CmenB compared with 0.2% of those receiving the routine pediatric vaccines. Fever was most often reported after the first and second vaccine doses, with onset within the first six hours post-vaccination and generally lasted less than 48 hours.[4-6] It is possible that acetaminophen use at the time of vaccination may prevent not only fever but also convulsions. For this reason, the CIQ recommended the use of prophylactic antipyretics in children under two years of age vaccinated with 4CMenB.[1]

As for arthralgia, 12% of the 84 children vaccinated at the age of 40–43 months reported severe transient arthralgia (no specific definition given).[7-8] This high incidence was reported in only one study but nevertheless raises concerns.

Post-vaccination absenteeism was reported in 12% of adolescents and in 9% of adults vaccinated with the 4CMenB vaccine.[9] A high percentage of absenteeism in vaccinated individuals or their parents due to the vaccine's side effects could considerably increase the social costs associated with the vaccination.

2 Vaccine Safety Surveillance Objectives

The overall objective of this surveillance was to monitor in real time the nature and incidence of AEFI in order to be able to promptly notify the MSSS and the DSP of RSS 02 about the emergence of a vaccine-related safety concern.

Safety surveillance of the 4CMenB vaccine involved two components:

1. Active surveillance via an electronic questionnaire sent to all vaccinated individuals who provided an email address;
2. Passive surveillance via the provincial passive reporting surveillance system (ESPRI) already in place for all vaccines administered in Québec.

2.1 Active Surveillance of Unexpected Clinical Events: Objectives

2.1.1 Primary Objective

The primary objective was to estimate in real-time the nature and incidence of AEFI resulting in absenteeism (either in vaccinees or a parent) or medical consultations related to the 4CMenB vaccine.

2.1.2 Secondary Objectives

Secondary objectives were to estimate the following during the seven-day period post-vaccination with 4CMenB:

1) Incidence of high-grade fever (≥ 40.5°C);
2) Protective effect of antipyretic prophylaxis on incidence and severity of fever in children under 2 years of age;
3) Incidence of febrile seizures;
4) Incidence of severe transient arthralgia;
5) Impact of AEFI on intention to receive the second dose of 4CMenB or other regularly scheduled vaccinations.

2.2 Passive surveillance of AEFIs (ESPRI): Objectives

2.2.1 Primary Objective

The primary objective was to estimate the incidence of AEFI, including Kawasaki disease, reported by healthcare professionals for all vaccinated individuals in RSS 02.

2.2.2 Secondary Objective

The secondary objective was to compare the type of AEFI reported to the ESPRI system with that reported to the active surveillance to ensure a comprehensive overview.

3 Methodology

3.1 Study Population

The meningococcal serogroup B vaccination campaign targeted children and young adults born between May 6, 1993, and December 31, 2014, residing or attending an educational institution in the Saguenay–Lac-Saint-Jean region (RSS 02). The active surveillance of AEFI described in this report includes residents or students of RSS 02 who received their first dose of the 4CMenB vaccine during the first wave of the campaign, namely between May 5 and June 17, 2014.

All individuals vaccinated in this meningococcal serogroup B vaccination campaign were asked to provide their email address in the vaccination consent form. Health and Social Services Centre (CSSS) vaccination staff entered the email address as well as vaccination information, such as vaccination date and vaccine lot number, into the provincial electronic measles database (V09), which was adapted to capture data about vaccination with 4CMenB.

3.2 Information about Active Surveillance and Checklist

Upon vaccination, individuals were given an information sheet describing the expected side effects of 4CMenB vaccine (Appendix 1). The information sheet also described the active surveillance to be performed and notified vaccinated individuals that they would be receiving an email seven days following vaccination inviting them to complete an on-line questionnaire. The sheet also included a checklist to help vaccines take note of fever or any other health problem that resulting in absenteeism or a medical consultation in the seven-day period post-vaccination. This information sheet also provided a section to record acetaminophen use for fever prevention (antipyretic prophylaxis).

3.3 Electronic Survey

Seven days post-vaccination, a personalized email message (e.g. name and vaccination date) with a brief description of the surveillance activities was sent to all vaccinees who provided an email address. The vaccinee or a parent were invited to complete an electronic questionnaire by clicking on a secure link (URL address) directing them the questionnaire. The surveillance used the Simple Sondage (OutSideSoft Solutions Inc., Saint-Jean-sur-Richelieu, Québec) survey software which included various components to manage the survey (e. g. electronic questionnaire platform, email and respondent management).

3.4 Information Collected

The electronic questionnaire gathered information about the concomitant administration of other vaccines and the use of antipyretic prophylaxis. It asked about fever onset as well as any other health problem resulting in the absenteeism of a parent or the vaccinee, or necessitating a medical consultation in the 7-day post-vaccination period. If an absence or medical consultation was reported, questions sought details about the nature of the problem and day(s) the problem occurred. Participants were also asked whether they intended to receive the next dose of the 4CMenB vaccine. In the case of respondents who stated "likely not” or "definitely not" intend to receive it were asked, they were asked the reason for their decision. Lastly, the questionnaire included a section for open-ended comments where participants could make aware public health authorities of health problems not resulting in absenteeism or a medical consultation.

3.5 Telephone Investigation of Serious Cases

The surveillance team analyzed questionnaires where participants reported an absence or medical consultation. Participants whose health problem met pre-established severity criteria (Appendix 2) received a phone call by a nurse in order to validate the information recorded in the electronic survey and to obtain additional information on the reported health problem.

3.6 Statistical Analysis

Participants were stratified into age categories. Children under the age of two years who are most likely to develop post-vaccination fever and for whom antipyretics were recommended were divided into two groups: 0–11 months and 12–23 months. The 2- to 4-year-olds corresponded to pre-schoolers, the 5- to 11-year-old group were the kindergarten to end-of-primary school group, the 12- to 16-year-olds were high school group, and the 17- to 20-year-olds were in the post-secondary or out of school group.

The maximum temperature in Celsius was adjusted according to the measurement method. For oral and axillary temperature readings, 0.5°C and 0.7°C, respectively, were added to make them comparable with rectal temperature readings.

Any health problem interrupted for at least one day was considered resolved.

Statistical analyses were done using SAS 9.3. The chi-square test was used to compare proportions and the chi-square trend test was used to evaluate trends. A value of $p < 0.05$ was considered significant.

A content analysis of the open-ended comments and reasons cites by participants who stated they “likely not” or “definitely not” intended to receive the second dose was performed using the N-Vivo 10 software.

3.7 Ethics

This safety evaluation of the 4CMenB vaccine during a targeted meningococcal serogroup B vaccination campaign in RSS 02 was legally mandated by the National Director of Public Health under the powers conferred by the Québec Public Health Act. Consent to take part in the electronic survey was obtained when the parent (or vaccinated individual if ≥ 14 years) agreed to complete the electronic questionnaire. Confidentiality was assured by ensuring anonymity of the collected data and their presentation in aggregate form.

3.8 Passive Surveillance of AEFI

Under the Québec Public Health Act, any healthcare professional qualified to make a medical diagnosis or assess a person’s health condition is required to report it to the regional public health unit (DSP) of all serious or unexpected clinical event possibly related to the vaccination. Moreover, a letter of the National Director of Public Health was sent to all physicians in RSS 02 before the start of the vaccination campaign advising them to pay special attention to all severe or unexpected adverse events, seizures and Kawasaki disease following vaccination. A weekly list of all AEFI reported under passive surveillance was shared with the active surveillance team to ensure complete follow-up of these patients.

4 Results of Active Surveillance

4.1 Participant Characteristics

Between May 5 and June 17, 2014, a total of 43,740 individuals aged of 2 months to 20 years residing in the Saguenay–Lac-Saint-Jean health region received an initial dose of the 4CMenB vaccine. Of this number, 29,853 (68%) provided email addresses, of which 1,349 (4.5%) were invalid or incorrect and 609 (2.0%) were entered too late for the individual to take part in the survey. Of the 27,895 vaccinated individuals with a valid email address to whom an email was sent, 12,332 (44.2%) completed the electronic questionnaire as of July 2, 2014, i.e. 28.2% of all vaccinated individuals (Table 1).

