

Summary of the Recommendation from the “Comité d’immunisation du Québec” (CIQ)

Advice on the appropriateness of an intervention to control a high invasive meningococcal serogroup B incidence in Eastern Quebec

Since the last outbreak of invasive meningococcal disease (IMD) caused by a virulent clone of serogroup C which resulted in a mass vaccination campaign with a conjugate (2001) vaccine, as well as the implementation of routine childhood (in 2002) and adolescents programs (2013), the vast majority of IMD in Canada are caused by strains of serogroup B (IIM-B). Quebec is the province where the incidence of IIM-B is highest and there are differences in the incidence rates at the regional level. In 2003, a particular clone of serogroup B, ST-269, was identified in Quebec and spread first among teenagers and young adults then reach young children. Currently, this clone represents a high proportion of strains circulating in the eastern province, three health regions (RSS) being particularly affected: the Saguenay-Lac-Saint-Jean (RSS 02), Capitale-Nationale (RSS 03) and Chaudière-Appalaches (RSS 12).

Faced with a situation of higher incidence prevailing in the eastern province of Quebec and availability in early 2014 of a potentially protective vaccine, the Ministry of Health and Social Services of Quebec (MSSS) asked the “Comité d’immunisation du Québec” (CIQ) to prepare an opinion on the appropriateness of a control intervention limited in time and space with the following objective: sustainably reduce the incidence IIM-B in the RSS most affected and to avoid, insofar as possible, an extension of the circulation of the virulent clone to other regions.

Epidemiology of IIM-B in Quebec

An analysis of surveillance data on notifiable diseases (MADO) and data from the Public Health Laboratory of Quebec (LSPQ) for the years 2006 to 2013 identified a total of 602 cases of IMD: 468 (78%) were serogroup B, 304 (65%) of whom occurred in individuals 20 years of age or less. The overall IIM-B in the population incidence rate was 0.7 / 100 000 p.-y, 2.1 / 100,000 p.-y in 20 and under and 0.3 / 100,000 p.-y in the population aged over 20 years.

During the same period, the incidence rate in the RSS 02, RSS 03 and RSS 12 were statistically higher than the provincial average. In the age group 20 years and under, these rates were 11.5, 5.2 and 2.1 per 100,000 respectively, in RSS 02, RSS 03 and RSS 12. In the group age 21 and older, these rates are respectively 1.1, 0.4 and 0.3 per 100,000 p.-y.

Among the 468 cases of IIM-B, 191 (41) came from 02 regions (74 cases: 16%), region 03 (77 cases: 16%) and region 12 (30 cases, 9%). The 3 most affected regions represent 46% of total cases of IIM-B in the 20 years and under age group.

Incidence rates observed in 2013 remain high, ie 10 per 100,000 p.-y in the region 02 and 5 in the 03 region. In RSS 12, a particularly high incidence was observed in 2007, but since

then, rates are comparable to the provincial average.

The IIM- B are serious diseases with lethality of the order of 4 to 6%. Lethality is higher in young children . Permanent physical sequelae occur in approximately 20% of survivors and neurological deficits in more than half .

The 4CMenB vaccine

A new vaccine prepared from meningococcal surface proteins and components of outer membrane vesicles was approved in Canada in December 2013 (Bexsero , Novartis Vaccines). It induces the appearance of bactericidal antibodies that are considered as a marker of protection . Studies comparing the phenotype and genotype of the proteins contained in the vaccine and those in the invasive strains circulating in Quebec suggests that the vaccine would cover at least two thirds of all strains and 90% of strains caused ST-269 clone.

The effectiveness of 4CMenB has not been evaluated in clinical trials. Vaccine efficacy was derived from immunogenicity studies demonstrating induction of bactericidal antibody responses in serum vis-à -vis each of the vaccine antigens . Immunization of infants with three doses and children, adolescents and young adults with two doses of 4CMenB induces bactericidal antibodies in the majority of vaccinees. One month after the primary vaccination course (2 , 4, and 6 months) , between 84 % and 100 % of the infants had bactericidal antibodies against the components included in the vaccine. The immunogenicity of 3 doses before age 6 months is comparable to that observed after vaccination of children aged 6 to 60 months with two doses. The immunization schedule with two doses spaced 6 months apart seems to induce higher antibody titers in a higher proportion of adolescents than the immunization schedule with intervals of one month or two months between doses.