Table 1 Characteristics of individuals vaccinated against meningococcal serogroup B disease as recorded in the V09 database by email address and response to the electronic questionnaire

	Total	Vaccinated individuals			
		Total	No email address	With email address	
				Non respondents	Respondents to questionnaire
	N = 56 819	**N = 43 740 N (77%)***	**N = 13 887 n (32%)****	**N = 17 521 n (40%)****	**N = 12 332 n (28%)****
Gender					
Female	27 877 (49%)	21 900 (50%)	6 739 (49%)	8 856 (51%)	6 305 (51%)
Male	28 941 (51%)	21 839 (50%)	7 147 (51%)	8 664 (49%)	6 028 (49%)
Age					
< 24 months	4 479 (8%)	3 886 (9%)	7%	1 355 (8%)	1 557 (13%)
2-11 months	2 018 (4%)	*1 797 (4%)*	*431 (3%)*	*620 (4%)*	*746 (6%)*
12-23 months	2 461 (4%)	*2 089 (5%)*	*543 (4%)*	*735 (4%)*	*811 (7%)*
2-4 years	8 395 (15%)	6 361 (15%)	1 816 (13%)	2 086 (12%)	2 459 (20%)
5-11 years	18 806 (33%)	16 708 (38%)	4 983 (36%)	6 658 (38%)	5 067 (41%)
12-16 years	12 927 (23%)	11 502 (26%)	4 562 (33%)	4 777 (27%)	2 163 (18%)
17-20 years	12 212 (21%)	5 283 (12%)	1 552 (11%)	2 644 (15%)	1 087 (9%)
Mean age ± s.d.	10,3 ± 5,7	9,9 ± 5,5	10,4 ± 5,4	10,5 ± 5,6	8,4 ± 5,4
Median age	10	9.8	10.8	10.6	7.7
CSSS of residence					
Chicoutimi	15 288 (27%)	11 875 (27%)	2 546 (18%)	5 008 (29%)	4 321 (35%)
Cléophas-Claveau	4 545 (8%)	3 569 (8%)	827 (6%)	1 736 (10%)	1 006 (8%)
Jonquière	13 026 (23%)	10 129 (23%)	2 964 (21%)	4 130 (24%)	3 035 (25%)
Lac-Saint-Jean-Est	11 456 (20%)	8 642 (20%)	3 252 (23%)	3 449 (20%)	1 941 (16%)
Maria-Chapdelaine	5 573 (10%)	4 312 (10%)	1 192 (9%)	1 925 (11%)	1 195 (10%)
Domaine-du-Roy	6 931 (12%)	5 213 (12%)	3 106 (22%)	1 272 (7%)	835 (7%)

* Percentage of the total number of individuals (row percent).

** Percentage of the number of vaccinated individuals (row percent).

Overall, there were few differences between the socio-demographic characteristics of individuals who provided an email address versus those who did not, except for some local CSSS that were marginally under-represented (Table 1). While the percentage of respondents aged 2 months to 11 years was higher in relation to their demographic weight, this was lower in the 12-20-year-old group. The mean age of vaccinees with a completed electronic questionnaire was8.4 years and the median age was 7.7 years.

4.2 Fever

Overall, fever within seven days post-vaccination was reported in 1,346 vaccinated individuals (10.9% of respondents). The incidence and prevalence of fever was highest on days 1 and 2 (Figures 1 and 2). Fever started within 48 hours post-vaccination in 9% (1,154) of vaccinees and for 1.9% (191), it started three to seven days ($p < 0.001$) post-vaccination. The vast majority (95%) of individuals who reported fever had only a single episode and 5% had two or three episodes of fever separated by at least a 24-hour period free of symptoms.

Figure 1 Incidence of fever by post-vaccination day and age

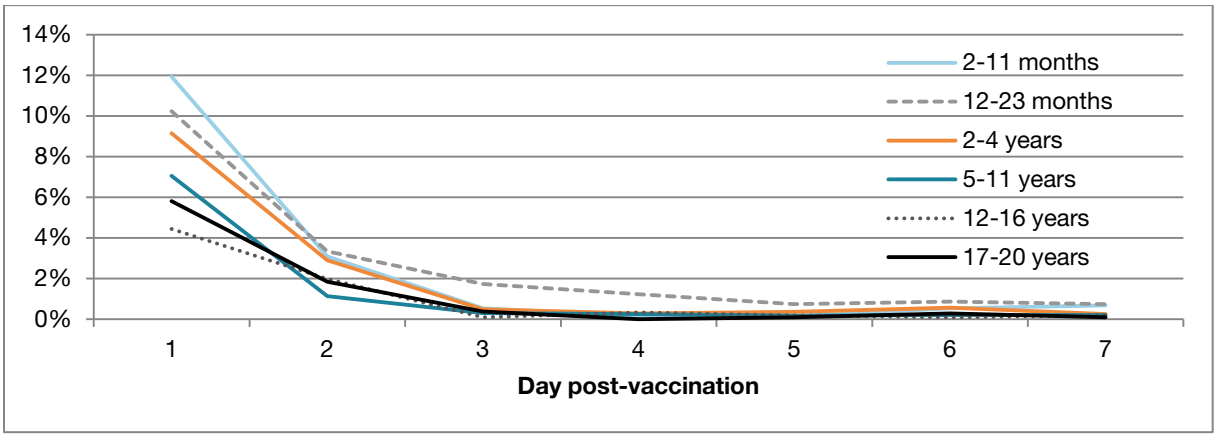
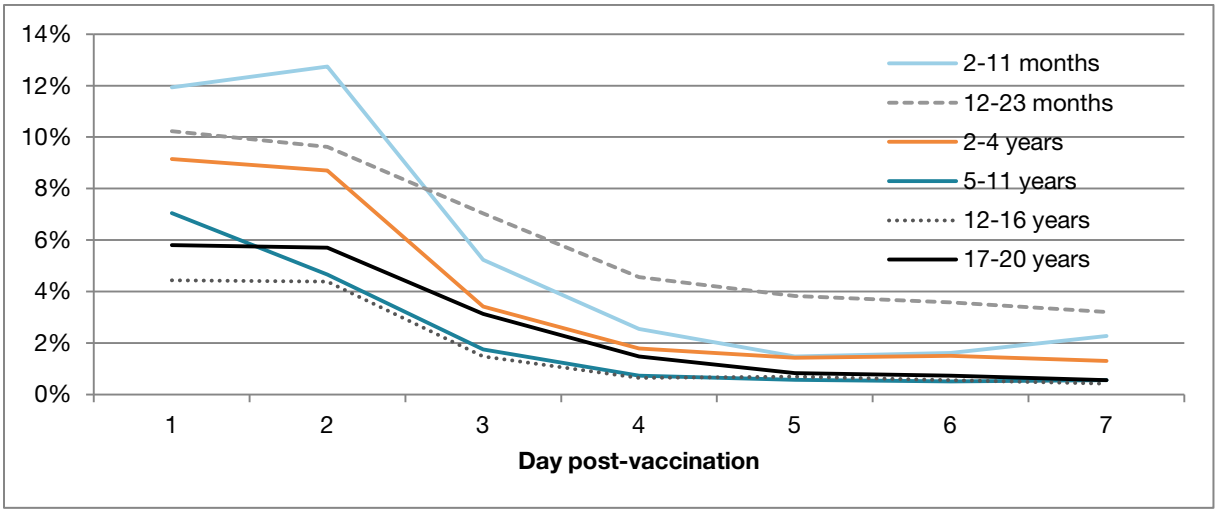


Figure 2 Prevalence of fever by post-vaccination day and age



4.2.1 PROPHYLACTIC ANTIPYRETICS: IMPACT ON INCIDENCE AND SEVERITY OF FEVER

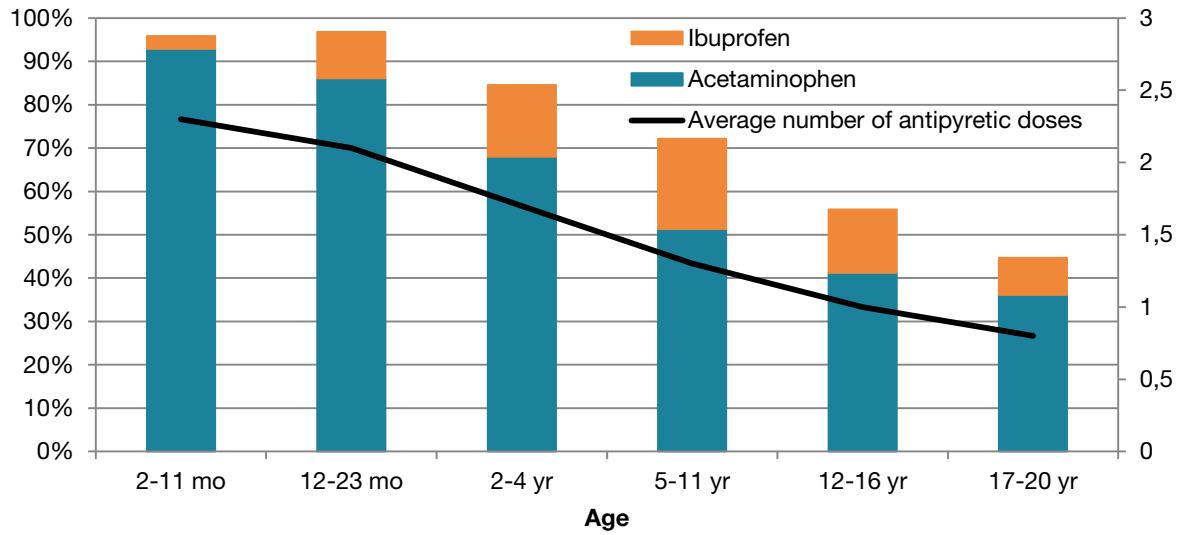
Although the use of medication to prevent fever was recommended in children aged < 2 years, 70% of all respondents reported taking such prophylaxis (67% of vaccinees > 2 years) (Table 2). However, this varied by age, ranging from 93% in those under 2 years of age to 43% in those over 17 years of age (Chi squared trend ($p < 0.001$) (Figure 3). In all age groups, acetaminophen was the drug taken most often (80% of antipyretics), followed by ibuprofen in 23% of respondents. In the target group of children under 2 years of age, 96% were given acetaminophen and 8% took ibuprofen. Twenty-six percent (26%) of those over two years of age took ibuprofen (Table 2).

Table 2 Vaccine co-administration and antipyretic prophylaxis by age

	2-11 months	12-23 months	2-4 years	5-11 years	12-16 years	17-20 years	Total
	N = 746	N = 811	N = 2 459	N = 5 067	N = 2 163	N = 1 086	N = 12 332
Coadministered with other vaccine(s)	234 (31%)	111 (14%)	55 (2%)	111 (2%)	22 (1%)	5 (0%)	538 (4%)
Antipyretic prophylaxis	707 (95%)	746 (92%)	1 997 (81%)	3 534 (70%)	1 181 (55%)	472 (43%)	8 637 (70%)
0 dose	32 (4%)	62 (8%)	435 (18%)	1 452 (29%)	898 (42%)	580 (53%)	3 459 (28%)
1 dose	127 (17%)	173 (21%)	649 (26%)	1 425 (28%)	513 (24%)	253 (23%)	3 140 (25%)
2 doses	159 (21%)	210 (26%)	629 (26%)	1 045 (21%)	351 (16%)	112 (10%)	2 506 (20%)
3 doses	421 (56%)	363 (45%)	719 (29%)	1 064 (21%)	317 (15%)	107 (10%)	2 991 (24%)
Timing of the 1st dose of antipyretics							
Before vaccination	166 (23%)	197 (26%)	523 (26%)	1 195 (34%)	304 (26%)	49 (10%)	2 434 (28%)
At the time of vaccination	154 (22%)	164 (22%)	363 (18%)	232 (7%)	91 (8%)	45 (10%)	1 049 (12%)
After vaccination	384 (54%)	379 (51%)	1 094 (55%)	2 037 (58%)	742 (63%)	345 (73%)	4 981 (58%)
Medication taken							
Acetamino-phen	693 (98%)	698 (94%)	1 672 (84%)	2 601 (74%)	892 (76%)	392 (83%)	6 948 (80%)
Ibuprofen	22 (3%)	87 (12%)	407 (20%)	1 054 (30%)	316 (27%)	93 (20%)	1 979 (23%)
Other	1 (< 1%)	0 (0%)	7 (< 1%)	10 (0%)	2 (< 1%)	6 (1%)	26 (< 1%)

Overall, 58% of respondents who took at least one dose of an antipyretic started the prophylaxis more than 15 minutes post-vaccination. This proportion was lower in children under 12 years of age (55.8%) than in those 12 years of age and older (65.8%). The average number of antipyretic prophylaxis doses was statistically higher in younger children, with 2.2 doses in the group aged < 2 years and 0.8 doses in the group aged 17 years and older.

Figure 3 Proportion of vaccinees who reported taking antipyretic prophylaxis, medication type and average number of doses by age



The frequency of fever with onset on days 1 or 2 was higher in the group under 2 years of age (14–15%) than in children aged 2 to 4 years (12%) and in children aged ≥5 years (6–8%) (Table 3, Figures 1 and 2).

In children under 2-years of age, the proportion of children who presented with fever within the first 48 hours was lower in those who received the meningococcal serogroup B vaccine alone than in those who received it co-administered with other pediatric vaccines, but this was not a statistically significant difference (13% vs. 19%, p = 0.09).

Table 3 Fever with onset on day 1 (D1) or day 2 (D2) and administration of antipyretic prophylaxis by age