Six months after the primary vaccination (at the age of 12 months), a significant proportion of vaccinated children no longer had antibody titers considered seroprotective: 18% against the fHbp and 39% against the NHBA (proteins present in the clonal complex ST 269).

One month after the booster dose given during the second year of life, 97-100 % of vaccinated children had antibody titers considered seroprotective . Twelve months after the booster dose, 38% and 64% of children vaccinated with 4 doses (0, 2, 6 and 12 months) no longer had titers considered seroprotective against fHbp and NHBA . Generally , the data indicate a more rapid decay of antibodies after vaccination of infants than after vaccination of young children and adolescents. It is not known whether the rapid decline of antibody titers after vaccination corresponds to a loss of protection against the disease.

Data from clinical studies suggest that the of 4CMenB vaccine is more reactogenic than routine vaccines currently used in Quebec , especially in infants less than 6 months. Coadministration of 4CMenB with some routine vaccines seems to increase the frequency of adverse effects, especially systemic effects such as fever . The majority of adverse events

after vaccination were of short duration and did not require medical attention. However, a significant proportion of vaccinated individuals reported adverse reactions (eg fever $\geq 39^{\circ}$ C) or absenteeism in the days following vaccination.

Cost-effectiveness evidence

The majority of simulations in economic analyzes indicate cost-effectiveness ratios unfavorable ($> \$ 40,000 / \text{QALY}$) when the price per dose is higher than \$ 30. It is in the RSS 02 that the cost-effectiveness ratios are most favorable in Quebec, given the higher incidence of the disease.

However, there remains some uncertainty to date regarding the use of 4CMenB vaccine and its effectiveness in reducing the burden of disease in a sustainable manner . The main uncertainties that have been discussed are:

- Actual vaccine efficacy and duration of protection by age groups;
- Capacity of the vaccine in reducing carriage, to limit transmission and to induce herd immunity affecting those vaccinated and the age groups not covered by a mass vaccination campaign;
- Number of birth cohorts needed to be vaccinated and coverage for herd immunity ;
- Capacity of a specific intervention limited in time and space to sustainably reduce the incidence of disease in the targeted region; impact on the acceptability of all of the routine immunizations when using a vaccine with higher reactogenicity.

Recommendation

Whereas :

The incidence of IIM- B is substantially higher in the RSS 02 than in the other RSS and that this situation continues since 2004 with no recent signs of decline.

A lethality of 9% in individuals less than 21 years of age has been observed in the last 8 years in SSR 02. The unpredictability of the disease and its rapid clinical course , even with the best treatments, are creating fear and raising anxiety in the region with the highest incidence.

The 4CMenB vaccine has the ability to cover a large proportion of meningococcal clones circulating in this region. The 4CMenB vaccine is a vaccine for which the clinical efficacy is not known , however it has the ability to induce bactericidal antibodies considered protective in the vast majority of vaccinees.

The 4CMenB vaccine may also reduce the transmission of meningococcal disease in the population and thereby induce herd immunity indirectly protecting unvaccinated people . However, the magnitude of this effect and its persistence following a mass immunization campaign are uncertain.

The reactogenicity of the 4CMenB vaccine is higher than vaccines currently used in Quebec, especially in young children, and particularly when coadministered with other vaccines. However, one can predict that the reactogenicity is reduced by prophylactic use of acetaminophen post- vaccination.

CIQ members unanimously recommend immunization of young people aged 20 years and under who reside in the RSS Saguenay-Lac -Saint- Jean, to control the endemic situation that persists. This public health intervention that is limited in time and space will be subject to rigorous evaluation and lessons learned from this intervention will be used to determine the future use of this vaccine. However, such a measure is expected to only marginally reduce the total burden of IIM- B across the entire Province of Québec.

For the other RSS in Québec, enhanced epidemiological surveillance must continue to analyze trends and, where appropriate, new recommendations on the use of 4CMenB vaccine may be issued.