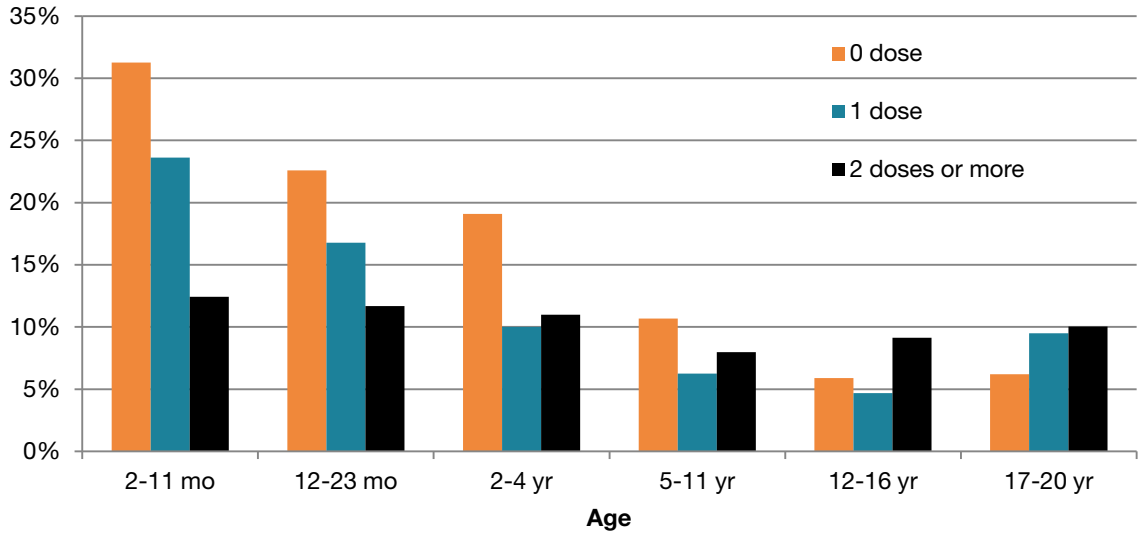
	2-11 months	12-23 months	2-4 years	5-11 years	12-16 years	17-20 years	Total
	N = 746	N = 811	N = 2 459	N = 5 067	N = 2 163	N = 1 086	N = 12 332
Fever (onset D1 or D2)	112 (15%)	110 (14%)	296 (12%)	414 (8%)	139 (6%)	83 (8%)	1 154 (9%)
Max. T°							
< 39 °C (%)	61 (54%)	51 (46%)	87 (29%)	105 (25%)	27 (19%)	10 (12%)	341 (30%)
39-40.4 °C (%)	29 (26%)	35 (32%)	87 (29%)	117 (28%)	27 (19%)	7 (8%)	302 (26%)
≥ 40.5 °C (%)	1 (< 1%)	0 (0%)	2 (1%)	4 (1%)	2 (1%)	5 (6%)	14 (1%)
Not measured	21 (19%)	24 (22%)	120 (41%)	188 (45%)	83 (60%)	61 (73%)	497 (43%)
Fever (onset D1 or D2)							
With prophylaxis	102 (14%)	96 (13%)	213 (11%)	257 (7%)	85 (7%)	46 (10%)	799 (9%)
No prophylaxis	10 (31%)	14 (23%)	83 (19%)	155 (11%)	53 (6%)	36 (6%)	351 (10%)
Mean Maximal T°in °C	38.8	38.9	38.9	39.0	38.9	39.1	38.9
With prophylaxis	38.8	38.9	38.9	39.0	38.8	39.0	38.9
No prophylaxis	38.6	38.5	38.9	39.1	39.1	39.4	39.0

In 43% of individuals who reported onset of fever on days 1 or 2, the maximum temperature was not taken or reported. Overall, the percentage of children, adolescents and young adults with a reported maximum fever of ≥ 40.5°C was 0.1% (n = 14) among all respondents and 1% in individuals reporting fever with onset on days 1 or 2 (Table 3). No cases of fever ≥ 40.5°C were observed in children who received the 4CMenB vaccine concomitantly with other vaccines. Overall, the mean maximum temperature adjusted for the measurement method was 38.9°C, which was similar in the under two years of age (38.8°C) and in the 2–20 years of age (39°C) groups. The mean duration of fever that started within 48 hours post-vaccination was 1.8 days, with a median duration of 2 days. The mean duration of a fever that started within 48 hours post-vaccination was slightly longer in children under two years of age than in the 2-20-year-old group (2.1 days vs. 1.8 days, $p < 0.001$).

Overall, the mean maximum temperature adjusted for the measurement method did not vary depending on whether or not an antipyretic was taken (38.9°C vs. 39.0°C) but the difference was slightly wider in children under 2 years of age (38.8°C vs. 38.5°C) than in those 2- to 20-year-old group (38.9°C vs. 39.0°C) (Table 3).

In children under the age of 2 years, administration of an antipyretic reduced the probability of fever in the first 48 hours by approximately 50% compared with children who were not given these drugs (2-11 months 14% vs. 31%; 12–23 months 13% vs. 23%, $p < 0.001$). The effect of the prophylaxis was more pronounced in children who had co-administration of other pediatric vaccines than in those who received 4CMenB alone. There was a greater reduction in the risk of fever with a higher number of doses of prophylactic antipyretics (Figure 4). In children younger than 2 years old who took 4CMenB alone, fever was reported by 17/83 (20%) who did not take prophylaxis, by 37/235 (16%) of those who took one dose and by 101/884 (11%) of those who took two or more doses ($p = 0.12$). In children who were co-administered other vaccines, fever was reported by 7/11 (64%) who did not take prophylaxis, by 22/64 (34%) who took one dose, and by 38/268 (14%) who took two or more doses ($p < 0.001$).

Figure 4 Proportion of vaccinees who reported fever on days 1 or 2 by age and number of antipyretic prophylaxis doses



Antipyretic prophylaxis also significantly reduced the risk of fever in children aged 2–4 years, and to a lesser extent in children aged 5–11 years (Table 3, Figure 4). However, no effect was noted in terms of the number of doses. In vaccines aged ≥12 years, prophylaxis did not reduce the risk of fever (Table 3, Figure 4).

4.3 Health Problems Causing Absenteeism or Resulting in a Medical Consultation

A total of 764 (6.2%) respondents reported a health problem that resulted in absenteeism (of the individual vaccinated or another individual in order to take care of the vaccinee) or a medical consultation within seven days post-vaccination (Table 4). Overall, absenteeism was reported for 6% of vaccinated persons and 1.2% consulted a physician. In 46% of the times when a vaccinee was absenteeism, another person also had to be absent to take care of him/her. This percentage was inversely proportional to the age of the vaccinated individual: 56% of absences in children under 5 years of age also involved an absence by another person, 48% in children aged 5–11 years, 25% in the 12- to 16-year-old category, and 12.5% in those ≥ 17 years of age.

On average, respondents who reported a medical consultation or absenteeism indicated two health problems in the electronic questionnaire: 9% had one, 19% had two, 23% had three and 18% reported four or more.

Table 4 Health problems resulting in absenteeism or a medical consultation by age

	2-11 months	12-23 months	2-4 years	5-11 years	12-16 years	17-20 years	Total
	N = 746	N = 811	N = 2 459	N = 5 067	N = 2 163	N = 1 086	N = 12 332
Absenteeism or consultation	33 (4%)	77 (9%)	212 (9%)	291 (6%)	117 (5%)	34 (3%)	764 (6%)
Absenteeism	23 (3%)	72 (9%)	198 (8%)	280 (6%)	114 (5%)	32 (3%)	719 (6%)
Vaccinated individual	17 (2%)	64 (8%)	192 (8%)	271 (5%)	112 (5%)	32 (3%)	688 (6%)
Another person	13 (2%)	49 (6%)	111 (5%)	140 (3%)	30 (1%)	4 (< 1%)	347 (3%)
Medical Consultation	19 (3%)	27 (3%)	43 (2%)	29 (1%)	13 (1%)	6 (1%)	137 (1%)
Absenteeism and consultation	9 (1%)	22 (3%)	29 (1%)	18 (< 1%)	10 (< 1%)	4 (< 1%)	92 (1%)
Hospitalization	2 (< 1%)	2 (< 1%)	2 (< 1%)	1 (< 1%)	1 (< 1%)	0 (0%)	8 (< 1%)

Problems most frequently reported were general malaise (56%), local reactions (49%), gastrointestinal problems (34%), respiratory problems (24%); 10% reported “Other health problems” (Table 5). In this last group, 84% included a comment describing this problem: 42% reported respiratory infections and 29% reported systemic events (general malaise, fever, headache). Three neurological events (loss of consciousness/vagal reaction), three allergic-like events (skin rash or eruptions), as well as one joint pain were also described in these comments.

Table 5 Health problems (not mutually exclusive) reported in the electronic questionnaire by individuals who reported absenteeism or a medical consultation within seven days post-vaccination, by age

	2-11 months N = 33	12-24 months N = 77	2-4 years N = 212	5-11 years N = 291	12-16 years N = 117	17-20 years N = 34	Total N = 764
Local reaction	12 (36%)	36 (47%)	101 (48%)	143 (49%)	66 (56%)	19 (56%)	377 (49%)
Mean duration (days)	2,7	2,4	3	3	3,9	4,8	3,2
Onset D1 or D2 and Duration ≥ 4 days	3 (9%)	8 (10%)	26 (12%)	46 (16%)	33 (28%)	13 (38%)	129 (17%)
General malaise excluding fever	21 (64%)	49 (64%)	109 (51%)	159 (55%)	70 (60%)	21 (62%)	429 (56%)
Mean duration (days)	2,9	3,7	2,8	2,3	2,5	3,6	2,7
Onset D1 or D2 and Duration ≥ 4 days	6 (18%)	19 (25%)	23 (11%)	22 (8%)	16 (14%)	10 (29%)	96 (13%)
Arthralgia	5 (15%)	7 (9%)	30 (14%)	49 (17%)	16 (14%)	8 (24%)	115 (15%)
Mean duration (days)	2,2	2,1	2,7	2,6	2,8	3,4	2,7
Cutaneous problems	5 (15%)	12 (16%)	20 (9%)	14 (5%)	9 (8%)	4 (12%)	64 (8%)
Mean duration (days)	2	2,8	2,2	3,6	3,8	5	3
Respiratory problems	11 (33%)	37 (48%)	56 (26%)	51 (18%)	21 (18%)	9 (26%)	185 (24%)
Mean duration (days)	2,7	3,9	4,4	3,4	3,1	4,3	3,8
Gastrointestinal problems	15 (45%)	21 (27%)	62 (29%)	99 (34%)	45 (38%)	16 (47%)	258 (34%)
Mean duration (days)	2,5	2,6	1,9	1,6	2,3	1,9	2
Neurological problems	0	1(1%)	0	1(< 1%)	0	1(3%)	3(< 1%)
Other problems	5 (15%)	8 (10%)	20 (9%)	28 (10%)	10 (9%)	3 (9%)	74 (10%)

4.3.1 Nurse Investigation of Health Problems

Among the 764 individuals who reported a medical consultation or an absence due to a health problem in their electronic questionnaire, 290 met the pre-defined severity criteria for being called by a nurse (Appendix 2). Of the 277 (96%) who were contacted, 86 (31%) did not meet the criteria and were excluded, while 191 cases met the criteria.

On average, these 191 individuals reported three health problems in their electronic questionnaire: 6% reported one, 16% reported two, and 70% reported three or more. Following validation by a nurse, a maximum of two main problems were kept: 73% had one and 27% had two. The majority of individuals with two problems experienced general malaise along with local reactions (n=32, 60%), respiratory symptoms (n=5, 9%) or gastrointestinal symptoms (n=4. 8%).

Table 6 Main health problems in patients meeting the criteria for a nurse telephone call (Appendix 2)

Health problem	Any absenteeism or medical consultation	Cases meeting the severity criteria in their electronic questionnaire					
		Total	Number reached	Number not meeting criteria after validation	Number meeting criteria after validation		
					Presence of the problem N = 191		Main problem N = 191
	N = 764	N = 290	N = 277		Initially reported	Reclassified**	
Local reaction	377	217	207	80	127	28	79 (41%)
General malaise	429	236	224	70	154	28	114 (60%)
Arthralgia	115	115	110	92	18	1	5 (3%)
Cutaneous ou allergic-like problems	64	45	44	27	17	0	10 (5%)
Respiratory problems	185	102	96	39	57	9	13 (7%)
Gastrointestinal problems	258	138	131	57	74	15	10 (5%)
Neurological problems	3	3	3	2	1	6	5 (3%)
Other problems	74	40	39	28	3	8	5 (3%)

* Health problem reported in the electronic questionnaire and validated by the nurse.

** Health problem not reported in the electronic questionnaire but reclassified after nurse validation.

The most frequent validated health problems were general malaise lasting ≥ 4 days (114), local reactions lasting ≥ 4 days (79), respiratory problems (13), allergic-like (8) or non-allergic-like (2) cutaneous problems, and arthralgia (5).

In the 113 cases with reported arthralgia, 3 (3%) were not contacted, 5 (4%) were excluded because they did not report absenteeism or medical consultation and 87 (77%) because their problem was in fact pain at the injection site involving an area up to the shoulder or elbow or generalized muscle pain without specific joint involvement. In the five cases where arthralgia was the main problem, (two in the 2-4-year-old group, one in the 5-11-year-old group, and two in the ≥12 years old group), the pain was short-lasting (average 2.9 days) and there were no signs of inflammation (redness, heat, swelling) suggestive of arthritis. One individual had trouble walking for a few days due to knee pain, whereas in another case, the individual stated the joint pain (ankle, knee, hip, elbow) interfered with sleeping. The severity of the other cases was mild or moderate.

Of the ten nurse-validated skin problems, eight involved allergic-like signs and symptoms (hives or non-pruritic plaque), including two individuals who started experiencing symptoms within four hours post-administration of the vaccine while the other six experienced onset of symptoms on average 17 hours post-vaccination (ranging from 12 to 36 hours). In one patient skin rash presented together with a dry, intermittent cough. The last two patients experienced other skin problems.

The three individuals who reported a neurological problem in their electronic questionnaire were contacted and two were excluded: the first experienced tingling from the injection site to the head immediately after being vaccinated causing no absenteeism or medical consultation, and the other had headaches and stiffness at the back of the neck. The third involved a one-year-old baby who was given one dose of antipyretic prophylaxis prior to the vaccination. The fever started a few hours later and was treated with two doses of antipyretic; the child vomited with the second dose just prior to having seizures. The convulsions lasted for less than one minute and occurred ten hours post-administration of the 4CMenB vaccine, co-administered with Priorix-Tetra (MMRV) and Infanrix (DaPT-Polio-Hib-HB) vaccines. The parents contacted a pharmacist but did not consult a physician.

Otherwise, neurological symptoms were identified in six individuals who did not report them in the electronic questionnaire. In two of these cases (one case involved confusion and the other a loss of consciousness), the neurological symptoms were not chosen as the main health problem. In the other four cases where the main problem was a neurological problem, this involved diminished or loss of consciousness. Three occurred at the time of vaccination and were attributed to vagal reactions according to the nurse who was present during the vaccination. The other case occurred the day after vaccination in an 8-year-old child who had two short episodes of diminished consciousness followed by a severe headache. The child stayed home that day to rest and had fully recovered by the end of the day.

In the eight patients with reported hospitalization, four spent less than 12 hours at the emergency room, one was hospitalized on day 10 (beyond the observation period) for otitis that began on day 7, and the other three were admitted for respiratory problems (one for bronchospasm on day 5 and two for infections) unlikely to be related to the vaccination.

4.3.2 Absenteeism Due to 4CMenB Vaccination

Overall, absenteeism was reported for 3.7% of vaccinees who had local reactions, fever or general malaise that began within 48 hours post-vaccination.

Absenteeism attributable to the side effects of 4CMenB, was calculated as the excess over the baseline occurrence of these problems. Given the high incidence of fever on days 1 and 2 which subsequently declined drastically, we assumed that fever and general malaise with onset on days 3 to 7 were unrelated to the vaccine and reflected the baseline frequency caused by non-vaccine etiologies. Since days 3 to 7 represent a five-day follow-up, we divided that latter incidence by 2.5 (percentage adjusted in Table 7) to make it comparable to the two-day follow-up on days 1 and 2.

Absenteeism attributed to 4CMenB's side effects was therefore estimated to be 4.4% for children aged 5–16 years, 3.1% for the 2-4-year-old category, and 0.9-2.2% for those aged 2-23 months (Table 7). Approximately 1% of individuals aged 17–20 years experienced absenteeism due to the side effects of the vaccine.

Table 7 Absenteeism due to local reactions or fever or general malaise with onset within the first 48 hours (day 1 or day 2) and attributed to 4CMenB vaccine

	2-11 months	12-23 months	2-4 years	5-11 years	12-16 years	17-20 years	Total
	N = 746	N = 811	N = 2 459	N = 5 067	N = 2 163	N = 1 086	N = 12 332
Onset D1 or D2	1,0%	2,5%	3,3%	4,6%	4,5%	1,1%	3,7%
Onset D3 to D7*	0,1%	0,8%	0,7%	0,3%	0,3%	0,2%	0,4%
Attributable to 4CMenB %	0,9%	2,2%	3,1%	4,4%	4,4%	1,0%	3,5%

* Adjusted percentage.

4.4 Open-ended Comments

Of the 12,332 individuals who completed the online questionnaire as of July 2, 2014, 20% (2,440) entered a comment at the end of the survey. Nearly 90% of them (n=2,194) reported a health problem that did not result in absenteeism or a medical consultation. The proportion of respondents who provided a comment varied slightly according to age group, with the group aged 17-20 years having the most comments (23%) and parents of 0- to 2-year-olds entering the fewest comments (15%).

Most comments involved local reactions which were mentioned by 85% (2,073) of them: 97% reported pain at the injection site while 3% wrote they experienced signs of inflammation (redness and swelling). Of those who reported pain at the injection site, 4% said that the pain was severe enough to interfere with their daily activities. Among individuals who reported a local reaction, 11% said this lasted for more than a week.

Systemic events (fever and change in overall health) were spontaneously reported by 32% (778) of those who provided a comment. In this group, 44% (342) reported fever, 35% (270) reported fatigue, irritability or crying, while 21% (166) said they had headaches in the week post-vaccination.

4.5 Intention to Receive the Next Dose

Of the 12,332 individuals who completed the questionnaire, 99% mentioned that they likely or definitely intended to receive the next dose of the vaccine, whereas this was 92% in the 764 individuals who reported absenteeism or a medical consultation (Table 8).

Table 8 Intention to receive the second dose by age at vaccination

Intention to receive the 2nd dose	2-11 months	12-23 months	2-4 years	5-11 years	12-16 years	17-20 years	Total
Of all vaccines	**N = 476**	**N = 811**	**N = 2 459**	**N = 5 067**	**N = 2 163**	**N =1 086**	**N = 12 332**
Definitely	630 (84%)	683 (84%)	2 060 (84%)	3 927 (78%)	1 540 (71%)	672 (62%)	9 512 (77%)
Likely	96 (13%)	107 (13%)	324 (13%)	974 (19%)	486 (22%)	337 (31%)	2 324 (19%)
Likely not	9 (1%)	6 (1%)	18 (1%)	39 (1%)	31 (1%)	25 (2%)	128 (1%)
Definitely not	0	2 (< 1%)	3 (< 1%)	5 (< 1%)	8 (< 1%)	8 (1%)	26 (< 1%)
In vaccinees with an absenteeism or a medical consultation	**N = 33**	**N = 77**	**N = 212**	**N = 291**	**N = 117**	**N = 34**	**N = 764**
Definitely	16 (48%)	49 (64%)	143 (67%)	174 (60%)	66 (56%)	9 (26%)	457 (60%)
Likely	14 (42%)	20 (26%)	53 (25%)	102 (35%)	37 (32%)	15 (44%)	241 (32%)
Likely not	3 (9%)	6 (8%)	13 (6%)	10 (3%)	6 (5%)	6 (18%)	44 (6%)
Definitely not	0	2 (3%)	2 (1%)	2 (1%)	3 (3%)	4 (12%)	13 (2%)

Among all vaccinated individuals who completed the electronic questionnaire, 154 indicated that they likely not or definitely not had the intention to receive the next dose. Of these, 131 (85%) provided a single reason, 16 (10%) gave two reasons and 7 (5%) gave three reasons. Following a review of the comments, only the main reason is presented (Table 9).

Table 9 Reasons given by the 154 vaccinees who likely or definitely have no intention of receiving the second vaccine dose

	N = 154
Adverse events (pain, general malaise, vomiting, headache, loss conscience, rash)	53%
Concerns with the vaccine (experimental or new vaccin, risk and safety, efficacy, negative influenza of medias)	11%
Leaves the region	6%
Risk of disease perceived as low (does not consider him/herself at risk)	4%
1 dose is enough	4%
Personal choice	3%
Did not know that there was a second dose	3%
Concerns regarding the usefulness of the mass campaign (number of cases in the Saguenay region, need for vaccination)	1%
Vaccine accessibility	1%
No response/ no reason	14%

Adverse effects following the first dose were the main reason (53%) indicated (Table 9).

5 Results of Passive Surveillance

5.1 Passive Surveillance (ESPRI)

Between May 5 and July 2, 2014, 56 AEFI associated with the meningococcal serogroup B vaccine were reported by physicians or nurses to the Direction de la santé publique for health region 02. As of July 7, 2014, 49 of these cases had been investigated, 39 were entered into the passive surveillance database (ESPRI database) and 37 belonged to the age group targeted by the mass vaccination. Among these 37 cases, 46% (n=17) involved allergic-like events, 30% (n=11) reported fever, and 19% (n=7) reported a large local reaction (Table 10). Two neurological problems were reported: one convulsion and one paresthesia. The convulsion occurred 8 hours after the vaccine was administered in a baby less than 6-months old who had not been given antipyretic prophylaxis; the convulsion lasted less than one minute and occurred shortly after taking an antipyretic treatment. This was medically diagnosed as febrile convulsions. Three other unexpected clinical events were reported, including two that could be considered neurological problems (memory loss), and the last one was an arthralgia in the elbow and knee lasting less than 24 hours that did not require a medical consultation (Table 10).

Mean time to onset of symptoms was 23 hours (median of 8 hours) with a mean duration of 5.1 days (median of two days). The severity of all reported cases entered was mild or moderate and recovery was noted for all cases at the time of investigation.

Two cases were considered to be serious adverse events. These cases presented allergic-like events (bronchospasm) within 4 and 6 hours post-vaccination and were hospitalized for 24 and 48 hours.

Table 10 Number and rate of AEFI reported in the ESPRI surveillance after the first dose of meningococcal serogroup B vaccine/10,000 doses administered in the Saguenay-Lac-Saint-Jean health region as of July 7, 2014

	2-11 months		12-23 months		2-4 years		5-11 years		12-16 years		17-20 years		Total	
	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	N	Rate
Total 1st doses administered	**1 906**		**2 141**		**6 488**		**16 890**		**11 579**		**5 450**		**44 454**	
Total AEFI	**6**	**31.5**	**3**	**14.0**	**10**	**15.4**	**4**	**2.4**	**7**	**6.0**	**7**	**12.8**	**37**	**8.3**
Fever	**5**	**26.2**	**1**	**4.7**	**3**	**4.6**	**1**	**0.6**	**0**	**0.0**	**1**	**1.8**	**11**	**2.5**
Local reaction (serious)	**0**	**0.0**	**1**	**4.7**	**0**	**0.0**	**0**	**0.0**	**1**	**0.9**	**5**	**9.2**	**7**	**1.6**
Systemic	**3**	**15.7**	**1**	**4.7**	**10**	**15.4**	**3**	**1.8**	**3**	**2.6**	**2**	**3.7**	**22**	**4.9**
Allergic-like	2	10.5	1	4.7	9	13.9	2	1.2	2	1.7	1	1.8	17	3.8
Rash	0	0.0	0	0.0	1	1.5	0	0.0	1	0.9	0	0.0	2	0.4
Anaphylaxis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Hypotonic/Hyporeactive	1	5.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Arthralgia/Arthritis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.8	1	0.2
Vomiting/Diarrhea	0	0.0	0	0.0	0	0.0	1	0.6	0	0.0	0	0.0	1	0.2
Incessant crying	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	**0**	0.0
Neurological problems	**1**	**5.2**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**1**	**0.9**	**0**	**0.0**	**2**	**0.4**
Convulsions	1	5.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Anesthesia/paresthesia	0	0.0	0	0.0	0	0.0	0	0.0	1	0.9	0	0.0	1	0.2
Other AEFI*	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**2**	**1.7**	**1**	**1.8**	**3**	**0.7**
Serious Adverse Event**	**0**	**0.0**	**0**	**0.0**	**2**	**3.1**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**2**	**0.4**

Source ESPRI: 2014-07-07.

V09: extraction 2014-07-02.

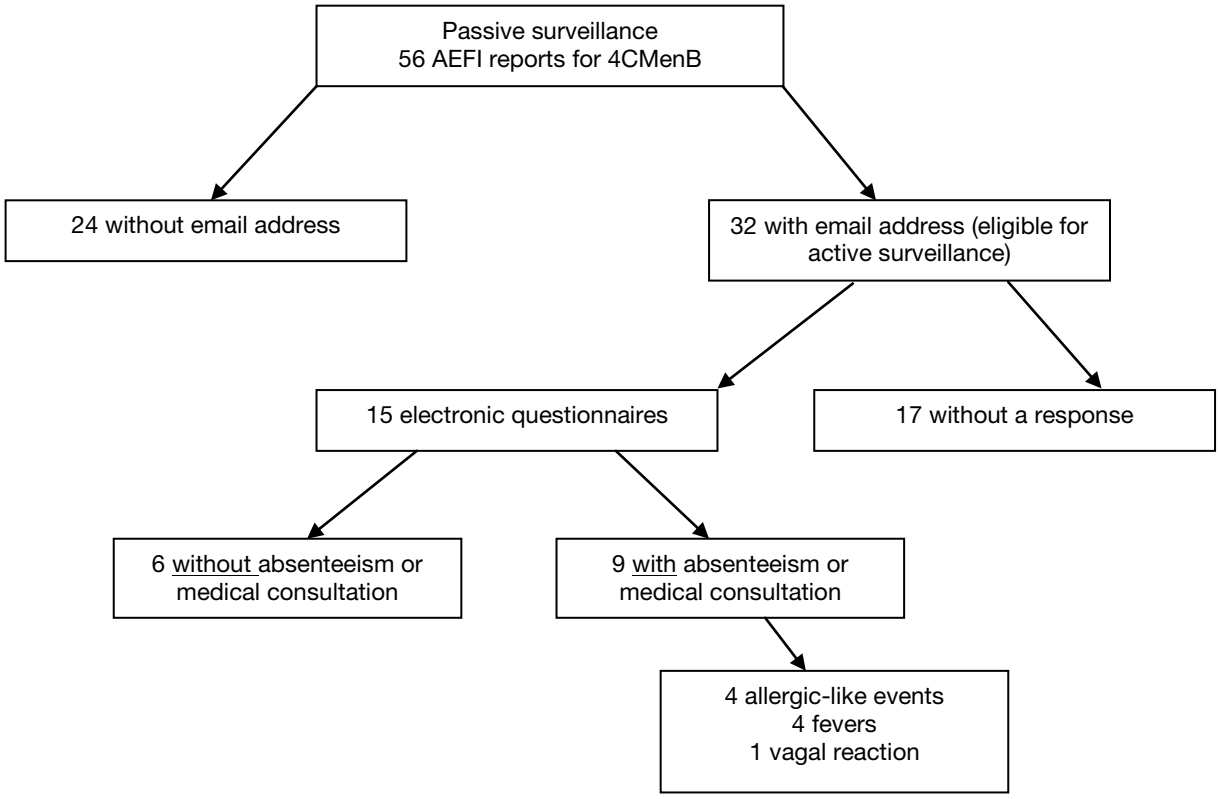
* Based on item 250 of the reporting form -Other serious AEFI.

** Serious adverse event: required hospitalization (24 hours or more), life threatening (eg. anaphylactic schock) or causing permanent disability or death.

5.2 AEFI Reported to both Active and Passive Surveillance

Among the 56 AEFI cases reported to the passive surveillance, 32 (57%) had an email address in the V09 database and 15 (27%) completed the online questionnaire. Of these, 9 (60%) appeared in both the passive and active surveillance (four with allergic-like events, four with fever and one with a vagal reaction). No active surveillance report was generated for six individuals: four (27%) did not have absenteeism or medical consultation and two (13%) did not report being sick in the week post-vaccination in their questionnaire.

Figure 5 Adverse events following the meningococcal serogroup B vaccine reported to passive and active surveillance between May 5 and July 2, 2014, in health region 02 (Saguenay–Lac-Saint-Jean)



6 Discussion

During the meningococcal serogroup B vaccination campaign targeting individuals aged ≤ 20 years living in the Saguenay-Lac-Saint-Jean region, we conducted an enhanced surveillance to ensure that the vaccine is safe. Although only one quarter of the vaccinees took part in active surveillance after the first dose of the vaccine was administered, these 12,332 individuals still represent a greater number than the total number of participants in pre-licensure studies conducted before the vaccine was marketed.[1] No serious or unexpected vaccine-related health problem was identified in our surveillance. However, the surveillance confirmed that the vaccine causes painful local reactions and there were numerous reports of fever and general malaise severe enough to result in absenteeism. Despite this, almost all of the individuals vaccinated intended to take the second dose.

In clinical trials, a non-significant excess of cases of Kawasaki disease (KD) was observed in approximately 90 cases per 100,000 person-years (PY), i.e. 6 out of 6,403 subjects who took the 4CMenB vaccine and approximately 60 cases per 100,000 P in the children (1/1,694 children) in the control group.[1] There was a single case of KD in the week post-vaccination. This disease essentially affects children 5 years of age and under. A retrospective evaluation of the MED-ECHO database for hospitalizations from 2008-2012 estimated a rate that ranged between 12 and 25 cases per 100,000 PY in children aged 5 years and under for the entire province (Deceuninck G, personal communication). In health region 02, the KD rate was 7.6 per 100,000 (6 cases over 5 years). Considering that the vaccine was administered to 12,511 children aged 2 months to 5 years between May 5 and June 17, 2014, the probability of detecting even a single case was very low since passive surveillance had a cumulative follow-up of 1,000 to 2,000 PY (assuming a 1- to 2-month follow-up for all vaccinees) and active surveillance accumulated less than 100 PY in follow-up (4,813 children x 1 week). Even though no cases of KD were detected, no definitive conclusion can be drawn and continued monitoring of the population is required to learn more about this.

In the clinical trials, there were four cases of seizures within 24 hours post-vaccination of 2,481 infants with the 4CMenB vaccine (1 convulsion per 620 infants) and no cases were reported in the 1,149 controls.[1, 5] If a similar risk had affected the 3,886 children aged 2–23 months who were vaccinated in RSS 02, we would have expected 6 seizures (3,886 children x 1 seizure/620 children). Two cases of simple febrile convulsion were reported, one in passive surveillance (1 in 3,886 children) and the other in active surveillance (1 in 1,557 children). Although these low numbers do not allow us to draw any solid conclusions, they suggest that the risk of febrile convulsions in health region 02 was not higher than expected.

In a clinical trial, severe transient arthralgia (no specific definition in the publication) was reported in 12% of the 84 children vaccinated at the age of 40–43 months.[7-8] In active surveillance, there were 113 reported cases of arthralgia (< 1% of vaccinees). After nurse validation by telephone, only 5 vaccinees truly suffered from arthralgia (two cases in the 2- to 4-year-old group, one in the 5- to 11-year-old group, two in the 12 years group) and none presented edema or redness of the joints compatible with arthritis. The risk of arthralgia in the week after the first dose of vaccine is therefore much lower than what was reported in the above-mentioned clinical trial and the reported cases of arthralgia were mild to moderate with no signs of arthritis.

In two clinical trials, post-vaccination absenteeism was reported in 12% of young people and in 9% of adults vaccinated with the 4CMenB vaccine.[6, 10] In our active surveillance, there was a gradual increase in the rate of absenteeism within seven days post-vaccination from 3% in the 17- to 20-year-old group to 5–6% in the 5- to 16-year-old group and 8–9% in the 1- to 4-year-old group. To conservatively estimate absenteeism likely attributed to vaccination, we only considered absenteeism

related to local reactions, fever, or general malaise with onset within 48 hours post-vaccination and subtracted the frequency of absenteeism related to fever and general malaise that took place on days 3 to 7 which was considered to be representative of the baseline risk. We found that these adverse reactions to the vaccine resulted in absenteeism in 3% to 4.4% of vaccinees aged 2 to 16 years. A parent or another person also had to be absent in about half of the absenteeism cases. This rate of absenteeism due to the vaccine is not trivial and significantly increases the societal cost of this vaccination.

Although fever was reported in all age groups, it was particularly important to monitor fever in the 2- to 23-month age group due to the risks of febrile seizures. Onset of fever within 48 hours post-vaccination was reported in 14–15% of children aged 2 to 23 months in active surveillance, which is lower than the rate of 40–48% observed in the clinical trials.[1, 11-12] Very high fever of ≥ 40.5°C was reported in less than 1% of the individuals vaccinated. In the 2- to 23-month age group, this high temperature was reported in only one of the 1,557 children. In the majority (54%) of children aged 2-23 months with reported fever, the maximum temperature was below 39°C. Administration of antipyretic prophylaxis in 93% of children in this age category may partly explain these results, since it reduced the frequency of reported fever by half. The impact of this prophylaxis was particularly pronounced in children who received the vaccine co-administered with other pediatric vaccines. Therefore, it seems useful to maintain this recommendation of antipyretic prophylaxis in children under 2 years of age. In individuals aged 2–20 years, prophylaxis was frequently used even if it was not recommended. Antipyretic prophylaxis also reduced the frequency of fever in the 2- to 11-year-old group, but not in the ≥12 year-old group. The Comité sur l'immunisation du Québec (CIQ) will need to review whether or not there this prophylaxis should be recommended in children aged 2–11 years.

This study has a number of limitations. Active surveillance has the advantage of improved sensitivity over passive surveillance in detecting targeted events. However, passive surveillance covers the entire population and not simply those with an email address who agree to participate. While active surveillance focused on the health problems that occurred within the week post-vaccination, passive surveillance did not have this restriction in terms of follow-up period. However, this may be a weak advantage since it is often difficult for healthcare professionals to make a connection between an adverse event and vaccination if there is a long interval between vaccination and symptom onset. Neither passive nor active surveillance have a control group of non-vaccinated individuals for baseline comparison to estimate the frequency of adverse events attributable to the vaccine. However, if our surveillance had detected an unexpectedly high frequency of a specific AEFI, we were already prepared to extract from the provincial database (RAMQ) the medical consultations for this AEFI and compare its frequency in vaccinated and non-vaccinated individuals. With slightly more than 43,000 vaccinees, of which 12,332 took part in active surveillance, this study did not have the sample size or statistical power to detect rare unexpected clinical events. The active surveillance received a completed electronic questionnaire from less than half of the individuals who provided an email address. It is possible that the individuals who experienced an AEFI were more inclined to participate, which would have overestimated the risk. However, active surveillance underestimated the frequency of all AEFI since it targeted only those with a severity sufficient enough to result in absenteeism or a consultation. There was also underestimation due to vaccinated individuals who were sick on Saturday or Sunday and therefore not absent from school or daycare, as well as children who do not attend these institutions.

Active surveillance via electronic means has the benefit of being able to cover a large population and to quickly provide information. Since participants could describe a number of AEFI, this information required validation. Since most of AEFI were unlikely to be caused by the vaccine (e.g. respiratory

infection); a nurse only called cases with severe and possibly vaccination-related AEFIs. The criteria to identify these cases were based on the severity of the AEFI as well as the plausibility of a causal relationship with the vaccine. This validation allowed a better identification of the AEFI primarily responsible for absenteeism or a medical consultation. Lastly, the results presented were observed after the first dose of the 4CMenB vaccine and should not be extrapolated to the second dose.

In conclusion, for the first dose, the surveillance identified no safety signal about the 4CMenB vaccine that could call into question the continuation of the vaccination campaign. In respect to the population, although a high number of vaccinees complained of pain at the injection site and general malaise associated with the vaccine, almost all of the vaccinated individuals intended to take the second vaccine dose. The second dose of vaccine will be administered in the fall and surveillance will continue to ensure that everything is done safely and meets expectations. This surveillance will include the same elements as with the initial dose but will also look for serious adverse events (resulting in hospitalization, persistent disability or life-threatening events) that had occurred between the first and second doses.

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Appendix 1

Information sheet for vaccinees

POST-VACCINATION MONITORING

You or your child has just received the meningococcal serogroup B vaccine. A number of studies have shown that this vaccine is safe. As with every new vaccine, post-vaccination monitoring is conducted by public health authorities with the assistance of health professionals.

If you provided your email address on the vaccination form, you will receive an email seven days after vaccination. You will be asked to complete a brief online questionnaire on the health status of the vaccinated person during the week after vaccination. Questions will address mainly the onset of **fever or a health problem serious enough to warrant medical attention or the absence of the vaccinated person or a parent from daycare, school, or work**. Simply click on the link in the email to access the questionnaire; it will take only 5 minutes to complete. Depending on your responses, a nurse may call you to obtain more information.

The email will be sent by Simple Sondage, but questionnaires will be evaluated only by Québec public health staff. Data will be kept strictly confidential.

CHECKLIST

We suggest using the checklist below. When the time comes, it will help you complete the questionnaire on post-vaccination health status. It is important to use the checklist even if you do not think the vaccinated person's health status is linked to administration of the vaccine. **Check off the days where the vaccinated person experiences fever (has a temperature) or health problems serious enough to warrant medical attention or the absence of the vaccinated person or a parent from daycare, school, or work.**

	Day of vaccination	DAYS AFTER VACCINATION					
		2	3	4	5	6	7
Fever (has a temperature) Enter the highest temperature: _____ **The temperature was taken:** ☐ In the mouth (orally) ☐ In the rectum (rectally) ☐ In the armpit (axillary) ☐ In the ear (tympanic)	☐	☐	☐	☐	☐	☐	☐

Other health problems experienced in the 7 days after vaccination that warranted **medical attention or the absence of the vaccinated person or a parent:**	Day of vaccination	2	3	4	5	6	7
Specify: _____	☐	☐	☐	☐	☐	☐	☐
Specify: _____	☐	☐	☐	☐	☐	☐	☐
Specify: _____	☐	☐	☐	☐	☐	☐	☐

<u>For children under age 2:</u>
If you used medication to <u>prevent</u> the onset of fever or pain (e.g., Tylenol, Tempra, Motrin, Advil), indicate when you administered the medication:

☐ I administered medication to <u>prevent</u> the onset of fever or pain.

Time of vaccination: _____

Name of medication: _____

Time(s) the medication was administered: _____/_____/_____/_____

This document is for your personal use only. It does not need to be sent to public health authorities.

Appendix 2

Criteria warranting a nurse telephone call to assess health problem

Criteria to determine individuals who had to be called by a nurse to evaluate their health problem

- Fever → Onset on days 1 or 2 and ≥ 40 °C
  → Onset on days 1 or 2 and lasting ≥ 4 days
- Local reaction → Onset on days 1 or 2 and lasting ≥ 4 days
- General malaise → Onset on days 1 or 2 and lasting ≥ 4 days
- Cutaneous problems → Onset on days 1 or 2
- Arthralgia → All
- Neurological problems → All
- Respiratory problems → None (except if other criteria met)
- Gastrointestinal problems → None (except if other criteria met)
- Other AEFI → Decided on a case-by-case basis
- Hospitalizations → All

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